

Additional Resources:

- Clinicians are encouraged to review the complete recommendations at www.cdc.gov/hiv/topics/testing/healthcare
- Mountain Plains AIDS Education and Training Center: www.mpaetc.org
- AIDS InfoNet: www.aidsinfonet.org/
- AETC National Resource Center: www.aidsetc.org/
- National HIV/AIDS Clinicians' Consultation Center: www.ucsf.edu/hivcntr/
- CDC HIV Website with many information links: <http://www.cdc.gov/hiv/>
- HIV InSite: <http://hivinsite.ucsf.edu/InSite>
- National HIV Testing Resources: <http://www.hivtest.org/>



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HIV Testing Recommendations



November 2006

This guide is based on: Centers for Disease Control and Prevention (CDC). (2006, September 22). Revised recommendations for HIV testing of adults, adolescents, and pregnant women in healthcare settings. Retrieved 22Sep06 from: www.cdc.gov/hiv/topics/testing/healthcare

Recommendations are based on best practices and meant to comply with ethical principles of informed consent. Recommendations do not take into account state, local, or institutional regulations.

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CDC Recommendation for HIV Testing: Opt-out HIV screening and HIV diagnostic testing should be a part of routine clinical care in all healthcare settings.¹

- “Screening” means that all patients in a certain population are tested for a disease regardless of the presence of signs, symptoms, or risk factors. The CDC recommends that HIV screening be a routine part of healthcare for all individuals in any of the following circumstances:
 - › between the ages of 13 and 64 years of age²
 - › in care for tuberculosis (TB)
 - › in care for other sexually transmitted diseases (STDs)³
 - › women considering conception and pregnancy
 - › pregnant women⁴
 - › women in delivery with undocumented HIV status at the onset of labor⁵
 - › infants born to mothers with undocumented HIV status.⁶

- “Opt-out testing” means that a test will be performed unless the patient specifically declines to have the test. The CDC recommends that:
 - › Oral or written information should be provided at the time of the test. Information should be at an appropriate health literacy level for the patient and in the patient’s primary language. Information should include:
 - An explanation of HIV infection
 - A description of ways to prevent HIV transmission
 - The meaning of positive and negative test results
 - › HIV testing should be voluntary and free from coercion. No patient should be tested without prior knowledge that the test will be done. The patient should then be given the opportunity to ask questions and to decline testing.
 - If a patient – especially one who is pregnant – refuses testing, providers should elicit reasons for that decision (i.e., fear

¹Healthcare settings include emergency and urgent care sites, primary care settings, corrections health care, substance use treatment services, outpatient clinics, and inpatient services in all public and private sectors.

²Unless the prevalence of undiagnosed HIV in clinic patients has been documented at < 1/1000 (0.1 %); if prevalence rates are not known, voluntary HIV screening should be implemented.

³Should be screened at each visit for a new STD complaint.

⁴Should be screened as soon as possible during pregnancy. Repeat testing during the third trimester (preferably at < 36 weeks) may be considered for all pregnant women but is recommended for women who live in jurisdictions with elevated rates of HIV in women between the ages of 15 and 45, in women who receive care in facilities with 0.1 % HIV infection prevalence in pregnant women, in women with known high risk factors, or in women who have signs and symptoms of HIV.

⁵Rapid testing is recommended in these cases.

⁶The recommendations are not specific about parental consent, which in many cases is dictated by specific state law.

- of stigma, lack of perceived risk, concerns about partner/family reactions, fear of a positive test, etc.) and discuss those concerns with the patient.
 - The decision to opt out of testing should be documented in the patient record.
 - Patients who decline testing – especially those who are pregnant – should be offered the test at subsequent clinic visits.
- › General consent for medical care is sufficient for HIV testing; separate, written consent for an HIV test should not be required.

- “Diagnostic testing” is performed when a patient presents with the signs and symptoms of a specific disease. The CDC recommends that:
 - › Patients with signs and symptoms of HIV be tested as part of the diagnostic workup⁷
 - › Patients at high risk for HIV, based on risk assessment, be screened every year⁸

CDC Recommendations for Communicating HIV Test Results:

- A negative HIV test result can be conveyed without direct personal contact. Patients known to have recent or continuing high-risk behaviors should be encouraged to have periodic testing, and provided with (or referred to) prevention counseling services.
- A positive HIV test result should be communicated in a private setting with direct contact between the patient and clinician.
 - › Assure confidentiality. Family members should not be used as translators.
 - › Help the patient find appropriate resources for healthcare, counseling, prevention services, and mental health/substance use care.
 - › Discuss partner notification and offer services to help in that process.⁹

⁷Clinicians should be familiar with the many manifestations of acute and chronic HIV infection, which include not only opportunistic infections but nonspecific abnormalities such as weight loss, lymphadenopathy, hypoalbuminemia, anemia, increased rate of community acquired pneumonia, etc. See also, Orenstein, R. (2002). Presenting syndromes of human immunodeficiency virus. Mayo Clinic Proceedings, 77, 1097. Available at: <http://www.mayoclinicproceedings.com/inside.asp?AID=196&UID=>

⁸People considered to be at high risk for HIV include injection drug users (IDUs) and their sex partners, those who have sex with more than one person or whose sex partner has sex with more than one partner, people who exchange sex for drugs or money, and sex partners of individuals known to have HIV infection.

⁹Funding for HIV care is available for infected patients. Local health departments can help with patient referrals to care services. Remember: The privacy rule under HIPAA prohibits disclosure of a patient’s health information, including HIV status, without the patient’s permission, except as required by local public health law.

- HIV test results should be documented in the patient’s confidential medical record.

CDC Recommendation about Counseling: Prevention counseling should not be required as a part of the HIV testing or screening process. Testing may, however, create an ideal opportunity to discuss risk and to provide (or arrange for) prevention counseling.

Why provide routine screening for HIV infection?

- 25% of people living in the U.S. with HIV do not know they are infected.
- HIV is a serious health problem that can be reliably diagnosed prior to symptom development and patients are more likely to be tested if it is suggested by a clinician.
- Routine testing helps to de-stigmatize the disease.
- Early entry into care increases the likelihood of a longer, healthier life. Unfortunately, an estimated 39% of people with HIV in the U.S. are not diagnosed until they are in the late stages of the disease.
- Transmission rates are higher in people who do not know they have HIV. Individuals who know their positive HIV status are more likely to engage in risk reduction efforts.
- Appropriate treatment during pregnancy can reduce the perinatal transmission rate to < 2%. Pregnant women who know they are infected are better able to make critical decisions about care for themselves and their infants.

Practical Considerations

- CDC recommendations do not supersede local laws about HIV testing and reporting. Providers should be aware of current local laws and should also be aware that these laws may need to be changed in order to implement these recommendations.¹⁰
- CDC recommendations do not consider facility/institution rules about HIV testing. Providers should be aware of these regulations as well.
- Rapid Testing can substantially decrease the large number of individuals who do not learn their HIV test results.
 - › Rapid test analysis can be completed in 20-30 minutes and reported to patients before they leave the testing site.
 - › Although positive rapid test results can be immediately reported to the patient, they must be confirmed with a more specific laboratory test before a diagnosis of HIV is made. A blood sample should be drawn for the confirming test at the time of the initial

¹⁰See a compendium of state HIV testing laws at: www.ucsf.edu/hivcntr

- test and arrangements made for the patient to return for those results.
- › A preliminary positive test can be frightening and care must be taken to provide support or counseling services to those who need it.¹¹
- › The following table discusses FDA-approved rapid tests.

FDA-Approved Rapid HIV Antibody Screening Tests

Test (manufacturer, approval date)	Specimen Type	CLIA * Category	Sensitivity+ (95% CI)	Specificity+ (95% CI)
OraQuick Advance Rapid HIV-1/2 Antibody Test (OraSure Technologies, 2004)	Whole blood**	Waived	99.6% (98.5–99.9)	100% (99.7–100)
	Oral fluid	Waived	99.3% (98.4–99.7)	99.8% (99.6–99.9)
	Plasma	Moderate complexity	99.6% (98.9–99.8)	99.9% (99.6–99.9)
Uni-Gold Recombigen HIV (Trinity Biotech, 2003)	Whole blood**	Waived	100% (99.5–100)	99.7% (99.0–100)
	Serum/plasma	Moderate complexity	100% (99.5–100)	99.8% (99.3–100)
Reveal G-2 (MedMira, 2003)	Serum	Moderate complexity	99.8% (99.2–100)	99.1% (98.8–99.4)
	Plasma		99.8% (99.0–100)	98.6% (98.4–98.8)
MultiSpot HIV-1/HIV-2 (BioRad Laboratories, 2004)	Serum/plasma	Moderate complexity	100% (99.9–100)	99.9% (99.8–100)
	HIV-2		100% (99.7–100)	

Adapted from Health Research and Education Trust (HRET). FDA-Approved Rapid HIV Antibody Screening Tests, January 10, 2005. Accessed September 27, 2006, from: www.hret.org/hret/programs/hivtransmrpd.html

* The Clinical Laboratory Improvement Amendments (CLIA) program categorizes tests as waived, moderate complexity, or high complexity. Tests approved as CLIA-waived tests may be done at the point of care after appropriate staff training and with procedures in place to insure quality control; results can be available in about 20 minutes. Other rapid tests are “non-waived” and must be performed in laboratories; results can be available in about an hour with available lab support.

**finger stick or venipuncture

+ Sensitivity is the probability that the test will be reactive if the specimen is a true positive

± Specificity is the probability that the test result will be non-reactive test if the a true negative

¹¹See also, Greenwald, J.L., Burstein, G. R., Pincus, J., & Branson, B. (2006). A rapid review of rapid HIV antibody testing. Current Infectious Diseases Report, 8, 125–131. Available at: www.cdc.gov/hiv/topics/testing/resources/journal_article/pdf/rapid_review.pdf

1 Signs and Symptoms

Fever within a week of ER or clinic visit

AND

One or more of the following:

SIGNS

- rash
- lymphadenopathy
- oral/genital/rectal ulcerations
- exudative pharyngitis
- aseptic meningitis (headache, photophobia, stiff neck)

SYMPTOMS

- myalgia/arthritis
- fatigue
- weight loss
- night sweats
- anorexia

Learn to recognize

Acute HIV Syndrome

2 Diagnosing it..

- Identify individuals at risk
- Obtain HIV ELISA test and HIV-PCR test*
- **If ELISA is negative and PCR is positive, diagnostic criteria have been met**

**diagnostic HIV-PCR is preferred, but if unavailable, a "viral load" HIV PCR(bDNA or RNA) may be obtained.*

3 Positive Diagnosis?

● COUNSEL THE PATIENT

- 1) This is a very early HIV infection
- 2) He/she may be extremely infectious
- 3) Transmission of HIV is very possible
- 4) Sex or drug partners should be notified

● ADVISE THE PATIENT

- 1) Significant benefit can result from *Early Expert Evaluation*
- 2) **Immediately** go to your **regional Acute HIV Study Center**
- 3) If there is no Acute HIV Study Center in your area, contact your local AETC listed below for a prompt referral.



National
HIV/AIDS Clinicians'
Consultation Center
which includes the
Warmline
(800-933-3413)
and PEpline
(888-HIV-4911)
with staffed clinical guidance
services 24 hours a day

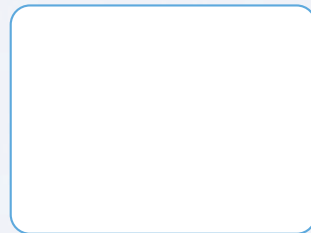
www.nynjaetc.org
212-305-8291



TIMING IS CRITICAL!

Contact your regional

Acute HIV Center



DIAGNOSIS AND MANAGEMENT OF ACUTE HIV INFECTION

What's New - January 2010 Update

- The Medical Care Criteria Committee recognized the need to raise clinical awareness for assessment and identification of acute HIV infection; consequently, these guidelines have been revised to emphasize the importance of testing for acute HIV infection, especially in the setting of a febrile, “flu”-, or “mono”-like illness that is not otherwise explained (see Section II. *Presentation and Diagnosis of Acute HIV Infection*).

Note: In the medical literature, as in this chapter, the terms acute HIV infection, acute retroviral syndrome, acute HIV seroconversion, and primary HIV infection are interchangeable. For consistency, the term acute HIV infection is used in these guidelines.

I. INTRODUCTION

Studies suggest that as many as 50% of HIV transmissions occur during the acute and early stage of the illness.¹⁻⁵ A number of factors contribute to the increased risk for transmission during acute infection:

- Markedly increased viral load levels during acute infection (often much greater than 10 million viral copies/mm³)
- Likelihood that risky behaviors are ongoing during this period because the individual is unaware of his/her HIV status
- The nonspecific “flu-” or “mono-like” symptoms of acute HIV infection that are frequently unrecognized as an indication of HIV infection

Detection of acute HIV infection provides an opportunity to follow patients prospectively soon after infection and thereby reduce disease progression and incidence of OIs. Because patients with a recent diagnosis of HIV are more likely to reduce risk behaviors if they are linked to primary HIV care than if they are not receiving care,⁶ early detection may also be a critical component of preventing further transmission.

II. PRESENTATION AND DIAGNOSIS OF ACUTE HIV INFECTION

RECOMMENDATIONS:

Clinicians should evaluate the following populations for acute HIV infection, particularly when they present with a febrile, “flu”-, or “mono”-like illness that is not otherwise explained:

- **Those who present for HIV testing (AIII)**
- **Those who report a recent sexual or parenteral exposure with a known HIV-infected partner or a partner of unknown HIV serostatus in the past 2 to 6 weeks (AII)**
- **Men who report having unsafe sexual practices with other men (AII)**
- **Those who report needle-sharing (AII)**
- **Those who present with a newly diagnosed sexually transmitted infection (AII)**
- **Those who present with aseptic meningitis (AII)**
- **Pregnant or breastfeeding patients (AIII)**

When acute HIV infection is suspected, a plasma HIV RNA assay should be used in conjunction with an HIV-1 antibody test to diagnose acute HIV infection. (AII) Low-level positive PCR results (<5000 copies/mL) are often not diagnostic of acute HIV infection and should be repeated to exclude a false-positive result. (AII)

Confirmatory HIV antibody testing should be performed 3 to 6 weeks after diagnosis by HIV RNA testing. (AII)

Key Point:

The diagnosis of acute HIV infection requires a high degree of clinical awareness. The nonspecific signs and symptoms of acute HIV infection are often not recognized. Diagnostic HIV RNA testing should be considered for patients who present with compatible symptoms (see Appendix A), particularly in the context of a sexually transmitted infection or a recent sexual or parenteral exposure with a known HIV-infected partner or a partner of unknown HIV serostatus.

A. Presentation

Patients acutely infected with HIV will often experience at least some symptoms of the acute retroviral syndrome. Fever and flu- or mono-like symptoms are common in acute HIV infection but are nonspecific. Rash, mucocutaneous ulcers, oropharyngeal candidiasis, and meningismus are more specific and should raise the index of suspicion. See Appendix A for a more extensive list of signs and symptoms. The mean time from exposure to onset of illness is generally 2 to 4 weeks, with a range of 5 to 29 days; however, some cases have presented with symptoms up to 3 months after exposure.⁷

B. Diagnosis

Acute HIV infection is often not recognized in the primary care setting because of the similarity of the symptom profile with that of the flu or other common illnesses. Furthermore, patients often do not recognize that they may have recently been exposed to HIV. Therefore, the clinician should have a high index of suspicion for acute HIV infection in a patient who may have recently engaged in behavior involving sexual or needle exposure and who is presenting with febrile, flu-, or mono-like illness.

When clinicians suspect acute infection (e.g., in a patient with a report of recent risk behavior in association with symptoms and signs of the acute retroviral syndrome), a test for HIV RNA should be performed. High levels of HIV RNA detected in plasma through use of sensitive amplification assays (PCR, bDNA, or NASBA), in combination with a negative or indeterminate HIV antibody test, support the diagnosis of acute HIV infection. Low-level positive PCR results (<5000 copies/mL) are often not diagnostic of acute HIV infection and should be repeated to exclude a false-positive result. HIV RNA levels tend to be very high in acute infection; however, a low value may represent any point on the upward or downward slope of the viremia associated with acute infection. Viremia occurs approximately 2 weeks prior to the detection of a specific immune response. Patients diagnosed with acute HIV infection by HIV RNA testing still require antibody testing with confirmatory Western blot 3 to 6 weeks later.

Key Point:

Patients undergoing HIV testing who are not suspected to be in the acute stages of infection should receive HIV antibody testing according to standard protocol (see [Diagnostic, Monitoring, and Resistance Tests for HIV](#)). Antibody test results that are initially negative should be followed up with HIV antibody testing at 3 months to identify HIV infection in individuals who may not yet have seroconverted at the time of initial presentation.

III. MANAGEMENT OF ACUTE HIV INFECTION

RECOMMENDATIONS:

Clinicians should offer assistance with partner notification, or refer patients to other sources for partner notification assistance (CNAP, PNAP).

Clinicians should counsel patients about the increased risk of transmitting HIV during acute HIV infection. (AII)

Clinicians should obtain baseline genotypic testing in the setting of acute infection, regardless of whether ARV therapy is being initiated. (AIII)

As part of the management of acute HIV infection, clinicians should:

- **Consult with a provider who has extensive experience in HIV treatment to determine whether to initiate treatment and to discuss possible ARV regimens** (see [Clinical Education Initiative](#) sites available for phone consultation) (AIII)
- **Refer for research opportunities as appropriate** (see Appendix A) (AIII)

- **Counsel patients regarding potential advantages and limitations of ARV therapy during acute infection (AIII)**

If the clinician and patient have made a decision to initiate ARV therapy to treat acute HIV infection, then:

- **Treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AII)**
- **Therapy should not be withheld while awaiting the results of recommended resistance testing; adjustments may be made to the regimen once resistance results are available (AII)**

Patients are at greatest risk for transmitting HIV during the period of viremia prior to the viral setpoint.^{1,8} Clinicians should counsel acutely infected patients about this increased risk of transmitting HIV during the 6-month period after infection.

Although evidence suggests that early ARV treatment has a beneficial effect on clinical outcome,⁹⁻¹¹ the long-term clinical effect of initiating potent treatment regimens early in HIV infection is currently unclear. The clinician and the patient should be aware that therapy for acute HIV infection is primarily based on theoretical considerations, and the potential benefits should be weighed against the potential risks (see Table 1). Data from ongoing clinical trials may help clarify the long-term benefits of treatment of acute infection (see Appendix B for a list of ongoing trials).

TABLE 1 THEORETICAL RATIONALE FOR AND DISADVANTAGES OF INITIATING ARV THERAPY DURING ACUTE INFECTION	
Rationale for ARV therapy	• To reduce the risk of viral transmission • To preserve HIV-specific immune function, including promoting the survival of CD4 cells that are involved in the initial response to HIV infection • To suppress the initial burst of viral replication and decrease the magnitude of viral dissemination • To potentially lower the initial viral setpoint, which may ultimately affect the rate of disease progression • To potentially reduce the emergence of viral mutations as a result of the suppression of viral replication
Disadvantages of ARV therapy	• Adverse effects on quality of life as a result of drug toxicities and complex treatment regimens • Potential for the development of drug resistance if therapy fails due to nonadherence or to insufficient suppression of viral replication, which may limit future treatment options • Earlier commitment to lifetime ARV therapy • Less time to educate the patient about ARV therapy • Insufficient data regarding effectiveness of early treatment

If the clinician and patient have made the decision to use ARV therapy for acute HIV infection, treatment should be implemented with the goal of suppressing plasma HIV RNA levels to below detectable levels. The patient should be counseled regarding potential limitations, and individual decisions should be made only after weighing the risks of therapy against the theoretical benefit of treatment.

Key Point:

Because there are insufficient data to make firm conclusions regarding specific drug recommendations for treating acute HIV infection, a provider with extensive experience in HIV treatment should be consulted when choosing an ARV regimen for a patient with acute HIV infection. The New York State Department of Health AIDS Institute's [Clinical Education Initiative line](#) is available for consultation.

Resistance testing should be obtained to optimize the initial ARV regimen. The increasing incidence of transmission of ARV resistance argues for resistance testing at baseline in all HIV-infected patients, including those who are acutely infected. If information about the source person is available, history of ARV drug resistance should be obtained to assist in selection of a regimen.

Key Point:

The use of a genotypic assay may be preferred in the setting of acute infection because of its more rapid turnaround time. However, if the decision to initiate treatment has been made, therapy should *not* be withheld while awaiting the results of resistance testing. Adjustments may be made to the regimen once resistance results are available (see [Antiretroviral Therapy: VI. 3. Resistance Assays](#)).

If therapy is initiated during acute HIV infection, many clinicians would continue to treat the patient with ARV therapy indefinitely because viremia has been documented to reappear or increase after discontinuation of such therapy; however, this view may change as new evidence becomes available. When discussing whether or not therapy should be continued, clinicians should provide the patient with information regarding current clinical data.

Regardless of whether or not ARV therapy for acute HIV infection is initiated, follow-up for standard HIV testing and HIV primary care should be arranged (see [Primary Care Approach to the HIV-Infected Patient](#)).

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FURTHER READING

- Hecht FM, Wang L, Collier A, et al. A multicenter observational study of the potential benefits of initiating combination antiretroviral therapy during acute HIV infection. *J Infect Dis* 2006;194:725-733. [[PubMed Abstract](#)]
- Patel P, Klausner JD, Bacon OM, et al. Detection of acute HIV infections in high-risk patients in California. *J Acquir Immune Defic Syndr* 2006;42:75-79. [[PubMed Abstract](#)]
- Streeck H, Jessen H, Kuecherer C, et al. Epidemiologically linked transmission of HIV-1 illustrates the impact of host genetics on virological outcome. *AIDS* 2009;23:259-262. [[PubMed Abstract](#)]

APPENDIX A

ACUTE RETROVIRAL SYNDROME: ASSOCIATED SIGNS AND SYMPTOMS (EXPECTED FREQUENCY AMONG PATIENTS WHO ARE SYMPTOMATIC)

- Fever (80%)
- Tired or fatigued (78%)
- Malaise (68%)
- Arthralgias (joint pain) (54%)
- Headache (54%)
- Loss of appetite (54%)
- Rash (51%)
- Night sweats (51%)
- Myalgias (pain in muscles) (49%)
- Nausea (49%)
- Diarrhea (46%)
- Fever and rash (46%)
- Pharyngitis (sore throat) (44%)
- Oral ulcers (mouth sores) (37%)
- Stiff neck (34%)
- Weight loss (>5 lb; 2.5 kg) (32%)
- Confusion (25%)
- Photophobia (24%)
- Vomiting (12%)
- Infected gums (10%)
- Sores on anus (5%)
- Sores on genitals (2%)

Data are from Hecht FM, Busch MP, Rawal B, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS* 2002;16:1119-1129.

* The most specific symptoms in this study were oral ulcers and weight loss. Best predictors were fever and rash. Index of suspicion should be high when these symptoms are present.

APPENDIX B

November 2009

CURRENT RESEARCH ON ACUTE HIV INFECTION BY NEW YORK HIV RESEARCH CENTERS CONSORTIUM*

Center	Type(s) of Research	Contact Information
Aaron Diamond AIDS Research Center (ADARC)	• Basic Laboratory Science • Clinical/Biomedical Science	Martin Markowitz, MD Clinical Director and Principal Investigator on Acute Infection and Early Disease Research Program Grant mmarkowitz@adarc.org
Center for AIDS Research (CFAR) New York University School of Medicine	• Basic Laboratory Science • Clinical/Biomedical Science • Behavioral/Prevention Science	First Call NYU firstcallnyu@nyumc.org 1-212-263-3544

* As of November 2009.

Who is at Risk for HIV?

PATIENTS WHO HAVE OR HAVE HAD:

SEX

- Any unprotected sex
- More than one sex partner ever
- Hx of any sexually transmitted infection

EXPOSURE TO INJECTION/PIERCING

- Unclean needles, particularly if shared
(e.g. IV drugs or injected steroids)
- Unclean drug equipment
- Tattoos inked with needles not properly cleaned & sterilized
- Piercing of ears or body parts with needles
not properly cleaned & sterilized

RECEIVED BLOOD

- Received blood or other blood products before 1985,
or from areas of the world without secure blood supply
- Handled blood or body fluids as a routine part of their job,
(i.e. doctors, dentists, nurses, lab technicians, and funeral workers)
- Infants whose mothers are infected with HIV

OR...

- A sex partner with one or more of the above risk factors

CDC Recommendations for HIV Testing Have Been Revised

The following recommendations were made:

Routine HIV screening for all adult/adolescent patients ages 13-64

Additionally test all patients:



- Tested or treated for a sexually transmitted infection
- Initiating tuberculosis treatment
- Pregnant women
- Women with undocumented HIV status at delivery

Repeat HIV screening is recommended at least annually for persons likely to be at high risk. All screening should be voluntary and conducted only after the patient is fully aware HIV testing is planned.

For more information on screening, consent, opt-out testing, counseling, and prevention recommendations:
www.cdc.gov/hiv/topic/testing/healthcare
State of California HIV testing information: www.dhs.ca.gov/AIDS/

References:

Centers for Disease Control and Prevention. Revised Recommendations for HIV Testing of Adults, Adolescents, and Pregnant Women in Health-Care Settings. *MMWR* 2006;55(No.RR-14):[1-13].

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All photos accessed at:
<http://www.hiv.va.gov/vahiv?page=im-00-00>

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The RED FLAGS of HIV & AIDS A Quick Reference Guide





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AIDS
Education and
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Keck School of Medicine
University of Southern California

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Alhambra, CA 91803
Phone: 626-457-4227
www.paetc.com

Acute (Primary) HIV Infection

Persistent or severe “Flu” like illness that generally occurs 2-8 weeks following exposure and may include the following:

Symptoms	Frequency
• Fever	96%
• Lymphadenopathy	74%
• Rash (erythematous maculopapular with lesions on face, trunk and sometimes extremities)	70%
• Myalgia or arthralgia	54%
• Diarrhea	32%
• Headache	32%
• Nausea and vomiting	27%
• Hepatosplenomegaly	14%
• Weight Loss	13%
• Thrush	12%
• Neurologic symptoms (meningoencephalitis or aseptic meningitis; peripheral neuropathy or radiculopathy; facial palsy; Guillain-Barre syndrome; brachial neuritis; or cognitive impairment or psychosis)	12%

Recommended HIV Tests for acute HIV:

HIV RNA PCR (“viral load”)

- Detects HIV infection earlier than antibody tests
- Tests for HIV virus
- Low level (<10,000) MAY suggest false positive, or may indicate chronic infection if ELISA w/confirmatory Western Blot are positive

ELISA w/confirmatory Western Blot

- If results negative, may not detect HIV infection in acute HIV infection (due to “window period”)
- Tests for HIV antibodies which may take up to 3 months to develop

Symptomatic Chronic HIV Infection

Clinical Presentation

- Thrush (oral candidiasis)
- Herpes zoster
- Oral hairy leukoplakia
- Thrombocytopenia
- Unexplained anemia/neutropenia
- Seborrheic dermatitis
- Unintentional weight loss > 10%
- Fever > 2 weeks
- Diarrhea > 1 month

Symptoms in Women

- The above PLUS:
- Recurrent vulvovaginal candidiasis
- Cervical dysplasia
- Carcinoma in situ of the cervix
- Pelvic Inflammatory Disease (PID)

Oral Hairy Leukoplakia



Photo Courtesy of Paul A. Volberding, MD; UCSF

Herpes Zoster



Photo Courtesy of Paul A. Volberding, MD; UCSF

Oral Candidiasis



Photo Courtesy of Arthur Amman, MD
Global Strategies for HIV Prevention

Recommended HIV Tests for symptomatic HIV

ELISA w/confirmatory Western Blot

- Likely to detect HIV at this stage
- Tests for HIV antibodies
- Confirm positive rapid HIV test results (rapid test is only an ELISA test) w/Western Blot

Advanced HIV Disease (AIDS)

Signs/symptoms

May indicate an opportunistic infection (OI) which is life threatening or may become life threatening if left untreated:

- Visual field defect (loss or distortion): r/o CMV retinitis
- Persistent cough or SOB: r/o *pneumocystis* pneumonia, tuberculosis
- Persistent headache, change in mental status, or focal neurologic changes: r/o cryptococcal meningitis, toxoplasmosis, CNS lymphoma, progressive multifocal leukoencephalopathy
- Diarrhea: r/o isosporiosis, cryptosporidia, microsporidia
- Persistent fever, night sweats, or weight loss: r/o all OIs

Recommended HIV Tests for advanced HIV/AIDS:

ELISA w/confirmatory Western Blot

- Likely to detect HIV at this stage
- Tests for HIV antibodies
- Confirm positive rapid HIV test results (rapid test is only an ELISA test) w/Western Blot

Helpful Numbers

National HIV Telephone Consultation Service

1-800-933-3413 (M-F)

National Clinicians’ Post-Exposure Prophylaxis Hotline

1-888-448-4911 (24 Hours)

How can VA health care providers help HIV+ patients who are resistant to practicing risk reduction behaviors?

- ♦ Assess why risky behaviors may be continuing. Some reasons may include intoxication, unavailability of condoms, lack of access to clean needles, domestic violence, depression, mental illness or disinhibition, hopelessness, homelessness, and knowledge or skill deficits that prevent negotiation of safer sex. Make referrals, when appropriate, to VA and non-VA services that can address these issues.
- ♦ Assess the patient's willingness to change their behaviors using techniques such as motivational interviewing and the stages of change model

For additional information on HIV prevention available through the VA:

visit

<http://vhaaidsinfo.cio.med.va.gov/aidsservice/>

contact the VA Depot and request copies of

The VA HIV Prevention Handbook:
A Guide for Clinicians

(Stock #P95644)

contact

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IB 10-53

PREVENTION FOR HIV+ PATIENTS



**Information for
VA Health Care Providers on
Prevention Activities
for Individuals with HIV**



As people with HIV are feeling better and living longer, HIV prevention has become an even more important part of chronic illness management. A greater quality of life and greater life expectancy for someone with HIV can mean increased relationships and sexual activity and in some instances, a return to substance-use activities. For these and other reasons, it is critical to engage HIV+ individuals in secondary prevention efforts.

What is secondary HIV prevention?

It consists of prevention activities directed towards people who are HIV+. It is sometimes referred to as prevention for positives. Secondary prevention differs from primary prevention, which focuses people who are not HIV infected.

What are the goals of secondary HIV prevention?

- ♦ To make sure people who are HIV+ do not transmit the virus to others
- ♦ To make sure people who are HIV+ remain healthy over time
- ♦ To prevent re-infection of people who are HIV+

Who in VA medical centers, clinics and Vet Centers can conduct secondary HIV prevention activities?

- ♦ Counselors in Vet Centers
- ♦ Nurse practitioners
- ♦ Nurses
- ♦ Physician assistants
- ♦ Physicians
- ♦ Psychiatrists
- ♦ Psychologists
- ♦ Social workers
- ♦ Substance abuse treatment providers
- ♦ Domiciliary counselors and staff
- ♦ Other health care providers

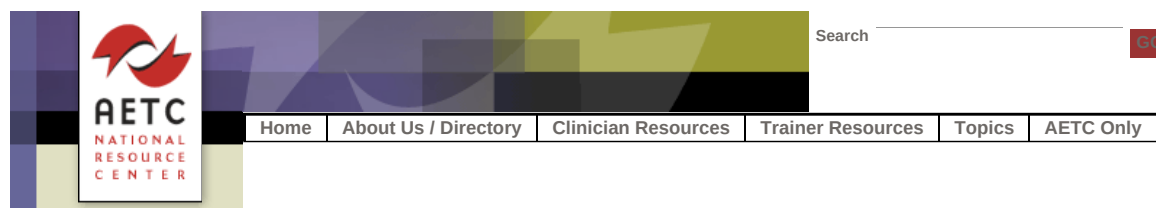
Why should VA health care providers practice secondary HIV prevention activities with their HIV+ patients?

- ♦ VA is the largest single provider of HIV care in the United States. In 1999, VA treated approximately 19,000 HIV+ veterans.
- ♦ The Centers for Disease Control and Prevention estimates that in the United States, 800,000-900,000 individuals are living with HIV and of these individuals, approximately 300,000 may not know they are HIV+.
- ♦ Secondary HIV prevention activities can help prevent disease transmission, reinfection and resistance.
- ♦ Secondary HIV prevention activities can help increase the life expectancy and quality of life for HIV+ individuals.



What are secondary HIV prevention activities that can take place in VA health care settings?

- ♦ Writing prescriptions for condoms for people who are HIV+ (male and female condoms are listed on the VHA National Formulary)
- ♦ Providing education on sexual behavior changes and safer sex practices
- ♦ Supporting medication adherence efforts
- ♦ Screening for substance abuse (drugs and alcohol) and when appropriate, referring patients to substance abuse treatment programs
- ♦ Providing information on high-risk substance abuse activities and harm-reduction techniques
- ♦ Providing mental health referrals to help with the diagnosis and treatment of conditions that affect patients' ability to adhere to medications and risk reduction practices, such as depression, PTSD, mania, anxiety disorders, psychosis, personality disorders, social skills deficits, or chronic stressors such as domestic violence
- ♦ Providing referrals to counselors or social workers who can help counsel patients on how to negotiate safer sex with a partner and/or disclose their HIV status
- ♦ Discussing the altruistic dimension of contributing to the health of one's family, friends and community by adopting safe behaviors
- ♦ Screening for STDs-the presence of STDs may indicate unprotected sexual activity. The treatment of STDs can protect against transmission of HIV.
- ♦ Providing HIV testing and counseling referrals for partners of patients who are HIV+
- ♦ Providing ongoing risk assessment as patients' sexual and substance-use behaviors and their risk for transmission may change over time



Guidelines

Clinical Manual

Clinician Support Tools

Reference Material

News & Events

Adverse Effects of Antiretroviral Drugs

[Print this page](#)

Author: Ian R. McNicholl, PharmD, University of California, San Francisco
Source: AETC National Resource Center and UCSF Center for HIV Information
Date: July 2009

Introduction

The following tables summarize the most common and most serious adverse events associated with antiretroviral medications used to treat HIV infection. For drug-drug interactions, see the [Database of Antiretroviral Drug Interactions](#).

Tables

Nucleoside Reverse Transcriptase Inhibitors

- NRTIs are associated with lactic acidosis, hepatic steatosis, and body fat redistribution (lipodystrophy).

Drug	Adverse Events	Comments
Abacavir	• Hypersensitivity syndrome (fever, myalgia, malaise, nausea, vomiting, symptoms suggestive of upper respiratory tract infection, anorexia); symptoms progressively worsen with each subsequent dose; rash occurs in about half of cases • Rash • Headache, nausea, vomiting, diarrhea	• Hypersensitivity reaction usually occurs in the first 6 weeks of treatment. • Hypersensitivity reaction may be more severe with once-daily abacavir dosing. • Risk of hypersensitivity related to certain genetic factors, particularly HLA B*5701; consider screening for this before prescribing abacavir. • Counsel patients on signs of hypersensitivity syndrome. • In case of hypersensitivity syndrome, abacavir must be discontinued permanently.
Didanosine	• Pancreatitis • Peripheral neuropathy • Nausea, diarrhea	• Concomitant alcohol use may increase risk of pancreatitis. • Lower frequency of diarrhea with enteric-coated capsules. • Increased risk of lactic acidosis and hepatic steatosis when combined with stavudine; this combination should be avoided when possible, especially during pregnancy. • Increased risk of peripheral neuropathy when combined with stavudine. • Adjust dosage for renal insufficiency or failure.
Emtricitabine	• Headache, nausea, insomnia • Hyperpigmentation of palms and soles (occurs most frequently in dark-skinned people)	• Active against hepatitis B virus (not approved by the U.S. Food and Drug Administration [FDA] for treatment of hepatitis B). In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of emtricitabine. • Adjust dosage for renal insufficiency or failure.
Lamivudine	• Headache, dry mouth	• Adverse effects occur infrequently. • Active against hepatitis B virus. In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of lamivudine. • Adjust dosage for renal insufficiency or failure.
Stavudine	• Peripheral neuropathy • Pancreatitis • Dyslipidemia • Diarrhea	• Of the NRTIs, stavudine appears to convey the greatest risk of lipodystrophy and other mitochondrial toxicity. • Increased risk of lactic acidosis and hepatic steatosis when combined with didanosine; this combination should be avoided when possible, especially during pregnancy.

		- Increased risk of peripheral neuropathy when combined with didanosine. - Consider dosage adjustment for peripheral neuropathy. - Adjust dosage for renal insufficiency or failure.
Tenofovir	- Flatulence, nausea, diarrhea, abdominal discomfort - Asthenia - Acute renal insufficiency, Fanconi syndrome - Chronic renal insufficiency	- Active against hepatitis B but not FDA approved for treatment of hepatitis B. In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of tenofovir. - Gastrointestinal symptoms may be worse in lactose-intolerant patients; tenofovir is formulated with lactose. - Case reports of renal insufficiency; association between tenofovir and renal insufficiency is not clear. - Adjust dosage for renal insufficiency or failure.
Zidovudine	- Anemia, neutropenia - Fatigue, malaise, headache - Nausea, vomiting - Myalgia, myopathy - Hyperpigmentation of skin and nails	- Twice-daily dosing preferred over thrice-daily dosing. - Fatigue, nausea, headache, and myalgia usually resolve 2-4 weeks after initiation. - Adjust dosage for renal insufficiency or failure.

Nonnucleoside Reverse Transcriptase Inhibitors

- NNRTIs are associated with rash, and may cause Stevens-Johnson syndrome and toxic epidermal necrolysis.
- All NNRTIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

Drug	Adverse Events	Comments
Delavirdine	- Fatigue - Elevations in liver function tests, hepatitis - Nausea, diarrhea	100 mg tablets can be dissolved in water. - Seldom used; less potent than other NNRTIs.
Efavirenz	- Elevations in liver function tests - Abnormal dreams, drowsiness, dizziness, confusion - Hyperlipidemia	- Central nervous system symptoms are common; severity usually decreases within 2-4 weeks. - Teratogenic in animal studies; contraindicated during pregnancy and for use by women who may become pregnant.
Etravirine	Elevations in liver function tests	- Tablets may be dissolved in water. - Has significant interactions with many other drugs (may differ from those of first generation NNRTIs); screen carefully for drug interactions before prescribing. - Does not interact with methadone.
Nevirapine	Elevations in liver function tests, hepatitis, liver failure	- Initial dose of 200 mg per day for first 14 days, then 200 mg twice daily, decreases frequency of rash. - Most rash develops within first 6 weeks of therapy; rash is most common in women. - Hepatotoxicity may be life threatening. It is more common at higher CD4 cell counts, in women, and in patients with hepatitis B or C. Nevirapine should not be initiated for women with CD4 counts of >250 cells/μL or men with CD4 counts of >400 cells/μL, unless the benefit clearly outweighs the risk. Monitor liver tests closely for the first 16 weeks of treatment.

Protease Inhibitors

- All PIs are associated with metabolic abnormalities including dyslipidemia, hyperglycemia, insulin resistance, and lipodystrophy. (Atazanavir is less likely to cause dyslipidemia.)
- PIs may increase the risk of bleeding in hemophiliacs.
- PIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

Drug	Adverse Events	Comments

Amprénavir	- Diarrhea, nausea, vomiting - Elevations in liver function tests - Rash	- May cause rash in patients sensitive to or intolerant of sulfonamides. - Capsule formulation no longer available in adult dosage; consider fosamprenavir. - Fosamprenavir formulation has a lower pill burden and a lower frequency of gastrointestinal side effects. - The oral solution should not be combined with metronidazole or disulfiram; it contains propylene glycol and may cause disulfiram-like reaction.
Atazanavir	- Hyperbilirubinemia, jaundice - Elevations in liver function tests - PR interval prolongation	- Proton pump inhibitors interfere with atazanavir absorption and are contraindicated for use by patients receiving atazanavir. - Other antacid medications and H₂ blockers also interfere with absorption of atazanavir and should be used with caution by patients receiving atazanavir. - Indirect hyperbilirubinemia; does not require discontinuation of atazanavir. - May have less effect than other PIs on lipid levels.
Darunavir	- Rash - Elevations in liver function tests	Increases pravastatin (and other statin) levels; no significant interaction with atorvastatin.
Fosamprenavir	- Diarrhea, nausea, vomiting - Elevations in liver function tests - Rash	- Prodrug of amprénavir. - May cause rash in patients sensitive to or intolerant of sulfonamides.
Indinavir	- Nephrolithiasis, flank pain - Hyperbilirubinemia - Elevations in liver function tests - Alopecia, dry skin, ingrown nails - Insomnia - Taste perversion	- To reduce risk of nephrolithiasis, patients should drink at least 1.5 liters of fluid daily. - When used as sole PI, should be taken on an empty stomach, 1 hour before or 2 hours after a meal, and should be taken every 8 hours (not 3 times per day).
Lopinavir/ ritonavir	- Diarrhea, nausea, vomiting - Dyslipidemia - Elevations in liver function tests - Taste perversion	- Available in tablets or oral solution. Tablets do not require refrigeration. - Oral solution contains 42% alcohol. - Avoid combining oral solution with metronidazole or disulfiram. Alcohol in the oral solution may cause disulfiram-like reaction.
Nelfinavir	- Diarrhea - Nausea, vomiting - Elevations in liver function tests - Fatigue	Diarrhea is very common. It usually can be managed with antidiarrheals such as loperamide and diphenoxylate/atropine.
Ritonavir	- Nausea, vomiting, diarrhea, abdominal pain - Elevations in liver function tests - Fatigue - Circumoral or peripheral numbness - Taste perversion - Hyperuricemia	- Capsules are stable at room temperature for up to 30 days. - Avoid combining oral solution with metronidazole or disulfiram. Alcohol in the oral solution may cause disulfiram-like reaction. - Has significant interactions with many other medications.
Saquinavir	- Nausea, vomiting, diarrhea - Elevations in liver function tests - Headache - Oral ulcerations	- Available in hard-gel capsules and tablets - Must be used in combination with low-dose ritonavir.
Tipranavir	- Nausea, vomiting, diarrhea - Elevations in liver function tests - Increased total cholesterol and triglycerides - Rash - Intracranial hemorrhage	- Must be coadministered with ritonavir; should never be used without ritonavir boosting. - Should be taken with food. - May cause rash in patients sensitive to or intolerant of sulfonamides. - Case reports of intracranial hemorrhage; association between tipranavir and intracranial hemorrhage is not clear. - Many drug-drug interactions. Certain drug combinations should be avoided. Consult current information before prescribing.

Fusion Inhibitors

Drug	Adverse Events	Comments
Enfuvirtide	• Injection site reactions; erythema, cysts, and nodules at injection sites • Neutropenia • Possible increased frequency of pneumonia	• Requires extensive patient counseling on injection technique, adherence, and management of possible side effects.

Chemokine Coreceptor Antagonists

Drug	Adverse Events	Comments
Maraviroc	• Diarrhea, nausea • Elevations in liver function tests, hepatitis • Upper respiratory tract infections, cough • Fatigue, dizziness, headache • Joint pain, muscle pain	• Many drug-drug interactions; dose adjustment needed with many other antiretrovirals and/or other medications. Consult current information before prescribing.

Integrase Inhibitors

Drug	Adverse Events	Comments
Raltegravir	• Nausea, diarrhea, flatulence • Elevations in amylase and liver function tests • Headache • Dizziness, abnormal dreams • Pruritus, rash • Fatigue, muscle pain	

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Clinical Manual for Management of the HIV-Infected Adult

2006 Edition

Updated July 2007

Providing Healthcare Professionals with
Quality Education to Improve HIV Care



AETC
AIDS EDUCATION &
TRAINING CENTERS
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About the AETC National Resource Center

The AETC National Resource Center (NRC) provides education and training resources for the regional AIDS Education and Training Centers (AETCs) to support their mission to offer timely, high-quality, state-of-the-art information to healthcare professionals working with existing and emerging populations affected by HIV. In partnership with the Center for HIV Information (CHI), the AETC NRC works to identify and develop information on HIV care, prevention, and policy through electronic media, including Internet and CD-ROM. The AETC NRC is administered by the François-Xavier Bagnoud (FXB) Center at the University of Medicine and Dentistry of New Jersey. The FXB Center provides clinical care, education and technical assistance in the United States and globally to support capacity development for addressing the HIV/AIDS epidemic.

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Clinical Manual for Management of the HIV-Infected Adult

About This Manual

This guide is the collaborative effort of clinical faculty associated with the AIDS Education and Training Centers. (*See the list of contributors below.*) The 2006 edition comes 13 years after the first edition, which was produced by the Midwest AETC (MATEC) and the Southeast AETC (SEATEC). The original manual was conceived to address the needs of the “midlevel” clinician—advanced practice nurses, physician assistants, etc—who comprise a significant proportion of the HIV primary care providers in the United States (and elsewhere). Experience has shown us that the whole range of providers—physicians, pharmacists, nurse practitioners and advanced practice nurses, physician assistants, dentists, and others, appreciate the nuts-and-bolts format of the guide. This edition maintains the practical approach of prior editions, but its content has been broadened somewhat, in recognition of its wide audience.

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Initial History

Background

This chapter includes essential points to cover during an initial clinic intake visit.

Conducting a thorough initial history and physical examination is important even if previous medical records are available. This is the best opportunity to get a complete picture of the patient’s HIV disease status and his or her physical and emotional condition, as well as to establish the basis for an ongoing relationship with the patient. Many of the conditions that put immunocompromised patients at risk for disease can be detected early, by means of a thorough assessment.

The information gathered through the initial history and physical examination will provide a comprehensive standardized database for the assessment and treatment of HIV-related problems, including acute intervention and ongoing supportive care. For essential aspects of the physical examination to cover in an initial clinic intake visit, see chapter *Initial Physical Examination*.

0: Objective

Document the patient’s full name, date of birth, date of assessment, and any other information standard to your practice (Tables 1 and 2). Perform a review of systems (Table 3).

Table 1. Patient Information

First Name:	Last Name:
Date of Birth: ____ / ____ / ____	Date of Assessment: ____ / ____ / ____

Table 2. Initial History Checklist

Category / Subject Matter	Questions
History of Present Illness	
HIV Testing	What was the date of your positive HIV test?
	Did you have a previous test? If so, when was the last negative HIV test?
	When do you think you were infected?
Treatment Status	Where do you usually receive your health care?
	Have you ever received care for HIV?
	What was the date of your last HIV care visit?
	Do you know what your first CD4 (T-cell) count was?
	What was your lowest CD4 count?
	What was your highest CD4 count?
	What is your current CD4 count?
	Do you know what your first viral load count was?
	What was your highest viral load count?
	What was your lowest viral load count?
	What is your current viral load count?
	Have you participated in any research protocols?
	Would you be interested in participating?

Risk for HIV and Other Sexually Transmitted Diseases	How do you think you were exposed to HIV?
Sexual	Please tell me about any experience you've had with unprotected anal, vaginal, or oral sex.
	Have you had sex with men? With women?
	Have any of your sex partners:
	Told you they were HIV infected or had AIDS?
	Told you they used injection drugs?
	Ever been in jail or prison?
	Had a sexually transmitted disease?
	Had hemophilia?
	Received a blood transfusion?
	Have you ever received donated sperm during artificial insemination?
Substance Use	Please tell me about your experience with injected substances.
	Have you shared your needles or injection equipment (works) with another individual?
Transfusion	Did you receive any blood or blood products between 1977 and 1985?
Occupational	Have you had an on-the-job injury that involved contact with a body fluid?
	What was the injury, and was HIV evaluation a part of the work injury follow-up?
Tattoos	Do you have any tattoos?
	Were sterile needles and ink-wells used to place your tattoo?
HIV-Related Illnesses	What opportunistic infection(s) have you had, if any? (PCP, MAC, cryptococcal meningitis, TB, etc)
	What year(s) were you diagnosed with the above?
	Have you had cancer(s)?
	What other HIV-related illnesses have you had?
Active Tuberculosis (TB) and TB Testing History	When was your last TB skin test (PPD)?
	What were the results of this test?
	Have you ever had a positive TB skin test?
	What year and what health care setting?
	What medications did you take and for how long?
	Have you ever had active tuberculosis?
Medications	Are you taking HIV medications now?
	If so, can you name them or describe them, and give their dosing frequency?
	How many doses have you missed in the last 3 days? The last week? The last month?
	What HIV medicines have you taken in the past (names or descriptions)? [If possible, have patient list all ARVs and ARV combinations, with dates and corresponding CD4 counts and viral loads.]
	When did you start and stop them (dates)?
	Do you know why you stopped these medications?
	Do you know what your HIV viral load or your CD4 counts were while you were taking your medications?
	Have you ever had a resistance test done?
	What other medications are you taking now?
	What herbs, over-the-counter (OTC) products, or vitamins are you taking now?

Past Medical and Surgical History		
Chronic Diseases	Do you have any chronic conditions, such as diabetes, high blood pressure, heart disease, cholesterol problems, asthma, emphysema, sickle cell disease, ulcers, acid reflux, irritable bowel syndrome, thyroid disorders, kidney or liver problems, or mental health disorders?	
	If so, do you receive medical care for these conditions?	
Previous Illnesses	Have you had any hospitalizations? Where, when, and for what reason?	
	Have you had any surgeries? When and where?	
	Have you had any major illnesses, including mental health conditions?	
Hepatitis	Have you ever had hepatitis? What type (A, B, C)?	
	Do you have chronic hepatitis?	
	Do you know your immunity status to hepatitis A or hepatitis B? Have you been vaccinated?	
Gynecologic	When was your last Papanicolaou (Pap) smear?	
	What were the results?	
	Have you ever had an abnormal Papanicolaou (Pap) smear?	
	When was your last menstrual period?	
	What is the usual length of your cycle?	
	Have you noticed changes in your menstrual cycle?	
	Have you had any lower abdominal pain?	
	Do you get yeast infections? How often?	
	Do you get urinary infections?	
	Have you ever had kidney stones?	
Obstetric	How many pregnancies have you had?	
	How many miscarriages or therapeutic abortions?	
	How many live births? Ages of children now?	
	Was HIV tested during any pregnancy?	
	Did you deliver an infant while you were HIV infected?	
	Was HIV medication given during pregnancy and delivery?	
	Do you have children who are HIV infected?	
	Do you intend to become pregnant?	
Anorectal History	Have you ever had an anal Papanicolaou (Pap) smear?	
	What were the results?	
Sexually Transmitted Infections (STIs)	Have you ever been treated for:	
	Syphilis?	Vaginitis?
	Genital herpes?	NGU (nongonococcal urethritis)?
	Gonorrhea?	Genital warts (HPV)?
	Chlamydia?	Proctitis?
	Pelvic inflammatory disease (PID)?	

Health-Related Behaviors	Do you smoke? How long have you smoked? How many cigarettes per day?
	Do you smoke anything besides tobacco?
	Do you chew tobacco?
	How much alcohol do you drink?
	Any experience with blackouts due to alcohol?
	Do you use any street drugs we haven't covered in earlier questions?
	If so, what drugs and how do you use them (inject, smoke, inhale, etc)?
	When did you last inject a substance?
	How about inhaled or snorted substances?
	Have you shared your equipment with another person?
	When did you last inhale a substance?
	Or smoked substances?
	Have you shared your equipment?
	When did you last smoke a substance?
	Are you interested in treatment for alcohol or drug use?
	What pain relievers do you use on a regular basis?
Immunizations	When was your last vaccination for:
	Tetanus?
	Streptococcal pneumonia (Pneumovax)?
	Influenza?
	Hepatitis A?
	Hepatitis B?
	Did you have chickenpox as a child, or were you vaccinated against chickenpox?
	What about measles, mumps, and rubella?
Allergies	What allergies do you have to medications?
	What was the reaction?
	What allergies to foods or environmental substances?
Family History	
	Do you have a family history of:
	Heart disease? Heart attacks or strokes?
	Cholesterol problems? Diabetes?
	Cancer?
	Mental health conditions (such as depression, anxieties, phobias)?
	Addictions?
	Which family member(s) and what is their health status currently?

Social History	
Relationship Situation	What is your relationship status (single, married, partnered, divorced, widowed)?
	Do you have children?
Living Situation	Do you live alone or with others? With whom?
Support System	Who knows about your HIV status?
	Which individual is the most supportive of your HIV diagnosis?
	Who is the least supportive of your status?
	Have you used any community support services such as support groups?
Employment	Are you currently employed?
	Where do you work?
	Describe your job task(s).
	What setting do you work in on a daily basis?
	Does your employer provide health insurance?
	If on disability: How long have you been on disability?
	What medical condition has made you disabled?
Travel	Where have you traveled outside the United States?
	When did travel take place?
Diet	Tell me what you eat during a typical day.
	Do you consume raw (unpasteurized) milk, raw eggs, raw or rare meat, deli meats, soft cheeses, or raw fish?
	How much water do you drink during the day?
	What is your source of water?
	How much caffeine do you drink during a typical day?
Pets	Do you have or have you had any pets?
	What kind of pets, and who cleans up after them?
Exercise	What kind of physical exercise and recreational activity do you participate in?
	How often?

Sensitive Sexual History Questions	
General Sexual	Do you have sex with men, women, or both?
	In the past, have you had sex with men, women, or both?
Sexual Identity	Do you consider yourself male or female?
	Have you had or considered treatment for sex change?
	Have you had hormone therapy?
	Have you had any sex-change surgery?
Sexual Practices	Do you have anal, vaginal, and/or oral sex?
	Do you protect yourself from sexually transmitted infections, or HIV reinfection? How?
	For men who have sex with men: Are you the receptive or insertive partner, or both?
	How often do you use alcohol or drugs before or during sex?
Prevention	Do you know the HIV status of your partner(s)?
	Do you protect your partners from HIV? How?
	In what situations do you or your partner use condoms or some other barrier?
Sex Trading	Have you ever exchanged sex for food, shelter, drugs, or money?
Contraception	What birth control measures do you use, if any?
	Do you use condoms or other latex barriers?
	Do you have plans for you or your partner to become pregnant?
Mental Health	
Coping	How do you handle your problems/stresses?
	What do you do to relax?
Therapy	Have you thought about seeing a mental health provider?
	Have ever been diagnosed with depression, anxiety, panic, bipolar disorder, etc?
	Have you taken or are you taking any medications for these conditions?
	Are you seeing a therapist or mental health professional?
	Have you had any previous counseling or mental health problems?
	Have you ever been hospitalized for a psychiatric condition?
	Have you ever thought about hurting yourself? If yes, probe for previous suicide attempts: Are you feeling that way now? (<i>See chapter Suicidal Ideation and prepare for immediate referral if necessary.</i>)
Violence	Have you ever been sexually abused, assaulted, or raped?
	In your adult life, have you lived in any situation with physical violence or intimidation?
	When has this occurred?
	Are you afraid for your safety now?
Childhood Trauma	Who reared you (one or both parents, other relatives, foster care)?
	Was there any alcoholism or drug abuse in your household when you were a child?
	Did you experience or observe violence; physical, sexual, or emotional abuse; or neglect?

Key to abbreviations: ARV = antiretroviral; HPV = human papillomavirus; MAC = *Mycobacterium avium* complex; PCP = *Pneumocystis jiroveci* pneumonia; PPD = purified protein derivative; TB = tuberculosis.

Table 3. Review of Systems

For each positive answer, document location, characteristics, duration of symptoms, and exacerbating and alleviating factors.

General	
General	Do you ever wake up feeling tired?
Fever	Do you have fevers? How high, and for how long?
Night Sweats	Do you ever sweat so much at night that it soaks your sheets and nightclothes?
Chills	Do you experience shaking or teeth-chattering when you feel cold?
Anorexia	How is your appetite?
Weight	What was your weight 1 year ago?
	What is a normal weight for you?
	Have you lost or gained weight unintentionally?
Body Changes	Have you noticed any changes in the shape of your body (describe)? For example, has there been an increase in your waist, collar, or breast size or a decrease in your arm, leg, or buttocks size?
	Have you noticed increased visibility of veins in your arms and legs?
	Have you noticed thinning of your face?
Head, Ears, Eyes, Nose, and Throat	
Vision	Have you noticed any changes in your vision, especially blurred vision or vision loss, double vision, new “floaters” or flashes of light?
	Have you noticed this problem in one or both eyes?
	When did you first notice these changes?
Mouth, Ears, Nose, Throat	Have you noticed any white spots in your mouth or a white coating on your tongue (thrush, oral hairy leukoplakia)?
	Do you ever get sores in your mouth or the back of your throat? Gum problems?
	Any nosebleeds?
	Hearing loss, ringing in your ears, ear pain?
Cardiovascular	
Cardiac	Any palpitations or chest pain?
	Any shortness of breath during activities or while you are lying down?
	How far can you walk or run before you get short of breath?
	Any swelling in feet or hands?
Pulmonary	
Cough	Do you have a cough?
	Can you describe it? Dry or productive, amount, color, odor, presence of blood in sputum? When is it the worst?
Dyspnea	Do you ever feel short of breath?
	Does that happen when you are sitting still, lying down, or moving around?
	How severe is your shortness of breath?
	Does it prevent you from doing anything?
	Do you ever wheeze?
Gastrointestinal	
Dysphagia	Do you have any problems with food sticking in your throat or being difficult to swallow?
	Do you notice it's easier to swallow liquids or solids?
	Do you gag or get nauseated when trying to eat?
Odynophagia	Do you have pain in your throat, esophagus, or behind your breastbone when you swallow?
Nausea/Vomiting	Do you have nausea or vomiting?
	When? Are there specific things that cause this?
Dyspepsia/Reflux	Do you ever have heartburn?
	When does it happen—after eating, lying down, on an empty stomach?
	Do you get the taste of stomach acid in your mouth?
Diarrhea	Do you have diarrhea, or more than 3-5 unformed stools a day?
	Stool characteristics: bloody, pus, mucus?
	Pain or cramping with diarrhea? Tenesmus?
Bowel Habits	How frequently do you have bowel movements?
	Do you have problems with constipation, blood in the stools, or other?
	Do you have problems with flatulence or belching after eating?

Genitourinary	
Genital	Do you have any lesions or sores on your genital area now, or have you in the past?
	Have you ever had genital herpes? If yes, how often do you have outbreaks?
	When was the most recent outbreak?
Women	Have you had any lower abdominal pain?
	Have you noticed a vaginal discharge or odor?
	Do you have any burning or pain on urination?
	Frequent urination?
Men	Do you lose control of your urine or have problems getting to the bathroom before you start to urinate?
	Have you noticed any swelling or testicular pain?
	Do you have difficulty starting your stream of urine?
	Are you getting up at night to urinate?
	Have you had burning or pain on urination?
	Do you lose control of your urine or have problems getting to the bathroom before you start to urinate?
	Have you ever had kidney stones?
	Do you have any difficulty developing an erection or maintaining one?
	Any discharge from your penis?
Musculoskeletal	
	Do you have any muscle aches or pains?
	Back pain, joint pain, and/or swelling?
	Have you ever broken any bones?
	Do you have chronic pain?
	Describe the pain—location, duration, rating (scale of 1-10), alleviation factors.
Skin	
Herpes Zoster	Have you ever had chickenpox (varicella)?
	Have you ever had “shingles” (zoster)?
	Where were the lesions?
Tinea	Do you have fungal infections on your skin, especially groin, fingernails, toenails, or feet?
Folliculitis	Do you have any itchy bumps on your face, back, or chest?
Seborrhea	Do you have flaking or itching on your skin or scalp?

Skin Lesions	Have you noticed any rash or skin problems? If so, where?
	Have you noticed any new moles, bruises, or bumps on your skin?
	Do you have any moles that changed shape, size, or color?
Neurologic	
Headache	How often do you get headaches?
	Describe the headaches—location, timing, duration, alleviating or aggravating factors.
	Do they cause nausea or vomiting?
	Does sensitivity to light lead to headaches?
Memory	Do you have difficulty with your memory or ability to concentrate? If so, describe.
Gait	Have you noticed any changes in the way you walk?
Neuropathy	Do you have any numbness, tingling, burning, or pain in your hands or feet?
Seizures	Have you ever had a seizure or “fit”?
	If so, describe the seizure—When? How long did it last? Loss of consciousness? Was medical care sought?
Weakness	Do you have or have you had any weakness in your arms or legs?
Endocrine	
Diabetes	Have you had any increase in thirst, hunger, or urination?
Thyroid	Have you noticed changes in your energy level?
	Do you have intolerance to heat or cold?
	Have you noticed changes in your hair (thinning, coarse texture)?
Sex Steroids	Have you noticed any changes in your libido?
Hematologic/Lymphatic	
Adenopathy	Do you have swollen glands?
	If so, describe—location, painful, size if measurable.
Bruising or Bleeding	Have you noticed easy bruising or prolonged bleeding after injury?
	Nosebleeds or bleeding gums?

Psychiatric	
Mood	Depression screening: Have you experienced a decrease in your interest or pleasure in your activities?
	Have you felt depressed, down, or hopeless?
	Do you feel more angry, sad, depressed, numb, irritable, or anxious than usual?
	Have any major life events have occurred to cause you to feel sad or depressed?
Sleep	When did these events occur?
	How is your sleep?
	How many hours do you sleep each night?
	What is your sleeping schedule—time to bed and time to rise?
	Do you take naps?

A: Assessment and Plan

- ◆ Conduct a physical examination, focusing on subjective findings elicited in the history. (See chapter *Initial Physical Examination*.) Note: If significant time has elapsed between the ROS and physical exam, perform another ROS.
- ◆ Compose a problem list. Initiate a medication list (if appropriate).
- ◆ Order baseline/intake laboratory work. (See chapter *Initial and Interim Laboratory and Other Tests*.)
- ◆ Refer the patient to social services, mental health, community and other resources, or other clinic services as needed.

During today's visit or a future visit:

- ◆ Perform PPD testing if not done in the last year, or if the patient was previously PPD negative. The patient can return to have the PPD read.
- ◆ Perform immunizations for pneumonia (Pneumovax), influenza (as appropriate), and other immunizations as indicated. (See chapter *Immunizations for HIV-Infected Adults and Adolescents*.)
- ◆ Provide counseling on prevention of HIV transmission (eg, safer sex and injection practices), as appropriate.

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Initial Physical Examination

Background

Many of the conditions that put immunocompromised patients at risk for disease can be detected early, by means of a thorough history and physical evaluation. This chapter presents essential aspects of the initial physical examination of the HIV-infected individual. (For essential aspects of the history to cover in an initial clinic intake visit, see chapter *Initial History*.)

S: Subjective

- ◆ When an HIV-infected patient presents for an initial examination, document the patient’s full name, date of birth, date of assessment, and any other information standard to your practice (Table 1).

Table 1. Patient Information

First Name:	Last Name:
Date of Birth: ____ / ____ / ____	Date of Assessment: ____ / ____ / ____

O: Objective

Assess the patient’s general appearance, affect, demeanor in answering questions, body language, and other relevant characteristics such as vital signs (Table 2). Perform a physical examination (Table 3).

Table 2. Vital Signs

Vital Sign	Recommendation
Weight	Record at each visit.
Height	Should be measured once.
Temperature	Document at each visit.
Blood Pressure	Use BP cuff size appropriate for the patient’s arm circumference.
Heart Rate	Provide a baseline rate for later evaluation of anemia, dehydration, and other physical conditions.
Waist, Hip	Waist and hip circumference should be measured for comparison in case the patient later develops metabolic complications of ART. Abdominal circumference: Waist-hip ratios: >102 cm (39”) in men = abdominal obesity >0.95 in men = increased risk of CHD >88 cm (35”) in women = abdominal obesity >0.85 in women = increased risk of CHD
Body Mass Index (BMI)	BMI can be helpful in determining obesity, wasting, and ART-related weight gain. Perform at baseline and upon changes in weight. BMI calculation: $\frac{[\text{weight in pounds}]}{[\text{height in inches}]^2} \times 703$ or $\frac{[\text{weight in kilograms}]}{[\text{height in meters}]^2}$ BMI <18.5 = underweight 18.5–24.9 = normal range 25–29.9 = overweight ≥30 = obese

Key to abbreviations: ART = antiretroviral therapy; BMI = body mass index; CHD = coronary heart disease.

Table 3. Physical Examination

Eyes	
• Visual acuity and visual fields by confrontation. • Tests of extraocular movements and pupillary size and reaction. • Funduscopic examination—with or without mydriatics; especially important if CD4 count is <100 cells/μL. • Note any retinal lesions, white or yellow retinal discoloration, infiltrates, or hemorrhages (could indicate cytomegalovirus retinitis, retinal necrosis, or ocular toxoplasmosis). • Referral to ophthalmologist for retinal examination every 6 months if the CD4 count is <100 cells/μL. • Refer immediately if the patient has retinal lesions or new visual disturbances.	
Ears/Nose	
• Examine ear canals and tympanic membranes. • Visualize nasal turbinates. • Palpate frontal and maxillary facial sinuses.	
Oral Cavity	
• Good lighting is essential. • Assess gingiva and teeth. • Assess mucosal surfaces (remove dentures, if present); note any lesions, discolorations, or skin abnormalities. • Have patient lift tongue to assess the posterior side. • Note whether tonsils are absent or present and any abnormality in tonsil size. • Pharynx—lesions, exudate?	
Endocrine	
• Check thyroid for enlargement, tenderness, nodules, and asymmetry.	
Lymph Nodes	
• Document site, size, and characteristic of each palpable node.	
Node Sites	Characteristics
• Posterior cervical chain • Anterior cervical chain • Submandibular • Submental • Supraclavicular • Axillary • Epitrochlear • Inguinal • Femoral	• Size (2 dimensions, in millimeters) • Consistency (hard, fluctuant, soft) • Tenderness • Mobility • Definition (discrete, matted) • Symmetry

Skin
• Examine the entire body, including scalp, axillae, palms, pubic and perianal areas, soles of feet. • Describe all lesions: size, borders, color, symmetry/asymmetry, distribution, raised/flat, induration, encrustation. • Note evidence of folliculitis, seborrheic dermatitis, psoriasis, Kaposi sarcoma, fungal infections, prurigo nodularis, etc.
Lungs
• Auscultate and percuss. • Note any abnormal sounds including crackles or wheezes (signs of infections, asthma, congestive heart failure, etc). • Note any absence of air movement (pneumothorax, pleural effusion, etc).
Heart
• Note rate and rhythm, heart sounds, murmurs, extra heart sounds. • Palpate for PMI (point of maximal impulse). • Examine for JVD (jugular venous distension).
Breasts
• Palpate for breast masses in both men and women. • Check for symmetry, discharge, dimpling, and masses.
Abdomen
• View—note distension, obesity, undernutrition, vascular prominence, petechiae. • Auscultate—note bowel sounds. • Percuss—record liver size. • Palpate—note hepatomegaly or splenomegaly; note any tenderness or rebound.

Genitals/Rectum - Inspect the genitalia and perirectal area; note lesions, warts, etc. - Culture discharges, ulcerative lesions, vesicles, and crusted lesions for herpes simplex virus, chancroid, chlamydia, and/or gonorrhea (GC), as appropriate, and send an RPR (rapid plasma reagin) or VDRL (Venereal Disease Research Laboratory) test.	Extremities/ Musculoskeletal - Joints—note any enlargement, swelling, or tenderness. - Muscles—for the major muscle groups, pay close attention to muscle bulk (normal or decreased), tenderness, or weakness. - Look for evidence of peripheral fat atrophy. - Consider measuring baseline arm, thigh, and chest circumferences for later comparison. - Note nail changes (clubbing, cyanosis, fungal infections). - Assess for pedal or leg edema.
Female Patients - Speculum examination—note any lesions on vaginal walls or cervix. - Obtain a Papanicolaou smear. (Note: Abnormal or inconclusive Papanicolaou smears require colposcopic follow-up, because invasive cervical cancer may progress rapidly in women with HIV. See chapter <i>Cervical Dysplasia</i>.) - Obtain endocervical swab for GC and chlamydia, and a posterior pool swab for wet mount evaluation for trichomoniasis, <i>Candida</i>, and bacterial vaginosis. - Bimanual exam—note size of uterus and ovaries, shape, and any tenderness or pelvic pain. - Rectal examination for anorectal lesions, warts, etc, and evaluation of uterine abnormalities. - Anal Papanicolaou smear.*	Habitus - Subcutaneous fat loss (face, extremities, buttocks). - Central fat accumulation (neck, dorsocervical, breasts, abdomen).
Male Patients - External genitalia—note whether male is circumcised; note any lesions, discharge, other abnormalities, as above. - Testicular examination for masses, tenderness. - Rectal exam—digital examination to evaluate rectal tone, discharge or tenderness, masses, lesions; prostate exam if appropriate. - Anal Papanicolaou smear.*	Neurologic - Mental status—including orientation, registration, recent and remote memory, and ability to calculate (serial subtraction) - Cranial nerves - Peripheral sensory examination should include pinprick, temperature, and vibratory stimuli. - Extremity strength and gait to discern myopathy, neuropathy, and cerebellar disease - Fine motor skills such as rapid alternating movements (often abnormal in dementia) - Deep tendon and plantar reflexes
* Anal Papanicolaou smear: Consider this test if follow-up evaluation of abnormal Papanicolaou test results is available. The suggested approach in HIV-infected women and men for anal dysplasia screening is similar to the cervical Papanicolaou screening guidelines for women: perform anal Papanicolaou test at initial diagnosis and, if normal, repeat at 6 months. If the first 2 anal Papanicolaou smears are normal, repeat annually. If a Papanicolaou test shows ASCUS (atypical squamous cells of undetermined significance) or SIL (squamous intraepithelial lesion), refer for anal colposcopy and biopsy. (See chapter <i>Anal Dysplasia</i>.)	Psychiatric - Patient's general mood (depressed, anxious, hypertalkative, etc) - Verbal content—answers questions appropriately; discussion of suicide - Inappropriate or unusual behavior, such as extremes of denial, hostility, or compulsiveness - See <i>Neuropsychiatric Disorders</i> section for more complete information on common pathologies. - Emergency situations, such as potential suicide or violence—refer to crisis mental health services for immediate evaluation

A: Assessment and Plan

After completing the initial history and physical examination:

- ◆ Complete the patient's database with the information garnered through the history and physical examination.
- ◆ Document a problem list, assessment, and plan for patient care.
- ◆ Complete follow-up or laboratory studies suggested by the history and physical exam. (See chapter *Initial and Interim Laboratory and Other Tests*.)
- ◆ Prescribe opportunistic infection (OI) prophylaxis as appropriate. (See chapter *Opportunistic Infection Prophylaxis*.)
- ◆ Refer for dental, nutrition, social services, and mental health care as appropriate.
- ◆ Refer for any additional specialty care identified in the history or physical exam.
- ◆ Order any appropriate vaccinations. (See chapter *Immunizations for HIV-Infected Adults and Adolescents*.)
- ◆ Make follow-up appointment with health care provider.
- ◆ Answer the patient's questions.

Patient Education

A very important aspect of caring for HIV-infected individuals is educating patients about HIV infection, including goals of care and ways of achieving those goals.

Review the following with each patient:

HIV disease

- ◆ Transmission and progression
- ◆ Significance of CD4 count and HIV viral load
- ◆ Possible treatment approaches
- ◆ Disclosure—whom the patient may need to tell about HIV status; approaches to disclosure

HIV transmission prevention and risk reduction for HIV-positive individuals

- ◆ Safer-sex approaches, including the use of condoms/latex barriers during all sexual contacts
- ◆ Safer use of recreational drugs

Nutrition

- ◆ Maintaining a healthy weight
- ◆ Nutritional support resources, if appropriate
- ◆ Importance of including a nutritionist in medical care

Mental health

- ◆ Stress reduction
- ◆ Rest and exercise to enhance a healthy mental state

Adherence

- ◆ Importance of keeping medical appointments
- ◆ Need for adhering to any medication regimen and the consequences of missed HIV medication doses
- ◆ Return appointment

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Initial and Interim Laboratory and Other Tests

Background

This chapter provides guidelines for monitoring patients with HIV infection.

Note that documentation of a confirmed HIV serologic test should be included in the chart.

O: Objective

Monitor patients with laboratory testing for HIV, hepatitis, sexually transmitted diseases, and other opportunistic infections (Table 1).

Table 1. Initial Laboratory Evaluations for HIV-Infected Patients

Test	Rationale	Result		Frequency and Comments
HIV Staging and Antiretroviral Therapy (ART) Monitoring				
CD4 Count	- For HIV staging and prognosis - Guides initiation of ART - Indicates risk of opportunistic illnesses and guides initiation of prophylaxis against opportunistic infections - Used to monitor immune reconstitution during ART	Reported in cells/μL		- Repeat every 3–4 months for patients not taking ART. - Repeat every 2–4 months for patients taking ART. - Repeat if results are inconsistent with the clinical picture or with previous trends. - See chapter <i>CD4 Monitoring and Viral Load Testing</i>.
CD4 Count Percentage	- Used in addition to the absolute CD4 count for monitoring trends; may be discrepant from absolute CD4 - PCP prophylaxis is indicated for CD4% <14 regardless of absolute count (see below).	CD4 count >500 200–500 <200	Expected CD4% >29% 14–28% <14%	Usually obtained with absolute CD4 count
Quantitative Plasma HIV RNA (HIV Viral Load)	- Estimates level of HIV replication - Monitors effect of ART - Diagnoses acute HIV infection (Not FDA approved for diagnosis of HIV, but has high sensitivity in setting of acute infection. Must be confirmed by positive HIV antibody test.)	- Reported in copies/mL. - In untreated patients, detectable (with rare exceptions) and measured to the upper limit of detection (usually >500,000 copies/mL). - In patients taking ART, ideally suppressed to undetectable levels (usually <50 or ≤75 copies/mL).		- Baseline. values (2 tests) - For patients on new or modified ART regimen: perform 2–8 weeks after initiation or change in ART. - For patients on stable ART: perform every 3–4 months. - For patients not taking ART: perform every 3–4 months; more frequently if CD4 count is low. <i>Factors that may temporarily alter viral load:</i> - Immunizations - Active infections
Drug Resistance Testing (Genotype, Phenotype)	To assess antiretroviral medications to which the patient’s HIV virus is likely to be resistant	- Genotype: detects specific mutations to ARV medications - Phenotype: measures HIV viral replication in the presence of ARVs		- Genotype (one time) is recommended in all ARV-naïve patients. For greatest accuracy, should be done as early as possible in the course of HIV infection. - Acute or primary infection: recommended - Chronic infection and treatment naïve: recommended before initiation of ART. - Pregnancy: recommended before initiation of ART or in those with detectable HIV RNA during ART. - Virologic failure: recommended (See chapter <i>Resistance Testing</i> for additional information.)

Complete Blood Count (CBC) with Differential and Platelets	• Detects anemia, thrombocytopenia, leukopenia	• Normal	• Repeat every 3-6 months.
		• Abnormal	• Requires follow-up evaluation as indicated; may influence choice of ARVs. • Repeat more frequently if the patient’s results are abnormal or he/she is taking bone marrow suppressive drugs.
Chemistry Profile (Electrolytes, Creatinine, Blood Urea Nitrogen, Liver Transaminases)	• Detects electrolyte abnormalities, renal insufficiency, hepatic enzyme elevations	• Normal/abnormal	• Repeat every 3-6 months, and as needed to monitor ART. • May influence ARV selection. • May be useful to monitor drug toxicities. • Abnormalities should prompt evaluation of cause.
Lipid Profile (Total Cholesterol, LDL, HDL, Triglycerides) Glucose (preferably fasting)	• Baseline before starting ART • Monitoring during ART	• Normal	• Repeat annually or more frequently (every 3-6 months) based on initial results, ARV use, or risk of cardiovascular disease.
		• Abnormal	• For interventions, see chapter <i>Dyslipidemia</i>.
Hepatitis Screening			
Hepatitis A Serology (HAV IgG)	• Screen for immunity to hepatitis A; vaccinate those not immune	• Negative	• Offer hepatitis A vaccine if indicated. (See chapter <i>Immunizations for HIV-Infected Adults and Adolescents</i>.)
		• Positive	• Immune; no vaccine necessary
Hepatitis B Serology	• Assess hepatitis B status		
Hepatitis B Surface Antigen (HBsAg)	• Indicates active hepatitis B	• sAg negative	• Consider vaccination if HBsAb negative (not immune).
		• sAg positive	• Indicates chronic or acute hepatitis B infection; requires further evaluation (check HBV DNA)
Hepatitis B Core Antibody (Anti-HBc, IgG)	• Indicates past exposure or ongoing infection	• Anti-HBc negative	• The patient most likely has not been infected with hepatitis B; consider vaccination if HBsAb negative and HBsAg negative.
		• Anti-HBc positive	• The patient most likely has been infected with hepatitis B; this test alone does not distinguish past exposure from active infection. • In rare cases, may be falsely negative in some with chronic infection. • If sAb negative and sAg negative, check HBV DNA to rule out active infection. • If sAb is positive, patient is immune.
Hepatitis B Surface Antibody (Anti-HBs)	• Indicates immunity status	• Anti-HBs negative	• The patient is not immune to hepatitis B; consider vaccination, unless patient has active hepatitis (sAg positive or HCV DNA positive).
		• Anti-HBs positive	• The patient is immune to hepatitis B either by previous infection or by immunization; may be negative in acute hepatitis B infection.

Hepatitis C Serology			
Anti-HCV Antibody (HCV Ab)	• Hepatitis C status	• HCV negative	• Patient is not infected with hepatitis C. • Consider annual screening in high-risk patients.
		• HCV positive	• Patient has chronic hepatitis C infection or past infection with immunity; confirm positive results with HCV RNA.
Other Opportunistic Infection Screening Tests			
<i>Toxoplasma gondii</i> IgG	• Detects exposure; if positive, increased risk of developing CNS toxoplasmosis if CD4 count <100 cells/μL	• Normal/negative	• Repeat if patient becomes symptomatic or when CD4 count drops to ≤100 cells/μL.
		• Abnormal/positive	• Note as baseline information. • Start toxoplasmosis prophylaxis when CD4 count drops to ≤100 cells/μL.
PPD (tuberculin skin test) (if no history of TB or positive PPD)	• Detects latent TB infection	• Normal	• Repeat every 6-12 months. • Repeat if CD4 count was <200 cells/μL on initial test but increases to >200 cells/μL.
		• Abnormal (induration ≥5 mm)	• Evaluate for active TB. (See chapter <i>Latent Tuberculosis</i> .)
Chest X-Ray (if pulmonary symptoms are present or positive PPD)	• Detects latent or active diseases	• Normal	• Repeat as indicated for pulmonary symptoms or positive PPD.
		• Abnormal	• Evaluate for TB, PCP, or other pathology.
Papanicolaou Smear (cervical for women; anal for women and men)	• Detects abnormal cell changes, dysplasia	• Normal	• Repeat in 6 months; then annually if negative on 2 smears and no ongoing risk factors.
		• Abnormal	• Perform workup, treat (see chapters <i>Cervical Dysplasia</i> and <i>Anal Dysplasia</i>) and follow up more frequently as indicated by condition.
STD Testing: Identify sexually transmitted infections in any patient at risk.			
Venereal Disease Research Laboratory (VDRL); or Rapid Plasma Reagin (RPR)	• Syphilis screening	• Negative titer	• Repeat every 3-12 months, depending on risk factors.
		• Positive titer: confirm with treponemal test	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex. • Perform serial testing if monitoring active disease. (See chapter <i>Syphilis</i> .)

Women			
Gonorrhea, Chlamydia, and Trichomoniasis Testing	• STD screening in sexually active women at risk	• Negative	• Counsel about safer sex and avoiding STDs. • Repeat every 6-12 months; more frequently if at high risk.
		• Positive	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Gonorrhea and Chlamydia Testing, Rectal	• STD screening in sexually active women at risk • STD screening in sexually active women who have receptive anal sex	• Negative	• Counsel about safer sex and avoiding STDs. • Repeat every 6-12 months; more frequently if at high risk.
		• Positive	• Treat patient; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Men			
Gonorrhea and Chlamydia Testing, Urethral	• STD screening in sexually active men who are at risk, especially men who have sex with men (MSM)	• Negative	• Retest every 3-6 months in patients with risk factors.
		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Gonorrhea and Chlamydia Testing, Pharyngeal	• STD screening in sexually active men who are at risk, especially MSM who have oral-genital contact	• Negative	• Retest every 3-6 months in patients with risk factors.
		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Gonorrhea and Chlamydia Testing, Rectal	• STD screening in sexually active men who are at risk, especially MSM who have receptive anal sex	• Negative	• Retest every 3-6 months in patients with risk factors.
		• Positive	• Treat; refer partner(s) of previous 60 days for evaluation and treatment; counsel about safer sex.
Consider/Optional			
G6PD Level	• Prevent hemolytic reactions by screening susceptible men of African, Mediterranean, Asian, Sephardic Jewish descent • Some would recommend screening all patients	• Normal range	• No intervention is necessary beyond documentation.
		• Abnormal range	• Avoid oxidant drugs such as dapsone, primaquine, and sulfonamides, if possible.
Cytomegalovirus (CMV) Antibody (anti-CMV IgG) for those at low risk of CMV, especially those who are not MSM or injection drug users	• Detects exposure; may reveal future disease risk	• Negative	• Avoid exposure by practicing safer sex. • If blood transfusion is required, use CMV-negative or leukocyte-reduced blood.
		• Positive	• Be aware of disease risk in advanced HIV infection, when CD4 count <50 cells/μL.
Prostate Specific Antigen (PSA)	• Prostate cancer screen (African American men over 45; other men over 50 with >10-year life expectancy)	• Normal	• Repeat annually.
		• Abnormal	• Refer to urology specialist for evaluation.
Urinalysis (UA)	• Detects proteinuria or pyuria	• Normal	• Repeat annually.
		• Abnormal	• Rule out HIV-associated nephropathy and other causes of nephropathy.
Dilated Retinal Examination	• Detects CMV, ophthalmic toxoplasmosis, or HIV retinopathy	• Normal	• CD4 count >100 cells/μL: repeat annually. • CD4 count <50 cells/μL or symptoms of retinal changes: repeat every 6 months.
		• Abnormal	• Follow up immediately with ophthalmologist.

Patient Education

- ◆ Discuss safer sex (review specifics appropriate to the patient's sexual practices and infections) to prevent the patient's exposure to herpes, hepatitis B, hepatitis C, and other sexually transmitted diseases, and to prevent the patient from exposing others to HIV or other pathogens. (See chapters *Preventing Transmission/Prevention with Positives* and *Preventing Exposure to Opportunistic and Other Infections*.)
- ◆ If toxoplasma IgG test result is negative, see chapter *Preventing Exposure to Opportunistic and Other Infections*.
- ◆ If cytomegalovirus (CMV) test result is negative, counsel the patient that CMV is shed in semen, vaginal and cervical secretions, saliva, and urine of infected people. Latex condoms will help reduce risk. For women considering childbearing, CMV should be avoided assiduously to prevent severe disease and even death of the neonate. (See chapter *Preventing Exposure to Opportunistic and Other Infections*.)
- ◆ For people who are hepatitis C negative and still use injection drugs, offer referral to a drug treatment program. (See chapters *Preventing Transmission/Prevention with Positives* and *Preventing Exposure to Opportunistic and Other Infections*.)

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Interim History and Physical Examination

Background

This chapter suggests information to gather and document for a standard written record of clinically important data over many visits. With this information, the clinician can track disease progression and formulate and maintain an appropriate care plan.

It is important to document new or ongoing symptoms and functional limitations at each visit. This information is particularly useful when outside agencies must

determine the patient's disability status. (See chapter *Karnofsky Performance Scale*.)

Table 1 lists the suggested frequency and follow-up intervals of the history and physical examination for monitoring HIV-infected patients. Note that specific medications and abnormalities may call for additional directed examinations.

Table 1. History and Physical Examination: Frequency and Follow-Up Intervals

History				Physical Examination	
Every visit (at least every 3 months)					
• New symptoms • Medications • HIV-related medications • Medications for other conditions • Over-the-counter medications • Herbs or vitamins		• Adherence to medications and clinical care visits • Risk reduction; prevention with positives		• Mood • Alcohol and recreational drug use • Tobacco use • Allergies • Pain	
		• Social supports • Housing • Insurance • Domestic violence		• Vital signs (temperature, blood pressure, heart rate, respiratory rate) • Weight • General appearance, body habitus (including evaluation for lipodystrophy) • Skin	
				• Oropharynx • Lymph nodes • Heart and lungs • Abdomen • Psychiatric—mood, affect • Neurologic	
Every 6 months					
As above		As above plus: • Visual and funduscopic exam • Ears/nose • Screening for chlamydia, gonorrhea, and syphilis in all patients at risk for these infections			
Every 6 months (twice) , and, if both are normal, annually thereafter (See chapters <i>Cervical Dysplasia</i> and <i>Anal Dysplasia</i> .)					
As above		• Women: cervical and anal Papanicolaou smear, pelvic exam		• Men: anal Papanicolaou smear	
Annually					
Update initial history: HIV-related symptoms, hospitalizations, major illnesses, family history				Complete physical to include: • Genitorectal exam • Prostate exam • Breast exam • Testicular exam	

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HIV Classification: CDC and WHO Staging Systems

Background

HIV disease staging and classification systems are critical tools for tracking and monitoring the HIV epidemic and for providing clinicians and patients with important information about HIV disease stage and clinical management. Two major classification systems currently are in use: the U.S. Centers for Disease Control and Prevention (CDC) classification system and the World Health Organization (WHO) Clinical Staging and Disease Classification System.

The CDC disease staging system (last revised in 1993) assesses the severity of HIV disease by CD4 cell counts and by the presence of specific HIV-related conditions. The definition of AIDS includes all HIV-infected individuals with CD4 counts of <200 cells/ μL (or CD4 percentage $<14\%$) as well as those with certain HIV-related conditions and symptoms. Although the fine points of the classification system rarely are used in the routine clinical management of HIV-infected patients, a working knowledge of the staging criteria (in particular the definition of AIDS) is useful in patient care. In addition, the CDC system is used in clinical and epidemiologic research.

In contrast to the CDC system, the WHO Clinical Staging and Disease Classification System (revised in 2005) can be used readily in resource-constrained settings without access to CD4 cell count measurements or other diagnostic and laboratory testing methods. The WHO system classifies HIV disease on the basis of clinical manifestations that can be recognized and treated by clinicians in diverse settings, including resource-constrained settings, and by clinicians with varying levels of HIV expertise and training.

S: Subjective

When a patient presents with a diagnosis of HIV infection, review the patient's history to elicit and document any HIV-related illnesses or symptoms (see chapter *Initial History*).

O: Objective

Perform a complete physical examination and appropriate laboratory studies (see chapters *Initial Physical Examination* and *Initial and Interim Laboratory and Other Tests*).

A: Assessment

Confirm HIV infection and perform staging.

P: Plan

Evaluate symptoms, history, physical examination results, and laboratory results, and make a staging classification according to the CDC or WHO criteria (see below).

CDC Classification System for HIV Infection

The CDC categorization of HIV/AIDS is based on the lowest documented CD4 cell count (Table 1) and on previously diagnosed HIV-related conditions (Tables 2 and 3). For example, if a patient had a condition that once met the criteria for Category B but now is asymptomatic, the patient would remain in Category B. Additionally, categorization is based on specific conditions, as indicated below. Patients in categories A3, B3, and C1-C3 are considered to have AIDS.

Table 1. CDC Classification System for HIV-Infected Adults and Adolescents

CD4 Cell Categories	Clinical Categories		
	A Asymptomatic, Acute HIV, or PGL	B Symptomatic Conditions,#* not A or C	C AIDS-Indicator Conditions*
(1) ≥ 500 cells/ μ L	A1	B1	C1
(2) 200-499 cells/ μ L	A2	B2	C2
(3) <200 cells/ μ L	A3	B3	C3

Key to abbreviations: CDC = U.S. Centers for Disease Control and Prevention; PGL = persistent generalized lymphadenopathy.
 # For symptomatic conditions, see Table 2.
 * For AIDS-indicator conditions, see Table 3.

Table 2. CDC Classification System: Category B Symptomatic Conditions

Category B symptomatic conditions are defined as symptomatic conditions occurring in an HIV-infected adolescent or adult that meet at least 1 of the following criteria:	
a) They are attributed to HIV infection or indicate a defect in cell-mediated immunity. b) They are considered to have a clinical course or management that is complicated by HIV infection.	
Examples include, but are not limited to, the following:	
- Bacillary angiomatosis - Oropharyngeal candidiasis (thrush) - Vulvovaginal candidiasis, persistent or resistant - Pelvic inflammatory disease (PID) - Cervical dysplasia (moderate or severe)/cervical carcinoma in situ - Hairy leukoplakia, oral	- Idiopathic thrombocytopenic purpura - Constitutional symptoms, such as fever ($>38.5^{\circ}\text{C}$) or diarrhea lasting >1 month - Peripheral neuropathy - Herpes zoster (shingles), involving ≥ 2 episodes or ≥ 1 dermatome

Table 3. CDC Classification System: Category C AIDS-Indicator Conditions

- Bacterial pneumonia, recurrent (≥ 2 episodes in 12 months) - Candidiasis of the bronchi, trachea, or lungs - Candidiasis, esophageal - Cervical carcinoma, invasive, confirmed by biopsy - Coccidioidomycosis, disseminated or extrapulmonary - Cryptococcosis, extrapulmonary - Cryptosporidiosis, chronic intestinal (>1-month duration) - Cytomegalovirus disease (other than liver, spleen, or nodes) - Encephalopathy, HIV-related - Herpes simplex: chronic ulcers (>1-month duration), or bronchitis, pneumonitis, or esophagitis - Histoplasmosis, disseminated or extrapulmonary - Isosporiosis, chronic intestinal (>1-month duration) - Kaposi sarcoma	- Lymphoma, Burkitt, immunoblastic, or primary central nervous system <i>Mycobacterium avium</i> complex (MAC) or <i>M. kansasii</i>, disseminated or extrapulmonary <i>Mycobacterium tuberculosis</i>, pulmonary or extrapulmonary <i>Mycobacterium</i>, other species or unidentified species, disseminated or extrapulmonary <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia (PCP) - Progressive multifocal leukoencephalopathy (PML) - Salmonella septicemia, recurrent (nontyphoid) - Toxoplasmosis of brain - Wasting syndrome due to HIV (involuntary weight loss $>10\%$ of baseline body weight) associated with either chronic diarrhea (≥ 2 loose stools per day ≥ 1 month) or chronic weakness and documented fever ≥ 1 month

WHO Clinical Staging of HIV/AIDS and Case

Definition

The clinical staging and case definition of HIV for resource-constrained settings were developed by the WHO in 1990 and revised in 2005. Staging is based on clinical findings that guide the diagnosis, evaluation, and management of HIV/AIDS, and does not require a CD4 cell count. This staging system is used in many

countries to determine eligibility for antiretroviral therapy. Clinical stages are categorized as 1 through 4, progressing from primary HIV infection to advanced HIV/AIDS (Table 4). These stages are defined by specific clinical conditions or symptoms. For the purpose of the WHO staging system, adolescents and adults are defined as individuals aged ≥ 15 years.

Table 4. WHO Clinical Staging of HIV/AIDS for Adults and Adolescents (Interim Definitions)

Primary HIV Infection		
• Asymptomatic		• Acute retroviral syndrome
Clinical Stage 1		
• Asymptomatic		• Persistent generalized lymphadenopathy
Clinical Stage 2		
• Moderate unexplained weight loss (<10% of presumed or measured body weight) • Recurrent respiratory infections (respiratory tract infections, upper respiratory infections, sinusitis, bronchitis, otitis media, pharyngitis) • Herpes zoster		• Minor mucocutaneous manifestations (angular cheilitis, recurrent oral ulcerations, seborrheic dermatitis, prurigo, papular pruritic eruptions, fungal fingernail infections)
Clinical Stage 3		
<i>Conditions for which a presumptive diagnosis can be made on the basis of clinical signs or simple investigations</i>		
• Severe weight loss (>10% of presumed or measured body weight) • Unexplained chronic diarrhea for >1 month • Unexplained persistent fever for >1 month (intermittent or constant) • Oral candidiasis (thrush) • Oral hairy leukoplakia • Pulmonary tuberculosis within the last 2 years		• Severe presumed bacterial infections (eg, pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) • Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
<i>Conditions for which confirmatory diagnostic testing is necessary</i>		
• Unexplained anemia (hemoglobin <8 g/dL) • Neutropenia (neutrophils <500 cells/μL)		• Thrombocytopenia (platelets <50,000 cells/μL)
Clinical Stage 4		
<i>Conditions for which a presumptive diagnosis can be made on the basis of clinical signs or simple investigations</i>		
• HIV wasting syndrome, as defined by the CDC (see Table 3, above) • <i>Pneumocystis jiroveci</i> (formerly <i>carinii</i>) pneumonia • Recurrent severe or radiologic bacterial pneumonia • Chronic herpes simplex infection (oral or genital, or anorectal site) for >1 month		• Esophageal candidiasis • Extrapulmonary tuberculosis • Kaposi sarcoma • Central nervous system toxoplasmosis • HIV encephalopathy
<i>Conditions for which a confirmatory diagnostic testing is necessary</i>		
• Cryptococcosis, extrapulmonary • Disseminated nontuberculosis Mycobacteria infection • Progressive multifocal leukoencephalopathy • Candida of the trachea, bronchi, or lungs	• Cryptosporidiosis • Isosporiasis • Visceral herpes simplex infection, cytomegalovirus infection (retinitis or organ other than liver, spleen, or lymph node)	• Any disseminated mycosis (eg, histoplasmosis, coccidioidomycosis, penicilliosis) • Recurrent nontyphoidal salmonella septicemia • Lymphoma (cerebral or B-cell non-Hodgkin) • Invasive cervical carcinoma • Visceral leishmaniasis

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Determining Risk of HIV Progression

Background

The absolute CD4 cell count and CD4 percentage are used for disease staging, and to determine when to start antiretroviral therapy (ART) and prophylaxis against opportunistic infections. The HIV RNA level (viral load), when used in conjunction with the CD4 count, also provides prognostic information in patients who are naive to ART.

Data from various cohort studies have demonstrated the strong relationship between lower CD4 count or higher viral load and the risk of progression to AIDS. Tables 1 and 2 and Figure 1 below show the risk of disease progression and death in patients who have not been treated with ART and in patients starting ART in several North American, European, and Australian cohorts. The data consistently indicate the importance of initiating ART before the CD4 count declines to <200 cells/ μ L, if possible.

Table 1. Relationship between CD4 Count or Viral Load and AIDS Progression

CD4 Count (cells/ μ L)	Viral Load (copies/mL)	AIDS Progression in Men (%)	
		Over 3 Years	Over 9 Years
<200	<10,000	14%	64%
	10,000-30,000	50%	90%
	>30,000	86%	100%
200-350	<10,000	7%	66%
	10,000-30,000	36%	85%
	>30,000	64%	93%
>350	<10,000	7%	54%
	10,000-30,000	15%	74%
	>30,000	40%	85%

Adapted from: Mellors JW, Rinaldo CR Jr, Gupta P, et al. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science*. 1996 May 24;272(5265):1167-70.

Figure 1. Prognosis according to CD4 Cell Count and Viral Load in the Pre-HAART and HAART Eras

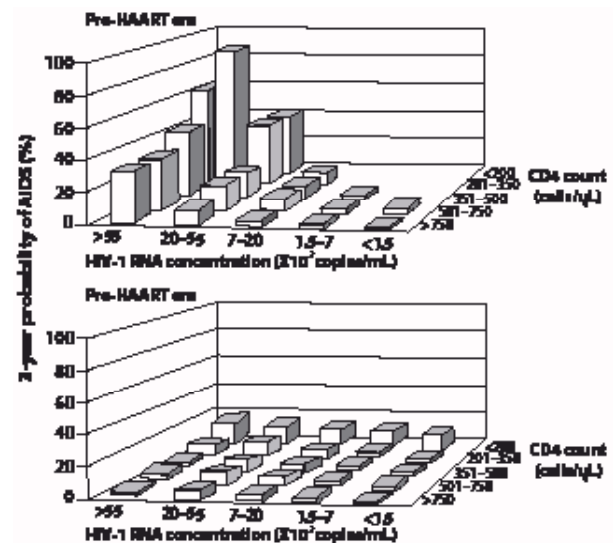


Figure shows Kaplan-Meier estimates of the probability of AIDS at 3 years.

HAART = highly active antiretroviral therapy

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Table 2. Predicted 6-Month Risk of AIDS according to Age and Current CD4 Cell Count and Viral Load, Based on a Poisson Regression Model

Viral Load (copies/ml)	Predicted Risk (%) at Current CD4 Cell Count ($\times 10^6$ cells/L)*									
	50	100	150	200	250	300	350	400	450	500
Age 25 years										
3,000	6.8	3.7	2.3	1.6	1.1	0.8	0.6	0.5	0.4	0.3
10,000	9.6	5.3	3.4	2.3	1.6	1.2	0.9	0.7	0.5	0.4
30,000	13.3	7.4	4.7	3.2	2.2	1.6	1.2	0.9	0.7	0.6
100,000	18.6	10.6	6.7	4.6	3.2	2.4	1.8	1.4	1.1	0.8
300,000	25.1	14.5	9.3	6.3	4.5	3.3	2.5	1.9	1.5	1.2
Age 35 years										
3,000	8.5	4.7	3.0	2.0	1.4	1.0	0.8	0.6	0.5	0.4
10,000	12.1	6.7	4.3	2.9	2.0	1.5	1.1	0.9	0.7	0.5
30,000	16.6	9.3	5.9	4.0	2.8	2.1	1.6	1.2	0.9	0.7
100,000	23.1	13.2	8.5	5.8	4.1	3.0	2.3	1.7	1.3	1.1
300,000	30.8	18	11.7	8.0	5.7	4.2	3.1	2.4	1.9	1.5
Age 45 years										
3,000	10.7	5.9	3.7	2.5	1.8	1.3	1.0	0.7	0.6	0.5
10,000	15.1	8.5	5.4	3.6	2.6	1.9	1.4	1.1	0.8	0.7
30,000	20.6	11.7	7.5	5.1	3.6	2.6	2.0	1.5	1.2	0.9
100,000	28.4	16.5	10.6	7.3	5.2	3.8	2.9	2.2	1.7	1.3
300,000	37.4	22.4	14.6	10.1	7.2	5.3	4.0	3.1	2.4	1.9
Age 55 years										
3,000	13.4	7.5	4.7	3.2	2.3	1.7	1.2	0.9	0.7	0.6
10,000	18.8	10.7	6.8	4.6	3.3	2.4	1.8	1.4	1.1	0.8
30,000	25.4	14.6	9.4	6.4	4.6	3.3	2.5	1.9	1.5	1.2
100,000	34.6	20.5	13.3	9.2	6.5	4.8	3.6	2.8	2.2	1.7
300,000	44.8	27.5	18.2	12.6	9.1	6.7	5.0	3.9	3.0	2.4

* Shading distinguishes risk: <2%, no shading; 2-9.9%, light gray; 10-19.9%, mid-gray; >20%, darkest gray.

Reprinted with permission from Lippincott, Williams & Wilkins [Phillips A; CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naïve individuals and those treated in the monotherapy era. *AIDS* 2004; 18 (1):51-8]. Lippincott, Williams & Wilkins online: <http://www.com>

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CD4 Monitoring and Viral Load Testing

Background

CD4 Monitoring

CD4 cells (also called T cells or T-helper cells) are the primary targets of the HIV virus. The CD4 count is the number of CD4 cells per microliter (μL) of blood. It is the standard test for assessing HIV stage and prognosis, and for monitoring progression to AIDS and risk of opportunistic illnesses. It also guides the provider in formulating differential diagnoses in symptomatic patients (see Table 1, below), deciding about initiating antiretroviral treatment (ART), and beginning prophylaxis for opportunistic infections.

Most laboratories report the CD4 count as part of a list of several types of lymphocytes, as both an absolute count and a relative percentage. The important numbers are the absolute number of CD4 cells per microliter and the CD4 cell percentage, which is the proportion of CD4 cells as a subset of all lymphocytes.

The CD4 count typically declines over time as HIV infection progresses. Many other factors may affect CD4 counts more transiently, including illness, vaccination, diurnal variation, laboratory error, and inter-laboratory differences (see “Patient Education” below). Because fluctuations in the absolute CD4 count are likely, definitive conclusions should rarely be drawn from a single CD4 value. When results are inconsistent with previous trends, tests should be repeated, and treatment decisions usually should be based on 2 or more similar values. The CD4 percentage sometimes is used in coordination with the absolute value to assess the significance of changes in the absolute CD4 count. The absolute CD4 count can fluctuate as overall lymphocyte counts vary, but the CD4 percentage often remains stable during insignificant CD4 fluctuations. CD8 cell (or cytotoxic T cell) counts do not appear to predict clinical outcomes.

As untreated HIV infection progresses, the CD4 count declines by approximately 4% per year. In response to successful ART, the CD4 count typically increases by >50 cells/ μL within weeks after viral suppression, and then increases by 50–100 cells/ μL per year thereafter until a threshold is reached. In some patients, CD4 counts may not increase this quickly or steadily, even with durable viral load suppression.

The CD4 count is one of many factors (including clinical status, viral load status, and medication adherence) that should be assessed before starting or changing ART. The U.S. Department of Health and Human Services has provided recommendations for starting therapy based on symptoms, CD4 count, and viral load (Table 2). (See chapters *Antiretroviral Therapy* and *Adherence*.) Prophylaxis against opportunistic infections also is based on CD4 count, and sometimes on CD4 percentage. For example, a CD4 count of <200 cells/ μL or a CD4 percentage of $<14\%$ is an indication for prophylaxis against *Pneumocystis jiroveci* pneumonia; a CD4 count of <50 cells/ μL is an indication for prophylaxis against *Mycobacterium avium* complex. (See chapter *Opportunistic Infection Prophylaxis*.)

For monitoring purposes, the CD4 count should be repeated approximately every 3–4 months both in stable untreated patients and in patients on stable ART. The CD4 count should be checked more frequently according to the clinical situation (Table 3).

Viral Load Testing

In untreated HIV infection, replication usually produces billions of new viral copies daily. Plasma HIV RNA (viral load) testing quantifies the HIV viral burden in the plasma. In areas of the world with access to viral load monitoring, the viral load is a standard tool used to monitor treatment response in patients taking ART and, in conjunction with the CD4 cell count, to assess HIV progression. In certain settings in which HIV antibody tests may be negative or misleading, such as in acute HIV infection or neonatal infection, the HIV viral load may be used to help diagnose HIV infection. In some situations, the viral load may factor into decisions to initiate or change ART.

Viral load assays include HIV RNA polymerase chain reaction (Amplicor HIV-1 Monitor; Roche Laboratories), the branched chain DNA (Versant HIV-1 RNA assay; Bayer), and nucleic acid sequence-based amplification (NucliSens HIV-1 QT test; bioMérieux). The lowest level of detection differs for each test. Ultrasensitive assays (which are preferred in most circumstances) measure viral loads to 50–80

copies/mL, depending on the specific test, whereas the older assays usually have a cut-off at <400 copies/mL. A viral load below the level of detection (“undetectable”) indicates inability of the assay to detect HIV in the plasma, but does NOT indicate absence or clearance of the virus from the body. Suppressing HIV RNA to an undetectable level (<50–75 copies/mL as measured by the ultrasensitive assay) is an important goal of ART. These assays also have different values for the highest levels of detection, ranging between 500,000 copies/mL and 750,000 copies/mL. Viral loads higher than these levels are reported, for example, as >500,000 copies/mL.

Whereas the absolute CD4 cell count is more predictive of clinical disease progression than is the baseline viral load, studies have shown that patients who have high plasma viral loads have an increased risk of progression to symptomatic disease and AIDS compared with patients who have low or undetectable levels. Patients with acute HIV infection who are undergoing seroconversion, and those with advanced disease, may have viral loads >500,000 copies/mL, whereas asymptomatic persons with chronic infection usually have considerably lower viral loads. Viral loads, like CD4 counts, are affected by laboratory variation, assay fluctuations, and patient variables such as acute illness and recent vaccinations. Variations less than approximately $0.5 \log_{10}$ copies/mL (3-fold) usually are not clinically significant. Viral load results that are inconsistent with previous trends should be repeated, and treatment decisions usually should be based on 2 or more similar values. If patients have had recent illnesses or vaccinations, viral load measurement should be deferred for 4 weeks, if possible.

Viral load should be checked at least twice at baseline, before starting an ART regimen. Follow-up viral load measurement should be performed at regular intervals, depending on the patient’s clinical situation (Table 3). In the stable patient, viral load should be monitored every 3–4 months. With new therapy or changes in therapy, significant change in viral load or CD4 count, or declining clinical status, the viral load should be measured at closer intervals.

S: Subjective

A patient presents with HIV infection.

O: Objective

Complete the initial or interim physical examination according to the protocol. (See chapters *Initial Physical Examination* and *Interim History and Physical Examination*.)

A: Assessment

See chapters *Initial History*, *Initial Physical Examination*, and *Initial and Interim Laboratory and Other Tests*.

P: Plan

Laboratory

- ♦ Obtain a CD4 count and perform viral load testing. See chapter *Initial and Interim Laboratory and Other Tests* for other recommended laboratory work.
- ♦ Monitor the results and manage patients using the schematic in Table 2 as a guide. See chapter *Antiretroviral Therapy* for more specific information.

Table 1. Correlation between CD4 Cell Counts and Complications of HIV Infection

CD4 Count* (cells/ μ L)	Infectious Complications	Noninfectious Complications#	
>500	- Acute retroviral syndrome - Candidal vaginitis	- Persistent generalized lymphadenopathy (PGL) - Guillain-Barré syndrome	- Myopathy - Aseptic meningitis
200-500	- Pneumococcal and other bacterial pneumonias - Pulmonary tuberculosis - Herpes zoster - Oropharyngeal candidiasis (thrush) - Cryptosporidiosis (self-limited) - Kaposi sarcoma (cutaneous) - Oral hairy leukoplakia - Herpes simplex (oral/genital)	- Cervical intraepithelial neoplasia - Cervical cancer - B-cell lymphoma - Anemia - Mononeuronal multiplex	- Idiopathic thrombocytopenic purpura - Hodgkin lymphoma - Lymphocytic interstitial pneumonitis - Fatigue
<200	<i>Pneumocystis jiroveci</i> pneumonia (PCP) - Disseminated histoplasmosis and coccidioidomycosis - Miliary/extrapulmonary tuberculosis - Progressive multifocal leukoencephalopathy (PML)	- Wasting - Peripheral neuropathy - HIV-associated dementia - Cardiomyopathy	- Vacuolar myelopathy - Progressive polyradiculopathy - Non-Hodgkin lymphoma
<100	- Disseminated herpes simplex virus - Toxoplasmosis - Cryptococcosis - Cryptosporidiosis, chronic - Microsporidiosis - Candidal esophagitis - Kaposi sarcoma (visceral/pulmonary)		
<50	- Disseminated cytomegalovirus (CMV) - Disseminated <i>Mycobacterium avium</i> complex (MAC)	Central nervous system (CNS) lymphoma	

* Most complications occur with increasing frequency at lower CD4 cell counts.

Some conditions listed as “noninfectious” are probably associated with transmissible microbes. Examples include lymphoma (Epstein-Barr virus) and cervical cancer (human papillomavirus). Adapted from Bartlett JG, Gallant JE. Medical Management of HIV Infection. Baltimore: Johns Hopkins University School of Medicine; 2005-2006. Used with permission.

Table 2. DHHS Guidelines for Initiating Antiretroviral Therapy in Chronically Infected Adults

Clinical Category	CD4 Count (cells/ μ L)	Plasma HIV Viral Load (copies/mL)	Antiretroviral Therapy Recommendations	Repeat CD4 and HIV Viral Load Test
Asymptomatic	>350	<100,000	Defer therapy	Every 3-4 months if not on ART (see below if on ART)
Asymptomatic	>350	$\geq$ 100,000	Most clinicians recommend deferring therapy, some may treat	Every 3-4 months until ART is started, then check for viral load response at 2-8 weeks; monitor CD4 and viral load every 3-4 months if satisfactory response
Asymptomatic	$\geq$ 200 but $\leq$ 350	Any value	Treatment should be offered	As above
Asymptomatic, AIDS	<200	Any value	Treat	As above
AIDS-defining illness or severe symptoms	Any value	Any value	Treat	As above

Adapted from U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 10, 2006.

Table 3. Indications for CD4 Count and Plasma HIV RNA (Viral Load) Testing

Clinical Indication	Test and Information Provided	Use
Syndrome consistent with acute or primary HIV infection	HIV viral load: establishes diagnosis when HIV antibody test is negative or indeterminate	Diagnosis (should be confirmed by standard HIV antibody test 2-4 months after initial test)
Initial evaluation of newly diagnosed HIV infection	Baseline CD4 and viral load values; disease staging	Decision to start or defer ART*
Every 3-4 months in patients not on therapy	CD4 cell count and viral load; disease monitoring	Decision to start or defer ART*
2-8 weeks after initiation of or change in ART	CD4 count and viral load: Initial assessment of drug regimen efficacy	Decision to start or defer ART*
3-4 months after starting ART	CD4 count and viral load: Assess treatment efficacy; viral load should be undetectable by 16-24 weeks; CD4 cell count likely to continue to increase	Decision to start or defer ART*
Every 3-4 months in patients on ART	CD4 count and viral load: Assess durability of immunologic response (CD4 increase) and virologic suppression (undetectable viral load)	Decision to start or defer ART*
Clinical event, or significant decline in CD4 cells or increase in viral load	CD4 count and viral load: Check for association of clinical events with changing or stable CD4 cell count and/or plasma HIV viral load; confirm changes in CD4 and viral load	Decision to initiate, continue, or change therapy*

* Decisions to initiate or change antiretroviral therapy (ART) should be based on 2 or more similar CD4 and viral load values.
Adapted from U.S. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents. October 10, 2006.

Patient Education

- ◆ CD4 counts are the best indicator of how healthy the immune system is and whether a person is at risk of getting certain infections.
- ◆ CD4 counts are variable. Caution patients not to pin emotions and hopes to a single lab result.
- ◆ The HIV viral load is the best indicator of how active HIV is in the patient's body.
- ◆ Several ARVs may be used in combination to reduce the amount of virus in the body of someone with HIV. For each of these regimens, it is important to take each dose on time, every time. (See chapters on *Antiretroviral Therapy* and *Adherence* if the patient is getting ready to start ART.)
- ◆ ART directly affects the activity of HIV in the body and will lower the viral load. With less HIV present, the body is able to produce more CD4 cells and improve the immune system.
- ◆ An undetectable viral load does not mean HIV is cured or that the patient is not infectious to others. It means that virus cannot be detected in the blood, although it exists in other parts of the body.
- ◆ If the patient's CD4 count increases with successful ART, he or she may be protected from infections and other illnesses related to HIV.

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Primary HIV Infection

Background

Primary HIV infection refers to the very early stages of HIV infection, or the interval from initial infection to the time that antibody to HIV is detectable. During this stage of HIV infection, patients typically have symptoms of acute HIV seroconversion illness, very high HIV RNA levels of >100,000 copies/mL, and negative or indeterminate HIV antibody tests.

The diagnosis of patients with primary HIV infection is a clinical challenge. The symptoms of primary HIV are nonspecific, and although many patients seek medical care for symptoms of HIV seroconversion illness, the diagnosis commonly is missed at initial presentation. The difficulties involve recognizing the clinical presentation of acute HIV infection and testing patients appropriately. In HIV treatment clinics, clinicians generally do not see patients with primary HIV infection, unless they are referred with this diagnosis already established. In other health care settings, clinicians may not be familiar with the signs and symptoms of acute HIV infection and often do not consider this diagnosis.

After infection with HIV, it takes a median of 25 days before the HIV antibody test becomes positive; in some individuals, it may be several months before seroconversion. Individuals with known exposures to HIV, whether occupational or not, should be monitored closely beginning at about 3 weeks after exposure (routine monitoring at 6 weeks, 3 months, and 6 months after exposure to HIV is likely to result in delayed diagnosis of HIV infection). For information on postexposure prophylaxis, see chapters *Nonoccupational Postexposure Prophylaxis* and *Occupational Postexposure Prophylaxis*.

S: Subjective

More than three quarters of patients who become infected with HIV develop symptoms consistent with primary HIV infection. Symptoms typically appear a few days to a few weeks after exposure to HIV, and generally include several of the following:

- ◆ Fever
- ◆ Rash, often erythematous maculopapular
- ◆ Fatigue

- ◆ Pharyngitis
- ◆ Generalized lymphadenopathy
- ◆ Urticaria
- ◆ Myalgia/arthralgia
- ◆ Anorexia
- ◆ Mucocutaneous ulceration
- ◆ Headache, retroorbital pain
- ◆ Neurologic symptoms (eg, aseptic meningitis, radiculitis, myelitis)

This symptomatic phase usually persists for 2–4 weeks or less, although lymphadenopathy may last longer. These symptoms and signs are similar to those of many other illnesses, including other viral syndromes. To diagnose early HIV infection, clinicians must consider HIV in the differential diagnosis for at-risk patients with symptoms resembling flu or mononucleosis. A history of recent risk behaviors should be obtained from all patients who present with symptoms consistent with acute HIV infection.

O: Objective

During the symptomatic phase of HIV seroconversion, the HIV antibody test is likely to be negative or indeterminate. For patients who have symptoms consistent with seroconversion illness and a recent high-risk history for HIV exposure, an HIV RNA (viral load) test should be performed, in addition to the HIV antibody test, as part of the evaluation. Patients with negative antibody tests but high HIV viral loads (>100,000 copies/mL) can be considered to be infected with HIV, although the antibody test should be repeated later to confirm seroconversion. False-positive HIV viral loads have been reported in approximately 5% of patients who were tested after HIV exposures. A low viral load (<1,000 copies/mL) usually indicates a false-positive result at this stage, because viral loads typically run very high (ie, >100,000 copies/mL and often millions of copies/mL) in acute infection. Patients who have indeterminate HIV antibody test results, low HIV viral loads, and no clear HIV risk factors or symptoms of primary HIV infection should have repeat antibody testing in 4–6 weeks, without other interventions. For patients without significant risk factors, indeterminate results rarely indicate evolving seroconversion.

A: Assessment and Plan

Patients with primary HIV infection will need additional medical evaluation, baseline laboratory testing, and intensive support, counseling, and education about HIV infection. See chapters *Initial History*, *Initial Physical Examination*, and *Initial and Interim Laboratory and Other Tests* for detailed information on the initial evaluation of HIV-infected patients.

Laboratory

The initial laboratory work should include the following:

- ◆ The CD4 count and HIV viral load should be checked on 2 occasions within several weeks.
- ◆ A baseline HIV genotype test should be obtained for all patients with primary HIV infection, even those who do not choose to start antiretroviral treatment (ART). In some cities in the United States and Europe, up to 15-20% of individuals infected in recent years have acquired HIV virus strains with mutations that confer resistance to antiretroviral medications. These resistance mutations may be identified by early resistance testing, but later may not be detectable. (See chapter *Resistance Testing*.)
- ◆ The HIV antibody test should be repeated in 4-6 weeks to document the HIV status of patients who are presumed to have primary HIV infection.

Treatment

It is reasonable to consider starting combination ART in patients with acute HIV infection, because some limited evidence suggests that treatment initiated during primary HIV infection may preserve HIV-specific immune function that would otherwise be lost as the infection progresses. However, it is not yet clear whether initiating early treatment yields long-term immunologic, virologic, or clinical benefits. The potential advantages of ART for primary infection must be weighed against the possibility of short- and long-term toxicities, the possibility of developing drug resistance, and the adherence challenges associated with starting antiretrovirals quickly in newly diagnosed patients. These issues are complex, and consultation with an HIV expert or referral to a clinical trial is recommended.

For patients who choose to start therapy during primary HIV infection, the choice of agents and the monitoring of patients on treatment are similar to those in the treatment of chronic HIV infection (see chapter *Antiretroviral Therapy*). The initial goal of therapy in

primary HIV infection is to suppress the HIV viral load to undetectable levels.

Clinical trials across the country currently are recruiting individuals to evaluate both the natural history of primary HIV infection and the possible benefits of treatment of acute HIV infection. Information on clinical studies of primary HIV may be obtained through the AIDS Clinical Trials Information Service (ACTIS) on its Web site at <http://www.aidsinfo.nih.gov/clinicaltrials> or by telephone at 800-HIV-0440. Issues concerning the possible treatment of primary HIV infection also are reviewed in the U.S. Department of Health and Human Services *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*.

Patient Education

Patients with primary HIV infection need support and counseling, as do all newly diagnosed patients. Intensive education about HIV infection, the course of disease, prognosis, and the risks and benefits of ART must be undertaken. Counseling about safer sex and drug injection techniques, as indicated, is especially important for these patients because they may have ongoing high-risk behaviors for HIV transmission and because they may be highly infectious during the primary infection period. (See chapter *Preventing HIV Transmission / Prevention with Positives* for more information about patient support and counseling in these areas.)

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Rapid HIV Testing

Background

It is estimated that as many as 300,000 individuals in the United States are unaware that they have HIV infection. It is also estimated that about 25% of these individuals account for approximately 55% of the 40,000 new infections occurring in the United States each year. Studies have shown that once individuals learn about their HIV infection, they substantially reduce their high-risk sexual behaviors. However, even when people are tested for HIV with standard HIV tests, many do not return to obtain the results. With rapid HIV testing, clients can receive their results during the same visit. A rapid test can allow referrals for urgent treatment, such as in pregnant women, as well as non urgent referrals to engage patients in medical care. Rapid testing also provides immediate information for making clinical decisions, such as whether to offer postexposure prophylaxis.

Clients and Settings for Rapid Testing

Rapid HIV testing is recommended for settings in which the availability of rapid HIV test results would influence medical care immediately, or HIV prevalence is high but clients are not likely to return for the results of HIV tests. These settings include labor and delivery settings (to allow intervention to reduce the risk of perinatal HIV transmission in women with undocumented or unknown HIV status) as well as hospital emergency departments, urgent care and acute care clinics, sexually transmitted disease clinics, drug treatment clinics, and clinical care or testing sites. Rapid HIV testing also is available or being implemented in employee health departments at many hospitals as part of evaluation for and provision of postexposure prophylaxis.

risk of perinatal HIV transmission in women with undocumented or unknown HIV status) as well as hospital emergency departments, urgent care and acute care clinics, sexually transmitted disease clinics, drug treatment clinics, and clinical care or testing sites. Rapid HIV testing also is available or being implemented in employee health departments at many hospitals as part of evaluation for and provision of postexposure prophylaxis.

Rapid HIV Tests

The U.S. Food and Drug Administration has approved 4 rapid tests for use in the United States (Table 1). Federal regulations under the Clinical Laboratory Improvement Amendments (CLIA) program categorize tests as waived, moderate complexity, or high complexity. Two rapid tests are approved as CLIA-waived tests, meaning that they may be done at the point of care after appropriate staff training and with procedures in place to insure quality control. These tests use whole blood or oral fluid and require a few simple steps to perform. Other rapid tests are “non waived” tests and must be performed in laboratories. Results for rapid tests done at the point of care are available in less than 30 minutes; results for those done in a laboratory should be available within 1 hour.

Table 1. FDA-Approved Rapid HIV Antibody Screening Tests

Test	Specimen Type	CLIA Category	Sensitivity (95% CI)*	Specificity (95% CI)	Manufacturer	Approved for HIV-2 Detection
OraQuick Advance Rapid HIV-1/2 Antibody Test	Whole blood (finger stick or venipuncture)	Waived	99.6% (98.5-99.9)	100% (99.7-100)	OraSure Technologies www.orasure.com	Yes
	Oral fluid	Waived	99.3% (98.4-99.7)	99.8% (99.6-99.9)		
	Plasma	Moderate complexity	99.6% (98.9-99.8)	99.9% (99.6-99.9)		
Uni-Gold Recombigen HIV	Whole blood (finger stick or venipuncture)	Waived	100% (99.5-100)	99.7% (99.0-100)	Trinity Biotech www.unigoldhiv.com	No
	Serum/plasma	Moderate complexity	100% (99.5-100)	99.8% (99.3-100)		
Reveal G2	Serum	Moderate complexity	99.8% (99.2-100)	99.1% (98.8-99.4)	MedMira www.medmira.com	No
	Plasma		99.8% (99.0-100)	98.6% (98.4-98.8)		
MultiSpot HIV-1/HIV-2	Serum/plasma	Moderate complexity	100% (99.9-100)	99.9% (99.8-100)	BioRad Laboratories www.biorad.com	Yes, differentiates HIV-1 from HIV-2
	HIV-2		100% (99.7-100)			

Adapted from Health Research and Education Trust (HRET). FDA-Approved Rapid HIV Antibody Screening Tests, January 10, 2005. Prepared by Stanger K, Margolin F, Lampe M, et al. Available at: <http://www.hret.org/hret/programs/hivtransmrpd.html>. Accessed May 25, 2006.

Interpreting Rapid Test Results

All of the rapid tests are highly sensitive and specific. The negative predictive value of all rapid HIV tests is close to 100%. This means that a client who receives a negative rapid test result is almost assuredly not infected, barring recent exposures (sexual contact or needle sharing with an infected person within 3 months). A client with a history of recent HIV risk behaviors or possible exposures should repeat the HIV test in the near future because it may take up to 3 months for HIV antibodies to be detectable after infection with HIV.

The positive predictive value of a single positive rapid HIV test depends on the specificity of the test and the HIV prevalence in the community. Given the high specificity of the rapid tests (Table 1), this means that if the rapid test result is positive, the likelihood that a client is truly HIV infected depends on the local HIV prevalence. In a population with a high HIV prevalence, a positive rapid test result is likely to be a true positive, but in a population with a low HIV prevalence, that result may be a false positive. For this reason, every positive rapid HIV test is considered a preliminary result and must be confirmed by either Western blot or immunofluorescence assay (IFA).

Information for the Client

Counseling the Client before Testing

Many clients believe the following:

- 1) they must consent to HIV testing to receive any medical care; or
- 2) they have been tested while getting medical care, and, because no one informed them otherwise, they must be HIV negative.

Because these assumptions are false, it is important to offer rapid HIV testing as a health screening test, to educate clients about the test and to give them an opportunity to ask questions and to decline testing. The provider should reassure clients that the rapid HIV test is just as accurate as the standard HIV test. When possible, rapid testing should be made available during the current office visit so that clients do not face additional waiting time. The provider should emphasize that a second test is always done to confirm a positive rapid test.

Giving Reactive (Preliminary Positive) Rapid Test Results

Example of simple language to use outside labor and delivery settings

The following wording is suggested when the client's rapid test result is positive:

"Your preliminary test result was positive, but we won't know for sure if you are infected with HIV until we get the results from your confirmatory test. In the meantime, you should take precautions to avoid transmitting the virus. This means protecting sexual partners from possible exposure (using condoms, for example), not sharing injection drug needles or syringes, and so forth."

Emphasize the importance of a confirmatory test, arrange for the confirmatory test to be done as soon as possible, and schedule a return visit for the results.

Language to use in labor and delivery settings

The following wording is suggested when the client's rapid test result is positive:

"Your preliminary HIV screening result was positive. You may have HIV infection. It is important to start medication to reduce the risk of passing HIV to your baby while we wait for the second (or confirmatory) test result. It is important to delay breast feeding until we have the second test result."

Follow-Up for Results of Confirmatory Tests

Clinical sites that offer rapid HIV testing should have a protocol for conveying the results of confirmatory HIV tests to clients. Rapid testing sites should either provide this service in-house or have mechanisms in place for referring clients to community-based HIV services. For example, when women have preliminary positive results on tests done during labor and delivery, confirmatory test results may be sent to their obstetrician, but often may be sent to the local health department. These women should be given appointments specifically for receiving their confirmatory test results. Clinicians should be familiar with community resources for referring clients with positive rapid test results. All clients with confirmed positive HIV test results should be referred for HIV care; testing sites should establish reliable referral pathways to qualified HIV care providers.

Patient Education

In general settings and in situations not involving labor and delivery, patient education should include the following points:

- ◆ Rapid HIV testing is an important health screening. Learning that you have HIV infection early can improve your prognosis (can keep you well).
- ◆ Knowing that you have HIV infection can help you take precautions to keep from passing HIV to others.
- ◆ You can refuse an HIV test, and it will not affect the care you receive.
- ◆ The results from the rapid tests are available at the same visit, usually in less than 1 hour.
- ◆ If the rapid test is positive, a second, confirmatory test is always done to be sure the rapid test was accurate.
- ◆ The rapid test is very accurate—as accurate as the standard HIV test.
- ◆ It is important that you come back for the results of the confirmatory test.
- ◆ If the test is negative, you do not have HIV infection, but the test may not show recent infection.
- ◆ The test results are kept confidential. However, if the confirmatory test is positive, the law requires that the results be reported to the health department (although this may not be the case in certain states). There are places you can go for more information and for counseling, care, or treatment.

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Immunizations for HIV-Infected Adults and Adolescents

Background

Immunocompromised individuals are at higher risk for many types of infections compared with immunocompetent people. Although HIV-infected persons could benefit greatly from immunization against preventable infections, little specific research on the effectiveness of immunizations in this population has been completed. In general, vaccines have better efficacy in HIV-infected patients when immune function is relatively well preserved, notably when the CD4 count is >200 cells/ μ L. Persons with advanced immunodeficiency (see Table 1) may have an impaired

humoral response, and may not respond to vaccines, or they may require supplemental doses to develop serologic evidence of protection. If possible, vaccines should be administered before the CD4 count decreases to <200 cells/ μ L.

Live vaccines generally should not be administered to those with HIV infection, particularly those with advanced immunodeficiency, unless the anticipated benefits of vaccination clearly outweigh possible risks.

Table 1 presents recommendations about vaccination for patients with HIV infection.

Table 1. Vaccine Recommendations

Vaccine Type	Recommendation
Pneumococcal (polysaccharide)	- Recommended for all; consider revaccination every 5 years. - If CD4 count is <200 cells/μL, may be less effective; revaccinate when CD4 count increases in response to ART.
Hepatitis A Virus (HAV)	- Recommended, for persons with chronic hepatitis C or hepatitis B, injection drug users, men who have sex with men, international travelers, and hemophiliacs. Consider for all, unless there is serologic evidence of previous disease. 2 doses (0, 6–12 months)
Hepatitis B Virus (HBV)	- Recommended, unless there is evidence of immunity (HBV surface Ab+) or active hepatitis B infection (HBV surface Ag+, or HBV core Ab+ and evidence of HBV activity). 3 doses (0, 1–2, 4–6 months)
Influenza (inactivated vaccine)	- Recommended (yearly) - Vaccination is most effective among persons with CD4 count >100 cells/μL and HIV RNA $<30,000$ copies/mL. - In patients with advanced disease and low CD4 count, inactivated vaccine may not produce protective antibodies. - Live, attenuated cold-adapted vaccine (LAIV, FluMist) is contraindicated in patients with HIV infection.
Tetanus-Diphtheria	Recommended (booster is recommended every 10 years in adults; or, if injured, after 5 years)
Measles, Mumps, Rubella (MMR)	- Recommended if indicated (eg, if contact with measles is likely through travel or other exposures). For live vaccine, use caution in those with low CD4 counts. - Consider for all susceptible people who are not severely immunosuppressed.* - Contraindicated in severe immunosuppression.
Varicella Zoster (VZV)**	- Consider for asymptomatic patients with relatively high CD4 counts, if they have no history of chickenpox and no evidence of immunity or significant exposure. - Avoid in patients with advanced immunosuppression. - Avoid exposure to VZV, if possible. If someone without immunity to VZV is exposed to VZV, administer VZIG as soon as possible, at least within 96 hours.

Key to abbreviations: ART = antiretroviral therapy; Ab = antibody; Ag = antigen.

* HIV-infected persons with CD4 counts <200 cells/ μ L, history of an AIDS-defining illness, or clinical manifestations of symptomatic HIV are considered to have severe immunosuppression. Asymptomatic HIV-infected persons with CD4 counts of 200–500 cells/ μ L are considered to have limited immune deficits.

** HIV-negative susceptible household contacts (especially children) of HIV-infected susceptible patients should be vaccinated against VZV, so that they will not transmit VZV to the HIV-infected patient. HIV-infected susceptible patients should limit their contact with recently vaccinated children or adults for 12–14 days after vaccination.

Immunizations for HIV-Infected Patients Traveling to Developing Countries

Routine vaccinations should be reviewed and updated before travel. All patients traveling to other countries should be evaluated for both routine and destination-specific immunizations and prophylaxes. Killed and recombinant vaccines (eg, diphtheria-tetanus, rabies, hepatitis A, hepatitis B, Japanese encephalitis) should be used for HIV-infected persons just as they would be used for HIV-uninfected persons anticipating travel. For further information, see the Centers for Disease Control and Prevention (CDC) Web page at <http://www.cdc.gov/travel/>. Recommendations specific to HIV-infected travelers are located in “The Immunocompromised Traveler” under the section called “Special Needs Travelers.” Select the “Traveler’s Health” option for regional travel documents and information on outbreaks.

Decisions about immunization for the HIV-infected traveler should take into consideration the traveler’s current CD4 count, history of an AIDS-defining illness, and clinical manifestations of symptomatic HIV. In the CDC recommendations, asymptomatic HIV-infected persons with CD4 counts of 200–500 cells/ μ L are considered to have limited immune deficits, whereas patients with CD4 counts >500 cells/ μ L are considered to have no immunologic compromise. For patients taking antiretroviral therapy, current CD4 counts rather than nadir counts should be used in deciding about immunizations.

The following should be noted about specific vaccinations:

- ◆ Inactivated (killed) enhanced potency-polio and typhoid vaccines should be given instead of the live, attenuated forms. In adults aged >18 years, vaccinate 8 weeks before travel to allow time for the initial 2 doses of polio vaccine.
- ◆ Measles or measles-mumps-rubella (MMR; omit if patient has evidence of immunity) should not be given to severely immunocompromised patients. Instead, immune globulin should be given to measles-susceptible, severely immunocompromised persons traveling to measles-endemic countries.
- ◆ Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy for HIV-infected persons and should be avoided if possible. Travelers with asymptomatic HIV infection and relatively high CD4 counts who cannot avoid potential exposure to yellow fever should be offered the choice of vaccination. If travel to a zone with yellow fever is necessary and vaccination is not administered, patients should be advised about the risk of yellow fever, instructed about avoiding the bites of vector mosquitoes, and provided with a vaccination waiver letter.
- ◆ The influenza season in the southern hemisphere is April through September, but in the tropics influenza is a year-round infection. Immunocompromised patients should be protected according to influenza risk at the destination. HIV-infected patients should not be given live intranasal influenza vaccine.

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Nutrition

Background

Maintaining good nutritional status is important to support overall health and immune system function in people with HIV/AIDS. Many HIV-related conditions affect and are affected by the body's nutritional status. These include conditions related to HIV itself (eg, opportunistic infections and other illnesses), comorbid conditions, and adverse effects of therapies.

Inadequate nutrition in people with HIV infection may result from many factors—including conditions such as nausea, vomiting, or anorexia—that may prevent adequate intake of nutrients and medications; diarrheal infections that prevent absorption of nutrients and medications; systemic illnesses (including HIV itself) that create a catabolic state; and psychological conditions (such as depression) that impair patients' ability to nourish themselves. In addition, financial constraints may limit patients' access to nutritious food.

Evaluation and enhancement of patients' nutritional status may help correct or compensate for deficiencies (eg, in the case of weight loss or nutrient deficits), may be a key treatment modality for certain conditions (eg, dyslipidemia, hyperglycemia), and may help to maintain good health and immune function. This chapter focuses on the evaluation of patients with nutritional deficiencies, particularly weight loss, and simple strategies for maintaining good nutrition in individuals with barriers to maintaining adequate weight.

Ideally, HIV-infected individuals will receive the services of HIV-experienced nutrition specialists, who may contribute to the patient care team in the following ways:

- ◆ Conducting routine screening to identify and treat nutritional problems
- ◆ Preparing a tailored nutritional plan to optimize patients' nutritional status, immune status, and overall well-being
- ◆ Screening and developing interventions for growth problems in children
- ◆ Developing strategies to prevent loss of weight and lean body mass
- ◆ Adapting dietary recommendations to help reduce the risk of comorbid conditions such as diabetes and heart disease, or treating these complications
- ◆ Educating patients about how to modify their dietary habits to maximize the effectiveness of medical and pharmacologic treatments
- ◆ Tailoring nutritional recommendations to fit patients' lifestyles and financial resources
- ◆ Counseling patients to promote nutrition self-care using available resources
- ◆ Providing nutritional support to patients may help to do the following:
 - ◆ Treat common problems associated with HIV disease and its treatment (eg, weight loss, wasting, fatigue, loss of appetite, adverse changes in taste, dental problems, gastrointestinal complaints)
 - ◆ Treat chronic comorbid conditions (eg, cardiovascular disease, hypertension, diabetes, cirrhosis)
 - ◆ Improve quality of life
 - ◆ Enhance immune responses, slow disease progression, and prolong life

S: Subjective

History

Identify nutrition risk factors through interview, questionnaire, or both at the start of care. Update the history at least annually. The history should record nutrition-related signs, symptoms, and habits (Table 1); dietary habits (Table 2); and symptoms suggesting nutritional deficiencies (Table 3).

Table 1. Nutrition-Related Questions for Patient History

Signs, Symptoms, and Comorbid Conditions: • Poor or sporadic appetite • Early satiety • Weight gain or loss • Trouble chewing or swallowing • Dental problems including poor dental hygiene • Gastrointestinal complaints, including nausea, diarrhea, constipation, heartburn, gas • Changes in body contours with fat gain in abdomen, back of neck, and breasts (lipodystrophy) and/or fat loss in extremities and face (lipoatrophy) • Depression, stress • Fatigue • Chronic pain • Other diseases affecting diet and nutrition Medication-Related Factors: • Medications, including over-the-counter and herbal products • Medication side effects • Difficulty coordinating meals with medicines • Use of nutritional supplements Social and Behavioral Factors: • Frequent eating out • Smoking • Alcohol or substance abuse • Erratic meal patterns • Unbalanced diet (eg, high intake of low-nutrient foods; deficiency in key nutrients) • Resources to ensure secure, continued food access • Availability of food storage and preparation facilities • Housing: stable, or homeless/marginally housed/in transition • Nutrition literacy

To develop a specific dietary history, use the following questions.

Table 2. Questions for Dietary History

Usual Dietary Intake • Frequency of intake of foods providing key nutrients (eg, dairy products, fortified or whole grains, fruits and vegetables, fluids, meat, eggs, beans) as well as those that perhaps should be limited (fast-food items, highly processed or salted products) • Usual meal patterns (number of times per day, snacks) and whether meals are prepared and eaten at home or eaten at restaurants or fast-food establishments • Specific information about nutritional supplements (eg, vitamins, minerals, herbs, protein), including contents, amounts, formulation (pills, powders, drinks), cost, and overlap among products Factors That May Affect or Limit Intake • Amount of money available for food, or participation in food assistance programs (eg, food stamps, food pantries) • Appetite, general well-being (eg, fatigue, pain, depression) • Food allergies, intolerances • Problems with dentition, swallowing, heartburn, diarrhea, constipation • Coordination of foods and supplements with medications (HIV or other)

Elicit symptoms that may be related to nutritional deficiencies.

Table 3. Symptoms with Possible Relationship to Nutritional Deficiencies

• General symptoms (eg, fatigue, decreased cognitive function, headache) • Behavioral changes (eg, irritability, apathy, decreased responsiveness, anxiety, attention deficit) • Body habitus changes (eg, loss or gain of fat) • Gastrointestinal symptoms (eg, diarrhea, constipation, bloating) • Changes in skin, nails, hair (eg, dryness, breaking, thinning) • Muscle loss • Neurologic symptoms (eg, weakness, sensory changes, gait abnormalities)

0: Objective

Physical Examination

Perform a careful physical examination, if possible with anthropometric and body composition testing as described below (Table 4). Compare current findings with past assessments and review at least every 6 months.

The physical examination should include the following:

- ◆ Vital signs, with orthostatic vital signs if dehydration is suspected
- ◆ Weight (compare with previous values) and body mass index (BMI)
- ◆ General appearance and gross nutritional status (eg, obesity, cachexia, wasting)
- ◆ Body habitus: loss of subcutaneous fat in face, buttocks, arms and legs and/or increase fat in abdomen, breasts, back of neck, and upper back (“buffalo hump”)

- ◆ Muscle mass
- ◆ Mouth: breakdown in oral mucosa, cheilosis, angular stomatitis, glossitis, papillar atrophy
- ◆ Abdomen: hepatomegaly (due to fatty infiltration)
- ◆ Skin: dryness, peeling, breakdown, pallor, hypopigmentation or hyperpigmentation
- ◆ Nails: pale nail beds, fissures or ridges
- ◆ Neurologic system, including strength, sensation, coordination, gait, deep tendon reflexes

Anthropometric and body composition tests are usually performed by registered dietitians. They can provide important information about patients’ nutritional status.

Table 4. Anthropometric Measurements for Adults and Children

	Height	Weight	Assessment for Changes over Time
Adults	Measure at baseline (self-report is not accurate).	Measure at least quarterly and consider intervention when small changes are observed. Do not wait until major amounts of weight have been lost or gained. Record sequentially at the front of the patient’s chart and monitor for trends.	Use healthy, premorbid weight to assess change, not the first clinic weight or the ideal weight. (Use the patient’s weight at a time when she or he is healthy, feels well, and can easily maintain that weight.)#*
Children	Measure at least quarterly using length board (0–2 years) or wall-mounted stadiometer (≥ 2 years).	Measure at least quarterly and consider intervention when small changes are observed. Do not wait until the patient has dropped significantly on the growth chart. Calculate age and plot the measurements on growth charts specific for age, sex, and country.*	Assessment of optimal growth is based on the observed pattern over time. General goals include a weight relatively “matched” for length or height (about the same percentile) and relative stability of percentile tracking over time.

* BMI (body mass index) is useful as an evaluative index. BMI can be calculated using the following formula: weight in pounds/(height in inches x height in inches) x 703; normal BMI = 19–25. See also the Centers for Disease Control and Prevention’s (CDC) Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion online calculators for BMI in adults, children, and teens. Available at: <http://www.cdc.gov/nccdphp/dnpa/bmi/index.htm>.

Growth charts for children in the United States are available online from the CDC at <http://www.cdc.gov/growthcharts>. A variety of growth charts are also available for children from specific ethnic groups (eg, Chinese, Vietnamese, Thai), children with selected conditions affecting growth (eg, Down syndrome), or those who are born prematurely. Percentiles for both height and weight should be recorded sequentially.

Body Composition Testing

Body composition is commonly tested by bioelectrical impedance analysis (Table 5) or skinfold thickness and circumference (Table 6).

Table 5. Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) testing is the standard of care for adults but has not been well validated for children:

- BIA is useful for assessing disease progression or health maintenance, documenting response to treatment, and justifying the cost of nutritional supplements and AIDS-wasting medications.
- The test is simple, noninvasive, and quick (<5 minutes). However, staff training and specialized software are required to interpret the results.
- Perform BIA at baseline. Update every 6-12 months, or more frequently if the patient is ill, has a decline in immune status, or has a weight change of 5-10%.
- The BIA test reports the following:
 - Body cell mass (BCM): the target component, reflecting cells in muscles, organs, and the circulation; losses may indicate AIDS wasting. BCM is recorded in pounds. Monitor for trends.
 - Fat: an index of energy stores; recorded in pounds and percentage.
 - Phase angle: a measure of cellular integrity, an independent indicator of morbidity and mortality in HIV-infected patients.

For a good BIA "primer", see also: AIDS Project Los Angeles. "Bioelectrical Impedance Analysis: Glossary of Terms". 2002. Available online at <http://www.apla.org/programs/nutrition.html>. Accessed June 1, 2006.

Table 6. Skinfold Thickness and Circumference Measures

Skinfold thickness and circumference measures can be used for adults and children in resource-limited settings, and when bioelectrical impedance analysis is not available. Circumference measures also can be used to monitor changes over time associated with lipodystrophy in adults.

- Skinfold thicknesses are measured with calipers.
- Circumference measures are taken at specific anatomical landmarks with nonstretchable tape.
- Tables of age- and sex-specific reference values (percentiles) are available at: <http://www.cdc.gov/nchs/products/pubs/pubd/series/ser.htm> (select Series 11, #238 and go to pages 41-50).

See also: AIDS Project Los Angeles. "Anthropometric Procedures". 2002. Available online at www.apla.org/programs/nutrition.html. Accessed June 1, 2006. The Web site includes an overview on how to take basic measurements, including skinfold thickness and circumference, and where to locate equipment and reference tables.

Laboratory Testing

Perform basic laboratory (blood) tests, including the following:

- ◆ Hemoglobin or hematocrit
- ◆ Total protein, albumin
- ◆ Fasting glucose
- ◆ Lipids (fasting triglycerides, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol)
- ◆ CD4 cell count and HIV viral load, if no recent values are available
- ◆ Specific vitamin and nutrient tests as indicated by symptoms (eg, iron studies in case of anemia, vitamin B12 in case of peripheral neuropathy)
- ◆ Others tests, such as testosterone and thyroid hormone levels as appropriate, to rule out other causes of symptoms

A: Assessment

Assess subjective information and objective findings to evaluate nutritional status.

Identify Nutrition Concerns

Several factors may influence nutrition:

- ◆ Barriers to good nutrition (eg, lack of knowledge or motivation for self-care, poor appetite, lack of money for food, lack of facilities for food storage and preparation)
- ◆ Lifestyle factors (eg, smoking, substance abuse, frequent eating out, erratic eating patterns, hectic schedule, high stress)
- ◆ Physical problems affecting food and nutrient intake (eg, poor appetite, nausea, fatigue, pain, weakness, mouth or throat pain, acid reflux, missing or decayed teeth, poorly fitting dentures, poor eyesight, constipation)

- ◆ Nutrient losses (eg, due to diarrhea, vomiting)
- ◆ Potential confounding factors (eg, use of multiple overlapping or questionable supplements)

Evaluate Dietary Intake

Assess the following diet-related issues:

- ◆ Expected excesses or deficiencies from dietary history or interview
- ◆ Rating of food security, including access to cooking and refrigeration
- ◆ Food intolerances, aversions, or allergies likely to affect adequacy of intake
- ◆ Special needs related to other conditions (eg, documented cardiovascular disease, diabetes, hypertension)

Evaluate Weight, Body Composition, and Weight Distribution

Assess physical findings of malnutrition and confirm with nutrition history, laboratory tests, and anthropometric evidence. Table 7 describes normal and abnormal findings of anthropometric tests and recommendations for monitoring changes over time.

Table 7. Evaluating the Findings of Anthropometric Tests

	Monitoring Trends and Recommendations
Adults	• Chart trends over time relative to previous measurements and the following population norms: • BMI (healthy range: 19-25) • BIA: • BCM (% of weight): women 30-35%; men: 40-45% • Fat (% of weight): women 20-30%; men 15-25% • Phase angle: women >5; men >6 • Skinfold thicknesses and circumferences: Chart changes in absolute measures and percentiles • Changes in body contours: Evaluate lipodystrophy (excess accumulation of fat in abdomen, breasts, dorsocervical area) and lipoatrophy (loss of subcutaneous fat in face, extremities, buttocks)
Children	• Plot measurements on growth charts and track percentiles over time (the consistency of percentiles rather than the absolute percentile is important) • Skinfold thicknesses and circumferences: Chart changes in absolute measures and percentiles

Key to abbreviations: BMI = body mass index; BIA = bioelectrical impedance analysis; BCM = body cell mass.

Evaluate Laboratory Findings

- ◆ Evidence of malnutrition (eg, low iron or protein stores)
- ◆ Evidence of disease or risk of disease for which dietary treatment is indicated (eg, high fasting glucose, hypertension, hyperlipidemia)

Develop a Problem List

Table 8 suggests a useful format for a nutrition-related problem list.

Table 8. Nutrition-Related Problem List Format

Problem #	Description of Problem (circle/describe)
	Nutrition barriers: insufficient knowledge, poor appetite, food insecurity, no food preparation or storage facilities, homelessness
	Lifestyle: substance abuse, smoking, erratic eating, frequent fast-food intake, high stress
	Weight or body composition: undesirable weight gain or loss (adult), changes in growth trajectory (children), loss of lean body mass (wasting), gain of excess fat (obesity), lipoatrophy or lipodystrophy
	Physical problems: fatigue, pain, early satiety, poor dentition, clinical signs of malnutrition
	Laboratory findings: low hematocrit or hemoglobin, low protein or albumin, low or high fasting glucose, high total cholesterol, high low-density lipoprotein, high triglycerides, low high-density lipoprotein, low testosterone
	Gastrointestinal: diarrhea, vomiting, reflux, constipation
	Poor diet: poor food choices, bingeing, skipping meals, high sugar intake, high alcohol consumption, high intake of refined foods, low fruit and vegetable intake, insufficient protein, insufficient calcium, food allergies or intolerances limiting intake
	Comorbid conditions: diabetes, hypertension, cardiovascular disease, cancer, gastroesophageal reflux disease (GERD)
	Medications: drug-drug or drug-nutrient interactions or difficulty coordinating medicines with meals
	Supplements: insufficient or excessive intakes, cost of supplements unaffordable, supplements with potential or unknown risks

P: Plan

Develop a nutritional plan and provide practical nutrition education for common problems. Some useful online sources for patient handouts include:

- ◆ AIDS Project Los Angeles Nutrition Fact Sheets Available at <http://www.apla.org/programs/nutrition.html>.
- ◆ Health Resources and Services Administration, HIV/AIDS Bureau. Health Care and HIV: Nutritional Guide for Providers and Clients; 2nd ed. Online manual, also in Spanish. 2002. Available at <http://www.aids-etc.org/aidsetc?page=et-30-20-01>.

- ◆ Association of Nutrition Services Agencies Available at <http://www.aidsnutrition.org>.

Evaluate and treat concurrent medical problems (eg, diarrhea, nausea, infections, malignancies, depression). For severe or persistent nutritional problems, or for specific needs, refer to a nutrition specialist for evaluation and treatment.

Table 9 lists of common nutrition-related problems and some simple suggestions that may help resolve them and help patients maintain adequate nutrition.

Table 9. Practical Interventions for Common Nutrition-Related Problems

Problem	Suggestions
Weight Loss (decrease in both body cell mass and fat)	• Early identification and ongoing monitoring are key. • Identify and treat underlying risk factors. • Try to add calories without adding “bulk”: • Fat (9 calories/gram): butter, margarine, avocado, cream, mayonnaise, salad dressing • Carbohydrate (4 calories/gram): jam, jelly, sugar, icing, gum drops • Protein (4 calories/gram): protein powders, cheese, nut butters, trail mix, powdered breakfast drinks, nonfat dry milk • Eat more frequently. • Maximize good days. • Use canned supplements (eg, Ensure, Boost). • For wasting or substantial weight loss, consider referral for therapies such as appetite stimulants or human growth hormone.
Diarrhea	• Increase soluble fiber; decrease insoluble fiber. • Replenish beneficial bacteria (eg, with lactobacilli preparations). • Avoid intestinal irritants and stimulants. • Decrease dietary fat. • Decrease or eliminate lactose. • Increase fluids and provide electrolytes (sodium, potassium). • Treat with pancreatic enzymes.
Early Fullness	• Take small, frequent meals. • Concentrate on solid foods, with liquids between meals. • Eat lower-fat, lower-fiber foods. • Wear loose-fitting clothing. • Sit up while eating. • Eat, walk, and eat again.
Nausea	• Take small, frequent meals. • Try dry snack foods. • Avoid fried foods, very sweet foods, spicy foods, and foods with strong odors. • Try cool, clear beverages, popsicles. • Try ginger-containing foods and drinks. • Keep liquids to a minimum at meals.
Changes in Taste	• Eat a variety of foods, not only favorite foods. • Try protein sources other than red meat. • Marinate foods, use sauces. • Use more and stronger seasonings. • Try tart foods. • Use sugar or salt to tone down the flavor of foods. • Try a mouth rinse of 1 teaspoon of baking soda in 1 cup of warm water before eating.
Loss of Appetite	• Rely on favorite foods. • Ask family members and friends to prepare meals. • Eat small, frequent meals. • Keep snacks handy for nibbling. • Eat before bedtime. • Eat in a pleasant place, with other people. • Make the most of good days. • Try light exercise to stimulate appetite. • Add extra calories without adding bulk. • Consider appetite stimulants (megestrol, stimulants).

Difficulty Chewing or Swallowing or Sore Mouth and Throat	• Choose soft, nutritious foods. • Blend or puree foods (eg, soup or stew, smoothies). • Add cream sauces, butter, or gravy for lubrication. • Sip liquids with foods. • Use a straw or drink foods from a cup.	• Choose bland, low-acid foods. • If hot foods cause pain, serve foods cold or at room temperature. • Avoid alcohol and tobacco. • Soothing lozenges or sprays may help.
Food Insecurity	• Refer to social services for assistance with accessing resources such as food stamps, community meals, or a food pantry program.	• Refer to a dietitian for assistance with low-cost food ideas. • Use materials at http://www.cheapcooking.com/index.htm
Unbalanced Diet and/or Other Conditions Requiring Dietary Modification	• Refer to a dietitian for counseling and education.	• Use materials at http://www.mypyramid.gov to assist with general counseling about dietary adequacy, balance, and portion size.

Nutrition Specialists

Whenever possible, nutritional services should be provided by a registered dietitian (RD) who is a qualified HIV care provider. In the United States, holding this status requires a nutrition degree from an accredited college, graduation from an approved internship or master's degree program, and maintenance with 75 continuing-education units every 5 years, including specific and ongoing HIV training. An RD with HIV/AIDS expertise in the United States can be located by going to <http://www.eatright.org>, clicking on "Find a Nutrition Professional," entering the patient's zip code or city, and selecting "HIV/AIDS" under areas of specialty. Membership in the HIV/AIDS Dietetic Practice Group (<http://www.hivaidsdpg.org>) also may indicate HIV experience.

Resources

The following online resources were referenced in this chapter:

- ◆ 2000 CDC Growth Charts: United States. CDC, National Health and Nutrition Examination Survey. <http://www.cdc.gov/growthcharts/>.
- ◆ Anthropometric Reference Data and Prevalence of Overweight: United States, 1976-80. Najjar, M. F., Rowland, M. October 1987. 84 pp. PB91-213033. PC A05 MF A01. CDC, National Center for Health Statistics. National Health Survey, Series 11, No. 238. Tables 31-41. <http://www.cdc.gov/nchs/products/pubs/pubd/series/sr11/240-221/240-221.htm>.
- ◆ Body Mass Index Home. CDC, Division of Nutrition and Physical Activity, National Center for Chronic Disease Prevention and Health Promotion. Online calculators for calculating BMI in adults, children, and teens. <http://www.cdc.gov/nccdp/dnpa/bmi/index.htm>.
- ◆ CheapCooking.com. Web site with recipes using low-cost ingredients and tips for frugal meal planning. <http://www.cheapcooking.com>.
- ◆ HIV/AIDS Dietetic Practice Group. Affiliate of the American Dietetic Association. Web site includes screening tool, Nutrition Screen and Referral Criteria for Adults (18+ Years) with HIV/AIDS. <http://www.hivaidsdpg.org>.
- ◆ MyPyramid.gov. U.S. Department of Agriculture Web site with dietary guidelines, tips, resources, and consumer-oriented information. <http://www.mypyramid.gov>.

References

- ◆ AIDS Project Los Angeles. *APLA Nutrition Fact Sheets*. Los Angeles: APLA; 2005. Available online at <http://www.apla.org/programs/nutrition.html>. Accessed June 1, 2006.
- ◆ Association of Nutrition Services Agencies. *ANSA Nutrition Guidelines and Fact Sheets*. (Select “Resources”, then “ANSA Publications”). Accessed June 1, 2006.
- ◆ Bartlett JG. Introduction. *Integrating nutrition therapy into medical management of human immunodeficiency virus*. Clin Infect Dis. 2003 Apr 1;36(Suppl 2):S51.
- ◆ Health Resources and Services Administration, HIV/AIDS Bureau. *Health Care and HIV: Nutritional Guide for Providers and Clients; 2nd ed*. Online manual, also in Spanish. 2002. Available online at <http://www.aids-etc.org/aidsetc?page=et-30-20-01>. Accessed June 1, 2006.

Nonoccupational Postexposure Prophylaxis

Background

Although avoiding exposure to HIV is the only reliable way of preventing HIV infection, postexposure prophylaxis (PEP) can decrease the risk of infection after exposure to HIV. Antiretroviral (ARV) therapy is an important prophylactic intervention in appropriate persons with nonoccupational exposures (eg, sexual contact; sharing of injection drug needles or other equipment), as well as those with occupational exposures (eg, needlesticks). The U.S. Department of Health and Human Services has established guidelines for nonoccupational PEP (nPEP) based on data from animal models, perinatal clinical trials, and observational studies.

Overall, the data suggest that nPEP is more likely to be effective when the exposure is a single episode and nPEP is initiated in a timely manner. It is not appropriate for cases of multiple sexual exposures or injection drug use (IDU) exposures over time or for exposures that occurred more than 72 hours before starting nPEP treatment (Figure 1).

The model for nPEP is derived in part from protocols for occupational PEP (eg, in terms of risk stratification, pretreatment testing, timing of treatment, treatment regimens, and duration of treatment). However, the recommendations for PEP and nPEP are distinct from each other and should not be confused. The nPEP guidelines exclude exposures to workers in health care, public safety, sanitation, and laboratory settings. Guidelines for the management of these occupational exposures to HIV, hepatitis B virus (HBV), and hepatitis C virus (HCV) are available at: <http://www.aidsinfo.nih.gov>.

S: Subjective

The patient reports potential exposure to HIV through a sexual encounter or the sharing of needles or other equipment for intravenous drug use.

Take a thorough history of the specific sexual or drug-use activities and the time the exposure occurred, the HIV status of the source person (if known), and HIV risk factors of the source person (if HIV status is not known). In cases of sexual assault, evidence collection and specific paperwork may be required as well.

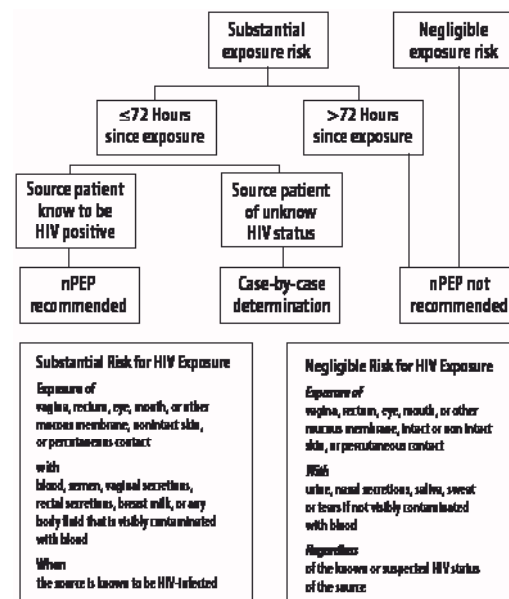
O: Objective

Examine for trauma and for signs or symptoms of sexually transmitted diseases (STDs), which may increase the risk of HIV transmission. In injection drug users, examine for abscesses and signs or symptoms of infection. For women who may be pregnant, perform a pregnancy test.

A: Assessment

Assess potential exposures to HIV, other STDs and bloodborne pathogens. The risk of HIV infection depends on the HIV status of the source and on the characteristics of the exposure. The estimated risk of HIV exposure will determine whether nPEP should be offered. Figure 1 presents an algorithm for risk evaluation and treatment decisions.

Figure 1. Algorithm for Evaluation and Treatment of Possible Nonoccupational HIV Exposures



Source: Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States, Recommendations from the U.S. Department of Health and Human Services. January 2005. See <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm#fig1> for original image.

P: Plan

Laboratory Testing

Provide pretest counseling and perform a baseline HIV antibody test. Evaluate and test for other infections transmitted through sexual or IDU exposures, including chlamydia, gonorrhea, syphilis, herpes simplex virus infection, hepatitis B (HBV surface antigen, surface antibody, core antibody), and hepatitis C (HCV antibody). Obtain complete blood count (CBC), liver function tests (LFTs), and chemistry panel at baseline before treatment with ARV medications.

Treatment

Follow the algorithm in Figure 1 to determine whether

the patient should be offered nPEP medications. If the patient is a candidate for treatment, counsel him or her about the potential risks and benefits of nPEP. If the patient elects to start therapy, see Table 1 for potential regimens. Select a regimen that is likely to be effective but tolerable; consider the potential adverse effects of ARV agents. Note that certain ARV agents, including nevirapine, should not be used for PEP. Avoid efavirenz in pregnant women.

If the HIV status of the source person is unknown and the exposure is considered to be of relatively low risk, consider 2-drug nPEP (eg, zidovudine + lamivudine) to minimize toxicity. If the source person is known or suspected to have infection with HIV that is resistant to ARV medications, seek expert consultation in selecting an appropriate nPEP regimen.

Table 1. Antiretroviral Regimens for Nonoccupational Postexposure Prophylaxis of HIV Infection

Preferred Regimens	
NNRTI-based	Efavirenz* + (lamivudine or emtricitabine) + (zidovudine or tenofovir)
PI-based	Lopinavir/ritonavir (co-formulated as Kaletra) + (lamivudine or emtricitabine) plus zidovudine
Alternative Regimens	
NNRTI-based	Efavirenz + (lamivudine or emtricitabine) + abacavir or didanosine or stavudine [#]
PI-based	Atazanavir + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or didanosine) or (tenofovir plus ritonavir [100 mg/day])
	Fosamprenavir + (lamivudine or emtricitabine) plus (zidovudine or stavudine) or (abacavir or tenofovir or didanosine)
	Fosamprenavir/ritonavir ^S + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Indinavir/ritonavir ^{S**} + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Lopinavir/ritonavir (co-formulated as Kaletra) + (lamivudine or emtricitabine) + (stavudine or abacavir or tenofovir or didanosine)
	Nelfinavir plus (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
Triple NRTI	Saquinavir (hgc or sgc)/ritonavir ^S + (lamivudine or emtricitabine) + (zidovudine or stavudine or abacavir or tenofovir or didanosine)
	Abacavir plus lamivudine + zidovudine (only when an NNRTI- or PI-based regimen cannot or should not be used)

Key to abbreviations: NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; hgc = saquinavir hard-gel capsule (Invirase); sgc = saquinavir soft-gel capsule (Fortovase); NRTI = nucleoside reverse transcriptase inhibitor.

† Efavirenz should be avoided in pregnant women and women of childbearing potential.

Stavudine may cause a higher incidence of lipodystrophy, hyperlipidemia, and mitochondrial toxicities than other NRTIs.

S Low-dose (100–400 mg) ritonavir. See Table 4 from the Adult Antiretroviral Guidelines (cited below) for doses used with specific PIs.

** Use of ritonavir with indinavir might increase the risk of renal adverse events.

Source: U.S. Department of Health and Human Services. *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States*.

Table 2. MMWR Recomm Rep. 2005 Jan 21;54(RR02);1–20. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=11>.

Once the decision is made to institute nPEP, do the following:

- ◆ Begin ARV prophylaxis as soon as possible after the exposure, but always within 72 hours. Treatment should be continued for 28 days.
- ◆ Provide counseling about the efficacy of nPEP, including the importance of protection against future HIV exposures, timely initiation of nPEP medications, and adherence to these medications for 28 days. Continued counseling about HIV risk reduction may be appropriate. In cases of sexual assault, refer the patient to a rape counselor.

Follow-Up

Patients should be evaluated at 1 week for review of all test results and further risk reduction counseling. For patients taking nPEP, this follow-up should include adherence assessment and evaluation of any adverse effects. A 2-week blood screening (CBC, LFTs, and chemistry panel) should be done for patients on the 28-day nPEP regimen to monitor for nPEP toxicity. Follow-up testing for HIV antibody in patients with a negative baseline HIV antibody test should be done at 6 weeks, 3 months, and 6 months after the exposure. Some patients may also need health education counseling and emotional support during their follow-up visits. If patients develop acute HIV infection or are discovered to be HIV seropositive at follow-up testing, refer to an HIV specialist for evaluation and care (see chapter *Primary HIV Infection*).

Prophylaxis against HBV and HCV

Prophylaxis against HBV is recommended for patients with potential exposure to HBV who have not been vaccinated against HBV. Give HBV immune globulin (HBIG) as a 0.06 mL/kg intramuscular injection and initiate the vaccination series. For patients who received the vaccine series but did not develop protective antibody (HBV sAb+), give HBIG at the time of the postexposure workup and repeat in 1 month. For patients with immunity to HBV (HBV sAb+), no treatment is indicated.

For HCV, no recommended prophylactic treatments are available. After potential exposure, check a baseline HCV antibody test. If the source is known to have HCV infection, consider alanine aminotransferase (ALT) and HCV viral load testing at 4–6 weeks. HCV antibody testing should be repeated at 4–6 months.

If HCV seroconversion occurs (indicated by ALT elevation, detectable HCV viral load, or confirmed positive HCV antibody test), refer the patient to a hepatologist because early treatment of acute HCV may be indicated.

Patient Education

- ◆ Patients should contact a medical provider or go to an emergency room as soon as possible after a potential HIV exposure has occurred. PEP may be effective if it is started within 72 hours of exposure, but the sooner medications are initiated, the better the chance for preventing HIV transmission.
- ◆ PEP medications should be taken as directed for the full 28 days. Adherence to PEP medications is essential for successful treatment.
- ◆ If patients are experiencing uncomfortable adverse effects, they should contact their providers. Providers may prescribe medications to alleviate the adverse effects or select other PEP medications.
- ◆ The most effective way to prevent HIV infection is to prevent exposure to HIV by practicing safer sex and safer IDU techniques. Using condoms and not sharing needles are successful preventive measures. It is crucial to the success of PEP treatment that patients not engage in risky sexual or needle-use behaviors. If patients have questions about access to condoms or clean needles, they should contact their health care providers for assistance.

References

- ◆ U.S. Department of Health and Human Services. *Antiretroviral Postexposure Prophylaxis After Sexual, Injection-Drug Use, or Other Nonoccupational Exposure to HIV in the United States*. MMWR Recomm Rep. 2005 Jan 21;54(RR02);1-20. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=11>. Accessed May 19, 2006
- ◆ U.S. Department of Health and Human Services. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis*. MMWR Recomm Rep. 2001 Jun 29;50(RR11). Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10>. Accessed May 19, 2006.

Occupational Postexposure Prophylaxis

Background

Health care workers (HCWs) and other employees in medical, public safety, sanitation, and laboratory settings are at risk of occupational exposure to HIV. Although avoiding exposure to HIV is the only reliable way of preventing HIV infection, postexposure prophylaxis (PEP), defined as antiretroviral (ARV) therapy initiated soon after exposure to HIV, has been highly effective in preventing HIV infection in exposed HCWs.

This chapter examines the general issues involved with PEP in occupational settings. The information is based on the U.S. Public Health Service (USPHS) guidelines for PEP (see “References” below). For information on PEP for nonoccupational HIV exposures (such as sexual exposure), see chapter *Nonoccupational Postexposure Prophylaxis*. Note that other bloodborne pathogens, particularly hepatitis B virus (HBV) and hepatitis C virus (HCV), also may be transmitted through occupational exposure; it is important to consider these potential infections when assessing occupational exposures. For information on the management of occupational exposures to HBV and HCV, refer to the 2001 USPHS PEP guidelines on (see “References” below). In addition, the National Clinicians’ Post-Exposure Prophylaxis Hotline (PEPline) is available 24 hours a day for telephone consultation at 888-HIV-4911 (888-448-4911).

The risk of HIV infection after exposure depends on several factors that are related to the exposure itself and to the source patient (see below). Before deciding whether to recommend PEP and what PEP regimen to recommend, the clinician must assess the risk of HIV infection from the particular exposure, as well as other factors such as the exposed worker’s willingness and ability to take ARV medications. After this assessment, the clinician and the exposed worker must weigh the possible benefit of PEP (in relation to the risk of HIV transmission from the injury) against the potential toxicity of the regimen. HCWs who are pregnant at the time of their exposure also must weigh the risk of fetal exposure to HIV against the potential teratogenic and other risks of the ARV drugs. The efficacy of PEP is related to the specific PEP regimen, the timing of PEP, and the exposed worker’s adherence to the PEP

regimen. PEP should be initiated within 72 hours of the exposure, but is more likely to be effective when it is initiated within hours of the exposure. The optimal duration of PEP is not known; studies support treatment for 28 days.

In the work setting, HIV infection may occur through percutaneous injuries (eg, needlesticks) or mucocutaneous exposures (eg, mucous membrane or nonintact skin exposure to blood or other infectious body fluids). The risk of HIV seroconversion after occupational exposure is best described for needlestick injuries: 0.3%, on average after a needlestick with an HIV-contaminated hollow-bore needle. The risk varies depending on the specific incident. In general, exposures that involve prolonged contact with larger volumes of infectious body fluids, or higher HIV RNA levels in the blood or fluid, convey a higher risk of HIV transmission. In a retrospective case-control study of HCWs with percutaneous exposure to HIV, the following exposure and source patient factors were associated with an increased risk of HIV transmission:

- ◆ Large-gauge (<18-gauge) hollow-bore needle
- ◆ Deep injury
- ◆ Visible blood on the device
- ◆ Procedure with needle in a blood vessel
- ◆ Terminal AIDS in the source patient

Compared with percutaneous injury, mucocutaneous exposure of infectious body fluids to mucous membranes (eg, eye or mouth) or to skin with an obvious impairment of integrity (eg, abrasion or wound) typically involves a lower risk of HIV transmission. However, mucocutaneous exposures that involve large volumes of blood or other infectious fluid from an HIV-infected patient with a high HIV RNA level may be significant.

S: Subjective

The HCW reports possible exposure to HIV through a needlestick injury or mucocutaneous exposure.

Ideally, the HCW immediately decontaminated the injured or exposed skin with soap and water, or flushed

the exposed mucous membranes with copious amounts of water or saline. The HCW should report the exposure immediately to the appropriate authorities in his or her health care institution (eg, the institution's needlestick hotline).

Take a thorough history of the specific exposure, including the type of exposure, the type and amount of body fluid involved, the point of entry or exposure, the time it occurred, the HIV status of the source patient (if known), and HIV risk factors of the source patient (if HIV status is not known).

A: Assessment

Assess potential exposure to HIV (as well as HBV and HCV). The HIV status of the source and the characteristics of the exposure should be assessed to estimate the risk of HIV infection. The decision about whether to offer PEP should be based on the estimated risk of HIV exposure. See Table 1 (percutaneous exposures) and Table 2 (mucocutaneous exposures) for recommendations about PEP.

Table 1. Recommended HIV Postexposure Prophylaxis after Percutaneous Injuries

Exposure Type	Infection Status of Source*				
	HIV Negative	HIV Positive (Class 1)	HIV Positive (Class 2)	Unknown HIV Status	Unknown Source
Less Severe (eg, solid needle, superficial injury)	No PEP warranted	Recommend basic 2-drug PEP	Recommend expanded ≥ 3 -drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP for source with HIV risk factors* [#] §	Generally, no PEP warranted; however, consider basic 2-drug PEP if exposure to HIV-infected persons is likely
More Severe (eg, large-bore hollow needle, deep puncture, visible blood on device, needle used in patient's artery or vein)	No PEP warranted	Recommend expanded ≥ 3 -drug PEP	Recommend expanded ≥ 3 -drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP for source with HIV risk factors	Generally, no PEP warranted; however, consider basic 2-drug PEP if exposure to HIV-infected persons is likely

* HIV positive (class 1): asymptomatic HIV infection or known low HIV RNA viral load (eg, $<1,500$ copies/mL); HIV positive (class 2): symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load; unknown HIV status: for example, a deceased source person with no samples available for HIV testing; unknown source: for example, a needle from a sharps disposal container.

The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the clinician regarding the risks versus benefits of PEP.

§ If PEP is offered and administered, and the source is later determined to be HIV negative, PEP should be discontinued.

Adapted from: Centers for Disease Control and Prevention. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR Recomm Rep. 2005 Sep 30; 54(RR09); 1-24. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10>.

Table 2. Recommended HIV Postexposure Prophylaxis after Mucous Membrane Exposures and Nonintact Skin Exposures*

Exposure Type	Infection Status of Source [#]				
	HIV Negative	HIV Positive (Class 1)	HIV Positive (Class 2)	Unknown HIV Status	Unknown Source
Small Volume (eg, a few drops)	No PEP warranted	Consider basic 2-drug PEP [§]	Recommend basic 2-drug PEP	Generally, no PEP warranted	Generally, no PEP warranted
Large Volume (eg, a major blood splash)	No PEP warranted	Recommend basic 2-drug PEP	Recommend expanded ≥ 3 -drug PEP	Generally, no PEP warranted; however, consider basic 2-drug PEP for source with HIV risk factors**	Generally, no PEP warranted; however, consider basic 2-drug PEP if exposure to HIV-infected persons is likely

* For skin exposures, follow-up is indicated only if evidence exists of compromised skin integrity (eg, dermatitis, abrasion, or open wound).

HIV positive (class 1): asymptomatic HIV infection or known low HIV RNA viral load (eg, $<1,500$ copies/mL); HIV positive (class 2): symptomatic HIV infection, AIDS, acute seroconversion, or known high viral load; unknown HIV status: for example, a deceased source person with no samples available for HIV testing; unknown source: for example, a needle from a sharps disposal container.

§ The recommendation "consider PEP" indicates that PEP is optional; a decision to initiate PEP should be based on a discussion between the exposed person and the clinician regarding the risks versus benefits of PEP.

** If PEP is offered and administered, and the source is later determined to be HIV negative, PEP should be discontinued.

Adapted from: Centers for Disease Control and Prevention. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR Recomm Rep. 2005 Sep 30; 54(RR09); 1-24. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10.

P: Plan

Laboratory Testing

Provide pretest counseling and perform a baseline HIV antibody test. Test for other infections transmitted through occupational exposure, particularly hepatitis B (HBV surface antigen, surface antibody, core antibody), and hepatitis C (HCV antibody). Obtain complete blood count (CBC), chemistry panel, and liver function tests (LFTs) at baseline, before treatment with ARV medications. For women who may be pregnant, perform a pregnancy test.

Treatment

Consult Table 1 or Table 2 to determine whether the worker should be offered PEP medications. For occupational exposures to infectious body fluids from an HIV-infected source patient, the USPHS guidelines state that PEP should be recommended or considered,

depending on the assessed risk. The assessed risk also helps to determine whether a “basic” 2-drug regimen or “expanded” ≥3-drug regimen should be selected. Other considerations in choosing the medications for a PEP regimen include:

- ◆ The likelihood that the source patient’s virus is resistant to ARV medication(s)
- ◆ Possible drug toxicities for the exposed HCW
- ◆ Drug–drug interactions with other medications the HCW may be taking

If the HCW is a candidate for PEP, counsel him or her about the potential risks and benefits of PEP. If the worker elects to start therapy, consider potential regimens (Table 3). Select a regimen that is likely to be effective but tolerable; consider the potential adverse effects of ARVs. Note that certain ARV agents, including nevirapine, should not be used for PEP. Efavirenz should be avoided in pregnant women.

Table 3. Antiretroviral Options for Occupational Postexposure Prophylaxis of HIV Infection

Basic 2-NRTI Regimens	
Preferred	
• Zidovudine 300 mg + lamivudine 150 mg twice daily (available as Combivir, 1 tablet twice daily) • Zidovudine 300 mg twice daily + emtricitabine 200 mg once daily	• Tenofovir 300 mg once daily + lamivudine 300 mg once daily • Tenofovir 300 mg once daily + emtricitabine 200 mg once daily (available as Truvada, 1 tablet once daily)
Expanded Regimens (one of the following may be added to a basic regimen)	
Protease Inhibitors	
Preferred	
• Lopinavir/ritonavir combination 400/100 mg twice daily	
Alternative	
• Atazanavir 300 mg once daily + ritonavir 100 mg once daily • Atazanavir 400 mg once daily*	• Fosamprenavir 1,400 mg twice daily • Fosamprenavir 700 mg twice daily + ritonavir 100 mg twice daily
NNRTI Regimen	
• Efavirenz 600 mg once daily (not recommended in pregnant women)	

Key to abbreviations: NRTI = nucleoside analogue reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor.

* Atazanavir cannot be used as a sole protease inhibitor if it is coadministered with tenofovir (use atazanavir + ritonavir).

Adapted from: Centers for Disease Control and Prevention. *Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis*. MMWR Recomm Rep. 2005 Sep 30; 54(RR09): 1–24. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=10.

If the HIV status of the source patient is unknown, a rapid HIV test may help in determining the need for PEP (see chapter *Rapid Testing*). Although a positive rapid test requires confirmation before the individual is diagnosed as HIV infected, for the purposes of PEP, it should be considered a true positive until proven otherwise, and the exposed worker should be counseled accordingly. If, upon further testing, the source patient is determined to be HIV uninfected, PEP can be discontinued. A negative rapid test is considered reliable unless the source reports recent high-risk HIV exposure or symptoms of primary HIV (see chapter *Primary HIV Infection*). If a rapid test is not available, PEP is considered “generally not warranted” for exposures involving source patients whose HIV status is unknown. However, PEP can be considered if the source patient has risk factors for HIV infection. PEP should not be delayed (beyond 1-2 hours) while awaiting information about the source patient. PEP is not recommended for exposures to HIV-seronegative source patients.

If the source patient is known or suspected to have infection with HIV that is resistant to ARV medications, seek expert consultation in selecting an appropriate PEP regimen. However, PEP should not be delayed while consultation is obtained.

Additional alternative ARVs are included in the USPHS guidelines, but certain ARVs are not recommended for PEP; including abacavir, delavirdine, nevirapine, and the combination of didanosine + stavudine. Refer to the appendix in the updated USPHS guidelines for a more complete discussion of the dosing, advantages, and disadvantages of the various ARV agents available for PEP.

Begin ARV prophylaxis as soon as possible after the exposure, but always within 72 hours. Treatment should be continued for 28 days.

Provide counseling about the efficacy of PEP, including the importance of protection against future HIV exposures, timely initiation of PEP medications, and adherence to these medications for 28 days. Counsel exposed workers to use latex barriers with their sexual partners until HIV infection has been ruled out.

Follow-Up

Exposed workers should be evaluated at 1 week for review of all test results. For patients taking PEP, adherence assessment and evaluation of any side effects also should be included. At 2 weeks, blood testing (eg,

CBC, LFTs) should be done for patients on a 28-day PEP regimen to monitor for PEP toxicity, as indicated by the particular ARV regimen. PEP is discontinued at 4 weeks, and generally no laboratory studies should be repeated unless there is a need to recheck an abnormal result. Follow-up HIV antibody testing should be done at 6 weeks, 3 months, and 6 months after the exposure. In addition to health-education counseling, some patients may need emotional support during their follow-up visits.

Symptoms of primary HIV infection such as fever, rash, and lymphadenopathy (see chapter *Primary HIV Infection*) may occur in HCWs who have been infected with HIV through occupational exposure. Every exposed HCW should be counseled about the symptoms of primary HIV infection and instructed to return for reevaluation as soon as possible if symptoms develop. If symptoms consistent with primary HIV appear within 4-6 weeks after an occupational exposure, the HCW should be evaluated immediately. If the worker is found to be infected with HIV, he or she should be referred immediately to an HIV specialist for further evaluation and care.

Expert Consultation

For consultation on the treatment of occupational exposures to HIV and other bloodborne pathogens, the clinician managing the exposed patient can call the National Clinicians' Post-Exposure Prophylaxis Hotline (PEpline) at 888-HIV-4911 (888-448-4911). This service is available 24 hours a day, at no charge (additional information on the Internet is available at <http://www.ucsf.edu/hivcntr>). PEpline support may be especially useful in challenging situations, such as when drug-resistant HIV strains are suspected or the HCW is pregnant.

Prophylaxis against HBV and HCV

Prophylaxis against hepatitis B is recommended for patients with potential exposure to HBV who have not been vaccinated against HBV. Give hepatitis B immune globulin (HBIG) as a 0.06-mL/kg intramuscular injection and initiate the vaccination series. For patients who received the vaccine series but did not develop protective antibody (HBV surface antibody positive), give HBIG at the time of the postexposure workup and repeat in 1 month. For patients with immunity to hepatitis B, no treatment is indicated.

For hepatitis C, no recommended prophylactic treatments are available. After potential exposure, conduct a baseline HCV antibody test. If the source is known to have HCV infection, consider alanine aminotransferase (ALT) and HCV viral load testing at 4–6 weeks. HCV antibody testing should be repeated at 4–6 months. If HCV seroconversion occurs (indicated by ALT elevation, detectable HCV viral load, or confirmed positive HCV antibody test), refer the patient to a hepatologist because early treatment of HCV may be indicated.

Addendum: Workplace Obligations

The health care institution has certain obligations to an exposed employee.* The institution should do the following:

- ◆ Evaluate the circumstances of the exposure, the type of fluid, and possible entry points.
- ◆ Evaluate the source patient.
- ◆ Perform baseline HIV antibody testing of the exposed worker, after appropriate pretest counseling.
- ◆ Counsel the exposed employee about the possible risks and benefits of PEP.
- ◆ Offer or recommend PEP as soon as possible after the exposure, preferably within the first several hours.
- ◆ Counsel the worker about avoiding secondary transmission to others (safer sex and other risk-reduction practices, as indicated).
- ◆ Support and maintain the confidentiality of the worker.
- ◆ For workers taking PEP, monitor for medication toxicity and adherence.
- ◆ Repeat HIV testing at 6 weeks, 3 months, and 6 months.
- ◆ Report the exposure as required by federal and state regulations (including Occupational Safety and Health Administration requirements).

** Legal issues vary from state to state. In many states, institutions and clinics have no obligation toward students or non-employees who have HIV exposures in their settings. In such situations, clinical supervisors or school or university officials often are the first contact for notification. However, anyone working in a health care setting should be familiar with the procedures and financial responsibility for HIV exposure management to avoid delays in HIV PEP treatment.*

Patient Education

- ◆ Persons who have possible exposures to HIV in the work setting should contact the PEP service of their employer or a qualified medical provider as soon as possible after the exposure, or they should go to an emergency room. Although PEP may be effective if it is started within 72 hours of exposure, the sooner medications are initiated, the better the chance for preventing HIV transmission.
- ◆ PEP medications should be taken as directed for the full 28 days. Adherence to PEP medications is essential for successful treatment.
- ◆ PEP recipients should be advised to contact their providers if they experience uncomfortable side effects. Providers may prescribe medications to alleviate the side effects, or may prescribe different PEP medications.
- ◆ Until HIV infection has been ruled out, exposed workers should be advised to use latex barriers to prevent transmission of HIV to their sex partners.
- ◆ Exposed workers should be counseled about the symptoms of primary HIV infection and instructed to contact their care providers immediately if symptoms develop.

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Preventing HIV Transmission/Prevention with Positives

Background

Helping patients to reduce the risk of transmitting HIV to others is an important aspect of medical care for HIV-infected individuals. Most people with HIV infection want to prevent others from being infected with HIV, but they may practice sexual or injection drug behaviors that put others at risk of infection. Most HIV-infected patients also want to protect themselves from acquiring sexually transmitted infections. This chapter offers recommendations for discussing HIV transmission and prevention with HIV-infected patients, with the goal of reducing HIV transmission. This aspect of care is often referred to as “prevention with positives” (PWP).

Taking responsibility for preventing HIV transmission is an important concern for most people with HIV, as well as for their health care providers. In fact, many HIV-infected individuals report that they want to discuss prevention with their health care providers. It is clear that information alone, especially on subjects such as sexual activity and drug use, cannot be expected to change patients’ behavior. However, health care providers can help patients understand the transmission risk of certain types of behavior and help patients establish personal prevention strategies (sometimes based on a harm-reduction approach) for themselves and their partners. Some patients may have difficulty adhering to their safer sex goals. In these cases, referrals to mental health clinicians or other professional resources such as prevention case management may be helpful.

Patient-education needs are variable and must be customized. Providers must assess the individual patient’s current level of knowledge as part of developing a prevention plan. All the information that a patient needs cannot be covered during a single visit. A patient’s prevention strategy should be reinforced and refined at each visit with the clinician. Clinicians also should ask patients questions to determine life changes (eg, a new relationship, a breakup, or loss of a job) that may affect the patient’s sexual or substance use practices. If the patient can read well, printed material can be given to reinforce education in key areas, but it cannot

replace a direct conversation with the clinician. Patient educators, nurses, peer counselors, social workers, and mental health providers also may be used to discuss prevention strategies with patients.

Sexual Transmission and Prevention of HIV

Begin the education process by learning what the patient and his or her immediate family (if the family is aware of the patient’s HIV status) believe about HIV transmission. Also be sure the patient understands how the virus is *not* transmitted (eg, sharing plates and eating utensils or using the same bathrooms) to allay any unnecessary fear.

Advise the patient not to share toothbrushes, razors, douche equipment, or sex toys to avoid transmitting HIV via blood or sexual secretions. This also will help prevent the transmission of other bloodborne or sexually transmitted infections, including hepatitis C, from coinfecting patients. The patient should not donate blood, plasma, tissue, organs, or semen because these can transmit HIV to the recipient.

There is no reason why a person with HIV cannot have an active, fulfilling, and intimate sex life. However, the patient must be counseled properly about the risk of transmission. This discussion between the provider and patient, should be client centered. This means that the provider should let the patient guide the discussion, starting from the patient’s current point of knowledge and practice, always addressing any presenting concerns the patient may have prior to proceeding with a discussion about sexual transmission and risk. The provider should ask open-ended questions, in a nonjudgmental manner, to elicit information about the patient’s relationships, sexual behaviors, and current means of reducing transmission risk.

It is important to recognize that not every patient seeks the complete elimination of risk (eg, via abstinence) but rather a reduction in risk, chosen after the options are discussed with the provider. The clinician may help the patient select and practice behaviors that are likely to

be less risky. There are many methods for reducing risk, including the following:

- ◆ Disclosing HIV status
- ◆ Reducing the number of sex partners
- ◆ Using condoms, particularly for anal or vaginal intercourse (insertive or receptive)
- ◆ Having sex only with other HIV-infected partners (serosorting)
- ◆ Avoiding drug use in conjunction with sex
- ◆ Using adequate lubrication to avoid trauma to genital or rectal mucosa
- ◆ Maintaining maximal suppression of HIV through antiretroviral therapy

If the patient requires more extensive counseling to support behavioral changes, the provider should refer the patient to support groups or prevention case management to meet those needs. Certainly, if the patient is dealing with a dual or triple diagnosis (including substance abuse or mental illness), a referral to address those needs also is indicated.

Several models of PWP are appropriate and realistic for the clinical setting, where prevention discussions must be conducted within severe time constraints. The Partnership for Health model developed by Jean Richardson and colleagues resulted in a 38% reduction in unprotected anal or vaginal sex among patients with multiple and casual partners after the implementation of “consequence frame messaging” in the context of a clinic-wide program. This program is being diffused nationally and soon will be included on the Centers for Disease Control and Prevention (CDC) Diffusion of Effective Behavioral Interventions Web site at: <http://www.effectiveinterventions.org>. Another model, developed by Fisher and Cornman for use in clinical settings, assesses deficits in HIV information, motivation, or behavioral skills using motivational interviewing techniques, complete with behavioral prescription writing at the end of the visit. This model involves a process that takes 5-10 minutes to complete. More information about the model is available at <http://www.chip.uconn.edu/interventions/k-options.pdf>. Finally, a model (called Act, Screen, Intervene) was generated from a work group developed in collaboration with the national HIV/STD Prevention Training Centers and the AIDS Education and Training Centers, based on the guidelines “Incorporating HIV Prevention into the Medical Care of Persons Living with HIV”

developed by the CDC, Health Resources and Services Administration, and HIV Medical Association. The new curriculum, with the same title, includes 4 modules designed to guide the clinician in implementing prevention and partner notification into clinical work. This model has been pilot tested in 5 U.S. cities and also is being diffused nationally. The guidelines can be found at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm>. Any of these models, or new models that are expected to emerge from the Special Projects of National Significance, may assist the provider in implementing prevention work in the context of clinical care.

Partner Notification

A good way to begin a discussion about HIV prevention and transmission is with an inquiry about any previous experiences disclosing to partners. The provider then can ask whether the patient currently has a need to disclose to one or more partners and whether he or she is ready and motivated to share information about HIV status. The provider should prompt patients to consider several questions about disclosure, including how they might approach the discussion, how their partners might react, what information they might offer their partners, whether partners are likely to keep their status confidential, and whether they have any concerns about personal safety (eg, if they fear a violent reaction). If patients fear a violent reaction or are not ready to share their status but want their partners to know, the provider may offer assistance with partner notification, for example through the local health department, in a confidential manner. As an alternative, patients may want the provider to talk with their partners, and that option can be offered as well. See the U.S. Department of Veterans Affairs HIV Web site at <http://www.hiv.va.gov/vahiv?page=sex-01-00> for a patient-oriented discussion of partner notification.

Helping Patients Reduce the Risk of Sexual Transmission

Standard Condom Use

Make sure that the patient understands how HIV is transmitted and which types of sexual acts are more and less risky than others. For vaginal or anal sex, correct use of latex or polyurethane condoms reduces the risk of HIV transmission considerably. Patients should be encouraged to use condoms as much as possible. For HIV-infected individuals, condom use is also effective in reducing the risk of contracting another illness (such

as hepatitis C or another sexually transmitted disease) and the (apparently low) risk of becoming reinfected with another strain of HIV. It should be noted that condoms are less effective in reducing the transmission of organisms such as human papilloma virus (HPV) and herpes simplex virus (HSV), which may result from viral shedding from skin. In the event of allergy to latex or other difficulty with latex condoms, polyurethane male or female condoms may be substituted. “Natural skin” or “lambskin” condoms are not recommended for HIV prevention.

Of course, condoms must be used correctly to be highly effective in preventing HIV transmission. Be sure that the patient knows exactly how to use a condom. Table 1 provides instructions for condom use.

Table 1. Instructions for Use of Standard Condoms

- Use a new latex or polyurethane condom with each act of sex (oral, anal, or vaginal). Make sure that the condom is undamaged, and that its expiration date has not passed.
- Carefully handle the condom to avoid damage from fingernails, teeth, etc.
- Being sure that the condom roll faces out, unroll the condom onto the erect penis before any genital contact with partner.
- Ensure that the tip of the condom is pinched when applying it to the top of the penis, to eliminate air in the tip that could cause breakage during ejaculation.
- Use only water-based lubricants with latex condoms. Oil-based lubricants (such as mineral oil, cooking oil, massage oil, body lotion, and petroleum jelly) can weaken latex or cause it to break, although they are fine with the use of polyurethane condoms. Adequate lubrication during intercourse helps reduce the risk of condom breakage.

Advise patients to avoid using nonoxynol-9 (N-9) spermicides. Recent data suggest that N-9 may increase risk of HIV transmission during vaginal intercourse and can damage the rectal lining. N-9 should never be used for anal intercourse.

For patients who complain about lack of sensitivity with condom use, the following techniques may help:

- ◆ Apply a drop of lubricant inside the condom (not more, because it increases the risk that the condom will come off).
- ◆ Use polyurethane condoms instead of latex because they conduct heat and may feel more natural.
- ◆ Use insertive (female) condoms, which are not as restrictive to the penis.

- ◆ Use specially designed condoms that do not restrict the top of the penis (eg, Inspiral, Xtra Pleasure).

For those patients who are unable or unwilling to use condoms, the following suggestions may help reduce HIV transmission risk:

- ◆ Use plenty of lubricant to reduce friction and microtrauma, which create portals of entry for the virus.
- ◆ Avoid spermicides that damage the vaginal or anorectal linings.
- ◆ Avoid douching products.
- ◆ Avoid recreational drugs, especially methamphetamine, which impair the ability to maintain “safer” sex behaviors.
- ◆ Avoid the use of drugs such as nitrates (poppers) that enhance blood flow to the genitals.

For HIV-infected women, consider avoiding hormonal birth control methods because of a possible increase in the risk of HIV viral shedding.

Insertive (Female) Condom Use

The insertive “female” condom (Reality) may be used for vaginal or anal intercourse. It is a thin polyurethane pouch with a flexible ring at the opening, and another unattached flexible ring that sits inside the pouch to keep it in position in the vagina (for use in the anus, the inner ring must be removed and discarded). The female condom may be an option for women whose male partners will not use male condoms or for couples who do not like standard condoms. Female condoms are more expensive than male condoms, but may be procured at a lower cost at some health departments or Planned Parenthood clinics. They generally are less well known to patients and may be unacceptable to some women whose culture or religion prohibits or discourages touching one’s own genitals. Note that the female condom cannot be used at the same time as a male condom.

Be sure the patient knows how to use the insertive condom before she or he needs it; after teaching, encourage practice when alone at home and unhurried. Women who have used the diaphragm, cervical cap, or contraceptive sponge may find it easy to use the female condom. Illustrated directions are included in each box

of insertive condoms. Table 2 gives instructions on the use of insertive condoms.

Table 2. Instructions for Use of Insertive (Female) Condoms

Vaginal Intercourse

- Open the pouch by tearing at notched edge of packet, and take out the female condom. Be sure that the lubricant is evenly distributed on the inside by rubbing the outsides together.
- Find a comfortable position, such as standing with one foot on a chair, sitting with knees apart, or squatting. Be sure the inner ring is inside, at the closed end of the pouch.
- Hold the pouch with the open end hanging down. While holding the outside of the pouch, squeeze the inner ring with your thumb and middle finger. Still squeezing, spread the labia with your other hand and insert the closed end of the pouch into the vagina.
- Now, put your fingers into the pouch itself, which should be inside the vagina, and push the inner ring and the pouch the rest of the way up into the vagina with your index finger. Check to see that the front side of the inner ring is just past the pubic bone. The back part of the inner ring should be up behind the cervix. The outer ring and about an inch of the pouch will be hanging outside the vagina.
- Until you and your partner become comfortable using the female condom, use your hand to guide the penis into the vagina, keeping it inside the pouch. If, during intercourse, the outer ring is getting pushed up inside the vagina, stop, remove the female condom, and start over with a new one. Extra lubricant on the penis or the inside of the female condom may help keep this from happening.
- After intercourse, take out the condom by squeezing and twisting the outer ring to keep the semen inside the pouch. Throw away in a trash can; do not flush. Do not reuse.
- If there are problems, call the manufacturer's toll-free customer assistance line at 800-274-6601, #230.
- More information is available on the manufacturer's Web site at: <http://www.femalehealth.com>.

Anal Intercourse

Remove the inner ring and discard it. Put the female condom on the penis of the insertive partner and insert the condom with the penis, being careful not to push the outer ring into the rectum. The outer ring remains outside the anus, for ease of removal after ejaculation.

Prevention with Positives and Oral Sex

Although there is evidence that some people have become infected through receptive oral sex, the risk of HIV transmission via oral sex, in general, is much lower than the risk of transmission by vaginal or anal sex. Thus, most public health and prevention specialists focus their attention on riskier sexual and drug-use behaviors. However, because HIV transmission can occur with oral sex, clinicians should address this issue with patients and help them make informed decisions about risk reduction. Sores or lesions in or around the mouth or on the genitals may increase the risk of HIV transmission, as may a concurrent sexually transmitted

infection. Patients (and their partners) should avoid oral-genital contact if they have these conditions. Similarly, patients and partners can further reduce risk by not brushing or flossing teeth before oral sex. Individuals who wish to reduce further the risk of HIV transmission during oral sex may use barriers such as condoms, dental dams, or flexible plastic kitchen wrap.

Individuals who smoke crack cocaine often develop open burns, cracked lips, or damaged mucous membranes inside the mouth and thus may be at elevated risk of HIV transmission via oral sex. HIV-infected crack users should be counseled about the risk of transmitting HIV to uninfected partners through those portals of entry during oral sex and should receive risk-reduction counseling. In addition, they (or their partners) may benefit from techniques such as insulating the end of the crack pipe to reduce burns while smoking (eg, with a rubber band or spark plug cap) and avoiding the brittle or sharp-edged copper scrubbing pads used as screens in the crack pipe.

Influence of Substance Use on Sexual Behavior

Alcohol and drug use can contribute significantly to the risk of sexual transmission of HIV, because of behavioral disinhibition. While intoxicated, substance users may, for example, forgo condom use, practice riskier sexual behaviors, have multiple partners, or use erectile dysfunction agents to sustain sexual activity. Addressing substance use issues is an important aspect of PWP. Patients should be assessed for HIV transmission risks associated with alcohol and injection or noninjection drug use, including crystal methamphetamine, in the context of their sexual behaviors (for injection drug use, see below). As always, it is important to approach the patient in a nonjudgmental manner. If alcohol or other drugs are posing barriers to practicing safer behaviors, the provider should counsel the patient to reduce or avoid substance use before engaging in sex, or refer the patient to prevention case management for more specialized risk reduction. Often, the provider can help the patient identify methods for reducing HIV transmission risk, including means that do not require abstaining from alcohol and drug use.

Injection Drug Use and Prevention of HIV

Clinicians should discuss substance use, including steroid use, and reinforce the patient's understanding of the adverse effects that these drugs can have on the body and the immune system. Assess whether referral

for treatment is appropriate, and be knowledgeable about referral resources and mechanisms. If the patient is using injection drugs, emphasize the fact that HIV is readily transmitted by sharing needles and other injection equipment and that reusing or sharing needles and syringes can cause additional infections (eg, endocarditis, hepatitis C). Assess the patient's readiness to change his or her drug injection practices, and refer to drug treatment programs as appropriate. Refer to an addiction counselor for motivational interviewing or other interventions, if available. After completion of substance abuse treatment, relapse prevention programs and ongoing support will be needed. If the patient continues to use needles, discuss safer needle-use practices (Table 3) and refer to a needle exchange program, if one is available, so that syringes and needles are not reused. A partial listing of needle exchange sites may be found at: <http://www.nasen.org>, although many states either do not have or cannot list their facilities. Local harm-reduction activists may be aware of specific programs for obtaining clean needles and syringes. Patient-education flyers on safer injection practices, safer stimulant use, overdose prevention, and other topics are available on the Midwest AIDS Education and Training Center's Web site at <http://www.uic.edu/depts/matec/resource.html>.

Table 3. Needle-Use Practices to Reduce the Risk of HIV Infection and Transmission

- Never reuse or share needles, syringes, water, or drug preparation equipment. If there is a need to reuse syringe equipment, it should be cleaned properly with bleach or water, with care taken not to share the materials (eg, container, water) used for cleaning.
- It is best to use only sterile syringes obtained from a reliable source (pharmacy, needle exchange program). In addition, reusing one's own syringes can lead to various bacterial infections, abscesses, etc.
- Use sterile or boiled water to prepare drugs. If unavailable, use clean water from a reliable source, such as fresh tap water.
- Use a new or disinfected container (cooker) and a new filter (cotton) to prepare drugs. Cooking the drugs before injecting can reduce the chances of transmitting HIV when sharing equipment.
- Clean the skin around the injection site with a new alcohol swab before injecting, and use a sterile or clean cotton pad to stop the blood flow after injecting. Also, using a tourniquet when injecting can help reduce damage to veins and assist the user in controlling the shot and avoiding overdose.
- Safely dispose of syringes after one use, either in a specially made sharps container, or a clean detergent container. Many pharmacies offer disposal programs for used syringes.
- For patient flyers on safer injection practices, safer stimulant use, overdose prevention, and other topics, go to <http://www.uic.edu/depts/matec/resource.html>.

Noninjection Drug Use and Prevention of HIV Transmission

Exposure to HIV through contaminated blood may also occur during noninjection drug use; for example, by sharing cocaine straws or sniffers through which cocaine is inhaled. These straws can easily penetrate fragile nasal mucosa and become contaminated with blood from one user before being used by another individual, who may then experience mucous membrane exposure or even a cut or break in the mucous membrane from the bloody object. Straws or sniffers should not be shared.

Tattoo, Piercing, and Acupuncture Equipment

Patients should be aware of the risk of contamination of tattoo equipment, inks, and piercing equipment, and avoid situations where they might either transmit HIV or pick up other bloodborne pathogens.

Acupuncturists generally use sterile needles, but clients should verify this before using their services.

Maternal-Infant HIV Transmission

HIV-positive women can have healthy pregnancies, with good health outcomes for both mother and baby. For this to occur, women must know their HIV status as early as possible, preferably before becoming pregnant. Although intervention to reduce the risk of perinatal infection is most effective if begun early in pregnancy, or preferably before pregnancy, it may be beneficial at any point in the pregnancy, even as late as during labor. For further information, see chapter *Reducing Maternal-Infant HIV Transmission*.

Postexposure Prophylaxis for Nonoccupational HIV Exposure

Postexposure prophylaxis (PEP) may be considered for certain sexual exposures, sexual assaults, and other nonoccupational exposures to HIV. As with occupational PEP, a risk assessment must be completed and antiretroviral therapy, if indicated, must be started in a timely manner. The risks and toxicities of antiretroviral drugs must be weighed against potential benefits, and the client's informed consent must be obtained. For further information, see chapter *Nonoccupational Postexposure Prophylaxis*.

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Preventing Exposure to Opportunistic and Other Infections

Background

Patients with HIV are more susceptible than others to certain infections. Exposure to some of the opportunistic pathogens may be minimized or avoided if patients are aware of the possible dangers associated with them.

Grouping transmissible infections by type of exposure is a useful way for patients and providers to conceptualize means of prevention.

Sexual Exposures

Patients should use latex or polyurethane condoms during every act of sexual intercourse to reduce the risk of exposure to cytomegalovirus (CMV), herpes simplex virus, hepatitis C, human papillomavirus, and other sexually transmitted pathogens. Although polyurethane male and female condoms have not been tested as thoroughly as latex condoms, they can greatly reduce risk if properly used. Correct use of condoms and other effective barriers, such as latex dental dams or flexible plastic film (eg, plastic food wrap) during oral sex on women also will prevent the transmission of HIV. Avoiding sexual contact when herpetic lesions are present (on the mouth or genitals) may help to reduce herpes simplex transmission, although herpes can be transmitted when no lesions are visible.

The most effective way to avoid the risk of sexually transmitted intestinal infections such as cryptosporidiosis, shigellosis, campylobacteriosis, amebiasis, and hepatitis A and B is to avoid sexual practices that may result in oral exposure to feces (eg, oral-anal contact, or “rimming”). Persons wishing to reduce their risk of exposure might consider using dental dams or other barrier methods (eg, plastic food wrap) for oral-anal contact; changing condoms after anal intercourse; and wearing latex, nitrile, or other intact waterproof gloves during digital-anal contact. Frequently washing hands and genitals with warm soapy water during and after activity that may bring them in contact with feces may further reduce the risk of illness.

Consistent and correct use of condoms greatly reduces the risk of sexually transmitted infections. See chapter *Preventing HIV Transmission/Prevention with Positives* for specific information on the use of condoms.

Injection Drug Use Exposures

Injection drug use with sharing of needles or other injection equipment puts HIV-infected persons at risk for infection with hepatitis C, additional strains of HIV (some of which may be drug-resistant), and other bloodborne pathogens. Injection drug use also conveys a risk of endovascular infections with skin and environmental flora, such as staphylococci, streptococci, *Candida*, and some gram-negative rods. Certain drugs, such as black-tar heroin, may be contaminated with anaerobic bacteria that can cause life- and limb-threatening anaerobic infections if injected. Finally, drug addiction may predispose patients to commercial sex work or trading of sex for drugs, which may increase their risk of acquiring sexually transmitted infections that are not injection related per se.

Assess each patient’s readiness to change his or her practices, and refer to drug treatment programs as appropriate. If the patient continues to use needles, discuss ways to avoid sharing needles and other drug equipment, refer to a needle exchange program so that syringes and needles are not reused, and teach proper cleaning of injection equipment. Specific recommendations about injection and other drug use can be found in the chapter *Preventing HIV Transmission/Prevention with Positives*. All injection drug users should be immunized against hepatitis A and hepatitis B if they are not already immune.

Environmental and Occupational Exposures

No specific measures are recommended to prevent exposure to *Pneumocystis jiroveci* pneumonia (PCP), *Mycobacterium avium* complex, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Candida* spp, or *Cryptococcus neoformans*.

Contact with Infected Populations

Certain activities or types of employment may increase the risk of exposure to tuberculosis. These include volunteer work or employment in health care facilities, correctional institutions, shelters for the homeless, and other settings identified as high-risk by local health authorities. The patient, along with the health care provider, should decide whether to continue such

activities while taking into account the patient's specific duties in the workplace, the prevalence of tuberculosis in the community, and the degree to which precautions are taken in the workplace to prevent the transmission of tuberculosis. These decisions will affect the frequency with which the patient should be screened for tuberculosis.

Child-care providers and parents of children in child-care facilities have an increased risk of acquiring CMV infection, cryptosporidiosis, and other infections (eg, hepatitis A and giardiasis) from children. Although the prevalence of CMV is high (50-70%) in the general adult population in the United States, it is higher (90%) in injection drug users, hemophiliacs, and men who have sex with men (MSM). Any HIV-infected child-care provider without an elevated risk of CMV (ie, no history of injection drug use, hemophilia, or sex with MSM) should be tested for CMV antibody. CMV-negative individuals can reduce the risk of acquiring infection by good hygienic practices, such as hand washing after contact with feces (eg, during diaper changing), urine, and saliva. Any CMV-negative person with HIV who needs a transfusion should receive blood that is CMV negative or leukocyte reduced.

HIV-infected children and adults who are susceptible to varicella-zoster virus (VZV) (ie, those with no history of chickenpox or shingles) should avoid exposure to persons with chickenpox or shingles. Household contacts, especially children, should be vaccinated against VZV if they are HIV negative and have no history of chickenpox so that they will not transmit VZV to their HIV-infected contact. If a susceptible HIV-infected person is in close contact with someone with chickenpox or shingles, varicella-zoster immune globulin (VZIG) should be administered as soon as possible (ideally within 48 hours, but at least within 96 hours) after the exposure. Anti-varicella titers can be performed after exposure if the HIV-infected person's VZV immunity status is unknown. The U.S. Centers for Disease Control and Prevention (CDC) no longer supports the alternative approach of giving acyclovir, 800 mg orally 5 times a day for 3 weeks instead of VZIG, because no data exist to support the efficacy of this approach.

Contact with Animals

Occupations involving contact with animals (eg, veterinary work and employment in pet stores, farms, or slaughterhouses) may pose a risk of cryptosporidiosis, toxoplasmosis, salmonellosis, campylobacteriosis, and

Bartonella infection. However, the available data are insufficient to justify a recommendation against work in such settings.

Contact with young farm animals, especially animals with diarrhea, should be avoided to reduce the risk of cryptosporidiosis.

Soil Exposure

Glove use and hand washing after gardening or other contact with soil may reduce the risk of cryptosporidiosis and toxoplasmosis.

In histoplasmosis-endemic areas, patients should avoid activities known to be associated with increased risk, such as stirring up dust when working with surface soil; cleaning chicken coops; disturbing soil beneath bird-roosting sites; cleaning, remodeling, or demolishing old buildings; and exploring caves.

In coccidioidomycosis-endemic areas, patients should consider avoiding activities associated with increased risk, such as extensive exposure to disturbed native soil (eg, at excavation sites, on farms, or in dust storms).

Pet-Related Exposures

Health care providers should inform HIV-infected persons of the potential risks posed by pet ownership. However, they should be sensitive to the possible benefits of pet ownership and should not routinely advise persons with HIV to part with their pets. They should advise their patients about the following.

General

Veterinary care should be sought when a pet develops a diarrheal illness. If possible, HIV-infected persons should avoid contact with animals that have diarrhea. A fecal sample should be obtained from an animal with diarrhea and examined for *Cryptosporidium*, *Salmonella*, and *Campylobacter*.

When obtaining a new pet, HIV-infected persons should avoid animals younger than 1 year, especially those with diarrhea. Because the hygienic and sanitary conditions in pet breeding facilities, pet stores, and animal shelters are highly variable, patients should exercise caution when obtaining a pet from these sources. Stray animals should be avoided. Animals less than 6 months of age, especially those with diarrhea, should be examined by a veterinarian for *Cryptosporidium*, *Salmonella*, and *Campylobacter* before

contact with the patient. Patients should wash their hands after handling pets (especially before eating) and avoid contact with pet feces to reduce the risk of cryptosporidiosis, salmonellosis, and campylobacteriosis.

Cats

Patients should consider the potential risks of cat ownership such as the risk of toxoplasmosis, *Bartonella* infection, and enteric infections. Those who elect to obtain a cat should adopt or purchase an animal that is more than 1 year of age and in good health to reduce the risk of cryptosporidiosis, *Bartonella* infection, salmonellosis, and campylobacteriosis.

Litter boxes should be cleaned daily, preferably by an HIV-negative, nonpregnant person; if the HIV-infected patient performs this task, he or she should wash hands thoroughly afterward to reduce the risk of toxoplasmosis. Also to reduce the risk of toxoplasmosis, cats should be kept indoors, should not be allowed to hunt, and should not be fed raw or undercooked meat. Flea control will help reduce the risk of *Bartonella* infection. Although declawing generally is not advised, patients should avoid activities that may result in cat scratches or bites to reduce the risk of *Bartonella* infection. Patients should wash the sites of cat scratches or bites promptly and should not allow cats to lick the open cuts or wounds.

Testing of cats for toxoplasmosis or *Bartonella* infection is not recommended.

Birds

Screening of healthy birds for *C. neoformans*, *M. avium*, or *Histoplasma capsulatum* is not recommended. Areas contaminated with bird droppings should be avoided if possible, and soil beneath bird-roosting sites should not be disturbed. Contact with chicks and ducklings has been associated with salmonellosis.

Other

Contact with reptiles (such as snakes, lizards, iguanas, and turtles) should be avoided to reduce the risk of salmonellosis.

Gloves should be used while cleaning aquariums to reduce the risk of infection with *Mycobacterium marinum*.

Contact with exotic pets, such as nonhuman primates, should be avoided.

Food- and Water-Related Exposures

Raw or undercooked eggs (including foods that may contain raw eggs, such as some preparations of hollandaise sauce, Caesar and certain other salad dressings, homemade mayonnaises, eggnog, uncooked cake batter, and cookie dough); raw or undercooked poultry, meat, or seafood, especially raw shellfish; unpasteurized dairy products; unpasteurized fruit juice; and raw seed sprouts (alfalfa, mung bean sprouts) may contain enteric pathogens such as *Salmonella*, pathogenic strains of *Escherichia coli*, and parasites including *Cryptosporidium*. Poultry and meat are safest if the internal temperature is verified with a meat thermometer to be at least 180°F (poultry) or 165°F (red meat). If a thermometer is not available, meats should be cooked until no traces of pink remain; however, color changes do not always correlate with internal temperature. Fruits and vegetables should be washed thoroughly, or cooked, before being eaten.

Cross-contamination of foods should be avoided. Uncooked meats should not be allowed to come into contact with other foods. Hands, cutting boards, counters, and knives and other utensils should be washed thoroughly after contact with uncooked foods.

Although listeriosis is uncommon in the United States, it is a serious disease that occurs more frequently among immunocompromised persons, including those with HIV disease. Persons at increased risk of listeriosis may elect to do the following:

- ◆ Avoid soft cheeses (eg, feta, brie, camembert, blue-veined, and Mexican-style cheeses such as queso fresco). Hard cheeses, processed cheeses, cream cheese, cottage cheese, and yogurt generally are safe from listeriosis.
- ◆ Cook leftover foods or ready-to-eat foods, such as hot dogs, until they are steaming hot before eating.
- ◆ Avoid foods from delicatessen counters, such as prepared meats, salads, and cheeses, or heat these foods until steaming before eating. Canned or shelf-stable pate and meat spreads need not be avoided.
- ◆ Avoid raw or unpasteurized milk or milk products, including goat's milk, or foods containing unpasteurized milk or milk products.

Patients should not drink water directly from lakes or rivers because of the risk of cryptosporidiosis and giardiasis. Even accidental ingestion of lake, river, or ocean water while swimming, rafting, boating, skiing, or engaging in other types of recreational activity carries this risk.

During outbreaks or other situations in which a community “boil water” advisory is issued, patients should boil water for 1 minute to eliminate the risk of cryptosporidiosis. Use of submicron personal-use water filters (home or office types) or bottled water may reduce the risk. Not all bottled water can be considered free of oocysts, however. Water is considered safe if it been distilled, filtered with an “absolute” 1-micron or submicron filter, or filtered by reverse osmosis. Current data are inadequate to recommend that all HIV-infected persons boil or otherwise avoid drinking tap water in non-outbreak settings.

Persons who wish to take independent action to reduce the risk of water-borne cryptosporidiosis may choose to take precautions similar to those recommended during outbreaks. Such decisions are best made in conjunction with the health care provider. Persons who opt for personal-use filters or bottled water should be aware of complexities involved in selecting the appropriate products, the lack of enforceable standards for the destruction or removal of oocysts, the cost of the products, and the difficulty of using these products consistently (eg, for toothbrushing, eating out, and travelling).

Patients taking precautions to avoid cryptosporidiosis in drinking water should be advised that ice made from tap water can be a source of infection. In addition, fountain beverages served in restaurants, bars, theaters, and other public places may pose a risk because these beverages, as well as the ice they contain, are made from tap water. Nationally distributed brands of bottled or canned carbonated soft drinks are safe to drink. Commercially packaged noncarbonated soft drinks and fruit juices that do not require refrigeration until after they are opened (eg, those that can be stored unrefrigerated on grocery shelves) also are safe. Nationally distributed brands of frozen fruit juice concentrate are safe if they are reconstituted with water from a safe source. Fruit juices that must be kept refrigerated from the time they are processed to the time of consumption may be either fresh (unpasteurized) or heat treated (pasteurized); only those labeled as being pasteurized should be considered safe. Other pasteurized beverages and beers also are considered safe to drink. No data are available concerning the survival of *Cryptosporidium* oocysts in wine.

Travel-Related Exposures

Travel, particularly to developing countries, may carry significant risks for HIV-infected persons, especially for patients who are severely immunosuppressed, in terms of exposure to opportunistic pathogens. There is little medical evidence to support recommending against travel to developing countries, however, as long as precautions are taken. Consultation with health care providers and/or experts in travel medicine will help patients plan itineraries.

During travel to developing countries, HIV-infected persons are at much higher risk of food-borne and water-borne infections than they are in the United States. Foods and beverages may be contaminated, especially raw fruits and vegetables, raw or undercooked seafood or meat, tap water, ice made with tap water, unpasteurized milk and dairy products, and items purchased from street vendors. Items that generally are safe include steaming-hot foods, fruits that are peeled by the traveler, bottled (especially carbonated) beverages, hot coffee or tea, beer, wine, and water brought to a rolling boil for 1 minute. Treatment of water with iodine or chlorine may not be as effective as boiling but can be used, perhaps in conjunction with filtration, when boiling water is not practical.

Water-borne infections may result from swallowing water during recreational activity. To reduce the risk of cryptosporidiosis and giardiasis, patients should avoid swallowing water during swimming and other recreational activities and should not swim in water that may be contaminated (eg, with sewage, animal waste, or human waste).

Antimicrobial prophylaxis for traveler’s diarrhea is not recommended routinely for HIV-infected persons traveling to developing countries. Such preventive therapy can have adverse effects and can promote the emergence of drug-resistant organisms. Nonetheless, several studies (none involving an HIV-infected population) have shown that prophylaxis can reduce the risk of diarrhea among travelers. Under selected circumstances (eg, when the risk of infection is very high and the period of travel is brief), the provider and patient may weigh the potential risks and benefits and decide that antibiotic prophylaxis is warranted.

When prophylaxis is offered, fluoroquinolones such as ciprofloxacin (500 mg daily) can be considered, although fluoroquinolones should not be used for pregnant women or children. Taking 1 double-strength

tablet daily of trimethoprim-sulfamethoxazole (TMP-SMX) has been effective, but resistance to this drug is now common in tropical areas. Persons already taking TMP-SMX for prophylaxis against PCP may gain some protection against traveler's diarrhea. For HIV-infected persons who are not already taking TMP-SMX, the provider should use caution when prescribing this agent for prophylaxis of diarrhea because of the high rate of adverse reactions and the possible need for the agent for other purposes (eg, PCP prophylaxis) in the future.

All HIV-infected travelers to developing countries should carry with them a sufficient supply of an antimicrobial agent to be taken empirically should significant diarrhea develop. One appropriate regimen is 500 mg of ciprofloxacin twice daily for 3-7 days. Alternative antibiotics (eg, TMP-SMX) should be considered as empirical therapy for use by pregnant women. Travelers should consult a physician if their diarrhea is severe and does not respond to empirical therapy, if their stools contain blood, if fever is accompanied by shaking chills, or if dehydration develops. Antiperistaltic agents such as diphenoxylate and loperamide are used to treat diarrhea; however, they should not be used by patients with high fever or with blood in the stool, and their use should be discontinued if symptoms persist beyond 48 hours.

Travelers should be advised about other preventive measures appropriate for anticipated exposures, such as chemoprophylaxis for malaria, protection against arthropod vectors, treatment with immune globulin, and vaccination. They should avoid direct contact of the skin with soil and sand (eg, by wearing shoes and protective clothing and using towels on beaches) in areas where fecal contamination is likely.

In general, live-virus vaccines should be avoided. An exception is measles vaccine, which is recommended for nonimmune persons, although not recommended for those who are severely immunocompromised. Immune globulin should be considered for measles-susceptible, severely immunocompromised persons traveling to measles-endemic regions. Inactivated (killed) poliovirus vaccine should be used instead of oral (live) poliovirus vaccine. Persons at risk for exposure to typhoid fever should be given inactivated parenteral typhoid vaccine instead of the live attenuated oral preparation. Yellow fever vaccine is a live-virus vaccine with uncertain safety and efficacy in HIV-infected persons. Travelers with HIV infection who are unvaccinated and for

whom travel is necessary should be advised of the risk, instructed in methods for avoiding the bites of vector mosquitoes, and provided with a vaccination waiver letter. Travelers with asymptomatic HIV infection who cannot avoid potential exposure to yellow fever should be offered the choice of vaccination after disclosure of its limitations.

In general, killed and recombinant vaccines (eg, diphtheria-tetanus, rabies, hepatitis B, hepatitis A, Japanese encephalitis) should be used for HIV-infected persons just as they would be for HIV-uninfected persons anticipating travel. Preparation for travel should include a review and update of routine vaccinations, including diphtheria-tetanus. The currently available cholera vaccine is not recommended for persons following the usual tourist itinerary, even if that includes travel to countries that have reported cases of cholera.

All patients traveling to other countries should be evaluated for both routine and destination-specific immunizations and prophylaxes. Travelers should be told about other area-specific risks and instructed about how to reduce those risks. Geographically focal infections that pose a high risk to HIV-infected persons include visceral leishmaniasis (a protozoan infection transmitted by the sandfly) and several fungal infections (eg, *Penicillium marneffei* infection, coccidioidomycosis, and histoplasmosis). Many tropical and developing areas have high rates of tuberculosis, which is a particular risk for HIV-infected persons.

For further information about health precautions for travelers, including vaccination information, check the CDC Web page at: <http://www.cdc.gov/travel/index.htm>. The "Special Needs Traveler" section contains a link for HIV-infected travelers. Select the "Travelers' Health" option for regional travel documents and outbreak information. Those without Internet access can call the CDC, toll free, at 1-877-FYI-TRIP or 888-232-3299.

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Opportunistic Infection Prophylaxis

Background

Prophylaxis against opportunistic infections (OIs) is treatment given to HIV-infected individuals to prevent either a first episode of an OI (primary prophylaxis) or the recurrence of infection (secondary prophylaxis). Prophylaxis is recommended to prevent 3 important OIs: *Pneumocystis jiroveci* pneumonia (PCP), *Mycobacterium avium* complex (MAC), and toxoplasmosis. Prophylaxis also is recommended to prevent tuberculosis (TB) in patients with latent *Mycobacterium tuberculosis* infection (See chapter *Latent Tuberculosis*). In certain situations, prophylaxis against some other OIs may be reasonable; see the OI prevention guidelines of the U.S. Public Health Service and the Infectious Diseases Society of America (USPHS/IDSA) (reference below) for additional information.

Pneumocystis jiroveci Pneumonia

Background

PCP remains the most common life-threatening infection among U.S. residents with advanced HIV disease.

Primary Prophylaxis: Indications

- ◆ Prophylaxis should be administered to all HIV-infected patients with a CD4 count of <200 cells/ μ L or a history of oral thrush. PCP prophylaxis may be indicated in patients with CD4 counts of >200 cells/ μ L in the presence of a CD4 percentage <14%, other OIs, or fever >100°F that persists for >2 weeks.
- ◆ In patients whose CD4 counts are declining toward 200 cells/ μ L, the CD4 count should be monitored closely. PCP prophylaxis should be considered for patients with a CD4 count between 200 and 250 cells/ μ L if laboratory monitoring will not be possible within 3 months.

Prophylaxis Options: Recommended Regimen

- ◆ The recommended regimen is trimethoprim-sulfamethoxazole (TMP-SMX; cotrimoxazole, Bactrim, Septra) 1 double-strength tablet daily. An alternative dosage is TMP-SMX 1 single-strength tablet daily, although the lower dosage may not be as effective. (Note: These regimens also are effective in preventing toxoplasmosis.)
- ◆ Warning: Many patients cannot tolerate sulfa medications. Severe reactions may include persistent neutropenia; rash, including severe erythroderma; and Stevens-Johnson syndrome (bullae and desquamation of the skin). Some patients with milder reactions (eg, rash without fevers or systemic symptoms) may undergo desensitization, but this must be done cautiously and requires diligence from the patient and careful management by the provider (see chapter *Sulfa Desensitization*).

Prophylaxis Options: Alternative Regimens

Other options for prophylaxis include the following:

- ◆ Dapsone 100 mg orally daily or 50 mg orally twice daily. (Note: These regimens do not prevent toxoplasmosis.)
- ◆ Dapsone 50 mg orally daily + pyrimethamine 50 mg orally once per week + leucovorin 25 mg orally once per week. (Note: This regimen also is effective in reducing the risk of toxoplasmosis.)
- ◆ Dapsone 200 mg orally + pyrimethamine 75 mg + leucovorin 25 mg, all once per week. (Note: This regimen also is effective in reducing the risk of toxoplasmosis.)
- ◆ Warning: Glucose-6-phosphate dehydrogenase (G6PD) deficiency can increase the risk of hemolytic anemia or methemoglobinemia in patients receiving dapsone. Screen for G6PD deficiency before starting dapsone. (G6PD deficiency is found in approximately 10% of African American males, and in 1-2% of males of Mediterranean, Indian, and Asian descent.)

- ◆ Aerosolized pentamidine 300 mg once per month, via Respigard II nebulizer. (Note: This regimen does not prevent toxoplasmosis.)
 - ◆ Warning: Aerosolized pentamidine may increase the risk of extrapulmonary pneumocystosis, pneumothorax, and bronchospasm. It increases the risk of TB transmission to others if the patient has active pulmonary tubercular disease, unless ventilation (negative pressurized facility with outside venting) is adequate. Do not use in patients in whom TB is suspected. The availability of treatment facilities offering aerosolized pentamidine may be limited.
- ◆ Atovaquone suspension 1,500 mg daily. (Note: This is also effective in reducing the risk of toxoplasmosis.) Atovaquone is more expensive than dapsone. It should be taken with high-fat meals for optimal absorption.
- ◆ TMP-SMX 1 double-strength tablet orally 3 times per week (eg, Monday, Wednesday, Friday).

Secondary Prophylaxis Indications

Prophylaxis should be given to all patients with a history of PCP.

Discontinuing Prophylaxis

Primary or secondary prophylaxis can be discontinued if the CD4 count has increased to >200 cells/ μ L for at least 3 months in response to effective antiretroviral therapy (ART), with the following cautions:

- ◆ If the patient had PCP in the past and the episode of PCP occurred at a CD4 count of >200 cells/ μ L, it may be prudent to continue PCP prophylaxis for life, regardless of how high the CD4 count rises as a consequence of ART.
- ◆ If PCP prophylaxis is discontinued, the patient's clinical status and CD4 count must be observed closely to determine when to resume prophylaxis.
- ◆ PCP prophylaxis should be reinitiated if the CD4 count decreases to <200 cells/ μ L or the patient meets other criteria as indicated above.

Prophylaxis during Pregnancy

TMP-SMX is the recommended agent for use during pregnancy; dapsone may be used as an alternative. Prophylaxis that includes pyrimethamine generally

should be deferred until after pregnancy. During the first trimester, aerosolized pentamidine can be used, if the potential teratogenicity of oral agents is a concern.

Disseminated *Mycobacterium avium* Complex

Background

Disseminated MAC (DMAC) is common in patients with advanced HIV disease and occurs in people with CD4 counts of <50 cells/ μ L.

Primary Prophylaxis: Indications

Prophylaxis should be administered to all HIV-infected patients with CD4 counts of <50 cells/ μ L. Before starting prophylaxis, rule out active MAC infection by clinical assessment and, if warranted, by acid-fast bacilli (AFB) blood cultures (see chapter *Mycobacterium avium Complex*). Review the current drug regimen for medications that may interact with DMAC prophylaxis.

Prophylaxis Options: Recommended Regimens

- ◆ Azithromycin 1,200 mg weekly or clarithromycin 500 mg orally twice a day.
(Note: Clarithromycin is not recommended during pregnancy, and it can have significant interactions with efavirenz and other drugs; see chapter *Drug-Drug Interactions with HIV-Related Medications*.)
Note that if breakthrough DMAC occurs, it may be macrolide resistant.

Prophylaxis Options: Alternative Regimens

- ◆ Rifabutin 300 mg daily, or azithromycin 1,200 mg daily + rifabutin 300 mg daily.
(Note: Rifabutin has significant interactions with many drugs; certain nonnucleoside reverse transcriptase inhibitors and protease inhibitors should be avoided or dose adjusted if used with rifabutin. See chapter *Drug-Drug Interactions with HIV-Related Medications*.)

Secondary Prophylaxis

Patients should receive lifelong chronic maintenance therapy, unless immune reconstitution occurs in response to ART. See chapter *Mycobacterium avium Complex*.

Discontinuing Primary Prophylaxis

Primary prophylaxis for DMAC can be discontinued in persons who have responded to effective ART with sustained increases in CD4 counts to >100 cells/ μ L for at least 3 months. Careful observation and monitoring are required, and prophylaxis should be restarted if the patient's CD4 count decreases to <50 – 100 cells/ μ L.

Secondary prophylaxis can be discontinued in patients who received at least 12 months of treatment for DMAC, are asymptomatic, and have sustained (for at least 6 months) CD4 counts of >100 cells/ μ L during ART.

Prophylaxis during Pregnancy

Azithromycin is the prophylactic drug of choice during pregnancy, although some providers withhold it during the first trimester. Clarithromycin is teratogenic in animals.

Toxoplasmosis

Background

Toxoplasmic encephalitis (TE) is usually caused by reactivation of latent *Toxoplasma gondii* infection in patients with advanced immunosuppression (especially those with CD4 counts of <100 cells/ μ L). The USPHS/IDSA guidelines recommend that all HIV-infected patients be tested for toxoplasmosis immunoglobulin G (IgG) antibody soon after the diagnosis of HIV infection. Toxoplasmosis IgG-negative patients should be counseled to avoid sources of infection (see chapter *Preventing Exposure to Opportunistic and Other Infections*), and should be retested for toxoplasmosis IgG when CD4 counts fall to <100 cells/ μ L to determine whether they have seroconverted and are therefore at risk for TE. (See chapter *Toxoplasmosis* for more information on active disease and secondary prophylaxis.)

Primary Prophylaxis: Indications

Prophylaxis should be administered to all HIV-infected patients with CD4 counts of <100 cells/ μ L who are seropositive for *Toxoplasma*. IgG-negative patients should avoid exposure to *Toxoplasma*; see “Patient Education” below.

Prophylaxis Options: Recommended Regimen

- ◆ TMP-SMX 1 double-strength tablet daily. (Note: This option is also effective in preventing PCP.)

Prophylaxis Options: Alternative Regimens

(Note: The following options also are effective in preventing PCP.)

- ◆ TMP-SMX, 1 single-strength tablet daily.
- ◆ Dapsone 50 mg daily + pyrimethamine 50 mg weekly + folinic acid 25 mg weekly.
- ◆ Dapsone 200 mg weekly + pyrimethamine 75 mg weekly + folinic acid 25 mg orally weekly.
 - ◆ Warning: G6PD deficiency can increase the risk of hemolytic anemia or methemoglobinemia in patients receiving dapsone. Screen for G6PD deficiency before starting dapsone. (G6PD deficiency is found in approximately 10% of African American males, and in 1–2% of males of Mediterranean, Indian, and Asian descent.)
- ◆ Atovaquone 1,500 mg orally daily, with or without pyrimethamine 25 mg daily + folinic acid 10 mg daily; however, this alternative is quite expensive.
- ◆ Neither aerosolized pentamidine nor dapsone alone provides protection against TE.

Secondary Prophylaxis

Patients should receive lifelong chronic maintenance therapy, unless immune reconstitution occurs in response to ART (see chapter *Toxoplasmosis*).

Discontinuing Prophylaxis

Primary prophylaxis for TE can be discontinued in patients who have responded to effective ART with sustained CD4 counts of >200 cells/ μ L for at least 3 months. CD4 counts should be monitored carefully, and prophylaxis should be restarted in patients whose CD4 counts decrease to <200 cells/ μ L.

Secondary prophylaxis may be discontinued if TE signs and symptoms have resolved with treatment and if patients have sustained (for at least 6 months) CD4 counts of >200 cells/ μ L during ART.

Prophylaxis during Pregnancy

TMP-SMX may be used as primary prophylaxis during

pregnancy. Prophylaxis that includes pyrimethamine generally should be deferred until after pregnancy, although pyrimethamine may be used with caution to treat active toxoplasmosis during pregnancy in sulfa-allergic patients.

Patient Education

- ◆ Discuss adverse effects of the selected medication(s) and how the patient should respond in the event of rashes, diarrhea, and other complications.
- ◆ Explain the purpose of each medication, and be sure that patients understand the dosage and frequency of administration.
- ◆ Reinforce the need to continue the medication indefinitely (potentially for life) to reduce the risk of the OI.
- ◆ OIs can occur despite prophylaxis. Instruct patients to call their health care providers if they become ill.
- ◆ Counsel patients who are *Toxoplasma* IgG negative to avoid exposure to *Toxoplasma*. Specifically, they should avoid eating raw or undercooked meat, especially pork, lamb, game, and venison. Patients should wash hands after handling raw meat and after gardening or contact with soil. Encourage patients not to adopt or handle stray cats, and, if they own cats, to wash hands thoroughly after cleaning litter boxes. (See chapter *Preventing Exposure to Opportunistic and Other Infections*.)
- ◆ For women of childbearing potential who are taking clarithromycin, emphasize the need for effective contraception to avoid potential teratogenic effects of clarithromycin.

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Latent Tuberculosis

Background

Latent (or inactive) tuberculosis (TB) infection occurs when an individual has dormant *Mycobacterium tuberculosis* organisms and no active disease, and can be diagnosed by a tuberculin skin test (TST). Persons with HIV or AIDS and latent TB infection (LTBI) have a much higher risk of developing active TB (estimated at 10% per year) than does the general population (estimated at 10% in a lifetime). The risk of developing active TB can be reduced dramatically with treatment of LTBI. Hence, identifying and treating HIV-infected persons for LTBI is a high priority. Treatment of LTBI not only reduces the risk of disease for the individual, but also reduces the risk of further TB transmission should the HIV/TB-coinfected person develop active pulmonary TB. Standard treatment with isoniazid (INH) is effective and safe.

Issues of concern regarding the treatment of LTBI among HIV-infected persons include the following:

- ◆ Excluding active pulmonary or extrapulmonary TB disease before treatment with INH alone
- ◆ Assessing the risk of latent infection with drug-resistant TB
- ◆ Avoiding or managing drug interactions if rifampin or rifabutin regimens are used
- ◆ Exercising great caution in the use of rifampin/rifabutin and pyrazinamide combinations for LTBI treatment

S: Subjective

HIV-infected persons who have no symptoms of active TB (ie, afebrile, stable weight, no cough) and who have not been treated previously for active or latent TB are eligible for LTBI treatment. When patients do have symptoms that could represent active TB, active TB must be evaluated and ruled out by appropriate diagnostic methods before initiating treatment (see “Assessment” below).

Persons who have had bacillus Calmette-Guérin (BCG) vaccine should be evaluated in the same way as those who have never had BCG. Immigrants from many countries will have had childhood vaccination.

History

Health care providers should ask about a history of potential exposure to TB, because this might indicate infection with drug-resistant TB. Such risk might occur when there is knowledge of a source patient or when the exposure occurred in a setting with known drug resistance or a location with ongoing TB transmission where others remain at risk for exposure).

O: Objective

Physical Exam

Current U.S. guidelines strongly recommend performing a TST in newly diagnosed HIV-infected persons. Repeat testing is recommended for those whose CD4 lymphocyte count increases from low numbers to counts of >200 cells/ μ L, and annual testing is suggested for those who initially test negative. The TST is administered as an intradermal injection of 0.1 mL (5 tuberculin units TUs) of purified protein derivative (PPD), which raises a wheal in the skin. This also is known as the Mantoux test. Multiple-puncture tests such as tine tests and the use of other strengths of PPD are considered unreliable. Anergy testing is not recommended routinely because a randomized controlled study in HIV-positive patients in the United States failed to show an advantage to treating anergic, tuberculin-negative persons.

PPD tests are not designed for reading by the patient; a trained health care worker must measure the area of induration (not erythema) 48–72 hours after the test is placed. Induration of 5 mm or more is a positive result in HIV-infected persons, other immunosuppressed persons, anyone with recent TB exposure, and anyone with fibrosis on chest x-ray consistent with previous TB. For HIV-uninfected health care workers, 10 mm of induration is positive; in various other populations, either 10 mm or 15 mm of induration may be considered positive. Many large HIV clinics find it challenging to get their patients to return for the PPD reading. One randomized study found that offering incentives (eg, a fast-food coupon) plus counseling was more effective than counseling alone in obtaining return visits for PPD readings.

Recently licensed tests for gamma-interferon, which is produced by peripheral blood T cells in response to TB antigens, have not been validated for use in HIV-infected persons and currently are not recommended for this population.

A: Assessment

TST-positive, HIV-infected persons without cough or other symptoms should have a chest x-ray. If the chest x-ray in an asymptomatic patient is negative, the patient should be offered treatment for LTBI. Persons with symptoms consistent with pulmonary or extrapulmonary TB, and those with abnormal findings on chest radiography, require further assessment. This assessment may include sending 3 sputum specimens on 3 separate mornings (using saline mist to induce cough for those not coughing spontaneously) for acid-fast bacilli stain and culture or obtaining other specimens, depending on the suspected site of extrapulmonary TB. If suspicion of TB is low, then those with negative sputum smears (or other biopsy or tissue samples) can begin LTBI treatment. If suspicion of active disease is high, treatment for active disease should be started

while the culture results are pending (see chapter *Mycobacterium tuberculosis: Treatment in the United States and other High-Income Nations*).

HIV-infected close contacts of patients with active pulmonary TB should receive preventive therapy regardless of PPD results or previous courses of preventive treatment, after active TB has been excluded. Such contacts should be tested with 5 TUs of PPD if previously negative and then started on preventive therapy. If the initial TST result is negative, the individual should be evaluated again 3 months after discontinuation of contact with the infectious source. If the contact is severely immunosuppressed, a full course of preventive treatment usually is provided even if that individual remains PPD negative. Contacts who are not immunosuppressed and who remain PPD negative may discontinue preventive treatment.

P: Plan

As with any treatment of TB, adherence with the regimen is required for success. Treatment regimens for LTBI are presented in Table 1.

Table 1. Treatment Regimens for Latent Tuberculosis

Drug	Dose (taken orally)	Frequency	Duration (minimum number of doses for completion)
Recommended			
Isoniazid*	Adults: 300 mg Children: 5 mg/kg	Daily	9 months OR 270 doses in 12 months
Alternative			
Isoniazid*	Adults: 900 mg Children: 15 mg/kg	Twice-weekly DOT**	9 months OR 76 supervised doses in 12 months
Exposure to isoniazid-resistant TB or intolerance to isoniazid			
Rifampin***	Adults: 600 mg Children: 10-20 mg/kg	Daily	4 months OR 120 doses in 6 months
Use only in special situations			
Rifampin*** and pyrazinamide	Highly toxic; to be used only by persons experienced in LTBI treatment in special situations		
Exposure to multidrug-resistant (MDR) TB			
Consider pyrazinamide with either ethambutol or a fluoroquinolone	Seek expert advice from public health authorities and those experienced in treatment of MDR TB. May be postponed or may be based on resistance pattern of index case, if known.		

*10–25 mg of pyridoxine (vitamin B6) should be given with each isoniazid dose to reduce the risk of isoniazid-induced peripheral neuropathy.

** DOT = directly observed treatment

*** Rifampin has significant interactions with antiretroviral drugs in the nonnucleoside reverse transcriptase inhibitor (NNRTI) and protease inhibitor (PI) classes and with other medications. See text about contraindicated combinations, dosage adjustments, and substitution of rifabutin for rifampin.

INH may cause liver toxicity and its use should be monitored carefully in patients with active alcohol use, liver disease, or chronic hepatitis B or C. INH is contraindicated in patients with acute hepatitis or decompensated liver disease. Before INH use, baseline liver and renal function tests should be checked. Routine monthly clinical monitoring for fever, fatigue, anorexia, nausea, vomiting, abdominal pain, jaundice, peripheral neuropathy, and rash should be performed. Alanine aminotransferase (ALT) should be monitored monthly in HIV-infected patients and others at risk for hepatitis. If patients develop abnormalities in liver transaminases while taking INH (ALT or aspartate aminotransferase >3 times the upper limit of normal with symptoms, or >5 times the upper limit of normal in the absence of symptoms), INH should be withheld. Obtain expert consultation before treating patients with abnormal liver function tests or advanced liver disease.

Before rifampin use, baseline liver and renal function tests and a complete blood count are suggested. Follow-up is the same as for INH use.

Drug Interactions with Antiretroviral Therapy

Rifampin and rifabutin have significant interactions with certain antiretroviral drugs, including nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). Rifampin can be used in persons taking efavirenz, although some experts recommend increasing the efavirenz dosage to 800 mg daily. Rifampin decreases the blood concentrations of nevirapine and all unboosted PIs (except ritonavir) and should not be used with these drugs. Standard ritonavir boosting of PIs fails to overcome the drug interaction, causes additional toxicity, or both. Although recommended in the past, rifampin should not be used in combination with ritonavir-boosted saquinavir because of high rates of hepatic toxicity. Adding more ritonavir to the fixed-dose combination of lopinavir/ritonavir (Kaletra) may overcome the pharmacokinetic effects of concurrent rifampin, but the regimen is poorly tolerated. Use of ritonavir-boosted PI regimens in combination with rifampin is best avoided and should be done only in consultation with an expert.

No data are available on the use of rifabutin for the treatment of LTBI. Nevertheless, rifabutin may be considered in place of rifampin for patients taking antiretroviral combinations that include NNRTIs (other than efavirenz) or PIs (other than ritonavir alone).

In these cases, the dosages of both rifabutin and the antiretroviral agent usually require adjustment.

Table 2 presents information on combining antiretroviral agents with rifampin or rifabutin.

Other Drug Interactions

Rifampin decreases the blood concentrations of estrogens, anticonvulsants, hypoglycemic agents, and many other drugs. Review all medications a patient is taking before initiating rifampin and make adjustments as necessary. (See Table 12: *Clinically significant drug-drug interactions involving rifamycins* at www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm#tab12.)

Pregnancy

HIV-infected pregnant women with a positive TST and no evidence of active TB should receive standard prophylaxis as soon as possible, even during the first trimester. The preferred prophylaxis in pregnancy is a 9-month INH regimen (with pyridoxine, as above). Alternative regimens, such as rifampin or rifabutin, should be used with caution because of limited experience. Neonates born to women who received rifampin during pregnancy should be given vitamin K (10 mg) to reduce the risk of hemorrhagic disease. Pyrazinamide generally is avoided during pregnancy because of lack of information about fetal effects.

Table 2. Combinations of Antiretroviral Medications with Rifampin or Rifabutin: Contraindicated Combinations and Dose Adjustments

	Rifampin	Rifabutin*
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz**	Rifampin dose unchanged, efavirenz dose 600-800 mg daily	No change in efavirenz dose Increase rifabutin to 450 mg/day or 600 mg 3 times weekly
Nevirapine	Generally not recommended; despite 25-50% reduction in nevirapine levels, 2 small studies claim standard doses are effective	Use standard dose of nevirapine Rifabutin 300 mg daily or 3 times weekly
Delavirdine	Never combine	Never combine
Protease Inhibitors (Nonboosted)		
Ritonavir	May be used at standard doses; limited clinical experience	Ritonavir at standard dose Rifabutin 150 mg alternate days or 3 times weekly
Amprenavir/fosamprenavir	Never combine	PIs at standard dose Rifabutin 150 mg/day or 300 mg 3 times weekly
Atazanavir	Never combine	Atazanavir at standard dose Rifabutin 150 mg alternate days or 3 times weekly
Indinavir	Never combine	Increase indinavir to 1,000 mg every 8 hours Rifabutin 150 mg/day or 300 mg 3 times weekly
Nelfinavir	Never combine	Increase nelfinavir to 1,000 mg every 8 hours Rifabutin 150 mg/day or 300 mg 3 times weekly
Saquinavir	Never combine	Never combine
Ritonavir-Boosted Protease Inhibitors		
Lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir (3 capsules twice daily) must be supplemented with additional ritonavir 300 mg twice daily; limited experience, not well tolerated	Standard dose of lopinavir/ritonavir Decrease rifabutin to 150 mg alternate days or 3 times weekly
Saquinavir/ritonavir	Due to high rates of hepatotoxicity this combination should not be used	Standard dose of lopinavir/ritonavir; Decrease rifabutin to 150 mg alternate days or 3 times weekly
All other ritonavir-boosted PIs	Should not be used (adequate dosing regimens not defined)	Standard dose of PI/ritonavir; Decrease rifabutin to 150 mg alternate days or 3 times weekly

Source: Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors. Updated January 20, 2004. (Nucleoside and nucleotide analogues are given in standard doses with either rifampin or rifabutin.)

* If available, rifabutin may be substituted for rifampin when TB treatment and antiretroviral therapy is combined.

** Avoid efavirenz during pregnancy or in women who may become pregnant during therapy. Both rifampin and rifabutin significantly reduce estrogen and progestin levels for women on hormonal contraceptives; efavirenz raises estrogen levels moderately. Two forms of birth control including one barrier method and either a mid- to high-dose hormonal contraceptive or intrauterine device are most often recommended. Barrier methods are also recommended for reducing HIV transmission in women who are infertile.

Patient Education

- ◆ Patients should know that although they have the TB germ in their bodies, they cannot pass the germ to others while TB is latent. However, because they have HIV infection, the TB germ is more likely to make them sick at some point in the future.
- ◆ The medicine patients are starting will help kill the TB germ and reduce their chances of getting sick with active TB.
- ◆ Patients must take all of their medicine, every day, to prevent the TB germ from spreading and making them sick.
- ◆ If patients have adverse effects, such as rash or itching, tell them to contact their health care providers immediately. Occasionally, INH can cause tingling or numbness in the hands or feet. The pyridoxine (vitamin B6) they are taking should help prevent that, but they should let their providers know if it occurs.
- ◆ Patients should avoid alcohol while taking these medications. The medicines for TB are processed by the liver and, when combined with alcohol, they easily can overload the liver. Acetaminophen (Tylenol) also is processed by the liver, so patients should keep their intake to a minimum. (Patients with hepatitis C, liver disease, or chronic alcohol use should not take more than 3.5 grams per day.)
- ◆ Blood tests will be done regularly to make sure the liver is working well, so it is important for patients to keep their follow-up appointments. They should take all their medications, vitamins, and supplements with them to the clinic so that their health care providers can review them and make sure there are no drug interactions.
- ◆ If patients experience nausea, vomiting, poor appetite, or abdominal pain, if they notice their urine darkening or becoming cola-colored, or if they notice their eyes or skin yellowing, they should return to the clinic immediately. These problems may indicate that the liver is being overwhelmed, and it is important to find out before permanent damage is done.
- ◆ Rifampin will cause sweat, tears, urine, and plastic contact lenses to turn orange.
- ◆ Rifampin will make birth control pills ineffective. Patients should use a backup method of contraception until treatment is complete. Condoms can help prevent HIV transmission and reduce the risk of pregnancy.

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Treatment of Latent Tuberculosis in Resource-Limited Settings

Background

Countries with a high prevalence of tuberculosis (TB), including resource-limited countries, traditionally relied on the bacillus Calmette-Guérin (BCG) vaccination rather than treatment of latent TB infection (LTBI) to prevent active TB. Because of the rapidly increasing rates of both TB and HIV in many countries, and the negative impact of each infection on the other, some pilot projects and national programs in resource-limited settings are now providing treatment of LTBI for HIV-infected persons. (See chapter *Latent Tuberculosis* for a general discussion of latent TB, including treatment options and patient education.)

Several issues should be considered in the treatment of LTBI among HIV-infected patients in resource-limited settings, including the following:

- ◆ Access to HIV test and tuberculin skin test (TST)
- ◆ The effect of previous BCG vaccination on the TST
- ◆ The need for TST before treatment of LTBI
- ◆ Criteria for isoniazid (INH) use, including the ability to rule out active TB before INH use
- ◆ The duration of treatment and the effectiveness of INH in treating LTBI
- ◆ Lack of access to preventive therapy other than INH
- ◆ Access to HIV and TB interventions

In some settings, a TST is not a prerequisite for INH use; in these settings the term “INH preventive therapy” (IPT) is used, rather than treatment of LTBI. To distinguish INH preventive therapy from intermittent prophylactic treatment of malaria in pregnancy (also abbreviated IPT), the acronym TB-IPT is used commonly.

Access to HIV Test and Tuberculin Skin Test

Interventions for HIV/TB-coinfected persons can occur only if both infections are diagnosed. Many countries are gradually expanding access to voluntary HIV counseling and testing at low or no cost, using either laboratory-based tests or rapid tests applied in the field. However, importation and use of purified protein derivative (PPD) for TB skin testing have been infrequent in many countries. An adequate supply of PPD and training in skin testing are required for programs that use the TST to identify patients who will be offered INH.

Several studies performed in sub-Saharan Africa have documented that the TST is effective in diagnosing TB infection, even in populations where previous BCG vaccination rates approached 100%.

Obtaining PPD test materials, training staff, and implementing a TST program can be formidable barriers to providing preventive treatment for LTBI. Some countries with very high rates of LTBI in their populations have decided not to require TSTs, but to offer IPT to all HIV-infected persons who meet certain criteria, without the use of TB skin testing.

Treatment with Isoniazid

Criteria for INH treatment of HIV-infected persons with suspected LTBI (positive TST or those from a high-prevalence population) require exclusion of active TB or risk factors for adverse events. Reliance on a chest x-ray to rule out active TB is prohibitively expensive for many resource-limited settings, however, and observational studies have shown that clinical criteria are 95% sensitive in ruling out active TB. Persons with cough, night sweats, fever, weight loss, loss of appetite, and lymphadenopathy are not offered INH preventive therapy. Instead, persons with those symptoms are evaluated for active TB or other conditions that require treatment. Other exclusion criteria include recent treatment for TB, active TB requiring combination therapy, unsatisfactory commitment to adherence with treatment; and preexisting liver disease, preexisting peripheral neuropathy, or previous severe adverse reaction to INH.

Randomized trials in Haiti, Zambia, and Uganda have demonstrated that a 6-month course of INH reduced the risk of active TB among HIV-infected persons by 60% over 1-5 years of follow-up. In resource-limited settings, the usual course of treatment is 6 months of daily INH treatment taken by the patient without observation, but with monthly clinic visits and prescription refills. A minimum of 180 doses taken within 9 months, or 80% of the doses within 6 months, is considered a complete regimen. Often, pyridoxine 10-25 mg daily also is provided. In studies of HIV-negative persons, the benefit of INH lasts 2 years. Current guidelines do not recommend prolonging INH preventive therapy beyond 6 months or repeating IPT in subsequent years; these issues are under study.

INH is the only treatment for LTBI that is available in much of the world. Rifampin and rifabutin combinations are very expensive and are not used for treatment of LTBI in resource-limited settings. The combination of rifampin and pyrazinamide is toxic and is not recommended in either industrialized or resource-limited settings.

Treatment of HIV/TB-coinfected persons requires adequate supplies of HIV test kits, materials for tuberculin testing, INH, pyridoxine, a trained staff, a mechanism for promoting adherence, and a system of record keeping, along with the willingness of patients to participate. In Uganda, only a small proportion of HIV-infected persons who were offered tuberculin testing eventually took a 6-month course of INH. Use of IPT requires substantial resources and planning. Projects and countries using this approach to TB prevention will have to identify resources for all of these requirements.

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Antiretroviral Therapy

Background

Potent combination antiretroviral therapy (ART), consisting of 3 or more antiretroviral drugs (ARVs), has greatly improved the health and survival rates of HIV-infected patients in areas of the world with access to ARVs.

More than 20 individual ARVs are available in the resource-sufficient world, in addition to several fixed-dose combination preparations. These can be combined to construct a number of effective regimens for initial and subsequent therapy. ART is not without limitations, however. ART does not cure HIV infection and it requires that multiple medications be taken for very long periods of time (usually for the duration of life). It is expensive, may cause a variety of adverse effects (some severe), requires close adherence to be effective and to prevent the emergence of resistance, and often fails (because of the patient's imperfect adherence or other factors). The failure of an ARV regimen when accompanied by drug resistance usually means that subsequent regimens are less likely to succeed.

Greatly overshadowing the limitations of ART, however, is the overwhelming evidence that ART saves lives and improves or restores immune system function. Mortality and morbidity benefits are particularly obvious in patients with relatively advanced immune suppression or with symptoms related to HIV infection. For asymptomatic patients with relatively high CD4 cell counts (>350 cells/ μ L), it is less clear whether or when to start ART. In deciding when to start ART for any patient, practitioners must weigh the expected benefits of ART for that individual (in terms of morbidity and mortality) against the possible risks (eg, toxicity, drug resistance, adverse drug interactions).

Although implementing ART is complex, a number of guidelines from expert panels are available to help practitioners select effective regimens for particular patients. The U.S. Department of Health and Human Services (DHHS) keeps a repository of “living documents” of frequently updated recommendations on the use of ARV medications in children, adults and adolescents, and pregnant women. All clinicians treating HIV-infected patients should be familiar with the most current versions of these treatment guidelines. They are available on the Internet at the AIDSinfo Web

site “Clinical Guidelines” section (<http://aidsinfo.nih.gov/Guidelines>). This chapter frequently references the *Adult and Adolescent ARV Guidelines*. (U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7.)

S: Subjective

Obtain the patient's history, including the following:

- ◆ CD4 cell count history, including nadir
- ◆ HIV viral load history, including before therapy if the patient is currently taking ARVs
- ◆ History of HIV-related conditions
- ◆ Previous and current ARV regimens, including regimen efficacy, toxicity, resistance, start and stop dates
- ◆ Current medications, including herbal preparations, supplements, and over-the-counter medications
- ◆ Medication allergies, intolerances, or prominent adverse effects
- ◆ Comorbid conditions (eg, hepatitis C, hepatitis B, depression)
- ◆ Occupation and daily schedule
- ◆ Current and previous substance use, including alcohol and recreational drugs
- ◆ Self-assessment of adherence to previous regimens
- ◆ Desire to start or continue an ARV regimen
- ◆ Commitment to adherence (see chapter *Adherence*)
- ◆ Indicators of ability to adhere to various types of regimens (eg, once daily, twice daily, every 8 hours, with or without food) given current life situation
- ◆ For women of childbearing potential: last menstrual period, current method of birth control (if any), current pregnancy status, thoughts on whether or when to have children
- ◆ History and review of systems (see chapter *Initial History*)

O: Objective

Perform the following objective tests:

- ◆ Complete physical examination (see chapter *Initial Physical Examination*)
- ◆ Current CD4 count and HIV viral load: preferably 2 or more separate results approximately 1 month apart
- ◆ Drug resistance test. To try to detect the presence of transmitted ARV resistance mutations, a genotype should be performed in all patients before initiating ART. This should be done as early in the course of infection as possible, because mutations may revert to wild type. Review the results of previous resistance testing or obtain a baseline resistance test, if this was not done earlier. (See chapter *Resistance Testing*.)
- ◆ Complete blood count (CBC) and platelet count, liver function tests (LFTs), renal function tests, fasting lipid panel (see chapter *Initial and Interim Laboratory and Other Tests*) fasting glucose, rapid plasma reagin (RPR), tuberculin skin test, hepatitis serologies

A: Assessment

Make the following basic decisions:

- ◆ The patient is or is not likely to benefit from ART at this time (ie, do potential benefits outweigh the risks)? See the *Adult and Adolescent ARV Guidelines* noted above, which thoroughly address the issue. A brief summary is included in the tables in the chapter *Determining Risk of HIV Progression* and in the chapter *CD4 Monitoring and Viral Load Testing*.
- ◆ The patient is or is not willing to start ARVs at this time (the choice to accept or decline therapy ultimately lies with the patient).
- ◆ The patient is or is not likely to adhere to an ARV regimen (an adherence counselor, with or without a mental health clinician, may be able to assist with this assessment and should be called upon if available). No patient should be automatically excluded from consideration of ART; the likelihood of adherence must be discussed and determined individually.

P: Plan

After educating the patient about the purpose and logistics of the proposed regimen and assessing the patient's potential for adherence, the ART regimen can be initiated, changed, or postponed accordingly.

The goals of therapy are to achieve maximal and durable viral suppression, restore or preserve immune function, improve quality of life, and reduce HIV-related morbidity and mortality.

Considerations before Initiating ART

No “average patient” exists. Some patients will do better during treatment and some will do worse than clinical studies would predict. Health care providers must work with each patient to develop a treatment strategy that is both clinically sound and appropriate for that individual's needs, priorities, and circumstances of daily life. Not all patients will be able to tolerate all drugs, and the patients understanding, readiness to commit to the regimen, and history of adherence to previous regimens must be considered when choosing ARV combinations. Major considerations are as follows:

- ◆ Willingness of the individual to begin therapy, coupled with understanding of the purpose and the mechanics of the planned regimen, and how it will fit into his or her life
- ◆ Degree of immunodeficiency and risk of disease progression as reflected by the CD4 count and HIV RNA level (see tables in the chapter *Determining Risk of HIV Progression* and the chapter *CD4 Monitoring and Viral Load Testing*)
- ◆ Potential benefits and risks of ARV drugs
- ◆ Likelihood of adherence to the prescribed regimen
- ◆ Resistance, if any, to ARV medications (obtain resistance testing prior to ARV initiation in ARV-naïve patients)

The patient has the right to decline or postpone ART. This decision should not affect any other aspect of care, and ART should be offered again at each visit to patients who meet the criteria for treatment. If mental health issues, addiction, or the patient's social situation are barriers to adherence, initiate appropriate referrals and reassess adherence barriers at regular intervals.

Initiating Therapy: DHHS ARV Guidelines

The following recommendations have been adapted from the DHHS *Adult and Adolescent ARV Guidelines*.

- ◆ ART is *recommended* for all patients with a history of AIDS-defining illness or severe symptoms of HIV infection regardless of the CD4 cell count.
- ◆ ART is also *recommended* for asymptomatic patients with a CD4 count of <200 cells/ μ L.
- ◆ Therapy *should be offered* to asymptomatic patients with CD4 counts of 201–350 cells/ μ L. The urgency of treatment recommendations may be based on various factors, including the following:
 - ◆ Rate of CD4 cell decline
 - ◆ Plasma HIV RNA >100,000 copies/mL
 - ◆ Patient's interest
 - ◆ Risk of toxicity
- ◆ Therapy should probably be *deferred* for asymptomatic patients with CD4 counts of >350 cells/ μ L and plasma HIV RNA <100,000 copies/mL.

The question of when to initiate ART in asymptomatic patients remains an area of research and debate. It is clear that ART should be initiated before the CD4 count declines to <200 cells/ μ L, if at all possible. However, it is not yet known at what CD4 threshold $\geq$ 200 cells/ μ L therapy should be started. Clinicians must weigh the anticipated benefits of immune reconstitution against the possible risks of ARV toxicity and the likelihood of emergent ARV resistance, in the individual patient. With the increasing availability of ARV regimens that are more tolerable, consist of fewer pills, and offer easier dosing schedules, many clinicians are choosing to initiate therapy earlier in the course of HIV infection.

Special Situations

- ◆ Pregnancy (see chapter *Care of HIV-Infected Pregnant Women*)
- ◆ Acute or primary HIV infection (see chapter *Primary HIV Infection*)
- ◆ Postexposure prophylaxis (see chapters *Occupational Postexposure Prophylaxis* and *Nonoccupational Postexposure Prophylaxis*)

Preparing the Patient for ART

Before starting ART, it is necessary to have a detailed discussion with the patient about his or her readiness to commit to a difficult, potentially toxic medication regimen, and to return for the required follow-up visits. The patient also must understand that the first treatment regimen offers the best opportunity for effective viral suppression, and immune reconstitution, which are the primary goals of ART.

Supporting Adherence

Numerous strategies are being tested for their effectiveness in supporting patients' adherence to the ART regimen. These may include extensive patient education, telephone contact with office staff members who can answer questions about adverse effects or other difficulties, family meetings, and peer support. Trust and accessibility appear to be important predictors of adherence, and some practitioners see the patient for 2 or 3 appointments before starting ART. Patients also may be given "test regimens" for a few weeks using inactive pills or mints, to help them understand how the medication schedule may fit into their lives before starting the actual ARVs. The choice to accept or decline ART ultimately lies with the patient (see chapter *Adherence*).

Anticipating Difficulties

Choosing an initial regimen that fits the patients' lifestyle and that is likely to be tolerable will improve the likelihood of long-term success with that regimen. If patients develop toxicities to 1 or more components of an initial regimen, substitutions typically can be made without limiting the success of the regimen. Close monitoring and "check-in" appointments allow these adjustments to be made under clinical supervision. Close monitoring also can help to identify medication toxicities that may limit treatment and to detect early signs of inadequate medication adherence; early intervention to treat adverse effects and to support adherence may increase the likelihood of treatment success.

Considerations in Regimen Selection

Regimens should be selected with consideration of both patient factors and medication factors. The patient's schedule, adherence history, and self-defined goals of ARV therapy should be considered in selecting

a regimen to which the patient will best adhere. The patient's comorbid conditions and potentially interacting medications should be evaluated for potential contraindications or synergism. The ARV history and any available resistance profiles should be reviewed carefully to choose a regimen that will be likely to achieve durable viral suppression. The CD4 cell count should be considered, especially if nevirapine will be used. In women who are pregnant or likely to become pregnant, ARV pregnancy categories and ARV teratogenicity should be taken into account. Table 9 of the *Adult and Adolescent ARV Guidelines* reviews the advantages and disadvantages of various drug classes and individual drugs in initial therapy.

Use of Multiple Classes of Drugs

For initial therapy, the *Adult and Adolescent ARV Guidelines* recommend the use of 2 nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Drug combinations that include only NRTIs generally do not reduce virus levels as effectively as 2-class combinations. The question of whether to use an NNRTI or a PI in initial therapy is a matter of debate. Some clinicians advocate using 2 NRTIs with an NNRTI to preserve the PI class for later and avoid PI-related toxicities. Others are more concerned about the potential toxicities of NNRTIs and their low genetic barrier to resistance and instead recommend starting with a PI-containing regimen. In the end, the regimen should be selected with the individual patient in mind because the only effective combination is the one that the patient is willing and able to take on a consistent basis. See the information on drug resistance and toxicities below as well as the full text of the *Adult and Adolescent ARV Guidelines* for more complete discussions.

Boosted Protease Inhibitors

Ritonavir may be used at low doses in combination with several other PIs to enhance or “boost” the serum level and prolong the half-life. This strategy generally decreases the dosing frequency and the number of pills required, and improves the activity of some PIs.

Preferred Starting Regimens

More than 20 ARVs in 4 drug classes have been approved by the FDA (see Tables 11, 12, and 13 in the *Adult and Adolescent ARV Guidelines*). In recent years, an

increasing number of fixed-dose combinations (FDCs) have become available to simplify dosing and reduce pill burden. These include 4 NRTI combinations:

- ◆ abacavir + lamivudine (Epzicom)
- ◆ abacavir + lamivudine + zidovudine (Trizivir)
- ◆ emtricitabine + tenofovir (Truvada)
- ◆ lamivudine + zidovudine (Combivir)

and 1 PI coformulation:

- ◆ lopinavir + ritonavir (Kaletra)

Also available is a 1-pill-per-day formulation of 2 NRTIs and 1 NNRTI:

- ◆ emtricitabine + tenofovir + efavirenz (Atripla).

The DHHS guidelines suggest “preferred” and “alternative” components for initial therapy (Table 1). Clinicians should note that these recommendations change over time as new data regarding efficacy or toxicity become available. In constructing a regimen with adequate potency (taking into account possible ARV resistance), drug selection should be guided by factors such as anticipated tolerability, pill burden, drug interactions, and the patient's comorbid conditions. Other agents or combinations may be appropriate in individual patients (see Table 6b of the *Adult and Adolescent ARV Guidelines*).

Avoiding Drug Resistance

ARV medications never should be given as single agents, in 2-drug regimens, in suboptimal regimens, or in lower doses than recommended because of the potential for development of resistance. High-level resistance to NNRTIs, as well as to emtricitabine and lamivudine, may develop quickly (ie, within days to weeks) in these situations. It may take longer for high-level resistance to develop with other NRTIs and PIs. Patients must be instructed to take the full dosage of all medications on schedule, and to avoid skipping doses or taking “days off” from their regimens. Careful medication dosing is important because resistance to 1 drug within a particular class may transfer to other drugs in the same class (cross-resistance). Cross-resistance can limit the options for future therapy significantly or require very complicated regimens in the future. Resistant viral strains, once developed, may be transmitted to other people.

Table 1. Initial Antiretroviral Regimens

Recommended Components of Initial ART					
To construct a regimen, choose 1 NNRTI or PI component from column A and 1 dual-NRTI combination from column B					
Column A: NNRTI or PI Options			Column B: Dual-NRTI Options		
Preferred Components	NNRTI • efavirenz ^a	or	PI • atazanavir + ritonavir • fosamprenavir + ritonavir (BID) • lopinavir/ ritonavir (BID)	+	Preferred Components • tenofovir/ emtricitabine ^b • zidovudine/ lamivudine
Alternative Components	NNRTI • nevirapine ^c	or	PI • atazanavir ^d • fosamprenavir • fosamprenavir + ritonavir (QD) • lopinavir/ ritonavir (QD)	+	Alternative Components • abacavir/ lamivudine • didanosine + (emtricitabine or lamivudine)

Key to abbreviations: ART = antiretroviral therapy; BID = twice daily; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside/nucleotide analogue; PI = protease inhibitor; QD=once daily.

a. Efavirenz is not recommended for use in the 1st trimester of pregnancy or in sexually active women with childbearing potential who are not using effective contraception.

b. Emtricitabine may be used in place of lamivudine and vice versa.

c. Nevirapine should not be initiated in women with CD4 cell count >250 cells/μL or in men with CD4 cell count >400 cells/μL because of increased risk of hepatotoxicity.

d. Atazanavir must be boosted with ritonavir if used in combination with tenofovir.

Adapted from U.S. Department of Health and Human Services. Table 6a. *Antiretroviral Components Recommended for Treatment of HIV-1 Infection in Treatment Naïve Patients*. In: *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10, 2006.

Acquired or “primary” resistance, in which a patient is infected with ARV-resistant virus, is common in parts of the United States. Because both multi- and single-class resistance has been found among drug-naïve persons in many U.S. cities, it is recommended that individuals with newly diagnosed HIV infection and those new to care should receive a baseline resistance test as early as possible, and before initiation of ART (see chapter *Resistance Testing*).

Drug Interactions

Many of the ARVs interact with one another as well as with other common medications. When starting or changing an ARV regimen, review all the patient’s current medications carefully for possible drug interactions. See chapter *Drug-Drug Interactions with HIV-Related Medications* for a summary of this issue and for references and resources to review medication lists and combinations. For further information on drug interactions involving ARVs, see Tables 20, and 22a-c, and 21a-b in the *Adult and Adolescent ARV Guidelines*.

Once-Daily Regimens

Convenient and simplified dosing is an obvious strategy to improve adherence, particularly with the availability of coformulations that reduce pill burden (see “Preferred Starting Regimens,” above). The *Adult*

and *Adolescent ARV Guidelines* currently include 2 once-daily combinations among “preferred” regimens, and list several other possibilities as “alternative” regimens.

The combinations indicated below (2 NRTIs + 1 NNRTI or PI) are likely to be effective in initial therapy (Table 2). Some of these combinations, however, have not been studied in clinical trials.

Table 2. Once-Daily Regimens for Initial Therapy

NRTI Combinations	NNRTI or PI
- Lamivudine or emtricitabine + abacavir - Lamivudine or emtricitabine + didanosine - Lamivudine or emtricitabine + tenofovir[#] - Didanosine + tenofovir^{*#}	- Efavirenz[*] - Nevirapine^{*^} - Atazanavir[#] - Atazanavir/ritonavir - Fosamprenavir/ritonavir - Lopinavir/ritonavir

Key to abbreviations: NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; PI = protease inhibitor.

* Didanosine + tenofovir should not be used with efavirenz or nevirapine.

^ Nevirapine is not FDA approved for once-daily dosing.

Tenofovir cannot be used with unboosted atazanavir. Adapted from Coffey S. *Options for Once-Daily Dosing of Antiretrovirals*. AETC National Resource Center Web site. Available at <http://aidsetc.org/aidsetc?page=et-03-00-01>.

Drugs and Drug Combinations That Should Not Be Used

Drugs with similar mechanisms of action and resistance mutations (eg, lamivudine and emtricitabine, or efavirenz and nevirapine) offer no significant advantage when combined and may increase toxicities. Drugs with additive or overlapping toxicities, such as stavudine and didanosine, should not be combined. Zidovudine and stavudine, which compete intracellularly and therefore cause antagonism, should not be used together. Most clinicians in the United States avoid using the NRTI stavudine if other options are available because of the high rate of metabolic abnormalities associated with that drug. Certain 3-drug combinations have suboptimal efficacy and are not recommended (eg, tenofovir + didanosine + NNRTI). Some ARVs require specific dosing intervals in particular patients. For example, once-daily dosing of lopinavir/ritonavir is not recommended in patients receiving concomitant efavirenz or nevirapine, and some once-daily PIs or combinations should not be used in treatment-experienced patients. For further information, see Table 7 and Table 8 of the *Adult and Adolescent ARV Guidelines*.

Follow-Up of Patients Starting ART

Patients who start a new ARV regimen should be seen at least twice within the first month to assess effectiveness, adherence, tolerability, and adverse effects of the regimen.

At 2 weeks on a new regimen, practitioners should check the following:

- ◆ CBC with platelets, especially for patients starting a zidovudine-containing regimen, to monitor for anemia
- ◆ LFTs, especially for patients starting a nevirapine-containing regimen, to monitor for hepatotoxicity

At 4-8 weeks on a new regimen, and every 3 months on a stable regimen, check the following:

- ◆ HIV viral load, to monitor initial virologic response to therapy
- ◆ CD4 cell count, to monitor initial CD4 response to therapy (note that CD4 response may lag behind virologic response)
- ◆ CBC with platelets (as above)
- ◆ LFTs (as above) and renal function tests

Patients should have glucose and lipid profiles (preferably when fasting) checked at baseline and, if normal, repeated every 4-6 months after starting ART. If the results are abnormal or if the patient has cardiac

risk factors, recheck every 3-4 months while on the regimen.

Regimen Failure

A treatment regimen may fail for several reasons.

Inadequate virologic response

- ◆ Viral load does not decline below the level of detection (<50-75 copies/mL, especially in patients taking initial therapy) within 6 months of initiating therapy. (In patients with previous treatment experience and in those with ARV resistance, it may not be possible to decrease plasma HIV viral load to undetectable levels, and stabilization of viral load below the previous baseline may be an appropriate goal of therapy.)

Virologic rebound

- ◆ Virus is repeatedly detected in plasma after initial suppression to undetectable levels. The degree of increase should be considered, however. Repeat testing is required to rule out “blips” of virus (isolated elevations in viral load of less than about 1,000 copies/mL) that are not clinically significant and to ensure that the increase is not due to infection, vaccination, or problems with test methodology.
- ◆ A reproducible, significant increase occurs in viral load, reaching 3-fold or greater from the lowest plasma HIV RNA level, that is not due to intercurrent infection, vaccination, or problems with test methodology.

Immunologic failure

- ◆ The CD4 cell count, measured on at least 2 separate occasions, shows a persistent decline.
- ◆ The CD4 cell count fails to increase by at least 25-50 cells/ μ L above baseline in the first year of ART.

Clinical deterioration or progression

- ◆ Recurrent, persistent, or new HIV-related illness occurs after at least 3 months on ART. Note that new or recurrent symptoms of opportunistic illness occurring in the first weeks to months after starting ART, especially in patients with severe immunosuppression, may not reflect a failure of ART. Rather, these symptoms could be due to persistence of severe opportunistic infections that may require longer treatment, or they could be due to an immune reconstitution syndrome (see chapter *Immune Reconstitution Syndrome*).

Responding to Apparent Treatment Failure

Refer to the *Adult and Adolescent ARV Guidelines* and consult with HIV-expert clinicians about the use of resistance testing and alternative regimens before discontinuing therapy.

Carefully assess patient adherence, because inadequate adherence to ARVs is a common reason for regimen failure. In some cases, adherence support, treatment of adverse drug effects, substitution for poorly tolerated ARVs, or other measures to enhance adherence may result in virologic suppression. In other cases, ARV resistance may have developed. Poor adherence may affect the decision to change therapy, and adherence issues should be addressed before a new regimen is initiated.

The availability of effective alternative ARVs is critical consideration in deciding whether or when to change therapies. If treatment possibilities are limited or nonexistent, it may be necessary to weigh the value of partial virologic suppression with the current regimen against the likelihood of further resistance. Consultation with an experienced HIV provider and use of HIV resistance testing are appropriate when considering changes in therapy. When no treatment options remain among currently approved drugs, refer the patient to an appropriate clinical trial if possible.

Susceptibility or Resistance Testing

It is fairly common for a first regimen to fail because of resistance to only 1 or 2 drugs in a multidrug combination (see chapter *Resistance Testing*). Resistance testing, although expensive and time consuming, can identify drugs that are less likely to be effective against the patient's virus. During resistance testing, the patient should still be taking the failing regimen so that resistant viral populations will be present in detectable numbers. Resistance testing is recommended before changing regimens because of virologic rebound during ARV therapy or suboptimal suppression of viral load on ARV therapy.

Cross-resistance exists among ARVs, such that resistance to 1 drug in a class of agents often extends to other agents in that class. For example, cross-resistance between efavirenz and nevirapine is almost complete, and resistance mutations to NRTIs and to PIs often decrease viral susceptibility to other drugs in those classes. As a result, selecting a new ARV regimen can be complicated because it requires knowledge of expected

resistance patterns. The likelihood of sustained viral suppression is lower when resistant virus is present even if a subsequent regimen contains new ARVs.

Guidelines for Changing an ARV Regimen for Suspected Drug Failure

The following recommendations are adapted from the *Adult and Adolescent ARV Guidelines*.

- ◆ Distinguish between the need to change a regimen because of drug intolerance or inability to adhere to the regimen and the failure to achieve the goal of sustained viral suppression. In the event of intolerance, single agents usually can be changed without resistance testing.
- ◆ In general, do not change a single drug or add a single drug to a failing regimen; it is important to use at least 2 or, preferably, 3 active drugs. If resistance testing (performed while the patient is taking the failing regimen) shows resistance to only 1 agent in a regimen, it may be possible to replace only that drug; however, this approach requires clinical validation.
- ◆ In general, the goal of ART is to suppress HIV RNA to undetectable levels, in order to improve or maintain immune function. This is increasingly possible even for patients with resistance to multiple drugs as new ARV agents and new classes of ARVs become available.
- ◆ However, many patients have limited options for new regimens that will achieve durable virologic suppression. In some of these cases it is rational to continue the same regimen if partial virologic suppression and clinical and immunologic stability were achieved.
- ◆ In some cases, it is reasonable to continue regimens identified as suboptimal for initial therapy in patients with limitations imposed by toxicity, intolerance, or nonadherence, especially in late-stage disease. Even when these patients fail to achieve durable viral suppression on these regimens, they may remain clinically stable, with stable CD4 cell counts. The risk of maintaining patients on a partially suppressive regimen, however, is the emergence of additional resistance mutations.
- ◆ Data are limited on the value of restarting a drug that the patient has previously received. Resistant virus can be archived and will reemerge for patients

who are rechallenged with regimens on which they had previously developed resistance. As a result, resistance tests from previous regimens should be used with current resistance tests to determine what drugs might be active in a new regimen.

- ◆ If virologic failure occurs on an NNRTI-containing regimen, avoid changing among NNRTIs because high-level cross-resistance is likely.
- ◆ The decision to change therapy and the choice of a new regimen require that the clinician have considerable expertise in the care of people with HIV infection. Those less experienced in the care of persons with HIV are strongly encouraged to obtain assistance by consulting with or referring to an expert clinician.

For a general strategy for selecting a new regimen after virologic failure of an initial regimen, see Table 25 in the *Adult and Adolescent ARV Guidelines*. Note that other possibilities exist, and resistance testing and expert consultation should be sought to help guide treatment choices.

Follow-Up of Patients Not Started on ART

Patients who may benefit from ART, but are not on therapy

These patients should continue their regular visits for monitoring, prophylaxis, and other medical treatment. Changes in laboratory results and the patients' condition should be taken as opportunities to reassess their decisions about ARVs, to educate them about new medications and research findings, and to discuss the risks of delayed treatment, including the risk of progression to AIDS or death. ARVs should be discussed again and offered at regular intervals to anyone who initially refuses treatment. If lack of readiness or probable adherence difficulties are issues, an adherence counselor (if available) or a mental health provider should be engaged to bolster the patients support and coping mechanisms (see the *Adult and Adolescent ARV Guidelines* or check tables in the chapter *CD4 Monitoring and Viral Load Testing*).

Patients who do not meet the DHHS criteria for starting ARVs

These patients should be monitored regularly with laboratory tests and physical examination (see Section 1, *Testing and Assessment* for chapters on physical examinations and laboratory tests), offered prophylaxis as appropriate, and reassessed for ARV therapy when they do meet the criteria for starting treatment.

Special Situations for ART

ART during acute or primary HIV infection

Patients with acute or primary HIV infection may experience symptoms such as rash, fever, lymphadenopathy, fatigue, weight loss, nausea, and headache within the first few weeks after becoming infected, and still have a negative or indeterminate result on the HIV antibody test. If a careful HIV risk history reveals the patient to be at significant risk for recent HIV infection, an HIV RNA test can be performed to ascertain whether viremia is present. (Note that a low viral load may suggest a false-positive result.) It is not yet known whether ART has a long-term benefit when started during primary HIV infection. However, for the appropriate patient, it is reasonable to consider starting therapy, with the goal of maximal virologic suppression. Before starting an ARV regimen, patients must be counseled carefully about potential limitations, such as toxicity, pill burden, cost, and the possible development of drug resistance. Patients should be monitored with HIV viral load, CD4 counts, and other parameters, as in patients with established infection who are taking ARV therapy. Because no definitive data exist on the clinical benefit of early treatment and because ART involves certain risks, including drug toxicity and resistance, persons with acute HIV infection ideally should be treated in controlled clinical trials. (See chapter *Primary HIV Infection*.)

Pregnant women

Since 1994, zidovudine has been recommended to reduce the risk of mother-to-child transmission of HIV, but zidovudine monotherapy is less effective than combination therapy in reducing perinatal transmission and is inadequate for treatment of the pregnant woman. Combination ARV regimens are now used during pregnancy, if possible, to reduce the risk of transmission to the infant and to treat HIV infection in the mother. Certain ARVs are recommended during pregnancy, whereas others should be avoided. Because of potential teratogenic effects, efavirenz should not be used. (See chapters *Reducing Maternal-Infant HIV Transmission* and *Care of HIV-Infected Pregnant Women*; also refer to the *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. October 12, 2006. Available online at <http://aidsinfo.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9>.)

ARV treatment in resource-limited settings

The discussion of ARV management is futile for the majority of people in the world today who are living with HIV/AIDS. According to the Joint United Nations Programme on HIV/AIDS, as of June 2005, only 11% of those needing ARV therapy in low- and middle-income countries were receiving treatment.

ARV medications are becoming available in many parts of the developing world, but the increase in availability is slow and in no way is occurring at the pace and with the efficiency warranted in this dire situation. Medication choices are limited by the availability and cost of drugs. Most resource-limited countries that are able to provide ARVs use an NNRTI-based combination for initial therapy. This regimen typically includes nevirapine or efavirenz plus 2 NRTIs such as zidovudine or stavudine plus lamivudine. Second-line therapies or substitutions needed because of toxicities or intolerance often are not readily available.

Widespread use of nevirapine to prevent mother-to-child transmission of HIV has lowered the rate of HIV transmission to infants, but the drug resistance that may emerge after even single-dose administration to the mother during labor has raised many concerns regarding effective treatment options for the mother. Without the availability of resistance testing, many women are subsequently started on an ARV regimen that includes an NNRTI. For women who have developed NNRTI resistance during previous nevirapine exposure, these regimens probably will be ineffective. In addition, NRTI resistance is likely to develop, further limiting treatment options.

Concern about adherence in resource-limited settings, although often cited as a treatment-limiting factor, has proven to be less of an issue than it is in the United States and western Europe. Many treatment programs require a lengthy educational process before ARVs are initiated. In addition, the limited availability of treatments paired with the widespread devastation of entire communities and countries has enhanced the motivation for strict adherence to therapies among patients able to acquire ARV therapy.

CD4 count and viral load testing to identify patients who should begin ART, and to monitor ARV effectiveness and potential drug toxicities, are severely limited by the lack of sufficient laboratories, equipment, and funds to perform costly blood tests. In some settings, patients are started on therapy based on clinical presentation alone, and monitoring is based solely on

clinical criteria. Success of treatment may be assessed by clinical response, such as resolution of opportunistic infections, weight gain, and improvements in quality of life. ARV toxicity may be assessed by clinical signs and symptoms of adverse effects such as anemia or hepatitis.

Comorbid conditions such as tuberculosis and malaria, and potential drug interactions associated with their treatments, often complicate therapy choices. Competing priorities of poverty, lack of clean water or sanitation, and overburdened health care settings and health care providers combine to complicate the distribution of effective ARV treatment. Regardless of the numerous challenges to treatment in resource-limited settings, human compassion and responsibility dictate that we find a way to provide care for those who require treatment.

Expert Consultation

The National HIV/AIDS Clinicians' Consultation Center (NCCC) is a valuable resource for any clinician seeking expert advice about ART, HIV clinical manifestations, laboratory evaluations, and other issues. Its National HIV Telephone Consultation Service (Warmline) is staffed by HIV-experienced physicians and pharmacists. The Warmline operates Monday through Friday, 8 AM to 8 PM EST and is available free of charge in the United States at 800-933-3413.

Patient Education

- ◆ Starting ARVs is rarely an emergency. Before starting ARVs, health care providers must work with patients to determine how important therapy would be for them, what goals of therapy are likely to be achieved, and which personal issues are pertinent for selecting the best regimen to fit their lifestyles.
- ◆ Providers should review the proposed drug regimen with their patients. Be sure patients understand the instructions about dosage, scheduling, food requirements or restrictions, drug storage, adverse effects, toxicities, and type of reactions that must be reported immediately, as well as remedies for common adverse effects.
- ◆ Providers should explain to patients that ART requires a commitment to taking the medications precisely as prescribed. There is a limited number of ARVs, and if they are taken incorrectly, the virus can quickly become resistant to the medications. This will mean even fewer choices and less effective treatment in the future. It might also mean that they

could transmit resistant virus to a partner or, if they are pregnant, to an infant.

- ◆ Patients should know that HIV medications do not prevent transmission of infection to others. Safer-sex recommendations must be followed and other high-risk activities (eg, needle sharing) must be carefully avoided to keep from spreading the virus to others (see chapter *Preventing HIV Transmission/Prevention with Positives* for more information).
- ◆ Experts recommend using latex barriers during sex (safer sex) and not sharing needles or other drug-using equipment, even with other HIV-infected persons. Patients should know that if their virus develops resistance to some ARVs and they pass that virus on to another person, HIV medications may not be effective in that person. If a patient's partner happens to have a drug-resistant strain of HIV, it is possible for the patient to become infected with a resistant virus in addition to the one he or she has already, and this may limit treatment options.
- ◆ Hepatitis C, hepatitis B, and other sexually transmitted infections such as syphilis and gonorrhea can be transmitted between partners who both have HIV.
- ◆ If ARVs must be discontinued, it is usually best to stop all ARVs at once. The exception to this recommendation may be NNRTI-containing regimens; in this case, the NRTIs should be continued for about 1 week after discontinuation of the NNRTI, if possible. Even carefully managed interruptions can cause drug resistance mutations. Again, this will limit future treatment options, and should be avoided if possible.
- ◆ Discuss contingencies in the event that the client is unable to take ARVs for a day or more (eg, illness, severe adverse effects, hospitalization, or other unexpected circumstances).

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Adherence

Background

For HIV-infected patients treated with antiretroviral therapy (ART), adherence to ART is a significant determinant of survival. Adherence is second only to the CD4 cell count as a predictor of progression to AIDS and death. Adherence rates approaching 100% are needed for optimal viral suppression, yet the average adherence rate to ART in the United States is approximately 70%. Patients with suboptimal adherence are at risk not only for HIV progression, but also for the development of drug resistance (see chapter *Resistance Testing*). Studies indicate that health care providers' assessments of their patients' adherence often are inaccurate and limited, so individualized assessment and planning for adherence are essential for patients to be successful with ART.

S: Subjective

Adherence assessment is most successful when conducted in a positive, nonjudgmental atmosphere. Patients need to know that their provider understands the difficulties associated with taking an antiretroviral (ARV) regimen. Within a trusting relationship, a provider may learn what is actually happening with the patient's ARV medication regimen rather than what the patient thinks the provider wants to hear. Important questions to ask a patient who is considering ART may be found in Table 1. Table 2 suggests important questions for patients who are receiving ART.

Common reasons for nonadherence include the following: experiencing adverse effects, finding the regimen too complex, having difficulty with the dosing schedule (not fitting into the daily routine), forgetting to take the medications, being too busy with other things, oversleeping and missing a dose, being away from home, not understanding the importance of adherence, and being embarrassed to take medications in front of family, friends, or coworkers. It is important to look for these and other potential barriers to adherence. (See chapter *Initial History*.)

O: Objective

Evaluate the following:

- ◆ CD4 cell count
- ◆ HIV viral load (indicating the effectiveness of ART in suppressing viremia; an indirect indicator of adherence)
- ◆ Current drug list (including over-the-counter medications, vitamins, and herbal remedies); check for adverse drug interactions with ARV medications
- ◆ Pharmacy refill records

A: Assessment

Assess adherence at each visit using questions such as those in Tables 1 and 2, and assessment scales such as those found in Tables 4, 5, and 6 (Appendix 1). Ask these questions in a nonjudgmental way and listen carefully to the patient to invite honesty about issues that may affect adherence.

Table 1. Important Questions to Ask Patients Considering Antiretroviral Therapy

- What is your attitude toward antiretroviral therapy?
- Do you believe that antiretroviral therapy is effective?
- What do you hope these medications will do for you?
- Are you ready to take the medication every day, around the same time each day?
- Are you committed and motivated to take the medication every day for the rest of your life?
- Who knows about your HIV status?
- What other medications are you taking: prescription, over-the-counter, herbals?
- Are you a morning or afternoon person?
- What is your daily routine, including waking and bed times?
- How many meals and snacks do you eat per day, and at what times?
- Do you use alcohol, marijuana, cocaine, or injectable drugs? If so, how much do you use and how long have you used them?

Table 2. Important Questions to Ask Patients Taking Antiretroviral Therapy

- Do you manage your own medications? If not, who manages them for you?
- What HIV medications do you take and what is their dosage? When do you take these?
- How do you remember to take your medications?
- How many doses of your HIV medication have you missed in the last 72 hours, last week, last 2 weeks, and last month?
- On a scale of 1 to 10, where would you say you are? A score of 1 indicates that you do not take your medicines right at all; for example, not every day or not at the same time every day; 10 indicates that you take your medications perfectly every day, at the same time every day. (Visual analog scales are also used to assess adherence; see Appendix 1.)
- If not a 10, what causes you not to be a 10?
- When are you most likely to miss doses?
- Do you have any adverse effects to from your HIV medications? If so, what are they?
- Are you comfortable taking medications in front of others?
- What is most difficult about taking your medications?
- How do you like working with your pharmacy?

The patient's self-report has been shown to be the most effective measure of adherence. Although, according to some studies, self-report of good adherence has limited value as a predictor of good adherence, self-report of suboptimal adherence should be regarded as a true predictor of poor adherence.

Before initiating (or changing) ART, it is important to assess the patient's readiness for ART. Patient factors that have been associated with poor adherence in the United States and western Europe include:

- ◆ Depression
- ◆ Active alcohol or drug use
- ◆ Low literacy
- ◆ Lack of social support
- ◆ Lack of belief in treatment efficacy
- ◆ Unstable housing
- ◆ Competing priorities
(eg, housing, childcare, food, work)

Most of these factors are modifiable. Before starting ART, appropriate interventions should be made, and sources of adherence support should be identified to help patients overcome potential barriers to adherence.

It is important to note that sociodemographic variables

such as sex, HIV risk factors, and education level generally are not associated with adherence. In addition, a history of substance or alcohol abuse is not a barrier to adherence.

Assess the patient's support system, and ask who knows about the patient's HIV status. Supportive family or friends can help remind patients to take their medications and assist with management of adverse effects. For patients who have accepted their HIV infection as an important priority in their lives, taking medications can become routine despite other potential adherence barriers such as alcohol or drug use.

Assess patients' willingness to accept and tolerate common adverse effects of ART. Patients may identify some adverse effects that they wish to avoid completely and others that they are willing to accept and manage; this may help in tailoring the selection of ARV medications to the individual patient. Describe strategies for the management of adverse effects before starting a regimen (see chapters *Patient Education* and *Adverse Reactions to HIV Medications*).

Before prescribing ARVs, some clinicians have their patients do adherence trials using placebo tablets or jelly beans to measure the patients' readiness to start therapy and their ability to adhere to a regimen. This trial allows patients to experience what a regimen will entail in real life, how therapy will affect their daily lifestyle, and what changes will be needed to accommodate the regimen. The shortcoming of placebo trials is that patients are not challenged with adverse effects as they might be with a true regimen.

For patients taking ART, it is important to assess adherence at every clinic visit. Tools such as those in Appendix 1 may be useful in predicting adherence. Adverse effects are a common cause of suboptimal adherence to ART. Continue to ask whether the patient has adverse effects from the ARV medications and assess his or her ability to accept and tolerate these. Work closely with the patient to treat adverse effects, and consider changes in ART if adverse effects are not tolerated. Continue to offer support to improve or maintain optimal adherence.

P: Plan

Start the ARV regimen only when the patient is ready. Starting it too early may result in poor adherence, failure of the regimen, and increased risk of ARV resistance. Comorbid conditions that interfere with

adherence, such as mental health issues or depression, must be treated initially. It is important to consider the patient's preferences in selecting the drug regimen. The regimen must fit into the patient's daily routine, and the patient must believe in the potential success of ART. Simplifying the ARV regimen to the extent possible with once-daily regimens and the lowest number of pills, while maintaining efficacy and minimizing adverse effects, is important for maximizing adherence and avoiding pill fatigue. Starting ART is rarely an emergency, so taking time to identify the patient's wishes for care, make a thorough readiness assessment, select the ARV regimen, and plan for adherence support is important in maximizing the likelihood of treatment success. (See Table 3 for additional suggestions.)

Table 3. Strategies to Improve Adherence to Antiretroviral Therapy

- Establish readiness to start therapy
- Provide education on medication dosing
- Review potential adverse effects
- Anticipate and treat adverse effects
- Utilize educational aids including pictures, pillboxes, and calendars
- Engage family, friends
- Simplify regimens, dosing, and food requirements
- Utilize team approach with nurses, pharmacists, and peer counselors
- Provide accessible, trusting health care team

Source: U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Table 16. October 10, 2006. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7>. Accessed July 7, 2007.

Patients who can identify their medications (in their own words) and describe the proper dosing and administration have higher adherence rates. Providing patient education before writing a prescription helps ensure adherence to ARV medications. Education can be provided in oral, written, or graphic form to assist the patient's understanding of the medications and their dosing. Basic information, including number of pills, dosages, frequency of administration, dietary restrictions, possible adverse effects, tips for managing adverse effects, and duration of therapy will help patients to understand their ARV regimens. Patients should understand that the success of ART depends upon taking the medications every day and that adherence levels of >95% are important in preventing virologic failure.

Close follow-up by telephone, clinic visits, or other contact with the patient during the first few days of

therapy is useful in identifying adverse effects, assessing the patient's understanding of the regimen, and addressing any concerns before they become significant adherence barriers. Individualized interventions should be designed to optimize outcomes for each patient. Pharmacists, peer counselors, support groups, adherence counselors, behavioral interventions, and community-based case managers are useful in supporting adherence for the HIV-infected patient. Multidisciplinary teams that include nurses, case managers, nutritionists, and pharmacists, in which each care provider focuses on adherence at each contact with the patient, are extremely effective in supporting adherence.

Many physical devices can be used to support adherence. The following are simple, inexpensive, and easy to incorporate into the routine of the HIV patient:

- ♦ Medication organizers include pillboxes and medisets. These are available in several shapes and sizes to fit the needs of the individual patient. They can be filled weekly so that the patient can easily determine whether a dose of medication was missed.
- ♦ Reminder devices include alarm watches, beepers, or cell phone alarms. They are effective in reminding the patient when to take medications. Medication diaries may be used for the patient to record doses that were taken.
- ♦ Visual medication schedules: are calendars with pictures of the patient's medications on them to remind the patient to take the doses.

Interventions for successful adherence are an ongoing effort, not one-time events. Studies have suggested that adherence rates decline when patient-focused interventions are discontinued. Therefore, positive reinforcement at each clinic visit or contact is extremely important. Reinforce what the patient has done well and assist the patient in identifying and problem-solving areas for improvement. Whenever possible, share positive information about the patient's health, such as improvements in quality of life, CD4 cell count, and viral load, to encourage a high level of adherence.

Special Populations and Issues

Mental Illness

Patients with mental health issues may have difficulty with adherence. In this population, it is particularly important to incorporate ARV medications into structured daily routines. Medication cassettes, reminder

signs, and calendars have been very effective for these patients. Nursing care providers and family members may be instrumental in filling medication boxes or ordering prescription refills.

Pediatrics

Adherence can be a challenge for young children who rely on parents and caregivers to provide their medications. Adolescents are more likely than younger children to have poor adherence. To improve adherence in this population, it is important to support the family. The *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection* review some of the adherence issues and considerations for this patient population.

Low Literacy

Health literacy is an important predictor of treatment adherence, particularly in low-income populations. Adherence interventions are necessary in this population to accommodate individuals who have difficulty reading and understanding medical instructions. Providers often fail to recognize this disability. In addition, adherence support is needed for patients who have difficulty navigating the health care system.

Resource-Limited Settings

Early research has shown that the level of adherence in resource-limited countries is at least as good as that in resource-rich settings and that rates of virologic suppression are equivalent or better. Lack of access to a consistent supply of ARV medications, including financial barriers that may cause interruptions in treatment, appears to be the primary obstacle to adherence in resource-limited settings.

Patient Education

- ◆ Providers must urge patients to take their ARV medications exactly as prescribed and to take every dose, every day.
- ◆ Patients must know that if they miss or skip doses of their ARV medications, they may not work well to fight HIV, and the virus may develop resistance to them.
- ◆ Tell patients to notify the clinic if they miss doses of their ARV medications.

- ◆ Discuss with patients how to improve their adherence, and support good adherence.
- ◆ Warn patients that some people have adverse effects from the medications, and tell them to notify the clinic if they develop adverse effects. Discuss ways to reduce these effects.

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Appendix 1. Scales to Assess Adherence to HIV Medication Regimens

Table 4. Visual Analog Scale Used in a Research Study to Assess Adherence to HIV Medication Regimens

Script for Interviewing Patient about Adherence	
Interviewer	Now I'm going to ask some questions about your HIV medications. Most people with HIV have many pills or other medications to take at different times during the day. Many people find it hard to always remember to take their pills or medicines. For example: • Some people get busy and forget to carry their pills with them. • Some people find it hard to take their pills according to all the instructions, such as "with food" or "on an empty stomach," "every 8 hours," or "with plenty of fluids." • Some people decide to skip taking pills to avoid adverse effects or to just not take pills that day. We need to understand what people with HIV are really doing with their pills or medicines. Please tell us what you are actually doing. Don't worry about telling us you don't take all your pills or medicines. We need to know what is really happening, not what you think we "want to hear." Which antiretroviral medications have you been prescribed to take within the last 30 days?
INTERVIEWER: LIST CODES FOR ALL ANTIRETROVIRALS THAT SUBJECT WAS PRESCRIBED TO TAKE IN LAST 30 DAYS. IDENTIFY UP TO 4 DRUGS.	
	DRUG A:
	DRUG C:
	DRUG B:
	DRUG D:
Interviewer	Now, I am going to ask you some questions about these drugs. Please put an "X" on the line below at the point showing your best guess about how much (DRUGS A-D) you have taken in the last 3-4 weeks. We would be surprised if this were 100% for most people.
HAND INSTRUMENT AND PEN TO RESPONDENT	
Interviewer	0% means you have taken no (DRUG A) 50% means you have taken half your (DRUG A) 100% means you have taken every single dose of (DRUG A)
Adherence Self Assessment Instrument	
Instructions for Patient:	Put an "X" on the line below at the point showing your best guess about how much of each drug you have taken in the last 3 to 4 weeks. 0% means you have taken none of the drug 50% means you have taken half of the drug 100% means you have taken every single dose of the drug
DRUG A:	0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% -----
DRUG B:	0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% -----
DRUG C:	0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% -----
DRUG D:	0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100% -----

Adapted from Machtinger EL, Bangsberg DR. *Adherence to HIV Antiretroviral Therapy*. HIV InSite, May 2005. Available online at hivinsite.ucsf.edu. Accessed June 1, 2006.

Table 5. Morisky Scale to Assess Adherence to HIV Medications: Dichotomous Response Options

Subjects were asked: “Thinking about the medications PRESCRIBED to you by your doctor(s), please answer the following questions.”		
	NO	YES
Do you ever forget to take your medications?		
Are you careless at times about taking your medications?		
When you feel better, do you sometimes stop taking your medications?		
Sometimes, if you feel worse when you take your medications, do you stop taking them?		

Adapted from Morisky DE, Green LW, Levine DM. *Concurrent and predictive validity of a self-reported measure of medication adherence.* Med Care 1986;24: 67-74.

Table 6. Morisky Scale to Assess Adherence to HIV Medications: 5-Point Response Options

Subjects were asked: “Thinking of the medications PRESCRIBED to you by your doctor(s), please answer the following questions.”					
Response options: never = 0; rarely = 1; sometimes = 2; often = 3; always = 4					
	0	1	2	3	4
Do you ever forget to take your medications?					
Are you careless at times about taking your medications?					
When you feel better, do you sometimes stop taking your medications?					
Sometimes, if you feel worse when you take your medications, do you stop taking them?					

Adapted from Morisky DE, Green LW, Levine DM. *Concurrent and predictive validity of a self-reported measure of medication adherence.* Med Care 1986;24: 67-74.

Resistance Testing

Background

As of mid 2006, 2 major types of resistance testing are available: genotype tests and phenotype tests.

Genotype Tests

Genotypic testing works by amplifying and sequencing HIV taken from a patient to look for mutations in the HIV reverse transcriptase and HIV protease genes, which are known to correlate with clinical resistance to antiretroviral drugs. This test generally can detect mutations in plasma samples with HIV RNA levels >1,000 copies/mL. Species representing 20% or more of the amplified product usually can be detected by current techniques. Minor species may not be detected. Resistance mutations acquired in the past, under the selective pressure of a previous drug, may be archived in minor species and remain invisible to genotypic testing. These resistance mutations may reemerge and cause drug failure, however, if the previous drug is used again.

A genotype test takes 1-2 weeks to complete. The results are reported as a list of the mutations detected; most reports also include an interpretation that indicates the drug resistance likely to be conferred by those mutations (see “Modifying Factors” below, for a discussion of the limitations of resistance testing).

Genotype results can be difficult to interpret. A thorough antiretroviral history and expert clinical review, therefore, are necessary to put the results of a genotype test in proper perspective and to identify options for further treatment. A compilation of the most common HIV mutations selected by the 3 classes of antiretroviral agents is available at: <http://hiv-web.lanl.gov>.

A “virtual phenotype” is a genotype that is compared with a databank of patients’ samples that have been analyzed by paired genotype and phenotype testing. The patient’s genotype is matched to a banked genotype, and the patient’s phenotype is then predicted based on the phenotypes paired to the banked genotype. A virtual phenotype can be completed in the same amount of time as a genotype. Results are reported as a genotype (listing the mutations detected) as well as a predicted fold change in the 50% inhibitory concentration (IC₅₀) of each drug to the patient’s virus (see “Phenotype

Tests” below). The predicted susceptibility of the patient’s virus to each drug is then reported, based on biologic and clinical cutoffs.

Phenotype Tests

Phenotypic testing works by splicing the HIV reverse transcriptase and HIV protease genes from a patient’s virus into a standardized laboratory strain, which is then grown in the presence of escalating concentrations of antiretroviral drugs. The test measures the IC₅₀ of each drug against the virus in vitro. Results are reported as fold-change in IC₅₀, as compared with a drug-susceptible control strain or with a previous test of the same patient’s blood. The predicted susceptibility of the patient’s virus to each drug is then reported, based on what is known about the correlation between fold-change in IC₅₀ of that drug and clinical resistance. As with genotypic testing, the phenotype may not be able to detect resistance if the HIV RNA is low (<1,000 copies/mL) and may not detect minor species. A thorough antiretroviral history and expert interpretation are essential in determining the significance of the results. A phenotype takes 2-3 weeks to complete.

Modifying Factors

Table 1 presents an overview of when genotype and phenotype testing is, and is not, recommended.

Limits of Resistance Testing

In a patient taking antiretroviral therapy (ART), drug-resistant HIV evolves in response to selective pressure applied by the antiretroviral drugs in the patient’s system. Specific resistance mutations develop in response to the pressure exerted by specific drugs (M184V, for example, evolves in response to lamivudine or emtricitabine). The presence of viral resistance suggests that a particular drug (and drugs with similar resistance patterns, or cross-resistance) is unlikely to be successful in suppressing viral replication.

In contrast, the absence of resistance to a drug does not necessarily indicate that the drug will be successful, particularly if that drug (or drugs sharing cross-resistance) has been used previously. If a particular

Table 1. Resistance Testing Recommendations

Clinical Setting/Recommendation	Rationale
Recommended	
Acute or primary HIV infection, if treatment is to be started	- Determine whether drug-resistant virus was transmitted, to help design an initial regimen or to change a regimen accordingly. - Consider resistance testing in all, even if treatment is deferred.
Chronic HIV infection before starting ART	- Determine whether drug-resistant virus was transmitted to help design an initial regimen. - Transmitted drug-resistant virus is more likely to be detected earlier in the course of HIV infection; consider resistance testing early.
Virologic failure during ART	Determine the role of resistance in drug failure and maximize the number of active drugs in the new regimen, if indicated.
Suboptimal suppression of viral load after starting ART	Determine the role of resistance and maximize the number of active drugs in the new regimen, if indicated.
Not Usually Recommended	
After discontinuation of drugs	Drug resistance mutations may decrease in number and become undetectable on assays.
Plasma viral load <1,000 HIV RNA copies/mL	Resistance assays may not be reliable because of the low number of RNA copies.

Key to abbreviations: ART = antiretroviral therapy.

Source: U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7.

drug is discontinued, the viral strains harboring the mutations that confer resistance to that drug may decrease below the threshold of detection by the resistance assay, so the resistance test may not reveal certain resistance mutations. In such situations, minority populations of resistant viruses may exist in reservoirs and may emerge rapidly under selective pressure if that drug is restarted, or if drugs with similar or overlapping resistance patterns are used. The implications of archived mutations are 2-fold: 1) Resistance tests are most reliable while the patient is still on the failing regimen; and 2) resistance testing should be interpreted in the context of both the drugs that the patient was taking at the time of the test and the drugs that the patient had been exposed to previously (ie, the patient's antiretroviral history).

Antiretroviral-Naive Patients

In treatment-experienced patients, as indicated above, resistance testing is most reliable when performed while the patients are still taking the failing antiretroviral medications. In treatment-naive patients, resistance testing may reveal resistance mutations that were acquired at the time of infection, through infection with a strain of HIV that had already developed antiretroviral resistance. Current guidelines recommend genotypic testing in recently infected patients and in antiretroviral-naive, chronically infected patients before

initiation of therapy. Many experts suggest testing as early as possible in the course of HIV infection, to increase the likelihood of detecting transmitted mutations. The rationale for resistance testing in antiretroviral-naive patients is 2-fold: 1) The incidence of primary resistance is rising, particularly in locations with a high prevalence of persons taking ART; and 2) unknowingly starting a patient on antiretroviral medications to which his or her virus is already resistant may risk failure of the initial regimen, rapid acquisition of additional resistance mutations, and curtailment of future treatment options.

Using Genotype and Phenotype Tests at the Same Time

Genotype and phenotype tests have a few complementary properties that may, in some circumstances, make it desirable to use both tests at the same time. This strategy is especially advantageous when trying to devise a regimen for patients who have been exposed to many antiretroviral agents and have few remaining treatment options, and for whom the development of additional resistance could be particularly dangerous. For example, early mutations may appear on a genotype before detectable increases in inhibitory concentrations, and these would not be detected on a phenotype. Phenotypic testing can detect loss or gain of drug efficacy caused by complex interactions of mutations that, by themselves, would not be predictive.

Resistance Testing in Patients with Virologic Failure

As discussed in the chapter *Antiretroviral Therapy*, factors other than nonadherence and resistance may cause failure of ART; these include drug-drug interactions and malabsorption. Therefore, before assuming that drug failure is due to resistance and ordering a resistance test, it is important to assess the causes of antiretroviral regimen failure. If resistance is still suspected after assessing all possible causes, resistance testing should be done while the patient is taking the failing regimen, for the reasons noted above.

Key Points

- ◆ There are 2 major types of resistance testing currently available: genotype and phenotype tests.
- ◆ In general, a patient's viral load must be at least 1,000 copies/mL for either test to be reliable.
- ◆ Both genotypic and phenotypic testing can detect resistance only if it exists in at least 20% of the viral species present in a patient (known as the dominant species). Minor species may harbor resistance that remains undetected by either test.
- ◆ Resistance tests are most reliable when performed while a patient is still taking a failing regimen, or within 4 weeks after stopping. Neither test predicts which drugs will be active in a particular patient, only drugs that are not likely to be active. Nevertheless, studies comparing the use of resistance testing to expert opinion alone have shown that resistance testing can improve virologic control of HIV. Most treatment guidelines recommend resistance testing in certain circumstances.

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Reducing Maternal-Infant HIV Transmission

Background

In the absence of antiretroviral (ARV) prophylaxis or other interventions, the rate of mother-to-child transmission (MTCT) of HIV in the United States ranges from 16% to 25%. Certain interventions, notably antiretroviral therapy (ART), are highly effective in reducing the risk of perinatal transmission of HIV. ART and may reduce the transmission rate to as low as 1.5% in selected groups. Pregnant women with HIV infection who wish to carry their pregnancies to term should be educated about the risks of perinatal HIV transmission and offered appropriate medical management and ARV medications to maintain or improve their own health and to reduce the risk of HIV transmission to their infants.

This chapter describes strategies to reduce the risk of MTCT of HIV and presents information on HIV testing during pregnancy. It is not intended to be a comprehensive discussion of these topics, and all HIV-infected pregnant women should be treated by an HIV-experienced obstetrician and an HIV specialist. For centers that do not have HIV specialists available, experts at the National Perinatal HIV Consultation and Referral Service Perinatal Hotline (888-448-8765) are available for consultation. For more information on caring for pregnant women, see chapter *Care of HIV-Infected Pregnant Women*.

Overview of Prevention of Perinatal HIV Transmission

In 1994, an interim analysis of Pediatric AIDS Clinical Trial Group study 076 (PACTG 076) found that ARV treatment during pregnancy could significantly reduce the risk of HIV transmission to the infant. Pregnant women in the intervention group took zidovudine (ZDV) orally during the last weeks of pregnancy, received it intravenously during labor and delivery, and gave it to their newborns for 6 weeks. Only 7.6% of those infants were infected with HIV, compared with 22.6% of infants whose mothers in the control group did not receive ZDV. ART for pregnant women with HIV infection rapidly became the standard of care in the United States and other high-income countries. A task force of the U.S. Public Health Service (USPHS) issued recommendations in August 1994 for the use

of ZDV for the reduction of perinatal transmission. Those recommendations were expanded to include guidelines for the medical management of pregnant women with HIV infection, including ARV treatment during pregnancy, as well as recommendations regarding other interventions that can further decrease transmission risk, such as cesarean section. The USPHS task force now meets regularly to review and update these guidelines as new research is published and new ARV drugs are approved. These guidelines, the *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States* are available online and in print (see “References” below).

Studies subsequent to PACTG 076 in resource-limited countries as well as resource-abundant areas found that other ARV regimens also reduced the risk of HIV transmission from mother to infant. The Petra study, a placebo-controlled trial in a breast-feeding population in Uganda, South Africa, and Tanzania, found a transmission rate of 9% among women who received oral ZDV plus lamivudine (3TC) intrapartum and for 1 week postpartum and whose infants also received 1 week of ZDV/3TC, compared with a rate of 15% in the placebo group. The HIV NET 012 trial in a breast-feeding population in Uganda compared the efficacy of a single dose of nevirapine (NVP) given to the mother at the onset of labor plus a single dose given to the newborn 48 hours postpartum with oral ZDV given to the mother during labor and to the newborn. The transmission rate was 9% in the NVP arm compared with 21% in the ZDV arm. The results of this study and the low cost of NVP led a number of resource-limited countries to institute NVP prophylaxis as the standard of care for preventing MTCT of HIV. Numerous other trials have demonstrated the efficacy of various ARV strategies, combining different ARVs with different treatment durations, and given to mothers, newborns, or both, in both breast-feeding and non-breast-feeding populations. Some trials have suggested that even late ARV interventions may decrease the infant’s risk of HIV infection. A retrospective study of subjects in New

York found that the rate of perinatal HIV transmission was 9.3-10% if ZDV was given to both the mothers intrapartum and their newborns or only to the newborn, compared with 26.6% if no ARV medication was given. This study supports the importance of offering ARV interventions to pregnant women with HIV infection whenever they are identified.

In the United States, the PACTG 076 regimen remains the standard of care for preventing perinatal HIV transmission, and usually is incorporated into combination ARV therapy for pregnant women. For international settings, other guidelines have been developed by global agencies such as the World Health Organization (see “References” below) and by individual governments.

Unless otherwise referenced, the information in this chapter is based on the most recent USPHS perinatal guidelines available at the time this chapter was written. The reader should consult the AIDSInfo Web site (<http://aidsinfo.nih.gov>) for the most current recommendations.

HIV Testing during Pregnancy

The success of interventions to reduce the risk of perinatal HIV transmission has underscored the importance of HIV testing and counseling of all pregnant women. Interventions to interrupt transmission can be effective only if women know their HIV status and can access treatment. The USPHS first recommended universal HIV counseling and testing for pregnant women in 1995. Many nationwide professional and governmental organizations, including the American Academy of Pediatrics, the American College of Obstetricians and Gynecologists, and the U.S. Preventive Services Task Force, have endorsed those recommendations. Current recommendations from the U.S. Centers for Disease Control and Prevention (CDC) urge 3 approaches to HIV testing during pregnancy:

- ♦ An “opt-out” approach to HIV testing during pregnancy, whereby a pregnant woman is tested unless she specifically declines testing
- ♦ Routine testing with a rapid HIV test for women with unknown or undocumented HIV status who present in labor, in order to offer those testing HIV positive ARV prophylaxis during labor
- ♦ Rapid HIV testing for newborns of mothers of unknown HIV status so that they can receive postexposure ARV prophylaxis, if indicated.

State laws regarding HIV testing during pregnancy vary widely, and many are under review. Clinicians should be familiar with their state laws regarding HIV testing during pregnancy, opt-out or consent provisions, and regulations about rapid HIV testing during the intrapartum or newborn period.

HIV Education and Counseling of Pregnant Women

Educating pregnant women about the importance of HIV testing is a critical element in preventing perinatal HIV transmission. However, extensive pretest counseling is not essential. A woman must be told that HIV testing is a standard part of prenatal care, that the clinician recommends the tests, and that all pregnant women should be tested for HIV because knowing about HIV infection is important for their health and the health of their babies. Research has shown that a provider’s strong endorsement of HIV testing is a major predictor of whether a woman receives an HIV test. Testing should be voluntary and free of coercion, and a woman should know that she can decline testing without the risk of being denied care. A woman’s age, cultural background, educational level, and primary language may influence her knowledge about HIV transmission and her willingness to be tested; the clinician should consider these factors carefully when providing education and information.

The following minimum information should be provided through an educational session with a health care provider or through written or electronic media (eg, brochures, videos):

- ♦ HIV is the virus that causes AIDS. Approximately 25% of women with HIV who are not treated can transmit the virus to their babies through pregnancy, during labor and delivery, or by breast-feeding.
- ♦ A woman could be at risk for HIV infection and not know it.
- ♦ Highly effective treatment can protect the infant from being infected with HIV and can improve the mother’s health.
- ♦ HIV testing is recommended for all pregnant women.
- ♦ Women who decline testing will not be denied care.

Women should also be told that test results are confidential to the extent allowed by law and that medical and other services are available for women with HIV infection. Reporting requirements for the specific state should be explained.

Some states require written informed consent before an HIV test is done. Others require patient education and a chart note from the providers. More recently, states are moving to the opt-out approach, whereby a woman is informed that an HIV test will be done unless she declines. Whatever the consent process, a woman should know that an HIV test is being done and should receive at least the information outlined above.

HIV testing should be performed as early in pregnancy as possible to allow for interventions to prevent transmission and for effective management of a woman's HIV infection, if the woman is found to be HIV seropositive. Repeat HIV testing is recommended in the third trimester for women at high risk for acquiring HIV (eg, a history of injection drug use, exchange of sex for money or drugs, multiple sex partners, a partner known to be HIV infected). Any pregnant woman with signs or symptoms of seroconversion should be evaluated for acute HIV infection (see chapter *Primary HIV Infection*). Some states, such as Florida, now mandate a third-trimester HIV test for all pregnant women. If a client declines testing, the clinician should ask her reasons and follow up at subsequent visits. If a provider is persistent, the woman may choose to have an HIV test at a later visit.

In the United States, the vast majority of pregnant women who are tested for HIV will be HIV seronegative. While giving test results to an HIV-negative woman, the clinician should take the opportunity to discuss risk-reduction strategies to help ensure that a woman remains uninfected by HIV. Women at high risk for HIV infection should be referred for more extensive counseling because recent research indicates that pregnancy may place her at greater risk for acquiring HIV infection.

Counseling a pregnant woman with a positive HIV test result requires knowledge and sensitivity. The clinician should explain that, even though the woman may feel well, she is infected with the virus. The woman should be told about the importance of medical management of HIV for her own health and for the prevention of perinatal transmission, and she should be guided to the medical and social services available in her local community. She also should be referred to an HIV obstetric specialist who can work closely with her primary obstetric and HIV providers to manage her care during the pregnancy. The patient may be surprised or shocked at the HIV diagnosis, or she may have known her status but been reluctant to disclose it. The

clinician should emphasize the importance of emotional and social support, assess the patient's social support resources, and offer her referrals as needed.

Rapid HIV Testing during Labor

As discussed earlier, beginning ART during pregnancy offers the greatest chance for preventing MTCT of HIV, but interventions during the intrapartum and neonatal periods still offer opportunities to decrease the risk of HIV transmission. Rapid HIV testing for women who present in labor with unknown or undocumented HIV status can identify HIV-infected women so that interventions can be offered. Newer rapid HIV antibody tests, which are both sensitive and specific, provide results in less than 1 hour. Women who should receive HIV testing during labor include those who have had little or no prenatal care, those who were not offered testing earlier in pregnancy, those who declined previously, and those whose HIV test results are not available at the time of labor. Education and counseling for the woman in labor who needs an HIV test should incorporate the information for prenatal education discussed earlier, and give consideration to the special circumstances of labor. Special educational formats such as flip charts have been developed to help with patient education. Confidentiality should be assured for the information and consent process and for treatment. If an opt-out approach is used in the labor setting, a woman of unknown serostatus should be told that no HIV test is found on her chart, that HIV testing is part of routine care, and that she can decline if she wishes, but that experts recommend HIV testing because interventions are available that decrease her baby's risk of becoming infected with HIV if she is found to be positive.

Factors Influencing Perinatal HIV Transmission

As stated earlier, the rate of MTCT in the United States ranges from 16% to 25% in the absence of ART or other interventions. Perinatal transmission is most likely to occur in the intrapartum period. Several factors influence the risk of transmission from mother to infant. The most influential factor seems to be the mother's HIV RNA level (viral load). Clinical trials and observational studies have shown a strong positive correlation between maternal HIV viral load during pregnancy or at delivery and the risk of perinatal HIV transmission, even among women treated with ARVs. Even for women with viral loads <1,000 copies/mL, in whom the risk of MTCT is lower than in women with

higher viral loads, ARV prophylaxis is a critical factor in reducing HIV transmission. One metaanalysis found that women with HIV RNA <1,000 copies/mL who were receiving ART had a transmission rate of only 1%, compared with a 9.8% transmission rate among women taking no ARVs. For that reason, ARV prophylaxis is recommended for all pregnant women with HIV infection. Other factors associated with increased risk of perinatal transmission include chorioamnionitis, low CD4 cell count, sexually transmitted infections, illicit drug use, cigarette smoking, and unprotected sex with multiple partners.

Obstetric factors also affect the risk of transmission. The risk of HIV infection increases linearly with the increased duration of ruptured membranes, although the effect of ruptured membranes in women with low viral loads is not known. Invasive procedures performed at any time during pregnancy, such as amniocentesis or placement of scalp electrodes, also increase the risk by exposing the fetus to maternal blood; these procedures should be avoided. The mode of delivery, whether vaginal or cesarean section, also influences the risk of HIV transmission. Cesarean section decreases the rate of perinatal infection, at least in the absence of other interventions (including ART); see “Mode of Delivery and Intrapartum Management” below for further information.

Breast-feeding increases the risk of HIV transmission by 5-20%. In the United States, where replacement foods and clean water routinely are available, women with HIV should not breast-feed. However, some women with HIV will be under tremendous cultural and family pressure to breast-feed and will need the clinician's ongoing support to use substitute formula.

Because many factors that affect the risk of perinatal HIV transmission may be modified, clinicians should educate pregnant women carefully about the importance of ARV prophylaxis and other strategies to reduce the risk of maternal-fetal transmission of HIV.

Antiretroviral Therapy during Pregnancy

The goals of ART for the pregnant woman are the same as those for any person living with HIV:

- ◆ To suppress the level of HIV to as low as possible for as long as possible
- ◆ To preserve and restore immune function
- ◆ To prolong life and improve quality of life

An additional goal in pregnant women is to reduce

the risk of perinatal HIV transmission. The USPHS recommendations discuss in detail the multiple issues that must be considered when balancing the woman's need for therapy for her own health and for decreasing the risk of transmission to the infant. Decisions about ART are complex and should be made by the woman and her health care provider after discussing of the risks and benefits. Clinicians are urged to consult an HIV specialist as well as the most current USPHS recommendations when making therapeutic decisions. The following discussion addresses some of the issues in determining ARV treatment and is taken from the current USPHS *Perinatal ARV Guidelines*.

A fundamental principle of the guidelines is that therapies of known benefit should not be withheld during pregnancy unless they may cause adverse effects to the woman, fetus, or infant and these adverse effects outweigh the potential benefit to the woman. The woman's clinical, virologic, and immunologic status should be the most important factor in guiding treatment decisions. Combination therapy with 3 ARVs, including agents from at least 2 ARV classes, is the standard therapy for adults and should be discussed with the pregnant woman. Special considerations in choosing drug regimens during pregnancy include changes in dosing requirements because of physiologic changes, the potential effects of ARVs on the woman, and the known and unknown potential effects of ARVs on the fetus or infant.

Safety and Toxicity of Antiretroviral Medications during Pregnancy

Only limited data are available on the safety of ARV drugs in pregnancy, particularly when ARVs are used in combination. The existing safety and toxicity information is derived from animal data, clinical trials, registry data, and anecdotal experience. A few drugs are of special concern when used during pregnancy (Tables 1-2). Efavirenz (Sustiva) is classified by the U.S. Food and Drug Administration (FDA) as a Pregnancy Class D drug because malformations have occurred in monkeys receiving efavirenz during the first trimester. Several cases of neural tube defects have been reported in humans after first-trimester exposure to efavirenz. Efavirenz should be avoided during the first trimester, and women taking efavirenz should be counseled about the risks and the importance of avoiding pregnancy. Use of efavirenz can be considered after the second trimester if other alternatives are unavailable. Amprenavir (Agenerase) oral solution is

contraindicated during pregnancy because the high levels of propylene glycol may not be metabolized well during pregnancy. The combination of didanosine (ddI) and stavudine (d4T) should be avoided unless no alternatives are available. Hydroxyurea, a drug previously thought to boost the response to ARVs, is a potent teratogen in various animal species and should not be used in the first trimester. Information on ARV toxicity during pregnancy should be consulted carefully before treatment choices are made.

The *USPHS Perinatal ARV Guidelines* maintain information on each ARV drug, including preclinical and clinical data, pharmacokinetic and toxicity data, and recommendations regarding use in pregnancy. These guidelines are updated routinely as information is received (Tables 1-2). Of course, numerous other medications are contraindicated during pregnancy, and potential toxicity should be considered carefully before any medication is given to a pregnant woman.

Table 1. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals during Pregnancy

Antiretroviral Drug	FDA Pregnancy Category*	Placental Passage (Newborn-to-Mother Drug Ratio)	Long-Term Carcinogenicity Studies in Animals	Teratogen Studies in Animals
Nucleoside and Nucleotide Analogue Reverse Transcriptase Inhibitors (NRTIs)				
Abacavir (Ziagen, ABC)	C	Yes (rats)	Positive: malignant and nonmalignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats	Positive: rodent anasarca and skeletal malformations at 1,000 mg/kg (35x human exposure) during organogenesis; not seen in rabbits
Didanosine (Videx, ddI)	B	Yes (human) [0.5]	Negative: no tumors, lifetime rodent study	Negative
Emtricitabine (Emtriva, FTC)	B	Unknown	Not completed	Negative
Lamivudine (Epivir, 3TC)	C	Yes (human) [~1.0]	Negative: no tumors, lifetime rodent study	Negative
Stavudine (Zerit, d4T)	C	Yes (rhesus monkey) [0.76]	Positive: liver and bladder tumors in mice and rats, at very high-dose exposure	Negative: but sternal bone calcium decreases in rodents
Tenofovir DF (Viread)	B	Yes (rat and monkey)	Positive: hepatic adenomas in female mice at high doses	Negative: but osteomalacia when given to juvenile animals at high doses
Zalcitabine (Hivid, ddC)	C	Yes (rhesus monkey) [0.30 - 0.50]	Positive: thymic lymphomas in rodents	Positive: hydrocephalus at high doses in rodents
Zidovudine† (Retrovir, AZT, ZDV)	C	Yes (human) [0.85]	Positive: noninvasive vaginal epithelial tumors in rodents	Positive at near lethal dose in rodents
Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)				
Delavirdine (Rescriptor)	C	Unknown	Positive: hepatocellular adenomas and carcinomas in male and female mice but not rats; bladder tumors in male mice	Positive: ventricular septal defect in rodents
Efavirenz (Sustiva)	D	Yes (cynomolgus monkey, rat, rabbit) [~1.0]	Positive: hepatocellular adenomas and carcinomas and pulmonary alveolar/bronchiolar adenomas in female but not male mice	Positive: anencephaly, anophthalmia, microphthalmia in cynomolgus monkeys
Nevirapine (Viramune)	C	Yes (human) [~1.0]	Positive: hepatocellular adenomas and carcinomas in mice and rats	Negative

Protease Inhibitors (PIs)				
Amprenavir (Agenerase)	C	Unknown	Positive: hepatocellular adenomas and carcinomas in male mice and rats	Negative, but deficient ossification and thymic elongation in rats and rabbits
Atazanavir (Reyataz)	B	Unknown	Positive: hepatocellular adenomas in female mice	Negative
Darunavir (Prezista)	B	Unknown	Not completed	Negative
Fosamprenavir (Lexiva)	C	Unknown	Positive: benign and malignant liver tumors in male rodents	Negative for fosamprenavir, but deficient ossification with amprenavir
Indinavir (Crixivan)	C	Minimal (humans)	Positive: thyroid adenomas in male rats at highest dose	Negative, but extra ribs in rodents
Lopinavir/Ritonavir (Kaletra)	C	Unknown	Positive: hepatocellular adenomas and carcinomas in mice and rats	Negative, but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses
Nelfinavir (Viracept)	B	Minimal (humans)	Positive: thyroid follicular adenomas and carcinomas in rats	Negative
Ritonavir (Norvir)	B	Minimal (humans)	Positive: liver adenomas and carcinomas in male mice	Negative, but cryptorchidism in rodents
Saquinavir (Fortovase)	B	Minimal (humans)	Negative	Negative
Tipranavir (Aptivus)	C	Unknown	In progress	Negative, but decreased ossification and weights in rats at maternally toxic doses
Fusion Inhibitors				
Enfuvirtide (Fuzeon)	B	Unknown	Not done	Negative

Key to abbreviations: FDA = U.S. Food and Drug Administration.

*Food and Drug Administration Pregnancy Categories:

A—Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and no evidence exists of risk during later trimesters).

B—Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate but well-controlled studies of pregnant women have not been conducted.

C—Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted, and the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.

D—Positive evidence exists of human fetal risk that is based on adverse-reaction data from investigational or marketing experiences, but the potential benefits from the use of the drug among pregnant women might be acceptable despite its potential risks.

X—Studies among animals or reports of adverse reactions have indicated that the risk associated with the use of the drug for pregnant women clearly outweighs any possible benefit.

Source: Centers for Disease Control and Prevention. *Table 2: Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy*. In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. July 6, 2006. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9>.

Table 2. Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetics, Toxicity Data, and Recommendations

Nucleoside/ Nucleotide Reverse Transcriptase Inhibitors			
Antiretroviral Drug	Pharmacokinetics during Pregnancy	Concerns during Pregnancy	Rationale for Recommended Use during Pregnancy
NRTI class concerns and comments		See text for discussion of potential maternal and infant mitochondrial toxicity.	NRTIs are recommended for use as part of combination regimens, usually including 2 NRTIs with either an NNRTI or 1 or more PIs. Use of single or dual NRTIs alone is not recommended for treatment of HIV infection (zidovudine alone may be considered for prophylaxis of perinatal transmission in pregnant women with HIV RNA <1,000 copies/mL).
Recommended Agents			
Zidovudine (Retrovir, AZT, ZDV)	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Preferred NRTI for use in combination antiretroviral regimens during pregnancy based on efficacy studies and extensive experience; should be included in regimen unless significant toxicity or stavudine use
Lamivudine (Epivir, 3TC)	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated for mother and infant.	Because of extensive experience with lamivudine in pregnancy in combination with zidovudine, lamivudine plus zidovudine is the recommended dual NRTI backbone for pregnant women.
Alternative Agents			
Didanosine (Videx, ddl)	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together.	Alternate NRTI for dual nucleoside backbone of combination regimens. Didanosine should be used with stavudine only if no other alternatives are available.
Emtricitabine (Emtriva, FTC)	No studies in human pregnancy.	No studies in human pregnancy.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Stavudine (Zerit, d4T)	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Cases of lactic acidosis, some fatal, have been reported in pregnant women receiving didanosine and stavudine together.	Alternate NRTI for dual nucleoside backbone of combination regimens. Stavudine should be used with didanosine only if no other alternatives are available. Do not use with zidovudine because of potential for antagonism.
Abacavir (Ziagen, ABC)	Pharmacokinetics are not significantly altered during pregnancy; no change in dose indicated.	Hypersensitivity reactions occur in ~5-8% of nonpregnant persons; a much smaller percentage are fatal and are usually associated with repeat challenge. Rate of such reactions during pregnancy is unknown. Patient should be educated regarding symptoms of hypersensitivity reaction.	Alternate NRTI for dual nucleoside backbone of combination regimens.
Insufficient Data to Recommend Use			
Tenofovir DF (Viread)	No studies in human pregnancy. Phase I study in late pregnancy in progress.	Studies in monkeys show decreased fetal growth and reduction in fetal bone porosity within 2 months of starting maternal therapy. Clinical studies in humans (particularly children) show bone demineralization with chronic use; clinical significance is unknown.	Because of lack of data on use in human pregnancy and concern regarding potential fetal bone effects, tenofovir should be used as a component of a maternal combination regimen only after careful consideration of alternatives.
Not Recommended			
Zalcitabine (Hivid, ddC) <i>Note: zalcitabine has been discontinued by the manufacturer.</i>	No studies in human pregnancy	Rodent studies indicate potential for teratogenicity and developmental toxicity (see Table 1).	Given lack of data and concerns regarding teratogenicity in animals, zalcitabine is not recommended for use in human pregnancy unless alternatives are not available.

Nonnucleoside Reverse Transcriptase Inhibitors			
Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Recommended Agents			
Nevirapine (Viramune)	Pharmacokinetics not significantly altered in pregnancy; no change in dose indicated.	No evidence of human teratogenicity. Increased risk of symptomatic, often rash-associated, and potentially fatal liver toxicity among women with CD4 counts >250 cells/ μ L when first initiating therapy; unclear whether pregnancy increases risk.	Because of the increased risk of potentially life-threatening hepatotoxicity in women with high CD4 counts, nevirapine should be initiated in pregnant women with CD4 counts >250 cells/ μ L only if benefit clearly outweighs risk. Women who begin pregnancy on nevirapine regimens and are tolerating them well may continue therapy, regardless of CD4 count.
Not Recommended			
Efavirenz (Sustiva)	No studies in human pregnancy.	FDA Pregnancy Class D; significant malformations (anencephaly, anophthalmia, cleft palate) were observed in 3 (15%) of 20 infants born to cynomolgus monkeys receiving efavirenz during the first trimester at a dose giving plasma levels comparable to systemic human therapeutic exposure. Three cases were reported of neural tube defects in humans after first-trimester exposure; relative risk is unclear.	Use of efavirenz should be avoided in the first trimester, and women of childbearing potential must be counseled regarding risks and avoidance of pregnancy. Because of the known failure rates of contraception, alternate regimens should be strongly considered in women of childbearing potential. Use after the second trimester of pregnancy can be considered if other alternatives are not available and if adequate contraception can be assured postpartum.
Delavirdine (Rescriptor)	No studies in human pregnancy.	Rodent studies indicate potential for carcinogenicity and teratogenicity (see Table 1).	Given lack of data and concerns regarding teratogenicity in animals, delavirdine is not recommended for use in human pregnancy unless alternatives are not available.
Protease Inhibitors			
Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
PI class concerns		Hyperglycemia, new onset or exacerbation of diabetes mellitus, and diabetic ketoacidosis reported with PI use; unclear if pregnancy increases risk. Conflicting data regarding preterm delivery in women receiving PIs.	
Recommended Agents			
Lopinavir/ritonavir (Kaletra)	Pharmacokinetic (PK) studies of standard ritonavir dose of lopinavir/ritonavir capsules (3 capsules twice daily) during 3rd trimester indicated levels were significantly lower than during postpartum period and in nonpregnant adults; an increased dose of 4 capsules of lopinavir/ritonavir twice daily starting in the 3rd trimester resulted in adequate lopinavir exposure; by 2 weeks postpartum, standard dosing was again appropriate. PK studies of the new lopinavir/ritonavir tablet formulation are under way, but data are not yet available.	No evidence of human teratogenicity. Well-tolerated, short-term safety demonstrated in phase I/II studies.	The capsule formulation is no longer available. PK studies of the new tablet formulation are under way, but there are currently insufficient data to make a definitive recommendation regarding dosing during pregnancy. Some experts would administer standard dosing (2 tablets twice daily) throughout pregnancy and monitor virologic response and lopinavir drug levels, if available. Other experts, extrapolating from the capsule formulation PK data, would increase the dose of the tablet formulation during the 3rd trimester (from 2 tablets to 3 tablets twice daily), returning to standard dosing postpartum. Once-daily lopinavir/ritonavir dosing is not recommended during pregnancy because there are no data to address whether drug levels are adequate with such administration.

Nelfinavir (Viracept)	Adequate drug levels are achieved in pregnant women with nelfinavir 1,250 mg, given twice daily.	No evidence of human teratogenicity. Well-tolerated, short-term safety was demonstrated for mother and infant. Nelfinavir dosing at 750 mg 3 times daily produced variable and generally low levels in pregnant women.	Given PK data and extensive experience with use during pregnancy compared with other PIs, preferred PI for combination regimens in pregnant women, particularly if ART is being given solely for perinatal prophylaxis. In clinical trials of initial therapy in nonpregnant adults, nelfinavir-based regimens had a lower rate of viral response compared with lopinavir/ritonavir or efavirenz-based regimens, but a similar viral response compared with atazanavir or nevirapine-based regimens.
Alternative Agents			
Indinavir (Crixivan)	Two studies including 18 women receiving indinavir 800 mg 3 times daily showed markedly lower drug levels during pregnancy compared with postpartum, although suppression of HIV RNA was seen.	Theoretical concern exists about increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, but minimal placental passage. Use of unboosted indinavir during pregnancy is not recommended.	Alternate PI to consider if unable to use recommended agents, but would need to give indinavir as ritonavir-boosted regimen. Optimal dosing for the combination of indinavir/ritonavir during pregnancy is unknown.
Ritonavir (Norvir)	Phase I/II study during pregnancy showed lower drug levels during pregnancy compared with postpartum.	Limited experience at full dose in human pregnancy, has been used as low-dose ritonavir boosting with other PIs.	Given low levels in pregnant women when used alone, ritonavir is recommended for use in combination with a second PI as low-dose “boost” to increase levels of second PI.
Saquinavir hard-gel capsule [HGC] (Invirase)/ ritonavir	PK studies of saquinavir soft-gel capsules (SGC) indicated that inadequate drug levels were observed in pregnant women given 1,200 mg of saquinavir SGC as a sole PI 3 times daily, but adequate levels were achieved when 800 mg saquinavir SGC boosted with ritonavir 100 mg was given twice daily. However, saquinavir SGC are no longer produced. Limited PK data on saquinavir HGC suggest that 1,000 mg saquinavir HGC/100 mg ritonavir given twice daily will achieve adequate saquinavir drug levels in pregnant women.	Well-tolerated, short-term safety demonstrated for mother and infant for both saquinavir SGC and HGC in combination with low-dose ritonavir.	Saquinavir SGC are no longer available. There are only limited PK data on saquinavir HGC during pregnancy. Ritonavir-boosted saquinavir HGC is an alternative PI for combination regimens in pregnancy, and is an alternative initial antiretroviral recommendation for nonpregnant adults. No data on saquinavir tablet formulation + ritonavir in pregnancy.
Insufficient Data to Recommend Use			
Amprenavir (Agenerase)	No studies in human pregnancy.	Oral solution is contraindicated in pregnant women because of high levels of propylene glycol, which may not be adequately metabolized during pregnancy.	Capsule formulation no longer available.
Atazanavir (Reyataz)	No studies in human pregnancy.	Theoretical concern exists about increased indirect bilirubin levels, which may exacerbate physiologic hyperbilirubinemia in the neonate, although transplacental passage of other PIs has been low.	Safety and pharmacokinetics in pregnancy data are insufficient to recommend use during pregnancy.
Darunavir (Prezista)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and PK data in pregnancy data are insufficient to recommend use during pregnancy.
Fosamprenavir (Lexiva)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.
Tipranavir (Aptivus)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and PK data in pregnancy are insufficient to recommend use during pregnancy.

Fusion Inhibitor			
Antiretroviral Drug	Pharmacokinetics in Pregnancy	Concerns in Pregnancy	Rationale for Recommended Use in Pregnancy
Insufficient Data to Recommend Use			
Enfuvirtide (Fuzeon)	No studies in human pregnancy.	No experience in human pregnancy.	Safety and pharmacokinetics data in pregnancy are insufficient to recommend use during pregnancy.

Source: Centers for Disease Control and Prevention. Table 3. *Antiretroviral Drug Use in Pregnant HIV-Infected Women: Pharmacokinetic and Toxicity Data in Human Pregnancy and Recommendations for Use in Pregnancy*. In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. October 12, 2006. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9>.

Key to abbreviations: HGC = hard-gel capsule; NNRTI = nonnucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NtRTI = nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; PK = pharmacokinetic; SGC = soft-gel capsule.

Adverse Antiretroviral Drug Events during Pregnancy

Concerns have been raised about complications and toxicities related to ART during pregnancy. For example, a European study found a 2-fold increase in preterm birth among mothers who started combination therapy before pregnancy. A metaanalysis of 7 U.S. clinical trials, however, found that ARV use was not associated with preterm labor, low birth-weight, low Apgar scores, or stillbirth. Until more is known, pregnant women who are taking combination regimens should be monitored closely for complications and toxicities and should be educated about the signs of premature labor.

Nucleoside reverse transcriptase inhibitors can cause mitochondrial dysfunction with long-term use. Clinical disorders linked to mitochondrial dysfunction include symptomatic lactic acidosis and hepatic steatosis, which are seen more commonly in women than in men. Three maternal deaths were reported in the United States in women taking ARV regimens that included ddI and d4T in combination with other ARVs. Patients with lactic acidosis with hepatic steatosis often present with 1-6 weeks of symptoms including nausea, vomiting, abdominal pain, dyspnea, and weakness. Because some of the symptoms of lactic acidosis/hepatic steatosis syndrome can mimic those of pregnancy, clinicians must be alert for early signs and symptoms of lactic acidosis and evaluate them promptly. The combination of ddI and d4T should be avoided during pregnancy, and used only when other effective options are not available (Table 2).

Women, including pregnant women, who begin nevirapine therapy when their CD4 count is >250 cells/

μL have a 9.8 times higher incidence of hepatotoxicity than women initiated on nevirapine at lower CD4 counts. Symptoms of hepatotoxicity include fatigue, malaise, anorexia, nausea, jaundice, liver tenderness, and hepatomegaly. Nevirapine should be initiated as part of an ARV regimen in pregnant women with CD4 cell counts >250 cells/μL *only* if the benefits clearly outweigh the risks (Table 2).

Hyperglycemia, new-onset diabetes, worsening diabetes, and diabetic ketoacidosis have been reported in patients taking protease inhibitors. In addition, pregnancy itself is a risk factor for hyperglycemia. Clinicians should monitor closely the glucose level of pregnant women taking PIs and should educate them about the symptoms of hyperglycemia. (See chapter *Care of HIV-Infected Pregnant Women*.)

Recommendations for Antiretroviral Chemoprophylaxis to Reduce Perinatal HIV Transmission

The Perinatal HIV Working Group has offered recommendations on ARV prophylaxis to reduce perinatal HIV transmission based on 4 clinical scenarios:

- ◆ HIV-infected women who have not received previous ARV therapy
- ◆ HIV-infected women receiving ARV therapy during the current pregnancy
- ◆ HIV-infected women in labor who have had no previous therapy
- ◆ Infants born to HIV-infected women who received no ARV therapy during pregnancy or intrapartum

Recommendations for ART in these 4 clinical scenarios are listed in Table 3.

Table 3. Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal HIV-1 Transmission

SCENARIO #1: HIV-1-infected pregnant women who have not received previous ARV therapy	SCENARIO #2: HIV-1-infected women receiving ARV therapy during the current pregnancy
• Pregnant women with HIV-1 infection must receive standard clinical, immunologic, and virologic evaluations. Recommendations for initiation and choice of ARV therapy should be based on the same parameters used for persons who are not pregnant, although the known and unknown risks and benefits of such therapy during pregnancy must be considered and discussed. • The 3-part ZDV chemoprophylaxis regimen, initiated after the first trimester, is recommended for all pregnant women with HIV-1 infection regardless of antenatal HIV RNA copy number to reduce the risk of perinatal transmission. • The combination of ZDV chemoprophylaxis with additional ARV drugs for treatment of HIV-1 infection is recommended for infected women whose clinical, immunologic, or virologic status requires treatment or who have HIV-1 RNA >1,000 copies/mL regardless of clinical or immunologic status, and can be considered for women with HIV-1 RNA <1,000 copies/mL. • Women who are in the first trimester of pregnancy may consider delaying initiation of therapy until after 10-12 weeks' gestation.	• HIV-1-infected women receiving ARV therapy in whom pregnancy is identified after the first trimester should continue therapy. ZDV should be a component of the antenatal ARV treatment regimen after the first trimester whenever possible, although this may not always be feasible. • For women receiving ARV therapy in whom pregnancy is recognized during the first trimester, women should be counseled regarding the benefits and potential risks of ARV administration during this period, and continuation of therapy should be considered. If therapy is discontinued during the first trimester, all drugs should be stopped and reintroduced simultaneously to avoid the development of drug resistance. • Regardless of the antepartum ARV regimen, ZDV administration is recommended during the intrapartum period and for the newborn.
SCENARIO #3: HIV-1-infected women in labor who have had no previous therapy	SCENARIO #4: Infants born to HIV-1-infected mothers who have received no ARV therapy during pregnancy or intrapartum
• Several effective regimens are available (see <i>USPHS Perinatal ARV Guidelines</i>, Table 5). These include: • Intrapartum intravenous ZDV followed by 6 weeks of ZDV for the newborn; • Oral ZDV and 3TC during labor, followed by 1 week of oral ZDV-3TC for the newborn; • A single dose of nevirapine at the onset of labor followed by a single dose of nevirapine for the newborn at 48 hours postpartum; • The single-dose maternal and infant nevirapine regimen combined with intrapartum intravenous ZDV and 6-week ZDV for the newborn. • If single-dose nevirapine is given to the mother, alone or in combination with ZDV, consideration should be given to adding maternal ZDV/3TC starting as soon as possible (intrapartum or immediately postpartum) and continuing for 3-7 days, which may reduce the development of nevirapine resistance. • In the immediate postpartum period, the woman should have appropriate assessments (eg, CD4 count and HIV-1 RNA copy number) to determine whether ARV therapy is recommended for her own health.	• The 6-week neonatal ZDV component of the ZDV chemoprophylactic regimen should be discussed with the mother and offered for the newborn. • ZDV should be initiated as soon as possible after delivery—preferably within 6-12 hours of birth. • Some clinicians may choose to use ZDV in combination with other ARV drugs, particularly if the mother is known or suspected to have ZDV-resistant virus. However, the efficacy of this approach for prevention of transmission has not been proven in clinical trials, and appropriate dosing regimens for neonates are incompletely defined for many drugs. • In the immediate postpartum period, the woman should undergo appropriate assessments (eg, CD4 count and HIV-1 RNA copy number) to determine whether ARV therapy is required for her own health. The infant should undergo early diagnostic testing so that, if HIV infected, treatment can be initiated as soon as possible.

Key to abbreviations: ARV = antiretroviral; ZDV = zidovudine; USPHS = U.S. Public Health Service; 3TC = lamivudine.

Adapted from: Centers for Disease Control and Prevention. *Table 4. Clinical Scenarios and Recommendations for the Use of Antiretroviral Drugs to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission*. In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. October 12, 2006. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9>.

The *USPHS Perinatal ARV Guidelines* emphasize that the PACTG 076 regimen is effective not only for women whose clinical status is similar to that of the participants in the original study, but also for women with advanced HIV disease, low CD4 counts, and previous ZDV therapy.

Because the goals of ART in a pregnant woman are not only to maintain her health, but also to prevent transmission to her infant, the considerations in ART differ from those in nonpregnant adults. Because the HIV viral load strongly influences the risk of HIV transmission, a primary goal of therapy should be to suppress the viral load to very low levels (preferably to undetectable levels) during pregnancy and throughout delivery; this goal guides treatment decisions. For nonpregnant adults, the *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents* recommend that treatment be deferred in certain persons, depending on the CD4 cell count and the HIV viral load. (See chapter *Antiretroviral Therapy*.) In contrast, the *USPHS Perinatal ARV Guidelines* recommend that all pregnant women, regardless of CD4 cell count, receive the 3-part ZDV prophylaxis regimen used in PACTG 076, that is, ZDV orally (200 mg 3 times a day or 300 mg twice a day) beginning after the first trimester, intravenous ZDV during labor, and ZDV given orally to the newborn for 6 weeks. The guidelines also recommend that women with an HIV RNA level >1,000 copies/mL (regardless of CD4 cell count) or with immunologic, virologic, or clinical indications for treatment be offered a combination ART regimen that includes ZDV and other ARV drugs. Even women with HIV RNA levels <1,000 copies/mL should be considered for combination therapy.

The specific ART regimen should be selected with a view to the limited information available about the efficacy and potential toxicities of ARV combinations during pregnancy. The USPHS offers recommendations on the use of specific ARV agents during pregnancy (Table 2).

Mode of Delivery and Other Intrapartum Management

All pregnant women with HIV infection should receive the intrapartum and neonatal components of ZDV prophylaxis used in the PACTG 076 protocol, as outlined earlier. ZDV should be given to the woman intravenously during labor in a 1-hour initial loading dose of 2 mg per kilogram body weight followed by a continuous infusion of 1 mg/kg body weight per hour until delivery. The newborn should receive ZDV syrup at a dose of 2 mg/kg body weight per dose every 6 hours beginning 8–12 hours after birth and continuing for the first 6 weeks of life.

Early studies before the availability of viral load testing found that cesarean delivery performed before the onset of labor or rupture of membranes significantly reduced the risk of perinatal transmission. However, now that many HIV-infected pregnant women in the United States and other high-income settings are receiving combination ART, transmission rates of 1.2–1.5%, unadjusted for mode of delivery, have been reported). Because the transmission rate is so low in women taking effective ART, it is difficult to determine whether cesarean section offers any additional benefit. For women with a viral load <1,000 copies/mL, it is unlikely that cesarean section would provide additional benefit.

The American College of Obstetricians and Gynecologists recommends consideration of cesarean section at 38 weeks for HIV-infected women with a viral load >1,000 copies/mL at or near the time of delivery. The woman and her health care providers should decide about mode of delivery before the onset of labor, based on her current viral load, her health status, and discussion about other concerns. Pregnant women who have not achieved optimal virologic control and whose viral load remains >1,000 copies/mL in the weeks before delivery, should be counseled about the risks and benefits of cesarean section. A planned cesarean section should be scheduled for 38 weeks' gestation, because the benefits of cesarean section once the membranes have ruptured are unknown. Intravenous ZDV should be started 3 hours before the scheduled cesarean section. Prophylactic antibiotics are recommended at the time of cesarean section in HIV-infected women, to decrease the risk of maternal infection. The *USPHS Perinatal ARV Guidelines* outline 4 scenarios in which the clinician must decide whether cesarean section is needed (Table 4). The data on the benefits of cesarean section are complex and must be balanced with the increased risk to the mother after surgery. The clinician may want to consult an obstetric/HIV specialist to discuss specific situations.

Questions remain about the management of labor when a vaginal delivery is planned. Because the duration of ruptured membranes is a risk factor for perinatal transmission, pregnant women with HIV infection should be counseled to go to a hospital for care at the first signs of labor or rupture of membranes. If the membranes rupture spontaneously before labor occurs or early in labor, the clinician should consider interventions to decrease the interval to delivery, such as administration of oxytocin. Procedures that increase the neonate's exposure to maternal blood, such as the use of scalp electrodes or artificial rupture of membranes, should be avoided.

Table 4. Clinical Scenarios and Recommendations regarding Mode of Delivery to Reduce Perinatal HIV-1 Transmission

Mode of Delivery Clinical Scenario	Recommendations
Scenario A: An HIV-1-infected woman presenting in late pregnancy (after about 36 weeks of gestation), known to be HIV-1-infected but not receiving ART, and who has HIV-1 RNA level and lymphocyte subsets pending but unlikely to be available before delivery	Therapy options should be discussed in detail. The woman should be started on ART, including at least the PACTG 076 ZDV regimen. The woman should be counseled that scheduled cesarean section is likely to reduce the risk of transmission to her infant. She should also be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and other surgical risks. If cesarean section is chosen, the procedure should be scheduled at 38 weeks of gestation, based on the best available clinical information. When scheduled cesarean section is performed, the woman should receive continuous intravenous ZDV infusion beginning 3 hours before surgery and her infant should receive 6 weeks of ZDV therapy after birth. Options for continuing or initiating combination ART after delivery should be discussed with the woman as soon as her viral load and lymphocyte subset results are available.
Scenario B: An HIV-1-infected woman who initiated prenatal care early in the third trimester, is receiving highly active combination ART, and has an initial virologic response, but has HIV-1 RNA levels that remain substantially >1,000 copies/mL at 36 weeks of gestation	The current combination ARV regimen should be continued because the HIV-1 RNA level is dropping appropriately. The woman should be counseled that, although she is responding to ART, it is unlikely that her HIV-1 RNA level will fall below 1,000 copies/mL before delivery. Therefore, scheduled cesarean section may provide additional benefit in preventing intrapartum transmission of HIV-1. She also should be informed of the increased risks to her of cesarean section, including increased rates of postoperative infection, anesthesia risks, and surgical risks. If she chooses scheduled cesarean section, it should be performed at 38 weeks' gestation according to the best available gestational dating parameters, and intravenous ZDV should be begun at least 3 hours before surgery. Other ARV medications should be continued on schedule as much as possible before and after surgery. The infant should receive oral ZDV for 6 weeks after birth. The importance of adhering to therapy after delivery for the woman's own health should be emphasized.
Scenario C: An HIV-1-infected woman taking combination ART with an undetectable HIV-1 RNA level at 36 weeks of gestation	The woman should be counseled that her risk of perinatal transmission of HIV-1 with a persistently undetectable HIV-1 RNA level is low, probably 2% or less, even with vaginal delivery. There is no information currently available to evaluate whether performing a scheduled cesarean section will decrease her risk further. Cesarean section increases the risk of complications for the woman as compared with vaginal delivery, and these risks must be balanced against the uncertain benefit of cesarean section in this case.
Scenario D: An HIV-1-infected woman who has opted for scheduled cesarean section but presents in early labor or shortly after rupture of membranes	Intravenous ZDV should be started immediately because the woman is in labor or has ruptured membranes. If labor is progressing rapidly, the woman should be allowed to deliver vaginally. If cervical dilatation is minimal and a long period of labor is anticipated, some clinicians may choose to administer the loading dose of intravenous ZDV and proceed with cesarean section to minimize the duration of membrane rupture and avoid vaginal delivery. Others might begin oxytocin augmentation to enhance contractions and potentially expedite delivery. If the woman is allowed to labor, scalp electrodes and other invasive monitoring and operative delivery should be avoided if possible. The infant should be treated with 6 weeks of ZDV therapy after birth.

Key to Abbreviations: ART = antiretroviral therapy; PACTG 076 = Pediatric AIDS Clinical Trial Group study 076; ZDV = zidovudine; ARV = antiretroviral.

Adapted from: Centers for Disease Control and Prevention. *Table 7. Clinical Scenarios and Recommendations Regarding Mode of Delivery to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV-1) Transmission.* In: *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States.* October 12, 2006. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9>.

Postpartum Follow-Up of the Woman with HIV Infection

Women with HIV infection who have delivered recently need access to a comprehensive array of services for themselves and their infants. The clinician should refer the postpartum woman not only to her primary obstetric and HIV providers for family planning and HIV management, but also to a pediatric HIV specialist for care for her infant. She should also be referred as needed for mental health, substance abuse, and social support services. The clinician should be alert for indications of postpartum depression and should offer treatment promptly. Adherence to ARV regimens may be particularly difficult in the immediate postpartum period because of the physical changes postpartum and the demands of a new baby.

Women should be evaluated for their ongoing need for ART postpartum. If combination ART was given only or primarily to reduce the risk of perinatal transmission, the woman and her clinician may wish to consider discontinuing therapy after pregnancy, with the option to resume ART when she meets the criteria for treatment. Generally, all drugs should be stopped at once, but if the drugs have very different half-lives, their discontinuation should be staggered to decrease the risk of resistance, (eg, in regimens containing nevirapine, which has a long half-life). Drugs with a short half-life should be continued for several days to 1 week after the nevirapine is discontinued.

Follow-Up of the HIV-Exposed Infant

The HIV-exposed infant should be referred to a pediatric HIV specialist for diagnostic testing and monitoring of health status. Newborns should be discharged home with a supply of ZDV oral syrup. The newborn should receive ZDV syrup at a dose of 2 mg/kg body weight per dose every 6 hours beginning 8-12 hours after birth and continuing for 6 weeks.

Traditional HIV antibody testing cannot be used in infants because maternal antibodies may persist for up to 18 months. Diagnosis of HIV infection in infants requires virologic testing with HIV DNA polymerase chain reaction (PCR) or HIV RNA PCR. The *DHHS Pediatric ARV Guidelines* recommend testing at birth to 14 days, at 1-2 months, and at 3-6 months. HIV DNA PCR is a sensitive test that detects viral DNA in the patient's peripheral monocytes. Although the sensitivity of DNA PCR is <40% if performed at <48 hours of age, by 2-4 weeks of age, the sensitivity is >90%. HIV RNA PCR detects extracellular viral RNA in the plasma

and is as sensitive as DNA PCR for early diagnosis in infants. Some clinicians recommend using the HIV RNA assay as a confirmatory test for an infant with a positive DNA PCR result. This approach confirms the diagnosis and can help guide treatment decisions. HIV viral culture is also sensitive, but it is expensive and results may not be available for 2-4 weeks.

HIV can be diagnosed in an infant on the basis of 2 positive virologic tests done on separate blood samples at any time. HIV reasonably can be excluded in an infant with 2 negative virologic tests done at >1 month of age, with 1 being done at >4 months of age. Antibody testing is recommended at age 12-18 months to document seroreversion.

Infants should have a baseline complete blood count and should be monitored for anemia while they are taking ZDV. The *DHHS Perinatal ARV Guidelines* recommend *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis for HIV-exposed infants beginning at 6 weeks (when the ZDV is completed) and continuing until age 6 months or until HIV infection can be ruled out.

Parents and family care givers need to be educated that the infant must be monitored closely until an HIV diagnosis is made or is ruled out. They also need to know that the infant's exposure to ARV agents in utero is an important part of the infant's medical history and should be shared with future health care providers. Although no long-term consequences of ARV exposure have been confirmed, the child may be at risk for long-term problems.

Antiretroviral Pregnancy Registry

To improve tracking of pregnancy-related adverse effects and fetal effects, an Antiretroviral Pregnancy Registry has been established as a collaborative project among the pharmaceutical industry, pediatric and obstetric providers, the CDC, and the National Institutes of Health. The registry collects observational data on HIV-infected pregnant women taking ARV medications to determine whether patterns of fetal or neonatal abnormalities occur. Pregnant women taking ARVs can be placed in this confidential follow-up study by calling 800-258-4263, 8:30 AM to 5:30 PM eastern time; the fax number is 800-800-1052. Information is confidential and patients' names are not used. Providers are encouraged to add to the available information on fetal risk by using this registry at first contact with a pregnant woman taking ARVs. More information can be obtained at <http://www.APRRegistry.com>.

Patient Education

- ◆ The clinician should provide the pregnant woman with the most current information on the risk of mother-to-child HIV transmission and the importance of ARV prophylaxis.
- ◆ The clinician and the pregnant woman should have a detailed discussion about whether she needs ART for her health and the ARV regimen that would be most appropriate for her to decrease the risk of perinatal transmission.
- ◆ The clinician should review the critical importance of adherence to ARV regimens before prescribing a regimen.
- ◆ Once a regimen is begun, the clinician should review possible adverse effects of the drugs and give the woman specific instructions about managing them if they are mild or getting medical advice if they represent a more serious adverse effect, such as ongoing fatigue, persistent nausea and vomiting, or signs of hyperglycemia.
- ◆ Early in the third trimester, the clinician and patient should discuss the risks and potential benefits of cesarean section based on her viral load and clinical status.
- ◆ Intrapartum management, including intrapartum ZDV, should be discussed with the patient so that she knows that she should tell the delivery team about her HIV status when she presents in labor.
- ◆ The signs of early labor should be explained to the pregnant woman and she should know that she should seek care immediately if her membranes rupture or she believes she is in labor.
- ◆ The clinician should discuss infant feeding plans with the mother and reinforce that she should not breast-feed. The clinician may need to provide ongoing support for formula feeding.
- ◆ The clinician should discuss follow-up plans and make referrals for the pregnant woman and her infant. If at all possible, the woman should meet the pediatric HIV team before delivery or in the postpartum period. The importance of ARV prophylaxis and follow-up for the newborn should be stressed.

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Care of HIV-Infected Pregnant Women

Background

This chapter describes the elements involved in caring for the pregnant woman with HIV infection, whether the woman was known to be HIV infected before conception or was found to be HIV infected during pregnancy. It is not intended to be a comprehensive discussion of this topic, and an HIV-experienced obstetrician and an HIV specialist should be involved in the management of all HIV-infected pregnant women. For centers that do not have HIV specialists available, experts at the National Perinatal HIV Consultation and Referral Service are available for consultation through the Perinatal Hotline (888-448-8765).

The first task in caring for an HIV-infected woman who is pregnant or is considering pregnancy is to provide counseling that will allow her to make informed reproductive choices. Taking a careful reproductive history and providing preconception counseling should be part of any woman's routine primary care. To make informed choices about pregnancy, the patient needs education and information about the risk of perinatal transmission of HIV, potential complications of pregnancy, continuation or modification (or possible initiation) of antiretroviral therapy (ART), and the support she will need to optimize maternal and fetal outcomes.

The goals of HIV management during pregnancy are to maintain and support the woman's health, provide optimal ART to preserve or restore her immune system and suppress viral replication, and offering interventions that decrease the risk of perinatal HIV transmission. ART has proven highly effective in preventing mother-to-child HIV transmission. After the results of the Pediatric AIDS Clinical Trial Group study 076 were released in 1994, ART tailored to the specific patient has been recommended to decrease perinatal transmission and optimize outcomes (see chapter *Reducing Maternal-Infant HIV Transmission*). In the United States, ART should be offered according to the U.S. Public Health Service (USPHS) Task Force guidelines (see "Antiretroviral Therapy" below).

Preconception Evaluation of the HIV-Infected Woman

Ideally, the evaluation of reproductive issues with an HIV-infected woman begins before pregnancy. The preconception evaluation should include the following elements:

- ◆ Reproductive history, including number of pregnancies, number of partners, pregnancies with each partner, and outcomes of each pregnancy
- ◆ Length of relationship with current partner, HIV serostatus of partner, and couple's sexual history, including condom use and sexual decision making or control of reproductive choices
- ◆ Patient's and partner's reproductive desires, and discussion of options

Any history of infertility or low fertility in either the patient or her partner also should be evaluated and discussed, including current information on gamete donation, other assisted reproductive techniques, and adoption. For a woman (or a couple) who has decided to try to conceive, several issues must be considered. Prominent among these is the HIV serostatus of both partners. If HIV infection is present in only one of the partners, the risk of transmission to the uninfected partner and techniques to minimize the risk should be discussed. (For further discussion and patient-education materials for HIV-discordant couples, see Aaron and Mercurius in "References" below.)

If ART is indicated, an appropriate regimen should be started before pregnancy, avoiding agents with increased risk for teratogenicity (eg, efavirenz), hepatotoxicity (eg, nevirapine), or metabolic complications such as lactic acidosis (eg, didanosine, stavudine, and zalcitabine). See chapter *Reducing Maternal-Infant HIV Transmission* and the *Public Health Service Task Force Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States*. Centers for Disease Control and Prevention. October 12, 2006. (<http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=9>) for further information. It should be noted that most fetal organogenesis occurs in the early weeks of pregnancy, before most women know that they are pregnant. Thus,

any medication with potential teratogenicity or fetal toxicity, whether an antiretroviral (ARV) or another drug, should be avoided in women who are intending to become pregnant or are at risk of pregnancy. Certain medications (eg, ribavirin) also should be avoided by male partners of women who may become pregnant.

Folate supplementation to reduce the risk of neural tube defects in the developing fetus should be started at least 1 month before conception, if possible, because the neural tube forms in the early weeks of pregnancy (see below).

Evaluation and Counseling of Pregnant Women

All HIV-infected pregnant women should receive thorough education and counseling about perinatal transmission risks, strategies to reduce those risks, and potential effects of HIV infection or HIV treatment on the course or outcomes of pregnancy.

- ◆ The goals of therapy for pregnant women treated with ART, as for all persons being treated for HIV infection, are to suppress the HIV viral load maximally (preferably to undetectable levels) for as long as possible, to improve quality of life, to restore or preserve immune function, and, for pregnant women specifically, to reduce the risk of perinatal transmission as much as possible.
- ◆ Therapy-associated adverse effects, including hyperglycemia, anemia, and hepatic toxicity, may have a negative effect on maternal and fetal health outcomes. Pregnant woman should be advised about possible ARV-related adverse effects and should be monitored regularly for these events.
- ◆ HIV-infected women should receive evaluation and appropriate prophylaxis for opportunistic infections (OIs), as well as vaccinations as indicated for persons with HIV infection (eg, pneumococcus vaccination) (see below).
- ◆ Some medications, both ARVs and other drugs, may cause fetal anomalies or toxicity when taken during pregnancy. These should be avoided in pregnant women, unless the anticipated benefit outweighs the possible risk. Consult with an HIV or obstetric specialist, a pharmacist, or the drug labeling information before prescribing medications for pregnant women.

Other evaluation and support for pregnant women should include the following:

- ◆ Screening for other potential maternal health problems, such as diabetes and hypertension
- ◆ Maternal nutritional evaluation and support, including initiation of a prenatal multivitamin containing folate (0.4-0.8 mg orally once daily) to reduce the risk of fetal neural tube defects. Pregnant women who are taking trimethoprim-sulfamethoxazole (Septra, Bactrim, cotrimoxazole) and women who may become pregnant who are taking trimethoprim-sulfamethoxazole should be given higher doses of folate. Some experts recommend a folate dose of 4 mg daily for women receiving trimethoprim-sulfamethoxazole.
- ◆ Screening for psychiatric and neurologic disease
- ◆ Counseling about the risks of tobacco smoking; smoking cessation support as indicated
- ◆ Counseling about the risks of alcohol or drug use and support for discontinuation of these substances as needed
- ◆ Domestic violence screening
- ◆ Review of medications, including over-the-counter and nutritional agents; discontinuation of medications with the potential for fetal harm
- ◆ Immunizations (eg, influenza, hepatitis B) as indicated
- ◆ Institution of the standard measures for evaluation and management (eg, assessment of reproductive and familial genetic history, screening for infectious diseases or sexually transmitted diseases [STDs])
- ◆ Planning for maternal-fetal medicine consultation, if desired or indicated
- ◆ Selection of effective and appropriate postpartum contraceptive methods if desired

Comprehensive Care of Pregnant Women with HIV Infection

Comprehensive care is important for pregnant women with HIV infection to achieve a healthy pregnancy and delivery. A multidisciplinary approach is the most effective way to address the medical, psychological, social, and practical challenges. For example, while her medical care is being managed by her obstetrician and an HIV specialist, the pregnant woman may need help from a social worker to find appropriate

social services for food, housing, child care, and parenting issues. The pregnant woman may need counseling and psychological support for herself and her partner, as well as referrals for substance abuse and detoxification programs. Peer counselors may be of particular assistance. Some patients may need legal or domestic violence services during and after pregnancy. Cooperation and communication between the obstetrician or nurse/midwife and the primary HIV provider are imperative throughout the pregnancy and early postpartum period. Referral to a maternal-fetal medicine specialist may be needed in complicated obstetric cases.

Prenatal Care

All of the pregnancy-related complications seen in HIV-uninfected women, such as hypertensive disorders, ectopic pregnancy, psychiatric illness, multiple

gestation, preterm delivery, and STDs also can occur in HIV-infected women. These problems must be recognized quickly and treated appropriately to avoid life-threatening complications. Ideally, HIV-infected pregnant women are managed by both an experienced obstetrician-gynecologist and an HIV specialist. Communication between these specialists about medications, expectations, and complications is vital for the health and well-being of both mother and baby. If complications occur or abnormalities are detected, they should be evaluated and treated as indicated by the condition, and referral should be made to a maternal-fetal medicine specialist, if possible. Antenatal fetal surveillance and testing to identify fetal abnormalities should be carried out using guidelines established by the American College of Obstetricians and Gynecologists.

Tables 1-3 present the suggested testing and monitoring practices for pregnant women with HIV infection, from the first trimester to labor and delivery.

Table 1. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Initial and Subsequent Visits

Initial Visit		Frequency/Subsequent Visits
History		
HIV History	Date of diagnosis	-
	Signs and symptoms	Every visit
	Nadir CD4 and current CD4 cell count; HIV viral load	-
	ARV history, including regimen efficacy, toxicity, and ARV resistance	-
	Opportunistic infections and malignancies	Every visit
	History of genital herpes (HSV-2)	-
	Adherence	Every visit
Obstetric History	Number of pregnancies; complications and outcomes	-
	History of genetic disorders	-
	Use of ARV prophylaxis during previous pregnancies	-
	HIV status of children	-
Current Pregnancy	Last menstrual period (LMP)	-
	Pregnancy: intended or not	-
	Contraceptive methods used, if any	-
	Gestational age (can be calculated in a woman with regular menses, counting weeks from LMP)	Every visit
	Estimated date of delivery	-
	Signs or symptoms of maternal complications: elevated blood pressure, headache, significant edema, gastrointestinal or genitourinary symptoms, vaginal discharge or bleeding, decreased fetal movement	Every visit
	Screen for intimate-partner violence	Every visit

Physical Examination		
General	Vital signs and weight, funduscopy, breast exam	Every visit
Gynecologic	Pelvic exam, STD screening, examination for perineal or vaginal lesions (discoloration, condyloma, ulcerative lesions, vaginal discharge), cervical lesions, discharge or bleeding	As indicated
	Fundal height, correlating with gestational age (concordant between 18 and 30 weeks)	Every visit
	Fetal heart beat and rate: audible with DeLee fetal stethoscope between 16 and 19 weeks, earlier with Doppler devices	Every visit
	Fetal movements and position in third trimester	Every visit
Laboratory Tests		
HIV	HIV enzyme-linked immunosorbent assay (ELISA) with Western blot confirmation (if HIV status is not known) or rapid test and confirmatory test	-
	HIV viral load and CD4 count (total and %)	Every 3 months (at least every trimester) or as indicated
	Fasting lipid measurement	As indicated
	Genotype if ARV naive or detectable HIV RNA while on ART	As indicated
	Cytomegalovirus (CMV) immunoglobulin G (IgG) if CD4 count <100 cells/μL or if at low risk for CMV	-
	Toxoplasmosis IgG	-
	Consider HSV-2 serology, if history suggests	-
General	Complete blood count (CBC); chemistries, liver enzymes (LFTs)	Every 3 months or more frequently based on ARV regimen or symptoms
	Blood group	-
	Rh antibody screen	-
	Rubella antibody	-
	Varicella IgG, if history unclear	As indicated
	Screening for syphilis: rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL)	As indicated
	Screening for gonorrhea and chlamydia	As indicated
	Urinalysis and clean-catch urine culture	As indicated
	Papanicolaou smear	As indicated
Hepatitis Serologies	Hepatitis A virus (HAV) antibody (IgG)	-
	Hepatitis B virus (HBV): HBsAg, HBcAb, HBsAb	-
	Hepatitis C virus (HCV) antibody	-
TB Screening	Tuberculin skin test (PPD); more reliable if CD4 >200 cells/μL (induration >5 mm is positive)	-
Disease Specific	G6PD level, especially if anemic	-
	Consider hemoglobin electrophoresis, if anemic and/or at increased risk for hemoglobinopathies	-
	Serum screening for Tay-Sachs disease—both partners—if at increased risk	-
	Urine toxicology screen	As indicated

Table 2. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Second and Third Trimesters

Test	Comment
Weeks 16-20	
Ultrasound	Confirm gestational age, screen for malformations, multifetal pregnancy.
Maternal serum alpha-fetoprotein (AFP) or triple screen (human chorionic gonadotropin [HCG], serum estriol, and AFP)	Screen for neural tube and abdominal wall defect, trisomy 21, trisomy 18. Abnormal test requires further investigation—consider amniocentesis only if abnormality is detected on expanded triple screen or level-2 sonogram. Voluntary and requires counseling.
STD screening: gonorrhea, chlamydia, wet mount	Repeat as indicated, according to the woman's risk factors.
Weeks 24-28	
Complete blood count	
Syphilis serology	
Diabetes screening	Consider at 20 weeks: check glucose 1 hour after a 50 g glucose load; perform 3-hour glucose tolerance test if screen is abnormal. If 3-hour test abnormal, perform regular glucose monitoring, especially in women taking protease inhibitors.
Bacterial vaginosis (BV) screening	BV increases the risk of preterm labor.
Weeks 32-36	
Streptococcus B screening	If positive, offer intrapartum chemoprophylaxis.
STD screening: gonorrhea, chlamydia, syphilis	Repeat tests to rule out risk of perinatal transmission of these infections.
CD4 count, HIV viral load	Results obtained at 35-36 weeks guide decisions on the mode of delivery.

Table 3. Recommended Evaluation and Routine Monitoring of the Pregnant Woman with HIV Infection: Labor and Delivery

Test	Comment
Record Review	- Documentation of HIV serostatus, blood type and Rh, hepatitis serologies, rapid plasma reagin (RPR) - Review of antiretroviral therapy, if any, during pregnancy - Review of HIV viral load results during pregnancy
Physical Evaluation	- Vital signs and fetal heart rate - Frequency and intensity of contractions - Fetal lie, presentation, attitude, and position - Vaginal examination: rule out herpes simplex virus (HSV) lesions; detect ruptured membranes; determine cervical effacement, dilatation, and position Avoid procedures that increase the risk of perinatal HIV transmission (eg, fetal scalp electrodes, scalp sampling, or assisted rupture of membranes)
Admission Laboratory Tests	- Complete blood count - Liver function tests - RPR or Venereal Diseases Research Laboratory (VDRL), if not done recently - Repeat hepatitis B and C testing, if at risk for acquisition of hepatitis B or C, to prevent perinatal transmission of these infections

Immunizations and Opportunistic Infection Prophylaxis

Immunizations during Pregnancy

Immunizations should be given before pregnancy, if possible. Immunizations should be considered during pregnancy when the risk of exposure to an infection is high, the risk of infection to the mother or fetus is high, and the vaccine is unlikely to cause harm. Some vaccinations (such as measles/mumps/rubella) are contraindicated, and others should be given only if the anticipated benefit of the vaccination outweighs its

possible risk. Special considerations for immunizations in HIV-infected individuals are discussed in chapter *Immunizations for HIV-Infected Adults and Adolescents*.

Some clinicians avoid giving immunizations during the third trimester of pregnancy because vaccinations may cause a transient increase in the HIV viral load and theoretically may increase the risk of perinatal HIV transmission. An increase in viral load may be prevented with effective ART, and some clinicians defer immunizations until ART is under way.

Recommendations related to immunizations during pregnancy are shown in Table 4.

Table 4. Immunizations and Postexposure Prophylaxis in Pregnant Women with HIV Infection

Immunization	Comment
Hepatitis A virus (HAV)	Recommended for susceptible patients at high risk of infection, those with chronic HBV or HCV, those traveling to endemic areas, injection drug users, or in the setting of a community outbreak
Hepatitis B virus (HBV)	Generally recommended for susceptible patients
Influenza	Generally recommended; give before flu season
Measles/Mumps/Rubella (MMR)	<i>Contraindicated</i>
Pneumococcus	Generally recommended, repeat every 5-7 years
Tetanus-diphtheria	Recommended; give booster every 10 years
Immune globulins (For postexposure prophylaxis in susceptible individuals)	Comment
Measles	Recommended after measles exposure, for symptomatic HIV-infected persons
Hepatitis A	Recommended after exposure to a close contact or sex partner, or in case of travel to endemic areas
Hyper immune globulins	Comment
Varicella-zoster virus immune globulin (VZIG)	Recommended after significant exposure to varicella-zoster virus (give within 96 hours)
Hepatitis B immune globulin (HBIG)	Recommended after needlestick or sexual exposure to a person with hepatitis B infection

Opportunistic Infection Prophylaxis

Some OIs can have an adverse effect on pregnancy. In turn, pregnancy can affect the natural history, presentation, treatment, and significance of some OIs. Women should be monitored carefully for OIs during pregnancy, with special attention given to nonspecific symptoms such as fatigue, back pain, and weight loss, which may be due to HIV-related illness rather than to pregnancy. Respiratory symptoms in particular merit rapid, aggressive investigation. Clinicians should follow the most current recommendations of the USPHS and the Infectious Diseases Society of America, which give

special consideration to pregnant women for each OI discussed. (*Guidelines for Prevention of Opportunistic Infections among HIV-Infected Persons—2002*. June 14, 2002. Available online at <http://aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=13>.) The indications and recommendations for OI prophylaxis generally should follow the guidelines for adults (see chapter *Opportunistic Infection Prophylaxis*). However, because of the risks of teratogenicity or harm to the developing fetus, some drugs routinely used for prophylaxis of OIs in nonpregnant adults are contraindicated during pregnancy.

Special Considerations for OI Prophylaxis during Pregnancy

Trimethoprim-sulfamethoxazole

Trimethoprim inhibits the synthesis of metabolically active folic acid. In pregnant women, folate deficiency increases the risk of neural tube defects in the developing fetus. Pregnant women, or women who may become pregnant, who are taking trimethoprim-sulfamethoxazole (Septra, Bactrim, cotrimoxazole) have an increased risk of folate deficiency and should be given folate supplementation to reduce the risk of neural tube defects. Some experts recommend high doses of folate (eg, 4 mg daily) to overcome the folate antagonism of trimethoprim-sulfamethoxazole. Because neural tube development occurs very early in pregnancy, folate supplementation should be started at least 1 month before conception, if possible.

Genital herpes

Women with HIV infection are more likely than HIV-uninfected women to experience outbreaks of herpes. If herpes simplex virus (HSV) is transmitted to the infant, neonatal infection can be severe, even if it is detected and treated early. Strongly consider obtaining HSV-2 serologies in a woman whose clinical history is unclear. Treatment for symptomatic HSV infections should be offered during pregnancy, and suppressive therapy should be given to women with frequent recurrences. If a woman has an active outbreak of genital HSV or experiences prodromal symptoms at the time of labor or membrane rupture, delivery by cesarean section is indicated. Prophylaxis with oral acyclovir late in pregnancy to prevent neonatal herpes transmission is controversial and is not routinely recommended.

Tuberculosis

Prophylaxis is recommended for any woman with either a positive purified protein derivative (PPD) skin test (≥ 5 mm induration) or a history of exposure to active tuberculosis, after active disease has been ruled out. Because of concern about possible teratogenicity from drug exposure, clinicians may choose to delay prophylaxis until after the first trimester. Patients receiving isoniazid also should receive pyridoxine to reduce the risk of neurotoxicity.

Toxoplasmosis

All HIV-infected persons should be tested for immunoglobulin G (IgG) antibodies to *Toxoplasma*

soon after HIV diagnosis, and this should be a part of antenatal testing for pregnant women with HIV infection. Women with a negative IgG titer should be counseled to avoid exposure to *Toxoplasma* (eg, by avoiding raw or undercooked meats, unwashed or uncooked vegetables, and cat feces). Women with previous exposure to *Toxoplasma* (positive IgG titer) may be given prophylaxis during pregnancy, if indicated. For women who require prophylaxis, trimethoprim-sulfamethoxazole is the preferred agent; some specialists advise against giving pyrimethamine during pregnancy.

Antiretroviral Therapy

Current USPHS guidelines for the use of ARV agents in pregnant women with HIV infection recommend treating HIV infection in pregnant women using the same principles and modalities as for nonpregnant individuals. The 3-part zidovudine (ZDV) regimen (antenatal, intrapartum, and neonatal) should be recommended as the minimum intervention to reduce the risk of perinatal HIV transmission. In addition to the 3-part ZDV regimen, the guidelines recommend offering effective combination ART to all pregnant women to maximally suppress viral replication, minimize the risk of developing resistant virus, and reduce the risk of perinatal transmission. The choice of ARV regimen should take into account the optimal regimen for the woman's health, the potential effect on the fetus and infant, the woman's previous experience, if any, with ARV treatment, and her stage of pregnancy. In most cases, the regimen should include ZDV, if possible. ARV agents with known teratogenic effects, such as efavirenz, should be avoided, especially in the first trimester. Some clients and HIV care providers may elect to withhold ARV therapies during the first trimester, because this is a period of rapid organogenesis and an increased risk of birth defects if teratogen exposure occurs. For women already taking ART at the time they become pregnant, the ARV regimen should be reevaluated for its appropriateness during pregnancy to avoid potentially toxic medications and to ensure maximal virologic suppression. If a decision is made to interrupt ART during the first trimester, the woman should be instructed how and when to stop and to restart ART and should be made aware of the risk of viral rebound during the ARV interruption.

Discussion of treatment options should include the known and unknown effects of ARV drugs on the fetus and newborn, recommendations for the woman's health,

and the known efficacy of ZDV in preventing perinatal transmission. Recommendations should be noncoercive, and the woman herself must make the final decision regarding the use of ARV drugs. A decision to decline ART should not result in punitive action or denial of care; nor should ART be denied to any woman who wishes to minimize the fetus's exposure to drugs and therefore chooses to receive only ZDV to reduce the risk of perinatal transmission. The woman should be informed that ZDV alone does not reduce the baby's HIV risk as much as a potent triple-drug therapy, and also that monotherapy with any ARV drug confers a risk of drug resistance that may affect the success of future treatment for her and for the infant (if HIV infected).

The *USPHS Perinatal ARV Guidelines* are updated regularly as clinical trial results are reported and ARVs are approved by the U.S. Food and Drug Administration. The guidelines include recommendations regarding ARV regimens, modes of delivery (vaginal vs cesarean section), and potential adverse events, as well as a detailed discussion of individual ARV agents. Pregnant women with HIV infection should be managed as a collaboration between an HIV specialist and the obstetric provider.

For further information about ARV treatment during pregnancy, see the chapter *Reducing Maternal-Infant HIV Transmission* and the *USPHS Perinatal ARV Guidelines*.

Antiretroviral Pregnancy Registry

To improve tracking of pregnancy-related adverse effects and fetal effects, an Antiretroviral Pregnancy Registry has been established as a collaborative project among the pharmaceutical industry, pediatric and obstetric providers, the CDC, and the National Institutes of Health. The registry collects observational data on HIV-infected pregnant women taking ARV medications to determine whether patterns of fetal or neonatal abnormalities occur. Pregnant women taking ARVs can be placed in this confidential follow-up study by calling 800-258-4263, 8:30 AM to 5:30 PM eastern time; the fax number is 800-800-1052. Information is confidential and patients' names are not used. Providers are encouraged to add to the available information on fetal risk by using this registry at first contact with a pregnant woman taking ARVs. More information can be obtained at <http://www.APREgistry.com>.

Pregnancy-Specific Complications and Management

Nutrition Risk and Inadequate Weight Gain

Maternal nutrition and weight must be monitored throughout the pregnancy. A food diary may be a useful tool in assessing intake, and nutritional counseling is recommended.

Nausea and Vomiting

Women with signs of dehydration should be assessed and treated appropriately in collaboration with the obstetrician or nurse-midwife. Any medication used for nausea and vomiting must be assessed for drug-drug interactions with all HIV-related medications the patient is already taking. Women who are not taking ART at the beginning of their pregnancy usually are assessed and placed on an ARV regimen at the end of the first trimester, when the nausea and vomiting of early pregnancy have improved.

Hyperglycemia

Pregnancy is a risk factor for hyperglycemia, and women treated with protease inhibitors (PIs) may have an even higher risk of glucose intolerance than other pregnant women and must be monitored carefully. New-onset hyperglycemia and diabetes mellitus, and exacerbation of existing diabetes, all have been reported in patients taking PIs. Clinicians should educate women taking PIs about the symptoms of hyperglycemia and closely monitor glucose levels. Some clinicians check glucose tolerance at 20-24 weeks and again at 30-34 weeks if the woman is taking PIs. The baby should be checked for neonatal hypoglycemia at 1 and 4 hours.

Lactic Acidosis

Lactic acidosis is a rare but life-threatening complication that has been reported in pregnant women taking nucleoside reverse transcriptase inhibitors, particularly didanosine and stavudine. The combination of didanosine and stavudine should be avoided during pregnancy and prescribed only when the potential benefit clearly outweighs the potential risk. Clinical suspicion of lactic acidosis should be prompted by vague symptoms such as malaise, nausea, or abdominal discomfort or pain. Lactate levels, electrolytes, and liver function tests should be monitored carefully, particularly in the third trimester.

Hyperbilirubinemia

Women who are taking indinavir may have an increased risk of nephrolithiasis, but evidence of harm to the newborns has not been demonstrated. Women taking indinavir or atazanavir frequently develop elevated indirect bilirubin, but it is not known whether treatment during pregnancy exacerbates physiologic hyperbilirubinemia in the newborn.

Pain Management

Pain management during labor and delivery may be complicated by drug interactions with ARVs and by the higher medication tolerance in women who have addictions. Additional pain medication may be needed for women with histories of drug use.

Perinatal Considerations

The risk of HIV infection of the fetus during invasive procedures (eg, amniocentesis, chorionic villus sampling, percutaneous or umbilical cord blood sampling) must be balanced against the possible benefits of these procedures. Invasive procedures should be performed only after discussion with and consent from the pregnant woman.

Postpartum Considerations

Because HIV can be transmitted to the infant through breast-feeding, breast-feeding is contraindicated in the United States and other resource-adequate countries where safe replacement feeding is available. Breast-feeding information should be removed from patient educational material pertaining to labor and delivery. Breast binding and ice packs can be used as needed to

reduce lactation discomfort. Clinicians should recognize that women in some cultural groups are expected to breast-feed and they may need additional support to use formula rather than breast-feed.

ART should be continued as indicated by the *USPHS Perinatal ARV Guidelines*. Maternal and infant medication adherence must be discussed with the new mother. Adherence barriers for the mother during the postpartum period may be different from those during pregnancy (eg, because of changes in daily routine, sleep/wake cycles, and meals).

New mothers should be observed carefully for signs of bleeding or infection. If the mother's glucose tolerance test was abnormal during pregnancy, she should be reevaluated (by 2-hour glucose tolerance test) 6 weeks postpartum and should be screened yearly for diabetes.

At the 2-week postpartum follow-up visit, the clinician should address the patient's concerns, screen for postpartum depression, assess adherence to her own and the infant's ARV medications, and ensure follow-up with the primary HIV care provider, pediatrician, and obstetric provider. This visit also affords an opportunity to address the woman's contraceptive needs and options, if this was not done previously.

Contraception

Many contraceptive choices are available for HIV-infected women; some considerations are discussed in Table 5. Depending on the woman's risk factors, consistent condom use should be emphasized, with or without other methods of contraception, to prevent the transmission of HIV and the acquisition or transmission of other STDs.

Table 5. Advantages and Disadvantages of Various Contraceptives

Contraceptive Type	Advantages	Disadvantages
Barrier Methods		
Male and female condom	Protect against transmission of HIV and STDs	- Requires partner cooperation and correct technique - High failure rate when used incorrectly
Diaphragm and cervical cap		- Requires partner cooperation and correct technique - High failure rate when used incorrectly
Sponge		Does not prevent STD or HIV transmission
Hormonal Methods		
Oral*	- Very effective - Lighter menstrual flow	- May have significant drug-drug interactions with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) that may affect the efficacy and toxicity of estradiol and norethindrone, and of certain PIs* - Consider alternative methods for women taking PIs or NNRTIs - Some concern about increased cervical proviral shedding
Injectable depot medroxyprogesterone acetate (DMPA, Depo-Provera)	Effective contraception for 3 months	- Possible increased risk of genital tract HIV shedding - Long-term concern about osteoporosis
Transdermal/Patch	- Effective - Lighter menstrual flow	- No studies to document pharmacokinetic interactions, but possible significance - Possible increased risk of HIV viral shedding
Vaginal ring	- Effective - Lighter menstrual flow	- No studies to document pharmacokinetic interactions, but possible significance - Possible increased risk of HIV viral shedding
Intrauterine devices (IUDs)	- Effective for long-term use - No evidence of increased HIV viral shedding	Possible blood loss with Copper T IUD
Surgical Methods		
Bilateral tubal ligation (female)	Effective; permanent	- Does not prevent STD or HIV transmission - No future fertility (usually not reversible)
Vasectomy (male)	Effective; permanent	- Does not prevent STD or HIV transmission - No future fertility (usually not reversible)
Spermicides		
Spermicides		- Not currently recommended - Nonoxynol-9 increases risk of HIV transmission - Do not prevent STD or HIV transmission

* See chapter *Antiretroviral Medications and Oral Contraceptive Agents* and U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7.

Patient Education

- ◆ Reinforce regularly and clearly the notion that, when the mother cares for herself, she is caring for her infant. Talk with the patient about stress, the importance of adequate mild-to-moderate exercise, and sufficient rest.
- ◆ Emphasize that regular prenatal care is extremely important to prevent complications of pregnancy.
- ◆ Use of a prenatal vitamin supplement is important, but cannot replace healthy food intake. Develop a plan with the patient for attaining the desired weight gain during pregnancy, while maintaining a healthy nutritional intake.
- ◆ Cigarette, alcohol, and drug use contribute to poor maternal nutrition and can harm the developing fetus. Illicit drug use also increases the risk of transmitting HIV to the infant. Injection drug use can transmit hepatitis B and C and cytomegalovirus (CMV) to the mother as well as to the baby. Encourage cessation of cigarette, alcohol, and drug use, and offer referrals for treatment, as needed.
- ◆ Be sure the woman understands all planned procedures and treatments and understands their potential risks and benefits both to herself and to the fetus.
- ◆ Discuss the risks and benefits (to the woman and fetus) of each medication to be taken during pregnancy, including those for which there are limited data on teratogenicity.
- ◆ Discuss ART as part of the strategy to reduce the risk of perinatal HIV transmission to the newborn. Allow the woman to choose whether to add ZDV to her combination ARV regimen (if applicable), or take it alone. The risk of developing ZDV-resistant HIV should be discussed if ZDV is used alone.
- ◆ For women at risk, diligent use of "safer sex" during pregnancy is important to prevent STDs and CMV, which can cause more complications when HIV is present. STDs can harm fetal development and may increase the risk of HIV transmission to the baby. New genital herpes infections during pregnancy can cause severe complications and even death in neonates.
- ◆ For women with negative *Toxoplasma* titers, explain the need to avoid undercooked meats, soil, and animal feces.
- ◆ Teach the pregnant woman how to obtain medical attention quickly at the first signs of OI or other complication. Discuss what to watch for and how to get help when emergencies arise in the evenings or on weekends or holidays.
- ◆ Help the patient clarify her child care options and encourage her to begin putting in place long-term child care and guardianship plans in case she becomes too sick to care for her child or children.

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Antiretroviral Medications and Oral Contraceptive Agents

Background

This chapter highlights the interactions between currently available antiretroviral agents and oral contraceptives.

The oral contraceptives ethinyl estradiol and norethindrone may interact in complex ways with protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs). The mechanism of these interactions may be multifactorial and includes the activity of these agents on cytochrome P450 enzymes. Pharmacokinetic studies have shown changes (either increases or decreases) in levels of ethinyl estradiol

and norethindrone in women who are taking certain PIs or NNRTIs. Other studies have shown decreases in levels of amprenavir (a PI) in women taking oral contraceptives.

The clinical significance of these drug interactions has not been evaluated thoroughly, but may cause oral contraceptive failure or antiretroviral failure, or medication toxicity, depending on whether drug levels are lowered or raised by the interacting drug.

Table 1 summarizes the available pharmacokinetic data. A more comprehensive review of oral and nonoral contraceptives for HIV-infected women can be found in the chapter *Care of HIV-Infected Pregnant Women*.

Table 1. Interactions between Antiretroviral Agents and Oral Contraceptives

Antiretroviral Agent	Pharmacokinetic Changes with Oral Contraceptives	Comments
Protease Inhibitors		
Atazanavir (ATV, TAZ, Reyataz)	- EE AUC increased 48% - NE AUC increased 110%	- Use lowest effective dose of each OC component and monitor for adverse effects. - Consider alternative methods of contraception to avoid OC adverse effects.
Fosamprenavir (FPV, Lexiva), Amprenavir (AMP, Agenerase)	C_{min} of EE/NE increased 32-45%; no significant change in AUC - Amprenavir AUC decreased 22% and C_{min} decreased 20%	- To avoid risk of ARV failure, do not coadminister amprenavir or fosamprenavir with OCs. - Consider alternative methods of contraception.
Indinavir (IDV, Crixivan)	- EE AUC increased 24% - NE AUC increased 26%	No dose adjustment is recommended.
Lopinavir/ritonavir (LPV/r, Kaletra)	- EE AUC decreased 42% - NE AUC decreased 17%	Use of alternative or additional method of contraception is recommended.
Nelfinavir (NFV, Viracept)	- EE AUC decreased 47% - NE AUC decreased 18%	Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.
Ritonavir (RTV, Norvir)	EE AUC decreased 40%	Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.
Saquinavir (SQV, Invirase, Fortovase)	- No data available regarding effect of SQV on EE or NE levels - SQV kinetics not affected by OC	Until more data are available alternative methods of contraception is recommended.
Tipranavir/ritonavir (TPV/r, Aptivus)	EE C_{max} and AUC decreased approximately 50%	Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz (EFV, Sustiva)	- EE levels increased 37% - No data available on NE component	Use of alternative method of contraception is recommended to avoid OC side effects.
Nevirapine (NVP, Viramune)	- EE AUC decreased 20% - NE AUC decreased 20%	Use of alternative or additional method of contraception is recommended to avoid contraceptive failure.

Key to abbreviations: EE = ethinyl estradiol; NE = norethindrone; AUC = area under the curve (drug concentration); C_{min} = minimum concentration; C_{max} = maximum concentration.

Adapted from U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10, 2006.

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- ◆ U.S. Department of Health and Human Services. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. October 10, 2006. Available online at aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?GuidelineID=7. Accessed July 7, 2007.

Abnormalities of Body-Fat Distribution

Background

Body-fat abnormalities are a recognized complication of antiretroviral therapy (ART). These include central fat accumulation, subcutaneous fat atrophy, and the development of lipomas. Taken together, these abnormalities in fat distribution and body shape have been noted in up to 40–50% of patients treated with ART. The etiology of these changes in body habitus is not well understood, but research to date suggests that it is multifactorial, with components related to specific antiretroviral (ARV) medications, HIV-related immune depletion and immune recovery, hormonal influences, individual genetic predispositions, and non-HIV-related factors such as diet and obesity. In fact, lipodystrophy probably is not a single syndrome, but rather several separate but interrelated clinical presentations.

Lipodystrophy may present as isolated fat accumulation (lipoaccumulation), fat wasting (lipoatrophy), or a combination of both. The most common morphologic changes seen in fat accumulation are an enlarged abdomen from central or visceral fat accumulation, breast enlargement (gynecomastia), and development of a dorsocervical fat pad (“buffalo hump”). Lipoatrophy is seen most commonly as the loss of subcutaneous fat in the face, arms, legs, and buttocks. Lipoatrophy differs from the generalized wasting seen in advanced AIDS, because lean cell mass generally is preserved.

Severe lipoaccumulation can cause discomfort and, in some cases, impairment of breathing or other bodily functions. It also may be associated with other metabolic abnormalities, including dyslipidemia and the metabolic syndrome. Both lipoaccumulation and lipoatrophy can be disfiguring, can damage self-image and quality of life, and can negatively influence ARV adherence.

Research into the causes and manifestations of lipodystrophy has yielded varying results, in part because there is no standard clinical case definition of lipodystrophy. The prevalence of and risk factors for lipodystrophy are not well understood. The condition seems to develop more frequently in patients who are older and have longer exposure to ART. In some studies, lipodystrophy has been associated with lower nadir CD4 count as well as with sex (central lipoaccumulation may be more common in women). It has been

associated with protease inhibitors (PIs) and with nucleoside reverse transcriptase inhibitors (NRTIs), but does not appear to be associated with nonnucleoside reverse transcriptase inhibitors (NNRTIs). However, it may develop in patients who have never received PIs, and occasionally in ARV-naïve individuals. PIs appear to be associated more commonly with fat accumulation, whereas NRTIs, most notably stavudine, are associated with lipoatrophy.

S: Subjective

The patient may report any of the following: abdominal fat accumulation with change in waist size, increased neck size, “buffalo hump,” and enlarged breasts; women may note an increase in bra size. The patient also may report sunken cheeks, temporal wasting, decreased arm or leg circumference, prominence of veins in the arms or legs, buttock flattening, and even pain in walking because of atrophy of fat padding around the soles of the feet. The patient may volunteer that these changes are causing emotional distress.

Inquire about CD4 nadir, ARV medication history, duration of and response to each regimen, and recent medication adherence. Ask about past medical and family history, specifically regarding hyperlipidemia, diabetes or insulin resistance, other metabolic disorders, and cardiovascular disease. Elicit the patient’s emotional responses to the body shape changes.

O: Objective

Compare past and current weights. Calculate body mass index. Measure and document waist and hip circumferences; check waist-to-hip ratio. An abdominal circumference >102 cm (39 inches) in men and >88 cm (35 inches) in women is the clinical definition of abdominal obesity and is associated with the metabolic syndrome. Waist-to-hip ratios >0.95 in men and >0.85 in women are associated with an increased risk of coronary heart disease.

Examine the head, neck, back, breasts, and abdomen for fat accumulation, especially looking for dorsocervical fat

pad and facial, neck, or breast enlargement. Examine the face and extremities for subcutaneous fat loss (eg, in the cheeks, temples, limbs, and buttocks).

Review laboratory history (glucose, lipid panel), to identify other metabolic disorders. (See chapters *Dyslipidemia* and *Insulin Resistance and Hyperglycemia on Antiretroviral Therapy*.)

A: Assessment

No uniform standard criteria are available for defining or grading lipodystrophy in clinical practice. Clinicians must base their assessment on physical examination (for characteristic body-shape changes) and lipodystrophy-associated symptoms and psychological consequences.

In research settings, modalities such as dual-energy x-ray absorptiometry (DEXA), computed tomography (CT), and magnetic resonance imaging (MRI) have been used to characterize lipodystrophy. Anthropometric measurements may be made in the clinic by trained personnel (eg, nutritionists), but do not measure visceral fat directly. Although measurements such as waist circumference cannot be used to assess lipodystrophy, they have been validated (in non-HIV-infected individuals) as an assessment of cardiovascular risk. Bioelectrical impedance analysis (BIA) does not measure regional body composition and thus is not used to measure abnormal body-fat changes.

P: Plan

Laboratory

Check for other metabolic abnormalities associated with the use of ART, such as dyslipidemia and impaired glucose metabolism. See chapters *Dyslipidemia* and *Insulin Resistance and Hyperglycemia on Antiretroviral Therapy* for further information about workup and treatment.

Evaluate the effect of body-shape changes on the patient's self-esteem, medication adherence, and interpersonal relationships. Refer the patient for psychological or adherence support and counseling, if indicated. If the patient is distressed enough to consider discontinuing or interrupting ART, review with the patient any gains he or she has made on ART and discuss treatment options (see below). In some cases the patient may insist on discontinuing ARV medications; in this situation, carefully review the risks and benefits of treatment interruption, as well as the alternatives to discontinuing treatment.

Treatment

Consistently effective treatments for lipodystrophy have yet to be identified. In general, patients with marked or severe lipodystrophy have shown poor or inconsistent responses to interventions. The best approaches to lipodystrophy are prevention and early intervention.

Clinicians can help to prevent lipodystrophy by avoiding, whenever possible, ARV agents known to confer a greater risk of this disorder (particularly stavudine). All patients who take ARVs should be monitored carefully for the development of lipodystrophy. If lipodystrophy is noticed, intervention should be initiated, if possible.

The optimal management of lipodystrophy is not known, although the following approaches can be considered. Also consider referring the patient to clinical studies of lipodystrophy treatment.

Drug Substitutions

Avoiding thymidine analogue NRTIs, particularly stavudine, and avoiding the NRTI combination stavudine + didanosine have been shown to reduce the risk of lipoatrophy. In patients with lipoatrophy, modest long-term improvement has been demonstrated after switching from thymidine analogues (stavudine and zidovudine) to nonthymidine analogues (such as abacavir or tenofovir) or to NRTI-sparing regimens. Before switching therapies, carefully assess the potential risk to the patient's long-term HIV management.

Nonpharmacologic Measures

Diet

The effects of diet on lipodystrophy have not been evaluated thoroughly. If overall weight reduction is needed, recommend dietary changes and exercise. Avoid rapid weight loss plans, as lean body mass is often lost disproportionately. Refer to a dietitian, to help the patient decrease his or her intake of saturated fat, simple sugars, and alcohol.

Exercise

Regular, vigorous cardiovascular exercise may help control central fat accumulation, whereas muscle-building (strength training) will improve the ratio between fat and muscle. Some studies of exercise have shown a reduction in visceral fat accumulation with minimal or no changes in peripheral lipoatrophy. Moderate aerobic exercise should be encouraged in all patients.

Pharmacologic Measures

Recombinant Human Growth Hormone

Treatment with recombinant human growth hormone (rHGH), 3-6 mg/d for 12 weeks followed by maintenance therapy with lower doses of 1-2 mg/d, has been shown to reduce visceral fat with minimal impact on peripheral fat wasting. However, the high cost of rHGH, the high rate of adverse effects (including insulin resistance), and the frequent recurrence of morphologic abnormalities once rHGH is discontinued have resulted in a limited role for this treatment.

Insulin-Sensitizing Agents

In diabetic and non-HIV lipodystrophy, treatment with thiazolidinediones may decrease visceral fat, increase peripheral fat, and improve glycemic control. Unfortunately, studies of rosiglitazone as treatment for lipoatrophy in HIV-infected patients have shown mixed results. Some small studies have reported improvement in peripheral fat loss; however, a larger, 48-week randomized trial of rosiglitazone in HIV-infected patients with lipoatrophy found no improvement in fat mass. Therefore, rosiglitazone cannot be recommended currently for the treatment of lipoatrophy.

Metformin has been somewhat effective in treating lipoaccumulation in patients with insulin resistance, but may cause worsening of lipoatrophy. Metformin should not be given to patients with an elevated risk of lactic acidosis.

Studies of insulin-sensitizing agents continue.

Plastic and Reconstructive Surgery

Various techniques have been investigated, but generally have limited applicability and efficacy. These include liposuction and breast reduction for lipoaccumulation, and cheek implants and autologous fat transfer for facial lipoatrophy. Poly-L-lactic acid (Sculptra, New-Fill) is approved by the U.S. Food and Drug Administration as a treatment for facial lipoatrophy. This injectable material has shown to good cosmetic results, at least in the short term.

Although plastic surgery can help some people with lipodystrophy, the treatments are expensive, may need to be repeated, and usually are not covered by private or public-payer sources. In some cases, they may be only a temporary solution, because abnormalities may reappear after treatment.

Patient Education

- ◆ Instruct patients who are receiving ARV medications to inform their health care providers if they notice changes in the shape or appearance of their bodies.
- ◆ Review the importance and benefits of ART and assess adherence to the regimen.
- ◆ For patients with lipoaccumulation, recommend aerobic and resistance exercise to build muscle and reduce fat. Assess resources in your area for safe muscle-strengthening possibilities.
- ◆ If weight reduction is needed, refer to a dietitian for consultation. Remind the patient that quick weight loss diets may result in excessive muscle loss.

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Dyslipidemia

Background

In HIV-infected people treated with antiretroviral therapy (ART), improved life expectancy and the aging process are likely to increase morbidity and mortality from coronary heart disease (CHD). Thus, identification and reduction of modifiable risk factors for CHD are important aspects of primary care for HIV-infected patients. Several risk factors for CHD are common among HIV-infected populations in the United States and Europe. Dyslipidemia is a well-described independent risk factor for CHD that occurs in a high proportion of patients treated with antiretroviral (ARV) medications. Other metabolic abnormalities such as insulin resistance and diabetes may be caused or compounded by ARVs. In addition, some traditional CHD risk factors, including smoking, hypertension, and inactivity, are prevalent in many HIV-infected populations.

Before the widespread use of ARV medications, increases in triglyceride (TG) levels and decreases in total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, and low-density lipoprotein (LDL) cholesterol were reported in individuals with HIV disease. The introduction of combination ART, particularly the use of protease inhibitors (PIs), increased the prevalence of dyslipidemia in HIV-infected patients. In fact, dyslipidemia is associated with certain agents in each of the 3 major classes of ARVs. In the PI class, ritonavir and ritonavir-boosted PIs (with the exception of atazanavir) are particularly likely to cause marked elevations of TG and LDL levels. Nonnucleoside reverse transcriptase inhibitors (NNRTIs) also may contribute to increases in TC, LDL, and TG levels although the effects, particularly with efavirenz, are more variable. Nucleoside analogue reverse transcriptase inhibitors (NRTIs), specifically stavudine, may increase TC and TG levels.

The pathogenesis of ARV-induced dyslipidemia is not well understood. Current research suggests that the dyslipidemia observed in patients taking ART is caused by a combination of factors related to HIV disease, ARV regimens, and individual patient characteristics. Lipid abnormalities may appear or worsen within

a few weeks to months after starting ART. Not all ARV-treated patients experience lipid abnormalities to the same degree. Patients with a personal or family history of dyslipidemia, glucose intolerance, diabetes, obesity, or a combination of these health problems may be genetically predisposed to lipid abnormalities that become evident once ART is initiated.

Published research regarding the relationship between ARVs and the risk of cardiovascular disease has not been conclusive. The largest prospective study of CHD events related to ARVs (the DAD study), showed a small but significant increase in the risk of myocardial infarction among HIV-infected patients treated with ART; moreover, the effect increased with cumulative years of ARV exposure. While awaiting definitive results from this and other studies, it is important to screen and treat patients for lipid abnormalities and for other known CHD risk factors. For patients with CHD or CHD risk equivalents (see below), ARV regimens should, if possible, be selected to minimize the risk of hyperlipidemia.

Guidelines for the evaluation and management of dyslipidemia have been developed by the National Cholesterol Education Program (NCEP). These recommendations and follow-up reports are based on studies of HIV-uninfected patients and may not be entirely applicable to HIV-infected patients. Despite this limitation, expert panels generally recommend similar treatment goals when evaluating and managing dyslipidemia in patients with HIV infection. (For recommendations on screening, see chapter *Initial and Interim Laboratory and Other Tests*.)

S: Subjective

The history should focus on factors indicating coronary artery disease or cardiovascular risk. CHD risk factors are conditions associated with a greater risk of serious cardiac events. A CHD risk equivalent, such as diabetes, is considered to be equal in risk to known CHD. Both CHD risks and CHD equivalents should be the focus of lifestyle modification strategies and lipid-normalizing treatment.

- ◆ Assess for CHD or CHD equivalents.
 - ◆ CHD includes a history of myocardial infarction, unstable angina, stable angina, CHD procedures, or evidence of clinically significant myocardial ischemia.
 - ◆ CHD equivalents include diabetes, peripheral vascular disease, carotid artery disease, abdominal aortic aneurysm, transient ischemic attacks, or 2 or more CHD risk factors with a 10-year risk of CHD >20% (see “Calculations to Estimate the 10-Year Risk of Cardiac Events for Men and Women”, below, or the online risk calculator at <http://hin.nhlbi.nih.gov/atpiii/calculator.asp?usertype=prof>).
- ◆ Assess CHD risks. Major risk factors include hypertension, diabetes, smoking, low HDL, age, and family history of CHD.
- ◆ Assess for causes of secondary dyslipidemias, including diabetes, hypothyroidism, obstructive liver diseases, chronic renal failure, and medications such as corticosteroids or progestins.
- ◆ Screen for other factors that contribute to

hyperlipidemia, including obesity, chronic liver diseases, alcohol abuse, high-fat or high-carbohydrate diet, and prothrombotic or proinflammatory states.

- ◆ Screen for health behaviors that increase CHD risk, including smoking, high-fat diet, sedentary lifestyle, and use of recreational drugs such as cocaine or methamphetamine.
- ◆ Review the patient’s family history for premature CHD, obesity, diabetes, and lipid abnormalities.
- ◆ Review the patient’s medications, with special attention to ARVs known to increase LDL or TG levels (particularly ritonavir and ritonavir-boosted PIs) or decrease HDL.

O: Objective

Check vital signs, weight, and height. Calculate body mass index (BMI). (See chapter *Initial Physical Examination* for information on BMI.)

Perform a focused physical examination with particular attention to signs of hyperlipidemia, such as xanthelasma, and to the cardiovascular system.

Table 1. Low-Density Lipoprotein Cholesterol Goals and Thresholds for Treatment*

Risk Category	Initiate Therapeutic Lifestyle Changes	Consider Drug Therapy	LDL Goal*
Lower risk: No CHD or CHD equivalents and <0-1 risk factor	LDL $\geq$ 160 mg/dL ($\geq$ 4.1 mmol/L)	$\geq$ 190 mg/dL ($\geq$ 4.9 mmol/L) (at 160-189 mg/dL, LDL drug therapy is optional)	<160 mg/dL (< 4.1 mmol/L)
Moderate risk: No CHD or CHD equivalents and $\geq$ 2 risk factors, with 10-year estimated risk <10%	LDL $\geq$ 130 mg/dL ($\geq$ 3.4 mmol/L)	$\geq$ 160 mg/dL ($\geq$ 4.1 mmol/L)	<130 mg/dL (< 3.4 mmol/L)
Moderately high risk: No CHD or CHD equivalents and $\geq$ 2 risk factors and 10-year estimated risk 10-20%	LDL $\geq$ 130 mg/dL ($\geq$ 3.4 mmol/L)	$\geq$ 130 mg/dL ($\geq$ 3.4 mmol/L)	<130 mg/dL (< 3.4 mmol/L) (optional goal of <100 mg/dL)
High risk: CHD or CHD equivalent	LDL $\geq$ 100 mg/dL ($\geq$ 2.6 mmol/L)	$\geq$ 100 mg/dL ($\geq$ 2.6 mmol/L)	<100 mg/dL (< 2.6 mmol/L) (optional goal of <70 mg/dL)

*Non-HDL cholesterol target levels are 30 mg/dL higher than corresponding LDL cholesterol levels.

Adapted from: Adult Treatment Panel III, National Cholesterol Education Program. Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. May 2001; NIH publication 01-3670. <http://www.nhlbi.nih.gov/guidelines/cholesterol/>

Table 2. Classification of Triglyceride Levels

Risk Category	Triglyceride Measurement
Normal triglycerides	<150 mg/dL
Borderline-high triglycerides	150-199 mg/dL
High triglycerides	200-499 mg/dL
Very high triglycerides	≥500 mg/dL

Hypertriglyceridemia is an independent risk factor for CHD. In addition, severe hypertriglyceridemia (eg, TG >1,000 mg/dL) increases the risk for pancreatitis. Patients with marked TG elevations should be treated to reduce this risk.

A: Assessment

Determine whether intervention is appropriate based on the patient's lipid values and identified CHD risks, as indicated in Tables 1 and 2. Aside from LDL, the following major CHD risk factors are listed by the NCEP as requiring intensive lipid management.

- ◆ Cigarette smoking
- ◆ Hypertension (systolic blood pressure ≥140 mm Hg or taking antihypertensive medication)
- ◆ HDL <40 mg/dL (if HDL is ≥60 mg/dL, subtract 1 risk factor)
- ◆ Patient age ≥45 for men, or ≥55 for women

Family history of premature CHD in first-degree relatives aged <55 (men) or <65 (women)

For patients who do not have diabetes or preexisting CHD and who have 2 or more CHD risk factors, calculate the "10-year risk of cardiovascular events" by using the risk-estimate page at the end of this chapter or the online tool at the National Institutes of Health Web site: <http://hin.nhlbi.nih.gov/atpiii/calculator.asp>.

P: Plan

Laboratory

Before starting ART, obtain baseline fasting lipid panel, fasting glucose, and comprehensive metabolic panel.

- ◆ Measure serum lipids after the patient has fasted at least 8 hours (ideally 12 hours). Include TC, HDL, TGs, non-HDL cholesterol with calculated LDL, and TC/HDL cholesterol ratio.

Repeat the fasting lipid panel within 3-6 months after starting an ARV regimen, and sooner (1-2 months) for patients who have abnormalities at baseline.

Patients with normal lipid values should receive annual

screening. Those with abnormal values may need more intensive monitoring (eg, every 4-6 weeks) until the LDL goal is met, after which monitoring every 4-6 months is adequate. If a new ARV regimen is begun, repeat the fasting lipid panel at 3-6 months.

Treatment of dyslipidemia usually involves a multimodal approach, including diet and exercise in all cases, and potentially including lipid-modifying medication, changes in ARV medication, or both as indicated. The primary goal of lipid-lowering therapy is to reduce LDL to target levels. Very high TG levels, may have to be reduced before LDL is treated directly (see below). Table 1 shows the LDL levels at which either therapeutic lifestyle change (TLC) or drug therapy should be initiated, as well as the target goals for LDL cholesterol. The response to therapy should be monitored and therapeutic interventions should be intensified or augmented until lipid targets are met.

Therapeutic Lifestyle Change

TLC, consisting of diet modification and exercise, is fundamental to the management of dyslipidemia in HIV-infected patients. Target goals for lipid abnormalities will be difficult to achieve without prioritizing these efforts. Although TLC is hard to maintain, it can yield significant results in reducing CHD risk and improving quality of life. Effective TLC is best achieved with a multidisciplinary team approach. HIV/AIDS primary care providers can be instrumental in identifying TLC as a treatment priority and providing referrals to nutritionists for dietary counseling, to mental health professionals for assessment of treatable mood disorders, and to social workers, peer counselors, or clinical nurse specialists for assistance with health-behavior changes, self-care strategies, and identification of resources in the community for smoking cessation support and exercise programs.

Treatment for Hypercholesterolemia

All patients with elevated lipid levels should initiate TLC. If pharmacologic intervention is indicated, hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are the first-line treatment for most patients. These agents can be effective in reducing TC, LDL, and non-HDL cholesterol levels in HIV-infected patients (Table 3).

In patients with serum TGs >400 mg/dL, the LDL cholesterol calculation is unreliable. In this situation,

non-HDL cholesterol (TC minus HDL) can be used as a surrogate target of therapy; the non-HDL goal is 30 mg/dL higher than the LDL goal. For these individuals, dietary intervention is warranted, and drug therapy to decrease LDL (or non-HDL) can be considered if TC is >240 mg/dL or HDL cholesterol is <35 mg/dL. For those with TG levels of 200-500 mg/dL, achieving the LDL cholesterol target is the primary goal and lowering non-HDL cholesterol levels is a secondary goal (see Table 1 for LDL intervention levels). (For treatment of high TGs, see “Treatment of Hypertriglyceridemia” below.)

Clinicians should note that PIs interact with most statins and can significantly increase serum statin levels, thus increasing the risk of rhabdomyolysis. Of the statin drugs, pravastatin is the least affected by PIs and is the recommended statin for patients with hypercholesterolemia without hypertriglyceridemia. Atorvastatin, if used, must be initiated cautiously and at a low dosage (note that atorvastatin may lower TGs as well as TC and LDL levels). Lovastatin and simvastatin should not be used in patients taking PIs (Table 4). Cerivastatin has been removed from the market in the United States because of reports of fatal rhabdomyolysis. Other available HMG-CoA reductase inhibitors include rosuvastatin and fluvastatin. These agents have not been as well studied as the others, but given their metabolic pathway, no significant interactions with PIs would be expected. Be aware that various formulations and combination products contain these statins. Check the generic name of components in new or unfamiliar cardiac prescriptions to determine whether they contain lipid-lowering agents.

Recommended starting dosages of statins in patients taking PIs are as follows:

- ◆ Pravastatin: 20 mg orally daily
- ◆ Atorvastatin: 10 mg orally daily

Niacin may be effective as adjunctive therapy, but may worsen insulin resistance. Ezetimibe (Zetia) has not been studied thoroughly in HIV-infected individuals, but in HIV-uninfected patients, it has been effective in combination with statins for patients whose cholesterol is not controlled adequately with a statin alone. Bile acid sequestrants generally should be avoided because they may interfere with the absorption of other drugs, and may increase TG levels. When given concomitantly, statins and fibrates increase the risk of rhabdomyolysis; these must be used cautiously and with careful monitoring.

Treatment of Hypertriglyceridemia

Patients with TG levels between 200 and 500 mg/dL should begin non-drug interventions such as diet modification, reduction in alcohol consumption, aerobic exercise, and smoking cessation. When TG level is >500 mg/dL, a low-fat diet (<15% of caloric intake) is recommended to help prevent pancreatitis, and pharmacologic therapy will probably be required. Patients with CHD or CHD equivalents, those at high risk of CHD, and those with TG levels >200 mg/dL may need pharmacologic therapy.

Fibrates are the first-line drug option for isolated hypertriglyceridemia and are an alternative treatment for combined hypertriglyceridemia and hypercholesterolemia. Fenofibrate or gemfibrozil reduce TG levels effectively in patients on ARVs. Because they are not metabolized by the cytochrome P450 hepatic enzyme system, they do not have significant drug interactions with ARVs. Fibrates are contraindicated in patients with renal failure. Recommended dosages of these agents are as follows:

- ◆ Fenofibrate: 50-200 mg orally daily
- ◆ Gemfibrozil: 600 mg orally twice daily, 30 minutes before meals

If a fibrate alone is inadequate in reducing TGs, several options are possible. A statin (notably atorvastatin, which acts on TGs as well as cholesterol) could be added cautiously, although there is an increased risk of skeletal muscle toxicity with concomitant use of a fibrate and a statin. N-3 (omega-3) fatty acid supplements, administered at 2 g 3 times a day, have decreased TG levels in patients taking ART. Niacin also decreases both TG and TC levels, although its clinical utility is restricted because of associated insulin resistance and flushing.

Switching Antiretroviral Therapy

In patients with CHD or CHD equivalents, ARV medications should, if possible, be selected to minimize the risk of hyperlipidemia. In patients with dyslipidemia caused by ARV agents, data suggest that it may be beneficial to discontinue the offending ARVs if reasonable alternatives exist. Substituting atazanavir or nevirapine in place of a lipogenic PI, or replacing stavudine with abacavir or tenofovir, may improve the lipid profile. Before making ARV substitutions, however, consider carefully the possible effect of the substitution on HIV virologic control and the potential adverse effects of new ARVs. In some cases, antihyperlipidemic agents may still be necessary after ARV substitution.

Table 3. Drug Treatments for Lipid Abnormalities

Lipid Abnormality	First Choice	Second Choice	Comments
Isolated high LDL, non-HDL cholesterol	Statin	Fibrate	Start with pravastatin or atorvastatin. Use low statin dosages and titrate upward; patients taking PIs may have increased risk of myopathy.
Isolated high triglycerides	Fibrate	Statin, N-3 (omega-3) fatty acids	Start with gemfibrozil or fenofibrate. Combined statin and fibrate may increase myopathy risk.
High cholesterol and triglycerides (TG level 200-500 mg/dL)	Statin	Fibrate	Start with pravastatin or atorvastatin. Use fluvastatin, rosuvastatin, gemfibrozil, or fenofibrate as alternative. Combined statin and fibrate may increase myopathy risk.
High cholesterol and triglycerides (TG level >500 mg/dL)	Fibrate	N-3 (omega-3) fatty acids, niacin, statin	Start with gemfibrozil or fenofibrate. Niacin is associated with insulin resistance. May need to add statin if cholesterol is not controlled adequately.

Table 4. Interactions between Statin Agents and Antiretroviral Medications*

Statin	Considerations
Atorvastatin	- Some CYP3A4 metabolism. - Large increase in atorvastatin levels when given with protease inhibitors (PIs). Use lowest possible dosage. Monitor antilipid activity and titrate the statin dosage cautiously. - Monitor closely.
Fluvastatin	Metabolized by CYP2C9, so no significant interactions with PIs or nonnucleoside reverse transcriptase inhibitors (NNRTIs) are expected. Decreased levels of nelfinavir are likely.
Lovastatin; Simvastatin	Extensively metabolized by CYP3A4. Statin levels are increased substantially if coadministered with PIs. These should not be used in patients taking PIs.
Pravastatin	- Renal excretion and some hepatic metabolism. Levels of pravastatin are increased 30% when it is given with lopinavir/ritonavir. Levels of pravastatin are decreased 35% when it is given with ritonavir/saquinavir and decreased 40% when it is given with efavirenz. The clinical significance of these changes in pravastatin levels is unknown. - PI and NNRTI concentrations are not affected. Titrate pravastatin dosage based on antilipid activity.
Rosuvastatin	Metabolized by CYP2C9 and CYP2C19. Mostly excreted in bile. No significant interactions with PIs or NNRTIs expected. Studies are ongoing.

* Note that various formulations and combination products contain statins and other lipid-lowering agents. Check the generic name of components in new or unfamiliar cardiac prescriptions to determine whether they contain lipid-lowering agents.

Calculations to Estimate the 10-Year Risk of Cardiac Events for Men and Women

To calculate the 10-year risk of cardiac events, add up points from the following 5 tables pertaining to age, HDL, systolic blood pressure, TC, and smoking status (Tables 5.1-5.5). Note that in Tables 5.3-5.5, women's points are in parentheses. After adding points from all of the tables, consult Table 5.6. (Alternatively, an online calculator is available at <http://hin.nhlbi.nih.gov/atpiii/calculator.asp>.)

Table 5.1. Estimate of 10-Year Risk of Cardiac Events: Age

Age (year)	Points—Men	Points—Women
20-34	-9	-7
35-39	-4	-3
40-44	0	0
45-49	3	3
50-54	6	6
55-59	8	8
60-64	10	10
65-69	11	12
70-74	12	14
75-79	13	16

Table 5.2. Estimate of 10-Year Risk of Cardiac Events: High-Density Lipoprotein Cholesterol

HDL (mg/dL)	Points—Men	Points—Women
≥60	-1	-1
50-59	0	0
40-49	1	1
<40	2	2

Table 5.3. Estimate of 10-Year Risk of Cardiac Events: Systolic Blood Pressure

Systolic Blood Pressure	Points if Untreated—Men (Women)	Points if Treated—Men (Women)
<120	0 (0)	0 (0)
120-129	0 (1)	1 (3)
130-139	1 (2)	2 (4)
140-159	1 (3)	2 (5)
≥160	2 (4)	3 (6)

Table 5.4. Estimate of 10-Year Risk of Cardiac Events: Total Cholesterol

Total Cholesterol (mg/dL)	Points for Men (Women)				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
160-199	4 (4)	3 (3)	2 (2)	1 (1)	0 (1)
200-239	7 (8)	5 (6)	3 (4)	1 (2)	0 (1)
240-279	9 (11)	6 (8)	4 (5)	2 (3)	1 (2)
≥280	11 (13)	8 (10)	5 (7)	3 (4)	1 (2)

Table 5.5. Estimate of 10-Year Risk of Cardiac Events: Smoking Status

Smoking Status	Points for Men (Women)				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Smoker	8 (9)	5 (7)	3 (4)	1 (2)	1 (1)

Table 5.6. Estimate of 10-Year Risk of Cardiac Events: Calculating Risk

Men		Women	
Point Total	10-Year Risk (%)	Point Total	10-Year Risk (%)
<0	<1	<9	<1
0	1	9	1
1	1	10	1
2	1	11	1
3	1	12	1
4	1	13	2
5	2	14	2
6	2	15	3
7	3	16	4
8	4	17	5
9	5	18	6
10	6	19	8
11	8	20	11
12	10	21	14
13	12	22	17
14	16	23	22
15	20	24	27
16	25	≥25	≥30
≥17	≥30		

Tables are adapted from: Adult Treatment Panel III, National Cholesterol Education Program. *Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults*. May 2001. NIH publication 01-3670.

Patient Education

- ◆ Review the importance of reducing cardiovascular risk factors.
- ◆ Educate patients about the benefits of diet and exercise in improving lipid levels and reducing cardiovascular risk.
- ◆ If lipid-lowering medications are prescribed, advise patients on possible adverse effects, and advise them to call the clinic if these develop.

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Insulin Resistance and Hyperglycemia on Antiretroviral Therapy

Background

Patients taking antiretroviral therapy (ART), particularly certain regimens containing a protease inhibitor (PI), appear to have an increased risk of hyperglycemia and diabetes mellitus. Hyperglycemia with or without diabetes has been reported in 3-17% of patients and has occurred at a median of about 60 days, with a range of 2 days to more than a year, after starting therapy. Disorders of glucose metabolism may present as the following:

- ◆ Insulin resistance, in which higher concentrations of insulin are required to exert normal effects; blood glucose levels may be normal but fasting insulin levels will be high because of compensatory insulin secretion by the pancreas
- ◆ Impaired glucose tolerance (ie, a glucose level of 140-199 mg/dL 2 hours after a 75-g oral glucose load)
- ◆ Impaired fasting glucose (ie, 110-125 mg/dL)
- ◆ Diabetes mellitus, which is diagnosed when the fasting blood sugar is ≥ 126 mg/dL, or the confirmed 2-hour glucose level is ≥ 200 mg/dL during glucose tolerance testing

The incidence of new-onset hyperglycemia in HIV-infected patients taking ART has been reported as about 5%, on average. Even if fasting glucose levels remain normal in patients taking ART, up to 40% of those on a PI-containing regimen will show impaired glucose tolerance. The etiology of insulin resistance and hyperglycemia in HIV-infected patients is probably multifactorial, with varying contributions from traditional risk factors (eg, obesity, family history), comorbid conditions (eg, hepatitis C virus infection), and antiretroviral-related factors (eg, direct effects of PIs, hepatic steatosis, and fat redistribution).

Patients who have preexisting diabetes must be monitored closely when starting ART; some experts would consider a PI-sparing regimen for these patients. Alternatively, PIs with favorable metabolic profiles (eg, atazanavir) may be preferred for such patients. Those with no history of diabetes should be advised about the warning signs of hyperglycemia (polydipsia, polyuria, and polyphagia) and the need to use diet and exercise to maintain an ideal body weight.

S: Subjective

The patient is about to begin ART, has been on an antiretroviral (ARV) regimen that includes a PI, or is overweight, has central fat accumulation, or has lipoatrophy. Although most patients with hyperglycemia are asymptomatic, some may report polydipsia, polyuria, and polyphagia.

History

Include the following in the patient's history:

- ◆ Fat redistribution on ART (see chapter *Abnormalities of Body Fat Distribution*)
- ◆ Family history of diabetes
- ◆ Obesity, or habitual physical inactivity
- ◆ Racial or ethnic heritages at higher risk: African, Hispanic, Native American, Asian-Pacific Islander
- ◆ Hypertension
- ◆ History of low level of high-density lipoprotein
- ◆ History of elevated triglycerides
- ◆ Gestational diabetes or delivery of infant weighing >9 lbs
- ◆ Current pregnancy
- ◆ Hepatitis C virus coinfection
- ◆ Polycystic ovary syndrome

O: Objective

Review previous or baseline blood glucose levels. Document weight and any weight changes or fat redistribution.

A: Assessment

Determine whether the patient has normal blood glucose, impaired fasting glucose, or diabetes (see laboratory recommendations and definitions below).

P: Plan

Laboratory

Most experts (eg, the International AIDS Society-USA) recommend monitoring routine fasting blood glucose levels at baseline and 3-6 months after starting therapy if baseline results are normal. Some recommend 2-hour postprandial measurements or a 75-g oral glucose tolerance test within the first 3-4 months of starting therapy and every 3-4 months thereafter. Monitoring should be more frequent if abnormalities are detected, or any additional risk factors exist, as noted earlier. Patients with these risk factors must be counseled about prevention of hyperglycemia before starting ART.

Treatment

Patients with insulin resistance

For patients with insulin resistance (impaired glucose tolerance) and normal blood glucose levels, current evidence is inadequate to recommend drug treatment. However, lifestyle modifications can be recommended, including exercise, weight loss, and diet changes. Weight loss is strongly recommended if the patient is overweight. Refer the patient to a dietitian. Some studies of insulin resistance in HIV-infected individuals are under way, and patients with access to clinical trials may be interested in these studies.

Patients with hyperglycemia and insulin resistance require treatment. A trial of lifestyle modifications may be attempted, including weight loss (if indicated), diet changes, and exercise. When drug treatment is required, because patients meet the diagnosis of diabetes and lifestyle changes are not adequate, the insulin sensitizers metformin or thiazolidinediones (pioglitazone or rosiglitazone) should be considered. Oral antidiabetic agents may increase the risk of hepatic and renal abnormalities, so patients should be monitored for hepatic toxicity (thiazolidinediones) and lactic acidosis (metformin). Thiazolidinediones should be avoided in patients with significant liver disease. Patients with elevated serum creatinine (>1.5 mg/dL in men or >1.4 mg/dL in women), hepatic impairment, or metabolic acidosis should not take metformin. In some cases,

insulin may be the safest drug therapy for symptomatic hyperglycemia, although episodes of hypoglycemia are much more common with insulin than with most oral agents. For hyperglycemia that is associated with the use of PIs, switching to an alternative agent (eg, a nonnucleoside reverse transcriptase inhibitor or a different PI) may be effective if the HIV treatment history and resistance profile permit.

Patients with diabetes

Treatment should be instituted to control blood sugar and to modify other cardiovascular risk factors, with the aim of preventing heart disease and other end-organ disease.

- ◆ Control glucose: maintain the glycosylated hemoglobin (HbA1c) level at $<7\%$.
- ◆ Treat dyslipidemia: maintain low-density lipoprotein (LDL) at <100 mg/dL and maintain triglycerides at <200 mg/dL.
- ◆ Treat hypertension: maintain systolic blood pressure at <130 mm Hg and diastolic blood pressure at <85 mm Hg.
- ◆ Reduce cardiovascular risk with lifestyle modifications: smoking and alcohol cessation, exercise, weight loss, nutritional counseling.
- ◆ Decrease the risk of end-organ complications:
 - ◆ Measure urine microalbumin and creatinine; if the urine albumin/creatinine ratio is >30 mg/g, treat with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker to slow the progression of nephropathy.
 - ◆ Schedule annual retinal examination by an ophthalmologist.
 - ◆ Perform an annual foot exam.
- ◆ Start aspirin therapy if the patient has evidence of macrovascular disease, a family history of coronary artery disease, a history of smoking, or previous vascular events.

For further information, see the American Diabetes Association, *Clinical Practice Recommendations, Diabetes Care*, at: <http://care.diabetesjournals.org>.

Patient Education

- ◆ Antiretroviral therapy can increase the risk of diabetes in some individuals. Patients should report any difficulty with excessive hunger and thirst and increased urination. Health care providers will monitor blood glucose when doing laboratory work, but it is important for the patient to call if any symptoms are present.
- ◆ Review exercise possibilities to determine what activities might be realistic and acceptable for the patient.
- ◆ Review the patient's eating habits and explain the need to work with a dietitian to keep blood glucose (and triglycerides) within normal limits. A proper diet can reduce the risk of permanent damage to the blood vessels of the eye, the kidney, the brain, and can reduce the risk of a heart attack.
- ◆ Emphasize other lifestyle modifications, such as weight loss (if appropriate).
- ◆ Provide medication-specific education, especially if the patient will be taking metformin or insulin.
- ◆ Consider referral to a diabetic clinic for specialty needs.

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Drug-Drug Interactions with HIV-Related Medications

Background

Drug-drug interactions are common concerns of both patients with HIV and their health care providers. The issues involved in evaluating and drug interactions are complex. Although many questions can be articulated simply (eg, “What antidepressant is least likely to have drug interactions with HIV medications?”), the responses to these questions involve more complex concerns (eg, “In choosing an antidepressant for my patient with HIV, I must consider efficacy, adverse effects, and tolerability as well as drug interactions.”).

This complexity is increased because antiretroviral agents, particularly protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), can cause and be affected by alterations in the activity of the cytochrome P450 enzymes in the liver. These enzymes are responsible for metabolizing many medications. Understanding the relevance of the influence of P450 enzymes is challenging because of several factors, including the following:

- ◆ Different drugs affect different P450 enzymes.
- ◆ Some medications have dosage-related responses that influence their effects on P450 enzymes.
- ◆ Formal pharmacokinetic studies on drug combinations are limited.
- ◆ Even when pharmacokinetic data exist for specific drug combinations, the clinical significance of any changes in pharmacokinetic parameters may not be clear.
- ◆ Patients taking HIV medications often have complex drug regimens. The interaction of only 2 drugs is rarely the concern; more often, patients are taking 3 or more medications that could influence interactions. Pharmacokinetic studies that evaluate the clinical significance of drug interactions involving more than 2 medications are less likely to be available.
- ◆ The P450 system is not the only influence on medication activity. Other influences include absorption, food-drug interactions, protein binding, altered activation of medications intracellularly, and altered efflux-pump activity.

Information on various drug-drug interactions is available in guidelines and via the Internet (see “Resources” below). Such resources can provide data regarding 2-drug combinations, but rarely consider all the complexities outlined above. What follows, therefore, is a suggested approach to considering drug-drug interactions in the management of HIV-infected patients and making patient-specific decisions.

S: Subjective

A new patient arrives for his clinic intake appointment. The patient receives his medical care from a local infectious-disease physician who has only a handful of HIV-infected patients in her practice. The patient was recently released from the hospital with a discharge diagnosis of pneumonia and *Mycobacterium avium* complex (MAC). He is not yet taking HIV medications, but is likely to start them in the next several weeks after the establishment of care and adherence support programs. Other problems include hyperlipidemia, erectile dysfunction, diabetes, depression, and herpes. The clinician wants to review the patient’s medication list to check for any potential drug-drug interactions.

O: Objective

Review the patient’s pharmacy records for current medications. As requested, the patient has brought in all his medications from home for review. His current medication list includes the following:

- ◆ Clarithromycin 500 mg twice daily
- ◆ Ethambutol 1,000 mg daily
- ◆ Rifabutin 300 mg daily
- ◆ TMP-SMX (Septra, Bactrim) DS 1 tablet daily
- ◆ Lovastatin 20 mg daily
- ◆ Metformin 500 mg twice daily
- ◆ Bupropion 150 mg daily
- ◆ Acyclovir 400 mg twice daily
- ◆ Milk thistle (*silymarin*)
(patient takes as needed for energy and liver health)

A: Assessment

Step 1: Identify interactions and classify them as follows:

- ◆ Definite interactions
- ◆ Probable interactions
- ◆ Possible interactions

Definite Drug Interactions

A drug interaction is definite if a high level of evidence is available regarding the drug combination, the clinical significance of the interaction is well understood, and consensus exists regarding the management strategy (eg, dosage adjustments). Common definite interactions for HIV patients include:

- ◆ Certain combinations of HIV agents (eg, boosted PIs, NNRTI + PI combinations)
- ◆ Rifamycins and PIs or NNRTIs
- ◆ Statins and PIs + NNRTIs
- ◆ Erectile dysfunction agents and PIs
- ◆ Methadone and PIs

Probable Drug Interactions

A drug interaction is probable if the limited available evidence suggests that an interaction may occur, even if the clinical outcome or significance may not be clearly established. Effective management of a probable interaction is based on assessment and clinical judgment about the risks and benefits of a particular combination for that patient. Examples of probable interactions with HIV-related medications include:

- ◆ Antidepressants and PIs or NNRTIs
- ◆ Oral contraceptives and PIs
- ◆ Warfarin and PIs or NNRTIs
- ◆ Proton pump inhibitors or H-2 blockers and atazanavir

Possible Drug Interactions

Possible drug interactions may be difficult to distinguish from probable drug interactions, but in these cases, only theoretical evidence is available. The proper management of such an interaction requires weighing the risks and benefits of the combination and making sound clinical judgments. Examples of possible drug interactions with HIV medications include:

- ◆ Herbal products and PIs or NNRTIs (except in the case of St. John's wort, for which definite information on interactions is available)
- ◆ Antidiabetic medications and PIs or NNRTIs
- ◆ Antifungal agents and PIs or NNRTIs (except in the case of voriconazole, for which definite information on interactions is available)
- ◆ Antiseizure medications and PIs or NNRTIs
- ◆ Antipsychotic agents and PIs or NNRTIs

Memorizing all the potential drug interactions is impossible. It is possible, however, to remember a few commonly used drug combinations with the potential for clinically significant interactions. The above examples of definite, probable, and possible interactions are reasonable "red flag" drug combinations that can be recalled easily. In addition, certain Internet resources allow you to submit all of a patient's current medications and planned additions (eg, lopinavir/ritonavir as part of a new antiretroviral regimen) and receive feedback on potential interactions (see "Resources" below). Finally, consultation with clinical pharmacists can aid in identifying and classifying potential interactions.

P: Plan

Step 2: The patient described above will start an antiretroviral regimen of lopinavir/ritonavir + zidovudine + lamivudine. The PI may cause problematic drug-drug interactions with some of his other medications. Develop a plan for management when lopinavir/ritonavir is added to this regimen.

For this patient, the following definite interactions should be of concern:

- ◆ Rifabutin and lopinavir/ritonavir
- ◆ Lovastatin and lopinavir/ritonavir

Refer to available references for management suggestions. Such references include:

- ◆ DHHS Adult and Adolescent Antiretroviral Treatment Guidelines
<http://www.aidsinfo.nih.gov/Guidelines/GuidelineDetail.aspx?MenuItem=Guidelines&GuidelineID=7>
- ◆ HIV InSite Database of Antiretroviral Drug Interactions:
<http://hivinsite.ucsf.edu/arvdb?page=ar-00-02>

- ◆ Toronto General Hospital Drug Interaction Tables
http://tthhivclinic.com/interact_tables.html
- ◆ Discover Drug Interaction Checker
<http://health.discovery.com/encyclopedias/checker/checker.jsp>
- ◆ Check my Meds on AIDSmeds.com
<http://aidsmeds.com/cmm/DrugsNewContent.asp>

Most of these sites include specific dosage adjustments or alternative agents to consider when managing these drug combinations. The following are suggestions for the above interactions:

- ◆ The rifabutin dosage should be 150 mg every other day with standard lopinavir/ritonavir dosing. Alternatively, discuss with the patient's primary care provider whether rifabutin is important to the current MAC regimen or whether the patient could be treated adequately with just clarithromycin + ethambutol to avoid the above interactions.
- ◆ Lovastatin should be discontinued in this patient when lopinavir/ritonavir is begun. To manage hyperlipidemia, the patient should be switched to safer statins such as pravastatin or low-dose atorvastatin.

Although this patient's current medication list does not contain an erectile dysfunction agent, the patient should be educated about the definite interactions and dosage adjustments recommended for patients using those agents with PIs. Some patients may obtain erectile dysfunction agents outside the care of their physician and, if unaware of the interactions and suggested dosage adjustments, may be at risk for life-threatening consequences.

Some additional probable or possible interactions should be considered if PIs are begun, including:

- ◆ Bupropion with lopinavir/ritonavir
- ◆ Milk thistle with lopinavir/ritonavir

The Web sites and references listed above include some information about these potential interactions, but no specific management or dosage adjustments are given. This patient should be monitored for increased effects of bupropion and educated about potential interactions with milk thistle. Clinical judgment and decision making with the primary care provider and other subspecialists (eg, psychiatrists) may be required. Consultation with clinical pharmacy services also may assist in evaluating the potential significance of an interaction and developing management strategies.

Patient Education

- ◆ Instruct patients that HIV medications, in particular PIs and NNRTIs, have a high potential for significant drug interactions.
- ◆ Tell patients to take all their medicines, including any herbal supplements and over-the-counter remedies, with them to all medical appointments. If they cannot take the actual bottles with them, they should make a list of current prescribed medications, supplements, and over-the-counter medications.
- ◆ Patients should have their primary care provider or pharmacist review any newly prescribed medications along with their current list of medicines. This is especially important if another physician prescribes a new medication.
- ◆ Patients should not "borrow" medications from friends or family. Assure patients that if they have a problem that needs medical treatment, their primary care provider will discuss it and choose the safest treatments for them.
- ◆ Tell patients that if they are considering buying a new nutritional or herbal supplement or an over-the-counter product, they should consult their pharmacist or primary care provider about interactions with drugs on their current medication list.
- ◆ Not all drug interactions are cause for alarm. Some drug combinations are safe for certain people, but less safe for others. Warn patients not to stop taking any medicines without the advice of their primary care provider.

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Resources

- ◆ *HIV InSite Database of Antiretroviral Drug Interactions*:
<http://hivinsite.ucsf.edu/arvdb?page=ar-00-02>
- ◆ *Toronto General Hospital Drug Interaction Tables*:
http://tthhivclinic.com/interact_tables.html
- ◆ *Discover Drug Interaction Checker*:
<http://health.discovery.com/encyclopedias/checker/checker.jsp>
- ◆ *Check my Meds on AIDSmeds.com*:
<http://aidsmeds.com/cmm/DrugsNewContent.asp>

Adverse Reactions to HIV Medications

Background

Clinicians and patients face many challenges associated with antiretroviral (ARV) therapy. These include decisions about when to start therapy, what regimen to start with, when to change medications, and how to switch if a regimen is failing. Although clinical research should guide the selection of ARV regimens, it is important to remember that the best regimen for any individual patient is the regimen he or she is willing and able to take. No regimen, no matter how potent, will be effective if the patient does not take it properly. Adherence to ARV therapy is one of the most important predictors of treatment efficacy. Although many factors may interfere with adherence to ARV therapy, adverse reactions to the medications are among the most important. In one trial, patients with adverse events were 13 times less likely than those without adverse events to have 95-100% adherence. Monitoring and managing adverse reactions to ARVs are crucial to establishing a successful HIV regimen.

Although adverse reactions are common and often predictable, their management must be individualized. Several factors will affect the management of adverse reactions, including comorbid conditions, the patient's other current medications, the availability of alternative regimens, and the patient's history of medication intolerance. In addition, the patient's report of severity can be inconsistent with the clinical interpretation (ie, some patients may overemphasize symptoms, whereas others underemphasize symptoms), and this must be considered when determining the management of adverse reactions.

This chapter reviews some of the most common adverse effects noted as patients start an ARV regimen and suggests strategies for the management of adverse effects. It is not intended as a comprehensive guide to adverse effects. For detailed information regarding assessment of symptoms, see the complaint-specific chapters found in Section 5 of this manual. For information on common adverse reactions to ARV agents and to medications used to prevent and treat opportunistic infections, see Section 10 of this manual. Consultation with an HIV expert also can help in determining the best management when symptoms may have multiple and overlapping causes. Finally, in each

case of suspected medication adverse effects, the patient should be evaluated for other possible causes of his or her symptoms.

S: Subjective

A patient presents 2 weeks after starting her new ARV regimen complaining of fatigue, nausea, and rash. Her current ARV medications include a combination of zidovudine (ZDV), lamivudine (3TC), and abacavir (ABC) (ie, Trizivir)—and nevirapine (NVP). She has continued her prophylactic medications, which include trimethoprim-sulfamethoxazole (TMP-SMX) and fluconazole. Although she reports that she had not missed any doses of her medications and she likes the low pill burden of this regimen, she does not want to continue because she has been feeling so sick that she cannot adequately care for her children. She is asking to stop her ARV therapy because of “too many side effects.”

The patient should be evaluated in the clinic for her complaints about adverse effects.

O: Objective

The following are suggestions for this evaluation; they are not intended to be a complete review of the workup and management of each symptom or objective finding. For more detailed information, refer to the complaint-specific chapters of this manual, as noted above.

- ◆ Vital signs: Fever may indicate a hypersensitivity reaction (HSR), acute hepatitis, or immune reconstitution syndrome related to starting ARV medications. See the chapter *Fever* for a more complete discussion about fever workup and considerations. Tachycardia or hypotension may suggest anemia, HSR, dehydration, or another illness.
- ◆ Physical examination: Pay special attention to the skin (rash, pallor), mucous membranes, and liver (enlargement or tenderness). Positive physical examination findings should be evaluated for severity and extent of involvement.

- ◆ Laboratory tests: Complete blood count is important when monitoring drugs that may cause bone marrow toxicity (eg, anemia, neutropenia). Perform a complete metabolic panel including electrolytes and liver function tests (LFTs). If the history suggests pancreatitis, evaluate amylase or lipase.
- ◆ Other studies: Perform as indicated by symptoms and examination (eg, chest x-ray if respiratory symptoms are present).

A: Assessment

Step 1: Clarify reports of adverse reactions by requesting the following information for each symptom the patient describes:

- ◆ Characterize the symptoms by asking about severity, onset, and frequency. It is also helpful to have the patient describe whether the symptom(s) have been improving or worsening over time.
- ◆ Ask whether the patient has tried any remedies to alleviate the symptom(s) and whether they were helpful.
- ◆ Explore how the patient is currently taking the regimen. Open-ended questions such as: "What are your current medications?" "How often do you take them?" "How many pills of each medicine do you take?" and "Do you take your medicines with or without food?" can be helpful in determining whether the patient has been taking medications correctly. Incorrect administration of medications (eg, taking higher dosages than recommended) can lead to adverse effects and is often overlooked by providers.

Step 2: Assess the severity of the reaction against the need to continue the current regimen. An understanding about the relative availability of alternative ARV regimens is important in this assessment

- ◆ Most adverse effects are self-limited and mild-to-moderate in severity. With supportive care, patients often are able to continue their current medications. This is particularly true for gastrointestinal symptoms (eg, nausea, vomiting, bloating). Supportive care for gastrointestinal adverse effects includes reminding the patient to take medications with food (if appropriate), suggesting the use of ginger-containing beverages or foods to relieve symptoms (see "Nausea," below), and prescribing antiemetics if needed. Other symptoms that can be

monitored carefully with supportive care include: fatigue, malaise, mild rashes, abdominal pain, and bloating.

- ◆ More severe reactions often require discontinuation of the offending medication. These include fever, LFT abnormalities, or severe systemic symptoms. Determining which of the medications is causing the reaction is often challenging, because patients are commonly taking several medications with overlapping toxicities.
- ◆ The threshold for stopping a medication depends in part on the availability of alternative agents for any given patient. Some patients have limited alternatives because their virus is resistant to other ARV agents (eg, patients on salvage ARV regimens). For other patients, alternatives are limited by past adverse effects. For patients who develop significant adverse effects when starting their first ARV regimen, substituting alternative ARV medications that are better tolerated should be considered as early as possible during therapy to avoid nonadherence due to adverse effects. For these situations, single-drug substitutions often improve tolerance and achieve long-term viral suppression.
- ◆ Some patients may refuse to attempt supportive care and refuse to continue treatment. In these situations, it may be best to discontinue all ARV medications and return to an adherence-readiness assessment (see chapter *Adherence*) to determine when to restart medications and what medications to restart (see chapter *Antiretroviral Therapy*).

Clarified Subjective and Objective Information

For the patient who reported nausea, fatigue, and rash 2 weeks after starting ZDV/3TC/ABC (Trizivir) and NVP (see above), additional history, physical examination, and laboratory work yielded the following information:

- ◆ Nausea: This was present since she started ARVs 2 weeks ago. She has had difficulty taking medications with food, because of nausea. No actual vomiting or other abdominal pain has occurred. She has not tried any remedies. The nausea is not worsening and perhaps has improved slightly over the past few days.
- ◆ Fatigue: This was present since she started ARVs 2 weeks ago. She is able to exercise and perform normal daily activities.

- ◆ Vital signs: Normal; no fever or signs of hemodynamic changes.
- ◆ Skin: Skin and conjunctival pallor is noted, along with mild to moderate maculopapular rash on the trunk, back, and extremities. These are associated with slight itching, but no pain. No mucous membrane involvement is noted. The rash has been present for 4 days, with slight improvement over the past day.
- ◆ Abdomen: Nontender, with normal liver size.
- ◆ Complete Blood Count: Normal, except for a slight increase in mean corpuscular volume (MCV), probably from ZDV therapy and not indicating macrocytic anemia.
- ◆ LFTs: Normal.

Availability of Alternative Regimens

A clarified ARV history yielded the following information. The patient took ZDV alone for 3 months a few years ago, during 1 of her pregnancies, and recalls similar feelings of nausea and fatigue that caused her distress at the time. She was able to continue ZDV through the end of her pregnancy. Otherwise, the patient is ARV naive and has many treatment options.

Assessment and Conclusion

The patient's symptoms are mild and are most likely related to starting ARV therapy. Thus, no additional workup is needed at this time. Careful monitoring is important because, if symptoms do not improve over the next few days, the patient should have a more extensive workup for other possible causes of the various symptoms. If other causes of her symptoms are ruled out and she is unable to tolerate supportive care, alternative ARV medications (eg, didanosine, tenofovir, protease inhibitors) can be substituted for medications in her current regimen. Given her ARV history, substitutions are likely to be effective.

P: Plan

Following is a suggested treatment plan for the mild adverse effects exhibited by the patient described above:

Fatigue

Fatigue is a common adverse effect among patients who are starting ARV therapy. It is usually self-limited, and, with reassurance that symptoms should improve

over a few weeks, most patients are able to continue their regimens without any changes. If fatigue does not resolve within the first weeks of treatment, it is important to rule out other causes of fatigue, including depression. For ZDV-containing regimens, practitioners should also rule out ZDV-induced anemia, especially when patients are also taking other medications that can cause bone marrow toxicity (eg, TMP-SMX). Some patients experience fatigue from ZDV even without anemia. If fatigue persists for several weeks or becomes debilitating and other causes are ruled out, consider replacing ZDV in this regimen. (See also chapter *Fatigue*.)

Nausea

Nausea is another common adverse effect described by patients starting a new ARV regimen. Like fatigue, it is usually self-limited, and patients without other systemic symptoms, acute hepatitis, or pancreatitis usually can continue their regimens. Supportive care is often helpful, however, in allowing patients to continue their ARVs. For example, patients should take their medications with food. Small, frequent snacks may be helpful for patients with significant nausea that prevents substantial meals. Clinical trials have suggested that ginger extract may relieve nausea symptoms. Patients can take ginger in a variety of forms, including ginger ale, tea, cookies, and candies. Among the medications that the current patient is taking, ZDV is the most likely culprit to cause persistent nausea. If nausea symptoms persist for several weeks despite taking medications with food, using ginger, or taking other antiemetics, and if other underlying causes are ruled out, consider replacing ZDV in this regimen. (See also chapter *Nausea and Vomiting*.)

Rash

Rash is a common adverse effect of certain ARVs and many other medications. It may present with a wide range of severity:

- ◆ Mild rash occurs with no other related symptoms and resolves over days or weeks.
- ◆ Moderate rash may be accompanied by systemic symptoms (eg, fever, LFT abnormalities, myalgias).
- ◆ Life-threatening rashes (eg, Stevens-Johnson syndrome) associated with pain, mucous membrane involvement, fever, LFT changes, and myalgias.

If a patient is taking 2 or more medications that have rash as a possible adverse effect, it may be difficult to

determine which of the medicines is the most likely cause of the rash. In the case of the patient described above, rash may be related to the following:

- ◆ Mild ABC rash: Usually a self-limited reaction that can be treated symptomatically
- ◆ Moderate to severe ABC HSR: Resolution of symptoms requires discontinuation of ABC, but repeat challenge can be life threatening (see below for more details)
- ◆ Mild NVP rash: Usually a self-limited reaction that can be treated symptomatically
- ◆ Moderate to severe NVP rash accompanied by hepatitis: Requires discontinuation of NVP
- ◆ Mild TMP-SMX reaction: Either delayed or part of an immune reconstitution reaction
- ◆ Other reactions: can be caused by other medications, contact dermatitis, folliculitis, immune reactivation or reconstitution effect and other causes

If the clinician discontinues all of the suspect medications and the rash resolves, the patient will be relieved, but the clinician will not be able to determine which medication caused the rash. In cases of mild rash, it is reasonable to try to identify the offending medication by discontinuing 1 medication at a time (generally, a substitution should be made for the discontinued ARV). This situation would require careful clinical judgment or consultation with an expert regarding the advantages or disadvantages of discontinuing each of the suspect medications.

Abacavir hypersensitivity reactions

Abacavir hypersensitivity reactions are a common cause of rash. The initial symptoms of possible ABC HSR are not life threatening, and it is important to try to distinguish true ABC HSR from isolated rash (without other hypersensitivity symptoms), self-limited adverse medication effects, or other illness (eg, influenza). This is often best accomplished by asking a patient who complains of mild gastrointestinal symptoms with or without rash to continue taking all medications while being monitored closely. Careful assessment of symptoms for a few days should clarify whether symptoms are lessening (indicating self-limited effects) or worsening (suggesting of ABC HSR). The pattern of symptom onset is also helpful. For patients with ABC HSR, symptoms usually begin after 10 days of therapy and worsen approximately 30-60 minutes after each ABC dose administration. When ABC is discontinued

because of suspected HSR, patients should never be rechallenged. Initial flulike symptoms are uncomfortable for patients, but not life-threatening. If, however, ABC is discontinued when HSR symptoms are present and is then restarted, life-threatening HSRs may occur.

Clinicians should report ABC HSRs to the following agencies:

- ◆ Abacavir Hypersensitivity Reaction Registry at Glaxo Wellcome at 1-800-270-0425
- ◆ FDA MedWatch program by telephone at 800-FDA-1088, via fax at 800-FDA-0178, via the Internet at <http://www.fda.gov/medwatch/report/hcp.htm>, or by mail at MedWatch HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857

Other Adverse Reactions

Patients may describe any number of adverse effects after starting new medications. Although some adverse effects are directly caused by the medications themselves, some symptoms may occur simply in the process of starting ARVs. The start of ARV therapy may precipitate a significant psychological shift in a patient's perception of self, in living with HIV infection, and in daily routine. In particular, patients who have kept their HIV infection distant from their "everyday" lives may notice significant internal changes as they take medications every day, go to the pharmacy to pick up medications, and make frequent visits to the clinic for evaluation and laboratory work. Some patients become depressed upon realizing that the severity of their illness now requires them to be on treatment. These psychological changes can cause significant symptoms that should be assessed and managed similarly to the pharmacologic adverse reactions.

These psychological effects can be considered "process" effects from starting ARVs, rather than adverse effects of the medications themselves. As with the self-limited adverse effects of early ARV therapy, process effects should become more tolerable over time as the medication regimen becomes routine for the patient. One of the most common process effects is fatigue. Many patients hope that their ARV regimen will give them increased energy and health, and they become frustrated when they notice increasing fatigue after starting the regimen. These patients must be evaluated to rule out common adverse effects that contribute to fatigue (eg, anemia, hepatitis, lactic acidosis). Equally important, especially for patients beginning a new

regimen, symptoms of fatigue could indicate depression or signal that the “process” of taking medications is emotionally difficult. Counseling, peer support, and antidepressant medications can be used to treat this type of fatigue. Often, once patients realize some of the goals of treatment (eg, the CD4 count increases, the HIV viral load becomes undetectable, or symptoms of HIV infection resolve), they recognize the benefits of ARV medications, and their fatigue or other adverse symptoms associated with the process of starting the regimen may lessen.

Clinicians are encouraged to report adverse reactions to medications to the FDA MedWatch program by telephone at 800-FDA-1088, via fax at 800-FDA-0178, via the Internet at <http://www.fda.gov/medwatch/report/hcp.htm>, or by mail at MedWatch HF-2, FDA, 5600 Fishers Lane, Rockville, MD 20857.

Patient Education

- ◆ All medications have potential to cause adverse reactions, which are defined as negative, unintended effects of medication use.
- ◆ Patients should be advised to report any adverse reaction to their medical care provider as soon as possible.
- ◆ Before starting a new medication, patients should be counseled by their medical care provider or pharmacist about the most common adverse effects and about any remedies available to minimize the severity of those effects.
- ◆ Nausea is one of the most common adverse effects. Nausea can be minimized by taking medications with food (if indicated, some medications should be taken on an empty stomach) or using ginger-based food or beverages (eg, ginger ale, tea, cookies). If these measures do not work, patients should talk with their medical care provider; they may need medications to treat the symptoms.
- ◆ Patients should not stop taking any medications unless instructed to do so by their medical care provider.

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Recreational Drugs and Antiretroviral Therapy

Background

Very few data are available on interactions between antiretroviral (ARV) medications and recreational drugs. No controlled trials have investigated this issue because of the legal and ethical issues regarding the use of illicit agents. Most available information on interactions between ARVs and recreational drugs has been derived from pharmacokinetic studies and from case reports. In addition, projections about ARV-drug interactions have been based on what is known about interactions between ARVs and similar agents.

Most phenomena related to drug-drug interactions arise from the pharmacokinetic properties of each interacting agent, specifically their metabolism and excretion.

One relevant issue is enzyme induction or inhibition, explained as follows:

- ◆ Different agents have different effects on the liver enzyme systems, specifically cytochrome p450 enzymes, used to metabolize the active form of many agents.
- ◆ Inducers are agents that *increase* the activity of these enzymes, resulting in increased metabolism and *decreased* serum concentration of the active drug form. This lower drug concentration could cause a loss of therapeutic efficacy of the interacting drug.
- ◆ Inhibitors are agents that *decrease* the activity of these enzymes, resulting in decreased metabolism and *increased* serum concentration of the active drug form. This higher drug concentration could lead to increased drug toxicity.
- ◆ Some agents have both inhibiting and inducing activity, making assessment of drug interactions more complicated.

Some agents exert most of their pharmacologic activity through their active metabolites, in which case inhibition and induction could affect the parent compound and the active metabolite in different or even opposite ways. For example, an agent that inhibits the metabolism of a parent drug would increase levels of the parent drug but decrease the concentration of active metabolites. If the parent compound has little pharmacologic effect compared with the active metabolite, the net effect could be decreased pharmacologic activity. This consideration further complicates drug-drug interactions and the understanding of their clinical significance. Further considerations include the following:

- ◆ Some agents are not metabolized by the liver, but instead are cleared by the kidneys and excreted in the urine.
- ◆ In the presence of hepatic or renal impairment, the metabolism and excretion of certain agents may be impaired, thus possibly increasing the amount of drug in the body or the amount of its toxic metabolites. Hepatic or renal dysfunction also may worsen drug-drug interactions.
- ◆ Street drugs are often impure, and sometimes are not what they are thought to be. They are frequently cut with substances that may themselves interact with ARVs or other drugs, and their potency can vary widely, even within the same batch.

Table 1 lists potential and documented drug interactions associated with commonly used recreational drugs. Pharmacokinetic properties and the interacting agents are discussed briefly.

Table 1. Potential and Documented Drug Interactions between Recreational Drugs and Antiretroviral Agents

Pharmacokinetics	Interactions	Significance	Comments
Alcohol			
Principally metabolized by alcohol dehydrogenase, but acute use can lead to enzyme inhibition, and chronic use may induce activity of CYP2E1 and CYP3A.	With induction of CYP3A, alcohol may increase the metabolism of PIs and NNRTIs. Because a common metabolic pathway is used by abacavir, there is theoretical concern that alcohol may compete for metabolism, thus increasing abacavir serum concentrations.	Inducing metabolism of specific medications may result in subtherapeutic levels, predisposing to resistance and decreasing efficacy.	Although the possibility of CYP3A induction is of theoretical concern, there may be little or no actual interaction between alcohol and ARV agents. Alcohol abuse and concomitant use of hepatotoxic agents may increase the risk of early and severe liver damage. Additionally, chronic alcohol abuse in the presence of didanosine markedly increases the risk of pancreatitis. There is no evidence of increased risk of abacavir-related toxicity or hypersensitivity reaction.
Amphetamine Compounds (crystal methamphetamine)			
Primarily metabolized by cytochrome P450 (CYP2D6). Under normal conditions, approximately 15% of a dose is eliminated renally, but as urine becomes more acidic, the proportion excreted renally may increase to 55%.	Inhibition of CYP2D6 can interfere significantly with hepatic metabolism of the amphetamine compound. Such inhibitors include: • Ritonavir (increases amphetamine levels 2- to 3-fold) • Delavirdine • Selective serotonin reuptake inhibitors (SSRIs) (primarily fluoxetine, fluvoxamine, sertraline, paroxetine)	Inhibition of amphetamine metabolism leads to increased levels of the compound. Effects similar to those seen with large doses may be anticipated. Response is variable from patient to patient and may include intense exhilaration, euphoria, agitation, panic, angina, cardiovascular collapse, convulsions, and cerebral hemorrhage. Amphetamines do not have any significant effect on ARV agents.	Patients who are taking ritonavir or other potent CYP2D6 inhibitors should be strongly urged to avoid using amphetamine compound(s).
Amyl Nitrate (poppers)			
Completely and rapidly metabolized in the liver by first-pass mechanism.	Pharmacodynamic property of this agent creates rapid and systemwide vasodilation. Agents that also cause vasodilation may create an additive effect. The use of erectile dysfunction (ED) agents such as sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra), and amyl nitrate may significantly decrease cardiac circulation.	Combinations of nitrates and ED agents can cause severe hypotension and may lead to loss of consciousness, ischemic angina, unstable angina, and myocardial infarction.	Nitrates and nitric oxide compounds are contraindicated with ED agents. Caution should be exercised with concomitant use of other vasodilators.

Benzodiazepines, Group I (alprazolam, clorazepate, clonazepam, diazepam, midazolam, triazolam)			
These agents are metabolized extensively in the liver by CYP3A4 isoenzymes.	Drugs inhibiting CYP3A4 could theoretically interfere with metabolism of these agents, causing a large increase in the area under the time-concentration curve (AUC). Ritonavir is the most potent CYP3A4 inhibitor.	Large increases in the AUC (>3-fold) of some of these compounds could have serious consequences, including sedation and respiratory depression.	Midazolam and triazolam are contraindicated for use with ritonavir; other PIs should be used with extreme caution. Other benzodiazepines may be administered safely with PIs, with close monitoring and dose adjustment.
Benzodiazepines, Group II (lorazepam, oxazepam, temazepam)			
These benzodiazepines are metabolized primarily by conjugation with glucuronic acid, which is mediated by glucuronosyltransferase enzymes.	Agents that increase glucuronosyltransferase enzyme activity may increase the metabolism of these compounds. Ritonavir may increase the metabolism of these drugs by this mechanism.	Concomitant use of these agents with ritonavir may decrease their therapeutic effectiveness. In patients who are abusing these agents, reduction in serum levels may cause symptoms of withdrawal, including: rebound insomnia, tremors, irritability, dysphoria, panic/paranoia, and convulsions.	Patients receiving these benzodiazepine agents for therapeutic purposes should be monitored for loss of effectiveness in the presence of ritonavir therapy. These benzodiazepine agents are likely to have less toxicity than the above (group I) agents. Patients who are known to be actively abusing these agents should be given an alternate PI or monitored for withdrawal.
Caffeine			
Thought to be extensively metabolized by the CYP1A2 enzyme group. Minor pathways include CYP2D6 and CYP3A4.	Drugs most likely to affect the metabolism of caffeine include those that inhibit its major metabolizing isoenzymes: ciprofloxacin (and potentially other fluoroquinolones) and macrolide antibiotics.	Elevations in caffeine levels may result in accentuated effects: increased blood pressure, increased central nervous system stimulation, tremors, and atrial dysrhythmias. CYP3A4 inhibitors such as ritonavir potentially elevate caffeine levels, but this is unlikely as it involves a very minor pathway in caffeine metabolism.	Recommend decreasing caffeine intake while concomitantly using agents that inhibit CYP1A2. No documented interaction between caffeine and PIs has been reported.
Cocaine			
Primarily metabolized by tissue and plasma enzymes. Small amount (10%) is metabolized by P450 enzymes (CYP3A3/4, CYP2B1) to hepatotoxic metabolite. Cocaine may induce some P450 enzymes with chronic use, and inhibit others with acute use. The isoenzymes involved are not related to ARV drug metabolism.	Potential interaction with: • Protease inhibitors (PIs) • Nonnucleoside reverse transcriptase inhibitors (NNRTIs) (nevirapine, efavirenz) • Macrolide antibiotics (erythromycin, clarithromycin)	Both inhibition and induction of P450 enzymes can lead to increased effects or toxicities of cocaine because of increased levels of the drug or active metabolites. However, given the minor role these enzymes play in overall cocaine metabolism, clinical significance is unlikely. Cocaine is unlikely to have any significant effects on ARV agents.	Monitor for increased cocaine effects and hepatotoxicity. Cocaine is also a known immunotoxic agent, significantly decreasing CD4⁺ cell production by as much as 3- to 4-fold, and increasing the rate of HIV reproduction up to 20-fold.

Ecstasy (X, MDMA) and GHB (gamma hydroxybutyrate)			
Ecstasy is an amphetamine-like compound that has similar metabolism as amphetamine compounds, with the major portion metabolized by CYP2D6. GHB is also thought to be metabolized through the CYP2D6 isoenzyme.	Inhibition of CYP2D6 is likely to impair detoxification of ecstasy and GHB because of large increases in serum levels. Such inhibitors include: • Ritonavir (increases ecstasy levels by 5- to 10-fold) • Delavirdine • SSRIs	At least 2 deaths from the combination of ritonavir and ecstasy have been reported. Ritonavir can increase the risk of life-threatening adverse effects from ecstasy (eg, heatstroke and dehydration) and GHB (eg, seizures, bradycardia, respiratory depression, loss of consciousness). Dehydration effects of these medications could increase the risk of renal stones in patients taking indinavir.	Strongly recommend avoiding the combination of ecstasy or GHB with ritonavir or other potent CYP2D6 inhibitors. Recent research has shown that ecstasy affects serotonin levels and can increase the potential for depression and anxiety disorders in individuals at risk. At least 68 deaths have been attributed to the combination of ecstasy and alcohol.
Heroin, Morphine, Hydromorphone, and Codeine			
Morphine and hydromorphone are extensively metabolized to glucuronides, mediated by glucuronosyltransferases. Codeine is mainly metabolized by glucuronidation, but minor pathways include a process mediated by CYP2D6. Heroin is converted to morphine in the blood rapidly and is metabolized similarly.	Plasma concentrations of all these agents may be decreased by agents that increase the activity of glucuronosyltransferases (eg, ritonavir). In the presence of ritonavir, heroin serum concentrations are reduced by as much as 50%. Administration of codeine with a CYP 2D6 inhibitor may inhibit the bioactivation of codeine into morphine.	Decreased levels of all these agents may result in loss of therapeutic effect when administered with ritonavir. Patients abusing these agents who add ritonavir may develop withdrawal symptoms, including lacrimation, rhinorrhea, irritability, tachycardia, elevated blood pressure, chills, flushing, sweating, seizures, myalgias, and arthralgias. There is also potential for an increase in a glucuronide metabolite, which is 45 times more potent than the parent compound. This increase in active metabolite could offset the above-described decreases in parent opiates.	Patients taking these agents with ritonavir or a CYP2D6 inhibitor (of codeine) should be monitored either for loss of therapeutic effect (in the case of prescribed opiates) or for withdrawal symptoms.
Ketamine (Special K)			
Undergoes extensive demethylation and hydroxylation in the liver, possibly via CYP3A4, and is excreted in the urine. Ketamine is structurally similar to phencyclidine and may undergo similar metabolism.	CYP 3A4 inhibitors could inhibit the metabolism of ketamine, resulting in elevated serum concentrations of the compound. A wide range of CYP3A4 inhibitors can play a significant role in interactions with ketamine, including: • Protease inhibitors • Macrolide antibiotics • Delavirdine	Ketamine has a reported wide margin of safety; however, elevated serum concentrations could result in increased heart rate, increased blood pressure, or respiratory depression. Chronic use of ketamine in the presence of ritonavir may increase ketamine concentrations and the potential for hepatotoxicity and drug-induced hepatitis.	Caution should be exercised with concomitant use of ketamine and agents that are CYP3A4 inhibitors. Two cases of drug-induced hepatitis have been reported in patients concomitantly using ketamine and ritonavir. Ketamine is often added to other illegal psychoactive substances such as ecstasy, marijuana, and others.

LSD, Mescaline, Psilocin, and Methyltryptamine			
Information about P450 metabolism is not available. LSD is structurally similar to serotonin and thus may be metabolized similarly. This means that LSD might be eliminated by the enzymes monoamine oxidase (MAO), aldehyde dehydrogenase, and alcohol dehydrogenase. Mescaline, psilocin, and dimethyltryptamine may have similar metabolic pathways.	Based on the postulated metabolism of LSD, MAO inhibitors could cause serious interactions by decreasing LSD metabolism and increasing serum levels. Because the metabolism of both abacavir and LSD involves alcohol dehydrogenase, it is possible that levels of either drug may be affected by the other; the clinical significance of any possible interactions is unknown.	Possible adverse effects of increased serum levels of LSD include respiratory insufficiency, acute anxiety, fear, vascular spasm, and potentially fatal malignant hyperthermia. The clinical significance of this possible interaction is unknown.	Because no data confirm these interactions in humans, the clinical significance of combining LSD with MAO inhibitors or abacavir is unknown.
Phencyclidine (PCP)			
PCP is mainly metabolized in the liver, mediated by CYP2C11. It is also speculated that PCP may inhibit CYP2B1.	Given the potential bidirectional effect on P450 enzymes, it is difficult to predict significant drug interactions.	The effects of PCP or PIs may increase with concomitant use. The clinical significance of this potential interaction is unknown.	No case reports have described interactions between PCP and P450 inhibitors. Caution should be exercised if combining PCP with ritonavir because of possible increased effects of both PCP and PIs.
Tetrahydrocannabinol (THC, marijuana, hashish, and hashish oil)			
Rapidly metabolized in the liver to an active metabolite (11-hydroxyl THC), which is then converted to inactive metabolites and excreted in the urine and stool. Levels of the active metabolite vary with route of administration. The oral route produces more of the active metabolite than either the intravenous or inhaled route. P450 isoenzymes are thought to be important in THC metabolism (CYP3A3/4, 2C9, 2C6).	Inhibiting agents that affect CYP3A3/4 could affect THC metabolism, thus increasing parent compound THC levels: • PIs • Macrolide antibiotics • Delavirdine Inducing agents of the same isoenzymes could reduce THC levels: • Efavirenz, nevirapine • Rifampicin compounds Fluconazole is an inhibitor of 2C9 and potentially increases THC levels. Clinical trials of THC in patients taking nelfinavir and indinavir suggested no change in THC levels, but some decrease in nelfinavir and indinavir levels. It is possible that more potent CYP3A3/4 inhibitors (eg, ritonavir) may change THC levels significantly.	Inhibition of selected isoenzymes may increase THC levels, producing higher parent THC levels but a lower amount of the active THC metabolite. The net effect on THC pharmacology is unknown. Symptoms of higher THC levels include frank hallucinations, delusions, paranoia, altered time sense, anxiety, panic, orthostatic hypotension, and increased heart rate. In the same way, medications that induce CYP3A4, 2C9 and 2C6 may increase or decrease THC effects. The clinical significance of changes in nelfinavir and unboosted indinavir with THC is unknown.	Recommend close monitoring of response to THC in patients who also take inhibitors and inducers of THC metabolism. To date, no clinically significant effects have been reported, despite widespread concomitant use of these agents.

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Immune Reconstitution Syndrome

Background

For most patients, initiating antiretroviral therapy (ART) improves immune responses to a wide range of opportunistic pathogens. The process of ART-induced immune reconstitution typically is uneventful. However, a small percentage of patients develop inflammatory disease in response to specific opportunistic pathogens within a few weeks or months of initiating therapy.

This exuberant inflammatory response has been called the immune reconstitution syndrome (IRS), and is also known as immune reconstitution inflammatory syndrome (IRIS) or immune reconstitution disease (IRD). IRS may present as the following:

- ◆ An exacerbation of a partially or successfully treated opportunistic infection (OI)
- ◆ A previously undiagnosed (subclinical) OI

IRS may occur in response to many pathogens, including *Mycobacterium tuberculosis* (TB), *Mycobacterium avium* complex (MAC), cytomegalovirus (CMV), *Cryptococcus*, *Pneumocystis*, *Toxoplasma*, hepatitis B, and varicella zoster virus.

Many of the IRS cases reported in the literature have occurred within a few months of initiating ART and in the context of a rapid and marked rise in CD4 count from very low pretreatment levels (often <50–100 cells/ μ L). The specific mechanisms involved in the pathogenesis of IRS are not well understood and may vary from one infection to another. However, experts believe that IRS is caused by an enhanced immune response to disease-specific antigens, which leads to an overproduction of inflammatory mediators.

IRS may be difficult to identify in clinical practice because the clinical presentation is nonspecific. IRS must be distinguished from other causes of disease such as the presentation of a new OI or other illness, failure of treatment of a previously identified OI, or drug toxicity. The severity of IRS varies widely, from mild to life threatening. Treatment varies according to the specific pathogen and clinical situation, but typically includes continuing ART if possible, treating the OI as indicated, and adding antiinflammatory therapy as needed.

Clinical Presentation

IRS is largely a clinical diagnosis. To consider IRS in the differential diagnosis, the clinician must recognize not only the clinical findings (typical or atypical) of a specific OI, but also the temporal association with initiation of ART and increase in the CD4 cell count. For example, in a patient with TB who has recently initiated ART after responding to treatment for TB, the “red flags” for a diagnosis of IRS (rather than progression of TB) would include new or worsening fever, new effusions, new or worsening lymphadenopathy, and other uncharacteristic signs or symptoms.

The clinical manifestations of IRS associated with some common OIs may include the following. (This is not an exhaustive list, but it includes most of the important IRS manifestations of patients with HIV infection.)

Tuberculosis

The signs and symptoms of TB IRS may include high fevers, new or worsening lymphadenopathy (mediastinal or peripheral), worsening of pulmonary symptoms and infiltrates, and new or increasing pleural effusions. Nonpulmonary presentations may include expanding central nervous system lesions, skin or visceral abscesses, bone lesions, or hypercalcemia. In a patient who is receiving therapy for active TB, the onset of TB IRS typically occurs 1–6 weeks after the patient begins ART. (See chapter *Tuberculosis Treatment in Resource-Limited Settings*.)

Mycobacterium avium Complex

Lymphadenitis and fever are the characteristic symptoms of MAC IRS, but pulmonary and other symptoms may develop. These and the other signs and symptoms of MAC IRS may be clinically indistinguishable from active MAC. In contrast to disseminated MAC, MAC IRS is associated with a rapid and striking increase in CD4 count (usually from <50 cells/ μ L to $\geq$ 100 cells/ μ L), and bacteremia usually is absent. MAC IRS can be mild and localized or it can be severe, requiring systemic antiinflammatory therapy in addition to anti-MAC therapy.

Cytomegalovirus

CMV retinitis

CMV retinitis may occur in patients with a history of CMV retinitis or in patients with no previous evidence of retinitis. In those with a previous diagnosis of CMV retinitis, a new opacified retinal lesion develops, frequently at the site of an earlier lesion. CMV retinitis IRS is identical to active CMV retinitis on ophthalmologic examination. Clinical information, therefore, will inform the diagnosis, and patients should be monitored closely. As with other IRS reactions, symptoms will be associated temporally with initiation of ART and a recent increase in CD4 count. In patients who were adequately treated for CMV and who experience IRS, serial ophthalmologic exams will reveal that the lesions clear without a new or different therapy for CMV. This clinical picture differs from that of retinal lesions caused by active CMV infection and uncontrolled CMV replication, in which lesions will increase in size or new lesions will appear, if CMV therapy has not been introduced or changed.

CMV vitreitis and CMV uveitis

CMV vitreitis and CMV uveitis are seen exclusively in people with previous CMV retinitis infection who responded to ART:

CMV vitreitis: IRS is an alarming syndrome but a benign one. Patients who are receiving anti-CMV therapy typically present with acute onset of blurred vision and “floaters” caused by posterior segment inflammation. Ophthalmologic exam reveals numerous inflammatory cells in the vitreous humor. Symptoms usually resolve in 1 month without specific treatment and without any lasting visual effects.

CMV uveitis: In patients with a history of CMV retinitis, CMV uveitis IRS may occur within months of ART initiation, but typically is a late complication, occurring about 3 years after patients begin ART. Uveitis is painless and primarily involves inflammation in the iris, the ciliary body, and the choroid layers. However, CMV uveitis may have serious sequelae. It often results in macular edema, epiretinal membrane formation, or cataracts, which can lead to permanent vision loss. Because of the risk of vision loss, clinicians should have a high index of suspicion for CMV uveitis.

Cryptococcal Meningitis

In patients with or without previously diagnosed cryptococcal meningitis, presentation of cryptococcal IRS typically includes fever, headache, and meningeal signs and symptoms. Onset has been reported between 1 week and 11 months after initiating ART. Lymphadenitis also has been reported. (See chapter *Cryptococcal Disease*.)

Pneumocystis jiroveci Pneumonia

Pneumocystis jiroveci pneumonia (PCP) IRS may occur in patients with current or recent PCP who are starting ART in the early weeks after initiation of PCP treatment. IRS may present as worsening pulmonary symptoms and high fever in patients who had been improving on PCP therapy or in patients with recent successful treatment of PCP. Chest x-rays may show worsening lung involvement, and oxygen saturation or arterial blood gas measurements may show worsening hypoxia or alveolar-arterial oxygen gradient. PCP IRS may sometimes cause severe acute respiratory failure. (See chapter *Pneumocystis Pneumonia*.)

S: Subjective

Symptoms of IRS will vary according to the specific illness.

Include the following in the history:

- ◆ Specific symptoms and time course of symptoms
- ◆ History of OIs including recently diagnosed OIs
- ◆ Treatment of OIs, including date of initiation, medication adherence, duration of therapy, and clinical response
- ◆ ART initiation: date, specific antiretroviral regimen, medication adherence, prior history of ART
- ◆ CD4 count and HIV viral load before ART initiation
- ◆ Current CD4 count and HIV viral load, if known
- ◆ Other medications, especially new medications, including over-the-counter and herbal preparations

O: Objective

Obtain vital signs, including temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation. Perform a thorough physical examination based on symptoms and suspicion of systems involved.

A: Assessment

In the appropriate clinical setting (especially in patients with advanced AIDS who recently initiated ART), IRS should be considered in the differential diagnosis of patients who present with new or worsening symptoms. In these patients, the differential often is broad, and causes other than IRS should be considered carefully.

- ◆ IRS: either a paradoxical worsening of a previously recognized OI or a new manifestation of a previously subclinical infection
- ◆ Worsening or progression of a known OI despite treatment
- ◆ A new infection or illness
- ◆ Drug toxicity; hypersensitivity reaction
- ◆ Failure of ART; progression of AIDS

Perform the appropriate diagnostic tests to exclude other etiologies. Consider consulting with an HIV specialist if the diagnosis is in question.

P: Plan

Diagnostic Evaluation

It is important to rule out new, incompletely treated, or untreated infections; malignancy; and other illnesses before concluding that the patient has IRS.

The workup of the patient with possible IRS will depend on the specific clinical presentation. Perform laboratory tests, blood cultures, and other diagnostic tests as appropriate to the individual patient. These may include the following:

- ◆ Complete blood count (CBC) with differential, electrolytes and creatinine, liver function tests
- ◆ CD4 cell count and HIV viral load
- ◆ Blood cultures for bacteria, acid-fast bacteria (MAC), fungi
- ◆ Chest x-ray; other radiographic studies
- ◆ Sputum stain and culture
- ◆ Biopsy or culture of skin or other lesions
- ◆ Lumbar puncture and cerebrospinal fluid studies
- ◆ Ophthalmologic examination

Treatment

Prevention and treatment recommendations from randomized, prospective trials are lacking for IRS. However, most cases of IRS reported in the literature appeared to resolve within a matter of weeks with the following:

- ◆ Continuing the current ART regimen (unless the clinical presentation was life threatening)
- ◆ Treating the OI as indicated (see below)
- ◆ If indicated, administering antiinflammatory medications (nonsteroidal drugs or systemic corticosteroids) to suppress the inflammatory process

For patients with recent OIs that resolved with a full course of appropriate therapy, it is not always necessary to resume antimicrobial therapy or to change maintenance therapy. For example, if a patient with TB IRS finished a full course of treatment for TB, repeat treatment is not indicated. If a patient with previously treated cryptococcal meningitis is receiving maintenance therapy and IRS develops, the therapy does not need to be altered. However, if IRS reveals a new, untreated OI, that infection should be treated appropriately. For instance, if new cryptococcal meningitis presents as IRS, the cryptococcus should be treated as indicated. If treatment is in question, consult with an HIV specialist.

Timing of Antiretroviral Therapy Initiation

The risk of IRS is not well understood for patients who start ART with low CD4 counts (<50–100 cells/ μ L) and new or recent OIs. In general, it appears that the risk of IRS is higher if ART is initiated soon after OI treatment is begun and if the CD4 count rises sharply in the early weeks or months of ART. However, the optimal timing of ART initiation in relation to treatment of the OI is not yet clear, and may depend in part on several variables. Prominent among these is the risk of AIDS progression if ART is deferred. Other considerations include the particular OI pathogen, the severity of the OI, and the medication burden and potential for drug toxicity or interactions if therapy with multiple drugs is initiated at the same time. For patients with cryptococcal or mycobacterial disease who are otherwise stable and in whom ART can be deferred temporarily, many specialists would recommend delaying ART until the patients have received appropriate OI treatment for 4–8 weeks. For decisions about initiating ART in patients with active OIs, consult with an HIV specialist.

Immune Reconstitution in Resource-Constrained Settings

As access to ART improves in resource-constrained countries, IRS is increasingly being recognized in patients receiving ART. Clinicians should include IRS in the differential diagnosis when evaluating patients who recently have begun ART and present with new or worsening symptoms of an OI. However, limited diagnostic testing resources may make it difficult to establish IRS or other diagnoses.

Given that coinfection with HIV and TB, is epidemic in many countries, and because IRS is not uncommon in patients with TB, clinicians should be particularly vigilant about symptoms that may signal IRS. As in resource-abundant countries, a consultation is recommended with a clinician trained in caring for patients with HIV if diagnosis or treatment is in question.

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Patient Education

- ◆ When patients are initiating ART, advise them to contact the clinic promptly if they experience new or worsening symptoms.
- ◆ Advise patients to take their antiretroviral medications exactly as prescribed.
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Anemia

Background

Anemia is usually characterized by a hemoglobin level of <14 g/dL in men and <12 g/dL in women. In people with HIV infection, anemia has been linked to poor quality of life and decreased survival, and correction of anemia can improve these parameters.

Anemia has many potential causes and, in HIV-infected individuals, several of these may occur concomitantly. Common causes include:

- ◆ Anemia of chronic disease
- ◆ Bone marrow suppression due to medications
- ◆ Bone marrow infiltration by infection or malignancy (eg, *Mycobacterium avium* complex, tuberculosis, cytomegalovirus, lymphoma, myelodysplasia)
- ◆ Nutritional deficiencies (eg, vitamin B12 or folate)
- ◆ Iron deficiency (eg, from blood loss)
- ◆ Hypogonadism

Anemia of chronic disease, due to HIV infection itself, is very common in patients with low CD4 counts (<200 cells/ μ L) and high HIV viral loads, as well as in those with low body mass index, and in women, African Americans, and older people (aged >50 years).

Medication-induced anemia, particularly from zidovudine (ZDV) and trimethoprim-sulfamethoxazole (TMP-SMX), is also common and may occur quickly after initiation of these medications. The risk of anemia with a ZDV-containing regimen is of particular concern in resource-limited settings where access to alternative antiretroviral (ARV) medications may be limited and the likelihood of advanced disease when starting ZDV is substantial. Careful monitoring of hemoglobin at 2–4 weeks after initiation of ZDV and regularly thereafter, and continued access to affordable alternatives, are crucial to the success of antiretroviral therapy (ART) in these settings.

S: Subjective

Patients who have gradual declines in hemoglobin may be able to compensate and remain asymptomatic even at very low hemoglobin levels. Others may complain of weakness, fatigue, shortness of breath, pallor, dizziness,

syncope, nausea, anorexia, headache, palpitations, chest pain, sleep disturbance, anxiety, malaise, or confusion.

History

Conduct a careful history, asking about symptoms listed above, as well as the following:

- ◆ Onset and duration of symptoms
- ◆ Previous anemia (and family history of anemia)
- ◆ Blood transfusions received (if any)
- ◆ HIV disease status, including CD4 cell count, history of opportunistic infections, other illnesses
- ◆ Abnormal bleeding; dark or tarry stools
- ◆ For women, date of last menses and amount of menstrual blood loss
- ◆ Jaundice
- ◆ Other symptoms: fever, sweats, weight loss, diarrhea, lymph node enlargement
- ◆ Current and recent medications (prescribed or over-the-counter), nutritional supplements, and herbal preparations
- ◆ Use of aspirin or nonsteroidal antiinflammatory drugs
- ◆ Dietary habits
- ◆ Alcohol abuse

O: Objective

Measure vital signs, with special attention to heart rate and blood pressure. Perform orthostatic measurements. Compare current weight with previous values. Perform a careful physical examination, including the following:

- ◆ General appearance (nutritional status, appearance of health or illness)
- ◆ Skin, conjunctivae: pallor, jaundice, icterus
- ◆ Mouth: stomatitis or glossitis (vitamin B12 or folate deficiency)
- ◆ Abdomen: liver or spleen enlargement, masses
- ◆ Lymph nodes

- ◆ Extremities: edema
- ◆ Neurologic: vibratory sensations, balance and gait, deep tendon reflexes, Babinski reflexes
- ◆ Rectal: check for occult blood

A: Assessment

Remember that more than one cause of anemia may be present. A partial differential diagnosis includes:

- ◆ Chronic disease: HIV/AIDS; other comorbid conditions
- ◆ Medications
 - ◆ ZDV or ZDV-containing drugs (Combivir, Trizivir)
 - ◆ TMP-SMX (Septra, Bactrim, cotrimoxazole)
 - ◆ Other hematotoxic medications (see list, below)
- ◆ Iron deficiency
- ◆ Vitamin B12 or folate deficiency
- ◆ Malnutrition
- ◆ Alcoholism
- ◆ Malignancy
- ◆ Renal disease
- ◆ Liver disease
- ◆ Blood loss (eg, gastrointestinal)
- ◆ Hemolysis (eg, in patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency who are exposed to dapsone, TMP-SMX, or other oxidants)
- ◆ Parvovirus B19
- ◆ Tuberculosis
- ◆ *Mycobacterium avium* complex (MAC)
- ◆ Histoplasmosis, cryptococcosis
- ◆ Malaria
- ◆ Sickle cell disease
- ◆ Thalassemia
- ◆ Hypogonadism
- ◆ Hypothyroidism
- ◆ Pregnancy
- ◆ Rheumatoid arthritis
- ◆ Systemic lupus erythematosus
- ◆ Inflammatory bowel disease
- ◆ Hookworm infection

P: Plan

Diagnostic Evaluation

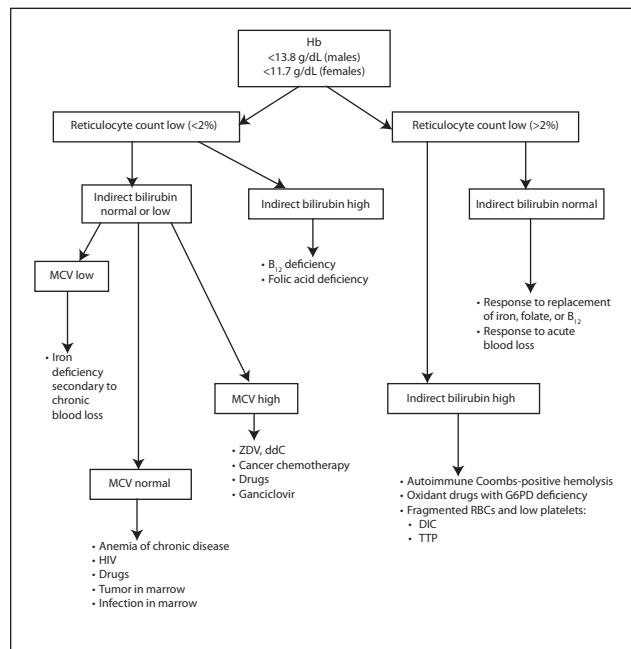
Recheck the hematocrit and hemoglobin to confirm anemia, and perform a complete blood count with differential to determine whether other cytopenias are present.

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. Consider the following as initial tests to determine the cause of anemia:

- ◆ Mean corpuscular volume
- ◆ Peripheral blood smear
- ◆ Reticulocyte count
- ◆ Bilirubin (total and direct)
- ◆ Iron studies: ferritin, iron, transferrin, total iron-binding capacity
- ◆ Hemoccult testing for fecal blood
- ◆ Pregnancy test if indicated

See Figure 1 for a possible diagnostic approach.

Figure 1. Diagnostic Evaluation for Anemia



Key to abbreviations: ZDV = zidovudine; ddC = dideoxycytidine; DIC = disseminated intravascular coagulation; HB = hemoglobin; MCV = mean cell volume; RBCs = red blood cells; TTP = thrombotic thrombocytopenic purpura

Adapted from: Volberding PA, Levine AM, Deiterich D, et al. *Anemia in HIV infection: clinical impact and evidence-based management strategies* (Figure 4. Simplified diagnostic approach to anemia in HIV-infected individuals). Clin Infect Dis. 2004 May 15;38(10):1454-63. Used with permission of the University of Chicago Press.

Check the testosterone level in individuals (both men and women) with anemia of uncertain cause, particularly if they have other signs or symptoms of hypogonadism. Perform further testing if indicated by the clinical presentation and results of the initial workup (eg, evaluation for parvovirus B19 or other infection, vitamin B12 deficiency, G6PD deficiency, malignancy, or gastrointestinal blood loss).

Consider bone marrow biopsy if the diagnosis is unclear, if the anemia is chronic or severe, if the initial evaluation does not determine the cause, or if the anemia is accompanied by pancytopenia. Bone marrow biopsy may also be performed to confirm a diagnosis.

Review the patient's medication list for drugs that may cause anemia. Some common medications that may cause anemia are the following:

- ◆ ZDV
- ◆ Ganciclovir, valganciclovir
- ◆ Sulfonamides
- ◆ Pyrimethamine
- ◆ Dapsone
- ◆ Ribavirin
- ◆ Interferon-alfa
- ◆ Antineoplastic agents

Refer the patient to hematology or oncology specialists as appropriate.

Treatment

The appropriate treatment depends on the cause and severity of the anemia. Refer to pertinent chapters in *Section 6: Disease-Specific Treatment* or primary care management guidelines as appropriate.

- ◆ Patients with severe anemia may require transfusion (unless hemolysis is suspected) with or without hospitalization for evaluation and treatment.
- ◆ Consider treating anemia of chronic disease with ART, if it is otherwise indicated, while avoiding medications associated with bone marrow toxicity. Mild anemia often resolves without intervention after the start of ART as the immune system is reconstituted.
- ◆ If drug-induced anemia is suspected, discontinue the offending medication, if possible. For example, for patients taking ZDV in whom other causes of anemia have been excluded, consider substituting another nucleoside/nucleotide analogue in place of ZDV. If it is not possible to alter therapy, consider using erythropoietin (EPO) or red blood cell transfusion to increase the hematocrit.
- ◆ EPO may be used to stimulate red blood cell production. A typical dosage of recombinant human EPO is 40,000 units weekly by subcutaneous injection. Note that EPO replacement is ineffective if the erythropoietin level is >500 international units per liter (check serum EPO levels before treatment) or if iron levels are low. For patients in whom EPO is started, monitor the hemoglobin and hematocrit regularly (eg, every week until stabilized, then every 4 weeks) and adjust the dosage as required.
- ◆ Treat hypogonadal patients with testosterone.
- ◆ Treat iron deficiency with ferrous sulfate 325 mg orally 3 times daily.
- ◆ Treat nutritional deficiencies as indicated. For folate deficiency, give folic acid 1-5 mg daily for 1-4 months; for vitamin B12 deficiency: administer cobalamin 1 g intramuscularly once daily for 7 days, then once weekly for 4 weeks, then once monthly, or 1-2 g orally once daily.

Patient Education

- ◆ Symptoms such as fatigue, weakness, and shortness of breath may be signs of anemia. Patients should notify their health care providers if they develop these or other symptoms.
- ◆ Anemia may be caused by an opportunistic infection or other illness; further evaluation may be necessary.
- ◆ Anemia often responds to treatment. For many patients, ART may be a successful treatment; encourage them to adhere to ART.
- ◆ Counsel patients to take their medications exactly as directed and to call their health care providers if they experience new or worsening symptoms.

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Diarrhea

Background

Diarrhea is a common condition in HIV-infected individuals that may have a variety of causes. Episodes may be acute and brief, intermittent or recurrent, or, in some cases, chronic and severe. If diarrhea persists, it may cause poor nutrition, dehydration, and weight loss. Diarrhea may diminish patients' quality of life significantly, and may interfere with adherence to and efficacy of antiretroviral (ARV) medications.

Diarrhea is defined in various ways, but commonly as more than 4 loose stools or watery stools per day for more than 3 days. Duration is classified as follows:

- ◆ Acute: <2 weeks
- ◆ Persistent: 2–4 weeks
- ◆ Chronic: >4 weeks

The causes of diarrhea, both infectious and noninfectious, found in HIV-positive individuals with normal or mildly depressed CD4 cell counts are likely to be similar to those in HIV-uninfected persons.

Among the noninfectious causes of diarrhea, adverse effects of ARVs and other medications are particularly common. Persons with advanced immunodeficiency are more likely to have infections, including opportunistic infections, as the cause of diarrhea.

Infectious diarrhea typically involves either the small or the large intestine, and the patient's history often suggests the site of the problem. Infections of the small intestine commonly produce generalized abdominal cramps, large-volume diarrhea without blood, and possibly dehydration. Large-intestine infections (colitis) often produce lower abdominal pain, an unproductive urge to defecate, and frequent small-volume stools with blood and pus.

S: Subjective

The patient complains of diarrhea. Take a thorough history, including the following:

- ◆ Onset of diarrhea
- ◆ Frequency (times per day, last episode)
- ◆ Stool consistency (soft vs liquid)
- ◆ Stool color (gray, white, or greasy stools: possible cholelithiasis or pancreatitis; dark stools: possible gastrointestinal bleeding)
- ◆ Bloody stools (possibly caused by invasive organisms, inflammation, ischemia, or neoplasm)
- ◆ Rectal bleeding
- ◆ Nausea or vomiting (if beginning within several hours of ingesting food, possible gastroenteritis)
- ◆ Weight loss: quantify amount and time frame
- ◆ Abdominal pain or cramping, and location if present
- ◆ Fever
- ◆ Other associated symptoms
- ◆ Allergies (to foods or medications)
- ◆ Aggravating factors
- ◆ Alleviating factors
- ◆ Treatments tried
- ◆ Contact with others with similar symptoms
- ◆ Previous episodes of diarrhea
- ◆ History of cytomegalovirus (CMV), *Mycobacterium avium* complex (MAC) or other infections involving the gastrointestinal tract
- ◆ Family history of inflammatory bowel disease, celiac disease
- ◆ Oral-anal sexual contact (males and females)
- ◆ Receptive anal intercourse
- ◆ Exposure to unsafely prepared food (eg, raw, undercooked, spoiled), unpasteurized milk or juices
- ◆ Exposure to possibly contaminated water (swimming in or drinking from well, lake, or stream)
- ◆ Exposure to non-toilet-trained infants and children (eg, daycare), pets, farm animals, reptiles

- ◆ Recent travel
- ◆ Antibiotic use or exposure in recent weeks or months
- ◆ ARV medications, especially ritonavir or nelfinavir; check relationship of diarrhea onset to initiation of ARVs
- ◆ Other current and recent medications, including supplements (prescribed or over-the-counter) and herbal preparations
- ◆ Dietary factors, especially “sugar-free” foods (containing nonabsorbable carbohydrates), fat substitutes, milk products, and shellfish, or heavy intake of fruits, fruit juices, or caffeine
- ◆ Alcohol and recreational drug use; withdrawal

O: Objective

Record vital signs, including temperature, orthostatic heart rate, blood pressure measurements, and weight. Compare these with recent or baseline values. Perform a thorough physical examination, including evaluation of the following:

- ◆ Hydration status (skin turgor, mucous membrane moistness)
- ◆ Nutritional status (body habitus, muscle mass, skin and hair integrity)
- ◆ Oropharynx (lesions, candidiasis, ulcerations, Kaposi sarcoma)
- ◆ Optic fundi (signs of CMV infection)
- ◆ Abdomen (distention, bowel sounds, tenderness, organomegaly, masses, adenopathy)
- ◆ Rectum (masses, tenderness, bloody stool)

Review recent CD4 cell counts. Low CD4 counts increase the risk of chronic or systemic illnesses and opportunistic infections.

A: Assessment

The differential diagnosis is broad, and includes the following infectious and noninfectious causes:

Infectious Causes

Acute diarrhea, any CD4 count

- ◆ Viruses (especially Norwalk virus)
- ◆ Viral hepatitis

- ◆ Herpes enteritis
- ◆ *Clostridium difficile* (suspect in patients who have recently been treated with antibiotics)
- ◆ *Salmonella*
- ◆ *Shigella*
- ◆ *Campylobacter*
- ◆ *Escherichia coli* O157:H7

Chronic diarrhea, any CD4 count

- ◆ *C difficile* (suspect in patients who have recently been treated with antibiotics)
- ◆ *Giardia lamblia*
- ◆ *Entamoeba histolytica*

Chronic diarrhea, CD4 count <300 cells/μL

- ◆ *Microsporidia*
- ◆ *Cryptosporidia*
- ◆ *Mycobacterium avium* complex (MAC) (CD4 count <50 cells/μL)
- ◆ *Iso spor a belli*
- ◆ CMV (CD4 count <100 cells/μL)

Adapted from: Infectious Causes of Diarrhea in Patients with HIV, Table 8-8. In: Bartlett JG, Cheever LW, Johnson MP, et al, eds. A Guide to Primary Care of People with HIV/AIDS. Rockville, MD: U.S. Department of Health and Human Services, Health Resources and Services Administration; 2004.

Noninfectious Causes

- ◆ Medication adverse effects, common with many medications including some ARVs:
 - ◆ Protease inhibitors (especially ritonavir and nelfinavir)
 - ◆ Didanosine buffered tablets (no longer available in the United States)
- ◆ Irritable bowel syndrome
- ◆ Inflammatory bowel disease (ulcerative colitis, Crohn disease)
- ◆ Lymphoma
- ◆ Lactose intolerance
- ◆ Celiac disease
- ◆ Small-bowel overgrowth
- ◆ Pancreatic insufficiency
- ◆ Diverticulitis
- ◆ Fecal incontinence

P: Plan

Diagnostic Evaluation

For suspected infections, perform laboratory studies including complete blood count with differential, electrolyte measurements, and liver function tests. Check stool for white blood cells and blood. Perform stool studies as indicated by the patient's presentation (bacterial culture, ova and parasites, *Microsporidia*, *Cryptosporidia*, and giardia: *C difficile* toxin assay). Order additional studies as suggested by the history (eg, blood cultures, MAC cultures, hepatitis serologies, retinal examination for CMV).

If the patient is febrile, perform a complete fever workup as appropriate (see chapter *Fever*).

Check the CD4 cell count and HIV viral load, if not checked recently.

If stool study results are negative (ova and parasite negative in 3 successive samples) and the patient has severe symptoms, particularly in the case of advanced immunodeficiency, refer to a gastroenterologist for colonoscopy or flexible sigmoidoscopy with biopsy. Endoscopy is the best procedure to identify certain conditions, including CMV colitis, and inflammatory bowel disease. If all studies are negative and the diarrhea persists, repeat endoscopy in 6-8 weeks regardless of the level of immunodeficiency. Pathogens may be difficult to identify.

Treatment

Once a diagnosis is made, initiate appropriate treatment. In seriously ill patients, presumptive treatment may be started while diagnostic tests are pending. See the appropriate chapter in *Section 6: Disease-Specific Treatment* or relevant treatment guidelines. If the cause of the diarrhea cannot be identified, consult with an HIV expert or a gastroenterologist.

For moderate to severe diarrhea, including dysentery (bloody diarrhea), empiric treatment can be given pending stool study results or in settings with limited resources for workup. Use fluoroquinolones in a 3-day regimen, including ciprofloxacin 500 mg twice daily, norfloxacin 400 mg twice daily, or levofloxacin 500 mg once daily. Monitor effectiveness and adjust therapy according to the results of diagnostic studies and clinical response.

For patients whose diarrhea is suspected to be due to ARV agents or other medications, symptomatic treatment may be tried (see below). Diarrhea from protease inhibitors often decreases after a few weeks without treatment. If the diarrhea cannot be controlled, a change in ARV regimen should be considered.

Symptomatic treatments

- ◆ Antimotility agents such as loperamide (Imodium) in over-the-counter or prescription strengths and atropine/diphenoxylate (Lomotil) are useful for many patients. The suggested dosage is 2 tablets after each loose bowel movement, not to exceed 8 tablets per day. These agents should not be used if patients have bloody diarrhea or if *C difficile* is suspected.
- ◆ Pharmaconutritional approaches include the use of calcium supplementation (500 mg 2-3 times daily). Patients with diarrhea related to protease inhibitors may find that taking calcium with each dose can decrease or prevent diarrhea. Note that magnesium supplements may worsen diarrhea.
- ◆ Pancrelipase (eg, Cotazym, Creon, Ultrase) can be useful in managing chronic diarrhea due to malabsorption. The dosage is 2-3 caplets 3 times daily with meals, titrated downward according to response.
- ◆ Cholestyramine (Questran) or psyllium (Metamucil) may reduce diarrhea by slowing peristalsis and adding bulk to stools. Avoid administering cholestyramine with other medications because it may impair their absorption.
- ◆ A combination of these treatments may be needed to control chronic diarrhea and can be continued for patients after an infectious process has been ruled out.

Nutrition and hydration

Encourage frequent intake of soft, easily digested foods such as bananas, rice, wheat, potatoes, noodles, boiled vegetables, crackers, and soups. Encourage hydration with fruit drinks, tea, "flat" carbonated beverages, and water. Patients should avoid high-sugar drinks, caffeinated beverages, alcohol, high-fiber foods, greasy or spicy foods, and dairy products. Many patients may benefit from a trial of a lactose-free, low-fiber, or low-fat diet. Patients should use nutritional supplements as needed or as recommended by a dietitian. In case of chronic or severe diarrhea, or significant weight loss, refer to a dietitian for further recommendations.

Patients with severe diarrhea must maintain adequate hydration, by mouth if possible. In severe cases, intravenous administration of fluids may be necessary. Oral rehydration solutions include the World Health Organization formula, Pedialyte, Rehydralyte, Rice-Lyte, and Resol. Homemade alternatives include the following:

- ◆ Combine 1/2 teaspoon of salt, 1 teaspoon of baking soda, 8 teaspoons of sugar, and 8 ounces of orange juice; add water to make 1 liter and drink.
- ◆ Drink 1 glass containing 8 ounces of apple, orange, or other juice; 1/2 teaspoon of corn syrup or honey; and a pinch of salt; then drink 1 glass containing 8 ounces of water and 1/4 teaspoon of baking soda.
- ◆ Mix 1/2 cup of dry, precooked baby rice cereal with 2 cups of water (boil first in areas with poor water quality); add 1/4 teaspoon of salt and drink.

Patient Education

- ◆ Diarrhea can have many causes. Instruct patients to notify their health care providers if they develop new or worsening symptoms.
- ◆ Instruct patients to take their medications exactly as directed and to call their health care providers if they experience worsening diarrhea, or other symptoms such as fever, nausea, vomiting, or pain.
- ◆ Patients must stay nourished and well hydrated even if they are having diarrhea. Instruct patients to eat small, frequent meals and to avoid dairy products, greasy food, and high-fat meals.

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Ear, Nose, Sinus, Mouth

Background

HIV-infected individuals frequently experience infections and neoplasms that affect the ears, nose, sinuses, and mouth. The degree of immunosuppression, as reflected by a patient's CD4 cell count, can affect the severity, likelihood of recurrence, and response to therapy for various infections and neoplasms.

Patients may present with ear, nose, sinus, or mouth complaints early in the course of HIV infection, perhaps even before they are aware of their infection. Some conditions arise more commonly in patients with advanced HIV infection. Certain complaints (eg, oral candidiasis) should prompt consideration of HIV testing in patients without known infection.

Ears

HIV-infected patients may experience recurrent acute otitis media and serous otitis media. Nasopharyngeal lymphoid hyperplasia, sinusitis, or allergies may contribute to dysfunction of the eustachian tubes. Unilateral and bilateral sensorineural hearing loss has been reported and may be caused by HIV infection involving the central nervous system (CNS) or the auditory nerve. Hearing loss may also be due to syphilis, other CNS infections, chronic otitis media, neoplasms, and certain medications (including some nucleoside analogues in rare cases). The pathophysiology, causative organisms, and incidence of external-ear infections appear to be the same in HIV-infected patients as in HIV-uninfected individuals.

S: Subjective

The patient may complain of ear pain, decreased hearing or hearing loss, a feeling of fullness in the ear, vertigo, or a popping or snapping sensation in the ear.

Obtain the following information during the history:

- ◆ Medications (prescription and over-the-counter), and herbal supplements, current and past
- ◆ Current or recent sinus infection
- ◆ Associated symptoms
- ◆ Drainage or blood from the ear
- ◆ Head or ear trauma

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether the patient is at risk for opportunistic infections as causes of ear complaints.

Perform visual and otoscopic inspection, including evaluation for skin abnormalities, lesions, cerumen impaction or foreign body, lymphadenopathy, adenotonsillar hypertrophy, etc.

Evaluate hearing and refer for an audiogram. Perform a neurologic examination and draw rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test.

A: Assessment and Plan

Otitis Externa/Interna

Proceed with care as with an immunocompetent patient. A chronic or atypical presentation in an HIV-infected patient warrants a thorough evaluation, including cultures, biopsy, radiographic scans, and referral to an ear, nose, and throat (ENT) specialist.

Hearing Loss

A patient with hearing loss should be referred for evaluation or treated depending on the cause. Avoid ototoxic medications (eg, furosemide, aminoglycosides).

Nose and Sinuses

Nasal and paranasal sinus conditions occur frequently in HIV-infected patients. Nasal obstruction, allergic rhinitis, nasal lesions, and sinusitis are common. Epistaxis can occur in patients with platelet disorders (eg, idiopathic thrombocytopenic purpura [ITP]).

S: Subjective

The patient may complain of “stuffy nose,” rhinorrhea, epistaxis, frontal or maxillary headaches (worse at night or early morning), pain in the nostrils, persistent postnasal drip, mucopurulent nasal discharge, general malaise, aching or pressure behind the eyes, or toothache-like pain.

Obtain the following information during the history:

- ◆ Medications (prescription and over-the-counter) and herbal supplements, current and past
- ◆ Current or recent sinus infection
- ◆ Previous sinus surgery
- ◆ Recent or current upper respiratory infection (URI)
- ◆ Nasal bleeding or discharge
- ◆ Facial trauma
- ◆ Allergic rhinitis
- ◆ Positional pain; worse when patient bends forward?
- ◆ Tobacco use
- ◆ Fever
- ◆ Headache
- ◆ Mucopurulent nasal drainage

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether the patient is at risk for opportunistic infections as causes of nasal and sinus complaints.

Examine the nose and sinuses. Check the nasal mucosa with a light and a speculum, looking for areas of bleeding, purulent drainage, ulcerated lesions, or discolored areas. Palpate or percuss the sinuses for areas of tenderness, look for areas of swelling over the sinuses, and visualize the posterior pharynx for mucopurulent drainage. Transillumination may be helpful. Examine the teeth and gums for caries and inflammation of the gingivae. Check maxillary teeth with the use of a tongue blade (5-10% of maxillary sinusitis is due to dental root infection). Refer to a dentist for tooth sensitivity or caries.

A: Assessment

Possible causes of epistaxis include coagulopathy, ITP, tumor, lesions of herpes simplex virus (HSV), and Kaposi sarcoma (KS). Suspect ITP if the platelet count is low and bleeding is difficult to control. HSV appears as painful, ulcerated vesicles in the nasal mucosa. Tumors may be caused by KS, squamous papilloma, or lymphoma; biopsy is necessary to determine the cause.

Acute infection of 1 or more of the paranasal sinuses is common. *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* are seen in both HIV-uninfected and HIV-infected patients, whereas *Staphylococcus aureus* and *Pseudomonas aeruginosa* are

found more often in HIV-infected patients. Fungi may be the causative agents, especially in patients with severe immunosuppression.

Chronic sinusitis occurs frequently in patients with HIV infection and may be polymicrobial or anaerobic. In patients with low CD4 cell counts, fungal sinusitis may occur.

Nasal obstruction may be caused by adenoidal hypertrophy, chronic sinusitis, allergic rhinitis, or neoplasm.

P: Plan

Epistaxis

Epistaxis caused by coagulopathy or tumor is managed the same as in the immunocompetent patient with these conditions. Cauterization of an identified bleeding point or packing may be necessary. ITP may be treated with antiretroviral therapy (ART) as chronic management, or with corticosteroids for acute management. Refer to a hematologist.

Acute Sinusitis

Combination therapy with antibiotics, decongestants, mucolytics, saline nasal spray, and topical nasal steroids may be effective. See chapter *Sinusitis* for details. Note: Avoid fluticasone (Flonase) and budesonide (Rhinocort Aqua) nasal spray in patients taking ritonavir or ritonavir-boosted protease inhibitors (eg, Kaletra), because significant increases in serum levels of these glucocorticoids may occur.

Chronic Sinusitis

Treat with a systemic decongestant (guaifenesin), saline nasal spray twice daily, and topical nasal saline spray. Patients with exacerbations of sinusitis should be treated as for acute sinusitis. For more detailed information, see chapter *Sinusitis*. Note: Avoid fluticasone (Flonase) and budesonide (Rhinocort Aqua) nasal spray in patients taking ritonavir or ritonavir-boosted protease inhibitors (eg, Kaletra), because significant increases in serum levels of these glucocorticoids may occur.

Nasal Obstruction

Perform magnetic resonance imaging (MRI) or computed tomography (CT) scan with biopsy for mass lesions or asymmetric nasal lymphoid tissue. Refer to an ENT specialist.

Mouth and Throat

The oral cavity is one of the most common areas of symptoms in patients with HIV infection. Conditions that arise in the oral cavity may be infectious, benign inflammatory, neoplastic, or degenerative processes.

S: Subjective

The patient may complain of white patches and red areas on the dorsal surface of the tongue and the palate, decreased taste sensation, white lesions along the lateral margins of the tongue, ulcerated lesions, nonhealing lesions at the corners of the mouth, sore gums, loose teeth, dysphagia, or odynophagia.

Obtain the following information during the history:

- ◆ Medications (prescription and over-the-counter) and herbal supplements (note that zalcitabine, dapsone, and other drugs may cause aphthous ulcers)
- ◆ Usual oral hygiene (toothbrushing, tongue brushing or scraping, flossing, use of mouthwash)
- ◆ Date of last dental examination
- ◆ Involuntary weight loss

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether the patient is at risk for opportunistic infections as causes of oral complaints.

Thorough examination of the mouth and throat with a tongue depressor and a good light is mandatory. Observe for white patches or plaques on the mucous membranes that can be partially removed by scraping with a tongue blade (candidiasis). Examine the dorsal surface of the tongue and hard and soft palates for red, flat, subtle lesions (erythematous candidiasis). Check for ulcerations, inflamed gums, and loose teeth. Look for discoloration or nodular lesions on the hard palate (Kaposi sarcoma). Look for ribbed, whitish lesions on the lateral aspects of the tongue that cannot be scraped off (oral hairy leukoplakia). Check the pharynx for adenotonsillar hypertrophy. Rule out HIV-unrelated causes of pharyngitis, including streptococci or respiratory viruses.

A: Assessment and Plan

Perform biopsy, culture, and potassium hydroxide (KOH) preparation of lesions as indicated.

Oral Candidiasis (Thrush)

Oral candidiasis is most likely to occur when the CD4 count is <300 cells/ μL , but it can occur at any CD4 level and in HIV-uninfected individuals. It may appear as creamy white plaques on the tongue or buccal mucosa or as erythematous lesions on the dorsal tongue or the palate. The most common treatment strategy is empiric therapy with topical or systemic antifungal agents. For more details, see chapter *Candidiasis, Oral and Esophageal*.

Angular Cheilitis

Angular cheilitis is also caused by *Candida* species, and is characterized by fissuring at the corners of the mouth. For treatment, see chapter *Candidiasis, Oral and Esophageal*.

Oral Hairy Leukoplakia

Oral hairy leukoplakia (OHL) is caused by Epstein-Barr virus and appears as raised, ribbed, “hairy” white lesions along the lateral margins of the tongue. Lesions are primarily asymptomatic, and treatment is generally not needed. Lesions often resolve with successful ART. For more details, see chapter *Oral Hairy Leukoplakia*.

Kaposi Sarcoma

Kaposi sarcoma appears as red, blue, or purplish lesions that are flat or nodular, and solitary or multiple. Lesions appear most commonly on the hard palate but may also occur on the gingival surfaces and elsewhere in the mouth. A definitive diagnosis requires biopsy and histologic examination. KS often resolves with ART and successful immune reconstitution. If lesions do not respond to ART or are severe or numerous, refer to an oncology specialist for chemotherapy. For more details, see chapter *Kaposi Sarcoma*.

Gingivitis

See chapters *Linear Gingival Erythema* and *Necrotizing Ulcerative Periodontitis and Gingivitis* for more details.

Herpes Simplex Virus

HSV lesions occur on the palate, gingivae, or other mucosal surfaces. They appear as single or clustered vesicles and may extend onto adjacent skin of the lips and face to form a large herpetic lesion. Lesions tend to be more common, persist longer, recur more often, and be larger and more numerous in HIV-infected patients, especially those with significant immunosuppression, than in healthy individuals. Empiric treatment with famciclovir, valacyclovir, or acyclovir is appropriate. For more details, see chapter *Herpes Simplex, Mucocutaneous*.

Aphthous Ulcers

Aphthous ulcers are eroded, well-defined lesions surrounded by erythema, ranging in size from <6 mm to several centimeters in diameter. The ulcers can appear anywhere in the oral cavity or pharynx and may be recurrent; they are extremely painful. Treatment may involve topical steroids or other methods. For more details, see chapter *Oral Ulceration*.

Oral Warts (human papillomavirus)

Oral warts may appear as solitary or multiple nodules. The lesions may be smooth, raised masses resembling focal epithelial hyperplasia, or small papuliferous or cauliflower-like projections. See chapter *Oral Warts*.

Other Conditions

Most of these complications also can occur in the esophagus. See chapters *Esophageal Problems*, *Candidiasis*, *Oral and Esophageal*, and *Cytomegalovirus Disease*.

If patient is having mouth pain, anorexia, or problems with taste, treat the condition appropriately and refer to an HIV-experienced dentist for evaluation and further treatment as needed. Refer to a dietitian for assistance with dietary needs (eg, nutritional supplements).

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Esophageal Problems

Background

Esophageal problems in HIV-infected patients include difficulty swallowing (dysphagia) or midline retrosternal pain when swallowing (odynophagia). Pain may be diffuse throughout the esophagus or localized in specific areas.

Several conditions may cause esophageal problems. Of the infectious causes of dysphagia in HIV-infected patients, *Candida* is the most common (50-70%). Drug-induced dysphagia, gastroesophageal reflux disease (GERD), vomiting, and hiatal hernia can also cause esophagitis. Less commonly, neoplasm or another cause of stricture may produce symptoms. Neuromuscular or neurological causes may be seen in patients with advanced AIDS.

If untreated, esophageal problems may result in esophageal ulcers, scarring of the esophagus, dehydration, and weight loss.

S: Subjective

The patient may complain of difficulty swallowing, a feeling of something being “stuck in the throat,” retrosternal pain when eating, “hiccups,” indigestion (“heartburn”), acid reflux, nausea, vomiting, or abdominal pain.

History

The history should include the following:

- ◆ Medications (prescription and over-the-counter) and herbal supplements, current and past
- ◆ Concurrent gastrointestinal (GI) symptoms, such as abdominal pain or diarrhea
- ◆ Recent dietary history
- ◆ Location and characteristics of pain (diffuse or focal)
- ◆ Oral thrush
- ◆ Aphthous ulcers
- ◆ Cytomegalovirus (CMV)
- ◆ *Candida* esophagitis
- ◆ GERD
- ◆ Hiatal hernia

O: Objective

Include the following in the physical examination:

- ◆ Measure vital signs (temperature may be elevated with certain infections, such as CMV, but not with herpes simplex virus [HSV], candidiasis, or idiopathic ulcers).
- ◆ Record weight (and compare with previous weights).
- ◆ Assess for oral candidiasis, lesions, and masses.
- ◆ Examine optic fundi to evaluate for CMV retinitis (in patients with CD4 counts of <50-100 cells/ μ L).
- ◆ Palpate for thyroid enlargement.
- ◆ Palpate the neck for lymphadenopathy.
- ◆ Assess the abdomen for masses, tenderness, and organomegaly.
- ◆ Perform a rectal examination to obtain stool for occult blood.
- ◆ Perform a neurologic examination.
- ◆ Check the CD4 count and HIV viral load to determine the level of immunosuppression and assess the risk of opportunistic infections as causes of esophageal complaints.

A: Assessment

Common causes of esophageal problems are as follows:

- ◆ Candidiasis (common with a CD4 count of <250 cells/ μ L or recent exposure to steroids or antibiotics)
- ◆ Most medications, including antiretroviral agents, can cause nausea and GI-related symptoms. The following medications are commonly associated with difficulty swallowing or heartburn: aspirin, nonsteroidal antiinflammatory drugs, potassium chloride, iron, tetracycline, theophylline, anticholinergic agents, calcium channel blockers, meperidine, and progesterone tablets.
- ◆ Foods can irritate the esophagus, including citrus fruits, mints, coffee, chocolate, and spicy foods.
- ◆ GERD

Less common causes of esophageal problems include:

- ◆ CMV; HSV; idiopathic or aphthous ulcers
- ◆ Kaposi sarcoma, lymphoma, tuberculosis, *Mycobacterium avium* complex (MAC), histoplasmosis
- ◆ Cardiac chest pain

P: Plan

Diagnostic Evaluation

Diagnosis often can be made on clinical grounds; in this case, empiric treatment may be initiated (see below). If the diagnosis is unclear, consider endoscopy or radiographic imaging (eg, CT or barium swallow).

Treatment

Determine whether the patient is able to swallow pills before giving oral medications. If pills are not tolerated, the patient may need liquids or troches.

For patients with severe oral or esophageal pain, viscous lidocaine 1% 5-10 mL 2-4 times daily (with swallowing precautions) or Magic Mouthwash (viscous lidocaine 1%, tetracycline, Benadryl, and nystatin compounded 1:1:1:1) may be tried.

Other treatments may depend on the underlying cause:

- ◆ Esophageal candidiasis: Fluconazole (Diflucan) is the drug of choice. If symptoms resolve within 7-10 days, no further testing is required. See chapter *Candidiasis, Oral and Esophageal* for more options and for dosing.
- ◆ Medication-related: Remove the offending drug(s), and institute a trial of H2 blockers or proton pump inhibitors (PPIs) as appropriate.*
- ◆ Food-related: Modify the diet and institute a trial of H2 blockers or PPIs as appropriate.*
- ◆ GERD: For nonpharmacologic treatment, in cases of obesity, counsel patients to lose weight, stop smoking, elevate the head of the bed, eat smaller meals, avoid eating food 2-3 hours before bedtime, and reduce fat in the diet to $\leq 30\%$ of calorie consumption.
- ◆ “Heartburn” or reflux: Patients whose primary symptoms are more typical of “heartburn” or reflux, especially those with a history of GERD, should receive a trial of H2 blockers or PPIs as

appropriate.* Some patients will require both an H2 blocker and a PPI to control symptoms. Reevaluate after 1-2 weeks; if symptoms are controlled, treat for 8 weeks, then reduce the dosage to the lowest effective amount. Patients may require maintenance therapy for an indefinite period because of the high likelihood of recurrence.

- ◆ CMV: Treat with anti-CMV medications (eg, oral valganciclovir). See chapter *Cytomegalovirus Disease* for details.
 - ◆ HSV: Treat with antiviral medications including acyclovir (Zovirax), famciclovir (Famvir), or valacyclovir (Valtrex). See chapter *Herpes Simplex, Mucocutaneous*.
 - ◆ Aphthous ulcers: These may respond to oral corticosteroids (prednisone 40 mg/d for 7-14 days, tapered to 10 mg per week for 4 weeks; a shorter course may be effective for small ulcers). Alternatively, a combination of H2 blockers* and sucralfate (Carafate) may be effective. In some circumstances, thalidomide 200 mg every 24 hours may be used. (Note: Thalidomide is teratogenic, and women of childbearing potential are not candidates for this therapy unless the benefits clearly outweigh the risks and appropriate prevention of pregnancy is undertaken.) Up to 40-50% of patients with aphthous ulcers experience relapse and require repeat treatment.
 - ◆ Neoplastic disease requires referral to an oncologist.
- * *Caution: PPIs and H2 blockers interfere with the absorption of atazanavir. PPIs are contraindicated in patients taking atazanavir (Reyataz). H2 blockers may be used cautiously in patients on ritonavir-boosted atazanavir, if they are separated from the atazanavir doses by 12 hours.*

Esophageal conditions that do not resolve with treatment require referral to a GI specialist for diagnostic endoscopy, with biopsy and brushing for histopathology and cultures as appropriate.

Diet

It is important that patients maintain adequate caloric intake, preferably with foods and liquids that can be swallowed easily. Nutritional supplements along with soft, bland, high-protein foods are recommended. Refer to nutritionist as needed.

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Eye Problems

Background

The immunosuppression caused by HIV infection increases the incidence of eye infections. However, serious eye problems associated with advanced immunosuppression, such as blindness due to cytomegalovirus (CMV) retinitis, are less common in patients treated with effective antiretroviral therapy (ART). Common problems not unique to HIV-infected patients include dry eye, blepharitis, keratitis, and presbyopia. Infectious processes affecting the eye include herpes simplex virus (HSV), herpes zoster virus (HZV), and syphilis. More severely immunocompromised patients (CD4 count <100 cells/ μ L) may experience CMV retinitis, *Toxoplasma* retinochoroiditis, cryptococcal chorioretinitis, and other conditions. Retinal detachment can result. Kaposi sarcoma (KS) also can affect the eye.

Immune reconstitution disease (IRD) may affect the eye in patients with advanced HIV disease soon after the initiation of effective ART. IRD may lead to exacerbation of a previously treated opportunistic infection or a new presentation (often with unusual manifestations) of a previously subclinical infection. In the case of CMV, IRD may present as retinitis, or less commonly as uveitis or vitreitis. IRD retinitis typically occurs in patients whose CD4 counts have increased from <50 cells/ μ L to 50–100 cells/ μ L during ART.

Drug-induced ocular toxicity can be caused by rifabutin (Mycobutin), ethambutol (Myambutol), and cidofovir (Vistide), and less often by high-dose didanosine (ddI, Videx), intravenous ganciclovir (Cytovene), intravenous acyclovir (Zovirax), and atovaquone (Mepron).

S: Subjective

The patient complains of dry eyes, blurred vision, floaters, sharp pains, flashing lights, central vision loss (“black holes”), vision field defects (“can only see half the page”), or peripheral vision loss (“looks like I’m in a tunnel”).

Ascertain the following during the history:

- ◆ Pain: clarify type and characteristics
- ◆ Unilateral or bilateral problem

- ◆ Visual defects (central or peripheral vision loss or distortion), scotomata (an area of lost or depressed vision surrounded by an area of less depressed or normal vision). Occurs with reading, distance, or both?
- ◆ Fever
- ◆ Headache
- ◆ Previous eye or vision problems
- ◆ Medications (prescription and over-the-counter), and herbal supplements, current and past
- ◆ Use of corrective lenses
- ◆ Date of last eye examination
- ◆ Recent or current varicella-zoster virus (VZV) or HZV infection

O: Objective

Recent CD4 count and HIV viral load are important measures of immunosuppression to determine whether patient is at risk for opportunistic infections as causes of eye complaints. Also do the following:

- ◆ Consider the patient’s age
- ◆ Check vital signs, including blood pressure and temperature
- ◆ Administer a visual acuity examination using the Snellen chart. Test the patient’s ability to read small print, such as classified ads.
- ◆ Consider using an Amsler grid to locate areas of retinal pathology.
- ◆ Examine the eyelids for lesions, inflammation, and swelling.
- ◆ Examine the external eye for edema, ptosis, conjunctival injection, and corneal clarity.
- ◆ Test cranial nerves II, III, IV, and VI.
- ◆ Perform funduscopic examination with pupillary dilatation if available. Note retinal appearance, lesions, and condition of the disc, vessels, and macula.

A: Assessment and Plan

Refer to an HIV-experienced ophthalmologist for dilated retinal or slit-lamp examination and definitive diagnosis. If symptoms raise suspicion of serious or vision-threatening conditions such as herpes ophthalmicus, CMV retinitis, or retinal necrosis, ophthalmologic evaluation should occur within 24-72 hours.

The differential diagnosis includes the following conditions:

Dry Eye (Keratoconjunctivitis Sicca)

The patient may complain of intermittent eye pain, intermittent blurred vision that clears with blinking, and mild eye irritation. The condition worsens with extended reading or computer use. Keratoconjunctivitis sicca is related to HIV-mediated inflammation with damage to the lacrimal glands. It occurs in 10-20% of HIV-infected patients, most often in those with advanced HIV disease. In patients with a CD4 count of >400 cells/ μ L and no other signs or symptoms, confirm that a recent eye examination was normal or refer for same, prescribe artificial tears, and monitor.

Blepharitis

Blepharitis is inflammation of the eyelids, a common condition with dry eyes. The patient may complain of discharge and erythema of the eyes or eyelids. Of the bacterial causes, *Staphylococcus aureus* is the most common. Treatment includes cleaning of the eyelashes with warm water and mild shampoo, and applying antibiotic ointment if indicated.

Infectious Keratitis

The patient may complain of photophobia, eye pain, decreased vision, and irritation. Infectious keratitis may be caused by VZV, HSV, CMV, bacteria, fungi, or *Microsporidia*. VZV and HSV are the most common infectious causes of keratitis in HIV-infected patients. Bacterial and fungal causes occur equally in HIV-infected and HIV-uninfected persons. Fungal infections are caused most frequently by *Candida* species, especially in intravenous drug users. Keratitis may be more severe and may recur more frequently in HIV-infected patients than in HIV-uninfected persons. Evaluation should include slit-lamp examination by an ophthalmologist.

Refraction Problems

The patient may complain of blurring vision with near or distance vision. Other findings include an abnormal Snellen test or inability to read fine print. The condition may be due to presbyopia or other causes. Refer for ophthalmologic examination.

Iridocyclitis/Anterior Uveitis

The patient may complain of redness or watering of the eyes, constriction of the pupil, and blurred vision. Anterior-chamber inflammation is fairly common among patients with HIV infection and is often associated with CMV or HSV retinitis. Ocular bacterial infections, syphilis, toxoplasmosis, and tuberculosis can cause severe symptoms. Fungal retinitis rarely causes iridocyclitis. Other causes include other systemic conditions (eg, reactive arthritis, sarcoidosis) and drug toxicity (eg, rifabutin, cidofovir, ethambutol). Evaluation should include slit-lamp examination by an ophthalmologist.

Treatment should be directed at the causative pathogen or illness. If drug toxicity is suspected, the offending drug should be discontinued or reduced in dosage. Topical steroids may be indicated as an adjunctive measure. CMV IRD may present as posterior uveitis; for suspected IRD, consult an HIV-experienced ophthalmologist.

HIV Retinopathy

The patient typically has no symptoms, but may complain of blurred vision, visual field defects, floaters, or flashing lights. Cotton wool spots on the retina appear as small fluffy white lesions with indistinct borders and without exudates or hemorrhages. Usually, these findings are benign and do not progress. Refer for ophthalmologic examination to rule out other causes.

CMV Retinitis

Patients with retinitis caused by CMV infection may be asymptomatic or may experience blurred vision, floaters, scotomata, or central or peripheral vision loss or distortion. Retinal examination shows creamy to yellowish lesions, white granular areas with perivascular exudates, and hemorrhages ("cottage cheese and ketchup"). The abnormalities initially appear in the periphery, but progress if untreated to involve the macula and optic disc. CMV is a common complication of advanced HIV infection in patients with CD4 counts

of <50 cells/ μ L. Vision loss is usually permanent. Urgent ophthalmology consultation and initiation of anti-CMV therapy are required. See chapter *Cytomegalovirus Disease*.

Acute Retinal Necrosis

The patient may complain of eye pain, decreased visual acuity, and floaters. Rapidly progressing peripheral necrosis frequently causes blindness. Retinal necrosis is usually caused by VZV, although HSV and CMV have also been implicated. Treatment should be initiated urgently.

Toxoplasma Retinochoroiditis

Toxoplasma retinochoroiditis may occur in patients with CD4 counts of <100 cells/ μ L and cause blurred vision, visual field defects, floaters, or flashing lights. In HIV-infected patients, ocular manifestations often appear after the infection of the central nervous system with toxoplasmosis (see chapter *Toxoplasmosis*). Retinal examination may reveal yellow-white infiltrates without hemorrhage and active vitreous inflammation. Evaluation requires consultation with an HIV-experienced ophthalmologist. If toxoplasmosis is confirmed or strongly suspected, treatment should be initiated as quickly as possible.

Neuro-Ophthalmologic Manifestations

Symptoms or signs of papilledema, optic neuritis, cranial nerve palsies, and visual field defects may indicate encephalopathy, increased intracranial pressure, neurosyphilis, toxoplasmosis, multifocal leukoencephalopathy, meningitis, or central nervous system lymphomas. A thorough neurologic examination is required to determine whether additional diagnostic testing, such as imaging studies or cerebrospinal fluid testing, is needed in addition to ophthalmologic evaluation.

Retinal Detachment

The patient may complain of flashes of light, sudden loss of vision or both. This condition requires immediate referral to an emergency department.

Patient Education

- ◆ Patients should report any changes in vision to their health care provider as soon as possible.
- ◆ Routine eye examinations should be part of the patient's primary care.

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Fatigue

Background

Fatigue is defined by Aaronson et al as “a decreased capacity for physical and/or mental activity due to an imbalance in the availability, utilization, and/or restoration of resources needed to perform activity.” Fatigue is one of the most common and debilitating complaints of HIV-infected people, with an estimated prevalence of 20–69%. The consequences of severe fatigue may include curtailment of work and other activities, need for frequent breaks, limitations in involvement with family and friends, and difficulty completing even the simplest household chores.

In HIV-infected individuals, fatigue may be caused by several comorbid conditions or by HIV itself. HIV-related fatigue is a broad term referring to fatigue that begins or significantly worsens after the patient is infected with HIV and that has no other identifiable causes. HIV-infected people with fatigue should be evaluated carefully for reversible causes, such as depression, anemia, hypogonadism, insomnia, and medication adverse effects, and should be treated aggressively if these are found. In some patients, fatigue may be related to advanced immunosuppression (with low CD4 cell counts) or to high levels of circulating HIV virus. Unfortunately, a specific cause of fatigue is not identified in many patients. Research to date suggests that fatigue in many HIV-infected individuals may result from a complex interplay between physiologic and psychosocial variables, and ongoing studies are being conducted to define factors related to the onset or worsening of fatigue.

S: Subjective

The patient complains of tiredness, easy fatigability, a need for frequent rest or naps, or waking in the morning feeling unrefreshed. The patient may complain of difficulty working, difficulty concentrating, inability to exercise without experiencing profound fatigue, or impairment in social relations because of fatigue.

Consider the following during the history:

- ◆ No objective clinical indicators exist for fatigue; thus, the diagnosis of fatigue rests on subjective data.

- ◆ Fatigue assessment tools may help to diagnose and estimate the severity of fatigue. One such tool, the HIV-Related Fatigue Scale, was developed specifically for use with seropositive individuals (see Barroso and Lynn reference below). The scale includes 56 items that assess the intensity of fatigue (on the day of the assessment and during the previous week), the circumstances surrounding fatigue (including patterns), and the consequences of fatigue.
- ◆ Take a thorough history of the fatigue symptoms, including onset, duration, exacerbating and alleviating factors, and associated symptoms. Evaluate for symptoms of other conditions that cause fatigue (eg, hypothyroidism, hypogonadism, anemia, heart failure, poor nutrition).
- ◆ Depression can cause significant fatigue and is common in HIV-infected patients with fatigue. Screen the patient for depression. A single question—“Are you depressed?”—has been shown to be as valid and reliable as most depression instruments. See the chapter *Depression* for further information.
- ◆ Evaluate the patient’s sleep patterns. HIV infection can interfere with sleep architecture early in the illness.
- ◆ Inquire about substance use or abuse.
- ◆ Obtain a list of all current medications, including herbal and over-the-counter preparations.
- ◆ Conduct a nutritional assessment.

O: Objective

Check vital signs and orthostatic blood pressure and heart rate measurements, if indicated. Perform a physical examination including evaluation of nutritional status, affect, conjunctivae and skin (for pallor), thyroid, lungs and heart, and deep tendon reflexes.

A: Assessment

The differential diagnosis includes the following:

- ◆ Anemia
- ◆ Hypothyroidism
- ◆ Hypogonadism
- ◆ Depression
- ◆ Insomnia or poor-quality sleep
- ◆ Substance use or abuse
- ◆ Malnutrition
- ◆ Medication adverse effects (eg, zidovudine, interferon)
- ◆ Opportunistic infections, malignancy, chronic hepatitis B or C, other illnesses

P: Plan

Diagnostic Evaluation

To rule out reversible causes of fatigue, perform laboratory tests, including:

- ◆ Hemoglobin and hematocrit
- ◆ Thyroid function tests
- ◆ Testosterone (in both men and women)

Fatigue assessment tools, as mentioned above, may be used to assess the intensity of fatigue, the circumstances surrounding fatigue, and the consequences of fatigue.

Treatment

If testing reveals a specific cause of fatigue, treat appropriately. For example:

- ◆ Treat anemia, hypothyroidism, or hypogonadism, as indicated. (See chapter *Anemia*.)
- ◆ Treat depression with antidepressant medication, psychotherapy, or both. (See chapter *Depression*.)
- ◆ Treat insomnia and review good sleep-hygiene practices with the patient. (See chapter *Insomnia*.)
- ◆ Refer for treatment of substance use or abuse, if possible.
- ◆ Treat malnutrition, ideally in conjunction with a nutritionist.
- ◆ Treat opportunistic infections and other illnesses. (See section *Disease-Specific Treatment*.)

- ◆ Control other symptoms that could be causing fatigue (eg, diarrhea).
- ◆ If fatigue seems to be related to antiretroviral medication(s), weigh the benefits of the medication(s) against the possible adverse effects, and discuss these with the patient.

If, after appropriate evaluation, the fatigue is thought to be related to HIV infection or no specific cause is identified, consider the following:

- ◆ If HIV infection is inadequately controlled, particularly if the CD4 count is low or the HIV viral load is high, consider antiretroviral therapy (ART), if otherwise appropriate.
- ◆ Patients taking effective ART may still experience HIV-related fatigue. Providers should not dismiss these symptoms or tell these patients that, because their CD4 counts are high or HIV viral loads are low or undetectable, they should be feeling fine.
- ◆ Encourage patients to track their patterns of fatigue with a fatigue diary if necessary. Once patients recognize their individual patterns, they can better cope with fatigue by planning their daily activities accordingly (eg, performing the most strenuous tasks during times of peak energy or staggering activities to avoid excessive fatigue).
- ◆ Recommend moderate exercise and frequent rest.
- ◆ Refer the patient to community-based agencies for assistance with housekeeping.
- ◆ Evaluate the need for occupational therapy (eg, energy conservation techniques) or physical therapy (eg, reconditioning and strengthening exercises).
- ◆ Medications, such as stimulants, may be helpful for some patients with severe or debilitating fatigue.

Patient Education

- ◆ Fatigue is often not related to the CD4 count or HIV viral load. Avoid telling patients that, because their CD4 counts are high or HIV viral loads are low or undetectable, they should be feeling well.
- ◆ Encourage patients to keep a fatigue diary to identify patterns of fatigue that may have gone unrecognized. This information can help patients cope with fatigue and plan activities appropriately.
- ◆ Patients should be asked what seems to aggravate their fatigue. This information, too, will help patients determine their patterns of fatigue and identify self-care actions they might take to avoid triggers that will worsen the fatigue.
- ◆ Screen fatigued patients for depression. If they are depressed, help them get appropriate treatment because this might reduce fatigue.
- ◆ Talk to patients about their sleep habits and recommend changes, as appropriate, to improve their sleep hygiene.

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Fever

Background

Although fever may accompany HIV infection at various stages of disease, fever in a patient with a low CD4 count (<200 cells/ μ L) should prompt the clinician to rule out opportunistic infections.

S: Subjective

The patient complains of persistent fever, or new-onset fever of $>101^{\circ}\text{F}$ (38.3°C).

Assess the following during the history:

- ◆ Duration of fever
- ◆ Associated symptoms, including chills, sweats, weight loss
- ◆ Visual disturbances (see chapter *Eye Problems*)
- ◆ Nasal or sinus symptoms
- ◆ Asymmetric, tender, or new lymphadenopathy
- ◆ Cough or shortness of breath (see chapter *Pulmonary Symptoms*)
- ◆ Diarrhea, tenesmus (see chapter *Diarrhea*)
- ◆ Vaginal or urethral discharge
- ◆ Rash, lesions, soft-tissue inflammation
- ◆ Pain (for headache, see chapter *Headache*)
- ◆ Neurologic symptoms (see chapter *Neurologic Symptoms*)
- ◆ Other localizing symptoms
- ◆ Unprotected sexual contacts
- ◆ Recent injection drug use
- ◆ Travel within the past 6-12 months
- ◆ Intravenous line or venous access device
- ◆ Medications (as a cause of fever)
- ◆ Use of antipyretic agents including acetylsalicylic acid, nonsteroidal antiinflammatory drugs (NSAIDs), and acetaminophen; when was most recent dose?
- ◆ Hepatitis history

O: Objective

Document fever. Check other vital signs, including orthostatic measurements. Check weight and compare with previous values. Search for evidence of an infectious focus. Perform a complete physical examination, including evaluation of the eyes (including fundus), sinuses, oropharynx, lymph nodes, lungs and heart, abdomen, joints, genitals, uterus, rectum, and neurologic system. Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses as a cause of fever.

A: Assessment

The differential diagnosis varies depending on the CD4 count. Partial lists are as follows.

Conditions More Likely with Low CD4 Count

- ◆ Aspergillosis
- ◆ Cryptococcosis
- ◆ Cytomegalovirus infection (CMV)
- ◆ Disseminated *Mycobacterium avium* complex (MAC)
- ◆ Disseminated histoplasmosis
- ◆ HIV infection itself
- ◆ Lymphoma, other neoplasms
- ◆ *Pneumocystis jiroveci* pneumonia (PCP)
- ◆ Sinusitis
- ◆ Toxoplasmosis
- ◆ Tuberculosis (atypical or extrapulmonary)

Conditions That May Occur at Any CD4 Count

- ◆ Acute hepatitis
- ◆ Bacterial pneumonia or bronchitis
- ◆ Tuberculosis (pulmonary)
- ◆ Urinary tract infection (UTI)
- ◆ Otitis
- ◆ Endocarditis
- ◆ Abscess, cellulitis
- ◆ Bacteremia or sepsis
- ◆ Disseminated herpes simplex virus; chicken pox

- ◆ Malaria
- ◆ Pelvic inflammatory disease (PID)
- ◆ Sexually transmitted infections
- ◆ Autoimmune process
- ◆ Immune reconstitution syndromes, related to opportunistic infections, are often associated with fever. (See chapter *Immune Reconstitution Syndrome*.)
- ◆ Drug-induced fever (common culprits include abacavir, nevirapine, sulfonamides, dapsone, amphotericin, pentamidine, thalidomide, penicillin, clindamycin, carbamazepine, phenytoin, barbiturates, and bleomycin)

P: Plan

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. These may include the following:

- ◆ CD4 count (if not done recently) to help with risk stratification for opportunistic illnesses
- ◆ Complete blood count (CBC) with differential
- ◆ Blood cultures (bacterial, mycobacterial, fungal)
- ◆ Urinalysis, urine culture if UTI symptoms are present
- ◆ Liver enzymes, renal panel
- ◆ Chest x-ray; sinus films if indicated by symptoms and physical examination findings
- ◆ If respiratory symptoms and signs are present: sputum evaluation (Gram stain and acid-fast bacilli smear, evaluation for PCP), with culture of sputum for bacterial pathogens, acid-fast bacilli, and fungi as indicated; consider sputum induction or bronchoscopy if indicated
- ◆ Serum cryptococcal antigen if CD4 count is <200 cells/ μ L and symptoms are consistent with cryptococcosis
- ◆ For new lymphadenopathy: aspirate with culture, including acid-fast bacilli and fungal; cytology
- ◆ For cytopenias: bone marrow aspirate and biopsy may be needed. See applicable treatment guidelines
- ◆ For fever of unknown origin (FUO), defined as persistent fever >101° F, for >3 weeks without findings on initial workup, more intensive workup may be needed, such as lumbar puncture, other scans or biopsies; consult with a specialist in infectious diseases or an HIV expert to determine whether hospitalization or other laboratory tests are needed.

- ◆ For patients taking abacavir or nevirapine, rule out hypersensitivity reactions (see chapter *Adverse Reactions to HIV Medications*).

Once a diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic tests are pending. In some cases, the source of fever cannot be identified. Consult with an HIV expert.

Symptomatic treatment may include NSAIDs, particularly naproxen (Naprosyn, Aleve) because it can be administered twice daily; acetaminophen; and analgesics. Monitor for gastrointestinal adverse effects with NSAIDs. Cold compresses also can be used to relieve fever symptoms. Refer to a dietitian to avoid weight loss during the hypermetabolic state. See *Section 6: Disease-Specific Treatment*, in this manual if an HIV-related cause is identified.

Patient Education

- ◆ Patients should report any new fever to their health care providers. They should measure their temperatures using a thermometer at home in order to report actual temperatures.
- ◆ Patients should know that fever is usually a sign that their bodies are battling an infection. Their health care providers may need to do special tests to find out what could be causing the fever.
- ◆ Many over-the-counter remedies are available to treat fevers. Patients should check with their care providers before taking these. Acetaminophen-containing products (eg, Tylenol) are generally well tolerated. Persons with liver disease should use acetaminophen only as prescribed. NSAIDs (eg, ibuprofen, naproxen, Advil, Motrin, Aleve) may also be used, but can cause gastrointestinal adverse effects, especially if taken without food. Patients should let their care providers know if they need to take these medicines for more than 2 or 3 days.

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Headache

Background

Headache may have many causes in HIV-infected persons, particularly those with low CD4 counts. Possible causes include infections (opportunistic and other) and central nervous system malignancies, HIV-related systemic illnesses, and medication toxicity. In addition, of course, headache may be caused by any of the processes that cause headaches in HIV-uninfected individuals. New or severe headache should be evaluated carefully.

S: Subjective

The patient complains of a new type of headache.

Determine the following during the history:

- ◆ History of headaches or migraines
- ◆ Characteristics of the headache (location, quality of pain, timing, duration, etc)
- ◆ Recent head trauma
- ◆ Allergies
- ◆ History of sinusitis
- ◆ Fevers
- ◆ Visual changes
- ◆ Dizziness, vertigo, nausea
- ◆ Mental status changes
- ◆ Seizures
- ◆ Focal or other neurologic symptoms (see chapter *Neurologic Symptoms*)
- ◆ New rashes or ulcerations
- ◆ Other symptoms
- ◆ Usual versus recent caffeine intake
- ◆ New medications (eg, zidovudine)
- ◆ Relief of headache by any medication
- ◆ Unprotected sex, new sex partner

O: Objective

Perform a physical examination as follows:

- ◆ Check vital signs. Look for fever, orthostasis, and hypertension.
- ◆ Examine the head and neck for trauma, sinus tenderness, and neck mobility; check lymph nodes.
- ◆ Check the eyes, including funduscopic examination, for lesions or papilledema.
- ◆ Look for oral lesions, dental abscess, thrush, and pharyngeal drainage.
- ◆ Examine the lungs for abnormal sounds.
- ◆ Check the skin, including palms and soles, for rashes or lesions.
- ◆ Perform a complete neurologic examination, including mental status examination.
- ◆ Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses as a cause of headache.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Cryptococcal meningitis
- ◆ Neurosyphilis
- ◆ Tuberculous meningitis; other meningitis
- ◆ Progressive multifocal leukoencephalopathy (PML)
- ◆ Toxoplasmic encephalitis
- ◆ Cytomegalovirus (CMV) meningoencephalitis or retinitis
- ◆ Other encephalitis
- ◆ Central nervous system lymphoma
- ◆ Systemic infection
- ◆ Sinusitis
- ◆ Anemia
- ◆ Fever
- ◆ Depression, anxiety disorder
- ◆ Medication adverse effect
- ◆ Stress or tension headache

- ♦ Migraine or cluster headache
- ♦ Caffeine withdrawal
- ♦ Hypertension
- ♦ Dehydration

Other causes of headache unrelated to HIV should be considered.

P: Plan

Diagnostic Evaluation

Evaluation should include the following:

- ♦ CD4 count (if not done recently), to help with risk stratification for opportunistic illnesses
- ♦ Complete blood count (CBC) with differential (if fever or suspected anemia); see chapters *Anemia* and *Fever*
- ♦ Blood chemistries, including liver function tests, electrolytes, creatinine, glucose
- ♦ Serum cryptococcal antigen (if fever is present and CD4 count is <200 cells/ μ L); see chapter *Cryptococcosis*
- ♦ Toxoplasma immunoglobulin G (IgG) (if previously negative and CD4 count is <200 cells/ μ L); see chapter *Toxoplasmosis*
- ♦ Syphilis testing: rapid plasma reagin (RPR) or Venereal Diseases Research Laboratory (VDRL) test; see chapter *Syphilis*

When indicated, also consider:

- ♦ Sinus imaging
- ♦ Computed tomography (CT) scan with contrast or magnetic resonance imaging of the head; see chapter *Neurologic Symptoms*
- ♦ Lumbar puncture with cerebrospinal fluid (CSF) studies to include cell count, chemistries, bacterial cultures; fungal and acid-fast bacilli (AFB) evaluations and cultures; India ink stain; cryptococcal antigen, VDRL, as indicated

Treatment

- ♦ Once diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be initiated while diagnostic test results are pending. In some cases, the source of headache cannot be identified. Consult with an HIV expert or a neurologist.
- ♦ Refer to disease-specific treatment guidelines or primary care management guidelines as appropriate.
- ♦ Treat symptomatically with nonsteroidal antiinflammatory drugs (NSAIDs), acetaminophen, or narcotics, if indicated, to control pain.

Patient Education

- ♦ Headaches can be a sign of an opportunistic infection, especially in patients with low CD4 cell counts. Patients should notify their health care providers if they develop a new headache.
- ♦ Providers should inform patients that they may have to do additional tests to determine the cause of the headaches.
- ♦ Many over-the-counter remedies are available for headache. Patients should check with their health care providers before taking these. Acetaminophen-containing products (eg, Tylenol) are generally well tolerated. Persons with liver disease should use acetaminophen only as prescribed. NSAIDs (eg, ibuprofen, naproxen, Advil, Motrin, Aleve) may also be used, but can cause gastrointestinal adverse effects, especially if taken without food. Patients should inform their care providers if they need to take these medicines for more than 2 or 3 days.

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Lymphadenopathy

Background

Lymphadenopathy is very common in HIV-infected individuals and may occur at any stage of HIV infection. It may be the first indication of a serious local or systemic condition, and should be evaluated carefully. Rapid enlargement of a previously stable lymph node or a group of nodes requires evaluation to identify the cause and to determine whether treatment is needed. Similarly, nodes that are abnormal in consistency, tender to palpation, fluctuant, asymmetrical, adherent to surrounding tissues, or accompanied by other symptoms should be evaluated promptly.

Lymphadenopathy may be generalized or localized and is usually characterized by lymph nodes that are >1 cm in diameter. A multitude of conditions can cause lymphadenopathy, including HIV itself, opportunistic or other infections, and malignancies. The likely causes of lymphadenopathy, and thus the diagnostic workup, will depend in part on the patient's degree of immunosuppression. The risk of opportunistic and certain malignant conditions increases at lower CD4 cell counts (see chapter *CD4 Monitoring and Viral Load Testing*).

Many individuals with primary HIV infection (see chapter *Primary HIV Infection*) may have generalized lymphadenopathy that may resolve or may persist for months to years. If lymphadenopathy of >2 cm in size occurs in 2 or more noncontiguous sites and persists for more than 3 months, and if appropriate evaluation reveals no other cause, the patient is diagnosed with persistent generalized lymphadenopathy (PGL). PGL is usually due to follicular hyperplasia from chronic HIV infection. As long as enlarged nodes are stable in number, location, and size, persons with PGL require no management other than monitoring of nodes at each physical examination. Changes in the character of the lymph nodes should prompt further evaluation. Rapid involution of PGL may occur with advanced HIV disease and is a poor prognostic sign.

S: Subjective

The patient complains of new, worsening, or persistent glandular swellings in the neck, axilla, groin, or elsewhere.

Ascertain the following during the history:

- ◆ Symptoms that accompany the lymphadenopathy, particularly constitutional symptoms such as fever, sweats, fatigue, and unintentional weight loss.
- ◆ Localized symptoms or conditions that involve areas of the body with lymphatic drainage into the area of abnormal lymph nodes (eg, in the case of axillary lymphadenopathy, ask about breast masses and skin conditions or trauma involving the arm)
- ◆ A full review of systems
- ◆ HIV-related or other malignancies, opportunistic illnesses
- ◆ Recent travel, country or region of origin, disease exposures (eg, tuberculosis [TB], sexually transmitted infections), and risk behaviors (eg, injection drug use)
- ◆ Trauma or injury (including cat scratches)
- ◆ Exposure to household pets
- ◆ Current medications

Review recent CD4 cell counts and HIV viral load measurements.

O: Objective

Check vital signs. Perform a complete examination of lymph nodes, including the cervical, submandibular, supraclavicular, axillary, epitrochlear, and inguinal sites. Document the location, size, consistency, mobility, and presence or absence of tenderness of all abnormal nodes. In cases of localized lymphadenopathy, examine the area drained by the node. Check for hepatosplenomegaly. Perform a focused examination (eg, lung, breast, skin, genitals) to identify signs of local or systemic illness.

A: Assessment

The differential diagnosis of lymphadenopathy in HIV-infected patients depends in part on the degree of immunosuppression. For further information, see chapter *CD4 Monitoring and Viral Load Testing*.

Infectious Causes

Generalized lymphadenopathy

- ◆ HIV infection, including PGL
- ◆ Mononucleosis; Epstein-Barr virus
- ◆ *Mycobacterium avium* complex
- ◆ TB
- ◆ Cytomegalovirus
- ◆ Secondary syphilis
- ◆ Toxoplasmosis
- ◆ Histoplasmosis, other fungal diseases
- ◆ *Bartonella* infection
- ◆ Hepatitis B
- ◆ Lyme disease
- ◆ Chlamydia (Lymphogranuloma venereum [LGV])
- ◆ Widespread skin infections
- ◆ Immune reconstitution syndrome
- ◆ Follicular hyperplasia

Localized lymphadenopathy

- ◆ Any of the above
- ◆ Oropharyngeal and dental infections
- ◆ Cellulitis or abscesses
- ◆ Chancroid
- ◆ TB (scrofula)

Neoplastic causes

- ◆ Lymphoma
- ◆ Acute and chronic lymphocytic leukemias
- ◆ Other malignancy; metastatic cancer
- ◆ Kaposi sarcoma

Other causes

- ◆ Reactive process (benign)
- ◆ Sarcoidosis
- ◆ Hypersensitivity reaction to medications
- ◆ Serum sickness
- ◆ Rheumatoid arthritis
- ◆ Castleman disease

P: Plan

Diagnostic Evaluation

After the history and physical examination, the cause of lymphadenopathy may be clear and further diagnostic testing may not be necessary. If the cause of the lymphadenopathy is still uncertain, perform diagnostic testing as indicated by the patient's presentation. This may include the following tests:

- ◆ CD4 count (with or without HIV viral load), to determine the risk of opportunistic illnesses
- ◆ Complete blood count with differential; liver function tests; urinalysis
- ◆ Chest x-ray
- ◆ Tuberculin skin test (purified protein derivative, or PPD)
- ◆ Rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test
- ◆ Blood cultures, if patient is febrile (bacterial, mycobacterial, and fungal, as indicated)
- ◆ Testing for specific infections if suspected (eg, *Bartonella* or LGV)

If a node is large, fixed, nontender, or otherwise worrisome, or if the diagnosis is unclear after initial evaluation, fine-needle aspiration (FNA) biopsy may provide a diagnosis. If FNA is nondiagnostic (false-negative results are relatively common), obtain an open biopsy for definitive evaluation. Biopsy specimens should be sent for bacterial, mycobacterial, and fungal cultures; acid-fast staining for mycobacteria; and cytologic examination.

If a node is large, inflamed, tender, or fluctuant, and a bacterial infection is suspected, consider initiating empiric antibiotic treatment and monitoring the patient over 1-2 weeks. If the node does not respond to antibiotic treatment or the patient becomes more symptomatic, arrange for FNA or open biopsy to establish the diagnosis.

Treatment

Treatment will depend on the cause of lymphadenopathy. Refer to the guidelines in *Section 6: Disease-Specific Treatment* or primary care management guidelines as appropriate. In the case of HIV-related lymphadenopathy, antiretroviral therapy may be effective.

Patient Education

- ◆ Lymphadenopathy may come and go throughout the course of HIV infection, but it may be a sign of a serious condition.
- ◆ Advise patients to notify their clinician if lymph nodes increase in size or change in character.

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Nausea and Vomiting

Background

Nausea with or without vomiting, and occasionally vomiting without nausea, can occur at any stage of HIV infection. Nausea is a common adverse effect of many antiretroviral (ARV) and other medications and often occurs within weeks of starting new medications. In some cases, nausea causes significant discomfort and may interfere with medication adherence. Nausea and vomiting may also be symptoms of a serious complication of ARV therapy, or a sign of an opportunistic infection or neoplasm in patients with late-stage AIDS. Clinicians must identify the cause of nausea and vomiting and institute appropriate treatment.

S: Subjective

The patient complains of nausea with or without vomiting, or vomiting without nausea.

Ascertain the following during the history:

- ◆ Duration of symptoms
- ◆ Characteristics, timing, and precipitating factors
- ◆ Fever
- ◆ Hematemesis
- ◆ Jaundice
- ◆ Abdominal pain
- ◆ Lightheadedness, dizziness, vertigo, or orthostatic symptoms
- ◆ Polyuria
- ◆ Polydipsia
- ◆ Headache
- ◆ Changes in vision
- ◆ Neck stiffness
- ◆ Pruritus
- ◆ Hepatitis history
- ◆ Pancreatitis history
- ◆ Toxoplasmosis encephalitis history
- ◆ Cytomegalovirus history
- ◆ Cryptococcal (or other chronic meningitis) history

- ◆ Central nervous system (CNS) lymphoma history
- ◆ Renal failure history
- ◆ Unprotected sex or missed menses in women
- ◆ Medications, new and ongoing
- ◆ Nutritional supplements and nonprescription medications
- ◆ Alcohol intake, substance use or abuse

O: Objective

Check vital signs, including orthostatic blood pressure and heart rate measurement.

Conduct a thorough physical examination, including evaluation of the following:

- ◆ Skin turgor
- ◆ Eyes and fundi (retinal abnormalities such as papilledema)
- ◆ Oropharynx (dryness of oral mucosa, thrush, ulcerations)
- ◆ Neck (stiffness or other signs of meningeal irritation)
- ◆ Abdomen (tenderness, distention, masses, organomegaly)
- ◆ Pelvis (tenderness, masses)
- ◆ Neurologic system (mental status, focal neurologic abnormalities)

Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses.

A: Assessment

A partial differential diagnosis includes the following conditions:

- ◆ Medication effect or reaction
- ◆ Drug-drug interactions
- ◆ Foodborne illness
- ◆ Pancreatitis
- ◆ Meningitis
- ◆ Pregnancy

- ◆ Adrenal insufficiency
- ◆ Toxoplasmosis encephalitis (see chapter *Toxoplasmosis*)
- ◆ Uremia
- ◆ Diabetic ketoacidosis
- ◆ Lactic acidosis due to nucleoside analogues
- ◆ Esophagitis (see chapter *Esophageal Problems*)
- ◆ CNS lymphoma
- ◆ Hepatitis, infectious or drug related (see chapters *Hepatitis B Infection* and *Hepatitis C Infection*)
- ◆ Appendicitis
- ◆ Pelvic inflammatory disease (see chapter *Pelvic Inflammatory Disease*)
- ◆ Myocardial infarction

P: Plan

Diagnostic Evaluation

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. Tests may include the following:

- ◆ Complete blood count (CBC) with differential
- ◆ Blood urea nitrogen (BUN), creatinine, electrolytes
- ◆ Glucose
- ◆ Amylase and lipase if symptoms of pancreatitis are present
- ◆ Liver function tests (LFTs) and hepatitis serologies for possible acute hepatitis
- ◆ Blood cultures and other fever workup as needed (see chapter *Fever*)
- ◆ Computed tomography (CT) scan of the brain if neurologic symptoms are present (see chapter *Neurologic Symptoms*)
- ◆ Cortisol and cortrosyn stimulation test if indicated (eg, fatigue, weakness, unexplained abdominal pain, weight loss, orthostasis; usually in late-stage AIDS)
- ◆ If odynophagia or dysphagia is present, see chapter *Esophageal Problems*
- ◆ Electrocardiogram if patient has chest pain or suspicious symptoms
- ◆ Lactic acid levels if lactic acidosis is suspected
- ◆ Pregnancy test if indicated
- ◆ Consult with an HIV expert to determine whether hospitalization or other laboratory tests are needed.

Treatment

Once the diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic test results are pending. See appropriate chapters in *Section 6: Disease-Specific Treatment* or other relevant guidelines.

In the case of significant adverse effects from ARVs or other medications, use a substitute for the offending medications, if possible (without compromising the efficacy of the treatment regimen). In the case of serious or life-threatening medication toxicities (eg, lactic acidosis or abacavir hypersensitivity reaction), discontinue the offending medication (see chapter *Adverse Reactions to HIV Medications*).

After the workup and exclusion of life-threatening illness, symptomatic treatment can be considered. If nausea and vomiting are due to medications that are vital to the patient, and these complications are not life-threatening, antiemetic therapy may be the best treatment. Chronic therapy is not always necessary. Some patients obtain adequate relief by breaking the “nausea cycle” with effective antiemetics for 1-2 days and then establishing meals or snacks with medications. Patients with dehydration may require administration of fluids (oral or intravenous) to relieve nausea. For patients with chronic nausea resulting in weight loss, refer to a nutritionist for assessment and nutritional support.

Symptomatic treatment

Consider the following strategies for symptomatic treatment:

- ◆ Ginger capsules have proven effective in clinical trials for the management of pregnancy-related and chemotherapy-related nausea. Foods and beverages containing ginger (eg, tea, cookies, ginger ale, candies) may help provide relief.
- ◆ Promethazine (Phenergan) may be given as a 25-mg oral tablet or a 12.5-mg rectal suppository, every 8-12 hours as needed.
- ◆ Prochlorperazine (Compazine) may be given as a 5-mg or 10-mg oral tablet, or a 25-mg rectal suppository, every 6-8 hours as needed. Extended-release Spansule, 10 mg every 12 hours or 15 mg every morning, can also be considered.

- ◆ Lorazepam (Ativan) may be given as a 0.5mg oral tablet one half hour before medications for symptoms of anticipatory nausea. Patients with anticipatory nausea develop significant nausea or vomiting when even thinking about medications or reaching for the medications.
- ◆ Dronabinol (Marinol) may relieve nausea, especially when nausea is accompanied by a loss of appetite. This remedy is best tolerated by patients who have tolerated inhaled marijuana. The starting dosage is 5mg 2 or 3 times daily.
- ◆ 5-Hydroxytryptamine (5-HT₃) receptor antagonists such as dolasetron (Anzemet) 50 mg and 100 mg, granisetron (Kytril) 1mg, and ondansetron (Zofran) 4-mg, 8-mg, and 24-mg tablets are highly effective in relieving severe nausea and vomiting due to chemotherapy and other causes. However, access to these medications is limited by their cost. Their use should be considered a short-term strategy.

Patient Education

- ◆ Nausea and vomiting can have many different causes. Patients should let their health care providers know if they are having these symptoms so that the most likely cause can be determined.
- ◆ Patients should stay nourished and well hydrated even if they are having nausea and vomiting. Eating small, frequent meals may be best tolerated, while avoiding dairy products, greasy foods, and high-fat meals.
- ◆ Tell patients not to stop taking any of their medications without first discussing it with their health care providers. Many medications must be continued despite nausea.
- ◆ Many patients wonder whether they should take their medicines again if they vomit after taking their dose. Generally, the medicines are still in the system unless the pills actually come back up. Patients should call their health care provider if they have any questions.
- ◆ Ginger may help to relieve nausea. Ginger can be taken in a variety of ways, including ginger ale, tea, cookies, candies, or ginger capsules. Patients can choose the form of ginger that works best for them.

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Neurologic Symptoms

Background

The nervous system may be a site of complications throughout the course of HIV infection, and neurologic complaints are common in people living with HIV/AIDS. Neurologic symptoms may be caused by many factors, including infections (opportunistic and other), central nervous system (CNS) malignancies, medication toxicities, comorbid conditions (eg, diabetes, cerebrovascular disease, chronic hepatitis, mental illness), and nervous system injuries related to HIV itself.

The risk of some conditions, such as CNS infection, malignancy, and dementia, increases with advancing immunosuppression, and the CD4 cell count will help to stratify the patient's risk of opportunistic illnesses (see Table 1 in chapter *CD4 Monitoring and Viral Load Testing*). This chapter presents a general approach to neurologic symptoms in HIV-infected patients, with reference to other chapters in this manual for more detailed reading. For information on peripheral neuropathy, see chapter *Pain Syndrome and Peripheral Neuropathy*.

S: Subjective

The patient, or a friend or family member on his or her behalf, reports new neurologic symptoms such as pain, headache, seizures, altered mental status, or weakness.

Ascertain the following during the history:

- ◆ Onset and duration: rapid (hours to days), subacute, chronic
- ◆ Characteristics of the symptoms (eg, location, quality, timing)
- ◆ Progression or stability of symptoms
- ◆ Constitutional symptoms: fever, night sweats, unintentional weight loss
- ◆ Associated symptoms, including other neurologic, muscular, psychiatric, or behavioral symptoms
- ◆ Recent trauma to the head or other area
- ◆ Visual changes, photophobia
- ◆ Dizziness, vertigo

- ◆ Mental status changes (including changes in behavior, personality, or cognition; short-term memory loss; mental slowing; reading comprehension difficulties; changes in personal appearance and grooming habits)
- ◆ Seizures (description, duration, number)
- ◆ Pain
- ◆ Sensory symptoms
- ◆ Weakness (distinguish weakness from fatigue or pain; determine whether bilateral or focal, proximal or distal)
- ◆ Bowel or bladder changes
- ◆ Rash or ulcerations
- ◆ Medications: current, past, and recently initiated medications, including antiretroviral therapy (ART)
- ◆ Alcohol or drug use; date of last use
- ◆ Exposures (sexual, environmental), travel history
- ◆ Psychiatric history and past psychiatric care
- ◆ Most recent CD4 cell count and HIV viral load, previous AIDS-defining illnesses
- ◆ Functional impact of the symptoms: social functioning, ability to work and perform activities of daily living

Differentiate delirium from dementia. Delirium presents as acute onset of clouded sensorium, disturbed and fluctuating level of consciousness, disorientation, cognitive deficits, and reduced attention, sometimes with hallucinations. Delirium is often due to medication toxicities, infections, hypoxia, hypoglycemia, electrolyte imbalances, or mass lesions, and is frequently is correctable. Dementia emerges more gradually and is characterized by cognitive impairment and behavioral, motor, and affective changes. See chapter *HIV-Associated Dementia and Minor Cognitive Motor Disorder*.

O: Objective

- ◆ Check vital signs (temperature, blood pressure, heart rate, and respiratory rate, oxygen saturation) and orthostatic measurements.
- ◆ Perform a careful physical examination as guided by the history, with special attention to the following:
 - ◆ General appearance: mood, affect, mannerisms
 - ◆ Head and neck: signs of trauma, sinus tenderness, lymph node status, neck mobility
 - ◆ Eyes, including fundi: lesions, papilledema
 - ◆ Lungs, heart: abnormal sounds
 - ◆ Extremities: muscle tone and bulk
 - ◆ Skin, mucous membranes: rash, lesions
- ◆ Conduct a thorough neurologic examination, including cranial nerves, motor function, sensory function, coordination, gait, and deep tendon reflexes.
- ◆ Conduct a mental status examination.
- ◆ Review recent CD4 measurements, if available, to determine the patient's risk for opportunistic illnesses.

A: Assessment

The differential diagnosis of neurologic abnormalities in patients with HIV infection may be broad, particularly if the CD4 count is low. Both HIV-related and HIV-unrelated causes should be considered; remember that more than one cause of symptoms may be present.

Causes related to the cerebrum or cranial nerves

- ◆ Toxoplasmic encephalitis
- ◆ Primary CNS lymphoma
- ◆ Cryptococcal meningitis
- ◆ Cytomegalovirus (CMV) encephalitis
- ◆ Other meningitis (bacterial, tuberculous, fungal, viral)
- ◆ Progressive multifocal leukoencephalopathy (PML)
- ◆ Neurosyphilis
- ◆ CNS coccidioidomycosis, histoplasmosis
- ◆ HIV-related dementia
- ◆ Alcohol or drug intoxication or withdrawal (medications or illicit drugs); chronic alcohol abuse
- ◆ Depression, mania, anxiety, psychosis

- ◆ Cerebrovascular accident; stroke
- ◆ Metabolic abnormalities, including hypo- or hyperglycemia, electrolyte abnormalities

Causes related to the spinal cord, nerve roots, peripheral nerves, and muscle

- ◆ Inflammatory demyelinating polyneuropathy (eg, Guillain-Barré syndrome)
- ◆ Polyradiculitis (eg, CMV, herpes simplex virus)
- ◆ Vitamin deficiency
- ◆ Myositis
- ◆ Myopathy (eg, due to zidovudine)
- ◆ Myelopathy (HIV vacuolar myelopathy)
- ◆ Epidural abscess or mass
- ◆ Mononeuritis multiplex
- ◆ Lactic acidosis
- ◆ Electrolyte abnormality (eg, hypokalemia)
- ◆ Peripheral neuropathy
- ◆ Distal sensory polyneuropathy
- ◆ Antiretroviral toxic neuropathy (especially stavudine, didanosine)
- ◆ Other neuropathy (eg, due to diabetes, alcohol, medications [isoniazid, dapsone, many others])

Note that organic causes of neurologic symptoms must be ruled out before concluding that symptoms are psychiatric in nature.

P: Plan

Diagnostic Evaluation

Unstable or seriously ill patients should be hospitalized for evaluation and treatment. Criteria for hospitalization include acutely altered mental status, fever with focal neurologic findings, and new or unstable seizures.

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. This may include the following:

- ◆ Establish the CD4 count (if not done recently) to help with risk stratification for opportunistic illnesses.
- ◆ Determine which laboratory tests are appropriate depending on the patient's presentation. The initial evaluation often includes a complete blood count with differential and monitoring of electrolyte and glucose levels.

- ◆ In patients with CNS symptoms or signs and low CD4 counts (<100 cells/ μ L), check serum levels of toxoplasma antibody (IgG) if not previously checked. Check serum cryptococcal antigen (CrAg) titer.
- ◆ In patients with symptoms of neuropathy or dementia, check serum levels of vitamin B12 and thyroid-stimulating hormone (TSH).
- ◆ In patients with cranial nerve abnormalities, meningoencephalitis, symptoms of dementia, or any symptoms of neurosyphilis, check syphilis serology by rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test.
- ◆ When CNS symptoms or signs are present, brain imaging by computed tomography (CT) scan with contrast is usually adequate as the initial test. Magnetic resonance imaging (MRI) is the modality of choice if the neurologic examination is nonfocal or if physical examination suggests a lesion in the posterior fossa.
- ◆ For patients with fever and CNS findings, perform lumbar puncture (LP) with cerebrospinal fluid (CSF) sampling. CT or MRI should be performed before the LP, if possible, to rule out a mass lesion that could cause herniation.
- ◆ Record the opening pressure, and send CSF for cell count and differential with protein and glucose measurements. Depending on the clinical suspicion, the fluid should also be sent for bacterial culture, India ink stain for fungal organisms (75-85% sensitive), acid-fast bacilli smear and culture, VDRL test, and CrAg titer (95% sensitive).
- ◆ If CMV is suspected, perform polymerase chain reaction (PCR) for CMV DNA (62-100% sensitivity; 89-100% specificity).
- ◆ If PML is suspected, perform CSF PCR analysis for JC virus DNA (sensitivity approximately 80%; specificity 92-100%).
- ◆ For suspected drug or alcohol use, perform urine or serum toxicology screen. (Note that alcohol usually has been metabolized by the time withdrawal symptoms set in, typically 7-48 hours after the last alcohol intake).
- ◆ For new-onset seizures, perform an electroencephalogram (EEG)
- ◆ Consult with neurology specialists if the workup or the diagnosis is in question.

Treatment

Specific treatment will depend on the cause of neurologic symptoms. Consult relevant chapters in this manual. For complex cases, consult with an HIV-experienced neurologist.

Patient Education

- ◆ Inform patients that keeping the CD4 count above 200 cells/ μ L with ART is the best way to prevent most HIV-associated neurologic diseases.
- ◆ Advise patients to take prophylaxis, as appropriate, to prevent opportunistic infections.
- ◆ When an antibiotic treatment is prescribed, advise patients to complete the entire regimen to prevent relapse of symptoms. Long-term treatment (prophylaxis) will be needed to prevent recurrence of certain infections.
- ◆ Advise patients who have seizures that driving and other potentially dangerous activities will be prohibited until the condition is stable.
- ◆ Counsel patients to avoid substances that impair the nervous system, such as alcohol and recreational drugs.
- ◆ If a patient is forgetful, educate other members of the household about the medication regimen and help devise a plan for adherence to medications and appointments.

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Pulmonary Symptoms

Background

Shortness of breath or cough may be common manifestations of acute or chronic respiratory diseases, but also may be symptoms of HIV-related opportunistic infections. Further, these symptoms may indicate nonpulmonary conditions such as anemia, cardiovascular disease, and sinusitis, or adverse effects of medications such as angiotensin-converting enzyme (ACE) inhibitors.

The onset and duration of symptoms, and the presence or absence of other factors such as sputum production, fever, and weight loss, will guide the evaluation. In addition, the patient's CD4 cell count will establish a context for the evaluation, because it will help to stratify the risk of opportunistic infections.

S: Subjective

The patient complains of dyspnea or cough. Determine the following factors relating to the patient's history.

Recent History

- ◆ Onset and duration of symptoms: rapid (hours to days), subacute, chronic
- ◆ Progression or stability of symptoms
- ◆ Dyspnea at rest or with exertion?
- ◆ Cough: productive (character of sputum), hemoptysis?
- ◆ Associated symptoms (chest pain, pleuritic pain, etc)
- ◆ Constitutional symptoms: fever, night sweats, unintentional weight loss
- ◆ Sinus congestion, facial tenderness, postnasal discharge, sore throat
- ◆ Orthopnea, paroxysmal nocturnal dyspnea (PND), peripheral edema
- ◆ Wheezing

Past History

- ◆ CD4 nadir (lowest documented CD4 cell count), current CD4 count
- ◆ If the CD4 count is <200 cells/ μ L, ask whether the patient is taking *Pneumocystis jiroveci* pneumonia (PCP) prophylaxis (primary or secondary); if taking PCP prophylaxis and adhering to the regimen, the diagnosis of PCP is less likely.
- ◆ Tuberculosis (TB): date and result of tuberculin skin test (purified protein derivative, or PPD), risk factors for *Mycobacterium* TB
- ◆ PCP, bacterial or other pneumonia, bronchitis
- ◆ Smoking
- ◆ Cardiovascular diseases, including congestive heart failure, coronary heart disease, arrhythmia, pulmonary hypertension
- ◆ Asthma, emphysema
- ◆ Pollen, dander, or dust allergies
- ◆ Drug allergies, specifically to penicillins and sulfa drugs
- ◆ Medications (eg, ACE inhibitors)
- ◆ Use of inhaled stimulants, injection drugs

O: Objective

Check vital signs, oxygen saturation (resting and after exercise), weight.

Conduct a thorough physical examination, to include evaluation of the following:

- ◆ Ears, nose, oropharynx
- ◆ Neck
- ◆ Lungs
- ◆ Heart
- ◆ Extremities

Note: If patients are coughing, strongly consider having them wear a surgical mask in the clinic or office until TB or other transmissible infection is ruled out. Covering both the nose and the mouth should prevent the discharge of large infectious droplets into the environment.

A: Assessment

The differential diagnosis of pulmonary symptoms is broad (Table 1). Both HIV-related and HIV-unrelated causes should be considered; the patient's risk of HIV-related causes is strongly influenced by the CD4 count. More than 1 cause of symptoms may be present.

Table 1. Partial Differential Diagnosis of Pulmonary Symptoms

CD4 Cell Count	Possible Cause
Any Count	- Upper respiratory tract illness - Upper respiratory tract infection (URI) - Sinusitis - Pharyngitis - Acute or chronic bronchitis - Bacterial pneumonia - TB - Influenza - Chronic obstructive pulmonary disease - Reactive airway disease, asthma - Non-Hodgkin lymphoma - Pulmonary embolus - Congestive heart failure - Pulmonary hypertension - Pneumothorax - Bronchogenic carcinoma - Anemia - Gastroesophageal reflux (may cause cough) - Lactic acidosis - Medication adverse effect
≤500 cells/μL	- Bacterial pneumonia (recurrent) - Pulmonary <i>Mycobacterium</i> pneumonia (nontuberculous)
≤200 cells/μL	- PCP <i>Cryptococcus neoformans</i> pneumonia or pneumonitis - Bacterial pneumonia (associated with bacteremia or sepsis) - Disseminated or extrapulmonary TB
≤100 cells/μL	- Pulmonary Kaposi sarcoma - Bacterial pneumonia (risk of gram-negative bacilli and <i>Staphylococcus aureus</i> is increased) <i>Toxoplasma</i> pneumonitis
≤50 cells/μL	- Disseminated histoplasmosis - Disseminated coccidioidomycosis - Cytomegalovirus pneumonitis - Disseminated <i>Mycobacterium avium</i> complex - Disseminated <i>Mycobacterium</i> (nontuberculous) <i>Aspergillus</i> pneumonia <i>Candida</i> pneumonia

Adapted from: Huang L. *Pulmonary Manifestations of HIV* (Table 4). In: Peiperl L, Coffey S, Volberding PA, eds. HIV InSite Knowledge Base [textbook online]; San Francisco: UCSF Center for HIV Information; May 1998. Available online at <http://hivinsite.ucsf.edu/InSite?page=kb-04-01-05>.

P: Plan

Diagnostic Evaluation

Perform laboratory work and other diagnostic studies as suggested by the history, physical examination, and differential diagnosis. This may include the following:

- ◆ Chest x-ray, especially if the patient has abnormal findings on chest examination, fever, or weight loss, or if the CD4 cell count is <200 cells/μL.
- ◆ Arterial blood gas (ABG) on room air, particularly if PCP is suspected.
- ◆ Complete blood count and white blood cell (WBC) count with differential, metabolic panel, and lactate dehydrogenase (LDH).
- ◆ If fever is present (especially temperature >38.5°C), obtain routine blood cultures (2 specimens) for bacteria. If the CD4 count is <50 cells/μL, obtain blood culture for acid-fast bacilli (AFB); if <100 cells/μL, check the serum level cryptococcal antigen (CrAg).
- ◆ Induced sputum (outside, or in negative-pressure room or area that is safely vented to the outside, to prevent TB aerosolization) for AFB smear and cultures (3 specimens), Gram stain and bacterial cultures, PCP stains, fungal stains and cultures, and cytology, as indicated.
- ◆ CD4 count and HIV viral load, if recent values are not known.
- ◆ Bronchoscopy with bronchoalveolar lavage (BAL) or biopsy if sputum studies are negative, if the diagnosis is unclear after initial evaluation, or the patient is not responsive to empiric therapy.
- ◆ Pulmonary function tests if no infectious or HIV-related pulmonary diagnosis is suspected and symptoms persist.
- ◆ Lactate level if lactic acidosis is suspected (eg, nausea, tachypnea, abdominal pain, fatigue, in the setting of long-term nucleoside analogue therapy).

Treatment

Once the diagnosis is made, appropriate treatment should be initiated. In seriously ill patients, presumptive treatment may be started while diagnostic test results are pending. See the appropriate chapter in *Section 6: Disease-Specific Treatment* or relevant guidelines. In some cases, the source of dyspnea or cough cannot be identified. In these cases, consult with an HIV expert or a pulmonologist.

Patient Education

- ◆ Shortness of breath and cough can be signs of an opportunistic illness, especially in patients with low CD4 counts. Patients should notify their health care providers if they develop new or worsening symptoms.
- ◆ Patients taking antibiotics should be instructed to take their medications exactly as directed and to call their care providers if they experience worsening fevers, shortness of breath, inability to take the prescribed medications, or other problems.
- ◆ Counsel smokers about the importance of smoking cessation; refer to tobacco cessation programs and prescribe cessation supports, as indicated.

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Vaginitis/Vaginosis

Background

Vaginitis is defined as inflammation of the vagina, usually characterized by a vaginal discharge containing many white blood cells (WBCs); it may be accompanied by vulvar itching and irritation. Vaginosis is characterized by increased vaginal discharge without WBCs or inflammation. Vaginal infections are common in HIV-infected women. This chapter focuses on 2 of the most common types of vaginal infections: trichomoniasis and bacterial vaginosis (BV). For information on the topic of vulvovaginal candidiasis, see the chapter *Candidiasis, Vulvovaginal*.

S: Subjective

The patient complains of vaginal discharge, with or without odor, itching, burning, pelvic pain, vulvar pain, or pain during intercourse.

Take a focused history, including the following:

- ◆ Duration of symptoms
- ◆ Sexual history, especially recent new partner(s), unprotected sex
- ◆ Relationship of symptoms to sexual contacts
- ◆ Contraceptive use, especially:
 - ◆ Vaginal contraceptive film
 - ◆ Other products containing nonoxynol-9 (N-9)
 - ◆ Condoms; type of condoms
- ◆ Use of feminine hygiene products (eg, sprays, deodorants)
- ◆ Douching
- ◆ Use of perfumed toiletries (eg, bath salts, scented toilet tissue or sanitary napkins)
- ◆ Use of any vaginal creams
- ◆ Postcoital bleeding
- ◆ Vulvar pain
- ◆ Pain or burning during urination
- ◆ Pain with intercourse
- ◆ Recent antibiotic use

- ◆ History of sexually transmitted infections (STIs), pelvic inflammatory disease (PID)
- ◆ Medications, including supplements

O: Objective

Perform a focused physical examination of the external genitalia, including perineum and anal area, for the following:

- ◆ Inflammation
- ◆ Edema
- ◆ Excoriation
- ◆ Lesions

Perform speculum examination for:

- ◆ Discharge (note color, quality)
- ◆ Erythema, edema, erosions, lesions
- ◆ Cervical friability
- ◆ Foreign body

Perform a bimanual examination for masses or tenderness, if indicated.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Bacterial vaginosis (BV)
- ◆ Candidiasis
- ◆ Trichomoniasis
- ◆ Pelvic inflammatory disease (PID)
- ◆ Latex or condom allergy
- ◆ Urinary tract infection (UTI)
- ◆ Condyloma
- ◆ Herpes simplex virus (HSV)
- ◆ Contact dermatitis from irritants, perfumes, etc
- ◆ Chlamydia
- ◆ Gonorrhea
- ◆ Normal vaginal discharge

P: Plan

Diagnostic Evaluation

- ◆ Obtain a cervical sample for STI testing, if indicated.
- ◆ Obtain smears from the vaginal wall for wet mounts and pH.
- ◆ Wet mounts: Perform microscopic examination of saline and potassium hydroxide (KOH) preparations for the following:
 - ◆ WBCs, clue cells, motile trichomonads (saline slide)
 - ◆ Yeast forms (KOH)
- ◆ Perform a whiff test of KOH preparation; if positive, check pH (if >4.5, presume BV).

Treatment depends on the specific diagnosis, and in general is the same as for HIV-negative women.

Trichomoniasis

Trichomoniasis is caused by the protozoan *Trichomonas vaginalis*. Many infected women have a diffuse, malodorous, yellow-green discharge. Most men who are infected with *T vaginalis* have no symptoms; others have symptoms of nongonococcal urethritis. The diagnosis is usually made by visualization of motile trichomonads on microscopic examination of wet mounts. Newer diagnostic tests using immunochromatographic or nucleic acid assays (eg, OSOM Trichomonas Rapid Test or Affirm VP III, respectively) have greater specificity and sensitivity than wet mount preparations. Culture of vaginal secretions is the most sensitive and specific diagnostic test for *T vaginalis*.

The sex partners of patients with trichomoniasis should be treated. Patients should avoid sexual intercourse until they and their partners have completed treatment and symptoms have resolved.

Treatment: Recommended regimen

- ◆ Metronidazole 2 g orally in a single dose
- ◆ Tinidazole 2 g orally in a single dose

Treatment: Alternative regimen

- ◆ Metronidazole 500 mg orally twice a day for 7 days

Treatment during pregnancy

- ◆ Pregnant women may be treated with a single dose of metronidazole 2 g orally.

Note: Patients must avoid alcohol while taking metronidazole. This combination may cause a disulfiram-like reaction. Patients taking ritonavir or tipranavir may also experience symptoms because of the small amount of alcohol in the capsules.

Treatment failure

Certain strains of *T vaginalis* have diminished susceptibility to metronidazole and must be treated with higher doses. If treatment failure occurs with either regimen, repeat treatment using metronidazole 500 mg orally twice daily for 7 days. If treatment failure occurs again, the patient should be treated with metronidazole 2 g once daily for 3-5 days. If this regimen is not effective, consult with a specialist.

Bacterial Vaginosis

BV is a clinical syndrome resulting from loss of the normal vaginal flora, particularly *Lactobacillus*, and replacement with anaerobic bacteria such as *Gardnerella vaginalis* and *Mycoplasma hominis*. BV appears as a homogeneous, white, noninflammatory discharge on the vaginal walls. The diagnosis is made by the detection of clue cells on the wet-mount slide, a vaginal fluid pH of >4.5, and a fishy odor to the vaginal discharge before or after the addition of KOH (whiff test).

Many studies have documented an association between BV and infections such as endometritis, PID, and vaginal cuff cellulitis after gynecologic procedures. Therefore, the U.S. Centers for Disease Control and Prevention (CDC) recommends screening for and treating BV before invasive gynecologic procedures.

The sex partners of women with BV do not need to be treated.

Treatment: Recommended regimen

- ◆ Metronidazole 500 mg orally twice daily for 7 days
- ◆ Metronidazole gel 0.75%, 1 full applicator (5 g) intravaginally at bedtime for 5 days
- ◆ Clindamycin cream 2%, 1 full applicator (5 g) intravaginally at bedtime for 7 days

Treatment: Alternative regimens

- ◆ Clindamycin 300 mg orally twice daily for 7 days
- ◆ Clindamycin ovules 100 g intravaginally at bedtime for 3 days

Treatment during pregnancy

- ◆ Pregnant women should be treated with oral metronidazole or oral clindamycin.

Note: Patients must avoid alcohol while taking metronidazole. This combination may cause a disulfiram-like reaction. Patients taking ritonavir or tipranavir may also experience symptoms because of the small amount of alcohol in the capsules.

Treatment Failure

Multiple conditions or pathogens may present concurrently. Perform testing for other conditions as suggested by symptoms, or if symptoms do not resolve with initial treatment:

- ◆ Perform herpes culture if indicated by lesions; see chapter *Herpes Simplex, Mucocutaneous*.
- ◆ Test for chlamydia and gonorrhea if indicated; see chapter *Chlamydia and Gonorrhea*.
- ◆ Perform urinalysis (with or without culture and sensitivities) if urinary symptoms are prominent.
- ◆ If an irritant or allergen is suspected, including N-9, discontinue use.
- ◆ If symptoms are related to the use of latex condoms, switch to polyurethane male or female condoms.
- ◆ For tenderness on cervical motion or other symptoms of PID, see chapter *Pelvic Inflammatory Disease*.
- ◆ Perform workup or obtain referral as needed for other abnormalities found on bimanual examination.

For information on other STIs or related conditions, see the CDC's treatment guidelines at <http://www.cdc.gov/std/treatment>.

Patient Education

- ◆ Patients must avoid any form of alcohol while taking metronidazole and for 24 hours after the last dose. Alcohol and metronidazole together can cause severe nausea, vomiting, and other immobilizing symptoms.
- ◆ Patients taking ritonavir may experience symptoms because of the small amount of alcohol in the capsules and should call their health care providers if nausea and vomiting occur.
- ◆ Clindamycin cream and ovules are oil based and will weaken latex condoms, diaphragms, and cervical caps. Patients should use alternative methods to prevent pregnancy and HIV transmission.
- ◆ Recurrence of BV is common. Patients should contact their health care providers and return for repeat treatment if symptoms recur.
- ◆ Instruct patients to avoid douching.
- ◆ To avoid being reinfected by *Trichomonas*, patients should bring their sex partners to the clinic for evaluation and treatment.

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Anal Dysplasia

Background

Anal cancer is a squamous cell cancer associated with human papilloma virus (HPV), the same virus that is associated with cervical cancer (see chapter *Cervical Dysplasia*). In the United States, the current incidence of anal cancer in the general population is approximately 1:100,000 per year, and rising. The incidence of anal cancer is significantly higher in HIV-infected women and men than in the general population. Rates are also higher in men who have sex with men (MSM), whether HIV infected or uninfected. Before the HIV epidemic, the anal cancer incidence in an MSM population was 35:100,000. Current rates in an HIV-infected MSM population are as high as 70-80:100,000. Thus, the incidence of anal cancer in this population is greater than the incidence of cervical cancer in women before the introduction of cervical cytology screening.

The cervical canal and anal canal share a common embryologic origin: Both have a squamocolumnar transition zone and are prone to infection with genitotropic HPV, a sexually transmitted virus. HPV infection, in combination with other cofactors, may stimulate dysplastic changes in the cervix or anus that may develop through precursor stages (squamous intraepithelial lesions [SIL]) into squamous cell cancer.

A small but growing body of literature suggests a high prevalence of anal HPV infection and dysplasia in HIV-infected individuals. Some studies have shown that, in HIV-infected individuals, anal HPV infection is present in 93% of MSM and 76% of women, and anal dysplasia (any grade) is present in 56% of MSM and 26% of women. Receptive anal intercourse (RAI) may increase the likelihood of anal HPV infection, but is not a prerequisite for anal HPV or dysplasia. In a study of HIV-positive heterosexual men with no history of RAI, anal HPV infection was found in 46% and anal dysplasia in 32%. Patients with lower CD4 cell counts appear to be at higher risk of developing anal dysplasia. It is not clear whether effective antiretroviral therapy (ART) and immune reconstitution offer protection against dysplasia.

Prevention of HPV infection is difficult. Latex or plastic barrier may be partially effective through bodily contact outside the area covered by the barriers. Vaccines against certain strains of HPV may be available soon, though

their efficacy in preventing anal dysplasia (as opposed to cervical dysplasia), and their efficacy in HIV-infected individuals, is unknown.

The field of anal dysplasia and anal cancer is a relatively new area of scientific investigation, and many questions about the disorder and its medical management remain unanswered. Because of the similarities between cervical and anal dysplasia, researchers postulate that many of the paradigms of managing cervical cytologic abnormalities may be translated to the anal canal. No national or international guidelines have been developed for anal cancer screening or the management of anal dysplasia. Further, many centers lack the resources for anal dysplasia screening and treatment. In areas with adequate diagnostic and treatment resources, some specialists recommend screening all HIV-infected individuals for anal dysplasia; and if indicated, intervening to prevent the development of anal cancer. Further investigation is needed to define appropriate screening intervals, diagnostic approaches, indications for therapy, and modalities of treatment.

S: Subjective

Patients with anal dysplasia are usually asymptomatic and the condition cannot be identified without screening tests. Exophytic anal condylomata may cause itching, discomfort, or bleeding, but are usually associated with low-risk phenotypes of HPV and low-grade dysplasia. Anal cancer may cause nonspecific symptoms such as pain, bleeding, and the development of a mass lesion.

Risk factors for anal dysplasia are not well understood, but include the following:

- ◆ Receptive anal intercourse (RAI)
- ◆ HPV infection
- ◆ Genital warts (or history of genital warts)
- ◆ HIV infection
- ◆ CD4 count <200 cells/ μ L
- ◆ Iatrogenic immunosuppression
- ◆ High-grade cervical or vulvar dysplasia
- ◆ Cigarette smoking

O: Objective

Examine the perianal and anal region, and perform digital anorectal examination. Look for lesions, masses, condylomata, and other abnormalities. In women, also examine the vulva, vagina, and cervix. Simple anoscopic examination with the naked-eye may not reveal any abnormality because dysplastic tissue tends to be flat and difficult to differentiate from normal anal tissue; application of 3% acetic acid is required (see below).

A: Assessment

HIV-infected individuals with anal dysplasia have an increased risk of progression to anal cancer. If the history or physical examination reveals abnormalities suggestive of anal dysplasia or anal cancer, an appropriate evaluation should be undertaken. Because most patients with anal dysplasia have no symptoms, anal cancer screening should be considered if follow-up evaluation of abnormal cytologic results is available.

P: Plan

Screening

No national or international guidelines for anal cytology screening in people with HIV infection. However, some experts recommend annual or biannual screening regardless of sex or sexual practices. Anal cytologic screening is performed using Papanicolaou (Pap) smears (for technique, see the study by Berry and Palefsky referenced below). Papanicolaou smear testing is sensitive for the detection of dysplastic anal cells, but does not reliably distinguish the grade of abnormality. Like cervical cytology, anal cytology is graded using the Bethesda 2001 system, which categorizes disease in increasing order of severity as follows:

- ◆ Negative for intraepithelial lesion or malignancy
- ◆ Atypical squamous cells of undetermined significance (ASCUS)
- ◆ Atypical squamous cells suggestive of high-grade (ASC-H)
- ◆ Low-grade squamous intraepithelial lesion (LSIL)
- ◆ High-grade squamous intraepithelial lesion (HSIL)
- ◆ Squamous cell carcinoma (SCC)

All individuals with abnormal anal cytology should be referred for high-resolution anoscopy (HRA) and biopsy to grade the lesion. If available, refer to an anal dysplasia specialty center.

Evaluation of Cytologic Abnormalities

HRA of the anal canal should be performed using a colposcope for magnification (x16) and the application of 3% acetic acid with or without Lugol's Iodine solution to aid in visualization of dysplastic lesions. Abnormal areas should be biopsied. Anoscopic features of high-grade disease are similar to those seen in the cervix; these include coarse punctation, mosaicism, and the presence of ring glands.

Treatment

The goal of treatment is to prevent progression to anal cancer. Treatment of high-grade anal dysplasia to prevent anal cancer is biologically plausible, following the model of cervical dysplasia treatment. However, the indications for treatment for anal dysplasia, the efficacy of treatment, and the optimal treatments have not been defined clearly.

The focus of treatment is high-grade, premalignant dysplasia. For patients with HSIL, refer to an anal dysplasia specialty clinic, if possible. If treatment is not available, or is not pursued, patients diagnosed with high-grade anal disease should be informed about the initial symptoms of anal cancer and asked to follow up promptly should these symptoms develop.

The optimal treatment for high-grade dysplasia is not known. Specific treatment may vary depending on the size, location, and extent of the lesions and the available treatment modalities. In some cases, treatment of small intra-anal lesions with 80% trichloroacetic acid or liquid nitrogen has been successful. More promising, infrared coagulation has shown 70% efficacy at 3 months in clinical cohorts. This office procedure involves identifying the lesion by HRA and applying an infrared energy source to destroy the lesion.

For perianal lesions, topical therapy with podophyllotoxin or imiquimod may be considered. For large or extensive lesions, surgical treatments such as cold-scalpel excision and electrofulguration are typically required. Unfortunately, postoperative pain and other complications may occur, and recurrence of dysplastic lesions is common. Low-grade dysplasia is not considered premalignant, but frequently progresses to high-grade dysplasia. Some specialists do not treat LSIL but monitor regularly instead with HRA, whereas others choose to treat LSIL to prevent progression.

Patient Education

- ◆ Women and men with HIV infection have an increased risk of developing anal dysplasia and cancer. MSM are at higher risk than other men of developing anal dysplasia.
- ◆ Emphasize the importance of keeping follow-up appointments to allow early detection of precancerous lesions and appropriate monitoring and treatment of abnormalities.
- ◆ Patients who have anal dysplasia should be informed about anal cancer symptoms, such as new-onset anal pain, bleeding, or the development of a mass. Patients should call their health care providers if these symptoms develop.

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Candidiasis, Oral and Esophageal

Background

Oropharyngeal candidiasis (“thrush”), a fungal disease of the oral mucosa and tongue, is the most common intraoral lesion in persons infected with HIV. In the absence of other known causes of immunosuppression, oral thrush in an adult is highly suggestive of HIV infection. Three clinical presentations of thrush are common in people with HIV: pseudomembranous, erythematous, and angular cheilitis. Thrush usually occurs with CD4 counts of <300 cell/ μ L and is not an AIDS-defining illness.

Candida may also infect the esophagus in the form of esophageal candidiasis which causes dysphagia (difficulty with swallowing) or odynophagia (pain with swallowing). Esophageal candidiasis is an AIDS-defining condition, generally occurs in individuals with CD4 counts of <100 cell/ μ L. It is the most common cause of esophageal infection in persons with AIDS.

Oropharyngeal and esophageal candidiasis are most commonly caused by *C. albicans*, although occasionally non-*albicans* species cause disease and may be resistant to first-line therapies.

S: Subjective

Oropharyngeal Candidiasis

The patient may complain of white patches on the tongue and oral mucosa, smooth red areas on the dorsal tongue, burning or painful areas in the mouth, a bad or unusual taste, sensitivity to spicy foods, or decreased appetite.

Esophageal Candidiasis

The patient complains of difficulty or pain with swallowing, or the sensation that food is “sticking” in the retrosternal chest. Weight loss is common, and nausea and vomiting may occur. Fever is not common with candidal esophagitis and suggests another cause.

O: Objective

Patients presenting with oral candidiasis may be totally asymptomatic, so it is important to inspect the oral cavity thoroughly. Lesions can occur anywhere on the hard and soft palates, under the tongue, on the buccal mucosa or gums, or in the posterior pharynx.

Pseudomembranous oral candidiasis appears as creamy white, curdlike plaques on the buccal mucosa, tongue, and other mucosal surfaces. Typically, the plaques can be wiped away, leaving a red or bleeding underlying surface. Lesions may be as small as 1-2 mm, or may form extensive plaques that cover the entire hard palate.

Erythematous oral candidiasis presents as 1 or more flat, red, subtle lesions on the dorsal surface of the tongue or the hard or soft palate. The dorsum of the tongue may show loss of filiform papillae.

Angular cheilitis causes fissuring and redness at 1 or both corners of the mouth and may appear alone or in conjunction with another form of oral *Candida* infection.

Patients with esophageal candidiasis usually have oral thrush and often have weight loss.

A: Assessment

A partial differential diagnosis for the 2 conditions is as follows:

Oropharyngeal Candidiasis

- ◆ Oral hairy leukoplakia
- ◆ Burn
- ◆ Bacterial gingivitis
- ◆ Periodontitis

Esophageal Candidiasis

- ◆ Cytomegalovirus (CMV)
- ◆ Herpes simplex virus (HSV)
- ◆ Aphthous ulceration

P: Plan

Diagnostic Evaluation

Oropharyngeal candidiasis

Clinical examination alone usually is diagnostic. If the diagnosis is unclear, organisms may be detected on smear or culture if necessary.

- ◆ Potassium hydroxide (KOH) preparation of a smear collected by gentle scraping of the affected area with a wooden tongue depressor. Visible hyphae or blastospheres on KOH mount indicate *Candida* infection.
- ◆ Culture is diagnostic and may detect non-*albicans* species in cases resistant to first-line therapies. Sensitivities may also be needed in such cases to diagnose azole-resistant infections.

Esophageal candidiasis

A presumptive diagnosis can usually be made with a recent onset of dysphagia, especially in the presence of thrush, and empiric antifungal therapy may be started. If the patient fails to improve clinically after 3-7 days of therapy, endoscopy should be performed for a definitive diagnosis.

Treatment

Treatment of oropharyngeal candidiasis

- ◆ Oral therapy is convenient and very effective as first-line treatment. Note that azole antifungal drugs are not recommended for use during pregnancy.
 - ◆ Fluconazole 100 mg once daily for 7-14 days
- ◆ Alternative topical therapy is less expensive, safe for use during pregnancy, and effective for mild to moderate disease. Such therapies include:
 - ◆ Clotrimazole troches dissolved in the mouth 5 times per day for 2 weeks
 - ◆ Nystatin oral suspension 5 mL “swish and swallow” 4 times daily for 2 weeks
- ◆ Other alternatives include the following:
 - ◆ Itraconazole oral solution 200 mg once daily for 7-14 days
 - ◆ Itraconazole capsules and ketoconazole 200 mg once daily for 7-14 days (less effective)

These agents present a greater risk of drug interactions and hepatotoxicity than do fluconazole or topical treatments.

Treatment of esophageal candidiasis

- ◆ Fluconazole 200 mg as an initial dose, then 100 mg by mouth once daily for 14 days. Intravenous therapy can be given if the patient is unable to swallow pills.
- ◆ Itraconazole oral suspension 200 mg once daily for 14 days
- ◆ Alternative (less effective) treatments include itraconazole capsules 200 mg once daily or ketoconazole 200 mg once daily for 14 days

Treatment of refractory candidiasis

Oral or esophageal candidiasis that does not improve after at least 7-14 days of azole antifungal therapy can be considered refractory to treatment. The primary risk factors for development of refractory candidiasis are CD4 counts <50 cell/ μ L and prolonged, chronic antifungal therapy (especially with azoles). In such cases, it is important to confirm the diagnosis of candidiasis. As noted previously, other infections such as HSV, CMV, and aphthous ulcerations can cause similar symptoms. Once refractory candidiasis is confirmed, several treatment options are available, including the following:

- ◆ Patients with candidiasis refractory to low-dose fluconazole (100-200 mg once daily) may respond to higher dosages (400-800 mg once daily)
- ◆ Itraconazole oral suspension 200 mg once daily
- ◆ Voriconazole 200 mg intravenously or by mouth twice daily. (Voriconazole therapy is contraindicated for patients taking protease inhibitors because of significant drug interactions.)
- ◆ Amphotericin B 100 mg/mL oral suspension, 1 mL 4 times daily
- ◆ Amphotericin B 0.5 mg/kg/d intravenously, or amphotericin liposomal complex 3-5 mg/kg/d intravenously
- ◆ Caspofungin 50 mg intravenously once daily

The choice of treatment depends upon the patient's preferences and tolerance, convenience, availability of medications, and the provider's experience. Consult with an HIV or infectious disease expert for advice about treatment regimens.

Maintenance therapy

Use caution when considering chronic maintenance therapy, because it has been associated with refractory and azole-resistant candidiasis, as noted above. Fluconazole 100-200 mg daily or weekly, or itraconazole solution, can be effective for patients who have had multiple recurrences of oral or esophageal disease (azole sensitive). Patients who achieve immunologic and virologic responses to antiretroviral therapy may be able to discontinue maintenance therapy.

Patient Education

- ◆ Patients should maintain good oral hygiene by brushing teeth after each meal.
- ◆ A soft toothbrush should be used to avoid mouth trauma.
- ◆ Advise patients to rinse the mouth of all food before using lozenges or liquid medications.
- ◆ Tell patients to avoid foods or liquids that are very hot in temperature or very spicy.
- ◆ Patients who have candidiasis under a denture or partial denture should remove the prosthesis before using topical agents such as clotrimazole or nystatin. At bedtime, the prosthesis should be placed in a chlorhexidine solution until reinsertion it into the mouth.
- ◆ Pregnant women or women who may become pregnant should avoid azole drugs (eg, fluconazole, itraconazole, voriconazole) during pregnancy because they can cause skeletal and craniofacial abnormalities in infants.

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Candidiasis, Vulvovaginal

Background

Vulvovaginal candidiasis is a yeast infection caused by several types of *Candida*, typically *Candida albicans*. This disease is common in all women, but may occur more frequently and more severely in immunocompromised women.

Although refractory vaginal *Candida* infections by themselves should not be considered indicators of HIV infection, they may be the first clinical manifestation of HIV infection, and can occur early in the course of disease (at CD4 counts >500 cells/ μ L). The frequency of vaginal candidiasis tends to increase as CD4 counts decrease; this may, however, be due in part to increased antibiotic use among women with advanced HIV infection.

Risk factors for candidiasis include diabetes mellitus and the use of oral contraceptives, corticosteroids, or antibiotics.

S: Subjective

The patient may complain of itching, burning, or swelling of the labia and vulva; a thick white or yellowish vaginal discharge; painful intercourse; and pain and burning on urination.

The most important elements in the history include:

- ◆ Type and duration of symptoms
- ◆ Previous vaginal yeast infection
- ◆ Oral contraceptive use
- ◆ Recent or ongoing broad-spectrum antibiotic therapy
- ◆ Recent corticosteroid therapy
- ◆ Sexual exposures (to evaluate for sexually transmitted infections)
- ◆ Diabetes history
- ◆ Cushing syndrome
- ◆ Obesity
- ◆ Hypothyroidism
- ◆ Pregnancy
- ◆ Use of douches, vaginal deodorants, or bath additives

O: Objective

A focused physical examination of the external genitalia may reveal inflammation of the vulva with evidence of discharge on the labial folds and vaginal opening. Speculum examination usually reveals a thick, white discharge with plaques adhering to the vaginal walls and cervix. Bimanual examination should not elicit pain or tenderness and otherwise should be normal.

A: Assessment

Rule out other causes of vaginal discharge and pruritus:

- ◆ Bacterial vaginosis
- ◆ Atrophic vaginitis
- ◆ Pediculosis
- ◆ Chemical or mechanical causes
- ◆ Trichomoniasis
- ◆ Gonorrhea, chlamydia, and other sexually transmitted infections
- ◆ Scabies
- ◆ Pediculosis

P: Plan

Diagnostic Evaluation

A presumptive diagnosis is made on the basis of the clinical presentation and potassium hydroxide (KOH) preparation:

- ◆ Perform microscopic examination of a KOH preparation of vaginal secretions. This exam usually reveals pseudohyphae and *Candida* spores (presumptive diagnosis).
- ◆ Definitive diagnosis is rarely needed, but may be made by a culture of vaginal secretions.
- ◆ In the presence of urinary tract symptoms (beyond external vulvar burning), perform urinalysis, culture, or both on a clean-catch urine specimen.
- ◆ Consider testing for gonorrhea and chlamydia in patients with a history of possible sexual exposure.

Treatment

Uncomplicated infections

Topical medications

- ◆ Prescribe topical vaginal antifungal agents in the form of cream or suppositories: butoconazole, clotrimazole, miconazole, nystatin, terconazole, tioconazole. Treat for 3-7 days and offer refills depending on the time to the next scheduled clinic visit. The creams may also be used on the vulva for pruritus.
- ◆ Nystatin vaginal pastilles 100,000 units; insert 1 daily for 14 days

Note that the mineral-oil base in topical vaginal antifungal preparations may erode the latex in condoms, diaphragms, and dental dams. Advise the patient to use alternative methods to prevent HIV transmission or conception, or to discontinue intercourse while using these medications. Nonlatex condoms (plastic and polyethylene only) or "female" condoms (polyurethane) can be used.

Oral medications

- ◆ Fluconazole 150 mg orally, 1 dose (see "Treatment notes" below)
- ◆ Itraconazole 200 mg orally twice daily for 1 day, or 200 mg orally once daily for 3 days (see "Treatment notes" below)

Complicated infections

Severe or recurrent candidiasis

Severe or recurrent candidiasis is defined as 4 or more episodes within 1 year. Consider the following treatments:

- ◆ Topical therapy as above, for 7-14 days
- ◆ Fluconazole 150 mg orally every 3 days for 3 doses (see "Treatment notes" below)

For severe cases that recur repeatedly, secondary prophylaxis can be considered, eg, clotrimazole vaginal suppository (500 mg once weekly) or oral fluconazole (100-200 mg weekly).

Non-*albicans* candidiasis

- ◆ Non-fluconazole azole for 10-14 days (see "Treatment notes" below)
- ◆ Boric acid 600 mg intravaginal gelatin capsules once daily for 2 weeks for refractory cases
- ◆ Consult with a specialist

Treatment notes

- ◆ Systemic azole drugs are not recommended during pregnancy, and women taking azoles should use effective contraception. Topical azoles are recommended for the treatment of pregnant women.
- ◆ Itraconazole interacts with some antiretroviral medications; check for adverse drug interactions before prescribing. Itraconazole should not be used by pregnant women or women considering pregnancy.
- ◆ Resistance to azole medications may develop, especially with prolonged use of oral agents.
- ◆ Avoid ketoconazole: Case reports have associated ketoconazole with a risk of fulminant hepatitis (1 in 12,000 courses of treatment with oral ketoconazole). Experts agree that the risks may outweigh the benefits in women with vulvovaginal candidiasis. Ketoconazole also interacts with many other drugs, including some antiretroviral drugs.

Patient Education

- ◆ Advise women to wash external genitals daily with a fresh washcloth or water-soaked cotton balls and to wipe the vulva and perirectal area from front to back after toileting. Women should not use baby wipes on inflamed vulval tissue because they may increase irritation.
- ◆ Women should avoid the use of perfumed soaps, bubble baths, feminine hygiene or vaginal deodorant products, and bath powders.
- ◆ Advise women not to douche.
- ◆ Women should wear cotton underwear and avoid tight, constrictive clothing, particularly pantyhose.
- ◆ If women are prescribed medication for vaginal candidiasis, they should take the medication exactly as prescribed and finish the medicine even during a menstrual period.
- ◆ Women who continue to have symptoms, can purchase Monistat or Gyne-Lotrimin medication over the counter. Advise patients to start using these as soon as symptoms come back, and to call the clinic if symptoms get worse on these medicines.
- ◆ Women taking fluconazole or ketoconazole must avoid pregnancy. Some birth defects have been reported.
- ◆ The mineral-oil base in topical vaginal antifungal preparations may erode the latex in condoms, diaphragms, and dental dams. Advise patients to use alternative methods to prevent HIV transmission or conception or to discontinue intercourse while using these medications. Nonlatex condoms (plastic and polyethylene only) or "female" condoms (polyurethane) can be used.
- ◆ Sex toys, douche nozzles, diaphragms, cervical caps and other items, can reinfect patients if not properly cleaned and thoroughly dried after use.
- ◆ Some studies have suggested that eating yogurt with live cultures (check labels) can reduce the occurrence of vaginal yeast infections.

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Cervical Dysplasia

Background

Cervical dysplasia and cancer are associated with human papilloma virus (HPV), a sexually transmitted virus. Carcinogenic strains of HPV may, in conjunction with other factors, cause dysplasia and cancer not only of the cervix, but also of the vulva, vagina, and anus. HIV-infected women have a higher prevalence of HPV infection than HIV-uninfected women, and are 5 times more likely to develop cervical dysplasia, or squamous intraepithelial lesion (SIL), precursors to cervical cancer. They may also have a higher risk of invasive cervical cancer and tend to have more aggressive forms of cervical cancer. Invasive cervical cancer is an AIDS-defining illness.

The risk of high-grade cervical lesions appears to be higher in women with advanced immunodeficiency than in women with preserved CD4 cell counts. Other risk factors for dysplasia and cervical cancer include African American ethnicity, a history of smoking, younger age at onset of sexual intercourse, and multiple sexual partners. Effective antiretroviral therapy (ART) with immune reconstitution has not been shown to prevent the progression of dysplasia.

Screening for cervical dysplasia and appropriate intervention in women with high-grade dysplasia are effective in preventing cervical cancer. Frequent monitoring and careful follow-up in women with low-grade lesions are essential for preventing progression to invasive disease. Papanicolaou testing should be performed routinely on all HIV-infected women, with testing initiated at diagnosis, repeated 6 months after the first test, then performed annually thereafter if the results are normal. (See chapter *Initial and Interim Laboratory and Other Tests*.) Because the risk of anal dysplasia is also increased in HIV-infected women, many experts recommend concurrent screening for anal dysplasia. For further information, see chapter *Anal Dysplasia*.

Prevention of HPV infection is difficult. Latex or plastic barriers may be partially effective, although infection may occur through bodily contact outside the area covered by the barriers. A vaccine against certain strains of HPV has been approved by the U.S. Food and Drug Administration and others are expected to follow, although their efficacy in HIV-infected women and men is not yet known.

S: Subjective

Patients with cervical dysplasia or early cervical cancer are usually asymptomatic and disease will not be diagnosed unless screening is performed. Genital condylomata (warts) indicate infection with HPV and are typically associated with low-risk types of HPV; however, women with genital warts may have concurrent dysplasia. The classic symptom of early invasive cervical neoplasia is intermittent, painless bleeding between menstrual periods, which may present initially as postcoital spotting. Late symptoms of invasive cervical carcinoma include flank and leg pain, dysuria, hematuria, rectal bleeding, and obstipation.

Ask all female patients about risk factors for, and previous history of, cervical dysplasia and cancer, including the following:

- ◆ Genital warts; previous or current HPV infection
- ◆ Previous abnormal cervical Papanicolaou smear
- ◆ Previous abnormal anal Papanicolaou smear
- ◆ Previous cervical cancer; when and how treated
- ◆ Sexual activity before age 20
- ◆ History of multiple sexual partners
- ◆ Cigarette smoking
- ◆ CD4 count <200 cells/ μ L
- ◆ Pregnancy
- ◆ Oral contraceptive use

O: Objective

Perform a focused examination of the abdomen and pelvis. Examine the external genital and perianal region. Perform speculum and bimanual examinations to evaluate the vagina and cervix. Look for lesions, masses, warts, and cervical inflammation or discharge, as well as exophytic or ulcerative cervical lesions with or without bleeding. Note that simple visual examination may not reveal abnormalities.

A: Assessment

HIV-infected women have an increased risk of cervical dysplasia with progression to cervical cancer. If abnormalities of cervical disease are suspected, an appropriate evaluation should be performed. Because most women with cervical dysplasia have no symptoms, routine screening should be performed in all women.

P: Plan

Screening

Perform screening Papanicolaou smear on all HIV-infected women. The initial smear should be taken at the time of HIV diagnosis, a second should be taken 6 months later, and the procedure should be repeated annually thereafter if all tests are normal. If a smear is abnormal, see below. Also consider screening for anal dysplasia, with an anal Papanicolaou smear (see chapter *Anal Dysplasia*).

Cervical (and anal) cytology is graded using the Bethesda 2001 system (see “References” below), which categorizes disease in increasing order of severity as follows:

- ◆ Negative for intraepithelial lesion or malignancy
- ◆ Atypical squamous cells of undetermined significance (ASCUS)
- ◆ Atypical squamous cells—cannot exclude HSIL (ASC-H)
- ◆ Low-grade squamous intraepithelial lesion (LSIL)
- ◆ High-grade squamous intraepithelial lesion (HSIL)
- ◆ Squamous cell carcinoma (SCC)

Other abnormalities may be noted, including:

- ◆ Atypical glandular cells of undetermined significance (AGUS)
- ◆ Infectious organisms such as *Trichomonas*

Evaluation of Cytologic Abnormalities

Atypical squamous cells of undetermined significance

If ASCUS is present without inflammation or suspected neoplastic process, several options for management exist. Most experts recommend referral for colposcopy and directed biopsy, regardless of the woman's degree of immunodeficiency. Patients who are considered reliable for follow-up may be monitored closely with repeat Papanicolaou smears every 4-6 months for 2 years until 3 consecutive tests have been negative. If a follow-up smear shows ASCUS (or higher-grade abnormalities), colposcopy with directed biopsy should be done. If the biopsy result is normal, the patient should be monitored as usual with Papanicolaou tests at 6 and 12 months. Another approach, available in some clinic settings, is to perform HPV DNA testing on a cervical sample; if HPV DNA testing shows an oncogenic HPV type, colposcopic examination should be performed.

Atypical squamous cells—cannot exclude HSIL

Women with abnormalities suggestive of high-grade dysplasia should be referred for colposcopy. HPV DNA testing can be considered to detect oncogenic HPV types.

Low-grade squamous intraepithelial lesion

Women with LSIL should be referred for colposcopy and directed biopsy.

High-grade squamous intraepithelial lesion or squamous cell carcinoma

Women with HSIL should undergo colposcopy with endocervical assessment and directed biopsy as soon as possible. Refer to an oncology specialist for treatment.

Atypical glandular cells of undetermined significance

Because of the high rate of significant lesions in patients with AGUS, colposcopy or endocervical curettage is recommended. Refer to an appropriate specialist for evaluation.

Treatment

The optimal management of precancerous cervical lesions has not been identified clearly for all classes of SIL. Consult with an HIV-experienced gynecologist, oncologist, or other dysplasia specialist.

Patient Education

- ◆ Patients who smoke should be advised to quit. Cigarette smoking appears to heighten the risk of cervical cancer, and makes HPV more difficult to treat. Discuss options for smoking cessation, and refer patients to the American Lung Association if programs are available in your area.
- ◆ Recommend the use of latex or polyurethane male or female condoms for vaginal or anal intercourse and plastic or latex barriers for oral sex to reduce the risk of transmitting HPV (the usual cause of cervical cancer) to partners. Barriers will also reduce the risk of exposure to other sexually transmitted pathogens.
- ◆ Emphasize the importance of keeping follow-up appointments for Papanicolaou smear or colposcopy to allow early detection of precancerous lesions and appropriate monitoring of abnormalities.
- ◆ For women with dysplasia who require treatment, emphasize that early treatment is essential to manage the disease and prevent the development of cancer. Advise patients to keep all medical appointments.

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Cryptococcal Disease

Background

Cryptococcosis is a systemic or central nervous system (CNS) fungal infection caused by the yeast *Cryptococcus neoformans*. The organism is ubiquitous, but is particularly plentiful in soils enriched with bird droppings. It may also be present in fruit skins or juices, as well as in unpasteurized milk. In immunocompetent patients, cryptococcal infection is usually asymptomatic, self-limited, and confined to the lungs. In persons with advanced HIV infection (eg, those with CD4 counts <100 cells/ μ L), *Cryptococcus* may cause life-threatening illness, either from a new exposure or through reactivation of a previously acquired latent infection.

In HIV-infected patients, *Cryptococcus* can infect almost all organs in the body, but most commonly causes meningitis or meningoencephalitis. Disseminated disease, pneumonia, and skin lesions may also be seen.

S: Subjective

Symptoms depend upon the locus of infection. In the case of meningitis, the patient typically complains of the subacute onset of fever, headaches, and malaise, which worsen over several weeks. These symptoms may be accompanied by nausea with or without vomiting. Meningeal signs, nuchal rigidity, and photophobia occur in only about 25% of cases. Cryptococcal meningitis may also cause confusion, personality or behavior changes, blindness, deafness, and, if left untreated, coma and death. If the disease involves the lungs, patients may complain of cough or shortness of breath, pleuritic chest pain, and fever. Skin lesions may also be present.

O: Objective

Perform a thorough physical examination with particular attention to the following:

- ◆ Vital signs, hydration status
- ◆ Funduscopic examination
- ◆ Neck (for nuchal rigidity, which is uncommon)
- ◆ Lungs, especially if respiratory symptoms are present
- ◆ Neurologic examination, including evaluation of cranial nerves, visual acuity, and mental status
- ◆ Skin

Cryptococcal meningitis

Physical examination may reveal papilledema with loss of visual acuity and cranial nerve deficits (particularly in cranial nerves III and VI).

Cryptococcal pulmonary disease

Examination may reveal tachypnea or fine rales.

Cutaneous infection

Skin lesions are variable and may appear as papules, nodules, or ulcers; they often resemble molluscum lesions.

A: Assessment

The differential diagnosis for serum cryptococcal meningitis or meningoencephalitis is broad and includes other infectious causes of meningitis (fungal, mycobacterial, bacterial, viral), syphilis, lymphoma, mass lesions, intoxication, HIV encephalopathy, and trauma. (See chapter *Neurologic Symptoms*.)

The differential diagnosis for cryptococcal pneumonia is broad and includes other infectious causes of pneumonia (fungal, mycobacterial, bacterial, viral), malignancy, and congestive heart failure. (See chapter *Pulmonary Symptoms*.)

P: Plan

Diagnostic Evaluation

The workup should include serum cryptococcal antigen (CrAg), which usually is very sensitive, and blood cultures, including acid-fast bacilli (AFB) and fungal cultures. Patients with symptoms of disseminated or pulmonary infection should be evaluated by chest x-ray (which may show diffuse or focal infiltrates, sometimes appearing as nodular or miliary; intrathoracic adenopathy; or pleural effusions), sputum culture (including fungal and AFB culture), and AFB stain. Bronchoscopy and bronchoalveolar lavage may be necessary for diagnosis. For cutaneous lesions, consider biopsy and histopathologic evaluation or culture. As part of the general fever workup, urinalysis and urine cultures should be checked.

Patients with a positive serum CrAg, another positive test for *Cryptococcus*, or signs or symptoms of meningitis should undergo analysis of the cerebrospinal fluid (CSF). If neurologic symptoms or signs are present, obtain a computed tomography (CT) scan of the brain before performing a lumbar puncture (LP) to rule out a mass lesion or increased intracranial pressure (ICP), which could cause herniation upon LP. Always measure the CSF opening pressure; a high ICP contributes to morbidity and mortality and determines the need for serial LPs to manage the increased ICP. Send the CSF for the following:

- ◆ CrAg (usually positive at high titer in meningitis)
- ◆ Fungal culture
- ◆ India ink stain (lower sensitivity than CrAg)
- ◆ Cell counts
- ◆ Glucose
- ◆ Protein

For exclusion of other etiologies, check CSF with the Venereal Disease Research Laboratory (VDRL) test, bacterial culture, AFB culture or polymerase chain reaction (PCR), if tuberculosis is suspected, and other tests as indicated by the patient's symptoms and exposures.

Treatment

Cryptococcal meningitis

Acute treatment of cryptococcal meningitis consists of 2 phases: induction and consolidation. Acute treatment is followed by chronic maintenance (suppressive) therapy.

Induction

Patients with cryptococcal meningitis should be hospitalized to start 2 weeks of induction therapy with amphotericin B (0.7 mg/kg/day) given intravenously plus flucytosine (25 mg/kg) given orally every 6 hours.

Amphotericin B causes many adverse effects, including fever, rigors, hypotension, nausea, nephrotoxicity and electrolyte disturbances, anemia, and leukopenia. The patient's hemoglobin, white blood cell (WBC) count, platelets, electrolytes, magnesium, and creatinine must be monitored closely during treatment. Note that liposomal forms of amphotericin (AmBisome and Abelcet) cause fewer adverse effects and appear to be effective. These liposomal forms should be considered for patients who have difficulty tolerating the standard amphotericin B. Because amphotericin B is highly

irritating to the veins, it should be given through a central line. High levels of flucytosine are associated with bone marrow toxicity, and levels should be monitored (target peak 70–80 mg/L; trough 30–40 mg/L). Note that the dosage of flucytosine must be adjusted for patients with renal insufficiency.

If amphotericin is not available, is contraindicated, or is not tolerated by the patient, alternative induction therapies may be considered. The primary alternative to amphotericin-based therapy is fluconazole (400–800 mg orally per day), with or without flucytosine. Of the newer antifungal agents, echinocandins have little activity against *Cryptococcus*. Voriconazole has good in vitro activity, but few clinical data are available and none suggest superiority over fluconazole. The efficacy of alternative regimens is not well defined.

Consolidation

After clinical improvement with 2 weeks of induction therapy (possibly sooner for patients with substantial improvement), the treatment can be switched to oral fluconazole (400 mg once daily to complete 8 weeks of acute treatment). Itraconazole (200 mg orally twice daily) sometimes is used as an alternative for patients who cannot take fluconazole. It should be noted that itraconazole is less effective than fluconazole and has significant drug interactions with commonly used medications.

Maintenance

After completing acute treatment, the patient should receive chronic maintenance therapy with fluconazole (200 mg orally once daily) to prevent recurrence of cryptococcosis. An alternative treatment is itraconazole (200 mg orally once or twice daily)—with the caution as indicated above.

Maintenance therapy should be continued for life, unless the patient has sustained CD4 cell recovery in response to effective antiretroviral therapy (ART) (CD4 count >100–200 cells/ μ L for at least 6 months during ART). Maintenance therapy should be restarted if the CD4 count declines to <100–200 cells/ μ L.

Management of elevated ICP

Elevated ICP significantly increases the morbidity and mortality of cryptococcal meningitis and should be treated by the removal of CSF. The CSF opening pressure should be checked on the initial LP. If the initial opening pressure is >250 mm H₂O, remove

up to 30 mL of CSF to lower the ICP by 50%, if possible. LP and CSF removal should be repeated daily as needed for ICP reduction. Ventriculostomy or a ventriculoperitoneal shunt may be needed if the initial opening pressure is >400 mm H₂O, or in refractory cases. There is no role for acetazolamide, mannitol, or steroids in the treatment of elevated ICP.

A repeat LP is not required for patients who did not have elevated ICP at baseline and are responding to treatment. If new symptoms develop, a repeat LP is indicated. Serum CrAg titers are not useful in monitoring response to treatment.

Cryptococcal pulmonary disease, with negative CSF CrAg and cultures

Treat with fluconazole (200–400 mg orally) if symptoms are mild or moderate. Otherwise, consider amphotericin induction, as above. Monitor fungal blood cultures and CrAg to verify the effectiveness of therapy. Itraconazole may be used as an alternative (200 mg orally twice daily capsules; 100–200 mg once daily for oral suspension). Therapy should be continued for life, unless the patient has sustained CD4 cell recovery in response to effective ART (CD4 count >100–200 cells/μL for at least 6 months during ART). Therapy should be restarted if the CD4 count declines to <100–200 cells/μL.

Cutaneous infection, with negative CSF CrAg and cultures

Treat with fluconazole 400 mg once daily for 6–10 weeks, then continue with 200 mg once daily for chronic maintenance therapy, as discussed above.

Other treatment notes

- ◆ ART: Immune reconstitution through ART is effective for preventing recurrence of cryptococcal infections. However, initiating ART within the first 1–2 months of cryptococcal infection may result in worsening or recurrence of symptoms because of immune reconstitution syndrome. Some experts recommend treating cryptococcosis with effective antifungal therapy for 1–2 months before starting ART. (See chapter *Immune Reconstitution Syndrome*.)
- ◆ Pregnancy: Fluconazole and other azole drugs are not recommended during pregnancy, especially in the first trimester. During the first trimester, pregnant women should be treated with amphotericin for both induction and consolidation therapy. Flucytosine is teratogenic at high doses in rats and should be used during pregnancy only if the benefits clearly outweigh the risks.
- ◆ Preventive therapy: Studies have suggested that routine primary prophylaxis for cryptococcal disease in patients with CD4 counts of <100 cells/μL is effective at preventing cryptococcal infection but is not cost efficient. Therefore, it is not routinely recommended. Trials of fluconazole prophylaxis in Asia and Africa are under way, but preservation of immune responses by the use of effective ART, when available, is the best form of prevention.

Patient Education

- ◆ Cryptococcosis is not curable in persons with low CD4 cell counts and may require lifelong treatment. Patients should be instructed to take their treatment without interruptions.
- ◆ Even with therapy, disease may recur. Patients should report fevers or recurrence of other symptoms immediately.
- ◆ Patients should avoid pregnancy while taking any oral antifungal drug. Fetal craniofacial and skeletal abnormalities have been reported.

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Cryptosporidiosis

Background

Cryptosporidiosis is caused by a species of protozoan parasite that typically infects the mucosa of the small intestine, causing watery diarrhea. Diarrhea may be accompanied by nausea, vomiting, abdominal cramping, and occasionally fever. The infection is spread by the fecal-oral route, usually via contaminated water, and is highly contagious. The course of infection depends on the immune status of the host. In immunocompetent individuals, cryptosporidiosis is usually self-limited and can cause a mild diarrheal illness. However, in HIV-infected patients with advanced immunosuppression, cryptosporidiosis can cause severe chronic diarrhea, electrolyte disturbances, malabsorption, and profound weight loss. It can also cause cholangitis and pancreatitis, through infection of the biliary tract and pancreatic duct. Those at greatest risk for cryptosporidiosis are patients with CD4 counts of <100 cells/ μ L.

S: Subjective

The patient may complain of some or all of the following: watery diarrhea (can be profuse), abdominal pain or cramping, flatulence, nausea, vomiting, anorexia, fever, and weight loss.

The history should include questions about the presence and characteristics of the symptoms listed above, as well as the following:

- ◆ Stool frequency (typically 6–26 bowel movements daily)
- ◆ Stool volume (mean 3.6 L, and up to 10 L/d in some patients with AIDS)
- ◆ Duration of symptoms (subacute or acute onset)
- ◆ Associated symptoms
- ◆ Exposures: recent travel to areas with unsafe water supply; ingestion of possibly contaminated water while swimming, boating, or camping; oral-anal contact
- ◆ Recent CD4 cell count (highest risk is in patients with CD4 count <100 cells/ μ L)

O: Objective

Perform a thorough physical examination with particular attention to the following:

- ◆ Vital signs
- ◆ Hydration status (eg, orthostatic vital signs, mucous membrane moistness, skin turgor)
- ◆ Weight (compare with previous values; document weight loss)
- ◆ Signs of malnourishment (eg, cachexia, wasting, thinning hair, pallor)
- ◆ Abdominal examination for bowel sounds (usually hyperactive), tenderness (can be diffuse), rebound
- ◆ Recent CD4 count (likely to be <150 cells/ μ L and can be significantly lower)

A: Assessment

In HIV-infected patients with advanced immunosuppression, the differential diagnosis includes other infectious causes of subacute or chronic diarrhea or cholangitis, such as *microsporidia*, *Isospora*, *Giardia*, *cytomegalovirus* (CMV), and *Mycobacterium avium* complex (MAC), as well as lymphoma.

P: Plan

Diagnostic Evaluation

- ◆ Test the stool for ova and parasites, including *Cryptosporidium*.
 - ◆ Be sure to ask that the laboratory look for *Cryptosporidium*; certain laboratories do not look for these parasites unless requested. For profuse diarrhea, a single sample is usually adequate for diagnosis; repeat sampling can be useful if the first round of test results is negative.
 - ◆ Test for fecal leukocytes. This is usually negative in cryptosporidiosis; if positive, consider the possibility of a second enteric infection, especially if the CD4 count is low.
- ◆ If the stool is negative for ova and parasites after 3 tests, consider a referral for biopsy of the gastrointestinal mucosa or flexible sigmoidoscopy.

- ◆ If cholangitis is suspected, consider abdominal ultrasound to detect biliary ductal dilatation, and endoscopic retrograde cholangiopancreatography (ERCP).
- ◆ Check electrolytes; conduct liver function studies including alkaline phosphatase and bilirubin.
- ◆ If fever is present, obtain blood cultures.
- ◆ Conduct other diagnostic testing as indicated by the history and physical examination (eg, evaluation for CMV, MAC, and other infectious causes of diarrhea or cholangitis) (see chapter *Diarrhea*).

Treatment

- ◆ Provide supportive care and symptomatic relief (this may require hospitalization in cases of severe dehydration), including the following:
 - ◆ Aggressive fluid and electrolyte replacement as needed
 - ◆ Oral rehydration (solutions containing glucose, sodium bicarbonate, potassium, magnesium, and phosphorus); in severe cases, intravenous hydration may be required
 - ◆ Antidiarrheal agents: atropine/diphenoxylate (Lomotil), loperamide (Imodium), tincture of opium (Paregoric)
 - ◆ Antispasmodics
 - ◆ Antiemetics
 - ◆ Topical treatment for the anorectal area, as needed (Tucks pads, sitz baths)
- ◆ No antiparasitic therapy has been proven to cure or prevent cryptosporidiosis. Most patients experience symptom improvement or resolution with immune reconstitution achieved by effective antiretroviral therapy (ART), especially if the CD4 count increases to >100 cells/ μ L. All patients with cryptosporidiosis should be treated with ART, unless it is contraindicated, as early in the course of cryptosporidiosis therapy as possible (see chapter *Antiretroviral Therapy*).
- ◆ Antiparasitic agents have not been proven effective, but are sometimes used. These include:
 - ◆ Paromomycin (Humatin), which may result in initial response, although its efficacy remains unclear. The usual adult dosage is 500 mg orally 4 times daily or 1,000 mg twice daily, with meals.
 - ◆ Paromomycin in combination with azithromycin. One study found substantial short-term benefit from this combination, although cure rates were low.
 - ◆ Nitazoxanide (Cryptaz), 500 mg orally twice daily. This agent is approved for use in children with diarrhea caused by *C parvum*. Its usefulness in adults and those with immunodeficiency has not been demonstrated consistently.
- ◆ For patients with weight loss, nutritional supplementation is usually an important aspect of treatment. In some cases, partial or total parenteral nutrition may be necessary while patients are awaiting clinical improvement in response to ART or other therapies. Consult or refer to a dietitian or nutritionist, if available. If not, assess food intake and counsel the patient about increasing caloric and nutritional intake.

Cryptosporidiosis in Resource-Limited Settings

Cryptosporidium infection in HIV-uninfected populations is more common in countries with overcrowding and poor sanitary conditions. The disease is also associated with rainy seasons and is frequent in children <2 years of age.

The prognosis for HIV-infected patients with cryptosporidiosis and without access to ART is poor. In one study, the mean survival time of coinfecting patients was 25 weeks.

Patient Education

- ◆ Recommend scrupulous handwashing for the patient and all contacts, especially household members and sexual partners.
- ◆ Explain that effective ART is the best treatment for alleviating symptoms and helping the immune system eradicate the parasite.
- ◆ Advise the patient to increase fluid intake (not alcohol), and avoid foods that aggravate diarrhea.
- ◆ Educate the patient about healthful food choices that increase calories and nutrition.
- ◆ Provide supportive counseling; discuss how to manage symptoms and the isolation that may accompany chronic diarrhea.

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Cytomegalovirus Disease

Background

Chronic infection with cytomegalovirus (CMV), a member of the human herpesvirus family, is common among sexually active adults. CMV is spread by sexual or other types of close personal contact, blood-to-blood contact (via transfusion or needle sharing), organ transplantation, and perinatal transmission. The estimated prevalence of CMV infection among adults ranges from 40% to 60% in resource-rich countries and from 80% to 100% in resource-poor countries. As with other herpesviruses, CMV is not cleared from the body, but is kept in a state of latency by an intact immune system. Chronic CMV infection rarely causes disease among immunocompetent persons, but it is a major cause of morbidity and mortality in HIV-infected patients with CD4 counts of <50 cells/ μL . CMV can cause several clinical illnesses in immunocompromised patients, including chorioretinitis, pneumonia, esophagitis, colitis, encephalitis, polyradiculopathy, adrenalitis, and hepatitis. Symptomatic disease represents either primary infection or reactivation of latent infection that has escaped immunologic control. Effective antiretroviral therapy (ART) greatly reduces the risk of CMV reactivation and disease.

S: Subjective

The patient may report symptoms including the following:

- ◆ Floaters, scotomata (blind spots), “flashing lights,” loss of peripheral or field vision (chorioretinitis)
- ◆ Headache, difficulty concentrating, sleepiness, personality changes (encephalitis, dementia)
- ◆ Mouth ulcerations
- ◆ Dysphagia or odynophagia (esophagitis)
- ◆ Abdominal pain and bloody diarrhea, weight loss, rectal ulcers, fever (colitis)
- ◆ Persistent fever, fatigue, weight loss (adrenalitis)
- ◆ Shortness of breath, dyspnea on exertion, dry cough (pneumonia; rare in patients with advanced HIV infection)
- ◆ Bilateral lower extremity weakness, urinary retention, incontinence, spasticity (polyradiculopathy)

- ◆ Low back pain, especially radiating to the perianal area (polyradiculopathy, myelitis)

Family members or caregivers may report confusion, apathy, lethargy, somnolence, withdrawal, or personality changes in the patient (CMV encephalitis, dementia).

The history should include questions about the presence and characteristics of the symptoms listed above, as well as the following:

- ◆ Duration of symptoms
- ◆ Associated symptoms
- ◆ Recent CD4 count; nadir CD4 count (risk is highest at <50 cells/ μL)
- ◆ Whether the patient is taking ART; if so, date initiated, specific medications, and CD4 and HIV RNA responses

O: Objective

Perform a thorough physical examination, with particular attention to the following:

- ◆ Vital signs: Document fever.
- ◆ Weight: Compare with previous values; document weight loss.
- ◆ Eyes: Funduscopic examination in patients with CMV retinitis may show pathognomonic “cottage cheese in ketchup” yellow-white lesions, representing vascular hemorrhages and exudates.
- ◆ Nervous system: Evaluate mental status and perform a complete neurologic examination, including cranial nerves, sensation (sensory deficits may occur with preserved vibratory sense and proprioception), motor, deep tendon reflexes, coordination, and gait.

A: Assessment

For HIV-infected patients with advanced immunosuppression, the differential diagnosis includes the following:

- ◆ For suspected CMV retinitis, consider cotton-wool spots and progressive outer or acute retinal necrosis.
- ◆ For suspected CMV enteritis, consider

gastrointestinal pathogens such as *Mycobacterium avium* complex, *Cryptosporidium*, other parasites, and lymphoma.

- ◆ For suspected CMV pneumonitis, consider *Pneumocystis jiroveci* pneumonia (PCP).
- ◆ For suspected CMV encephalitis, consider causes of neurologic deterioration such as progressive multifocal leukoencephalopathy, toxoplasmosis, central nervous system lymphoma, and other mass lesions.

P: Plan

Diagnostic Evaluation

CMV can be detected by serology, culture, antigen testing, nucleic acid amplification, or examination of tissue samples. However, serologic tests are not reliable for diagnosing CMV disease because most adults are seropositive and because patients with advanced AIDS may serorevert while remaining infected. Furthermore, for HIV-infected patients, demonstration of CMV in the blood, urine, semen, cervical secretions, or bronchoalveolar lavage (BAL) fluid does not necessarily indicate active disease, although patients with end-organ disease are usually viremic.

Diagnosis of end-organ disease generally requires demonstration of tissue invasion. The recommended evaluation is as follows.

CMV retinitis

Dilated retinal examination should be performed emergently by an ophthalmologist experienced in the diagnosis of CMV retinitis. The diagnosis is usually based on the identification of typical lesions.

Gastrointestinal CMV disease (esophagitis or colitis)

Perform endoscopy with visualization of ulcers, and conduct tissue biopsy showing viral inclusions to demonstrate viral invasion.

Pulmonary CMV disease

Perform chest radiography showing interstitial pneumonia, and conduct lung tissue biopsy showing inclusion bodies.

Neurologic CMV disease

- ◆ Encephalitis: Magnetic resonance imaging (MRI) of the brain should be done to rule out mass lesions.

Periventricular or meningeal enhancement may be detected with CMV disease. Lumbar puncture should be performed; cerebrospinal fluid (CSF) should be analyzed for CMV (by polymerase chain reaction, which is sensitive and specific), cell count (may show lymphocytic or mixed lymphocytic or polymorphonuclear pleocytosis), glucose (may be low), and protein (may be high). A brain biopsy may be performed if the diagnosis is uncertain after imaging and CSF evaluation.

- ◆ Polyradiculopathy: Spinal MRI should be done to rule out mass lesions. In CMV disease, nerve root thickening may be present. Lumbar puncture with CSF analysis should be performed, as described above.
- ◆ Myelitis: Spinal MRI should be done to rule out mass lesions. Cord enhancement may be present. Lumbar puncture with CSF analysis should be performed, as described above.

Other sites

Detection of CMV at other sites requires BAL, visualization with endoscopy, or tissue biopsy. Viral inclusions (“owl’s eye cells”) in biopsied tissue demonstrate invasive disease (as opposed to colonization). Because retinitis is the most common manifestation of CMV disease, patients with gastrointestinal, central nervous system, or pulmonary disease should undergo ophthalmologic evaluation to detect subclinical retinal disease.

Treatment

Ganciclovir, valganciclovir, foscarnet, and cidofovir may be effective for treating CMV end-organ disease. The choice of therapy depends on the site and severity of the infection, the level of underlying immunosuppression, the patient’s ability to tolerate the medications and adhere to the treatment regimen, and the potential medication interactions.

Immune reconstitution through ART is also a key component of CMV treatment and relapse prevention. The optimal timing of ART initiation in relation to the treatment of CMV is not clear. CMV flares may occur if patients develop immune reconstitution inflammatory syndrome (see chapter *Immune Reconstitution Syndrome*), but in most cases of nonneurologic disease, ART probably should not be delayed.

CMV retinitis

Treatment consists of 2 phases: initial therapy and chronic maintenance therapy.

Initial therapy

Before the advent of valganciclovir, the preferred strategy for treating CMV retinitis involved ganciclovir intraocular implants and systemic therapy. Because implants deliver a higher dose of drug to the retina than any other modality (1.4 mcg/hour for up to 8 months), many experts still prefer them for patients with sight-threatening (zone 1) disease. About half of patients treated with implants develop disease in the contralateral eye, and a third experience systemic disease, within 3 months of implantation. Therefore, patients with implants should be treated systemically with valganciclovir (900 mg once daily; some experts increase this to 900 mg twice daily for patients with vision-threatening disease).

For patients with peripheral retinitis (beyond zone 1), oral valganciclovir (see below) is the preferred treatment because it is easy to administer and is not associated with the surgery- or catheter-related complications seen with intraocular treatments and intravenous therapies. This formulation quickly converts to ganciclovir in the body and has good bioavailability. Valganciclovir should be used only if the patient is thought to be capable of strict adherence. Other possible intravenous treatments include ganciclovir, ganciclovir followed by oral valganciclovir, foscarnet, and cidofovir. See below for dosing recommendations.

For sight-threatening disease, treat with ganciclovir intraocular implants plus valganciclovir 900 mg orally once daily or twice daily.

For peripheral disease, treat with valganciclovir 900 mg orally twice daily for 14-21 days.

Alternatives for initial therapy

- ◆ Intravenous ganciclovir 5 mg/kg every 12 hours for 14-21 days
- ◆ Intravenous foscarnet 60 mg/kg every 8 hours or 90 mg/kg every 12 hours for 14-21 days
- ◆ Intravenous cidofovir 5 mg/kg weekly for 2 weeks, then every other week (must be given with probenecid [2 g orally 3 hours before, 1 g orally 2 hours after, and 1 g orally 8 hours after the cidofovir infusion] and intravenous saline to decrease the risk of renal toxicity)

Note: Valganciclovir, ganciclovir, and foscarnet require dosage adjustment in patients with renal insufficiency. Cidofovir is contraindicated in patients with renal insufficiency or proteinuria.

Monitor patients closely to gauge the response to therapy. Repeat the dilated retinal examination after the completion of induction therapy, 1 month after initiation of therapy, and monthly during anti-CMV therapy. Consult with a specialist if the response to therapy is suboptimal.

Note: Retinal detachment may occur in up to 50-60% of patients in the first year after diagnosis. Regular follow-up with an ophthalmologist is required for all patients. Patients should report any vision loss immediately.

Chronic maintenance therapy

After initial CMV treatment, lifelong maintenance therapy with valganciclovir or intravenous foscarnet should be given to prevent recurrence, and the patient needs regular reevaluation by an ophthalmologist. Recommended dosages for maintenance therapy are as follows:

- ◆ Valganciclovir 900 mg orally once daily
- ◆ Intravenous foscarnet 90-120 mg/kg once daily

Discontinuation of maintenance therapy can be considered for patients with inactive CMV and sustained immune reconstitution during ART (CD4 count of >100-150 cells/ μ L for at least 6 months). However, the decision should be guided by factors such as the extent and location of the CMV lesions and the status of the patient's vision. An ophthalmologist who is experienced in caring for HIV-infected patients should be involved in making any decision to discontinue therapy, and patients should receive regular ophthalmologic follow-up. Maintenance therapy should be resumed if the CD4 count drops below 100-150 cells/ μ L or the patient develops other signs of HIV progression.

Gastrointestinal and pulmonary CMV disease

These infections are usually treated with intravenous ganciclovir or foscarnet for 21-28 days unless the patient is able to absorb oral medications, in which case oral valganciclovir is an option (refer to the dosing suggestions above). Some specialists recommend a follow-up endoscopy to verify regression of lesions before discontinuing therapy. Many experts do not recommend maintenance therapy for gastrointestinal CMV infections unless the disease recurs.

Neurologic CMV disease

The optimal treatment of neurologic disease has not been determined. Prompt initiation of dual therapy with intravenous ganciclovir and foscarnet may be effective in some patients.

Monitoring CMV therapies

The medications used to treat CMV have several important potential adverse effects, and monitoring for these is required. Valganciclovir and ganciclovir have been associated with bone marrow suppression, neutropenia, anemia, thrombocytopenia, and renal dysfunction. Foscarnet has been associated with cytopenia, renal insufficiency, electrolyte abnormalities, and seizures. For patients taking these medications, perform complete blood count with differential and check electrolytes and creatinine twice weekly during initial therapy and once weekly during maintenance therapy. Cidofovir has been associated with renal insufficiency and ocular hypotony. For patients taking cidofovir, check creatinine and blood urea nitrogen and perform urinalysis (for proteinuria) before each dose. Intraocular pressure must be checked at least every 6 months.

Patient Education

- ◆ Educate patients about the importance of ART in treating CMV. Urge patients to start ART if they have not done so already.
- ◆ Patients with CMV retinitis may have to remain on suppressive therapy for life to prevent blindness. Patients with CMV esophagitis or enteritis usually see improvements within 2-4 weeks of therapy.
- ◆ Treatment of CMV retinitis halts progression of the infection but does not reverse the damage already done to the retina. Warn patients that vision will not return to pre-CMV status.
- ◆ Advise patients to report any visual deterioration immediately. Retinal detachment or progression of CMV must be treated immediately to avoid further vision loss.
- ◆ With gastrointestinal disease, recurrence of symptoms warrants repeat endoscopy. Advise patients to report any recurrence of symptoms.
- ◆ Adverse reactions to current therapies are common. Educate patients about these and advise them to promptly report any adverse reactions.
- ◆ Help patients cope with the possibility of therapeutic failure, and, in the case of CMV retinitis, permanent loss of vision.
- ◆ Teach patients how to maintain indwelling venous access lines, if used. Have patients demonstrate these techniques before discharge.

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Dermatologic Staphylococcal Infections

Background

Staphylococcus aureus is the most common cause of community-acquired (CA) or hospital-acquired (HA) bacterial skin and soft-tissue infections (SSTIs) among patients with HIV infection. Staphylococcal infection may present as cellulitis, folliculitis, furuncles, abscesses, ecthyma, bullous impetigo, or plaques resembling hidradenitis suppurativa. Staphylococcal SSTIs can occur in isolation or as a complication of other skin pathology. HIV-positive patients are at risk of superinfection, bacteremia, and metastatic infection from SSTIs that might be considered trivial in other patients.

Most CA staphylococcal infections involve methicillin-susceptible *S aureus* (MSSA). However, a strain of CA methicillin-resistant *S aureus* (MRSA) is increasingly common; MRSA is now found in up to 50% of CA SSTIs in many localities. This strain carries an SSTI virulence gene (the Panton-Valentine leucocidin gene), is more aggressive in causing SSTIs, and appears more likely to result in serious pneumonia than was previous CA *S aureus*. Resistance is conferred by the *mec IV* gene (different from *mec III* of HA MRSA). CA MRSA is commonly sensitive to tetracyclines, rifampin, trimethoprim-sulfamethoxazole (TMP-SMX), quinolones, and clindamycin.

The treatment of SSTIs is determined by the extent, depth, and speed of progression of the infection. Hospital admission for intravenous antibiotic therapy is indicated when systemic toxicity accompanies a staphylococcal skin infection, the infection is rapidly advancing, or there is concern about compartment syndrome, necrotizing fasciitis, or other complications.

S: Subjective

The patient complains of inflammation (erythema and tenderness) of the skin and subcutaneous tissue, itchy rash (folliculitis), furuncles, pustules, or abscesses.

Inquire about the following:

- ◆ Risk factors, including other recent skin infections, trauma, hospitalization, close skin contact with other people (especially those with skin infections), injection drug use, diabetes mellitus, chronic venous insufficiency
- ◆ Constitutional symptoms, such as fever
- ◆ Localizing pain
- ◆ Symptoms distant from the index lesion, which may suggest systemic spread

Review medications, supplements, and herbal preparations.

O: Objective

Physical Examination

Note: SSTIs may be highly contagious. During examination of any skin lesions, the health care worker should wear gloves and wash hands thoroughly after glove removal.

Check vital signs. Perform a focused physical examination of the skin, lymph nodes, and other areas as indicated (eg, the heart for signs of endocarditis, the mucous membranes for lesions, or the joints for signs of septic arthritis).

Cellulitis

Findings include swelling, tenderness, erythema, and warmth of localized tissue, most commonly on the face and extremities. Cellulitis may be associated with other types of lesions.

Furuncles/abscesses

Palpation of the affected area reveals a firm nodule or a fluid collection in the subcutaneous tissue, often surrounded by cellulitis. Most abscesses or furuncles with more than a few mm³ of pus should be drained.

Folliculitis

Follicular pustules are pruritic, often very painful lesions that may be present on the face, trunk, axillae, or groin. A tiny central pustule may be visible when the skin is stretched, although sometimes the lesions are almost urticarial. These may extend below the skin surface, forming abscesses or, in rare cases, large, violaceous hidradenitis-like plaques with pustules. Note that excoriations may obscure primary lesions.

Ecthyma

This appears as a superficially ulcerated “punched out” or eroded lesion with an extremely adherent crust. A purulent layer of material is usually found under the crust.

Bullous impetigo

Superficial blisters or erosions, often with yellow crusts, appear on the face, groin, or axillae.

A: Assessment

A partial differential diagnosis of cellulitis, abscess, eruptions, or ulcerations includes the following:

- ◆ Streptococcal or other bacterial SSTI
- ◆ *Candida albicans* or other fungal infection (particularly in the groin and perineal area and under pendulous breasts, or as a cause of folliculitis)
- ◆ Eosinophilic folliculitis
- ◆ Syphilis
- ◆ Herpes simplex, herpes zoster
- ◆ Cutaneous hypersensitivity reactions to drug therapy
- ◆ Deep vein thrombosis in the calf, causing swelling with apparent cellulitis
- ◆ Pyogenic granuloma
- ◆ Angiosarcoma
- ◆ Kaposi sarcoma, particularly if femoral or inguinal lymph node enlargement is present
- ◆ Bacillary angiomatosis
- ◆ Gout

P: Plan**Diagnostic Evaluation**

Often, SSTIs can be diagnosed and treated on the basis of the history and physical examination, and diagnostic testing is not required.

For exudative or pustular lesions, obtain exudate for Gram stain, culture, and sensitivity, to identify the organism and to choose the optimal antibiotic therapy. Note that CA MRSA is common among HIV-infected patients in most urban and many rural areas.

If systemic illness is suspected, check complete blood count with differential, blood cultures, and a metabolic panel.

Order tests to rule out other causes of skin infection, as indicated (eg, syphilis, herpes). Consider biopsy if the diagnosis is unclear after initial workup or if the lesion does not respond to empiric treatment.

Treatment

If the patient has extensive, spreading cellulitis or systemic illness, or is suspected to have deep abscess, necrotizing infection, compartment syndrome, or other deep soft-tissue infection, hospitalize immediately for intravenous antibiotic therapy (consult an infectious disease specialist for antimicrobial therapy) and obtain urgent surgical consultation. Mild and moderate SSTIs can usually be treated on an outpatient basis.

Abscesses and fluctuant lesions should be incised and drained, if possible. Antibiotic therapy may not be necessary if the abscess is drained adequately.

For suspected *S aureus* infections, initiate empiric antibiotic treatment, if indicated; consider the local prevalence of MRSA when selecting antibiotics (see “Treatment note” below).

Impetigo

Treat impetigo for 7-14 days.

- ◆ Dicloxacillin 250 mg orally 4 times per day
- ◆ Cephalexin 250 mg orally 4 times per day
- ◆ Erythromycin 250 mg orally 4 times per day
- ◆ Clindamycin 300-450 mg orally 4 times per day
- ◆ Doxycycline 100 mg orally twice daily

Known or suspected MSSA SSTI

Treat known or suspected MSSA SSTIs for 7-14 days.

- ◆ Dicloxacillin 500 mg orally 4 times per day
- ◆ Cephalexin 500 mg orally 4 times per day
- ◆ Clindamycin 300-450 mg orally 4 times per day; if the patient has been taking azithromycin for *Mycobacterium avium* complex prophylaxis, staphylococcal infections may be resistant to clindamycin
- ◆ Doxycycline 100 mg twice daily orally
- ◆ TMP-SMX 2 double-strength tablets orally twice daily

Known or suspected MRSA SSTI

Treat according to the patient's culture and sensitivity results, or according to local trends in MRSA susceptibility (see "Treatment note" below). The following are often effective:

- ◆ Clindamycin 300-450 mg orally 4 times per day
- ◆ Doxycycline 100 mg orally twice daily
- ◆ TMP-SMX 2 double-strength tablets orally twice daily

For severe infections, use intravenous antibiotics selected according to *S aureus* susceptibility. For MRSA, consider vancomycin, clindamycin, linezolid, or daptomycin, if available.

Recurrent lesions may indicate MRSA carriage in the nose or elsewhere. Nasal carriage can be treated with topical mupirocin ointment to the anterior nares 3 times daily for 7 days. If nasal mupirocin fails and MRSA SSTI recurs frequently, consider the addition of a quinolone or TMP-SMX (2 double-strength tablets twice daily) plus rifampin (600 mg twice daily) to mupirocin nasal ointment for 14-21 days may be effective. With all treatments, staphylococcal eradication may be temporary.

Treatment note

To guide empiric antimicrobial therapy, monitor the percentage of staphylococcal isolates that are MRSA in the particular clinical setting, as well as local MRSA antibiotic sensitivities. (The laboratory must perform the "D-test" to rule out erythromycin induction of clindamycin resistance.)

Patient Education

- ◆ Patients should be informed that impetigo and some other staphylococcal infections are highly contagious. Patients should avoid hand contact with lesions, and should not allow other people to touch the affected areas.
- ◆ Antibiotics should be taken exactly as prescribed.
- ◆ Patients should call or return to the clinic if symptoms do not improve in 3-5 days or if symptoms worsen.
- ◆ Instruct patients to wash the affected area with antibacterial soap (such as Hibiclens, Betadine, or benzoyl peroxide wash). If living quarters are shared, patients should clean contaminated surfaces to protect others from MRSA colonization or infection.
- ◆ Instruct patients to use of warm soaks in aluminum acetate astringent solution (Domeboro solution) if needed for discomfort or irritation.

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Gonorrhea and Chlamydia

Background

Gonorrhea, caused by *Neisseria gonorrhoeae* (GC), and chlamydia, caused by *Chlamydia trachomatis* (CT), are sexually transmitted infections (STIs). These infections may be transmitted during oral, vaginal, or anal sex; they can also be transmitted from the mother to baby during delivery and cause significant illness in the infant.

Both organisms can infect the urethra, oropharynx, and rectum in women and men; the epididymis in men, and the cervix, uterus, and fallopian tubes in women. Untreated GC or CT in women may lead to pelvic inflammatory disease, which can cause scarring of the fallopian tubes and result in infertility or ectopic pregnancy (tubal pregnancy). The organisms can also affect other sites; *N gonorrhoeae* can cause disseminated infection involving the skin, joints, and other systems.

Certain strains of CT can cause lymphogranuloma venereum (LGV). This infection is common in parts of Africa, India, Southeast Asia, and the Caribbean. Outbreaks among men who have sex with men (MSM) have been reported over the past several years in Europe and the United States. LGV may cause genital ulcers followed by inguinal adenopathy; it can also (as in the recent cases in MSM) cause gastrointestinal symptoms, notably anorectal discharge and pain.

Patients with symptoms of gonorrhea or chlamydia should be evaluated and treated as indicated below. Although GC or CT urethritis in men typically causes symptoms, urethral infection in women and oral or rectal infections in both men and women often cause no symptoms. In fact, a substantial number of individuals with GC or CT infection have no symptoms. Thus, sexually active individuals at risk for GC and CT should receive regular screening for these infections as well as for syphilis and other STIs. Patients are frequently infected with both *N gonorrhoeae* and *C trachomatis*, so they should be tested and treated for both.

S: Subjective

Symptoms will depend on the site of infection (eg, oropharynx, urethra, cervix, rectum). Symptoms are not present in all patients.

If symptoms are present, **women** may notice:

- ◆ Vaginal discharge
- ◆ Urinary hesitancy
- ◆ Pain with sexual intercourse
- ◆ Pain or burning on urination
- ◆ Abdominal or pelvic pain
- ◆ Sore throat
- ◆ Mouth sores
- ◆ Rectal discharge
- ◆ Anal discomfort

If symptoms are present, **men** may notice:

- ◆ Increased urinary frequency or urgency
- ◆ Urethral discharge
- ◆ Red or swollen urethra
- ◆ Incontinence
- ◆ Pain on urination
- ◆ Testicular tenderness or pain
- ◆ Rectal discharge
- ◆ Anal discomfort

During the history, ask the patient about the following:

- ◆ Any of the symptoms listed above, and their duration
- ◆ Previous diagnosis of gonorrhea or chlamydia
- ◆ New sex partner(s)
- ◆ Unprotected sex (oral, vaginal, anal)
- ◆ Use of an intrauterine device
- ◆ Last menstrual period, and whether the patient could be pregnant

O: Objective

Physical Examination

During the physical examination, check for fever and document other vital signs.

In **women**, focus the physical examination on the mouth, abdomen, and pelvis. Inspect the oropharynx for discharge and lesions; check the abdomen for bowel sounds, distention, rebound, guarding, masses, and suprapubic or costovertebral angle tenderness; perform a complete pelvic examination for abnormal discharge or bleeding; check for uterine, adnexal, or cervical motion tenderness; and search for pelvic masses or adnexal enlargement. Check the anus for discharge and lesions; perform anoscopy if symptoms of proctitis are present. Check for inguinal lymphadenopathy.

In **men**, focus the physical examination on the mouth, genitals, and anus/rectum. Check the oropharynx for discharge and lesions, the urethra for discharge, the external genitalia for other lesions, and the anus for discharge and lesions; perform anoscopy if symptoms of proctitis are present. Check for inguinal lymphadenopathy.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Urinary tract infection
- ◆ Dysmenorrhea
- ◆ Appendicitis
- ◆ Cystitis
- ◆ Proctitis
- ◆ Pelvic inflammatory disease (PID)
- ◆ Irritable bowel syndrome
- ◆ Pyelonephritis

P: Plan

Diagnostic Evaluation

Test for oral, urethral, or anorectal infection, according to symptoms and possible exposures. Perform concurrent testing for both gonorrhea and chlamydia. The availability of the various testing methods depends on the clinical site. Consider the following:

- ◆ Gram stain (pharyngeal, cervical, or urethral discharge)
- ◆ Culture (oropharynx, endocervix, urethra, rectum)
- ◆ Nucleic acid amplification test (NAAT): urine specimens (first stream) and urethral, vaginal, and endocervical swab specimens; has also been used for pharyngeal and rectal swab specimens, although it is not currently approved for this use
- ◆ Nucleic acid hybridization assay (DNA probe): endocervical and male urethral swab specimens
- ◆ Serologic tests (microimmunofluorescence test or complement fixation test) for suspected LGV

Treatment

Treatments for gonorrhea and chlamydia are indicated below. High rates of fluoroquinolone-resistant *N. gonorrhoeae* exist in California, Hawaii and the Pacific Islands, Asia, and Great Britain. Fluoroquinolone-resistant GC is also common among MSM in the United States. Thus, the U.S. Centers for Disease Control and Prevention (CDC) recommends that fluoroquinolones not be used for treatment of GC in MSM or in any patient infected in the areas listed above, unless antimicrobial susceptibility test results are used to guide therapy.

Because dual infection is common, patients diagnosed with either GC or CT should receive empiric treatment for both infections, unless the other infection has been ruled out. Reinfection is likely if reexposure occurs. Any sex partners within the last 60 days, or the most recent sex partner from >60 days before diagnosis, also should receive treatment. Patients should abstain from sexual activity for 7 days after a single-dose treatment or until a 7-day treatment course is completed.

Adherence is essential for treatment success. Single-dose treatments maximize the likeliness of adherence and are preferred. Other considerations in choosing the treatment include antibiotic resistance, cost, allergies, and pregnancy. For further information, see the CDC STD treatment guidelines and the revised recommendations (references below).

Treatment of Gonorrhea

Treatment options include the following. (See the full CDC STD treatment guidelines, referenced below.)

Recommended regimens

- ◆ Ceftriaxone 125 mg or 250 mg intramuscular (IM) injection in a single dose (some providers recommend 250 mg because of slightly higher cure rates)
- ◆ Cefixime 400 mg orally in a single dose (tablet formulation not currently available in the United States)

Alternative regimens

- ◆ Spectinomycin 2 g IM injection in a single dose (for urogenital or anorectal GC; not sufficiently effective to treat pharyngeal GC)
- ◆ Cefpodoxime 400 mg orally in a single dose (insufficient data to be recommended by the CDC)
- ◆ Ciprofloxacin 500 mg orally in a single dose (see “Note” below)
- ◆ Ofloxacin 400 mg orally in a single dose (see “Note” below)
- ◆ Levofloxacin 250 mg orally in a single dose (see “Note” below)
- ◆ Azithromycin 2 g orally in a single dose (not recommended by the CDC; high rate of gastrointestinal intolerance)

Note: Fluoroquinolones are not recommended for treatment of gonococcal infection in MSM or in any patient who acquired GC infection in California, Hawaii, Massachusetts, New York City, or outside the United States, because of the high prevalence of fluoroquinolone resistance.

Treatment of Chlamydia

(See the full CDC STD treatment guidelines, referenced below.)

Recommended regimens

- ◆ Azithromycin 1 g orally in a single dose
- ◆ Doxycycline 100 mg orally twice daily for 7 days

Alternative regimens

- ◆ Erythromycin base 500 mg orally 4 times daily for 7 days
- ◆ Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days

- ◆ Ofloxacin 300 mg orally twice daily for 7 days (see note above)
- ◆ Levofloxacin 500 mg orally once daily for 7 days (see note above)

Treatment of LGV

Recommended regimens

- ◆ Doxycycline 100 mg orally twice daily for 21 days

Alternative regimens

- ◆ Erythromycin base 500 mg orally 4 times daily for 21 days
- ◆ Azithromycin 1 g orally once a week for 3 weeks (limited data)

For recent sex partners (within 30 days of the onset of symptoms), treat with azithromycin 1 g orally in a single dose or doxycycline 100 mg orally twice daily for 7 days.

Treatment during Pregnancy

Fluoroquinolones and tetracyclines should be avoided during pregnancy. For the treatment of GC in pregnant women, the CDC advises using either a recommended cephalosporin or spectinomycin. For the treatment of CT in pregnant women, see the following.

Recommended CT regimens

- ◆ Erythromycin base 500 mg orally 4 times daily for 7 days
- ◆ Amoxicillin 500 mg orally 3 times daily for 7 days

Alternative CT regimens

- ◆ Erythromycin base 250 mg orally 4 times daily for 14 days
- ◆ Erythromycin ethylsuccinate 800 mg orally 4 times daily for 7 days
- ◆ Erythromycin ethylsuccinate 400 mg orally 4 times daily for 14 days
- ◆ Azithromycin 1 g orally in a single dose

Follow-up

- ◆ Evaluate sex partners and treat them if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms.
- ◆ Most recurrent infections come from sex partners who were not treated.
- ◆ If symptoms persist, evaluate for the possibility of reinfection, treatment failure, or a different cause of symptoms. If treatment failure is suspected, perform culture and antimicrobial sensitivity testing.

- ◆ For pregnant women with chlamydia, retest (by culture) 3 weeks after completion of treatment.
- ◆ Screen for chlamydia, syphilis, and other STIs at regular intervals according to the patient's risk factors. The sites of sampling (eg, pharynx, urethra, endocervix, anus/rectum) will depend on the patient's sexual exposures.
- ◆ Evaluate each patient's sexual practices with regard to the risk of acquiring STIs and of transmitting HIV; work with the patient to reduce sexual risks.

Patient Education

- ◆ Instruct patients to take all of their medications. Advise patients to take medications with food if they are nauseated, and to call or return to clinic right away if they have vomiting or are unable to take their medications.
- ◆ Sex partners from the previous 60 days need to be tested for sexually transmitted pathogens, and treated as soon as possible with a regimen effective against gonorrhea and chlamydia, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated. Otherwise, patients may be reinfected.
- ◆ Advise patients to avoid sexual contact until the infection has been cured (at least 7 days).
- ◆ Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent reinfection with gonorrhea or chlamydia, to prevent other STIs, and to prevent transmission of HIV to sexual partners.

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Hepatitis B Infection

Background

Hepatitis B virus (HBV) is the most common cause of chronic liver disease worldwide. HBV is a DNA virus that is transmitted primarily through blood exposure, sexual contact, and from mothers to their children. Because HIV and HBV share transmission routes, up to 90% of HIV-infected patients have evidence of previous or current HBV infection.

Most people who become infected with HBV are able to clear the virus without treatment, and they subsequently become immune to HBV. A small proportion of individuals infected with HBV (approximately 10% in the general population) develop chronic HBV infection. Over time, chronic HBV can cause hepatic fibrosis and eventually cirrhosis, end-stage liver disease (ESLD), and hepatocellular carcinoma (HCC). HIV infection appears to increase the risk of developing chronic HBV infection after HBV exposure. Patients coinfect with HBV and HIV also tend to have faster progression of liver disease, with associated morbidity and mortality.

To identify patients with HBV coinfection, and to identify and vaccinate susceptible individuals, all HIV-infected persons should be tested for HBV. Table 1 outlines routine baseline HBV serologic screening tests for HIV-infected individuals:

Table 1. Interpreting Hepatitis-B-Related Laboratory Tests

Name of Test	Interpretation of Positive Results	Interpretation of Negative Result
Hepatitis B surface antigen (HBsAg)	Active HBV	Usually indicates absence of HBV infection; may be falsely negative in some patients with active HBV
Hepatitis B surface antibody (HBsAb)	Immune to HBV (through past exposure or vaccination)	Not immune; if active HBV disease is not present, consider vaccination
Hepatitis B core antibody (HBcAb), IgG	Past exposure to HBV; does not indicate whether patient has active infection or has cleared infection (check HBsAg and HBsAb)	Probably has not been infected with HBV

A positive result for hepatitis B surface antigen (HBsAg) that persists longer than 6 months indicates chronic infection. In some cases of active HBV infection, a positive result for hepatitis B core antibody (HBcAb) may be the only detectable marker, because HBsAg may be negative. Ongoing viral replication and infectiousness is indicated by the presence of HBV DNA or a positive result for hepatitis B envelope antigen (HBeAg).

S: Subjective

Symptoms of acute HBV infection may include fatigue, nausea, vomiting, arthralgias, fever, right upper quadrant pain, jaundice, dark urine, and clay-colored stools. Some patients may have no symptoms.

Patients with chronic HBV are often asymptomatic until ESLD has developed. Progressive HBV can lead to decompensated liver disease, portal hypertension, cirrhosis, esophageal varices, coagulopathy, thrombocytopenia, hepatic encephalopathy, and HCC, or some combination of these conditions. Patients may experience fatigue, right upper quadrant pain, or complications of ESLD such as jaundice, increased abdominal girth, easy bruising, gastrointestinal bleeding, and altered mentation.

O: Objective

Perform a thorough physical examination, with special attention to the eyes and mouth (icterus, gum bleeding), skin (jaundice, palmar erythema, petechiae, ecchymoses), abdomen (caput medusa, distention, ascites, hepatomegaly, splenomegaly), heart and lungs (signs of congestive heart failure), extremities (edema), and the neurologic system.

A: Assessment

A partial differential diagnosis includes:

- ◆ Medication-induced hepatotoxicity
- ◆ Alcohol- or drug-related liver injury
- ◆ Fungal, bacterial, or other viral infection

P: Plan

Diagnostic Evaluation

- ◆ Assess the severity of liver disease at the time of diagnosis and at least every 6 months with alanine aminotransferase (ALT), albumin, bilirubin, prothrombin time, platelet count, and complete blood count.
- ◆ Consider checking the HBV DNA (viral load). DNA levels are usually high in persons with active HBV (in the absence of treatment) and can be used to confirm active disease (in those not taking effective treatment) and monitor the response to treatment (in patients taking HBV treatment). Note, however, that HBV DNA levels apparently do not predict the progression of liver disease.
- ◆ Check for HBeAg; this test indicates active infection and infectiousness, as does the HBV viral load.
- ◆ Persons with chronic HBV are at elevated risk for HCC. Consider screening for HCC every 6-12 months with the serum alpha-fetoprotein (AFP) level or imaging of the liver (ultrasound, computed tomography, or magnetic resonance imaging). Screening is especially important if the patient is in a high-risk group (eg, patients aged >45 years, those with cirrhosis, or those with a family history of HCC).
- ◆ Liver biopsy is the only definitive test to assess the grade (inflammation) and stage (degree of fibrosis) of liver disease. Many experts recommend liver biopsy to guide decisions about therapy, whereas others start therapy based on ALT and HBV DNA, without liver biopsy.

Treatment

The optimal treatment strategies for patients with HIV and HBV coinfection have not been defined, and individual patient characteristics should be used to guide therapy. The patient's need for HIV treatment (antiretroviral therapy [ART]) should be considered carefully because it will influence the selection of HBV therapy. When ART is indicated, agents that have activity against both HIV and HBV (eg, lamivudine, emtricitabine, tenofovir) can be considered for inclusion in the ART regimen. Patients who need HBV treatment but are not candidates for HIV treatment can be given agents that do not have activity against HIV at standard doses (eg, interferon, adefovir, entecavir). For some therapies, data on efficacy and safety are

limited, the proper duration of treatment is not yet clear, and the role of combination therapy has not been defined. Studies of treatment in HIV/HBV-coinfected populations are ongoing. Consider consulting with an HBV treatment expert to determine the best approach to HBV treatment for a particular patient.

Some experts treat all patients with proven chronic HBV, whereas others consider treatment for patients with both of the following:

- ◆ Positive HBeAg or HBV DNA >10,000 copies/mL
- ◆ ALT >2 times the upper limit of normal, or inflammation or fibrosis on liver biopsy

Table 2 describes the possible treatments for HBV.

Treatment considerations

- ◆ Adefovir and interferon are preferred for HIV/HBV coinfecting patients who do not require ART.
- ◆ A case series suggests entecavir may be active against HIV as well as HBV. It also describes the emergence of the M184V mutation, which confers cross-resistance to lamivudine and emtricitabine, in a patient on entecavir monotherapy. At present, entecavir should be used only for patients who are receiving effective ART.
- ◆ For HIV/HBV-coinfecting patients who require ART, consider agents with both anti-HIV and anti-HBV activity.
- ◆ When lamivudine is used as a single agent, HBV resistance develops in many patients by 1-2 years. Although combination therapy has not been well studied, specialists recommend using 2 nucleoside/nucleotide combinations that have activity against HBV (lamivudine + tenofovir, or emtricitabine + tenofovir [Truvada]) as part of the antiretroviral regimen, to treat HBV and to prevent HBV resistance.
- ◆ For patients infected with hepatitis C virus (HCV) as well as HBV and HIV, evaluate the need for HIV therapy first. If ART is not required, consider treating HCV first, because interferon therapy is active against both HCV and HBV. If interferon-based therapy for HCV has failed, consider treating chronic HBV with an oral agent.
- ◆ Patients taking therapy should be monitored regularly for changes in ALT. If possible, HBeAg (if initially positive) and HBV DNA should also be monitored.

- ◆ Some patients treated with ART may experience worsening of HBV symptoms and laboratory markers in the weeks after ART initiation, because of immune reconstitution. Hepatic decompensation due to immune reconstitution must be distinguished from other causes, such as medication toxicity, or other infection. Liver function tests should be monitored closely in patients starting ART.
- ◆ Some antiretroviral medications are hepatotoxic and should be avoided or used cautiously. These include nevirapine, tipranavir, and high-dose ritonavir.
- ◆ Numerous other medications (eg, fluconazole and isoniazid) are known to be hepatotoxic and can pose problems for people with impaired liver function.
- ◆ For patients with treatment failure, consult an HBV specialist.
- ◆ *Caution:* Discontinuation of HBV medications in patients with HIV/HBV coinfection may cause a flare of liver disease. If this occurs, consider reinstating HBV therapy as soon as possible. Be very cautious when discontinuing HBV-active medications from an HIV ART regimen. In this scenario, consider continuing or substituting the HBV-active medications to avoid rebound liver inflammation and decompensation. For example, if it is decided to discontinue HIV treatment for an HIV/HBV-coinfected patient taking lamivudine + tenofovir + lopinavir/ritonavir, consider starting adefovir or entecavir to maintain activity against HPV.

Other care issues

Acute hepatitis A virus (HAV) or HCV in persons with chronic HBV infection can cause decompensated liver disease. All patients with HBV infection should be tested for immunity to HAV and HCV. Patients who are not immune to HAV should be vaccinated and patients who are not immune to HCV should be counseled about how to avoid the acquisition of HCV.

All HBV-infected individuals should be taught how to reduce the risk of HBV transmission to others. As appropriate, patients should be counseled to adopt “safer sex” approaches, avoid blood exposures (eg, from sharing razors or tattoo equipment), and practice safe drug injection techniques. Persons with HBV infection should be counseled to avoid exposure to hepatotoxins, including alcohol and hepatotoxic medications (eg, acetaminophen in large doses, fluconazole, and isoniazid).

Table 2. Hepatitis B Treatment Regimens

Medication	Treatment Regimen	Comments
Interferon-alfa 2a or 2b	5 million units (MU) daily or 10 MU 3 times weekly for 4-6 months*	• Interferon is contraindicated in patients with decompensated cirrhosis. • Expect the CD4 count to drop by 100-150 cells/μL or more during treatment with interferon or pegylated interferon. (The CD4 percentage usually remains stable).
Pegylated interferon-alfa 2a (Pegasys)	180 micrograms per week for 4-6 months*	
Lamivudine (Epivir, 3TC) [#]	150 mg twice daily or 300 mg daily (dosage as part of ART regimen) for 1 year or more*	• Use only as part of an effective HIV ART regimen. • High rate of HBV resistance occurs after 1-2 years of treatment. Lamivudine-resistant HBV is also resistant to emtricitabine. • Most specialists recommend combination with a second agent (eg, tenofovir or emtricitabine).
Tenofovir (Viread) [#]	300 mg daily: treatment duration unknown*	• Use only as part of an effective HIV ART regimen. • Active against lamivudine-resistant strains of HBV. • Most specialists recommend combination with a second agent (eg, lamivudine or emtricitabine).
Emtricitabine (Emtriva) [#]	200 mg daily: treatment duration unknown*	• Use only as part of an effective HIV ART regimen. • Emtricitabine-resistant HBV also is resistant to lamivudine. • Most specialists recommend combination with a second agent (eg, tenofovir or lamivudine)
Adefovir (Hepsera)	10 mg daily: treatment duration unknown*	• Active against lamivudine-resistant strains of HBV.
Entecavir (Baraclude)	0.5-1.0 mg daily: treatment duration unknown*	• Active against lamivudine-resistant strains of HBV. • May have activity against HIV; pending further studies, should not be used in patients who are not on effective HIV ART regimen.

[#] Agents are active against both HIV and HBV.

* The duration and expected efficacy of treatment vary according to the treatment strategy and the individual patient characteristics.

Patient Education

- ◆ Most patients with HBV will remain asymptomatic for several years. However, ongoing injury to the liver occurs during this time, and can culminate in liver failure. Patients can slow the damage by avoiding alcohol and any medications (including over-the-counter drugs and recreational drugs) that may damage the liver. Instruct patients to call their pharmacist or health care provider if they have questions about a specific medication or supplement.
- ◆ As with HIV, patients must avoid passing HBV to others. Instruct patients not to share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment, or personal care items that may have blood on them. Emphasize the importance of safer sex to protect themselves and their partner(s).
- ◆ Tell patients to discuss HBV with their sex partner(s), and suggest that partner(s) get tested for HBV.
- ◆ Certain antiretroviral drugs are more likely to cause problems with the liver because of HBV. Advise patients that if they start an ART regimen, their liver function tests should be watched carefully to determine whether the body is able to process the medicines.
- ◆ Patients who have not been vaccinated against HAV, will need to receive 2 vaccinations 6 months apart. HAV can cause severe illness, liver damage, or even death, in people with HBV.
- ◆ Patients who have not been tested for HCV should be tested for this virus.
- ◆ HCV can worsen liver function greatly if it is acquired in addition to HBV. Patients with HCV should use safe sex practices (latex barriers) to avoid exposure. Patients who use injection drugs should not share needles or injection equipment.
- ◆ If children were born after women were infected with HBV, consider having them tested. Even though their risk is low, they should be screened for HBV.
- ◆ HBV treatments may cause adverse effects. Most of these are treatable with medications. Patients should contact their health care provider know right away if they experience adverse effects or new symptoms.

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Hepatitis C Infection

Background

Hepatitis C virus (HCV) is a single-stranded RNA virus that is transmitted primarily through blood exposure. The virus can also be transmitted perinatally and through sexual contact, although the latter appears to occur rarely. In some populations of HIV-infected injection drug users (IDUs) and hemophiliacs in the United States, up to 90% may be coinfecting with HCV. Rates of HCV are approximately 15% among HIV-infected men who have sex with men and 2-3% among monogamous heterosexual partners of HCV-infected individuals. HIV infection appears to increase the rate of progression of chronic HCV, and increases the risk of developing end-stage liver disease. It is not yet clear whether HCV affects the progression of HIV disease.

Impact of Coinfection on Vertical Transmission of HIV and HCV

Women coinfecting with HIV and HCV have a higher risk of transmitting HIV to their infants; some studies have shown a 10% (or greater) rate above that of women infected with HIV alone. Coinfecting women are also more likely to pass HCV to their infants. Approximately 20% of babies born to HIV/HCV-coinfecting mothers acquire HCV, compared with 5-6% of infants born to HCV-infected women without HIV. Breast-feeding is not known to transmit HCV, although HIV-infected women are advised against breast-feeding because of the risk of transmitting HIV.

O: Objective

Acute HCV Infection

Acute HCV infection is usually not recognized. In most cases, patients with acute HCV infection are asymptomatic or have nonspecific symptoms such as fatigue and, occasionally, jaundice and scleral icterus. Acute HCV infection is sometimes discovered on the basis of elevations in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) in asymptomatic patients who receive regular monitoring of hepatic transaminases. Most patients with acute HCV will not resolve the infection and will progress to chronic infection, but symptomatic patients generally have a higher likelihood of clearing the virus than do asymptomatic patients (see “Treatment for Acute HCV,” below).

Chronic HCV Infection

About 60-85% of people who become infected with HCV are unable to clear the virus and become chronically infected. Major manifestations are usually not seen in immunocompetent people for 15-20 years, although ALT may be transiently elevated during earlier stages of disease. The virus can cause gradual hepatic fibrosis and eventual cirrhosis, end-stage liver disease, and hepatocellular carcinoma (HCC). Death can occur from decompensated liver disease; the consequences of portal hypertension, esophageal varices, coagulopathy, and thrombocytopenia; HCC; or some combination of these conditions. HIV-infected patients who are not treated with antiretroviral (ARV) medications tend to have faster progression of liver disease than those who are treated.

P: Plan

Diagnostic Evaluation

Enzyme immunoassay

According to the 2002 guidelines of the United States Public Health Service and the Infectious Diseases Society of America, all HIV-infected patients should be tested for anti-HCV antibodies using the enzyme immunoassay (EIA) test. HCV EIA tests are sometimes falsely negative in HIV-infected patients, although the third version of the test is highly sensitive and specific; it is also the least expensive screening test currently available. HIV-infected people who test positive on the EIA should be tested to determine whether they have circulating virus (ie, detectable HCV RNA). Falsely negative HCV viral load testing is uncommon.

Genotyping

Genotyping of HCV is helpful in assessing the likelihood of response to therapy. Patients with genotype 1 have much lower rates of response to treatment than do patients with genotype 2 or 3. Some specialists use the genotype to determine the type and duration of treatment, whereas others treat all HIV/HCV-coinfecting patients similarly.

Alanine aminotransferase

Monitoring of ALT is used to assess liver inflammation, although levels may be low in patients with advanced liver disease.

Imaging

Ultrasonography can be performed to screen for cirrhosis or mass lesions. Computed tomography (CT), magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT) are more expensive and are generally reserved for evaluation of liver masses. Some specialists recommend screening for HCC every 6 months.

Liver biopsy

Liver biopsy is used to stage the degree of inflammation and fibrosis to determine the need for HCV treatment. Biopsy should be considered in patients who are candidates for HCV treatment, after education about HCV therapy (including the expected success rates given the genotype, potential adverse effects, and the duration and logistics of treatment). Recently, blood tests have been used as noninvasive markers of hepatic fibrosis and have shown reasonable ability to identify patients with either mild or advanced liver fibrosis (currently about 40% of patients with HCV), allowing them to avoid liver biopsies.

Treatment**Treatment of chronic HCV**

The recommendations of the National Institutes of Health (NIH) from June 2002 suggest that current alcohol users, pregnant women, patients with untreated depression, patients with renal disease, and patients with advanced cirrhosis are not candidates for HCV treatment. However, more recent data suggest that patients in several of these “special groups” can be treated on a case-by-case basis. Although pregnant women and persons with active alcohol use should not receive HCV treatment, certain individuals with renal disease, depression, injection drug use, and lower degrees of hepatic fibrosis (ie, Child-Pugh class A) should be considered for HCV treatment. These comorbid conditions should, of course, be treated to the degree possible.

HIV-infected patients with low CD4 counts should not be excluded from HCV treatment on the basis of CD4 count alone. Some studies do not support an association between absolute CD4 cell counts and treatment response.

Patients with a high risk of progression to cirrhosis should receive higher priority for treatment. Risk is indicated by portal or bridging cirrhosis, moderate inflammation and necrosis, measurable HCV RNA levels, or persistently elevated ALT levels. However, because ALT levels do not correlate with liver damage and some patients with normal ALT levels have abnormal liver biopsies, many experts treat patients who have normal ALT levels. For patients with minimal findings on liver biopsy and minimal ALT elevations, therapy should be deferred and the patients should be monitored. Patients with decompensated liver disease generally should not receive HCV treatment; appropriate candidates can be considered for clinical studies of liver transplantation in HIV/HCV-coinfected patients.

The most effective treatment for HCV in patients with or without HIV is combination therapy with pegylated interferon-alfa (PEG-IFN) plus ribavirin. Among HIV-uninfected patients, approximately 50% with genotype 1 achieve HCV viral clearance using this combination. HCV/HIV-coinfected patients with genotype 1 have a 22% rate of sustained virologic response to PEG-IFN plus ribavirin if treated for 48 weeks, whereas patients with other genotypes have approximately a 55% rate of sustained virologic response. Data suggest that early virologic response (EVR), defined as a $\geq 2 \log_{10}$ decrease in HCV viral load 12 weeks into treatment, predicts sustained virologic response to treatment; treatment may be stopped if patients do not demonstrate EVR. The recommended duration of treatment in patients with genotype 1 HCV and EVR is 48 weeks. For genotype 2 or 3, the optimal duration of treatment is not clear; some specialists treat for 24 weeks, whereas others treat for 48 weeks.

Adverse effects of treatment

HCV therapy may cause significant adverse effects. IFN reduces total white blood cell counts, and can cause neutropenia. It also decreases CD4 cell counts, although the CD4 percentage usually does not change. IFN can reduce HIV RNA somewhat (approximately a 0.5 $\log_{10}$ decrease). IFN may also produce flulike symptoms, depression, peripheral neuropathy, and other symptoms. Ribavirin can cause anemia and other adverse effects. Zidovudine and didanosine should be avoided, if possible, in patients taking HCV treatment.

HCV treatment should not be given during pregnancy, and women receiving HCV treatment should avoid

pregnancy. Ribavirin is teratogenic, and both women and men must use contraception consistently during treatment with ribavirin and for 6 months after treatment. IFN may cause fetal growth abnormalities, and is abortifacient in animals.

Treatment of acute HCV

Treatment of acute HCV is associated with a much higher response rate than treatment during the chronic phase. However, delaying therapy for 12 weeks to ascertain whether spontaneous clearance will occur does not affect treatment response rates. Treatment with PEG-IFN monotherapy has been associated with viral eradication in >90% of patients. Treatment for 24 weeks appears to be sufficient to clear HCV.

Timing of HCV treatment and HIV treatment

The decision of whether and when to treat HCV among people infected with HIV must be determined individually. When coinfecting patients require treatment for both infections, some experts begin with HIV treatment in hope that by improving CD4 counts, they may enhance the response to HCV therapy, even though CD4 cell counts by themselves are not firmly associated with an increased likelihood of a sustained virologic response. Other experts choose to treat HCV before initiating ARV therapy (ART) in those with high CD4 counts and low HIV viral loads to simplify treatment and improve the tolerability of ART. Consult with an HCV treatment expert to determine the appropriateness and timing of HCV treatment.

Some patients with HCV will experience worsening of hepatic function during ART, and liver function tests should be monitored closely. Some ARV medications are hepatotoxic and should be avoided or used cautiously; these include nevirapine, tipranavir, and high-dose ritonavir. Numerous other medications (eg, fluconazole and isoniazid) are hepatotoxic and can pose problems for people with impaired liver function.

Other Care Issues

Acute hepatitis A or hepatitis B infection in persons with chronic HCV can cause fulminant liver disease. All patients with HCV infection should be tested for immunity to hepatitis A and hepatitis B; patients who are not immune should be vaccinated.

Persons with HCV infection should be counseled to avoid exposure to hepatotoxins, including alcohol and hepatotoxic medications (eg, acetaminophen in large doses, fluconazole, and isoniazid). All patients should

be counseled to reduce the risk of transmitting HCV to others. As appropriate, patients should be advised to adopt “safer sex” approaches, avoid blood exposures (eg, from sharing razors or tattoo equipment), practice safe drug injection techniques, and avoid pregnancy.

Patient Education

- ◆ Most patients with HCV will remain asymptomatic for several years. However, ongoing injury to the liver occurs during this time and can culminate in liver failure. Patients can slow the damage by avoiding alcohol and any medications (including over-the-counter drugs and recreational drugs) that may damage the liver. Patients should contact their pharmacist or health care provider if they have questions about a specific medication or supplement.
- ◆ As with HIV, patients must avoid passing HCV to others. Instruct patients not to share toothbrushes, dental appliances, razors, sex toys, tattoo equipment, injection equipment, or personal care items that may have blood on them. Emphasize the importance of safer sex to protect themselves and their partner(s).
- ◆ Tell patients to discuss HCV with their sex partner(s), and suggest that partner(s) get tested for HCV.
- ◆ Pregnant women have a high risk of transmitting HIV or HCV infection to the baby because each virus makes it easier to transmit the other. Women who are pregnant or considering pregnancy should talk with a specialist in HIV and HCV to discuss ways to decrease the infection risk for the baby.
- ◆ HCV medications (ribavirin and interferon) should not be given during pregnancy. Both men and women who are taking ribavirin should use contraception consistently during ribavirin therapy and for 6 months after completion of treatment.
- ◆ If children were born after women were infected with HCV, consider having them tested as well. Even though their risk is low, they should be screened for HCV.
- ◆ Certain ARV drugs are more likely to cause problems with the liver because of HCV. Advise patients that if they start an ARV regimen, their liver function tests should be watched carefully to be sure that the body is able to process the medicines.
- ◆ Patients who not been vaccinated against hepatitis A need to receive 2 vaccinations 6 months apart.

Hepatitis A can cause severe illness damage, or even death, in people with HCV.

- ◆ Patients who have not been vaccinated against hepatitis B should complete the vaccine series, which requires 3 shots. If patients have been vaccinated in the past, they should have the anti-HBV titer checked to make sure that they are still protected.
- ◆ Hepatitis B can worsen liver function greatly if it is acquired in addition to HCV. Patients who are not immune to hepatitis B should use safer sex (latex barriers) to avoid exposure. Patients who use injection drugs should not share needles or injection equipment.
- ◆ Patients who use injection drugs should consider entering a treatment program. Quitting drug use will reduce the strain on the liver, protect patients from other blood-borne illnesses that can affect the liver, and help prevent transmission of HCV to others. Patients who are not ready to stop injection drug use should let their providers know so that they can try to help find a source for clean, single-use needles.
- ◆ Hepatitis C is not spread by coughing, sneezing, hugging, sharing food and water, or other casual contact.
- ◆ The HCV treatments interferon alfa and ribavirin can cause flulike symptoms, body aches, fevers, anemia, neuropathy, and depression. Most of these adverse effects are treatable with medications. Patients should contact their medical provider right away if they experience depression. Antidepressant medications that can help relieve depression, but the medications take a couple of weeks to become effective.

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Herpes Simplex, Mucocutaneous

Background

Herpes simplex virus (HSV) types 1 and 2 cause both primary and recurrent oral and genital disease. HSV usually appears as a vesicular eruption of the mucous membranes of the oral or perioral area, vulva, perianal skin, rectum, and occasionally the inguinal or buttock areas. The eruption develops into tender or painful ulcerated lesions that are frequently covered with a clear yellow crust. In some patients, however, the typical painful vesicular or ulcerative lesions may be absent. Persons with HIV disease and low CD4 counts have more frequent recurrences of HSV and more extensive ulcerations than HIV-uninfected people. Persistent HSV eruption (>1 month) is an AIDS-indicator diagnosis.

S: Subjective

The patient may complain of eruption of red, painful vesicles or ulcers (“fever blisters”) with or without an exudate in the mouth, on the genitals, or in the perianal area. The patient may complain of burning, tingling, or itching before eruption of the lesions.

The vesicles will rupture and ulcerate, generally crusting over and healing in approximately 7-14 days. The lesions may be pruritic and are often painful. As immunosuppression progresses, the lesions may recur more frequently, grow larger or coalesce, and become chronic and nonhealing.

Perform a history, asking the patient about the symptoms above, duration, associated symptoms, and history of HSV or similar symptoms.

O: Objective

Look for punctate, grouped vesicular or ulcerative lesions on an erythematous base on the mouth, anus, or external genitals, or are visible on speculum or anoscopic examination. When immunosuppression is severe, lesions may coalesce into large painful ulcerations that spread to the skin of the thighs, lips, face, or perirectal region. Recurrent lesions may start atypically, first appearing as a fissure, pustule, or abrasion.

A: Assessment

A partial differential diagnosis includes:

- ◆ Oral aphthous ulcers
- ◆ Chancroid
- ◆ Syphilis
- ◆ Cytomegalovirus
- ◆ Candidiasis
- ◆ Drug-related eruption

P: Plan

Diagnostic Evaluation

The diagnosis of HSV is usually based on the clinical appearance and symptoms, without laboratory testing.

If the diagnosis is uncertain, obtain a specimen from a freshly opened vesicle or the base of an ulcer for culture confirmation. Note that lesions that are >72 hours old or are beginning to resolve may not show HSV in culture.

Polymerase chain reaction (PCR) is also a sensitive diagnostic test for detection of herpes DNA in ulcerative lesions, but is more expensive and less widely available than viral culture.

If culture is not available, perform a Tzanck smear by staining scrapings from the base of the lesion with Giemsa or methylene blue to reveal multinucleated giant cells. Note that this test is fairly insensitive.

If cultures are negative and there is a high suspicion of HSV infection, skin may be taken from the edge of the ulcer for biopsy. Biopsy material may also be cultured.

Single serologic tests that detect HSV-1 or HSV-2 antibodies can determine whether a patient has ever been infected with herpes, and a 4-fold or greater rise in antibody titer between acute and convalescent serum specimens may diagnose primary HSV. However, only about 5% of persons with recurrences will develop a 4-fold rise in titer.

Strongly consider checking for syphilis with a rapid plasma reagin (RPR) or Venereal Disease Research Laboratory (VDRL) test in any patient who presents with genital, anal, or oral ulceration.

Treatment

Empiric treatment for suspicious lesions is often initiated in the absence of laboratory confirmation. In some instances, treatment can be started empirically and, if no response is seen within 7-10 days, laboratory studies could be undertaken.

Episodic outbreak

- ◆ Acyclovir (Zovirax) can be given 400 mg orally 3 times daily or 200 mg orally 5 times daily until ulcers heal, usually within 5-10 days. This treatment helps the healing of lesions but does not prevent recurrences. Large, extensive ulcers may need to be treated for a longer period of time.
- ◆ Famciclovir (Famvir) 500 mg orally for 5-10 days is another option but is more expensive than acyclovir.
- ◆ Valacyclovir (Valtrex) 1,000 mg orally twice daily for 5-10 days is also more expensive than acyclovir.

Adjust the dosage for renal impairment.

Severe disease

- ◆ Treat initially with intravenous acyclovir.

Acyclovir-resistant HSV

- ◆ The diagnosis of acyclovir-resistant HSV should be confirmed with culture and sensitivities. Cross-resistance to famciclovir, valacyclovir, and ganciclovir will be present as well. The usual alternative is foscarnet (40 mg/kg every 8 hours intravenously); other possibilities include topical trifluridine and topical cidofovir.

Chronic suppressive therapy

- ◆ Consider suppressive therapy with acyclovir (400-800 mg orally 2-3 times daily), famciclovir (500 mg orally twice daily), or valacyclovir (500 mg orally twice daily) for patients with frequent or severe recurrences. Treatment should be continued indefinitely. Note that suppressive therapy also reduces the risk of transmission of HSV.

HSV during Pregnancy

Acyclovir appears to be safe and effective for use by pregnant women. Few data are available on valacyclovir and famciclovir during pregnancy.

It is important to avoid peripartum transmission of HSV. For women with recurrent or new genital HSV late in pregnancy, obstetric and/or infectious disease specialists should be consulted. All women should be evaluated carefully for symptoms or signs of genital HSV.

Patient Education

- ◆ Patients should be told that HSV has no cure, and outbreaks may occur at intervals for the rest of their lives.
- ◆ HSV is easily spread through kissing (if mouth or lips are infected) and sexual contact (oral, anal, or vaginal). HSV is often transmitted when no lesions are present, so it is important that patients inform their sex partners of their herpes infection before sex. Patients must avoid all sexual contact while lesions are visible, because a lot of virus is present at those times. Condom use at each sexual encounter offers the best chance of preventing HSV transmission. If HSV is transmitted, sexual partners also will have it for life.
- ◆ Instruct patients to avoid use of occlusive dressings or ointments, which can prevent healing of sores.
- ◆ Treatment is most effective when taken early in the outbreak, so patients not taking suppressive therapy should keep medication on hand and start treatment at the first signs of eruption.
- ◆ Genital HSV in a pregnant woman around the time of delivery can cause severe illness in the newborn. Women must inform their obstetricians and pediatricians if they have a history of HSV or are exposed to or infected with HSV during pregnancy. Pregnant women who do not have HSV should avoid having sex with partners who have HSV, and men who have HSV should avoid having sex with pregnant women who do not have HSV.

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Herpes Zoster/Shingles

Background

Shingles is a skin or mucosal infection caused by the varicella-zoster virus (VZV) that occurs along a dermatome and represents a reactivation of varicella (chickenpox). Zoster is common in patients with HIV infection, including apparently healthy individuals before the onset of other HIV-related symptoms. The incidence may be higher at low CD4 cell counts and also within 4 months of initiating effective antiretroviral therapy.

Zoster may be particularly painful or necrotic in HIV-infected individuals. Disseminated infection, defined as outbreaks with >20 vesicles outside the primary and immediately adjacent dermatomes, usually involves the skin and the visceral organs. Neurologic complications of zoster include encephalitis, transverse myelitis, and vasculitic stroke.

S: Subjective

The patient complains of painful skin blisters or ulcerations along 1 side of the face or body. Loss of vision may accompany the appearance of facial lesions. Pain in a dermatomal distribution may precede the appearance of lesions by many days (prodrome).

Assess the following during the history:

- ◆ Duration of pain or blisters (average of 2-3 weeks if untreated)
- ◆ Location of pain or blisters; severity of pain
- ◆ History of chickenpox (usually in childhood)

O: Objective

Perform a skin and neurologic examination to include the following:

- ◆ Vesicular lesions with erythematous bases in a dermatomal distribution; may be bullous or hemorrhagic
- ◆ Necrotic lesions; may persist for as long as 6 weeks
- ◆ Dermatomal scarring (particularly in dark-skinned individuals)

- ◆ Lesions in the eye area or tip of nose, along the trigeminal nerve represent ophthalmic nerve involvement, which requires immediate evaluation and intravenous treatment (see below)

A: Assessment

- ◆ Rule out other causes of vesicular skin eruptions (eg, herpes simplex virus, severe drug reactions).
- ◆ Assess contact exposures (see below).

P: Plan

Diagnostic Evaluation

The diagnosis is usually clinical and is based on the characteristic appearance and distribution of lesions. If the diagnosis is uncertain, perform viral cultures or antigen detection by direct fluorescent antibody from a freshly opened vesicle or biopsy from the border of a lesion.

Treatment

- ◆ Treatment ideally should begin within 72 hours of an outbreak or while new lesions are appearing. Famciclovir (Famvir) 500 mg orally 3 times per day for 7-10 days or valacyclovir (Valtrex) 1 g orally every 8 hours for 7 days is the preferred regimen and may attenuate a herpes/VZV attack if started early.
- ◆ An alternative treatment is acyclovir 800 mg orally 5 times per day.
- ◆ Dosage reductions of these drugs are required for patients with renal impairment.
- ◆ If new blisters are still appearing at the end of treatment, repeat course of oral therapy or consider intravenous treatment. Adjunctive corticosteroids aimed at preventing postherpetic neuralgia are not recommended.
- ◆ Consult an ophthalmologist immediately if lesions appear in the eye area or on the tip of the nose, or if patient complains of visual disturbances, because VZV-related retinal necrosis can cause blindness. Because of the rapid progression associated with this diagnosis, hospitalization for intravenous acyclovir and possibly foscarnet is recommended.

- ◆ VZV from zoster lesions is contagious, and contact or airborne spread from vesicle fluid may cause chickenpox in nonimmune people. If a zoster patient's household includes a pregnant woman (HIV infected or uninfected) or an HIV-infected child, consult with a specialist immediately for advice on management of exposed household members. (See "Postcontact Chickenpox Prevention" below.)
- ◆ Give analgesics for pain; narcotics may be required.
- ◆ Antiviral therapy may reduce the risk of postherpetic neuralgia, but if it does occur, special pain control techniques will be required:
 - ◆ Nortriptyline 10-20 mg should be taken every night at bedtime and increased until pain is controlled and adverse effects remain tolerable. Other tricyclics may be used.
 - ◆ Lidocaine 5% patches provide good local relief with minimal systemic absorption. Up to 3 patches may be applied simultaneously to the affected area for up to 12 hours in a 24-hour period.
 - ◆ Gabapentin is given at 100-300 mg orally 3 times per day; this may be increased until reaching 3,600-mg total daily dosage.
 - ◆ Sustained-release opiates may be required.

(See chapter *Pain Syndrome and Peripheral Neuropathy* for more options and specific recommendations.)

Severe or unresponsive cases

- ◆ Intravenous acyclovir may be indicated if:
 - ◆ The patient is severely immunocompromised
 - ◆ The ophthalmic branch of the trigeminal nerve is affected (as noted above)
 - ◆ Dissemination has occurred
 - ◆ Lesions are not responsive to oral therapy
 - ◆ Pain is intractable
- ◆ The usual adult dosage is 10-12 mg/kg every 8 hours for 7-14 days; dosage reduction is required for patients with renal impairment. Refer to an infectious disease specialist.
- ◆ Acyclovir resistance may occur in patients previously treated with acyclovir or related drugs, and foscarnet may be required for effective treatment. Resistance should be suspected if lesions are not resolving after 10 days of therapy or if they develop a verrucous appearance. Such lesions should be cultured and drug sensitivities should be obtained.

Postcontact Chickenpox Prevention

All persons, including pregnant women, who have close contact with a patient who has chickenpox or shingles must be treated to prevent chickenpox. Those who have no history of chickenpox or shingles or no detectable antibody against VZV should be administered varicella zoster immune globulin as soon as possible, but at least within 96 hours after contact. Even immunocompetent adults with primary VZV (chickenpox) can develop viral dissemination to the visceral organs. HIV-infected patients may develop encephalitis, pneumonia, or polyradiculopathy during primary zoster (chickenpox) or reactivated zoster (shingles).

Patient Education

- ◆ Patients should bathe the skin lesions in mild soap and water. For necrotic lesions, patients should use warm, moist compresses 2-3 times a day to remove debris.
- ◆ Antibiotic ointments may help prevent secondary infection and keep dressings from sticking.
- ◆ Advise patients to take their medications as directed, and to call the clinic if symptoms worsen.

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Histoplasmosis

Background

Histoplasmosis is caused by *Histoplasma capsulatum*, a fungus that thrives in soil contaminated by certain bird and bat droppings. In the United States, *H capsulatum* is found most often along the Ohio and Mississippi river valleys, and in the central, mid-Atlantic and south-central states, from Alabama to southwest Texas. In highly prevalent areas, such as Indianapolis and Kansas City, more than 80% of the population has been exposed to *Histoplasma* through inhalation of airborne infectious elements. Histoplasmosis is also found in the Canadian provinces of Quebec and Ontario, Mexico, Central and South America, Africa, East Asia, and Australia.

The initial infection usually causes no symptoms or only in mild flulike illness. However, immunosuppressed individuals may develop disseminated disease. Progressive disseminated histoplasmosis often represents a reactivation of latent infection, occurs late in the course of HIV disease (the CD4 count usually is <150 cells/ μ L), and is an AIDS-defining illness. Pulmonary histoplasmosis (without dissemination) may occur in people with higher CD4 counts. Within endemic areas, histoplasmosis accounts for 5% of opportunistic infections among AIDS patients. In hyperendemic areas, the prevalence of histoplasmosis may reach 25% among patients with AIDS. The incidence of histoplasmosis in the United States has declined with the use of effective antiretroviral therapy (ART).

Table 1 describes common clinical features that may be associated with histoplasmosis.

S: Subjective

Histoplasmosis may be difficult to diagnose because the symptoms are nonspecific. In addition, clinicians may not suspect this diagnosis in low-prevalence areas.

The patient complains of fever, weight loss, fatigue, cough, and shortness of breath. He or she may also note skin lesions, adenopathy, central nervous system (CNS) changes, oropharyngeal ulcers, nausea, diarrhea, or abdominal pain. Symptoms usually begin several weeks before presentation. On occasion, histoplasmosis presents abruptly as a sepsis-like syndrome.

The following activities are associated with significant risk of exposure (note that absence of reported exposures does not rule out histoplasmosis):

- ◆ Residence or travel in endemic areas (or coastal AIDS centers of New York, Los Angeles, San Francisco, and Miami)
- ◆ Occupational history of farming or construction/remodeling
- ◆ Hobbies that involve contact with caves, bird roosts or nests, or farm areas
- ◆ Contact with soil with a high organic content and undisturbed bird droppings, such as around old chicken coops and bird roosts

Table 1. Common Clinical Manifestations of Histoplasmosis

Symptom Group	% Cases	Examples
Constitutional	95%	• Weight loss • Fever
Gastrointestinal	>10%	• Splenomegaly • Hepatomegaly • Diarrhea • Abdominal pain
Respiratory	50-60%	• Pneumonia • Pneumonitis
Hematologic	>50%	• Anemia • Leukopenia • Thrombocytopenia
Neurologic	15-20%	• Meningitis, cerebritis • Encephalopathy • Focal parenchymal lesions
Septic	10-20%	• Hypotension • Respiratory insufficiency • Renal or hepatic failure • Disseminated intravascular coagulopathy • High fever
Dermatologic	<10%	• Follicular, pustular, maculopapular, or erythematous lesions

O: Objective

Measure vital signs and document fever. Perform a complete physical examination, with special attention to the lymph nodes, lungs, abdomen, skin, and neurologic system. Common findings include enlargement of the liver, spleen, and lymph nodes. Skin lesions and oropharyngeal ulcers may be seen.

A: Assessment

A partial differential diagnosis includes:

- ◆ Other deep-seated fungal infections, such as cryptococcosis and coccidioidomycosis
- ◆ Mycobacterial disease (*Mycobacterium tuberculosis* or *Mycobacterium avium* complex)
- ◆ Pneumocystic pneumonia
- ◆ Lymphoma

P: Plan

Diagnostic Evaluation

- ◆ The *H capsulatum* polysaccharide antigen test is sensitive and specific. The test is most sensitive for urine samples, but can be used on serum, bronchial fluids, or cerebrospinal fluid specimens. Results may be obtained in a few days. Urine antigen levels can be used to monitor the response to therapy. The antigen test is available from a private laboratory, MiraVista Diagnostics (<http://www.miravistalabs.com>).
- ◆ Cultures of blood, bone marrow, and specimens from other sources have reasonable sensitivity but may take several weeks. Wright stain of buffy coat of blood may reveal intracellular organisms.
- ◆ Biopsies of lymph nodes, liver, cutaneous lesions, and lungs may be diagnostic in up to 50% of cases; bone marrow can be stained with methenamine silver to show the organism within macrophages.
- ◆ Lactate dehydrogenase (LDH) and ferritin, although not specific, may be markedly elevated in disseminated disease.
- ◆ Complete blood count and chemistry panels may show pancytopenia, elevated creatinine, or abnormal liver function tests.

Treatment

Treatment consists of 2 phases: induction and chronic maintenance.

Induction therapy

Mild to moderate disseminated histoplasmosis without CNS involvement

Administer itraconazole 200 mg orally 3 times daily or 300 mg orally twice daily for 3 days, followed by itraconazole 200 mg twice daily for 12 weeks. (See “Treatment note” below regarding itraconazole.) Induction therapy must be followed by maintenance therapy (see below).

Severe disseminated histoplasmosis

Severe infection requires intravenous induction therapy with amphotericin B 0.7-1.0 mg/kg/d (or a lipid formulation 3-5 mg/kg/d). After 3-10 days of therapy and stabilization of the patient’s clinical status, therapy may be switched to itraconazole 200 mg twice daily to complete 12 weeks of therapy. If itraconazole is not available or is not tolerated, fluconazole 800 mg orally once daily can be used as an alternative. (See “Treatment note” below regarding itraconazole and fluconazole.) CNS infection must be treated with a full course of amphotericin B, because of poor penetration of itraconazole into the CNS. Induction therapy must be followed by maintenance therapy (see below).

Maintenance/suppressive therapy

Lifelong maintenance therapy must be given to prevent relapse after the 12-week course of induction therapy and typically includes itraconazole 200 mg orally once daily or twice daily. Amphotericin B 50 mg once weekly or fluconazole 400-800 mg daily are alternatives for those who cannot tolerate or cannot obtain itraconazole. (See “Treatment note” below regarding itraconazole and fluconazole.)

It is not known whether maintenance therapy can be discontinued safely in patients who achieve immune reconstitution during antiretroviral therapy.

Treatment note

Itraconazole and fluconazole may cause fetal abnormalities if taken during the first trimester of pregnancy. Check pregnancy status in women of childbearing potential before starting these medications, and ensure that women are using appropriate birth control. Note the possibility of drug interactions involving itraconazole, especially with rifamycins.

Patient Education

- ◆ Histoplasmosis is not transmitted from person to person, so isolation is not necessary.
- ◆ Patients should take all of their medications exactly as prescribed by their health care providers.
- ◆ Even with maintenance therapy, relapses can occur. Patients should call their providers immediately if symptoms worsen.
- ◆ Itraconazole and fluconazole may cause birth defects. Women who are taking either of these medicines should avoid pregnancy. In addition, itraconazole interacts with some other medications; patients should tell their providers if they begin any other new medicines while taking itraconazole.

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Kaposi Sarcoma

Background

Kaposi sarcoma (KS) is an endothelial neoplasm that usually occurs as skin or oral lesions but may involve the internal organs. It is the most common AIDS-associated neoplasm and is an AIDS-defining disease. AIDS-associated KS is 1 of 4 types of KS, along with classic, endemic, and organ transplant-associated KS. Although the types vary in epidemiology and clinical presentation, all are associated with human herpesvirus type 8 (HHV-8), also known as KS-associated herpesvirus. The clinical manifestations of AIDS-associated KS (sometimes called epidemic KS) range in severity from mild to life threatening. The progression of disease may be rapid or slow, but the overall prognosis is poor in the absence of treatment. The skin lesions of KS, even when they do not cause medical morbidity, may cause significant disfigurement and emotional distress.

AIDS-associated KS usually occurs in HIV-infected persons with advanced immunosuppression (CD4 count <200 cells/ μ L), but may occur at any CD4 count. In the United States and Europe, KS occurs in all HIV risk groups, but most frequently in men who have sex with men (MSM). Risk factors in MSM include multiple sexual partners and a history of sexually transmitted infections (STIs); risk factors in other groups have not been clearly identified. The transmission of HHV-8 is not well understood. Although experts believe HHV-8 is transmitted sexually, it apparently also passes from person to person by other routes.

The incidence of KS in resource-abundant countries has declined markedly since the early 1990s, in part because of the widespread availability of effective combination antiretroviral therapy (ART). In parts of sub-Saharan Africa, where endemic KS has long existed in people with normal immune function, the incidence of KS has risen sharply in people with HIV/AIDS. ART appears to be effective in reducing the risk of AIDS-associated KS, particularly when initiated before the development of advanced immunosuppression.

S: Subjective

The cutaneous presentation of KS is the most common, occurring in 95% of cases. The patient may complain of a new painless pigmented (often purplish) lesion or lesions on the skin (usually of the extremities, face, or torso), or in the mouth. Lesions on the lower extremities, genitals, or face may be accompanied by swelling and pain. The patient may complain only of swelling or edema, without skin lesions, or may note enlarged lymph nodes. Oral lesions, if extensive, may cause tooth loss, pain, and ulceration.

Pulmonary KS may cause intractable cough, bronchospasm, hemoptysis, chest pain, and dyspnea.

Gastrointestinal KS may cause no symptoms, or the patient may have bleeding, pain, and symptoms of bowel obstruction.

During the history, ask about the symptoms noted above and associated characteristics, including the following:

- ◆ Duration of lesion(s)
- ◆ Pain
- ◆ Frequency of new lesions
- ◆ Respiratory or gastrointestinal symptoms
- ◆ Edema or swelling
- ◆ Recent CD4 cell counts.

O: Objective

Physical Examination

Perform a careful physical examination, with particular attention to the following:

- ◆ Vital signs
- ◆ Skin (examine the entire skin surface)
- ◆ Oropharynx
- ◆ Extremities and external genitals (look for lesions, edema)
- ◆ Lymph nodes

Examine the lungs, abdomen, rectum, and other systems as indicated.

Common Manifestations

Skin lesions

Skin lesions may occur anywhere on the skin. Common sites include the face (under the eyes and on the tip of the nose), behind the ears, and on the extremities and torso. Lesions may be macules, papules, plaques, or nodules. At first, the lesions are small and may be flat. Their color may vary from pink or red to purple or brown-black (the latter particularly in dark-skinned individuals), and they are nonblanching, nonpruritic, and painless. Over time, the lesions often increase in size and number, darken, and rise from the surface; they may progress to tumor plaques (eg, on the thighs or soles of the feet), or to exophytic tumor masses, which can cause bleeding, necrosis, or extreme pain.

Oral lesions

Oral lesions may be flat or nodular and are red or purplish. They usually appear on the hard palate, but may develop on the soft palate, gums, tongue, or elsewhere.

Lymphedema

Lymphedema associated with KS usually appears in patients with visible cutaneous lesions, and edema may be out of proportion to the extent of visible lesions. Lymphedema may also occur in patients with no visible skin lesions. Common sites include the face, neck, external genitals, and lower extremities. Usually, a contiguous area of skin is also involved. Lymph nodes may be enlarged.

Pulmonary KS

Pulmonary KS usually causes severe, pneumonia-like symptoms and is rapidly progressive. The patient may exhibit difficulty breathing, bronchospasm, cough (sometimes with hemoptysis), and hypoxemia. The chest x-ray typically shows diffuse interstitial infiltrates, often accompanied by nodules or pleural effusion.

Gastrointestinal KS

Gastrointestinal KS may arise anywhere in the gastrointestinal tract. Patients are usually asymptomatic except in cases of intestinal obstruction or bleeding. KS may also cause protein-losing enteropathy. Visceral disease is uncommon in the absence of extensive cutaneous disease.

A: Assessment

The partial differential diagnosis depends on the type of symptoms present.

For cutaneous, oral, and lymph node presentations, consider the following:

- ◆ Bacillary angiomatosis
- ◆ Lymphoma
- ◆ Dermatofibromas
- ◆ Bacterial or fungal skin infections
- ◆ Stasis

For pulmonary symptoms, consider:

- ◆ *Pneumocystis jiroveci* pneumonia (PCP)
- ◆ Cytomegalovirus (CMV) pneumonia
- ◆ Pulmonary lymphoma (rare)

P: Plan

Diagnostic Evaluation

For cutaneous or oral KS, a presumptive diagnosis can often be made by the appearance of skin or mucous membrane lesions. Biopsy of a lesion (or a suspect lymph node) is recommended to verify the diagnosis and rule out infectious or other neoplastic causes. Biopsy is particularly important if the lesions are unusual in appearance or if the patient has systemic or atypical symptoms.

If respiratory symptoms are present, obtain chest x-rays or computed tomography (CT) studies. Radiographic findings may be suggestive of KS, but cannot provide a definitive diagnosis. Bronchoscopy with visualization of characteristic endobronchial lesions is usually adequate for diagnosis.

For patients with gastrointestinal symptoms and suspected KS, perform endoscopy.

Review recent CD4 cell counts. The CD4 count is typically low (<200 cells/ μ L) but KS can occur with any CD4 count.

If the patient has fever or respiratory, gastrointestinal, or constitutional symptoms, evaluate for other infectious and malignant causes (eg, by culture or biopsy) as suggested by the history and physical examination.

Treatment

Treatment of KS is not considered curative, and no single therapy is completely efficacious. ART is a key component of the treatment of KS and should be initiated (or maximized) in all persons with KS, unless contraindicated (for further information, see chapter *Antiretroviral Therapy*). KS often regresses and sometimes resolves in patients treated with effective ART. Other treatment modalities may be used concurrently, depending on the severity of KS and the speed of progression. Consult with a KS-experienced oncologist or dermatologist.

Specific treatment of KS depends on various factors such as the number, extent, severity, and location of lesions; cosmetic considerations; and presence of visceral involvement. The goals of therapy may also vary according to the clinical presentation and may include controlling symptoms, improving cosmetic appearance, reducing edema, eliminating pain, and clearing lesions.

Local treatment (preferably in conjunction with ART) is usually given to patients who have a few small lesions causing only minor symptoms. Systemic therapy (in conjunction with ART) is needed for more extensive or more severe disease, including symptomatic visceral disease, widespread skin involvement, significant edema, and rapidly progressive KS.

Local treatment of limited disease

Options for local treatment of limited disease include the following:

- ◆ ART followed by observation for response (limited, stable cutaneous disease may require no specific treatment)
- ◆ Topical treatment with alitretinoin gel (Panretin) 0.1%
- ◆ Intralesional chemotherapy (eg, vinblastine)
- ◆ Radiation therapy, for localized or facial lesions (may cause mucositis when used for oropharyngeal lesions)
- ◆ Cryotherapy
- ◆ Laser therapy

Treatment of extensive or rapidly progressing disease

Extensive or rapidly progressing disease may include lymphedema, intraoral or pharyngeal disease that interferes with eating, pulmonary KS, and painful or bulky lesions. Options for treatment include:

- ◆ Intralesional chemotherapy (eg, vinblastine)
- ◆ Systemic chemotherapy (eg, liposomal formulations of doxorubicin or daunorubicin, vincristine, paclitaxel [Taxol], etoposide [VP16], or bleomycin; these agents can be used alone or in combination for visceral or extensive cutaneous disease)
- ◆ Interferon- α

Patient Education

- ◆ KS often responds to treatment. Educate patients that ART is a cornerstone of treatment; encourage them to start and adhere to ART.
- ◆ Swollen or edematous lesions increase the risk of cellulitis, whereupon lesions can become infected and progress rapidly. Advise patients to avoid injuring swollen or edematous lesions, to keep them clean, and to call their health care provider if lesions appear to be spreading or if swelling worsens.
- ◆ Advise patients to return to the clinic if respiratory or gastrointestinal symptoms develop.
- ◆ Patients may use cosmetic preparations to cover facial lesions. Refer patients to support groups or counseling services if they are having difficulty coping with their physical appearance.

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Molluscum Contagiosum

Background

Molluscum contagiosum is a benign viral infection of the skin, caused by a double-stranded DNA virus of the Poxviridae family. Transmission occurs by direct bodily contact (eg, through sexual activity), fomites (eg, underwear), or self-inoculation. The incubation period is 14-50 days. The infection is most common in children, sexually active adults, and immunocompromised persons and occurs in 5-18% of HIV-infected patients. In immunocompetent persons, the infection usually lasts 6 to 12 months, although genital lesions in HIV uninfected adults may persist longer. Persons with HIV infection may have extensive lesions and a strong correlation exists between the degree of immunosuppression and the risk of molluscum, the number of lesions, and their resistance to treatment.

S: Subjective

The patient complains of new or increased papular lesions on the face, upper trunk, or genitals. Papules of molluscum contagiosum may cause no symptoms or can be pruritic or tender to the touch. Genital lesions are transmitted sexually; the patient may recall seeing such lesions on the genitals of a previous partner. Ask about fever or other systemic symptoms.

O: Objective

Perform a thorough evaluation of the skin, the genitals, and the mouth. Molluscum lesions are white, pink, or flesh-colored; smooth-surfaced, firm, pearly, and spherical (dome-shaped) papules (2-5 mm) or nodules (6-10 mm), with umbilicated centers. Lesions are usually found on the head or neck and the genital area, but may affect every part of the body except the palms and soles of the feet. Molluscum may occur intraorally. Molluscum commonly presents as multiple lesions. Patients with HIV infection may develop giant lesions (>1 cm) or clusters of hundreds of small lesions.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Disseminated cryptococcosis
- ◆ Other fungal infection
- ◆ Folliculitis
- ◆ Syphilis, condyloma acuminata, vulvar syringoma for multiple small molluscum genital lesions
- ◆ Squamous or basal cell carcinoma for large, solitary genital lesions

P: Plan

Diagnostic Evaluation

The diagnosis of molluscum is usually based on the characteristic appearance of the lesions. Perform laboratory testing, if indicated, to exclude other infections or malignancies.

Treatment

Because molluscum does not cause illness and rarely causes symptoms, the goal of treatment is primarily cosmetic. Molluscum is difficult to eradicate in HIV-infected patients, and lesions often recur, particularly if immune suppression persists. Effective antiretroviral therapy may achieve resolution of lesions or significant improvement in the extent or appearance of molluscum. Refer complex cases to a dermatologist. Other therapeutic options include:

- ◆ Local excision may be done by electrocautery, evisceration, curettage, or cryotherapy. Adverse effects include pain, irritation, soreness, and mild scarring. Repeated treatments are necessary.
- ◆ Imiquimod 5% (Aldara), an immune response modifier, stimulates production of interferon-alpha and other proinflammatory cytokines, inducing a tissue reaction known to be associated with viral clearance from the skin. Apply 3 times per week for up to 16 weeks or nightly for 4 weeks. Clearing can take up to 3 months.
- ◆ Tretinoin (Retin-A) 0.1% cream can be applied to lesions twice daily. Adverse effects include drying, peeling, irritation, and soreness.

- ◆ Podophyllum resin (podophyllin) is administered by a health care provider and washed off after 1–4 hours. This treatment is caustic and may cause significant irritation, is contraindicated in pregnancy, and has limited effectiveness.
- ◆ Patient-administered podophyllotoxin (Podofilox) may be a safer alternative to podophyllum. Adverse effects include burning, pain, inflammation, erosion, and itching.
- ◆ Trichloroacetic acid is administered by a health care provider. Controlling the depth of acid penetration is difficult. Adverse effects include pain, irritation, and mild scarring are common.
- ◆ Laser therapy may be used to remove lesions.
- ◆ Cidofovir 1% to 3% topical cream, combined with a vehicle, is applied twice daily for 2 weeks, followed by a 30-day rest period and then 2 additional cycles. This treatment was effective in several small studies and case reports, but it is expensive and difficult to compound. No systemic adverse effects are noted.
- ◆ Investigational treatments include 5-aminolevulinic acid with subsequent photodynamic therapy and intravenous cidofovir.

Patient Education

- ◆ Molluscum infection is benign but may be distressing.
- ◆ Patients should avoid shaving in areas with lesions because shaving could spread the lesions to other areas.
- ◆ Molluscum infection may be transmitted both sexually and nonsexually, through direct contact with lesions. Patients should avoid close contact between their molluscum lesions and the skin, mouth, and genitals of other people. Latex condoms may not prevent transmission.

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Mycobacterium avium Complex

Background

Mycobacterium avium complex (MAC) is an opportunistic infection caused by species of *Mycobacterium* that can cause severe illness in people with advanced AIDS but rarely affects others. The risk of disseminated MAC (DMAC) is directly related to the severity of immunosuppression. DMAC typically occurs in persons with CD4 counts of <50 cells/ μ L, and its frequency increases as the CD4 count declines. In the absence of antibiotic prophylaxis, DMAC occurs in up to 40% of AIDS patients with CD4 counts of <50 cells/ μ L. Antimicrobial therapy, especially if given in conjunction with antiretroviral therapy (ART) that achieves immune reconstitution, can be successful in treating MAC disease. Specific antimicrobial prophylaxis and effective ART may also be used to prevent MAC in patients with advanced AIDS (see chapter *Preventing Exposure to Opportunistic and Other Infections*).

Mycobacterium organisms are common in the environment. They are found worldwide and have been isolated from soil, water, animals, birds, and foods. They usually enter the body through the respiratory or gastrointestinal tract and disseminate to cause multisystem infection, typically manifested by nonspecific symptoms and signs such as fever, sweats, weight loss, abdominal pain, fatigue, chronic diarrhea, and anemia and other cytopenias. MAC can also cause local disease such as central nervous system infection, soft-tissue or bone infections, or endocarditis. In patients with subclinical or incompletely treated MAC who have recently started ART, an immune reconstitution inflammatory syndrome may occur with localized lymphadenitis or paradoxically worsening symptoms may (see chapter *Immune Reconstitution Syndrome*).

S: Subjective

The patient complains of 1 or more of the following symptoms:

- ◆ Persistent or cyclic fever
- ◆ Night sweats
- ◆ Unintentional weight loss

- ◆ Anorexia
- ◆ Chronic diarrhea
- ◆ Weakness
- ◆ Fatigue
- ◆ Abdominal pain

During the history, ask about the following:

- ◆ Any symptoms as above, including duration and intensity. Ask about other symptoms of infection.
- ◆ Whether the patient is taking MAC prophylaxis or ART

O: Objective

Perform a full physical examination with particular attention to the following:

- ◆ Vital signs (temperature, heart rate, blood pressure, respiratory rate)
- ◆ Weight (compare with previous measurements)
- ◆ General appearance (cachexia, wasting, signs of chronic illness, jaundice, pallor)
- ◆ Lymph nodes (lymphadenopathy)
- ◆ Abdomen (hepatosplenomegaly, tenderness)

Review previous laboratory values, particularly the CD4 cell count (usually <50 cells/ μ L).

A: Assessment

Rule out other infectious or neoplastic causes of constitutional symptoms, anemia, or organomegaly. A partial differential diagnosis would include the following:

- ◆ *Mycobacterium tuberculosis*
- ◆ Cytomegalovirus
- ◆ Lymphoma
- ◆ *Bartonella*
- ◆ Disseminated fungal infection
- ◆ Pyogenic abscess
- ◆ Other septicemia

P: Plan

Diagnostic Evaluation

A definitive diagnosis requires isolation of MAC from the blood or other normally sterile body fluids or tissues (*M avium* cultured from sputum, bronchial washing, or stool may represent colonization rather than infection). Send blood for acid-fast bacilli (AFB) culture (2-3 samples drawn at different times will increase sensitivity).

Because MAC may take weeks to grow in culture, ancillary studies should be performed. These are not specific, but may be helpful in reaching a presumptive diagnosis:

- ◆ Complete blood count (CBC) for anemia, lymphopenia, thrombocytopenia
- ◆ Serum alkaline phosphatase (often elevated in DMAC)
- ◆ Computed tomography (CT) scan of the chest and abdomen (intra-abdominal and mediastinal lymphadenopathy or hepatosplenomegaly are often present)

If blood cultures are negative and MAC is suspected, consider biopsy of the lymph nodes, bone marrow, liver, or bowel (via endoscopy) to detect DMAC by microscopic examination for AFB and culture. If the evidence suggests pulmonary MAC, consider bronchoscopy and bronchoalveolar lavage.

Perform additional studies as indicated to rule out other causes of the patient's symptoms, including bacterial blood cultures, sputum for *M tuberculosis*, *Bartonella* studies, lymph node cytology for lymphoma, and stool cultures.

Treatment

Because antimicrobial resistance develops quickly with single-drug therapy, multidrug regimens must be administered for DMAC.

The U.S. Centers for Disease Control and prevention recommends the following 2-drug regimens:

- ◆ Clarithromycin 500 mg twice daily + ethambutol 15 mg/kg once daily,
- ◆ Azithromycin 500-600 mg once daily + ethambutol 15 mg/kg once daily

Some experts recommend including a third agent for more advanced disease or for patients not taking effective ART. The addition of rifabutin (300 mg daily) has been associated with increased mycobacterial clearance, but no survival benefit. A fluoroquinolone (eg, ciprofloxacin, levofloxacin) or amikacin may be used instead of rifabutin as a third agent, or in addition to rifabutin as a fourth agent; however, studies have not confirmed the clinical benefit of these medications.

Because immune reconstitution is essential for controlling MAC, all patients not already taking ART should begin ART, if possible. Patients taking suboptimal ART should be evaluated for enhancement of their regimen. The optimal timing of ART initiation in relation to MAC treatment is unclear. Because immune reconstitution from effective ART may cause a paradoxical inflammatory response if started during active DMAC infection, some experts recommend treating DMAC for about a month before adding antiretroviral (ARV) medications (see chapter *Immune Reconstitution Syndrome*). This strategy also helps to avoid or forestall interactions between DMAC and ARV drugs and the additive toxicities of these medications.

Clarithromycin is often considered the macrolide of choice for use in combination therapy for MAC, but azithromycin is equally efficacious and may cause fewer gastrointestinal adverse effects and drug interactions. In particular, clarithromycin should not be combined with efavirenz because the interaction will result in decreased efavirenz drug concentrations.

Rifabutin has significant interactions with many drugs, including ARV medications and therefore dosage adjustments or alternative agents may be needed (Table 1).

Table 1. Interactions between Rifabutin and Antiretroviral Medications: Contraindicated Combinations and Dosage Adjustments

Antiretroviral Agent	Management When Used with Rifabutin
Nonnucleoside Reverse Transcriptase Inhibitors	
Efavirenz	Use standard efavirenz dosage; increase rifabutin to 450-600 mg daily.
Nevirapine	Use standard dosage of nevirapine; give rifabutin at 300 mg daily or 3 times weekly.
Delavirdine	Do not combine.
Ritonavir-Boosted Protease Inhibitors	
Lopinavir/Ritonavir (Kaletra)	Give standard dosage of lopinavir/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly.
All Other Ritonavir-Boosted PIs	Give standard dosage of PI/ritonavir; decrease rifabutin to 150 mg on alternate days or 3 times weekly.
Unboosted Protease Inhibitors	
Ritonavir	Use ritonavir at standard dosage; give rifabutin at 150 mg on alternate days or 3 times weekly.
Amprenavir, Fosamprenavir	Use PIs at standard dosages; give rifabutin at 150 mg/day or 300 mg 3 times weekly.
Atazanavir	Give atazanavir at standard dosage; give rifabutin at 150 mg on alternate days or 3 times weekly.
Indinavir	Increase indinavir to 1,000 mg every 8 hours; give rifabutin at 150 mg/day or 300 mg 3 times weekly.
Nelfinavir	Increase nelfinavir to 1,000 mg every 8 hours; give rifabutin at 150 mg/day or 300 mg 3 times weekly.
Ritonavir	Give ritonavir at standard dosage; give rifabutin at 150 mg on alternate days or 3 times weekly.

Source: HIV InSite. Database of Antiretroviral Drug Interactions. San Francisco: UCSF Center for HIV Information. Available online at <http://hivinsite.ucsf.edu/arvdb?page=ar-00-02>. Accessed April 26, 2006.

The patient should show clinical improvement within the first weeks of treatment. If the patient is not responding to treatment after 2-4 weeks of therapy, assess adherence, consider adding 1 or more drugs, and consider evaluation for other or additional causes of the patient's symptoms. Consider repeating a blood culture with antimicrobial sensitivities in patients whose clinical status has not improved after 4-8 weeks of treatment. If immune reconstitution inflammatory reactions are suspected, consider adding anti-inflammatory medications (see chapter *Immune Reconstitution Syndrome*).

Treatment of MAC is generally required for the remainder of the patient's life, although it may be reasonable to discontinue MAC therapy if patients complete at least 12 months of MAC treatment, have no further symptoms, and demonstrate immune restoration in response to ART (an increase in CD4 counts to >100 cells/ μ L for at least 6 months). If MAC treatment is discontinued, the patient must be monitored carefully for any decrease in CD4 cell count or recurrence of MAC symptoms. Some clinicians verify negative AFB cultures before discontinuing therapy. Treatment should be resumed if the CD4 count drops to <100 cells/ μ L or if symptoms recur.

Patient Education

- ◆ Advise patients that antimycobacterial therapy alone will not eradicate MAC infection, but should decrease symptoms and improve quality of life. A response to treatment may take up to 4 weeks. If medications are discontinued, the disease almost always recurs, unless the CD4 count has increased to >50-100 cells/ μ L in response to ART.
- ◆ Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, *Mycobacterium* can develop resistance to the medications. If patients are having trouble taking the medications on schedule, they should contact their health care providers immediately.
- ◆ Educate patients about the benefits of ART in strengthening the immune system and preventing opportunistic infections such as DMAC.
- ◆ Urge patients to contact the clinic immediately if they notice worsening symptoms, or new symptoms.
- ◆ DMAC is an opportunistic infection of late-stage HIV and indicates profound immune suppression. Some patients may not respond to MAC treatment or to ART. Because this is a life-threatening disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate this discussion.

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Mycobacterium tuberculosis: Treatment in the United States and Other High-Income Nations

Background

Tuberculosis (TB) is an infection caused by organisms in the family *Mycobacteria*. These organisms grow slowly and can be identified only with special staining techniques, a trait that led to the name “acid-fast bacteria.” Organisms in the *Mycobacterium tuberculosis* (MTB) group cause human disease, usually a chronic pneumonia. The destruction of MTB may produce holes or cavities in the lung containing huge numbers of organisms. MTB can also cause disease in other individual organs (eg, lymph nodes, meninges, bone, pericardium, peritoneum, intestines, urogenital tract) and can disseminate to multiple organs, often including the lungs, blood, liver, and spleen.

TB is almost always transmitted by persons with active pulmonary TB who release large numbers of organisms in their sputum. The organisms remain suspended in the air for hours or days, making TB one of the most easily transmitted respiratory pathogens. Most immunologically healthy persons who are infected with MTB do not develop active TB but remain infected with inactive organisms (latent TB infection); only about 10% of infected persons develop active disease during their lifetimes. Persons with HIV infection have much higher rates of active TB and develop active disease at a rate approximating 10% per year.

Before the development of effective treatment, half of all persons with TB disease died within about 5 years; others recovered but were prone to relapse. Appropriate application of modern chemotherapy to drug-susceptible MTB disease cured at least 95% of persons in the pre-HIV era.

HIV and TB cause more deaths than any other infectious diseases worldwide, each claiming millions of lives annually. A biologic synergy exists between these infections: HIV-induced immunosuppression increases susceptibility to TB infection, and active TB infection enhances HIV replication through immunologic stimulation. The populations infected by these 2 pathogens overlap in many respects, creating epidemiologic synergy. Poverty, crowded living conditions, and inadequate efforts to reduce transmission combine to enhance the transmission of both organisms.

In the United States, most cases of TB occur among immigrants, and TB is a relatively infrequent AIDS-defining illness. Nevertheless, TB remains important to HIV clinicians in the United States because it is highly infectious yet curable with proper treatment and because improper treatment leads to drug resistance both in the original patient and in those to whom that patient transmits. Although other conditions (eg, malnutrition, diabetes, end-stage renal disease, pulmonary silicosis, iatrogenic immunosuppression) increase the risk of TB disease, HIV is by far the most important risk factor.

Classic pulmonary TB, with upper-lobe infiltrates and cavitory lesions, may occur in HIV-infected persons with relatively intact immunity. As the CD4 cell count decreases, TB is more likely to manifest atypically in the chest (without cavitory disease, or with lower-lobe disease, adenopathy, pleural effusions, or interstitial or miliary infiltrates), as extrapulmonary disease (particularly in lymph nodes, as meningitis, and as disseminated infection), or both. Bone, joint, and urogenital sites of TB are less commonly associated with HIV-induced immunosuppression. Symptoms and signs of TB in HIV-infected person therefore can vary widely.

Improper or erratic treatment may cause resistance to TB medications. MTB resistance to a single drug may complicate treatment, but usually does not prevent successful treatment. Resistance to several drugs (polydrug resistance) requires a longer course of therapy using medications that are less potent and cause more adverse effects, and markedly reduces the chance of cure. Resistance to both isoniazid and rifampin is called multidrug resistance (MDR) and makes treatment especially difficult. It is extremely important to try to avoid the development of drug resistance, especially MDR. Treatment of drug-resistant TB should be managed by experts or in consultation with experts.

S: Subjective

Persons with TB generally describe an illness lasting several weeks to months, associated with systemic features such as high fever, night sweats, loss of appetite, and weight loss. These symptoms may be nonspecific, but should raise the possibility of TB.

- ◆ Pulmonary TB causes a chronic productive cough, sometimes with hemoptysis; shortness of breath occurs late in the disease.
- ◆ TB adenitis causes enlargement of the lymph nodes (usually asymmetric involvement in 1 region) which may suppurate and drain but usually are not painful, hot, or erythematous.
- ◆ TB meningitis causes headache, gradual change in mental status, and sometimes cranial nerve abnormalities such as double vision or decreased hearing.
- ◆ Disseminated TB may occur with only systemic manifestations such as fever, sweats, and weight loss, with no localizing features.

Risks for TB include known previous contact with an active case, previous positive result of a tuberculin skin test (TST, also known as a purified protein derivative test [PPD]), exposure in congregate settings (such as homeless shelters and prisons, but also health care facilities), or travel or residence in countries with high rates of endemic TB. In the United States, persons with active or past substance use disorders and persons of color are more likely than others to have had TB exposure.

O: Objective

- ◆ Measure vital signs, including oxygen saturation.
- ◆ Measure weight; compare with previous values.
- ◆ Perform thorough physical examination with particular attention to the lungs, heart, abdomen, lymph nodes, and neurologic system.

Systemic signs of chronic disease and inflammation are common, including fever, night sweats (which may occur without awareness of the high fever that precedes them), and weight loss.

In patients with pulmonary TB, the breath sounds may be normal or focally abnormal; tachypnea and hypoxia occur only with extensive lung damage.

Extrapulmonary TB may present with focal adenopathy without local signs of inflammation, but perhaps with a draining sinus.

TB meningitis causes subacute or chronic symptoms, with neck stiffness and changes in mental status, with or without cranial nerve palsies caused by inflammation at the base of the brain or increased intracranial pressure.

Pericardial disease can be associated with the pain and friction rub of pericarditis or signs of pericardial tamponade.

Patients with disseminated TB may have diffuse adenopathy and hepatic or splenic enlargement.

A: Assessment

The differential diagnosis of TB is extensive and depends in part on the degree of immunosuppression (as indicated by the CD4 cell count) of the individual. It includes a broad range of bacterial, mycobacterial, viral, and fungal infections in addition to noninfectious causes. A partial differential diagnosis of pulmonary TB includes:

- ◆ Bacterial pneumonia
- ◆ Pulmonary *Mycobacterium* pneumonia (nontuberculous)
- ◆ *Pneumocystis jiroveci* pneumonia (PCP)
- ◆ *Cryptococcus neoformans* pneumonia/pneumonitis
- ◆ Pulmonary Kaposi sarcoma
- ◆ *Toxoplasma* pneumonitis
- ◆ Disseminated histoplasmosis
- ◆ Disseminated coccidioidomycosis
- ◆ Cytomegalovirus pneumonia
- ◆ Bronchogenic carcinoma
- ◆ Non-Hodgkin lymphoma
- ◆ Influenza
- ◆ Pulmonary embolus
- ◆ Chronic obstructive pulmonary disease
- ◆ Reactive airway disease
- ◆ Congestive heart failure
- ◆ Lactic acidosis

P: Plan

Diagnostic Evaluation

During the initial evaluation, check complete blood count (CBC) and differential, sputum gram stain, sputum AFB stain and culture (see below) blood cultures, and chest x-ray. For patients with lymphadenopathy, consider fine needle aspiration biopsy for bacterial and AFB stains and culture, and cytologic evaluation. For patients with meningitis or central nervous system abnormalities, perform lumbar puncture (LP) and cerebral spinal fluid (CSF) analysis including cell count, protein, glucose, AFB smear, AFB, bacterial and fungal cultures. If focal neurologic abnormalities are present, obtain computed tomography (CT) scan of the head to rule out mass lesion before doing the LP. Perform other diagnostic tests as suggested by the clinical presentation.

Pulmonary TB can be associated with any chest x-ray appearance, including a normal x-ray. However, the chest x-ray classically demonstrates upper-lobe infiltrates with or without cavities. Patients with HIV-associated immunosuppression are more likely to have atypical chest x-rays, including absence of cavities, lower-lobe disease, hilar or mediastinal adenopathy, and pleural effusions. In disseminated TB, the chest x-ray may show a miliary pattern with small nodules (“millet seeds”) scattered throughout both lungs.

Suspected TB should be evaluated aggressively. Diagnosis of TB should include identification of the organism in stained sputum smears or stains of biopsied tissue and confirmed by culture or nucleic acid amplification (such as polymerase chain reaction). All positive cultures should be tested for drug susceptibility. Proof of the diagnosis is important because other opportunistic diseases can mimic TB, and other mycobacterial infections requiring different treatment can occur in HIV-infected persons. Drug susceptibility testing is necessary because improper treatment of drug-resistant TB will lead to treatment failure, more severe drug resistance within the patient, and increased risk of transmission of drug-resistant TB.

A presumptive diagnosis of TB is made on acid-fast stains of expectorated sputum; 3 specimens should be sent for acid-fast staining and mycobacterial culture on 3 successive days (preferably first morning specimens). Sputum induction with nebulized saline can be used for patients who do not have spontaneous sputum

production. Patients with suspected pulmonary TB and negative sputum smears should undergo bronchoscopy and transbronchial biopsy (which is more sensitive than bronchoalveolar lavage for TB). Young children cannot not produce sputum, so gastric lavage on 3 successive mornings can be performed to obtain swallowed sputum for smear (although false-positive smears occur) and culture.

The diagnosis of extrapulmonary TB generally requires microscopic examination of tissue and culture. An aspirate of a suspect lymph node will often be positive on smear, on histopathologic examination, and on culture. Specimens of organs with suspected TB can be obtained by CT-guided aspiration and biopsy, liver biopsy, bone marrow biopsy, “blind” needle biopsies of pleura or peritoneum, or thoracoscopy or laparoscopy-guided biopsies of pleura or peritoneum. At times an open surgical procedure is required to obtain appropriate specimens. Blood cultures for *mycobacteria* (using appropriate mycobacterial media rather than standard blood culture media) may be positive in disseminated TB; the technique is the same as in culturing blood for *M avium* complex organisms. Urine culture is used to diagnose renal TB, which is rare among HIV-infected persons.

Some laboratories will perform a nucleic acid detection test on positive sputum smears and can confirm MTB in positive smears within 1 or a few days. The test is not sufficiently sensitive to use on negative smears, and drug sensitivity testing requires growth in culture. Initial growth may occur within 3–8 weeks. A nucleic acid probe can confirm a positive culture as MTB within a few days of culture growth; otherwise speciation may take several weeks. Susceptibility testing generally takes 3–4 weeks after the initial culture growth, depending on the laboratory procedures used.

Note that a positive TST result indicates TB infection but does not prove active disease (see chapter *Latent Tuberculosis*). Similarly, a negative test can occur in HIV-infected persons with active TB and this was common among persons with disseminated TB prior to the HIV epidemic. A positive TST provides supporting evidence of TB disease; a negative test is not as informative in HIV-infected persons.

Respiratory Precautions

Respiratory infection control precautions should be implemented for HIV-infected patients with an undiagnosed chronic cough or undiagnosed inflammatory infiltrate on chest x-ray. Individual institutions have specific guidelines that should be followed; usually patients are housed in single negative-pressure rooms and persons entering the rooms are required to wear individual protective respirators. If 3 sputum smears are negative on acid-fast staining, or if a single deep specimen (bronchial lavage or tracheal aspirate) is smear negative, infectious TB is unlikely and respiratory precautions can be discontinued. Patients who are highly suspect for MTB and lack an alternative diagnosis should be kept on precautions and empiric treatment may be started. Persons who have responded to treatment for an alternative diagnosis (eg, bacterial pneumonia) and who cannot produce the requisite 3 sputum samples, may be released from the TB precautions.

The impact of TB transmission is severe in a health care setting, where immunosuppressed persons may be exposed. Children aged <5 years and immunosuppressed persons in the home are at increased risk.

Treatment

Treatment should be instituted when TB is considered likely and the proper specimens to determine the diagnosis have been obtained. It is ideal to have a positive smear and confirmation by nucleic acid amplification before initiating treatment, but empiric treatment can be started after the specimens have been collected if the suspicion of TB is high, the patient is severely ill, or a positive smear is unlikely (eg, cerebrospinal fluid smears).

Once the decision to treat is made and an appropriate regimen is selected, adherence becomes the most important issue. The treating clinician must ensure that the patient completes a full course of therapy. Therefore, it is strongly recommended that patients be referred to public health departments for TB treatment. Health departments usually provide free TB treatment and have specific resources and systems to promote adherence. All patients should receive directly observed therapy (DOT), whereby the taking of every dose of anti-TB medication is observed and documented. The intermittent TB therapies in Table 1 (regimens 1b, 2, and 3) were designed to simplify DOT. Clinical trials have documented that DOT with enhancements to

maximize adherence improves the rate of completion of therapy and reduces mortality in HIV-infected TB patients. If the health department manages the TB treatment, the HIV clinician must coordinate with the health department to do the following: 1) avoid drug interactions; 2) provide antiretroviral therapy (ART), if indicated, that does not conflict with the TB treatment; 3) ensure that immune reconstitution inflammatory syndrome (IRS) or incident opportunistic diseases are not misinterpreted as progression of TB; and 4) maximize adherence with the TB medications, ART, and any other medications.

The U.S. guidelines for TB treatment in HIV-infected persons are shown in Table 1; dosages are given in Table 2. Four anti-TB drugs are administered for the first 2 months, and then 2 drugs are administered for an additional 4 months (if the organism is susceptible to standard medications). The initial phase of TB treatment usually consists of isoniazid, rifampin, pyrazinamide, and ethambutol; the continuation phase typically is simplified to isoniazid and rifampin. If drug resistance or MDR is suspected, more drugs can be used initially, and treatment should be directed by, or in consultation with, experts. Resistance may be suspected among persons who were exposed to TB in countries with high rates of endemic resistance, those who failed previous treatment, those who have used treatment erratically, those who may have had a specific exposure to drug-resistant TB, or those who were diagnosed during an MDR outbreak. Treatment is extended in certain circumstances. Cavitary TB or TB in an HIV-infected person who remains sputum-culture positive after 2 months of treatment should be treated for a total of 9 months; bone and joint TB are treated for 6-9 months; and meningeal TB is treated for 9-12 months. If cultures obtained before treatment demonstrate drug resistance, the regimen and the duration of therapy may need to be changed. In patients with TB meningitis or pericarditis, and for persons with adrenal insufficiency, a course of corticosteroids is given in addition to specific anti-TB therapy.

Considerations in pregnancy

Pyrazinamide has not been formally proven safe during pregnancy although no problems have been reported with its use during pregnancy. Some health departments in the United States avoid pyrazinamide in pregnant women and extend the continuation phase to 7 months. Others prescribe the standard regimens in Table 1 during pregnancy. Streptomycin and certain second-line

Table 1. Regimens for Treatment of Tuberculosis among HIV-Infected Persons in the United States

Initial Phase		Continuation Phase			Complete Therapy
Drugs	Interval and Doses (minimum duration)	Regimen	Drugs	Interval and Doses (minimum duration)	Range of Total Doses (minimum duration)
1. Preferred Regimen					
Isoniazid Rifampin* Pyrazinamide Ethambutol	• 7 days/week for 56 doses or 5 days/week for 40 doses (8 weeks)	1a.	Isoniazid Rifampin*	7 days/week for 126 doses or 5 days/week for 90 doses (18 weeks)#	182-130 doses (28 weeks)
		1b. if CD4 count >100 cells/μL	Isoniazid Rifampin*	Twice weekly for 36 doses (18 weeks)** #	92-76 doses (28 weeks)
2. Acceptable Alternative if CD4 >100 cells/μL					
Isoniazid Rifampin* Pyrazinamide Ethambutol	• 7 days/week for 14 doses (2 weeks) followed by twice weekly for 12 doses (6 weeks) <i>OR</i> • 5 days/week for 10 doses (2 weeks) followed by twice weekly for 12 doses (6 weeks)	2. if CD4 count >100 cells/μL	Isoniazid Rifampin*	Twice weekly for 36 doses (18 weeks)** #	62-58 doses (28 weeks)
3. Acceptable Alternative					
Isoniazid Rifampin* Pyrazinamide Ethambutol	3 times weekly for 24 doses (8 weeks)	3.	Isoniazid Rifampin*	3 times weekly for 54 doses (18 weeks)#	72 doses (28 weeks)

Source: American Thoracic Society, CDC, and Infectious Disease Society of America. *Treatment of Tuberculosis. Morb Mort Weekly Rpts Recommendations and Reports*. June 20, 2003, 52(RR11);1-77.

* See Table 2 for dosages. See Table 3 for contraindications, substitutions, and dosage adjustments of rifampin. Rifampin should not be used with nevirapine or with HIV protease inhibitors other than ritonavir; rifabutin may be substituted with appropriate dosage adjustments.

** Twice-weekly regimens (1b and 2) should not be used in persons with HIV and a CD4 lymphocyte count $\leq$ 100 cells/ μ L.

For patients who are slow to respond, or in whom sputum cultures are still positive after the initial 2 months of treatment, the continuation phase may be extended to 7 months, for a total of 9 months of treatment. Pediatric patients should be treated for a 7 months in the continuation phase, for a total of 9 months of treatment. TB meningitis caused by susceptible organisms should be treated for 9-12 months. Bone and joint TB should be treated for 6-9 months; the longer time may be prudent when multiple bones and joints are involved or when it is difficult to document a response to treatment.

Table 2. Dosages of First-Line Antituberculous Drugs Used in the United States

Agent	Regimen 1 or 2: Daily or 5 times/week Dosage (maximum)		Regimen 1b or 2: 2 times/week Dosage (maximum)		Regimen 3: 3 times/week Dosage (maximum)	
	Adults	Children	Adults	Children	Adults	Children
Isoniazid* (tabs: 100 and 300 mg)	5 mg/kg (300 mg max)	10-15 mg/kg (300 mg max)	15 mg/kg (900 mg max)	20-30 mg/kg (900 mg max)	15 mg/kg (900 mg max)	NA
Rifampin** (caps 300 mg)	10 mg/kg (600 mg max)	10-20 mg/kg (600 mg max)	10 mg/kg (600 mg max)	10-20 mg/kg (600 mg max)	10 mg/kg (600 mg max)	NA
Pyrazinamide (tabs 500 mg)	20-25 mg/kg (2 g max)	10-30 mg/kg (2 g max)	35-50 mg/kg (3 g max)	10-30 mg/kg (2 g max)	35-55 mg/kg (4 g max)	NA
Ethambutol (tabs 100 and 400 mg)	15-20 mg/kg (1,600 mg max)	10-20 mg/kg (1 g max)	20-30 mg/kg (2,400 mg max)	10-20 mg/kg (1 g max)	35-50 mg/kg (4,000 mg max)	NA
Rifamate[#] (caps isoniazid 150 mg, rifampin 300 mg)	2 caps daily	NA	NA	NA	NA	NA
Rifater^{##} (tabs isoniazid 50 mg, rifampin 120 mg, pyrazinamide 300 mg)	$\leq$ 44 kg: 4 tabs 45-54 kg: 5 tabs 55-90 kg: 6 tabs	NA	NA	NA	NA	NA

Source: American Thoracic Society, CDC, and Infectious Disease Society of America. *Treatment of Tuberculosis. Morb Mort Weekly Rpts Recommendations and Reports*. June 20, 2003, 52(RR11);1-77.

Typical daily dosage for a 60 kg patient: isoniazid 300 mg (2 tabs), rifampin 600 mg (2 caps), pyrazinamide 1,500 mg (3 tabs), ethambutol 1,200 mg (3 tabs)

* Add pyridoxine 10-25 mg per dose of isoniazid.

** See Table 3 for dosage adjustments or rifabutin substitution when combined with ART.

Suitable for daily dosing during the continuation phase.

May be part of daily initial phase combined with ethambutol tablets.

drugs should be avoided during pregnancy. HIV-infected women in the United States are instructed not to breast-feed, so there are usually no issues regarding TB treatment of HIV-infected women during breast-feeding.

Treatment of pediatric patients

Children are often treated with a 7-month continuation phase for a total treatment time of 9 months, although there are no data on this issue. Some experts avoid ethambutol in young children who cannot be tested for the adverse event of color blindness; others consider the risk so small with current ethambutol dosages that the drug can be included safely. Treatment of children for TB should be done in consultation with an expert.

Coordinating with Antiretroviral Therapy

ART and TB treatment must be coordinated for both to be successful. Rifampin is a potent inducer of cytochrome p450 enzymes and has clinically important interactions with many medications, including certain

antiretrovirals and oral contraceptives. Rifampin reduces the blood concentrations of nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs), but does not affect nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) or the entry inhibitor enfuvirtide. Some NNRTIs and PIs cannot be used with rifampin while others require dose adjustment when coadministered (Table 3). Triple-nucleoside regimens can be administered safely during rifampin treatment but are less potent than other first-line antiretroviral (ARV) combinations. The safest ARV combination to use with rifampin is a 2-drug nucleoside backbone with efavirenz. Some clinicians increase the efavirenz dosage to 800 mg/day because efavirenz blood concentrations may be reduced 25% by concomitant rifampin. Note that efavirenz is teratogenic; women who take efavirenz should avoid pregnancy by using birth control methods that use are not affected by rifampin (preferably condoms plus injectable progestins or condoms plus an intrauterine device).

Table 3. Interactions of Antiretroviral Medications with Rifampin or Rifabutin: Contraindicated Combinations and Dosage Adjustments

	Rifampin	Rifabutin*
Nonnucleoside Reverse Transcriptase Inhibitors		
Efavirenz**	Rifampin dosage is unchanged; give efavirenz dosage of 600-800 mg daily	No change in efavirenz dosage; increase rifabutin to 450-600 mg 3 times daily
Nevirapine	Generally not recommended; despite 25-50% reduction in nevirapine levels, 2 small studies claim standard dosages are effective	Use standard dosage of nevirapine; rifabutin 300 mg daily or 3 times weekly
Delavirdine	Never combine	Never combine
Unboosted Protease Inhibitors		
Ritonavir	May be used at standard dosages; limited clinical experience	Ritonavir at standard dosage; rifabutin 150 mg alternate days or 3 times weekly
Amprenavir, fosamprenavir	Never combine	PIs at standard dosage; rifabutin 150 mg/day or 300 mg 3 times weekly
Atazanavir	Never combine	Atazanavir at standard dosage; rifabutin 150 mg alternate days or 3 times weekly
Indinavir	Never combine	Increase indinavir to 1,000 mg every 8 hours; rifabutin 150 mg/day or 300 mg 3 times weekly
Nelfinavir	Never combine	Increase nelfinavir to 1,000 mg every 8 hours; rifabutin 150 mg/day or 300 mg 3 times weekly
Ritonavir-Boosted Protease Inhibitors		
Lopinavir/ritonavir (Kaletra)	Lopinavir/ritonavir (3 caps twice daily) must be supplemented with additional ritonavir 300 mg twice daily; limited experience, not well tolerated	Standard dosage of lopinavir/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly
Saquinavir/ritonavir	Should not be used because of high rates of hepatotoxicity	Standard dosage of lopinavir/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly
All other ritonavir-boosted PIs	Should not be used (adequate dosing regimens not defined)	Standard dosage of PI/ritonavir; decrease rifabutin to 150 mg alternate days or 3 times weekly

Adapted from *Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nonnucleoside Reverse Transcriptase Inhibitors*. Updated January 20, 2004. Nucleoside and nucleotide analogues are given in standard dosages with either rifampin or rifabutin.

* If available, rifabutin may be substituted for rifampin when TB treatment and antiretroviral therapy is combined.

** Avoid efavirenz during pregnancy or in women who may become pregnant on therapy. Both rifampin and rifabutin significantly reduce estrogen and progestin levels for women on hormonal contraceptives; efavirenz raises estrogen levels moderately. Two forms of birth control including one barrier method and either a mid-high dose hormonal contraceptive or intrauterine device are most often recommended. Barrier methods are also recommended for women who are infertile to reduce HIV transmission.

Rifabutin may be substituted for rifampin to avoid rifampin-ARV interactions. Rifabutin has less marked effects on the pharmacokinetics of other drugs compared to rifampin, although its own blood concentrations can be affected by certain ARVs. See Table 3 for dosing recommendations for coadministration of rifabutin with ARVs. Rifabutin is expensive; some public health systems do not provide rifabutin as part of TB treatment and it generally is not available in resource-limited countries. The U.S. Food and Drug Administration characterizes rifabutin in pregnancy category B: it has been safe in animal studies of pregnancy but has not been proven safe in humans. For pregnant women who require both TB and ARV therapy, the use of rifabutin rather than rifampin allows the use of non-efavirenz-based ARV regimens.

Persons who are already taking ART when TB treatment is begun should have their ARV regimens reassessed. The appropriate dosages of rifampin or rifabutin must be chosen and the ARV regimen may need to be modified, at least until the completion of TB treatment.

In HIV/TB coinfecting patients the optimal timing of ART initiation in relation to TB therapy is not known. For patients who are not taking ART at the time they start TB therapy, many specialists recommend postponing ART for the first 4–8 weeks of TB therapy. This strategy decreases the pills burden, adherence problems, the risk of drug adverse effects, and the risk of IRS (see below). Some experts recommend that persons with very low CD4 cell counts (<50–100 cells/ μ L) start ART 2 weeks after initiating TB treatment, although others believe that an increased risk of complications remains. International studies are under way, and others are planned, to inform this decision.

Persons who do not require immediate ARV treatment (eg, those with CD4 counts >350 cells/ μ L) may be best served by completing TB treatment first and then reassessing the need for ARVs.

Monitoring for efficacy

Ideally, every dosing of anti-TB therapy is observed and documented by a health care agent or responsible individual. A member of the health care team should evaluate patients' adherence at least weekly during the initial phase or monthly during the continuation phase. If gaps in medication use occur, the cause must be evaluated and a plan to improve adherence must be implemented.

During the treatment of pulmonary TB, monthly sputum specimens should be obtained for smear and culture until 2 sequential specimens are sterile on culture. Patients with extrapulmonary and disseminated TB are usually monitored clinically and with imaging studies. Biopsies are not repeated but other specimens (cerebrospinal and other body fluids) may be obtained for repeat laboratory study including acid-fast bacilli smear and culture, cell counts, and protein levels. Monitoring of patients with extrapulmonary and disseminated TB should be done in consultation with an expert.

Managing immune reconstitution syndrome

Patients in the initial months of treatment for active TB who begin ART may experience a paradoxical increase in signs and symptoms of TB (fever, dyspnea, increased cough, enlarging lymph nodes, worsening chest x-ray findings, increased inflammation at other involved sites, or enlargement of central nervous system tuberculomas). In many cases, this phenomena is caused by an enhanced immune response against remaining MTB organisms because of immunologic improvement from ART. IRS often occurs within 2 weeks up to several months after ARVs are begun and is usually accompanied by a sharp decline in the HIV viral load and at least a 2-fold increase in the CD4 cell count. TB treatment failure (potentially due to an inappropriate treatment regimen, inadequate adherence, or drug resistance) must be ruled out and the possibility of drug toxicity should be considered. If IRS is diagnosed, TB and ARV treatment should be continued and symptoms should be managed with nonsteroidal anti-inflammatory drugs, or in severe cases, with a short course of corticosteroids. See chapter *Immune Reconstitution Syndrome*.)

Monitoring for toxicity

Antituberculous medications may have significant adverse effects. Table 4 lists the most important adverse reactions reported for the commonly used anti-TB medications. Before initiating TB treatment, check complete blood count with platelet count, serum creatinine, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], bilirubin, alkaline phosphatase), and hepatitis B and C serology. Newly diagnosed TB patients with unknown HIV status should be encouraged to undergo testing for HIV infection. Thereafter, all patients taking TB therapy should be monitored monthly with a symptom review to assess possible toxicity.

Although HIV-uninfected persons without risks for liver disease do not require routine laboratory monitoring, HIV/TB coinfecting patients have a higher risk of drug toxicity. Laboratory monitoring may be repeated after 1 month of treatment and every 3 months thereafter, unless symptoms or laboratory abnormalities warrant more frequent testing. Persons with symptoms and AST or ALT elevations ≥ 3 times the upper limit of normal, and asymptomatic persons with aminotransferase elevations ≥ 5 times the upper limit of normal, should have therapy interrupted and should be managed thereafter in consul-

tation with an expert. Patients should be monitored for isoniazid-induced peripheral neuropathy; this adverse effect is rare if pyridoxine is administered with isoniazid, as recommended (Table 2). Testing of visual acuity and red-green color discrimination is recommended at the start of therapy with ethambutol. Persons taking standard ethambutol doses who have normal baseline examinations should be asked monthly about visual disturbances. Those taking higher ethambutol dosages or prolonged ethambutol treatment (>2 months) should have periodic eye examinations for acuity and color discrimination.

Table 4. Adverse Events Associated with Common Antituberculous Medications

Drug	Frequent (≥ 5 per 100 patients)	Common ($\geq 1-5$ per 100 patients)	Infrequent (≥ 1 per 1,000 patients and <1 per 100 patients)
Isoniazid	• Liver enzyme elevations		• Hepatitis • Peripheral neuropathy • Drug fever
Rifampin	• Bilirubin elevations in the beginning of treatment • Orange discoloration of urine and tears • Liver enzyme elevations		• Hepatitis • Pruritus • Flu syndrome • Drug fever
Pyrazinamide	• Arthralgias	• Nausea	• Hepatitis • Rash • Nausea
Ethambutol			• Retrobulbar neuritis • Periaxial ocular toxicity
Streptomycin	• Vestibular toxicity	• Cochlear toxicity • Hypersensitivity reactions	• Renal damage

Adapted from IUATLD slide sets and Reider H.L. *Interventions for Tuberculosis Control and Elimination*. 2002. International Union Against Tuberculosis and Lung Disease.

Available at: www.tbrieder.org. Accessed July 4, 2005.

Note: Rare adverse events (≤ 1 per 1,000 patients) are not included in this table.

Patient Education

- ◆ All patients with TB-positive sputum or bronchoscopy specimens can infect others with TB. All close contacts, especially children, should be screened for TB as soon as possible and given medication to prevent (or treat) active disease.
- ◆ The health department will be notified of each TB case and will provide the required follow-up care.
- ◆ Patients must take all medicines exactly as prescribed. If doses are missed, or if the medication is stopped and restarted, the TB bacteria can develop resistance to even the best medications and become even more dangerous. If patients are having trouble taking the medication on schedule, they should contact their health care providers immediately.
- ◆ If patients become ill, if their skin or eyes turn yellow, or if their urine darkens to a cola color, they should see their health care providers immediately.
- ◆ Patients must keep all follow-up appointments. Blood tests will be done regularly to be sure the liver is working well, and patients will be checked for medication adverse effects. They should show their health care providers all medications, vitamins, and supplements that they are taking so that the providers can check for drug interactions.
- ◆ Rifampin will make urine, sweat, and tears turn orange; this is not harmful. It will also stain plastic contact lens; patients should avoid wearing these if they are taking rifampin.
- ◆ Rifampin will cause birth control pills to fail. An alternate method of contraception should be used when the patient is under treatment.
- ◆ Alcohol should be avoided during treatment with TB drugs to avoid liver damage.

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Tuberculosis Treatment in Resource-Limited Settings

Background

Tuberculosis (TB) is the most common severe opportunistic infection associated with HIV in many resource-limited areas such as sub-Saharan Africa. The enormous and increasing number of cases of TB associated with HIV infection has greatly increased the demands on TB treatment programs. TB treatment in HIV-infected patients is different in resource-limited settings than in resource-abundant settings, and treatment details may differ by country. In general, the emphasis of TB treatment and control in resource-limited areas has been on diagnosing sputum smear-positive patients (ie, those with infectious pulmonary TB) to minimize the need for expensive technology and to maximize the public health impact of treatment. The target for many national TB control programs is to diagnose 70% of new cases, and for 85% of newly diagnosed patients to complete a course of therapy. The following recommendations for diagnosis and treatment are derived from guidelines by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease.

See the *Treatment of Latent Tuberculosis in Resource-Limited Settings* chapter for a discussion of isoniazid preventive treatment (IPT) for HIV-infected persons.

For more information on tuberculosis, including diagnosis and treatment, see chapter *Mycobacterium tuberculosis: Treatment in the United States and Other High-Income Nations*.

Diagnosis

HIV counseling and voluntary testing should be encouraged for every person diagnosed with TB. In addition, screening for TB symptoms should occur at every health care interaction with HIV-infected persons. Patients with both conditions should be referred between the TB and HIV treatment facilities in order to access both treatments appropriately. Coordination between TB and HIV treatment is crucial because of potential drug interactions, increased risk of toxicity, risk of immune reconstitution inflammatory syndrome (IRS), and increased adherence challenges. In many countries, an effort to coordinate HIV and TB care is just beginning.

Three sputum smears should be examined for acid-

fast bacilli (AFB) in all patients with chronic cough. The presence of other respiratory symptoms (eg, breathlessness, chest pain, hemoptysis) or systemic symptoms (eg, fever, night sweats, weight loss, loss of appetite) increase the likelihood of pulmonary TB. For outpatients, an initial (spot) sputum specimen should be obtained on the day a patient presents for evaluation. The patient then is sent home with a sputum cup to collect a sample immediately after awakening the next morning. The patient brings the morning specimen back to the health facility the day it is collected. On that day, the patient provides a second spot specimen in the health facility, so that 3 specimens are collected in 2 days. All 3 are stained and examined microscopically for AFB.

HIV-infected patients with TB, especially those with advanced immunosuppression, often have either smear-negative pulmonary disease or extrapulmonary disease. In such cases, diagnosis relies on clinical judgment and radiographic imaging, and sometimes on aspirates and biopsies. In some locations, x-rays may be unavailable, so TB treatment may be instituted in smear-negative patients in whom pulmonary TB is suspected (eg, in patients in whom at least 1 trial of standard antibiotics has been ineffective and a medical doctor or an appropriately trained clinician has not made an alternative diagnosis). In some cases, diagnostic testing may not be available, and AIDS patients with a wasting febrile disease may be treated empirically for TB.

TB lymphadenitis often can be diagnosed on an AFB smear of a needle aspirate of a suspicious lymph node, or on the gross appearance of caseous necrosis in a biopsied lymph node. AFB smears are usually negative in pleural, pericardial, peritoneal, joint, and cerebrospinal fluids of patients with TB in those compartments. Diagnosis is based on clinical presentation and on cell counts and chemistry tests of the fluids. (Where chemistry tests are not available, the fluid may be observed for formation of protein clots over the course of several hours, indicating elevated fluid protein levels.) Liver and bone marrow biopsy may be helpful in diagnosing disseminated TB, revealing granulomas if not acid-fast organisms. If possible, these fluids and biopsied tissues should be cultured for *Mycobacterium tuberculosis*.

Young children do not produce sputum, and usually are treated on the basis of clinical presentation and chest x-ray findings. A point system has been used to assist in selecting children for treatment, especially where x-ray facilities are not available. However, this point system may not be very specific in HIV-infected children, who may have other illnesses unrelated to TB. Children exposed to TB in the home need to be assessed for symptoms and signs of active disease, and should receive either IPT (see the *Treatment of Latent Tuberculosis in Resource-Limited Settings* chapter) or empiric treatment for active TB.

Treatment Adherence

Directly observed therapy—short course (DOTS) is recommended. The DOTS framework includes systems for

- ◆ Standardized short-course (6-month) chemotherapy promoting adherence and observing each dose of medication;
- ◆ Access to quality-assured sputum microscopy;
- ◆ Uninterrupted access to appropriate drugs;
- ◆ A quality-assured data and monitoring system; and
- ◆ The political will and resources to implement a national TB control program.

Therapy may be directly observed by health care workers, family members, lay community volunteers or activists, or coworkers. The treatment supporter documents the observation of doses using forms and procedures analogous to those used for this purpose by health care workers. The treatment supporter accompanies the patient to the TB treatment visits, bringing remaining medications and treatment documentation paperwork each time.

Treatment Regimens

The TB treatment regimens recommended by the WHO for HIV-infected persons are shown in Table 1. Where DOTS can be assured, regimens for new patients are the same as those used in industrialized countries. Fixed-dose combination (FDC) tablets are available in some countries for both initial and continuation phases of treatment, for both adults and children, and may be available in blister packs. Use of the FDCs reduces the time demands on health care workers, ensures more accurate weight-based dosing, simplifies assessment of adherence, and eliminates the option for patients to avoid individual medications in their regimen.

Patients who are smear positive after completing TB treatment (“relapse”) or return after a 2-month gap in treatment having had at least 1 month of prior exposure to TB medications (“return from default”) are considered retreatment cases (Category II; see Table 1) and receive an expanded and extended regimen. If possible, sputum for culture and sensitivity is obtained at the beginning of a retreatment regimen. In some countries with high rates of multidrug resistance, these patients may be referred directly to second-line treatment (Category IV).

Ethambutol is included in regimens for HIV-infected persons. However, it may be omitted in HIV-uninfected persons with smear-negative pulmonary TB without cavities and without suspicion of drug resistance. Some countries do not include ethambutol in the treatment of young children with TB.

TB meningitis is treated with streptomycin instead of ethambutol during the initial phase of therapy.

Corticosteroids are recommended for patients with TB meningitis, pericarditis, severe or bilateral pleural effusions, TB laryngitis threatening the airway, massive TB adenopathy with dangerous pressure effects, severe IRS, and severe drug toxicity (prednisone 1 mg/kg with tapering over the course of weeks to months). For patients with adrenal insufficiency due to TB, stress-doses of corticosteroids will need to be followed by chronic replacement doses.

Thiacetazone was previously widely used in Africa as part of TB treatment. Its use is discouraged now because of a high rate of severe skin reactions including fatalities from Stevens-Johnson syndrome and toxic epidermal necrolysis, especially in HIV-infected persons.

Table 1. World Health Organization's Recommended First-Line Regimens for Tuberculosis Treatment

TB Category	TB Patients	TB Treatment Regimens	
		Initial Phase (daily or 3 times weekly)	Continuation Phase (daily or 3 times weekly)
I	New smear positive; new smear negative with extensive chest x-ray abnormalities, severe HIV disease, or severe extrapulmonary TB	Isoniazid,* rifampin,** pyrazinamide, ethambutol*** for 2 months	Isoniazid* and rifampin** for 4 months Isoniazid and ethambutol† daily for 6 months
II	Previously treated smear-positive pulmonary TB# • relapse • return after default • treatment failure	Isoniazid,* rifampin,** pyrazinamide, ethambutol and streptomycin for 2 months, followed by isoniazid,* rifampin,** pyrazinamide and ethambutol for 1 month	Isoniazid,* rifampin,** and ethambutol for 5 months
III	Smear-negative TB and extrapulmonary TB less severe than category I##	Isoniazid,* rifampin,** pyrazinamide, ethambutol for 2 months	Isoniazid* and rifampin** for 2 months Isoniazid* and ethambutol† daily for 6 months
IV	Chronic and multidrug-resistant TB (smear positive after supervised retreatment)	Multidrug-resistant or individualized regimen per country protocol	

Source: Harries A, Maher D, Graham S. *TB/HIV: A Clinical Manual*, second edition. 2004. WHO, Geneva.

* Pyridoxine 10 mg daily is added to each dose of isoniazid.

** Rifampin is called rifampicin in other countries. It is recommended that every rifampin dose be supervised (directly observed therapy). Rifampin should not be used with nevirapine or protease inhibitors; rifabutin may be substituted with appropriate dosage adjustments.

*** In TB meningitis, the World Health Organization recommends substituting streptomycin for ethambutol.

† Isoniazid and ethambutol is expected to have a higher failure rate than isoniazid and rifampin; however, it is included for treatment when continuation-phase therapy cannot be directly supervised, to avoid the risk of promoting resistance to rifampin.

Culture and susceptibility testing (if available) should be performed at the beginning of Category II treatment.

HIV-infected patients in Category III will take the same treatment as persons in Category I.

Pregnancy

The WHO considers all Category I medications to be safe in pregnancy. Avoid streptomycin (Category II treatment) if possible, as it can cause 8th cranial nerve damage to the fetus.

Breastfeeding

The WHO considers all anti-TB medications to be safe during breast-feeding.

Hepatic Disease

Pyrazinamide should be avoided in patients with preexisting liver disease. For mild-to-moderate liver disease, an initial 2-month regimen of isoniazid, rifampin, ethambutol, and streptomycin can be followed by a 6-month course of isoniazid and rifampin. For severe liver disease, 2 months of isoniazid, ethambutol, and streptomycin is followed by 10 months of isoniazid and ethambutol. If these regimens are not tolerated, or if drug resistance is suspected, consult an expert.

Renal Disease

Ethambutol should be dose-adjusted or avoided altogether in severe renal insufficiency. Streptomycin doses must be adjusted in patients with abnormal renal function.

Polydrug or Multidrug Resistance

Patients with polydrug or multidrug resistance may be treated with standardized Category IV regimens or individualized regimens, depending on the country protocol. Category IV patients should be treated according to expert advice or in specialized centers.

Monitoring for Treatment Effectiveness

Patients who are smear positive initially should be monitored by repeat sputum smears (Table 2). Young children, smear-negative pulmonary TB patients, and extrapulmonary TB patients can be followed clinically. Repeat chest x-ray is not recommended for routine follow-up and is considered a poor use of resources. Chest x-ray should be repeated only for a patient with new or progressive symptoms.

Table 2. Timing of Sputum Smears

When to Monitor	Category I (6-month regimen)	Category II (8-month regimen)
At diagnosis	3 specimens	3 specimens
End of initial phase	1 spot specimen	1 spot specimen
End of additional month of initial phase, if needed*	1 spot specimen	1 spot specimen
In continuation phase	1 spot specimen at end of month 5	1 spot specimen at end of month 5
During last month of treatment	1 spot specimen during month 6	1 spot specimen during month 8

Source: Harries A, Maher D, Graham S. TB/HIV: A Clinical Manual, second edition. 2004. World Health Organization, Geneva. *See text.

Patients who were previously sputum smear-positive with 2 subsequent negative sputum smears and completion of 6–8 months of treatment are considered cured. Previously sputum smear-negative patients, or patients who cannot produce sputum, who respond clinically (cessation of cough and fever, weight gain) and complete 6–8 months of treatment are considered “completers.” Successful treatment includes all cured patients and “completers.”

Patients who are smear positive at the end of the initial phase (2 months of Category I treatment or 3 months of Category II treatment) should continue on the initial phase for 1 additional month. Patients who are smear positive after the additional month need 2 sputum samples sent for culture and sensitivity (if available) and progress to the continuation phase for the usual 4 months (Category I) or 6 months (Category II).

Patients who are smear positive at 5 months are considered treatment failures; sputum is sent for culture and sensitivity and they progress to the retreatment regimen.

Those who have a gap in treatment are called “interrupters,” and efforts must be made to get them back into treatment. Those who have at least a 2-month gap in treatment are “defaulters,” and must be reassessed with new sputum smears.

Monitoring for Toxicity

(See Table 4 in chapter *Mycobacterium tuberculosis*: Treatment in the United States and Other High-Income Nations for information on adverse effects of TB therapy.)

Standard guidelines for anti-TB therapy in resource-limited settings do not require baseline or follow-up laboratory tests as a matter of routine. Rather, clinical assessment should be performed at least monthly and should include evaluation of symptoms or signs such as gastrointestinal intolerance, minor and major cutaneous drug reactions, joint pain, hepatitis (nausea, vomiting, abdominal pain, jaundice), peripheral neuropathy, changes in visual acuity, or development of blind spots (Table 3). Where laboratory facilities and financial resources allow, many clinicians prefer to check baseline and periodic complete blood counts with differential, alanine/aspartate aminotransferase (ALT/AST) or bilirubin, and baseline creatinine. Laboratory monitoring is more important in persons with preexisting liver disease or those on concomitant ART although TB treatment should not be withheld for lack of access to hematology or chemistry laboratory testing.

Management of severe rash includes discontinuation of TB therapy, supportive care, administration of corticosteroids for severe or life-threatening desquamation, and gradual reintroduction of escalating dosages of medications after resolution. Drugs are reintroduced in the reverse order of their likelihood of causing severe rash: isoniazid, rifampin, pyrazinamide, ethambutol, streptomycin. Avoid thiacetazone because of high risk of severe cutaneous reactions. Seek expert advice.

Management of liver toxicity includes cessation of therapy until bilirubin and ALT return to normal levels. If laboratory testing is not available, wait until 2 weeks after the resolution of jaundice. Treat with ethambutol, streptomycin, rifampin (if tolerated), and isoniazid (if tolerated). See the discussion of hepatic disease, above, for 2 possible treatment regimens. If the TB is severe, treatment may have to be resumed early without hepatotoxic drugs (ethambutol and streptomycin), until additional drugs can be reintroduced to the regimen. Seek expert advice.

Table 3. Monitoring for Toxicity

Side Effects	Drugs Likely Responsible	Management
Minor Side Effects		
Anorexia, nausea, abdominal pain	Rifampin	Give dose last thing at night
Joint pain	Pyrazinamide	Aspirin or nonsteroidal anti-inflammatory drugs
Burning in feet, neuropathy	Isoniazid	Pyridoxine 50-75 mg daily
Orange/red urine	Rifampin	Reassurance
Major Side Effects		
Severe rash or skin itching	Thiacetazone, streptomycin	Stop TB therapy for severe reactions; give supportive care; after resolution of symptoms, reinstitute therapy (see text)
Decreased hearing, deafness (rule out wax in ears)	Streptomycin	Substitute ethambutol or other
Dizziness, vertigo, nystagmus	Streptomycin	Substitute ethambutol or other
Jaundice	Pyrazinamide, isoniazid, rifampin	Stop TB treatment until jaundice resolves (see text)
Vomiting and confusion	Pyrazinamide, isoniazid, rifampin	Stop TB treatment and perform liver function tests
Visual impairment	Ethambutol	Stop ethambutol
Generalized hypersensitivity reaction with shock and purpura	Rifampin	Stop rifampin

Source: Harries A, Maher D, Graham S. *TB/HIV: A Clinical Manual*, second edition. 2004. World Health Organization, Geneva.

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Non-Hodgkin Lymphoma

Background

Non-Hodgkin lymphoma (NHL) is a diverse group of more than 20 malignant diseases originating in the cells of the immune system. The incidence of NHL is up to 60 times higher in HIV-infected patients than in HIV-noninfected persons, and the risk of NHL increases with declining immune function. In the United States, rates of NHL among HIV-infected persons increased dramatically in the early years of the HIV epidemic, but the rate has stabilized since the advent of antiretroviral therapy (ART).

Ninety percent of HIV-related NHL cases are of B-cell origin and they are frequently high-grade in nature. Although B-cell lymphomas may occur at any stage of HIV disease, they are seen more frequently in patients with lower CD4 cell counts (particularly CD4 counts of <100 cells/ μ L). Central nervous system (CNS) lymphoma typically is seen only in patients with advanced AIDS (the CD4 count usually is <50 cells/ μ L). NHL is an AIDS-defining condition. A viral factor, the Epstein-Barr virus (EBV), is linked to CNS and some types of systemic NHL in people with AIDS.

The majority of patients with NHL present with unexplained fever, sweats, or weight loss (“B symptoms”), and lymphadenopathy. Extranodal disease often is present at the time of diagnosis. Common sites of extranodal disease include the CNS, gastrointestinal (GI) tract, lungs, and bone marrow.

S: Subjective

Patients may complain of enlarged lymph nodes and often report B symptoms such as fever, weight loss, and night sweats. B symptoms are present in 80% of patients with systemic AIDS-related NHL. In patients with these complaints, it is important to exclude opportunistic infections (OIs) when evaluating for lymphoma.

Headaches, seizures, and altered mental status often are present in patients with CNS lymphoma.

Other symptoms may include changes in bowel habits, GI bleeding, abdominal pain, and early satiety, shortness of breath, and cough.

Take a careful history, asking about the symptoms described above, their duration, severity, progression,

and any associated symptoms.

Inquire about current or recent CD4 cell counts and the CD4 nadir. Ask whether the patient is taking ART or OI prophylaxis.

O: Objective

Measure vital signs and weight; compare with previous values.

Perform a complete physical examination with special attention to:

- ◆ General appearance and nutritional status (appearance of illness, cachexia)
- ◆ Skin (pallor, jaundice)
- ◆ Lungs (effusion, abnormal sounds)
- ◆ Abdomen (hepatosplenomegaly)
- ◆ Lymph nodes (note size, consistency, mobility, and degree of tenderness)
- ◆ Nervous system, including mental status

A: Assessment

The differential diagnosis is broad and is determined in part by the patient’s CD4 count. It includes both infectious and noninfectious etiologies, such as:

- ◆ Other malignancies, including Hodgkin disease
- ◆ HIV infection; persistent generalized lymphadenopathy
- ◆ Immune reconstitution syndrome
- ◆ Mononucleosis; Epstein-Barr virus infection
- ◆ *Mycobacterium avium* complex (MAC)
- ◆ Tuberculosis
- ◆ Histoplasmosis, other fungal diseases
- ◆ Toxoplasmosis (for CNS disease)
- ◆ Progressive multifocal leukoencephalopathy (PML) (for CNS disease)
- ◆ *Bartonella*
- ◆ Lymphogranuloma venereum
- ◆ Castleman disease

P: Plan

Diagnostic Evaluation

Definitive diagnosis of lymphoma requires identification of lymphomatous cells, usually obtained by excisional biopsy.

Biopsy of lymph node or other site

Rapidly expanding or otherwise abnormal lymph nodes or masses should be biopsied. Fine needle aspiration (FNA) biopsy may determine the diagnosis, but excisional biopsy should be obtained if the FNA is unrevealing. (Also, FNA may not yield enough cells for definitive diagnosis). See chapter *Lymphadenopathy* for more information.

Other that studies help to determine the extent of involvement, rule out other diseases, and determine the patient's clinical status include complete blood count (CBC) with differential, liver function tests, electrolyte and lactate dehydrogenase (LDH) measurements, and peripheral blood smear. (Otherwise-unexplained cytopenias and peripheral blood smear abnormalities may suggest bone marrow involvement. Elevated LDH is nonspecific but may be seen in patients with lymphoma.)

Perform blood cultures, MAC culture, tuberculosis studies, serum cryptococcal antigen, or other laboratory work as indicated by the patient's symptoms.

Radiographic studies

Patients with unexplained CNS symptoms or signs should receive brain imaging by computed tomography (CT) scan with contrast or magnetic resonance imaging (MRI); MRI is the more sensitive study. See chapter *Neurologic Symptoms* for more information.

Perform chest x-ray and CT scans of other areas as indicated by the patient's presentation. Positron emission tomography or gallium scanning also may be used to assess the extent of the disease.

Cerebrospinal fluid studies

Lumbar puncture (LP) should be performed in all persons diagnosed with NHL and in those suspected of having CNS lymphoma (brain imaging should be obtained first to rule out the presence of mass lesions that might cause herniation upon LP). Studies should include cytology, cell count, protein and glucose measurements, and any studies needed to rule out infections or other causes of the patient's symptoms (eg, bacterial, mycobacterial, and fungal cultures).

Bone marrow biopsy

This procedure may yield the diagnosis if other studies are negative. It also should be performed for patients with known NHL to assess for bone marrow involvement.

Treatment

If possible, patients should be evaluated and treated by an oncologist experienced in the treatment of HIV-related malignancies. Systemic chemotherapy is the only curative treatment, but the optimal treatment for AIDS-related NHL has not been defined. The standard regimen for advanced disease is R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), though the specific treatment will depend on the specific type of lymphoma and on patient characteristics. In patients with very low CD4 cell counts, rituximab may be withheld because of the risks of further immunosuppression. Patients with meningeal involvement should receive concomitant intrathecal chemotherapy (medication given directly into the CNS via a lumbar puncture or Ommaya reservoir) using methotrexate and cytarabine.

Patients treated with ART in addition to chemotherapy appear to have better survival rates than do those treated with chemotherapy alone. Therefore, all patients should receive ART, if possible, in addition to chemotherapy.

Prognosis is dependent on the type and stage of the lymphoma and on the stage of HIV disease. A CD4 count of <200 cells/ μ L, extranodal disease including bone marrow, and a poor performance status are indicative of a poor prognosis. Patients with Stage IV NHL and very low CD4 counts usually have a life expectancy of <6 months. However, 50% of those patients may die from an OI rather than from the lymphoma. Patients who achieve a complete response with chemotherapy have a survival benefit that may range from 6 to 20 months or longer. In general, outcomes are better in patients taking ART for their HIV infection.

Patient Education

- ◆ Successful treatment of NHL requires meticulous adherence to the treatment plan. Patients who sporadically receive treatment put themselves at risk for the adverse effects of treatment but may receive little of the benefit. Advise patients to take all of their medications exactly as prescribed and to attend all of their scheduled chemotherapy and follow-up clinic appointments.
- ◆ Different chemotherapy regimens have different side effect profiles. Not all patients who receive chemotherapy will be nauseous or lose their hair. Educate patients about the possible side effects of chemotherapy and other medications and advise them to call their health care providers if they develop these.
- ◆ Encourage patients who are not taking ART to agree to start; emphasize the importance of close adherence.
- ◆ Emphasize to patients the importance of medications in preventing OIs, if these are indicated.

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Pelvic Inflammatory Disease

Background

Pelvic inflammatory disease (PID) is the syndrome resulting from the ascent of microorganisms from the vagina and cervix to the uterine endometrium, fallopian tubes, ovaries, or contiguous abdominal structures. Many episodes of PID go unrecognized, because of lack of symptoms or mild, nonspecific symptoms (eg, dyspareunia, abnormal bleeding, and vaginal discharge). Infecting organisms may include *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, which are sexually transmitted, and anaerobic bacteria (*Gardnerella vaginalis* or *Haemophilus influenzae*), gram-negative rods (*Escherichia coli*), *Streptococcus agalactiae*, gastrointestinal flora, and mycoplasmas (*Mycoplasma hominis*), which may not be sexually transmitted. PID is coepidemic with HIV among some urban populations of reproductive age. Data on PID outcomes in HIV-infected women are limited. Many studies have documented no difference in length or severity of lower abdominal pain, vaginal discharge, fever, abnormal vaginal bleeding, or low back pain between HIV-positive and HIV-negative women with PID. However, there is a higher rate of tubo-ovarian abscesses and severe salpingitis and pyosalpinx in HIV-positive women.

Clinical presentation may include salpingitis, endometritis, tubal and/or ovarian abscess, and pelvic peritonitis, although PID may present with subtle or mild symptoms even in HIV-infected women. Long-term complications of PID may include infertility, ectopic pregnancy, pelvic adhesions, and chronic pain.

S: Subjective

The patient may complain of mild-to-moderate lower abdominal pain and tenderness, pain with intercourse, vaginal discharge, fever, chills, heavy menstrual bleeding, or other abnormal vaginal bleeding.

Inquire about the following during the history:

- ◆ Symptoms listed above, and duration
- ◆ New sex partner(s), unprotected sex
- ◆ Use of intrauterine device
- ◆ Last menstrual period

- ◆ Previous diagnosis of gonorrhea or chlamydia
- ◆ Previous abdominal or gynecologic surgery

O: Objective

Perform a focused physical examination, documenting fever (temperature may be elevated or normal) and other vital signs. Check abdomen for bowel sounds, distention, rebound, guarding, masses, suprapubic and costovertebral angle (CVA) tenderness; perform complete pelvic examination looking for abnormal bleeding or discharge; uterine, adnexal, or cervical motion tenderness; pelvic masses or adnexal enlargement.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Pregnancy, uterine or ectopic
- ◆ Ruptured or hemorrhagic ovarian cyst
- ◆ Dysmenorrhea
- ◆ Appendicitis
- ◆ Pyelonephritis
- ◆ Diverticulitis
- ◆ Irritable bowel syndrome
- ◆ Cystitis
- ◆ Uterine fibroids/leiomyomas
- ◆ Ovarian torsion
- ◆ Mittelschmerz
- ◆ Kidney stones
- ◆ Pyelonephritis

P: Plan

Diagnostic Evaluation

- ◆ Gram stain of endocervical discharge
- ◆ Microscopic examination of saline preparation of vaginal secretions
- ◆ Endocervical and rectal cultures, urine for *N gonorrhoeae*
- ◆ Endocervical and rectal culture, or nucleic acid amplification test, for endocervical swab or first void urine
- ◆ Pregnancy test (if menses is late or pregnancy is possible)

Treatment

Because clinical diagnostic criteria for PID are not always conclusive, presumptive diagnosis and early treatment is common. The positive predictive value of a clinical diagnosis is 65-90%. The absence of infection from the lower genital tract, where samples are usually taken, does not exclude PID and should not influence the decision to treat.

Empiric treatment for PID should be initiated in sexually active women at risk for sexually transmitted infection if the following minimum criteria are met:

- ◆ Uterine or adnexal tenderness
- ◆ Cervical motion tenderness
- ◆ Additional criteria that support the diagnosis of PID include:
 - ◆ Oral temperature >101° F
 - ◆ Abnormal cervical or vaginal mucopurulent discharge
 - ◆ Presence of white blood cells in vaginal secretions
 - ◆ Elevated erythrocyte sedimentation rate
 - ◆ Elevated C-reactive protein
 - ◆ Laboratory documentation of infection with *N gonorrhoeae* or *C trachomatis*
- ◆ Definitive criteria:
 - ◆ Endometrial biopsy with histopathologic evidence of endometritis
 - ◆ Transvaginal sonogram showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex

- ◆ Laparoscopic abnormalities consistent with PID

Treatment considerations

Antimicrobial regimens must provide broad-spectrum coverage of likely pathogens (Table 1). HIV-infected women respond equally well to standard antibiotic regimens as HIV-negative women. Whether the management HIV-infected women with advanced immunocompromise requires more aggressive interventions (eg, hospitalization or parenteral antimicrobial regimens) has not been determined. Decisions about whether to use oral or parenteral therapy must be individualized.

In moderate to severe cases of PID, intrauterine devices (IUDs) should be removed, if present.

The goals of treatment are to:

- ◆ Alleviate the pain and systemic malaise associated with infection
- ◆ Achieve microbiological cure
- ◆ Prevent development of permanent tubal damage with associated problems, such as chronic pelvic pain, ectopic pregnancy, and infertility
- ◆ Prevent the transmission of infection to others

Indications for hospitalization of patients with PID include:

- ◆ Unsure diagnosis; surgical emergency cannot be excluded
- ◆ Tubo-ovarian abscess
- ◆ Severe illness with nausea and vomiting or high fever
- ◆ Pregnancy
- ◆ Inability to follow outpatient regimen
- ◆ Immunosuppression (low CD4 count or significant comorbidity)

Pregnancy

If the patient is pregnant, aggressive treatment is essential to prevent preterm delivery, fetal loss, and maternal morbidity. Certain medications should be avoided to reduce the risk of fetal toxicity; these include doxycycline, fluoroquinolones, and gentamicin. Hospitalization for parenteral antibiotic therapy is recommended.

Table 1. Treatment Regimens for Pelvic Inflammatory Disease

Antibiotic Regimens	
Oral / Outpatient Treatment (see CDC STD Treatment Guidelines, referenced below)	
Regimen 1	• Ofloxacin* 400 mg orally twice daily for 14 days <i>or</i> • Levofloxacin* 500 mg orally once daily for 14 days <i>with or without</i> • Metronidazole 500 mg orally twice daily for 14 days (provides activity against anaerobes)
Regimen 2	• Ceftriaxone 250 mg intramuscular (IM) injection in a single dose <i>or</i> • Cefoxitin 2 g IM injection in a single dose, administered concurrently with probenecid 1 g orally in a single dose <i>or</i> • Other parenteral third generation cephalosporin (eg, ceftizoxime or cefotaxime) <i>plus</i> • Doxycycline 100 mg orally twice daily for 14 days <i>with or without</i> • Metronidazole 500 mg orally twice daily for 14 days
Parenteral / Inpatient Treatment	
Regimen 1	• Cefotetan 2 g intravenously (IV) every 12 hours <i>or</i> • Cefoxitin 2 g IV every 6 hours <i>plus</i> • Doxycycline 100 mg orally or IV every 12 hours (oral form is preferable because of the irritant qualities of the IV solution)
Regimen 2	• Clindamycin 900 mg IV every 8 hours <i>plus</i> • Gentamicin loading dose IV or IM injection (2 mg/kg of body weight) followed by maintenance dose (1.5 mg/kg) IV every 8 hours or 5-7 mg/kg IV daily
Alternative Parenteral Regimens	
Regimen 1	• Ofloxacin* 400 mg IV every 12 hours <i>or</i> • Levofloxacin* 500 mg IV daily <i>with or without</i> • Metronidazole 500 mg IV every 8 hours
Regimen 2	• Ampicillin/Sulbactam 3 g IV every 6 hours <i>plus</i> • Doxycycline 100 mg orally or IV every 12 hours (oral form is preferable due to the irritant qualities of IV solution)

* Fluoroquinolones should not be used to treat PID infections acquired outside the United States, or in California, Hawaii, or other areas with high rates of fluoroquinolone-resistant gonorrhea.

Follow-Up

- ◆ Patients should show significant clinical improvement within 3 days of initiation of therapy (eg, improvement in fever, abdominal tenderness, and uterine, adnexal, and cervical motion tenderness). If the patient has not improved, consider hospitalization, additional diagnostic testing, or surgical intervention. Patients who are initially hospitalized for treatment may be switched to an oral regimen and discharged on oral therapy after they have improved clinically.
- ◆ Evaluate sexual partners and offer them treatment if they had sexual contact with the patient during the 60 days preceding the patient's onset of symptoms. Treat empirically for both chlamydia and gonorrhea.
- ◆ Some specialists recommend rescreening for *C trachomatis* and *N gonorrhoeae* after therapy is completed in women with documented infection with these pathogens.
- ◆ Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent becoming reinfected with chlamydia or gonorrhea, to prevent other sexually transmitted infections, and to prevent passing HIV to sexual partners.

Patient Education

- ◆ Instruct patients to take all of their medications. Advise patients to take medications with food if they are nauseated, and to call or return to clinic right away if they have vomiting or are unable to take their medications.
- ◆ Sexual partners from the previous 60 days need to be tested for sexually transmitted pathogens, and treated as soon as possible with a regimen effective against gonorrhea and chlamydia, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated. Otherwise, they may be reinfected.
- ◆ Advise patients to avoid sexual contact until the infection has been cured.
- ◆ Provide education about sexual risk reduction. Instruct patients to use condoms with every sexual contact to prevent becoming reinfected, to prevent other sexually transmitted infections, and to prevent passing HIV to sexual partners.

- ◆ Advise patients that PID can recur, and that they should call or return to the clinic if symptoms such as pain or fever develop.
- ◆ Patients must not drink beer, wine, or any other alcoholic beverage during treatment while taking metronidazole, and for at least 24-48 hours after the last dose. Metronidazole may cause a disulfiram reaction, resulting in severe nausea and vomiting. Note that patients taking ritonavir may experience symptoms due to the small amount of alcohol in the capsules; advise patients to call if nausea and vomiting occur.

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Pneumocystis Pneumonia

Background

Pneumocystis jiroveci pneumonia (previously called *Pneumocystis carinii* pneumonia, and still abbreviated PCP), is caused by an unusual fungus, *Pneumocystis jiroveci*. Many humans appear to be infected in childhood, but clinical illness occurs only in people with advanced immunosuppression, either through new infection or reactivation of latent infection. Cases of PCP in otherwise healthy young homosexual men were among the first recognized manifestations of AIDS, in 1981. The organism can affect many organ sites, but pneumonia is far and away the most common form of disease. In the United States, the incidence of PCP has declined sharply since the use of prophylaxis and effective antiretroviral therapy (ART), but PCP is still many patients' initial presenting opportunistic infection and a significant cause of morbidity and mortality in HIV-infected patients.

S: Subjective

The patient complains of fever, shortness of breath, particularly with exertion, nonproductive cough, night sweats, weight loss, or fatigue. Typically, the symptoms worsen over days to weeks. Pleuritic pain and retrosternal pain or burning also may be present. There may be minimal symptoms if early in the course of PCP.

Note: Given the possibility of HIV-associated tuberculosis (TB), patients with cough should be kept in respiratory isolation until TB is ruled out.

Ask patient about fever, fatigue, and weight loss, which may be present for weeks, with gradual worsening of shortness of breath. PCP may present less commonly with acute onset symptoms of fevers, chills, sweats, dyspnea, and cough.

O: Objective

Perform a full physical examination with particular attention to the following:

- ◆ Vital signs including temperature, heart rate, blood pressure, respiratory rate, oxygen saturation at rest and after exertion (there is often a sharp drop in oxygen saturation with exertion)
- ◆ Appearance
- ◆ Lung examination

Patients may appear relatively well, or acutely ill. Tachypnea may be pronounced, and patients may exhibit such a high respiratory rate (>30 breaths per minute) that they are unable to speak without stopping frequently to breathe. Chest examination may be normal, or reveal only minimal rales, although coughing is common on deep inspiration. Cyanosis may be present around the mouth, in the nail beds, and on mucous membranes. Cough is either unproductive, or productive of a thin clear or whitish mucus.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Pneumococcal pneumonia
- ◆ Other bacterial pneumonias
- ◆ Tuberculosis
- ◆ *Mycobacterium avium* complex
- ◆ Lymphocytic interstitial pneumonitis
- ◆ Bronchitis
- ◆ CMV pneumonitis
- ◆ Histoplasmosis
- ◆ Other fungal pneumonia, especially *cryptococcus*
- ◆ Pulmonary Kaposi sarcoma
- ◆ Asthma, chronic obstructive pulmonary disease
- ◆ Congestive heart failure
- ◆ Pulmonary hypertension

P: Plan

Diagnostic Evaluation

- ◆ CD4 count is usually <200 cells/ μ L (>90% of PCP cases occur in patients with CD4 counts <200 cells/ μ L).
- ◆ Arterial blood gas (ABG): hypoxemia is common, as is elevation in alveolar-arterial O₂ gradient (A-a gradient). Generally, PO₂ levels and A-a gradient are associated with disease severity. Poorer outcomes are seen with PO₂ <70 mm Hg and A-a gradient >35 mm Hg.
- ◆ Elevated serum lactate dehydrogenase (LDH) (>300-500 IU is common.)
- ◆ Thin-section chest computed tomography (CT) scan may show ground glass opacities; in a patient with clinical signs or symptoms of PCP, these are suggestive but not diagnostic of PCP.
- ◆ Chest x-ray typically shows bilateral interstitial infiltrates, but atypical patterns with cavitation, lobar infiltrates, nodules, or pneumothorax may occur, and chest x-ray may be normal in some cases. Upper lobe predominance is common if the patient is receiving aerosolized pentamidine for PCP prophylaxis.
- ◆ Sputum induction: The patient inhales saline mist to mobilize sputum from the lungs. The respiratory therapist collects expectorated sputum, which is stained with Giemsa and examined for *P. jiroveci* organisms. This technique is useful because of its noninvasive approach, but requires an experienced technician, and may not be available at all centers. Sensitivity varies widely (10-95%) depending on the expertise of the center. If there is any chance that the patient has TB, sputum induction should be done in a confined space in a negative pressure area or near an exhaust fan vented safely outside.
- ◆ Bronchoscopy with bronchoalveolar lavage (BAL): If induced sputum is negative for PCP organisms, definitive diagnosis is made through detection of organisms in BAL fluid obtained during bronchoscopy. Sensitivity is >95% in experienced centers. BAL fluid can be evaluated for bacteria, *mycobacteria*, and fungi, as well as for *P. jiroveci*.
- ◆ Transbronchial biopsy may be done if lung disease is progressive despite treatment, to look for diagnoses other than PCP. Open lung biopsy is rarely done.

Treatment

Presumptive treatment is often initiated based on clinical presentation, chest x-ray findings, and ABG results, while definitive diagnostic tests are pending. Table 1 shows the standard and alternative treatment regimens.

Standard Therapy

Trimethoprim-sulfamethoxazole

Trimethoprim-sulfamethoxazole (TMP-SMX, Bactrim, Septra, cotrimoxazole) is the drug of choice: 15-20 mg/kg of the TMP component and 75-100 mg/kg of the SMX component, divided into 3 or 4 doses daily intravenously or orally for 21 days (a typical oral dose is 2 double-strength tablets 3 times daily). Adverse effects of TMP-SMX are common (eg, rash, fever, leukopenia, anemia, gastrointestinal intolerance), mostly mild, and can usually be “treated through.” Patients who have had previous reactions to sulfa drugs also may be successfully desensitized (see chapter *Sulfa Desensitization*). TMP-SMX requires dose adjustment in cases of renal insufficiency.

Adjunctive corticosteroids

Adjunctive corticosteroids should be given if the room air PO₂ is <70 mm Hg or the A-a gradient is >35 mm Hg. Corticosteroids should be given as early as possible (preferably before or with the first dose of antibiotic therapy) and within 36-72 hours of the start of antipneumocystis therapy:

- ◆ Prednisone 40 mg twice daily days 1-5; 40 mg once daily on days 6-10; 20 mg once daily on days 11-21. Intravenous methylprednisolone can be given, as 75% of the prednisone dose.

Table 1. Standard and Alternative PCP Therapy

Drugs	Dosages	Notes
Standard Therapy		
Trimethoprim + sulfamethoxazole (TMP-SMX)	TMP: 15-20 mg/kg plus SMX: 75-100 mg/kg divided into 3 or 4 doses daily intravenously (IV) or orally for 21 days	Patients who have had previous reactions to sulfa drugs may be successfully desensitized. Adjust dose in renal insufficiency.
Alternative Therapies		
Pentamidine	4 mg/kg IV daily for 21 days	Similar efficacy to TMP-SMX but greater toxicity (nephrotoxicity, pancreatitis, glucose dysregulation, cardiac arrhythmias). Usually reserved for patients with severe disease who require intravenous therapy.
Dapsone + trimethoprim	Dapsone* 100 mg orally daily plus trimethoprim 15 mg/kg orally daily for 21 days	Appropriate for mild-to-moderate disease
Clindamycin + primaquine	Clindamycin 600-900 mg IV every 6-8 hours (or 300-450 mg orally every 6-8 hours) plus Primaquine* base 15-30 mg orally once daily for 21 days	Appropriate for mild-to-moderate disease.
Atovaquone	750 mg orally twice daily for 21 days	For mild-to-moderate PCP only; not as potent as TMP-SMX
Trimetrexate (+ leucovorin)	Trimetrexate 45 mg/m ² (or 1.2 mg/kg) IV daily plus Leucovorin 25 mg orally every 6 hours for 21 days	Not as potent as TMP-SMX. Leucovorin must be continued for 3 days beyond completion of trimetrexate

* Screen for G6PD deficiency (most common in patients of African or Mediterranean descent).

Other therapy notes

- ◆ Patients started on intravenous therapy can be switched to an oral treatment regimen to complete the 3-week course when they are afebrile, have improved oxygenation, and are able to take oral medications.
- ◆ Paradoxical worsening of PCP due to presumed immune reconstitution inflammatory syndrome (see chapter) has been reported in patients who initiated ART close to the time of diagnosis and treatment for PCP. At present, there is no consensus on whether initiation of ART during an acute episode of PCP is preferable to delaying ART, and clinical trials are under way to explore this question.
- ◆ Many providers prefer to wait until completion of PCP therapy and clinical stabilization of the patient before initiating ART. Consultation with HIV experts is advisable when considering starting ART in the setting of PCP.

Treatment failures

The average time to clinical improvement in hospitalized patients is 4-8 days, so avoid premature change in therapy. In patients who fail to improve on appropriate therapy, it is important to exclude other diagnoses, rule out fluid overload, and consult an infectious disease specialist. Some patients do not respond to any therapy, and the mortality rate of hospitalized patients is about 15%.

Secondary Prophylaxis

Anti-PCP prophylaxis (chronic maintenance therapy) should be given to all patients who have had an episode of PCP. Prophylaxis should be continued for life, unless immune reconstitution occurs as a result of ART, and the CD4 count has been >200 cells/ μ L for at least 3 months.

Standard prophylactic therapy

TMP-SMX, 1 double-strength tablet orally daily, or 1 single-strength tablet orally daily

Alternative prophylactic therapy

- ◆ Dapsone* 100 mg orally once daily, or 50 mg orally twice daily
- ◆ Dapsone* 50 mg orally once daily + pyrimethamine 50 mg orally once per week + leucovorin 25 mg orally once per week
- ◆ Dapsone* 200 mg orally + pyrimethamine 75 mg + leucovorin 25 mg, all once per week
* *Warning:* Screen for G6PD deficiency before starting dapsone.
- ◆ Aerosolized pentamidine 300 mg once per month, via Respigard II nebulizer (note: does not prevent toxoplasmosis)
Warning: May increase the risk of extrapulmonary pneumocystosis, pneumothorax, and bronchospasm.
- ◆ Atovaquone suspension 1,500 mg orally once daily
- ◆ TMP-SMX: 1 double-strength tablet orally 3 times per week (eg, Monday, Wednesday, Friday)

Primary Prophylaxis

Primary prophylaxis against PCP should be given to all HIV-infected patients with CD4 counts <200 cells/ μ L or CD4 percentages <14%, or a history of oral candidiasis. See chapter *Opportunistic Infection Prophylaxis*.

Patient Education

- ◆ Instruct patients to take all medications exactly as prescribed.
- ◆ Patients should call their health care providers if symptoms worsen.
- ◆ Patients being treated with TMP-SMX who develop rash, fever, or other new symptoms, should call their providers to be evaluated for a drug reaction.
- ◆ Explain to patients that taking anti-PCP prophylaxis is extremely important to prevent repeat episodes of illness. Patients should not stop taking these medicines without talking with their health care providers, and should not let their prescriptions run out.

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Progressive Multifocal Leukoencephalopathy

Background

Progressive multifocal leukoencephalopathy (PML) is a rare demyelinating disease of the central nervous system (CNS) to which immunocompromised hosts are vulnerable. It is caused by the JC virus, a polyomavirus that infects and lyses oligodendrocytes. Disease is thought to result from reactivation of latent infection. Among HIV-infected patients, PML occurs most frequently in those with CD4 counts of <100 cells/ μL . They typically present with deficits of the cerebrum and brainstem, such as cognitive decline, focal weakness, and cranial nerve palsies, which progress over the course of subsequent weeks. Among untreated patients, the interval between the first manifestation of neurologic symptoms and death may be as short as 3–4 months. Although the prognosis for patients with PML has improved with the use of potent antiretroviral therapy (ART), there is no specific treatment for PML and mortality rates remain high. Patients who survive PML are likely to have permanent neurologic deficits.

Whereas PML in the absence of ART usually is not an inflammatory condition, initiation of ART may cause an immune reconstitution-like syndrome, involving new or worsening neurologic deficits and inflammatory changes seen on brain imaging and biopsy specimens. (See chapter *Immune Reconstitution Syndrome*.) The initiation of ART in a patient with late-stage HIV-related disease may even unmask previously silent PML. Although many patients with inflammatory PML improve or at least stabilize, some suffer exacerbation of symptoms, rapid progression of disease, and death.

S: Subjective

The patient or a caregiver may note symptoms such as weakness, gait abnormalities, difficulties with speech, visual changes (eg, field deficits, nystagmus, and blindness), altered mental status, personality changes, and seizures. The onset is likely to be subacute, though neurologic disturbances may be profound.

O: Objective

- ◆ Measure vital signs.
- ◆ Perform a full physical examination, including a thorough neurologic and mental status and evaluation. Look for focal or nonfocal neurologic deficits, particularly cranial nerve abnormalities, visual field defects, weakness, gait abnormalities, and abnormalities in cognitive function, speech, or affect. The patient typically is alert, and deficits are likely to be multiple.
- ◆ Review previous laboratory values, particularly CD4 count (usually is <100 cells/ μL in patients with PML).

A: Assessment

Rule out other causes of the patient's neurologic changes. A partial differential diagnosis includes:

- ◆ CNS lymphoma
- ◆ Toxoplasmosis
- ◆ HIV encephalopathy
- ◆ HIV dementia
- ◆ Other (non-HIV) forms of dementia
- ◆ Cerebrovascular disease
- ◆ Neurosyphilis
- ◆ CNS opportunistic infection (eg, tuberculosis, cryptococcosis, and cytomegalovirus)
- ◆ Multiple sclerosis

P: Plan

Diagnostic Evaluation

Definitive diagnosis requires a brain biopsy and identification of characteristic pathological changes, or detection of JC virus DNA in cerebrospinal fluid (CSF) of patients with radiographic and clinical findings consistent with PML.

Presumptive diagnosis often is made on the basis of clinical presentation, brain imaging, and laboratory tests. A brain biopsy should be considered with patients for whom a diagnosis is unclear.

Radiographic studies

CNS imaging may reveal changes typical of PML, but is nonspecific. Magnetic resonance imaging (MRI) is more sensitive than computed tomography (CT) for detecting PML. PML presents as single or multiple hypodense lesions in the subcortical white matter, with no surrounding edema. On MRI, lesions show increased T2 signal and little or no enhancement with gadolinium. On CT, PML lesions typically are nonenhancing. In some patients, and particularly in patients taking ART, PML lesions may show inflammatory changes, such as enhancement.

CSF evaluation

- ◆ CSF cell count, protein level, and glucose level generally are normal or show mild pleocytosis and slightly elevated protein.
- ◆ A JC virus polymerase chain reaction (PCR) assay is approximately 75-85% sensitive; detection of JC virus in a patient whose clinical presentation and radiographic imaging results are consistent with PML is adequate to make a diagnosis. A negative result with JC virus PCR does not rule out PML.

Other studies

- ◆ Other diagnostic tests should be performed as indicated to rule out other potential causes of the patient's symptoms.
- ◆ A brain biopsy should be considered if the diagnosis is unclear.

Treatment

- ◆ There is no specific treatment for JC virus. Potent ART with effective immune reconstitution is the only treatment that may be effective for patients with PML. Even with ART, however, mortality rates approach 50%, and neurologic deficits are unlikely to be reversible.
- ◆ Initiate ART for patients who are not already receiving treatment. It is not clear whether antiretroviral agents with good CNS penetration are more effective than those that are less likely to cross the blood-brain barrier.
- ◆ For patients who are taking ART with incomplete virologic suppression, change the ART regimen appropriately to achieve virologic suppression, if possible. For patients on ART with poor immunologic response, consider changing or intensifying therapy with the goal of improved immunologic recovery. (See chapter *Antiretroviral Therapy*.)

- ◆ If symptoms are caused by immune reconstitution, consider adding corticosteroids (eg, dexamethasone) to help decrease inflammation.
- ◆ Depending on the patient's cognitive and physical status, he or she may need a care provider in the home to assure that medications are taken on schedule.
- ◆ The patient is likely to need supportive care for personal hygiene, nutrition, safety, and prevention of accidents or injury; refer as indicated.

Patient Education

- ◆ When a diagnosis of PML has been established or suspected, the clinician should initiate a discussion of plans for terminal care (including wills, advanced directives, and supportive care and services) with the patient and family members or caregivers. Supportive treatment will be necessary for an undetermined period of time, and hospice referral should be considered if the patient does not show clinical improvement in response to ART.
- ◆ If the patient is receiving ART, the clinician should be sure that family members or friends are taught about the medications and are able to help the patient with adherence.

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Seborrheic Dermatitis

Background

Seborrheic dermatitis is one of the most common skin manifestations of HIV disease. It occurs in <5% of the general HIV-uninfected population, but in 34-83% of those with advanced HIV disease. It may flare and subside over time, and tends to worsen after severe illness. Seborrheic dermatitis is characterized by reddish or pink patches of skin, accompanied by greasy flakes or scales. It most commonly occurs in the scalp and on the face, especially at the nasolabial folds, eyebrows, and forehead, but also may develop on the ears, chest, upper back, axillae, or groin. Occasionally, seborrheic dermatitis may be severe and may involve large areas of the body.

The etiology of seborrheic dermatitis is not entirely clear. *Malassezia* yeast (formerly called *Pityrosporum ovale*) may play a causative role, as may high sebum levels.

S: Subjective

The patient complains of a new rash, sometimes itchy, or of “dry skin” that will not go away despite the application of topical moisturizers.

O: Objective

Perform a thorough evaluation of the skin with special attention to the scalp, nasolabial folds, ears, eyebrows, eyelashes, central chest, back, axillae, and groin. Seborrheic dermatitis appears as greasy or waxy flakes of skin over red or pink patches of skin. The distribution often is symmetrical.

A: Assessment

The diagnosis of seborrheic dermatitis usually is based on the characteristic appearance. A partial differential diagnosis includes psoriasis and rosacea.

P: Plan

Treatment

- ◆ Antiretroviral therapy, if otherwise indicated.
- ◆ Topical antifungal medications: various preparations are available; selection can be based on cost and availability. Antifungals may be used in combination with topical corticosteroid therapy (see below). Effective antifungals are not limited to this list.
 - ◆ Ketoconazole (Nizoral) 2% cream or shampoo. Studies suggest this is as effective as 1% hydrocortisone cream. Ketoconazole is one of the most widely studied of all topical treatments.
 - ◆ Bifonazole ointment, miconazole cream (Monistat), terbinafine (Lamisil) 1% solution, or clotrimazole (Lotrimin) 1% cream, lotion, or solution.
 - ◆ Ciclopiroxolamine (Loprox) 1% shampoo, gel, or cream.
 - ◆ Zinc pyrithione (keratolytic/antifungal) shampoo or cream.
- ◆ Topical corticosteroids are generally effective and may be used in combination with topical antifungal therapy (see above). Low-potency agents (eg, hydrocortisone 1%) rather than high-potency corticosteroids (eg, betamethasone dipropionate, triamcinolone), are recommended, especially for the face, to reduce the adverse effects associated with all corticosteroids (eg, atrophy, telangiectasias, and perioral dermatitis).
- ◆ Selenium sulfide/sulfur preparations (the most common is selenium sulfide shampoo).
- ◆ Whole coal tar and crude coal tar extract.
- ◆ Lithium succinate ointment, available in some countries as a combination of 8% lithium succinate and 0.05% zinc sulfate (may have antifungal or anti-inflammatory effects).
- ◆ Antibiotic agents:
 - ◆ Metronidazole 1% gel
- ◆ Honey, 90% diluted with warm water, may be useful to treat seborrheic dermatitis and dandruff.

- ◆ Noncorticosteroid topical immunomodulators (eg, tacrolimus, pimecrolimus) are helpful in atopic dermatitis and may be useful for seborrheic dermatitis.
- ◆ Oral therapy may be used for patients refractory to topical treatment (check for possible drug-drug interactions with antiretroviral and other medications before prescribing).
 - ◆ Itraconazole 200 mg once daily for 7 days (safest and best option)
 - ◆ Ketoconazole 200 mg once daily for no more than 4 weeks (prolonged use may cause hepatotoxicity)
 - ◆ Terbinafine 250 mg once daily for 4 weeks

Patient Education

- ◆ Although topical and oral medicines can relieve symptoms, recurrence of symptoms is common. Effective antiretroviral therapy also should be considered to control the effects of HIV on the immune system and thereby treat the underlying cause of seborrheic dermatitis.

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Sinusitis

Background

Sinusitis is defined as an inflammation involving the membrane lining of any sinus, and is a frequent finding in people with HIV disease. It occurs very commonly as part of a viral upper respiratory infection (URI), and usually is self-limited. Bacterial sinusitis usually occurs as a secondary complication of a viral URI, which causes decreased patency of the nasal ostia, decreased nasal ciliary action, and increased mucus production. Acute sinusitis is defined as lasting up to 4 weeks, whereas chronic sinusitis persists for at least 12 weeks.

HIV-infected patients are susceptible to sinusitis for a number of reasons related to their immunosuppression. Pathophysiologic mechanisms for this susceptibility may include proliferation of lymphatic tissue contributing to nasal obstruction, defects in B-cell and T-cell immunity due to HIV, and defects in production of immunoglobulins, specifically IgE, resulting in an exaggerated allergic response in the nasal mucosa. As in the general population, the most common pathogens causing acute bacterial sinusitis are *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and *Haemophilus influenzae*. However, HIV-infected patients have a greater incidence of sinusitis caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*. The bacterial causes of chronic sinusitis are not well understood, but may involve more polymicrobial and anaerobic infections. In patients with severe immunosuppression, particularly those with CD4 counts ≤ 50 cells/ μ L, sinusitis may be caused by *Aspergillus* and other fungal pathogens.

S: Subjective

The patient may complain of facial pain, frontal or maxillary headache, postnasal drip, or fever.

Ask the patient about specific symptoms, the duration and progression of symptoms, and treatments attempted.

- ◆ Fever
- ◆ Facial pain or pressure, headache; positional pain (worse when patient bends forward)
- ◆ Purulent or bloody nasal discharge
- ◆ Postnasal drip

- ◆ Nasal congestion
- ◆ Recent URI
- ◆ Malaise
- ◆ Chronic cough
- ◆ Maxillary tooth pain
- ◆ Ear pressure
- ◆ History of chronic sinusitis, seasonal allergies, antibiotic allergies, atopy
- ◆ Tobacco use, inhaled recreational drugs

O: Objective

- ◆ Document vital signs.
- ◆ Perform a careful physical examination focusing on the head and face, neck, and lungs. Examine the nose, mouth, ears, and sinuses; look for nares inflammation, drainage from sinus ostia; examine the tympanic membranes and external auditory canals, evaluate the oropharynx for mucous drainage, lesions, exudates; check the teeth and gums for tenderness and erythema; palpate for tenderness over frontal and maxillary sinus cavities; examine the face and orbits for swelling or erythema.
- ◆ Perform cranial nerves examination.
- ◆ Auscultate the chest for abnormal lung sounds.

A: Assessment

Partial differential diagnosis includes:

- ◆ Allergic rhinitis
- ◆ Sinus blockage by other lesions such as Kaposi sarcoma or lymphoma (particularly if the CD4 count is <200 cells/ μ L) or fungal infections (if CD4 count is <50 cells/ μ L)
- ◆ Dental abscess, caries
- ◆ Meningitis
- ◆ Trauma

P: Plan

Diagnostic Evaluation

Uncomplicated acute sinusitis is usually a clinical diagnosis. There are no symptoms, physical findings, or tests that reliably distinguish bacterial from viral sinusitis. Patients can generally be assumed to have bacterial sinusitis if symptoms do not resolve, or if they worsen, over the course of 7-10 days. Any patient with high fever or severe or unusual symptoms should be evaluated urgently for other causes of illness.

Imaging studies usually are not indicated for uncomplicated acute sinusitis. In patients with a poor response to empiric antibiotic therapy and/or worsening symptoms, and those with suspected chronic sinusitis, computed tomography (CT) scans of the paranasal sinuses are the best initial radiologic study. Standard x-rays (sinus series) can detect cloudiness or air-fluid levels and will show mucosal thickening (a nonspecific finding in HIV-infected individuals).

Cultures of nasal aspirates are not useful for diagnosis, because nasal fluids do not accurately represent pathogens in the paranasal sinuses. Sinus aspirate cultures will give definitive diagnosis of a specific organism in the majority of cases; this may be considered in complicated cases. Definitive diagnosis of invasive fungal sinusitis requires tissue for culture.

Treatment

Treatment is multimodal. For viral sinusitis, treatment is based on symptom suppression; for bacterial sinusitis, an antibiotic is added to other therapies:

- ◆ Antihistamine: chlorpheniramine or other
- ◆ Decongestant: pseudoephedrine
- ◆ Nonsteroidal anti-inflammatory drugs (NSAIDs): ibuprofen or other
- ◆ Cough suppressant as needed
- ◆ Mucolytic agent: guaifenesin
- ◆ Inhaled steam and saline nasal irrigation to promote sinus drainage

If acute bacterial sinusitis is suspected, treat as above and add an antibiotic for a 10-14 day course of therapy:

- ◆ Amoxicillin 500-1,000 mg 3 times daily
- ◆ Amoxicillin/clavulanate (Augmentin) 825/125 mg twice daily
- ◆ Cefpodoxime 200-400 mg twice daily

- ◆ Doxycycline 100 mg twice daily
- ◆ Levofloxacin 500 mg once daily or moxifloxacin 400 mg once daily

For chronic sinusitis, administer multimodal treatments and an antibiotic as listed above for 3-4 weeks; add a nasal steroid such as budesonide, fluticasone, mometasone, or triamcinolone.

Note: Avoid fluticasone (Flonase) and budesonide (Rhinocort Aqua) nasal spray in patients taking ritonavir (including ritonavir-boosted protease inhibitors such as Kaletra), because significant increases in serum levels of these glucocorticoids may occur.

If symptoms persist or worsen, refer patients to an otolaryngologist for further evaluation and treatment.

Patient Education

- ◆ Instruct patients in the correct use of medications used to treat sinusitis, including proper technique for nasal irrigation or steam inhalation, as required.
- ◆ Instruct patients to take antibiotics on schedule until the entire prescription is gone in order to prevent recurrence of the infection.
- ◆ Advise patients that drinking 8 glasses (8-12 oz each) of fluid daily helps to keep the mucus thin enough to drain the sinus passages.
- ◆ Advise patients to call or return to clinic for swelling of the face or swelling around the eyes, increased facial tenderness, new or worsening fever, or other concerning symptoms.

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Syphilis

Background

Syphilis is a sexually transmitted infection (STI) caused by the spirochete *Treponema pallidum*. It is a complex disease with protean variations that can mimic many common infections or illnesses. HIV infection may alter the natural history and management of syphilis, causing a more rapid course of illness, higher risk of neurologic complications, and greater risk of treatment failure with standard regimens. Because many individuals with syphilis have no symptoms, or have symptoms that subside without treatment, sexually active individuals at risk for syphilis should receive regular screening for syphilis as well as for other STIs. Many clinicians strongly recommend routine syphilis testing every 3–6 months in patients at risk for syphilis.

In recent years, increasing numbers of syphilis cases have been reported in HIV-infected men who have sex with men (MSM), predominantly in major metropolitan areas. This trend reflects reduced use of safer sex practices, and is concerning both because syphilis can have major health consequences if it is undetected and untreated, and because it is associated with increased risk of new HIV infections. Risk assessment should be conducted at each patient visit for unprotected sex (including oral sex), multiple sexual partners, and use of recreational drugs (methamphetamine and cocaine, in particular, are associated with high-risk sexual practices in MSM). Asymptomatic persons at risk of acquiring syphilis should be screened at regular intervals (with rapid plasma reagin [RPR] or Venereal Diseases Research Laboratory [VDRL] testing, as below), depending on their risk factors. MSM with multiple partners should be tested every 3–6 months.

The natural history of untreated syphilis infection is divided into several different stages based on length of infection.

Primary Syphilis

Primary syphilis usually manifests after an incubation period of 1–3 weeks from exposure and is characterized by a painless self-limiting ulcer (chancre) at the site of sexual contact. HIV-infected individuals may have multiple or atypical chancres that might be misidentified. Some patients have no primary lesion, or have a primary lesion that is not visible. Associated

regional lymphadenopathy can occur. HIV-infected individuals sometimes have a chancre concurrently with rash typical of secondary syphilis.

Secondary Syphilis

Secondary syphilis usually develops 2–8 weeks after initial infection and is caused by ongoing replication of the spirochete, with disseminated infection that may involve multiple systems. Rash is the most common presenting symptom; skin lesions may be macular, maculopapular, papular, or pustular, or may appear as condyloma lata. The rash often appears on the trunk and extremities and may involve the palms and soles of feet. Constitutional symptoms, lymphadenopathy, arthralgias, and myalgias are common and neurologic or other symptoms may occur. In the absence of treatment, the manifestations of secondary syphilis last days to weeks, then usually resolve to the latent stages.

Latent Syphilis

Latent syphilis follows resolution of secondary syphilis. As in HIV-uninfected individuals, latent syphilis is asymptomatic and the diagnosis is determined by positive serologic tests. Latent syphilis is further classified as “early latent” if the infection is known to be less than 1 year in duration, “late latent” if the infection is known to be greater than 1 year in duration, or “latent syphilis of unknown duration” if the duration of infection is not known.

Late or Tertiary Syphilis

Late or tertiary syphilis is due to chronic infection with progressive disease in any system causing serious illness and death in untreated patients. The most common manifestations include neurosyphilis, cardiovascular syphilis, and gummatous syphilis.

Neurosyphilis

Neurosyphilis can occur at any time after initial infection, due to spread of the spirochete to the central nervous system (CNS). In HIV-infected individuals, neurosyphilis may occur more commonly early in the course of infection, during secondary or latent syphilis. It is associated with neurologic symptoms, including cranial nerve abnormalities (particularly extraocular

or facial muscle palsies, tinnitus or hearing loss) or symptoms of meningitis. Uveitis or other eye disease may occur in conjunction with neurosyphilis.

S: Subjective

Symptoms will depend on the site of initial infection, the stage of disease, and whether neurosyphilis is present. Symptoms are not present in all patients.

If symptoms are present, the patient may complain of:

- ◆ Painless sore(s) or ulcer(s) in the genital area, vagina, anus, or oral cavity
- ◆ New rash, usually on the trunk, soles, and/or palms; patchy hair loss
- ◆ Fever, malaise, swollen glands, arthralgias, myalgias
- ◆ Altered mental status, weakness, paralysis
- ◆ Neurosyphilis: vision changes, eye pain, hearing loss, headaches, dizziness, generalized weakness, seizures, confusion, changes in personality or affect

Conduct a targeted history, asking the patient about symptoms listed above, including duration; inquire about other or associated symptoms. Ascertain the following:

- ◆ Previous diagnosis of syphilis
- ◆ New sex partner(s) in past 90 days (for primary or secondary syphilis)
- ◆ Unprotected sex (oral, vaginal, anal)
- ◆ Date of last syphilis test
- ◆ Possible pregnancy

O: Objective

Check for fever, document other vital signs

Perform a complete examination including:

- ◆ Skin and mucosal areas (including the genitals, palm, and soles): rash, gummas, granulomas, patchy hair loss
- ◆ Oropharynx: chancres, mucous patches, condyloma lata
- ◆ Lymph nodes
- ◆ Heart: murmurs
- ◆ Ophthalmic examination
- ◆ Neurologic examination (mental status, cranial nerves [including visual acuity], sensory, motor, reflexes, coordination, gait): abnormal mental status, visual acuity changes, extraocular movement

abnormalities, neurosensory hearing loss, facial palsy, paraesthesias, paralysis, hemiplegia, hyperactive reflexes, ataxia

A: Assessment

Because syphilis has a wide range of manifestations, the differential diagnosis is broad. It is important to consider syphilis as a possible cause of many presenting illnesses. A partial differential diagnosis includes:

- ◆ Other causes of maculopapular rashes: pityriasis, drug eruption, condyloma, folliculitis, psoriasis, acute HIV infection
- ◆ Other causes of genital ulcerative disease: herpes simplex virus (HSV), chancroid
- ◆ Other causes of ocular disease: glaucoma, cytomegalovirus (CMV) retinitis, CMV immune reconstitution uveitis, HSV keratitis
- ◆ Other causes of neurologic disease: stroke, Bell's palsy, CNS lymphoma, toxoplasmosis, meningitis
- ◆ Other causes of cardiac murmurs: bacterial endocarditis, congenital abnormalities
- ◆ Other causes of systemic symptoms (eg, fever, malaise, adenopathy): acute HIV infection, acute hepatitis, other infections or malignancies

P: Plan

Diagnostic Evaluation

Darkfield examination and direct fluorescent antibody

Darkfield examination and direct fluorescent antibody (DFA) testing of a sample from suspicious genital or anal chancres or moist dermatologic lesions (not oral lesions) are definitive tests for syphilis.

Serologic tests

Nontreponemal tests (RPR or VDRL) are most sensitive in primary and secondary syphilis when titers are high, though the response may be delayed in HIV-infected patients (typically nontreponemal tests are positive within 3 months after infection). Because false-positive results may occur, positive nontreponemal test results must be confirmed with a treponemal test. Titers may be used to follow response to treatment; a fourfold change in titer is considered a significant change. Note that the same nontreponemal test should be used consistently for a single patient; RPR titers cannot be compared with VDRL titers.

Treponemal antibody tests (TP-PA [T pallidum particle agglutination] or FTA-ABS [fluorescent treponemal antibody absorption]) confirm a positive nontreponemal test.

A false-negative RPR or VDRL test may occur, usually when the test is performed in early infection, before a sufficient antibody response has developed. Another possible cause of a false-negative nontreponemal test is the prozone phenomenon, seen when antibody concentrations are very high (usually in secondary syphilis) and the specimen is not diluted sufficiently. If serologic tests are negative and suspicion of syphilis is high, perform other diagnostic tests (biopsy, etc) and/or request that the laboratory perform additional dilutions on nontreponemal test specimens.

Cerebrospinal fluid (CSF) evaluation

HIV-infected patients with clinical evidence of neurologic or ocular syphilis, late latent syphilis, syphilis of unknown duration, or tertiary syphilis should receive lumbar puncture (LP) and CSF analysis. LP also is indicated for patients in whom treatment for early syphilis fails (see below). Some specialists recommend CSF evaluation for all HIV-infected patients with syphilis of any stage. CSF analysis should include:

- ◆ CSF-VDRL: this test is specific but is not very sensitive; a positive test is diagnostic but a negative test does not rule out neurosyphilis.
- ◆ Leukocytes: elevated white blood cell count (>10 cells/ μL) is suggestive but is not specific. Note that mononuclear pleocytosis (up to 5-20 cells/ μL) is not uncommon in patients with HIV infection, particularly those with higher CD4 cell counts.
- ◆ Some recommend checking CSF FTA-ABS. This is very sensitive but not very specific; a negative test indicates that neurosyphilis is very unlikely.

Other testing

All patients who test positive for syphilis should be tested for gonorrhea and chlamydia, with sampling sites based on sexual practices and exposures (oropharyngeal, urethral, vaginal, or anorectal testing). Patients not known to be HIV-infected also should be tested for HIV.

Treatment

Treatment of syphilis in HIV-infected individuals essentially is the same as in HIV-uninfected individuals, and depends on stage and the presence or absence of neurosyphilis. It is important to follow patients closely to assure the success of treatment. For further information, see the Centers for Disease Control and Prevention (CDC) Sexually Transmitted Diseases Treatment Guidelines (reference below).

Early syphilis

Less than 1 year duration, ie, primary, secondary, and early latent; nonneurologic

- ◆ **Recommended:** benzathine penicillin G, 2.4 million units intramuscularly (IM) (single dose).
- ◆ **Alternatives:** In penicillin-allergic, nonpregnant patients, consider the following. Note that these therapies are not as well proven in HIV-infected individuals; close monitoring for treatment response is recommended.
 - ◆ Doxycycline, 100 mg orally twice daily for 14 days
 - ◆ Tetracycline, 500 mg orally 4 times daily for 14 days
 - ◆ Ceftriaxone, 1 gm IM or intravenously (IV) daily for 8-10 days
 - ◆ High rates of treatment failure have been reported in patients treated with azithromycin (2 grams, single dose); this regimen should be used only if other options are contraindicated and close follow-up is possible

Late latent syphilis

More than 1 year duration or of unknown duration; nonneurologic

- ◆ CSF examination to rule out neurosyphilis should be done on all patients with a history of syphilis of more than 1 year or of unknown duration.
- ◆ If CSF examination is negative, treat with benzathine penicillin G, 2.4 million units IM weekly for 3 consecutive weeks (7.2 million units total).
- ◆ In penicillin-allergic clients, refer for desensitization to penicillin. As an alternative, some consider doxycycline 100 mg orally twice daily for 28 days. Referral to infectious disease specialist and close clinical monitoring are required, as treatment is not proven in HIV-infected individuals.

Tertiary syphilis

Consult with specialists.

Neurosyphilis

Syphilis at any stage with neurologic or ocular symptoms or CSF findings of neurosyphilis

Ideally, patients should be hospitalized and given 2 weeks of penicillin IV under close observation. Penicillin-allergic patients should be referred for desensitization, if possible.

- ◆ **Recommended:** aqueous crystalline penicillin G, 18–24 million units IV per day (3–4 million units every 4 hours [or continuous infusion] for 10–14 days).
- ◆ **Alternatives** (require strict adherence with therapy):
 - ◆ Procaine penicillin 2.4 million units IM per day, plus probenecid 500 mg orally 4 times daily, both for 10–14 days.
 - ◆ Some consider use of ceftriaxone, 2 gm IM or IV once daily for 10–14 days with close clinical monitoring.
- ◆ Some specialists recommend administration of benzathine penicillin, 2.4 million units IM weekly for 3 weeks, after completion of the standard 10- to 14-day course of therapy for neurosyphilis.
- ◆ Recheck CSF leukocyte count every 6 months until the cell count normalizes (if CSF pleocytosis was present at initial evaluation). If the leukocyte count is not lower at 6 months, consider retreatment (consult with a specialist).

Note that a Jarisch-Herxheimer reaction may occur after initial syphilis treatment, especially in primary, secondary, or even latent syphilis. This self-limited treatment effect should not be confused with an allergic reaction to penicillin. It usually begins 2–8 hours after the first dose of penicillin and consists of fever, chills, arthralgias, malaise, tender lymphadenopathy, and intensification of rash. It resolves within 24 hours and is best treated with rest and acetaminophen. Patients should be warned about the possibility of Jarisch-Herxheimer reaction.

Pregnancy

Pregnant women should be treated with penicillin, if possible, using a regimen appropriate to the stage of infection (see above). Penicillin-allergic pregnant women should be referred for desensitization to penicillin. Doxycycline and tetracycline may cause fetal

toxicity and should not be used during pregnancy; erythromycin is not sufficiently effective in treating syphilis in the fetus. The efficacy of azithromycin and ceftriaxone in pregnancy is uncertain.

Women treated during the second half of pregnancy are at risk of contractions, early labor, and fetal distress if they develop a Jarisch-Herxheimer reaction; thus, they should be monitored carefully.

Sex partners

Syphilis is transmitted sexually only when mucocutaneous lesions of syphilis are present; this is uncommon after the first year of infection. Nevertheless, sex partners of a patient who has syphilis in any stage should be evaluated.

- ◆ Persons exposed within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively, as they might be infected with syphilis even if they are seronegative.
- ◆ Persons exposed more than 90 days before the diagnosis of primary, secondary, or early latent syphilis should be treated presumptively if serologic test results are not available immediately and the patient's follow-up is in doubt. Otherwise, they should receive serologic testing and be treated appropriately if the test result is positive. Note that some experts recommend presumptive treatment of all persons potentially exposed to syphilis. For patients with primary syphilis, this means partners within the previous 3 months; for secondary, within 6 months; for early latent, within 1 year.

Follow-up

All HIV-infected patients treated for syphilis should be evaluated clinically and serologically at 3, 6, 9, 12, and 24 months (at 6, 12, 18, and 24 months for late syphilis) to rule out treatment failure. Treatment success is determined by a fourfold decrease in RPR or VDRL titer by 6–12 months (for early syphilis) or 12–24 months (for late syphilis) after treatment. Patients whose titers do not decrease appropriately probably either experienced treatment failure or were reinfected. Any patient with apparent treatment failure should undergo an LP for CSF analysis and be re-treated as appropriate. If, at any time, symptoms develop or nontreponemal test titers increase fourfold, CSF examination should be performed and appropriate treatment should be given.

Some patients retain reactive (low-titer) nontreponemal test results after successful treatment for syphilis. In these “serofast” individuals, reinfection with syphilis is indicated by a rise in test titer of at least 4-fold.

Risk-reduction counseling

All patients with syphilis should receive risk evaluation and risk-reduction counseling. Evaluate each patient’s sexual practices with regard to risk of acquiring STIs and of transmitting HIV. Work with the patient to reduce sexual risks.

Patient Education

- ◆ Instruct patients to go to clinic for treatment at the intervals recommended. If patients are given oral antibiotics (penicillin-allergic individuals), instruct them to take their medications exactly as prescribed.
- ◆ Warn patients about the possibility of Jarisch-Herxheimer reaction and advise them about self-management of associated symptoms (eg, acetaminophen or aspirin at usual doses, fluids, and rest).
- ◆ Instruct patients about the required follow-up laboratory and clinical evaluations necessary to document adequate treatment. Emphasize the need for regular evaluation of treatment efficacy.
- ◆ Sexual partners from the previous 3–6 months (sometimes longer, depending on the stage of syphilis) need to be evaluated and treated as soon as possible, even if they have no symptoms. Advise patients to inform their partner(s) that they need to be tested and treated.
- ◆ Syphilis is a reportable communicable disease in the United States. Patients will be contacted to assist with partner tracing and to ensure appropriate treatment.
- ◆ Provide education about sexual risk reduction. Review sexual practices and support patients in using condoms with every sexual contact to prevent becoming reinfected with syphilis or infected with other STIs, and to prevent passing HIV to sexual partners.

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Toxoplasmosis

Background

Toxoplasma gondii is a common intracellular protozoan that preferentially infects the central nervous system (CNS) of immunodeficient patients, causing severe neurologic disease. *T. gondii* also can cause local disease such as chorioretinitis or pneumonia. *Toxoplasma* has an infectious reservoir in almost all animals; humans acquire infection either through ingestion of tissue cysts contained in undercooked meat (usually pork or lamb) or oocysts on contaminated vegetables or through exposure to cat feces containing oocysts. There is no transmission by person-to-person contact.

Clinical disease usually occurs through reactivation of latent infection in patients who have CD4 counts of <100 cells/ μ L. Seroprevalence varies widely, from 15% in the United States to 75% in some European countries, and even higher in certain resource-limited countries. In the absence of prophylaxis, toxoplasmic encephalitis occurs in more than 30% of patients with advanced HIV disease who are seropositive for *T. gondii*.

CNS toxoplasmosis is an AIDS-defining condition that can be progressive and fatal. However, antimicrobial therapy, especially if given in conjunction with antiretroviral therapy (ART) that results in immune reconstitution, can be successful in treating toxoplasmosis. Specific prophylaxis and effective ART also may be used to prevent toxoplasmosis in patients with advanced AIDS who have latent *T. gondii* infection (as demonstrated by the presence of anti-Toxoplasma immunoglobulin G [IgG] antibodies; see chapter *Preventing Exposure to Opportunistic and Other Infections*).

S: Subjective

The patient may complain of subacute onset of dull, constant headache, fever, visual changes or other focal neurologic symptoms, confusion, or disorientation. Seizures may occur. Caregivers may report subtle alterations in mental status or mood.

Take a careful history from the patient and caregivers about the symptoms listed above and their duration, progression, and severity. Inquire about other related symptoms. Ask whether the patient is taking *Toxoplasma* prophylaxis or ART.

O: Objective

- ◆ Measure vital signs (temperature, heart rate, blood pressure, respiratory rate).
- ◆ Perform a full physical examination including a thorough neurologic examination, looking for focal or nonfocal neurologic deficits, particularly weakness, cranial nerve abnormalities, visual field defects, gait disturbances, and abnormalities in speech, cognitive, or affective functions.
- ◆ Review previous laboratory values, particularly:
 - ◆ CD4 count (which usually is <50-100 cells/ μ L in patients with toxoplasmosis)
 - ◆ Toxoplasma IgG (>95% of patients with toxoplasmosis have positive IgG)

A: Assessment

Rule out other infectious or neoplastic causes of headache, fever, and neurologic changes. A partial differential diagnosis includes:

- ◆ CNS lymphoma
- ◆ Cryptococcal meningitis
- ◆ Progressive multifocal leukoencephalopathy (PML)
- ◆ Tuberculous meningitis
- ◆ Brain abscesses of bacterial, fungal, or mycobacterial etiologies
- ◆ Herpes simplex virus or cytomegalovirus (CMV) encephalitis
- ◆ Primary HIV encephalopathy
- ◆ AIDS dementia complex
- ◆ Cerebrovascular accident secondary to hemorrhage, hypoxia, or emboli from vegetative endocarditis
- ◆ Neurosyphilis
- ◆ Other causes of chorioretinitis such as CMV, HIV, and cryptosporidiosis

P: Plan

Diagnostic Evaluation

Definitive diagnosis requires identification of *T gondii* in tissue biopsy or body fluid samples. Brain biopsy usually is not performed if toxoplasmosis is strongly suspected; instead, presumptive diagnosis is made on the basis of clinical presentation, laboratory and imaging tests, and response to therapy. Brain biopsy should be considered in patients who do not respond to therapy or in whom the diagnosis is unclear.

- ◆ Serum *Toxoplasma* IgG antibody test results are positive in nearly all patients with toxoplasmic encephalitis. A negative IgG test result makes the diagnosis very unlikely but does not rule it out. (Antibody titer changes are uncommon in reactivation disease and are not useful in making a diagnosis.)
- ◆ CNS imaging with computed tomography (CT) typically shows multiple contrast-enhancing mass lesions, but may show a single lesion or no lesions. Magnetic resonance imaging (MRI) is more sensitive than CT for CNS toxoplasmosis. Other imaging studies, such as single photon emission CT (SPECT), may be useful in distinguishing toxoplasmic lesions from CNS lymphoma.
- ◆ Polymerase chain reaction (PCR) tests for *T gondii* in the cerebrospinal fluid have poor sensitivity.
- ◆ Other diagnostic tests should be performed as indicated to rule out other potential causes of the patient's symptoms.
- ◆ Patients with toxoplasmic encephalitis typically respond quickly to treatment. If clinical improvement is not seen after 10-14 days of appropriate treatment, or if clinical worsening is seen in the first week, consider brain biopsy for alternative diagnoses.

Treatment

Treatment consists of 2 phases: acute therapy and chronic maintenance therapy.

Presumptive treatment often is begun on the basis of clinical presentation, positive *Toxoplasma* IgG, and results of brain imaging studies. If patients do not respond quickly to treatment, other diagnoses should be considered. The following recommendations are based on treatment guidelines published by the Centers for Disease Control and Prevention, National Institutes of Health, and HIV Medicine Association/Infectious Diseases Society of America (see References below).

Acute Therapy

Preferred

- ◆ Pyrimethamine 200 mg orally as a single loading dose, then 50 mg (<60 kg body weight) to 75 mg (>60 kg body weight) daily + sulfadiazine 1,000 mg (<60 kg body weight) to 1,500 mg orally every 6 hours (>60 kg body weight) + folinic acid (leucovorin) 10-20 mg daily.

Dosage adjustments to the lower end of therapeutic range of pyrimethamine and sulfadiazine may be considered for patients who have significant bone marrow suppression despite folinic acid supplementation. Monitor patients carefully for cytopenias, especially if they are on other agents that cause bone marrow suppression, such as zidovudine, valganciclovir, and ganciclovir.

Note: Patients at risk for G6PD deficiency should be checked for G6PD deficiency before starting pyrimethamine.

Alternatives

- ◆ Pyrimethamine + folinic acid (administered as described above) + 1 of the following:
 - ◆ Clindamycin 600 mg orally or intravenously every 6 hours; recommended for patients with significant allergic reactions to sulfa medications
 - ◆ Atovaquone 1500 mg orally every 12 hours
 - ◆ Azithromycin 900-1,200 mg orally once daily
- ◆ Trimethoprim-sulfamethoxazole (TMP-SMX) 5 mg/kg TMP and 25 mg/kg SMX orally or intravenously every 12 hours. This can be considered when the availability of other regimens is limited or when patients need intravenous therapy.

- ◆ Atovaquone 1,500 mg orally twice daily + sulfadiazine 1,000-1,500 mg orally every 6 hours.

Note: The regimens that contain sulfadiazine, TMP-SMX, or atovaquone also are effective in preventing *Pneumocystis jiroveci* pneumonia (PCP), so patients on these regimens do not need additional PCP prophylaxis.

Adjunctive corticosteroids (eg, dexamethasone 4 mg orally or intravenously every 6 hours) may be indicated for patients with significant CNS edema or mass effect. Use is based on clinical judgment and should be discontinued as soon as clinically feasible.

Anticonvulsant therapy should be given to patients with seizures.

Ventilatory support may be necessary if severe CNS symptomatology is present.

Chronic Maintenance Therapy

After at least 6 weeks of initial therapy, and significant clinical and radiologic improvement, chronic maintenance therapy can be considered.

Preferred

- ◆ Pyrimethamine 25-50 mg orally once daily + sulfadiazine 500-1,000 mg orally every 6 hours + folinic acid 10 mg orally once daily (also effective as PCP prophylaxis).

Alternatives

- ◆ Pyrimethamine 25-50 mg orally once daily + clindamycin 300-450 mg orally every 6-8 hours + folinic acid 10 mg orally once daily.
- ◆ Pyrimethamine 25-50 mg orally once daily + atovaquone 1,500 mg orally once daily + folinic acid 10 mg orally once daily (also effective as PCP prophylaxis).

Chronic maintenance therapy generally should be continued for life. For patients who complete acute therapy successfully, have resolution of signs and symptoms of toxoplasmosis, and have immune reconstitution (with CD4 counts >200 cells/ μ L) for more than 6 months on ART, it is reasonable to consider discontinuing maintenance therapy. Some specialists would require resolution of CNS lesions on radiologic studies before discontinuation of therapy. Patients must be observed for recurrence of symptoms, and treatment should be restarted if the CD4 count decreases to <200 cells/ μ L.

Considerations in Pregnancy

All pregnant women should be tested for *T gondii*. If the result is positive, evaluate the mother for toxoplasmosis and the neonate for evidence of congenital infection. Perinatal transmission usually occurs only with acute maternal infection, but in advanced HIV, it may occur with reactivation of chronic infection. If *T gondii* infection occurs during pregnancy, consult with a maternal-fetal specialist. Treatment for pregnant women is the same as for nonpregnant adults (see above). Note that sulfadiazine taken at the time of delivery may increase the risk of neonatal hyperbilirubinemia and kernicterus.

Patient Education

- ◆ Advise patients that antimicrobial therapy alone will not eradicate toxoplasmosis, but should decrease symptoms and improve quality of life. If medications are discontinued, the disease is likely to recur, unless the CD4 count increases to >100-200 cells/ μ L in response to ART.
- ◆ Inform patients that suppressive therapy must be continued to prevent recurrence. This therapy may be lifelong.
- ◆ It is essential for patients to take all medicines exactly as prescribed. If doses are missed, or if the medications are stopped and restarted, *Toxoplasma* can develop resistance to the medications. If patients are having trouble taking the medication on schedule, they should contact their health care providers immediately.
- ◆ Educate patients about the benefits of ART in strengthening the immune system and preventing opportunistic infections such as toxoplasmosis.
- ◆ Advise patients to return to clinic promptly if symptoms worsen or new symptoms develop.
- ◆ Toxoplasmosis is a late-stage HIV opportunistic infection and indicates profound immune suppression. Some patients may not respond to treatment or to ART. As with any patient who is at risk for a life-threatening HIV-related disease, clinicians should discuss advance directives and durable power of attorney with patients. Referral to a social worker, mental health clinician, or chaplain experienced in such issues may facilitate this discussion.

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Linear Gingival Erythema

Background

Linear gingival erythema is inflammation of the margins of the gingiva. It is characterized by a 2-3 mm band of intense erythema around the necks of the teeth that does not resolve with routine oral hygiene. The erythematous changes usually are generalized, but may be confined to a few teeth. This condition is one of the most common oral manifestations of advanced HIV/AIDS. It also may be referred to as HIV gingivitis or red-band gingivitis.

S: Subjective

The patient may complain of bleeding, tender gums, and a bad taste in the mouth.

O: Objective

Examine the oral cavity carefully for inflamed gingival tissues, which bleed easily upon manipulation (including brushing). This condition is seen most commonly in the buccal area of lower anterior teeth, as a continuous red band around the necks of teeth.

A: Assessment

The differential diagnosis includes necrotizing gingivitis, periodontitis, and Kaposi sarcoma. (See chapters on *Necrotizing Ulcerative Periodontitis and Gingivitis* and *Kaposi Sarcoma* for more information.)

P: Plan

The diagnosis is based on clinical features; perform additional testing to rule out other causes, as indicated. Recommend patient education and counseling, meticulous home care, frequent dental visits during treatment phase, and regular recall visits. Refer for nutrition counseling as needed.

Treatment

Linear gingival erythema should be treated aggressively to prevent progression to necrotizing periodontal disease; referral should be made for prompt dental care and the patient should be educated in oral hygiene techniques.

A chlorhexidine gluconate (0.12%) rinse twice daily for 2 weeks will relieve some of the symptoms. Refer to a dentist or dental hygienist for a thorough dental prophylaxis (cleaning). If this combination is not successful, it may be appropriate to add an antibiotic such as:

- ◆ Metronidazole 250 mg orally 4 times daily for 7 days
- ◆ Amoxicillin-clavulanate (Augmentin) 875 mg orally twice daily for 7 days
- ◆ Clindamycin 150-300 mg orally 4 times daily for 7 days

Patient Education

- ◆ Good oral hygiene is essential to management, especially with concomitant periodontitis. Advise patients to brush and floss after every meal. Any rinses prescribed by care providers should be used after brushing.
- ◆ Advise patients not to eat or drink for 30 minutes after rinsing with chlorhexidine gluconate.
- ◆ Urge regular dental checkups and cleaning at least every 3-6 months.
- ◆ Patients should not drink alcohol while taking metronidazole, and for at least 48 hours after the last dose.

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Necrotizing Ulcerative Periodontitis and Gingivitis

Background

Necrotizing ulcerating periodontitis (NUP) is a marker of severe immunosuppression that affects the gums and extends to the underlying bone or periodontium. It may or may not be distinct from necrotizing ulcerative gingivitis (NUG), which is considered to be confined to the gums. This discussion will focus primarily on NUP, but the microbial profiles and treatment recommendations for these two periodontal diseases are similar.

NUP in HIV-infected individuals is believed to be an endogenous infection that progresses to necrosis of the gingiva. Pathogens may include anaerobic bacteria and fungi. NUP usually presents as “blunting” at interdental papillae, but rapidly progresses to destruction of underlying alveolar bone. It usually is associated with severe pain and spontaneous bleeding. Several case reports have described extensive destruction leading to exfoliation of teeth within 3–6 months of onset, with sequestration of necrotic alveolar bone and necrotic involvement of the adjacent mandible and maxilla. Patients may present with concomitant malnutrition due to inability to take food by mouth. The prevalence of NUP in the HIV-infected population has been reported as 0–5%. NUP is the most serious form of periodontal disease associated with HIV.

S: Subjective

The patient complains of painful, spontaneously bleeding gums, diminished or metallic taste, bad breath, or loose teeth (with a prevalence toward anterior teeth and first molars). “Deep jaw pain” is a common complaint and may reflect extension to adjacent mucosa.

O: Objective

Examine the oral cavity carefully. NUP and NUG present with fiery red, ulcerated gingival tissues, and grayish exudate. Teeth may be very loose or missing and there will be a fetid odor from the mouth. The ulcerated tissues can extend past the attached gingiva to the adjacent mucosa. Necrosis of adjacent bone also is common.

A: Assessment

The differential diagnosis includes other causes of gingival ulceration, such as herpes simplex virus, herpes zoster, cytomegalovirus, and Kaposi sarcoma. (See relevant chapters on these conditions.)

P: Plan

Treatment

Treatment usually is divided into the acute phase and the maintenance phase. The primary concern in the acute phase is pain control. For the maintenance phase, treatment is directed toward reducing the burden of potential pathogens, preventing further tissue destruction, and promoting healing.

- ◆ For uncomplicated NUP or NUG, perform local debridement with irrigation and periodontal curettage (extending below the marginal gingiva).
- ◆ Chlorhexidine gluconate rinse (0.12%) twice daily after brushing and flossing (the alcohol-free preparation is preferred).
- ◆ Antibiotic therapy (preferably narrow spectrum, to leave gram-positive aerobic flora unperturbed).
 - ◆ Metronidazole or penicillin is the drug of choice, 250 mg orally 3 times daily for 10–14 days.
 - ◆ Coadminister with amoxicillin-clavulanate (Augmentin) 875 mg orally twice daily for 10–14 days, if no hypersensitivity or allergy to either drug exists.
- ◆ Refer to a dentist for the following:
 - ◆ Removal of plaque and debris from the site of infection and inflammation
 - ◆ Debridement of necrotic hard and soft tissues, with a 0.12% chlorhexidine gluconate lavage

Patient Education

- ◆ Advise the patient of the following: Good oral hygiene is critical to arresting gum, periodontium, and tooth loss. Avoid smoking and try to eliminate emotional stress. When primary stabilization is achieved, resume daily brushing and flossing after every meal. This may be difficult during the acute phase, but it is very important to keep the mouth as clean as possible. Nutrition supplements (liquid diet, plus vitamins/minerals) are recommended.
- ◆ Frequent professional cleaning (every 2-3 months) may be needed during the maintenance phase.
- ◆ Patients taking metronidazole should not drink alcohol during treatment with metronidazole, and for at least 24-48 hours after last dose, in order to avoid severe nausea and vomiting from a disulfiram reaction.
- ◆ Instruct patients not to drink, eat, or rinse their mouths with water for 30 minutes after rinsing with chlorhexidine.
- ◆ Bleeding gums may transmit HIV (or hepatitis C) during "deep kissing" or other activities (oral-genital contact). Advise patients/clients to avoid exposing partners to HIV by taking all necessary precautions, including abstaining from risky activities until this condition is healed and stable (no oozing of oral fluids).

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Oral Health

Background

Examination of the oral cavity should be included in both the initial and interim physical examination of all HIV-infected patients. Patients with lesions suspected to be oral manifestations of HIV disease should be referred to a dental health expert with experience in treating oral lesions associated with HIV/AIDS. Other oral lesions may be a sign of a systemic disease, a side effect of medications, or a result of poor oral hygiene.

The following is an overview of conditions commonly seen in patients with HIV infection. See chapters *Oral and Esophageal Candidiasis*, *Oral Hairy Leukoplakia*, *Oral Warts*, *Oral Ulceration*, *Linear Gingival Erythema*, and *Necrotizing Ulcerative Periodontitis and Gingivitis* for more information about those conditions.

Aphthous Ulceration

S: Subjective

The patient complains of a painful ulcer or ulcers in the mouth.

O: Objective

The typical appearance of an aphthous ulcer is a “red raised border with a depressed, necrotic (white to yellow pseudomembrane) center.” Aphthous ulcers may be small or large, solitary or in clusters, and can resemble intraoral herpetic lesions.

A: Assessment

The differential diagnosis includes traumatic ulcers and herpes simplex virus ulcers.

P: Plan

The diagnosis usually is based on appearance. For further information, see the chapter on *Oral Ulceration*.

Atrophic Glossitis: Burning Mouth Syndrome;

S: Subjective

The patient may complain of a constant burning sensation in the mouth or a numbness or tingling feeling of the tongue. Eating certain foods or spices may trigger the burning sensation. The patient also may complain of dry mouth or a metallic taste in the mouth.

O: Objective

The tongue and oral mucosal tissues may be normal in appearance or there may be a slight redness on the tip and lateral margins of the tongue. In other cases, the tongue may appear “bald” due to the loss of papillae on the dorsal surface, and it may be “beef red” in color.

A: Assessment

Possible systemic etiologies include nutritional and vitamin deficiencies (atrophic glossitis), chronic alcoholism, medication adverse effects, diabetes mellitus, and gastric reflux. Local etiologies include denture irritation, oral habits such as tongue or cheek biting, and excessive use of certain toothpastes or mouthwashes. Psychological factors and nerve damage also may cause burning mouth. Erythematous candidiasis also can present as a burning sensation.

P: Plan

Identify the cause of the burning sensation, if possible, by review of the medical history and by performing diagnostic tests as indicated (eg, complete blood count, biopsy, or oral cytological smears). Once the underlying cause is identified, treatment may be as simple as changing a dentifrice or eliminating the identified irritant, or the condition may require systemic treatment.

Bruxism

S: Subjective

The patient may complain of chronic facial or jaw pain, sensitive teeth, earache, or waking up with a headache or facial pain. Often, the patient is not aware that he or she is clenching or grinding the teeth. Bruxism very often is a result of increased stress or anxiety, causing the patient consciously or unconsciously to clench or grind the teeth. However, some people may be “nighttime bruxers” and grind their teeth while sleeping, often loudly enough to wake others sleeping in the same room.

O: Objective

Perform a focused evaluation of the oropharynx, jaw, and facial muscles. The teeth may appear shortened, flattened, or worn down as a result of chronic grinding or clenching of the teeth. There may be hyperkeratotic lesions on the inside of cheeks due to chronic grinding or biting. There may be tenderness with palpation of facial muscles.

A: Assessment

The differential diagnosis includes other causes of facial or jaw pain, including caries, dental abscesses, and trauma.

P: Plan

Refer the patient to a dentist for treatment. Treatment may include wearing a bite guard and/or psychological or behavioral management therapy.

Dental Caries due to “Meth Mouth”

Background

Meth mouth refers to dental decay seen in individuals who smoke methamphetamine or use cocaine orally.

S: Subjective

The chief complaint may be pain in 1 or more teeth. However, if the condition is chronic, the patient may not complain of pain.

O: Objective

In meth mouth, the enamel on all teeth or multiple teeth is grayish-brown to black in color (due to decay), and appears “soft” (this has been described as a “texture less like that of hard enamel and more like that of a piece of ripened fruit”). Oral mucosal tissues appear dry due to decreased salivary flow. The gingiva appears red or inflamed, and there may be spontaneous bleeding of the gingiva around the teeth.

Another pattern of dental decay can be seen in cocaine users who rub the drug along the gingiva in order to test its strength or purity. This can lead to localized dryness of the gingival tissues. Consequently, plaque sticks to the cervical portion of the teeth in the area where the cocaine is rubbed, resulting in dental caries along the cervical portion of the teeth.

A: Assessment

The differential diagnosis includes other causes of caries and dental decay.

P: Plan

Refer to a dentist for restorative or endodontic therapy. In severe cases, extraction of the involved teeth and replacement with a partial or complete denture may be necessary. Encourage proper oral hygiene; evaluate sucrose intake.

Maxillary Tori; Mandibular Tori

S: Subjective

The patient may complain of a “lump” in the roof of the mouth or floor of mouth, behind the lower front teeth.

O: Objective

Exostosis of normal bone (covered by oral mucosal tissue) can appear as a nodular or lobulated protuberance centrally located on the hard palate (maxillary tori) or unilaterally or bilaterally located behind the mandibular incisors (mandibular tori). This develops slowly and the patient may become aware of exophytic growth only if the area is inadvertently traumatized.

A: Assessment

Differential includes other benign or malignant lesions including oral cancer and Kaposi sarcoma.

P: Plan

No treatment is indicated unless the exostosis interferes with speech or swallowing, or removal is needed for fabrication of dentures or a partial denture.

Recurrent Herpes Simplex

S: Subjective

The patient complains of a locally painful ulcer(s) on the lips or intraoral areas.

O: Objective

Herpes lesions are located on the lips and around the mouth, the gums, or gingival or hard palate. They may appear as small vesicular lesions that rupture, forming small ulcers. They may rupture and coalesce into larger lesions.

A: Assessment

The differential diagnosis includes aphthous ulcer and traumatic ulcer.

P: Plan

The diagnosis usually is based on appearance. For further information, see chapters *Oral Ulceration* and *Herpes Simplex, Mucocutaneous*.

Oral Cancer

S: Subjective

Oral malignancies may be symptomatic or asymptomatic. They are more common in users of tobacco products than in nonusers of tobacco. The patient may complain of a mouth sore that fails to heal or that bleeds easily, or a persistent white or red (or mixed) patch. The patient may note a lump, thickening or soreness in the mouth, throat, or tongue; difficulty chewing or swallowing food; difficulty moving the jaw or tongue; chronic hoarseness; numbness of the tongue or other areas of the mouth; or a swelling of the jaw causing dentures to fit poorly or become uncomfortable.

O: Objective

Perform a thorough evaluation of the oropharynx, as well as lymph nodes in the head and neck. Suspicious lesions may occur on the lips, tongue, floor of the mouth, palate, gingiva, or oral mucosa, and may appear as an ulcer or a soft-tissue mass or masses that can be pink, reddish, purple, white, or mixed red and white. The lesion typically is indurated and may be painful. It may enlarge rapidly between examinations.

A: Assessment

The differential diagnosis includes oral cancer, traumatic ulcer, hyperplasia or hyperkeratosis, and Kaposi sarcoma.

P: Plan

An ulcerated lesion or symptom described above that is present for 2 weeks or more should be evaluated promptly by a dentist or physician. If cancer is suspected, a biopsy should be obtained to make a definitive diagnosis. Treatment will be based on the specific diagnosis.

Oral Piercing

S: Subjective/Objective/Assessment

Jewelry worn in piercings in the tongue, lips, or cheeks can chip or fracture the teeth. Chronic rubbing of jewelry against the gingiva can cause the gingiva to recede, leading to periodontal problems. (These complications occur apart from procedure- or technique-associated complications associated with body piercing, such as inflammation and infection, bleeding, or transmission of bloodborne pathogens.)

P: Plan

Refer the patient to a dentist for treatment. Removal of the jewelry may be warranted.

Periodontal Disease

Background

The medical evaluation of patients with HIV infection should include assessment of periodontal health. Whereas the same type of plaque-induced periodontal diseases can be seen in both immunocompetent and immunosuppressed individuals, periodontal disease in HIV-infected patients can be a marker of HIV disease progression. In the HIV-infected patient with periodontal disease, it is important to distinguish whether or not the periodontitis represents an aggressive and/or chronic presentation unique to those with HIV disease. In addition, it is important to determine whether the patient has an inflammatory oral disease process that may further compromise his or her health.

Various illnesses and systemic factors (eg, diabetes mellitus, hormonal abnormalities, medications, and malnutrition) can complicate the clinical presentation of periodontal disease. If significant periodontal disease is suspected, refer to an experienced dentist for diagnosis and treatment. Gingivitis, a milder form of periodontal disease, usually is reversible with proper professional and home oral health care. For further information on linear gingival erythema, necrotizing ulcerative gingivitis, or necrotizing ulcerative periodontitis, see chapters *Linear Gingival Erythema* and *Necrotizing Ulcerative Gingivitis or Periodontitis*.

S: Subjective

The patient may complain of red, swollen, or painful gums, which may bleed spontaneously or with brushing; chronic bad breath or bad taste in the mouth; loose teeth or teeth that are separating; or a “bite” that feels abnormal.

O: Objective

Examine the gums. Periodontitis appears as localized or generalized gingival inflammation. The gingivae appear bright red or reddish-purple, ulcerated, and/or necrotic. Spontaneous gingival hemorrhage and purulent discharge may be evident around the teeth, especially if pressure is applied to the gingivae. Feter oris may be present.

A: Assessment

The differential diagnosis includes gingivitis, periodontitis, trench mouth, and oral abscesses. Diagnosis usually is based on appearance. Patients with severe or recalcitrant disease should be referred to a dental care provider for definitive diagnosis and treatment.

P: Plan

Treatment may include:

- ◆ Warm saline rinses
- ◆ Daily brushing and flossing
- ◆ Antimicrobial mouth rinse (eg, Listerine, chlorhexidine)
- ◆ Antibiotic therapy

For further information, see chapters *Linear Gingival Erythema* and *Necrotizing Ulcerative Periodontitis or Gingivitis*.

Xerostomia (Dry Mouth)

S: Subjective

The chief complaint may be a dry, “sticky,” or burning sensation in mouth, or an inability to “taste” food. The patient may present with difficulty swallowing.

O: Objective

The oral mucosal tissues appear dry and sometimes “shiny” in appearance. The lips may be dry and cracked, and the tongue is dry. Dental decay may be present on the cervical portion of the teeth. Oral candidiasis (thrush) may or may not be present.

A: Assessment

The differential diagnosis includes medication side effects (eg, from anticholinergics), systemic diseases (eg, Sjögren's syndrome), and adverse effects of radiation therapy.

P: Plan

Identify the cause of xerostomia and modify, if possible. Treat with artificial saliva products or oral lubricant products (eg, Salivart, Biotene Oral Balance Dry Mouth Relief Moisturizing Gel, or TheraSpray). Discourage sucking on hard candies, as that can promote dental caries. Promote good oral hygiene with flossing and brushing with a fluoride toothpaste, and encourage regular (every 3–4 months) dental recall visits. Severe cases of xerostomia may be treated by prescribing cholinergic stimulants such as pilocarpine (Salagen).

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Oral Hairy Leukoplakia

Background

Oral hairy leukoplakia (OHL) is an oral infection caused by Epstein-Barr virus (EBV). It appears as white corrugated lesions (sometimes “hairy” in appearance) on the lateral aspects of the tongue. This infection may spread across the entire dorsal surface, onto the ventral surface of the tongue, and occasionally may be found on buccal mucosa. It is common in people with HIV infection, particularly in those with advanced immunosuppression (CD4 count <200 cells/ μ L).

S: Subjective

The patient notices new, white lesions on the tongue that cannot be wiped off or removed by scraping or brushing. The OHL lesions usually are asymptomatic, but occasionally may cause alteration in taste, discomfort, or other symptoms.

O: Objective

Perform a focused examination of the oropharynx. OHL appears as unilateral or bilateral white plaques or papillary lesions on the lateral, dorsal, or ventral surfaces of the tongue or on buccal mucosa. The lesions may vary in appearance from smooth, flat, small lesions to irregular, “hairy” or “verrucous” lesions with prominent vertical folds or projections.

A: Assessment

A partial differential diagnosis for OHL includes:

- ◆ Oral candidiasis
- ◆ Squamous cell carcinoma
- ◆ Geographic tongue
- ◆ Lichen planus
- ◆ Smoker's leukoplakia
- ◆ Epithelial dysplasia
- ◆ White sponge nevus

P: Plan

Diagnostic Evaluation

A presumptive diagnosis of OHL usually is made on the basis of the clinical appearance of the lesions. Because OHL is often confused with candidiasis, the diagnosis of OHL should be considered for lesions that resemble oral candidiasis but do not respond to treatment for candidiasis (see chapter *Candidiasis, Oral and Esophageal*). Definitive diagnosis of OHL requires biopsy and demonstration of EBV.

- ◆ Biopsy lesions if they are ulcerated or unusual in appearance, to distinguish OHL from cancer or other causes.

Treatment

- ◆ Because OHL usually is asymptomatic, specific treatment generally is not necessary.
- ◆ Consider initiation of HIV treatment (antiretroviral therapy [ART]), if otherwise indicated, for immune system reconstitution. OHL may respond to ART.
- ◆ If specific treatment is required, the following may be considered. Relapse is common after discontinuation of treatment.
 - ◆ Acyclovir 800 mg orally 5 times per day for 2 weeks; famciclovir and valacyclovir may be considered.
 - ◆ Topical tretinoin (Retin-A) 0.025-0.05% solution, podophyllin 25% in tincture of benzoin, and other treatments also have been used.
 - ◆ For relapse of severe OHL, consider maintenance therapy with high-dose acyclovir, famciclovir, or valacyclovir.
- ◆ For severe symptomatic cases, surgical treatment (cryosurgery, excision, etc) may provide temporary resolution.
- ◆ Candidiasis may be present concurrently; treat candidiasis if it is present (see chapter *Candidiasis, Oral and Esophageal*).

Patient Education

- ◆ Advise the patient that OHL rarely is a problem in itself, but may be a marker of HIV progression.
- ◆ If treatment is given, review possible drug side effects and interactions, and advise the patient to call if new symptoms develop.
- ◆ Instruct the patient to comply with regular dental and medical care regimens.

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Oral Ulceration

Background

Oral ulcerations appear as necrotic or eroded areas on the oral mucosa, including the tongue. Most such lesions are idiopathic (aphthous) or of viral etiology (eg, herpes simplex virus [HSV]; rarely herpes zoster [VZV]). Oral ulcerations also may be caused by fungal, parasitic, or bacteriologic pathogens; by malignancy; or by other systemic processes. This chapter will focus on herpetic and aphthous ulcers.

Herpetic ulcerations tend to appear on keratinized tissues such as the hard palate or gingiva. Aphthous ulcerations tend to manifest on nonkeratinized tissues such as buccal mucosa, soft palate, and lingual (bottom) surface of the tongue.

S: Subjective

The patient complains of painful ulcerated areas in mouth. He or she may have difficulty eating, drinking, swallowing, or opening the mouth, and also may complain of sore throat.

History

Inquire about previous occurrences of oral ulcerative disease as well as ulcerative gastrointestinal diseases, including HSV, cytomegalovirus (CMV), or histoplasmosis. Ask about recent sexual exposures. Inquire about recent trauma or burns. Note current medications and any recent changes in medications; obtain history of tobacco (smoked and chewed) and alcohol use.

O: Objective

Look for red or white-bordered erosions or ulcerations varying in size from 1 mm to 2 cm on the buccal mucosa, oropharynx, tongue, lips, gingiva, and hard or soft palate. Lesions due to HSV tend to be shallow and occur on keratinized tissues. HSV lesions may appear as clusters of vesicles that may coalesce into ulcerations with scalloped borders. Aphthous ulcers present with a white or grey pseudomembrane surrounded by a halo of inflammation.

A: Assessment

Rule out recurrence of previous gastrointestinal or oral lesions, such as HSV and aphthous ulcers. Rule out syphilis and other suspected pathogens.

P: Plan

Diagnostic Evaluation

The diagnosis of HSV and aphthous ulcers usually is made on the basis of characteristic lesions. If diagnosis is uncertain, it is possible to perform HSV culture or HSV antigen detection using direct fluorescent antibody (DFA) testing on oral ulcerations that appear on keratinized tissues or the dorsal and lateral surfaces of the tongue, scraping near the margin of the lesion or unroofing a fresh vesicle, if available, and scraping the base. The sensitivity of HSV testing decreases when collections are taken from older, resolving herpetic areas; herpetic lesions >72 hours old usually will not yield a positive culture.

If other diagnoses are suspected, perform culture or biopsy as indicated.

Note that syphilis is very common in some HIV-infected populations. For patients in whom primary syphilis (manifested by an oral chancre) is suspected, perform (or refer for) darkfield examination; check Venereal Disease Research Laboratory (VDRL) or rapid plasma reagin (RPR) results (note that VDRL or RPR may be negative in primary syphilis); see *Syphilis* chapter for further information

Treatment

If HSV culture is positive, or if HSV is strongly suspected due to the appearance of the lesions or the patient's history, treat with HSV antiviral medication (eg, acyclovir, famciclovir, or valacyclovir) while awaiting results of culture. Do not use topical steroids without a concomitant oral HSV antiviral if the lesion is of possible herpetic etiology. Refer to *Herpes Simplex, Mucocutaneous* chapter for more complete information regarding management and treatment of HSV lesions.

Recalcitrant aphthous ulcerations should be treated with topical corticosteroids (eg, fluocinonide 0.05% or clobetasol 0.05% ointments mixed 1:1 with Orabase).

For multiple small lesions or lesions in areas where topical ointments are difficult to apply, consider dexamethasone elixir (0.5 mg/5 mL). Rinse 3 times daily with 5 mL for 1 minute, then expectorate. As with all oral topical steroids, advise the patient not to drink or eat for 30 minutes after rinsing. Continue treatment for 1 week or until lesions resolve.

Some aphthous ulcers may respond to one of the various “magic mouthwashes” that contain combinations of antibiotic, antifungal, corticosteroid, antihistamine, and anesthetic medication. The inclusion of an antihistamine (eg, diphenhydramine) and/or anesthetic (eg, lidocaine) may be helpful in treating pain associated with these ulcers.

For large or extensive aphthous ulcers, systemic corticosteroids may be needed: prednisone 40–60 mg orally daily for 1 week followed by a taper should prove beneficial. If this is ineffective, refer for biopsy to rule out CMV, other infection, or neoplastic disease.

For patients with major oral aphthous ulcers that are recalcitrant to other therapies, thalidomide 200 mg daily for 2 weeks may be considered. Thalidomide should not be used in women of childbearing potential due to its teratogenicity. It must be used very carefully with thorough patient education and 2 concomitant methods of birth control.

Pain control may be needed in order for the patient to maintain food intake and prevent weight loss. Most of the topical treatments noted above will ease pain as well as treat the ulcer. Additional considerations for pain control include:

- ◆ For small accessible ulcerations, topically apply Orabase Soothe-N-Seal (2-octyl cyanoacrylate) directly to the lesion every 4–6 hours. (This is an over-the-counter product.)
- ◆ Oral anesthetics: Various products are available such as gels, viscous liquids, or sprays (eg, benzocaine, lidocaine). These may be applied topically or swished and expectorated. They will provide temporary relief, but also may lead to a temporary loss of taste sensation.
- ◆ Systemic: If topical treatments are inadequate, consider systemic analgesics, eg, nonsteroidal anti-inflammatory drugs or opiates. Refer to the Pain Syndrome and Peripheral Neuropathy chapter.

Assess nutritional status and consider adding liquid food supplements. Suggest soft, nonspicy, or salty foods if the ulcer is interfering with food intake. Refer to a registered dietician if client is having pain, problems eating, or weight loss.

Refer to an oral health specialist or an HIV-experienced dentist as needed.

Patient Education

- ◆ Advise patients to report any oral pain or difficulty swallowing to their health care provider.
- ◆ Instruct patients in the application of topical ointments, and that they may require assistance if the lesion is difficult for the patient to see on his or her own.
- ◆ It is important for patients to maintain good nutrition and food intake while their oral ulcers heal. Advise them to eat soft, bland foods, and refer to a nutritionist if they have difficulty.

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Oral Warts

Background

Oral warts are caused by human papillomavirus (HPV) and may appear anywhere within the oral cavity or on the lips. They occur more frequently and more extensively in people with HIV infection than in those with normal immune function, especially in patients with advancing immune suppression (CD4 count <200–300 cells/ μ L). Oral warts in patients with CD4 counts <100 cells/ μ L may be refractory to therapy. The frequency of oral warts may increase, at least temporarily, in patients treated with antiretroviral therapy.

S: Subjective

The patient notices new raised lesions in the mouth or on the lips. Warts are not painful unless they have been traumatized.

O: Objective

Examine the oral cavity carefully for abnormalities. Wart lesions may vary in appearance from smooth, small, and slightly raised lesions to cauliflowerlike or spiked masses with prominent folds or projections. They may be single or multiple.

Review recent CD4 counts. In patients with oral warts, the CD4 count usually is <300 cells/ μ L.

A: Assessment

Partial differential diagnosis: squamous cell carcinoma, lichen planus, traumatic hyperkeratinized areas due to cheek biting or tongue thrusting.

P: Plan

Diagnostic Evaluation

- ◆ The diagnosis of oral warts usually is based on the appearance of the lesions. If lesions are unusual in appearance, are ulcerated, or have grown rapidly, perform biopsy to rule out cancer. If there is suspicion of other causes, perform other diagnostic evaluations as indicated.

- ◆ HPV may be demonstrated with electron microscopy or in situ hybridization; this testing is not required routinely.
- ◆ Observation of these lesions is important due to the potential, however minimal, for development of squamous cell carcinoma.

Treatment

- ◆ Treatment is difficult, as these lesions tend to recur. Treatment options include cryosurgery and surgical or laser excision. Care must be taken when using laser excision, as HPV can survive in an aerosol. Extraoral lesions (lip or corner of mouth) may be treated with topical agents such as podofilox topical solution (Condylox) or fluorouracil 5% topical (Efudex). Imiquimod 5% cream (Aldara) may help to prevent recurrence once the lesions have resolved.
- ◆ Refer to an oral health specialist or dentist for treatment.

Patient Education

- ◆ Instruct patients to comply with regular dental and medical care regimens.
- ◆ Instruct patients to use medications exactly as prescribed.

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Pain Syndrome and Peripheral Neuropathy

Background

The International Association for the Study of Pain defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Pain is subjective, it is whatever patient says it is, and it exists whenever the patient says it does. Pain is a common symptom in people with HIV infection, especially in those with advanced HIV disease. It occurs in 30-60% of HIV/AIDS patients and can diminish their quality of life significantly. Like cancer patients, HIV patients experience, on average, 2.5 to 3 types of pain at once. Pain in HIV-infected patients may have many causes (as discussed below).

Peripheral Neuropathy

Pain from HIV-associated peripheral neuropathy is particularly common, and may be debilitating. Peripheral neuropathy is clinically present in approximately 30% of HIV-infected individuals and typically presents as distal sensory polyneuropathy (DSP). It may be related to HIV itself (especially at CD4 counts <200 cells/ μ L), to medication toxicity (eg, from certain nucleoside analogues such as didanosine or stavudine), or to the effects of chronic illnesses (eg, diabetes mellitus). Patients with peripheral neuropathy may complain of numbness or burning, a pins-and-needles sensation, shooting or lancinating pain, and a sensation that their shoes are too tight or their feet are swollen. These symptoms typically begin in the feet and progress upward; the hands may be affected. Patients may develop difficulty walking because of discomfort. Factors associated with increased risk of peripheral neuropathy include the following:

- ◆ Previous peripheral neuropathy
- ◆ Low CD4 count (≤ 100 cells/ μ L)
- ◆ Prior AIDS-defining opportunistic infection or neoplasm
- ◆ Vitamin B12 deficiency
- ◆ Concomitant use of other drugs associated with peripheral neuropathy (eg, isoniazid)
- ◆ Use of neurotoxic agents (eg, alcohol)

Patients should be assessed carefully before the introduction of a potentially neurotoxic nucleoside analogue (eg, didanosine, stavudine) to avoid the use of these medications in patients at greatest risk of developing peripheral neuropathy.

Pain is significantly undertreated, especially in HIV-infected women, because of factors ranging from providers' lack of knowledge about the diagnosis and treatment of pain to patients' fear of addiction to analgesic medications. Pain, as the so-called fifth vital sign, should be assessed at every patient visit.

S: Subjective

The patient complains of pain. The site and character of the pain will vary with the underlying cause. Ascertain the following from the patient:

History

- ◆ Duration, onset, progression
- ◆ Distribution, symmetry
- ◆ Character or quality (eg, burning, sharp, dull)
- ◆ Intensity
- ◆ Severity (see below)
- ◆ Neurologic symptoms (eg, weakness, cranial nerve abnormalities, bowel or bladder abnormalities)
- ◆ Exacerbating or relieving factors
- ◆ Response to current or past treatments
- ◆ Past medical history (eg, AIDS, diabetes mellitus)
- ◆ Alcohol intake (amount, duration)
- ◆ Medications, current and recent (particularly zalcitabine, didanosine, stavudine, and isoniazid)
- ◆ Nutrition (vitamin deficiencies)
- ◆ Meaning of the pain to the patient

O: Objective

Measure vital signs (an increase in blood pressure,

respiratory rate, and heart rate can correlate with pain). Perform a symptom-directed physical examination, including a thorough neurologic examination. Look for masses, lesions, and localizing signs. Pay special attention to sensory deficits (check for focality, symmetry, and distribution [such as “stocking-glove”]), muscular weakness, reflexes, and gait. Patients with significant motor weakness or paralysis, especially if progressive over days to weeks, should be evaluated emergently.

A: Assessment

Pain assessment includes determining the type of pain: nociceptive or neuropathic. Nociceptive pain occurs as a result of tissue injury (somatic) or activation of nociceptors resulting from stretching, distention, or inflammation of the internal organs of the body. Nociceptive pain usually is well localized; may be described as sharp, dull, aching, throbbing, or gnawing in nature; and typically involves bones, joints, and soft tissue. Neuropathic pain occurs from injury to peripheral nerves or central nervous system structures. Neuropathic pain may be described as burning, shooting, tingling, stabbing or like a vise or electric shock; it involves the brain, central nervous system, nerve plexuses, nerve roots, or peripheral nerves.

Assess the severity of the pain. Have the patient rate the pain severity on a numeric scale of 0-10 (0 = no pain and 10 = worst imaginable pain), a verbal scale (none, small, mild, moderate, or severe), or a pediatric faces pain scale (when verbal or language abilities are absent). Note that pain ratings >3 usually indicate pain that interferes with daily activities. Use the same scale for evaluation of treatment response.

Although pain in HIV-infected patients is often due to opportunistic infections, neoplasms, or medication-related neuropathy, it is important to include non-HIV-related causes of pain in a differential diagnosis. Some of these other causes may be more frequent in HIV-infected individuals. A partial list for the differential diagnosis includes:

- ◆ Anorectal carcinoma
- ◆ Aphthous ulcers
- ◆ Appendicitis
- ◆ Arthritis, myalgias
- ◆ Candidiasis, oral or esophageal
- ◆ Cholecystitis

- ◆ Cryptococcal disease
- ◆ Cytomegalovirus colitis
- ◆ Dental abscesses
- ◆ Gastroesophageal reflux disease (GERD)
- ◆ Ectopic pregnancy
- ◆ Herpes simplex
- ◆ Herpes zoster
- ◆ Kaposi sarcoma
- ◆ Lymphoma
- ◆ Medication-induced pain syndromes (eg, due to growth hormone, granulocyte colony-stimulating factor)
- ◆ Medication-induced peripheral neuropathy (eg, due to didanosine, stavudine, isoniazid, vincristine)
- ◆ *Mycobacterium avium* complex
- ◆ Myopathy
- ◆ Other neuropathy
- ◆ Pancreatitis
- ◆ Pelvic inflammatory disease
- ◆ Toxoplasmosis

P: Plan

Perform a diagnostic evaluation based on the suspected causes of pain.

Treatment

Treatment should be aimed at eliminating the source of pain, if possible. If symptomatic treatment of pain is needed, begin treatment based on the patient's pain rating scale, using the least invasive route. The goal is to achieve optimal patient comfort and functioning with minimal medication adverse effects. Use the 3-step pain analgesic ladder originally devised by the World Health Organization (WHO).

Nonpharmacologic Interventions

Interventions such as relaxation techniques, guided imagery, massage, reflexology, acupuncture, thermal modalities, prayer, deep breathing, and meditation can be used as adjunctive therapy at any step in the treatment plan.

Pharmacologic interventions

The following 3 steps are adapted from the WHO analgesic ladder.

Step 1: Nonopioids for mild pain (scale 1-3)

- ◆ The most common agents in this step include acetaminophen and nonsteroidal antiinflammatory drugs (NSAIDs), and cyclooxygenase-2 (COX-2) inhibitors.
- ◆ Acetaminophen has no effect on platelets and no antiinflammatory properties; avoid use in patients with hepatic insufficiency.
- ◆ Note that COX-2 inhibitors have been associated with an increased risk of cardiovascular events and should be used with caution.
- ◆ Tramadol (Ultram) is a centrally acting nonopioid that can be combined with NSAIDs. Avoid coadministration with selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) because of serotonin syndrome; also avoid in patients with a seizure history.

Step 2: Mild opiates with or without non-opioids for moderate pain (scale 4-6)

- ◆ Most agents used to treat moderate pain are combinations of opioids and Step 1 agents.
- ◆ The most common agents are acetaminophen combined with codeine, oxycodone, or hydrocodone.
- ◆ Meperidine (Demerol) should be avoided because its active metabolite, normeperidine, has activating properties that may cause delirium and seizures.
- ◆ Chronic pain is more likely to be controlled when analgesics are dosed on a continuous schedule rather than "as needed." Sustained-release formulations of opioids should be used whenever possible.
- ◆ For breakthrough pain, use "as needed" medications in addition to scheduled-dosage analgesics.

Step 3: Opioid agonist drugs for severe pain (scale 7-10)

- ◆ Morphine is the drug of choice in this step. Others used are oxycodone, hydromorphone, fentanyl, levorphanol, methadone, codeine, hydrocodone, oxycodone, and buprenorphine.
- ◆ Avoid meperidine because of the increased risk of delirium and seizures.
- ◆ Around-the-clock, oral, sustained-release dosing will achieve optimum pain relief. Patients unable to take oral therapy may use transdermal fentanyl patches or rectal administration of sustained-release tablets.

- ◆ Anticipate and treat complications and adverse effects of opioid therapy, such as nausea, vomiting, and constipation.

Adjunctive Treatments

The addition of antidepressant medications can improve pain management, especially for chronic pain syndromes. These agents, and anticonvulsants, are usually used to treat neuropathic pain (discussed in more detail below), but should be considered for other chronic pain syndromes as well.

Treatment of Neuropathic Pain

Assess the underlying etiology, as discussed above, and treat the cause as appropriate. Review the patient's medication list for medications that can cause neuropathic pain. Discontinue the offending agents, if possible. Consider dosage reductions of stavudine to reduce peripheral neuropathy (consult with an HIV expert). For isoniazid regimens, ensure that patients are taking vitamin B6 (pyridoxine) regularly to avoid isoniazid-related neuropathy.

Nonpharmacologic interventions for neuropathic pain

The nonpharmacologic interventions described above also can be useful in treating neuropathic pain.

Pharmacologic interventions for neuropathic pain

Follow the WHO ladder of pain management described above. If Step 1 medications are ineffective, consider adding antidepressants, anticonvulsants, or both before moving on to opioid treatments.

Antidepressants

Antidepressant medications often exert analgesic effects at dosages that are lower than those required for antidepressant effects. However, as with antidepressant effects, optimum analgesic effects may not be achieved until several weeks of therapy.

- ◆ Tricyclic antidepressants (TCAs): Doses may be titrated upward every 3-5 days, as tolerated.
- ◆ Amitriptyline (Elavil): Starting dose is 10-25 mg at bedtime. Usual maintenance dosage is 25-150 mg at bedtime.
- ◆ Desipramine (Norpramin): Starting dose is 25 mg at bedtime. Usual maintenance dosage is 25-250 mg at bedtime.

- ◆ Nortriptyline (Pamelor): Starting dose is 10 mg at bedtime. Usual maintenance dosage is 20-150 mg at bedtime.
 - ◆ Adverse effects include sedation, anticholinergic effects (eg, dry mouth, urinary retention), and orthostatic hypotension. There is a risk of overdose if taken in excess.
- ◆ SSRIs: See chapter *Depression* for dosing, side effects, and drug interactions associated with this class of agents. SSRIs are less effective than TCAs in treating chronic pain.
- ◆ Venlafaxine (Effexor): Starting dosage is 37.5 mg daily. Usual maintenance dosage is 75-300 mg daily in divided doses or by extended-release formulation (Effexor XR).

Anticonvulsants

The following may be effective for neuropathic pain.

- ◆ Gabapentin (Neurontin): Starting dosage is 100-300 mg 2 or 3 times daily. Usual maintenance dosage is 1,200-3,600 mg/day in divided doses. Monitor response and increase the dosage every 1-2 weeks by 300-600 mg/day. Adverse effects include somnolence, dizziness, fatigue, and nausea.
- ◆ Lamotrigine (Lamictal): Starting dosage is 25 mg twice daily. Usual maintenance dosage is 50-300 mg/day in divided doses. Adverse effects include sedation, dizziness, ataxia, confusion, nausea, blurred vision, and rash.
- ◆ Valproic acid (Depakote): Starting dosage is 500 mg twice daily. Usual maintenance dosage is 500-1,500 mg 2 or 3 times daily. Monitor valproic acid serum levels. Adverse effects include weight gain, sedation, ataxia, nausea, and diarrhea.
- ◆ Although phenytoin and carbamazepine have some effectiveness in treating neuropathy, they have significant drug interactions with protease inhibitors and nonnucleoside reverse transcriptase inhibitors, and their use in HIV-infected patients is limited.

Substance Abuse, HIV, and Pain

Some health care providers hesitate to treat pain in patients with current or past substance abuse because of concern about worsening these patients' dependence on opioids or suspicion that such patients are seeking pain

medications for illicit purposes. However, the following points should be considered:

- ◆ Many patients with current or past substance abuse do experience pain, and this pain should be evaluated by care providers and treated appropriately.
- ◆ Failure to distinguish among addiction, tolerance, and dependence can lead to undertreatment of chronic pain by health care providers.
 - ◆ Addiction (substance abuse) is a complex behavioral syndrome characterized by compulsive drug use for the secondary gain of euphoria.
 - ◆ Pharmacologic tolerance refers to the reduction of effectiveness, over time, of a given dosage of medication.
 - ◆ Physical dependence is the consequence of neurophysiologic changes that take place in the presence of exogenous opioids.
- ◆ Aberrant use of pain medications, if it develops, is best managed by an interdisciplinary team of providers from HIV clinical care, psychiatry, psychology, pharmacy, social services, and drug addiction management.
- ◆ Drug-drug interactions between certain antiretroviral medications and methadone can decrease methadone serum concentrations (see chapter *Drug-Drug Interactions with HIV-Related Medications*). If this occurs, methadone dosages may need to be increased to prevent opiate withdrawal.
- ◆ As part of chronic pain management in patients with substance abuse, consider establishing a written pain-management contract to be signed by the clinician and the patient. The contract should:
 - ◆ Clearly state limits and expectations for both the patient and provider
 - ◆ Identify a single clinician responsible for managing the pain regimen
 - ◆ Tell the patient what to do if the pain regimen is not working
 - ◆ Describe the procedure for providing prescriptions (eg, 1 prescription given to the patient, in person, for a limited period of time, such as 1 month).
 - ◆ List the rules for dealing with lost medications or prescriptions

Patient Education

- ◆ Pain management is part of HIV treatment and patients should give feedback to allow the best treatment decisions. If pain persists for more than 24 hours at a level that interferes with daily life, patients should call so that their health care provider can change the plan and try additional measures if needed.
- ◆ Patients should not expect full pain relief in most cases, but enough relief that they can perform their daily activities.
- ◆ "Mild" pain medications (eg, NSAIDs, aspirin, acetaminophen) usually are continued even after "stronger" medications are started because their mechanism of action is different from that of opiates. This combination of pain medication has additive effects, so that pain may be controllable with a lower narcotic dosage.
- ◆ Patients taking "around the clock" medications, should take them on schedule. Those taking "as needed" medications should take them between doses if they have breakthrough pain.
- ◆ Opiates are noted for causing severe constipation. Patients must remain hydrated and may need stool softeners, laxatives, or other measures. They should call their health care provider quickly if constipation occurs.
- ◆ Patients should avoid recreational drugs or alcohol when taking opiates because opiates can interact with them or cause additive adverse effects, possibly resulting in central nervous system depression, coma, or death.
- ◆ Patients taking opiates should avoid driving and operating machinery.

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Palliative Care and HIV

Background

Palliative care is not curative care, but is supportive, symptom-oriented care. It is usually needed throughout the course of disease progression to relieve patients' suffering and promote quality of life. Palliative care is important for patients with any medical condition. It may be used in conjunction with disease-specific care or as the sole approach to care. Palliative care includes the following:

- ◆ Management of symptoms (eg, fatigue, pain)
- ◆ Treatment of adverse effects (eg, nausea, vomiting)
- ◆ Psychosocial support (eg, depression, advance care planning)
- ◆ End-of-life care

Following is the widely used definition of palliative care according to the World Health Organization:

Palliative medicine is the study and management of patients with active, progressive, far advanced disease for whom the prognosis is limited and the focus of care is the quality of life. [It is] the active total care of patients whose disease is not responsive to curative treatment. Control of pain, of other symptoms, and of psychological, social, and spiritual problems, is paramount. The goal of palliative care is achievement of the best quality of life for patients and their families.

Palliative care in AIDS patients comprises a continuum of treatment consisting of therapy directed at AIDS-related illnesses (eg, infection or malignancy) and treatments focused on providing comfort and symptom control throughout the life span. This care may involve multidimensional and multidisciplinary services, including HIV medicine, nursing, pharmacy, social work, complementary/alternative medicine, and physical therapy.

Palliative Care in the Era of Antiretroviral Therapy

With advances in HIV-specific therapy and care, HIV infection is no longer a rapidly fatal illness. Instead, those patients who are able to tolerate antiretroviral therapy (ART) often experience a manageable, chronic illness.

The death rate from AIDS, however, continues to be

significant: approximately 15,000–16,000 per year in the United States. In many parts of the world, patients are not able to obtain specific treatments for HIV or for opportunistic illnesses, and supportive or palliative care may be the primary mode of care available to patients with advanced AIDS. Regardless of access to disease-specific treatment, people living with HIV continue to experience symptoms from HIV disease and its comorbid conditions, and those taking ART may experience adverse effects. Integrating palliative care with disease-specific care is important in the treatment of patients with HIV to promote quality of life and to relieve suffering.

S: Subjective

The patient with advanced HIV disease complains of 1 or more of the following:

◆ Agitation	◆ Delirium	◆ Increased secretions
◆ Anorexia	◆ Dementia	(<i>"death rattle"</i>)
◆ Chronic pain	◆ Depression	◆ Nausea
◆ Constipation	◆ Diarrhea	◆ Pruritus
◆ Cough	◆ Dry skin	◆ Sweats
◆ Decubitus ulcers or pressure sores	◆ Dyspnea	◆ Vomiting
	◆ Fatigue	◆ Weakness
	◆ Fever	◆ Weight loss

O: Objective

Conduct a complete symptom-directed physical examination.

A: Assessment and P: Plan

Treatment

Table 1 lists common symptoms of AIDS and their possible causes. Also included are disease-specific treatments and palliative interventions. Depending on the situation, either or both of these treatments may be appropriate. Consider the patient's disease stage and symptom burden, the risks and benefits of therapies, and the patient's wishes. Practitioners should note that some of the palliative treatments may have substantial long-term adverse effects and should be used to alleviate symptoms only in late-stage or dying patients.

Table 1. Common Symptoms in Patients with AIDS and Possible Disease-Specific and Palliative Interventions

Symptom	Possible Causes	Disease-Specific or Curative Treatment	Palliative Treatment*
CONSTITUTIONAL			
Fatigue, weakness	• AIDS • Opportunistic infections (OIs) • Anemia	• ART • Treat specific infections • Erythropoietin, transfusion	• Psychostimulants (methylphenidate, pemoline, dextroamphetamine, modafinil) • Testosterone/androgens • Corticosteroids (prednisone, dexamethasone)
Weight loss/anorexia	• HIV • Malignancy	• ART • Chemotherapy • Nutritional support/enteral feedings	• Testosterone/androgens • Oxandrolone • Megestrol acetate • Dronabinol • Recombinant growth hormone • Corticosteroids
Fevers, sweats	• Disseminated MAC and other infections • HIV lymphoma, and other malignancies	• Specific treatment of OIs or malignancy • ART	• Nonsteroidal anti-inflammatory drugs (NSAIDs, ibuprofen, naproxen, indomethacin) • Anticholinergics (hyoscine, thioridazine) • H2-antagonists (cimetidine)
PAIN			
Nociceptive, somatic, visceral	• Opportunistic infections • HIV-related malignancies, nonspecific	• Specific treatment of disease entities	• NSAIDs • Opioids • Corticosteroids
Neuropathic	• HIV-related peripheral neuropathy • Cytomegalovirus (CMV) • Varicella zoster virus (VZV) • Medications (eg, dideoxynucleosides: didanosine, zalcitabine, stavudine), isoniazid, vincristine	• ART • Discontinue offending medication; • Change antiretroviral or other regimen	• NSAIDs • Neuropathic pain medications: • tricyclics (amitriptyline, imipramine) • benzodiazepines (clonazepam) • anticonvulsants (gabapentin, lamotrigine) • Opioids (eg, methadone) and adjuvants • Corticosteroids • Acupuncture

GASTROINTESTINAL			
Nausea, vomiting	• Antiretroviral medications • Esophageal candidiasis • CMV	• Specific treatment of disease entities • Change antiretroviral regimen	• Dopamine antagonists (prochlorperazine, haloperidol) • Prokinetic agents (metoclopramide) • Antihistamines (diphenhydramine, promethazine) • Anticholinergics (hyoscine, scopolamine) • Serotonin antagonists (granisetron, ondansetron, dolasetron) • H2 blockers (cimetidine) • Proton pump inhibitors (omeprazole) • Somatostatin analogues (octreotide) • Benzodiazepines (lorazepam) • Marijuana, dronabinol
Diarrhea	• MAC • Cryptosporidiosis • CMV microsporidiosis • Other intestinal infections • Malabsorption • Medications (eg, protease inhibitors)	• Specific treatment of disease entities • Discontinue offending medication	• Bismuth, methylcellulose • Psyllium • Kaolin • Diphenoxylate + atropine • Loperamide • Calcium carbonate • Ferrous sulfate • Octreotide • Tincture of opium
Constipation	• Dehydration • Malignancy • Anticholinergic medications • Opioids	• Hydration • Radiation and chemotherapy • Medication adjustment	• Activity/diet • Prophylaxis for patients taking opioids • Peristalsis-stimulating agents: • anthracenes (senna) • polyphenolics (bisacodyl) • Softening agents: —surfactant laxatives (docusate) —bulk-forming agents (bran, methylcellulose) —osmotic laxatives (lactulose, sorbitol) —saline laxatives (magnesium hydroxide)
RESPIRATORY			
Dyspnea	• PCP • Bacterial pneumonia • Anemia • Pleural effusion, mass, or obstruction • Decreased respiratory muscle function	• Specific treatment of disease entities • Erythropoietin, transfusion • Drainage, radiation, or surgery	• Use of fan, open windows, oxygen • Opioids • Bronchodilators • Methylxanthines • Benzodiazepines (eg, lorazepam)
Cough	• PCP, bacterial pneumonia • TB • Acid reflux • Postnasal drip	• Specific treatment of disease entities	• Cough suppressants (dextromethorphan, codeine, other opioids) • Decongestants, expectorants (various)
Increased secretions (“death rattle”)	• Fluid shifts • Ineffective cough • Sepsis • Pneumonia	• Antibiotics as indicated	• Atropine, hyoscine, transdermal scopolamine, glycopyrrolate • Fluid restriction, discontinue intravenous fluids

DERMATOLOGIC			
Dry skin	• Dehydration • End-stage renal disease • End-stage liver disease • Malnutrition • Medications (eg, indinavir)	• Hydration • Dialysis • Nutritional support • Discontinue offending medication	• Emollients with or without salicylates • Lubricating ointments or creams (eg, petrolatum, Eucerin)
Pruritus	• Fungal infection • End-stage renal disease • End-stage liver disease • Dehydration • Eosinophilic folliculitis	• Antifungal agents (itraconazole for eosinophilic folliculitis) • Dialysis • Hydration • Topical corticosteroids	• Topical agents (menthol, phenol, calamine, doxepin, capsaicin) • Antihistamines (doxepin - oral, diphenhydramine) • Corticosteroids (topical or systemic) • Serotonin antagonists (ondansetron) • Opioid antagonists (naloxone, naltrexone) • Antidepressants • Anxiolytics • Neuroleptics • Thalidomide
Decubitus ulcers, Pressure sores	• Poor nutrition • Decreased mobility, prolonged bed rest	• Increase mobility • Enhance nutrition	• Prevention (nutrition, mobility, skin integrity) • Wound protection (semipermeable film, hydrocolloid dressing) • Debridement (normal saline, enzymatic agents, alginates)
NEUROPSYCHIATRIC			
Delirium/agitation	• Electrolyte imbalances, glucose abnormalities • Dehydration • Toxoplasmosis • Cryptococcal meningitis • Sepsis • Medication adverse effects (eg, benzodiazepines, opioids, efavirenz) • Intoxication	• Correct imbalances • Hydration • Specific treatment of disease entities • Discontinue offending medications	• Neuroleptics (haloperidol, risperidone, chlorpromazine) • Benzodiazepines (eg, lorazepam, midazolam) (Note: in some patients, these may have adverse effects.)
Dementia	• AIDS-related dementia • Other dementia	• ART	• Psychostimulants (methylphenidate) • Low-dose neuroleptics (haloperidol)
Depression	• Chronic illness • Reactive depression, major depression	• Antidepressants (SSRIs, tricyclics, other)	• Psychostimulants (methylphenidate, pemoline, dextroamphetamine, modafinil) • Corticosteroids (prednisone, dexamethasone)

Key to abbreviations: ART = antiretroviral therapy; MAC = *Mycobacterium avium* complex; NSAIDs = nonsteroidal antiinflammatory drugs; CMV = cytomegalovirus; PCP = *Pneumocystis jirovecii* pneumonia; TB = tuberculosis; SSRI = selective serotonin reuptake inhibitor.

* Some of the palliative treatments may have substantial long-term adverse effects and should be used to alleviate symptoms only in late-stage or dying patients.

Adapted with permission from Selwyn PA, Rivard M. Palliative care for AIDS: Challenges and opportunities in the era of highly active anti-retroviral therapy. *Innovations in End-of-Life Care*. 2002;4(3). Available at <http://www.edc.org/lastacts>.

Advance Care Planning

Advance care planning involves planning for future medical care. Two main documents are produced:

- ◆ Advance directive (living will)
- ◆ Health care proxy (a person to speak for the patient or make decisions if the patient is too sick to do so)

The clinician should initiate these conversations and make referrals to helpful resources.

Patient Education

- ◆ Discuss advance care planning with patients, and the option of hospice care, if appropriate.
- ◆ Provide the patient and his or her family with detailed information so that they understand the illness and associated treatments.
- ◆ Instruct patients to discuss their pain or other bothersome symptoms with their health care providers.
- ◆ Encourage patients to talk with their health care providers if they are feeling anxious, depressed, or fearful.
- ◆ Discuss with patients what their death might be like. Some patients may feel relieved to be able to talk openly about their last days. Assure them that their pain will be controlled and that their health care providers will be there to help them.

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Anxiety Disorders

Background

Anxiety symptoms can develop because of a patient's uncertainty about HIV infection and treatment or because of issues unrelated to HIV. Symptoms can include mild distress, full-blown panic attacks, generalized anxiety disorder, or other disorders. The criteria for a diagnosis of generalized anxiety disorder include unrealistic or excessive worry about 2 or more life circumstances for more than 6 months, and at least 6 of the subjective complaints listed below.

It is important to differentiate between anxiety with and without panic attacks. Symptoms of anxiety can mimic symptoms of physical illness, and an appropriate workup should be performed to rule out other illnesses. (For more information about panic disorders, see chapter *Panic Disorder*.)

S: Subjective

The patient complains of the following:

- ◆ Difficulty concentrating
- ◆ Dizziness or lightheadedness
- ◆ Dry mouth
- ◆ Easy fatigability
- ◆ Exaggerated startle response
- ◆ Feeling anxious or on edge
- ◆ Flushes or chills
- ◆ Frequent urination
- ◆ Irritability
- ◆ Muscle tension, aches, or soreness
- ◆ Nausea, diarrhea, or other abdominal distress
- ◆ Palpitations or accelerated heart rate
- ◆ Restlessness
- ◆ Shortness of breath or smothering sensations
- ◆ Skin rashes
- ◆ Sweating or cold, clammy hands
- ◆ Trembling, twitching, or feeling shaky
- ◆ Trouble falling or staying asleep
- ◆ Trouble swallowing or "lump in the throat"

History

Obtain the following information during the history:

- ◆ Anxiety patterns (eg, constant or intermittent; timing)
- ◆ Caffeine intake
- ◆ Concomitant illnesses
- ◆ Family history of similar problems
- ◆ Medications, supplements, and herbal preparations
- ◆ New or recurrence of previous episodes
- ◆ Onset: sudden or gradual
- ◆ Recent stressors
- ◆ Recreational drugs or alcohol use (current or recent)
- ◆ Sleep disturbances
- ◆ Other physical symptoms

O: Objective

Perform a physical examination, including mental status and neurologic examination. Note heart rate, respiratory rate (shortness of breath, hyperventilation), tremor, rashes.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Allergic reactions
- ◆ Anemia
- ◆ Central nervous system (CNS) or opportunistic infections or malignancies
- ◆ Electrolyte imbalances
- ◆ Excessive caffeine intake
- ◆ Heart disease, arrhythmias
- ◆ Hyperthyroidism
- ◆ Hypoglycemia
- ◆ Immune disorders
- ◆ Medications such as efavirenz, isoniazid, steroids, theophylline
- ◆ Respiratory disease
- ◆ Sleep disturbances or sleep deprivation
- ◆ Substance use (eg, amphetamines, cocaine)
- ◆ Substance withdrawal (eg, alcohol, benzodiazepines)
- ◆ Systemic or other infections
- ◆ Vitamin B12 deficiency

P: Plan

Laboratory and Diagnostic Evaluation

Perform the following tests:

- ◆ Electrocardiogram (EKG)
- ◆ Thyroid studies
- ◆ Blood glucose
- ◆ Arterial blood gases (if frank difficulty breathing is not self-limited)
- ◆ Other tests as indicated based on symptoms and physical examination

Treatment

Once other diagnoses have been ruled out and the diagnosis of anxiety disorder is established, several options are available:

Cognitive-behavioral interventions

Options include individual cognitive-behavioral therapy, a stress-management group, relaxation therapy, visualization, and guided imagery. Refer the patient to available community-based support.

Psychotherapy

Psychotherapy may be indicated if experienced professionals are available and the patient is capable of forming an ongoing relationship. If possible, refer to an HIV-experienced therapist.

Pharmacotherapy

Patients with advanced HIV disease, like geriatric patients, may become more vulnerable to the CNS effects of certain medications. Medications that affect the CNS should be started at low dosage and titrated slowly. Similar precautions should apply to patients with liver dysfunction.

Interactions may occur between selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and HIV medications. Consult with an HIV expert or pharmacist before prescribing.

- ◆ SSRI-type antidepressants, including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro) may be effective. Venlafaxine timed-release formulation (Effexor XR), at dosages of 75-225 mg/d, has been approved for the treatment of generalized anxiety

disorder. Note: There is a risk of hypertension at the higher dosages of venlafaxine; monitor blood pressure.

- ◆ Buspirone (BuSpar) is a nonaddictive anxiolytic. Start at 5 mg orally 3 times per day. If symptoms persist, the dosage can be increased by 5 mg per dose each week to a maximum of 10-15 mg orally 3 times per day (for a total daily dosage of 30-45 mg). It will take several weeks for patients to notice a decrease in anxiety; low-dose benzodiazepines may be used during this interval. The major potential adverse effects of buspirone are dizziness and lightheadedness.
- ◆ Treatment may include intermediate half-life benzodiazepines such as oxazepam (Serax) 10 mg orally every 6 hours or lorazepam (Ativan) 0.5 mg orally every 8 hours, if buspirone is not tolerated or to alleviate anxiety symptoms until buspirone takes effect. Longer-acting benzodiazepines such as clonazepam (Klonopin) also may be useful at dosages of 0.25-0.5 mg orally twice a day.
- ◆ Benzodiazepines should be used only for acute, short-term management because of the risk of tolerance and physiologic dependence. These risks are even more problematic in patients with a history of addiction.
- ◆ Note that protease inhibitors and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines. If benzodiazepines are used, they should be started at low dosages, and other CNS depressants should be avoided. Consult with a clinical pharmacist before prescribing.
- ◆ Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors and with delavirdine and efavirenz.
- ◆ Some sedating antidepressants are effective, nonaddictive anxiolytic agents. These include trazodone (Desyrel) 25-100 mg at bedtime or imipramine (Tofranil) 25 mg at bedtime. Note that imipramine is contraindicated with ritonavir or in advanced HIV disease. Neurontin 200-400 mg 2 times daily or 4 times daily can also be used.

Patient Education

- ◆ Behavioral interventions can help to reduce anxiety, but may take practice. Patients should seek help from a therapist, an experienced source, or a friend.
- ◆ Some patients develop problems with sexual function because of antianxiety medications. Patients should report any problems to their prescribers.

References

- ◆ American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Washington: American Psychiatric Association; 1994.
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Depression

Background

Major depression is a cause of significant morbidity among people with HIV disease. Management of this condition may be complicated by its multifactorial etiology. A diagnosis of HIV may not only cause psychological crisis, but may also complicate underlying psychological or psychiatric problems (eg, preexisting depression, anxiety, or substance abuse). In addition, direct viral infection of the central nervous system (CNS) can cause several neuropsychiatric syndromes. Finally, both constitutional disease and medications can impair neurologic function and mood.

The clinician's task is 4-fold:

- ◆ Maintain a high index of suspicion for depression and screen frequently for mood disorders.
- ◆ Elicit any history of psychiatric diagnoses or treatment.
- ◆ Rule out organic causes of mood or functional alterations.
- ◆ Refer for appropriate psychiatric evaluation and psychosocial support, including substance abuse counselors and domestic violence service providers.

Patients with untreated depression experience substantial morbidity and may become self-destructive or suicidal. They are also at continuing risk for unsafe behaviors that may lead to HIV transmission.

Major depression in persons with comorbid medical illness, including HIV infection, has been associated with numerous adverse events, such as the following:

- ◆ Decreased survival
- ◆ Impaired quality of life
- ◆ Decreased treatment adherence
- ◆ Longer hospital stays
- ◆ Increased risk behaviors
- ◆ Suicide

Although depression occurs independently of physical symptoms, recent research has concluded that it is associated with higher mortality rates in HIV-infected individuals. Stress and depressive symptoms, especially when they occur jointly, are associated with diminished immune defenses in HIV-infected individuals.

S: Subjective

The patient may complain of the following:

- ◆ Appetite changes with weight changes (increase or decrease)
- ◆ Decreased ability to concentrate
- ◆ Depressed mood, sadness, hopelessness
- ◆ Diminished interest or pleasure in activities
- ◆ Fatigue or loss of energy
- ◆ Feelings of worthlessness or guilt
- ◆ Insomnia or hypersomnia
- ◆ Psychomotor agitation or retardation
- ◆ Recurrent thoughts of death or suicide

History

Inquire about the symptoms listed above, and about associated symptoms. If 5 of these symptoms occur on most days for at least 2 weeks, a clinically significant major affective disorder is present and requires intervention. Depressed mood or diminished interest or pleasure must be 1 of the 5 symptoms present.

Take a careful history of the timing of symptoms, their relationship to life events (eg, HIV testing, loss of a friend) and any other physical changes noted along with the mood changes. Elicit personal and family histories of depression or suicidal behavior. Probe for suicidal thoughts, plans, and materials to execute the plans. Inquire about hallucinations, paranoia, and other symptoms. Take a thorough history of medication use and substance abuse.

O: Objective

Perform mental status examination, including affect, mood, orientation, appearance, agitation, or psychomotor slowing; perform neurologic examination if appropriate.

A: Assessment

Partial Nonpsychiatric Differential Diagnosis

Rule out nonpsychiatric causes of symptoms, which may include the following:

- ◆ Vitamin B12, folate (B6), zinc, or vitamin A deficiency
- ◆ Hypothyroidism or hyperthyroidism
- ◆ Endocrine disorders such as Addison disease or hypotestosteronism (hypogonadism)
- ◆ HIV dementia or minor cognitive motor disorder
- ◆ HIV encephalopathy
- ◆ Neurosyphilis
- ◆ Opportunistic illnesses affecting CNS (eg, toxoplasmosis, cryptococcal disease, CNS cytomegalovirus, progressive multifocal leukoencephalopathy)
- ◆ Medication adverse effects (eg, from steroids, efavirenz, isoniazid, interferon-alfa)
- ◆ Substance-induced mood disorder (intoxication or withdrawal)

Partial Psychiatric Differential Diagnosis

- ◆ Adjustment disorder (eg, acute reaction to a life crisis, such as HIV diagnosis, bereavement, job loss)
- ◆ Anxiety disorders
- ◆ Bereavement
- ◆ Dysthymia (depressed mood of long duration with less intensive symptoms)
- ◆ Psychotic depression

P: Plan

Laboratory Tests

Check thyroid function tests and vitamin B12, folate, and testosterone levels.

Treatment

Make sure that the patient has been referred to available community organizations for support.

Refer immediately for psychiatric evaluation or treatment if the patient is:

- ◆ Suicidal (see chapter *Suicidal Ideation*)

- ◆ Displaying psychotic symptoms
- ◆ Debilitated or functionally impaired by severe symptoms
- ◆ Not responding to treatment

Psychotherapy

Individual psychotherapy with a skilled, HIV-experienced mental health professional can be very effective in treating depression. The combination of psychotherapy and antidepressant medication is more effective than either treatment modality alone.

Pharmacotherapy

When selecting antidepressant medications, consider their side effect profiles as a means to treat other symptoms. For example, activating medications can be taken in the morning if the patient complains of low energy; medications that increase appetite may be useful for patients with wasting syndrome; sedating medications may be taken at bedtime if the patient complains of sleep problems.

Monitor patients closely after starting antidepressant medications. Some patients may be at risk of worsening depression, including suicidality, after initiation of therapy.

Because of the potent inhibition of the microsomal cytochrome P450 isoenzymes by protease inhibitors (especially ritonavir), antidepressants used concomitantly with protease inhibitors should be started at low dosages and titrated cautiously to prevent antidepressant adverse effects and toxicity. Interactions between selective serotonin reuptake inhibitors (SSRIs) and HIV medications are fairly common. For patients who are starting antiretroviral medications (particularly protease inhibitors) and are on a stable antidepressant regimen, an empiric dosage reduction of antidepressant therapy should be considered, especially if the antidepressant dosage is at the high end of the range or the patient is having adverse effects of the antidepressant before starting antiretroviral therapy. Consultation with an HIV expert, psychiatrist, and clinical pharmacist can assist in developing an effective antidepressant and HIV therapy combination.

A therapeutic trial consists of treatment for 4-6 weeks at a therapeutic dosage. Medications should be continued for 6-9 months beyond the resolution of symptoms to reduce the risk of recurrence. After this time, treatment may be gradually tapered if the patient wishes, with careful monitoring for recurrence.

of symptoms. The risk of recurrence is higher if the first depressive episode is inadequately treated or if the patient has had multiple depressive episodes.

Table 1 lists the available antidepressant medications (SSRIs and serotonin/norepinephrine reuptake inhibitors [SNRIs]), including therapeutic dosages and possible positive and negative effects.

Table 1. SSRI and SNRI Antidepressant Medications and Possible Positive and Negative Effects

Medication: Usual Dosage	Possible Positive Effects	Possible Negative Effects
Fluoxetine (Prozac): 10–40 mg once daily	Rarely sedating, often energizing, no cardiovascular adverse effects, no anticholinergic effects, nonfatal in overdose	Insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life
Paroxetine* (Paxil): 10–40 mg once daily	May be sedating (for patients experiencing sedation with paroxetine, dose at bedtime; can be useful with depression-associated insomnia)	Insomnia, agitation (for patients experiencing these effects, administer dose in mornings), nausea, headache, sexual dysfunction in men and women
Sertraline (Zoloft): 50–100 mg once daily	May have lower incidence of significant drug-drug interactions compared with fluoxetine and paroxetine; nevertheless, start with lower dosages when this medication is used with protease inhibitors	Insomnia, agitation, nausea, headache, sexual dysfunction in men and women, long half-life
Venlafaxine XR** (Effexor XR): 75–375 mg once daily	May have lower risk of significant drug-drug interactions compared with SSRIs	Nausea, headache, nervousness, sexual dysfunction
Citalopram (Celexa): 10–60 mg once daily or escitalopram (Lexapro): 10–20 mg once daily	May have lower risk of significant drug-drug interactions than other SSRIs	Mild nausea, possible sedation

* When discontinuing paroxetine therapy, carefully titrate the dosage reduction to avoid serious adverse effects associated with abrupt discontinuation. Such effects include confusion, agitation, irritability, sensory disturbances, and insomnia.

** Note: Monitor blood pressure at higher dosages of venlafaxine.

Other Agents

Newer antidepressants such as mirtazapine may be particularly useful in patients who have significant insomnia and in those who have experienced sexual dysfunction with other antidepressant agents such as SSRIs.

- ♦ Mirtazapine (Remeron) should be administered at bedtime because of its sedating effects. Sedation is commonly noted with the starting dosage of 15 mg once daily, but may be lessened by increasing the dosage to 30 mg at bedtime. Individuals may also experience an increase in appetite, weight gain, and dry mouth. Mirtazapine has minimal drug-drug interactions. The therapeutic dosage range is 15–45 mg once daily. Consider starting with 15 mg at bedtime for 7 days, then increasing to 30 mg if sedation is problematic.
- ♦ Bupropion (Wellbutrin) sustained-release (SR) or extended-release (XL) formulation may be used in individuals with depression who experience sexual dysfunction with other antidepressant agents.

Bupropion SR or XL dosing should not exceed 400 mg per day (the SR formulation should be administered twice daily in divided doses) because of an increased risk of seizures at higher bupropion dosages, particularly in individuals who have other risk factors for seizures. For patients taking protease inhibitors, caution should be used as the dosage approaches 300–400 mg per day because of possible increases in levels of bupropion. Bupropion may have an activating effect, which some patients may experience as agitation, insomnia, or both, and also may have an appetite suppressant effect.

- ♦ Nefazodone (Serzone) may cause liver toxicity and generally is not recommended as an antidepressant for patients with HIV/AIDS because of the high rates of preexisting liver abnormalities in HIV-infected patients. This medication has recently received a black box warning regarding severe liver toxicity from the U.S. Food and Drug Administration. If the patient has ever had liver toxicity from the drug, restarting is contraindicated.

- ◆ Tricyclic antidepressants may be effective, but in general have a higher risk of adverse effects than SSRIs and are dangerous if overdosed.
- ◆ Treatment may involve antidepressant combinations, including psychostimulants.
- ◆ Patients with prominent insomnia may benefit from the addition of trazodone 25-50 mg, given 1-2 hours before bedtime.
- ◆ St. John's wort is an herbal antidepressant that is contraindicated for use with protease inhibitors and nonnucleoside reverse transcriptase inhibitors. St. John's wort can significantly decrease serum concentrations of these HIV medications.

Patient Education

- ◆ Providers should explain to patients that illness (physical or emotional) is not a character flaw or a moral or spiritual weakness. It is an expected aspect of HIV infection. Sadness is a normal part of life, but major depression is always abnormal and often can be alleviated with medication, therapy, or both.
- ◆ Antidepressants typically are given for a long time, usually for a year or longer, to help patients with the chemical imbalances associated with depression.
- ◆ When starting an antidepressant medication, patients should expect that it will take 2-4 weeks for them to notice any improvement. Their symptoms should continue to decrease over the following weeks. If they do not have much improvement in symptoms, their providers may choose to adjust the dosage of the medication or to change medications. Patients must continue taking their medications so that the symptoms of depression do not return.
- ◆ Some patients develop problems with sexual function while they are taking antidepressants. They should report any problems to their prescribers.
- ◆ Patients should note the major symptoms of depression and be aware of what factors led them to seek treatment. They will need to monitor themselves for recurrences and get help if the symptoms come back. Providers should explain to patients that if they notice changes in their sleep, appetite, mood, activity level, or concentration, or if they notice fatigue, isolation, sadness or helplessness, it is time to get help.

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Panic Disorder

Background

Panic disorder is persistent fear that interferes with the ability to conduct activities of daily living. A patient is diagnosed as having panic disorder when he or she has experienced 4 panic attacks within a 4-week period, or at least 1 panic attack followed by a month of persistent fear. Panic attacks are discrete, sudden-onset episodes of intense fear or apprehension accompanied by specific somatic or psychiatric symptoms (eg, palpitations, shortness of breath, or fear of losing control).

Patients may associate panic attacks with various activities, such as leaving home, driving, and even visiting health care providers for medical appointments. The symptoms of panic disorder usually begin in late adolescence to the mid-30s and may coincide with the presentation of major depressive disorder, social phobia, or generalized anxiety disorder. Symptoms may mimic physical illness. Patients with panic disorder have an increased incidence of suicide.

S: Subjective

The patient complains of panic attacks, or describes episodes of:

- ◆ Chest pain or discomfort
- ◆ Depersonalization or derealization
- ◆ Dizziness, lightheadedness, faintness, or feeling of unsteadiness
- ◆ Fear of dying
- ◆ Fear of going crazy or losing control
- ◆ Hot flashes or chills
- ◆ Nausea or abdominal distress
- ◆ Numbness or tingling sensations
- ◆ Palpitations or accelerated heart rate
- ◆ Sensation of choking
- ◆ Shortness of breath or smothering sensation
- ◆ Sweating
- ◆ Trembling or shaking

In the absence of physical causes, 4 or more of the above symptoms accompanying multiple panic attacks are diagnostic of panic disorder. Panic attacks are, by definition, self-limited and they peak quickly, usually within 10 minutes. Symptoms that persist continuously for longer periods suggest other causes.

History

Inquire about the following:

- ◆ Any associated or concurrent symptoms, such as rash, cough, or fever
- ◆ Current medications, herbal products, and supplements
- ◆ Family history of mood and psychiatric illnesses, particularly anxiety and panic
- ◆ Frequency, duration, and onset of panic episodes
- ◆ Any relationship to food or hunger
- ◆ Settings in which attacks occur to determine whether there are triggers, such as being outdoors (agoraphobia)
- ◆ Intake of caffeine, recreational drugs, and alcohol (current and recent)
- ◆ New onset versus previous incidents
- ◆ Sleep disturbances
- ◆ Concomitant illnesses

O: Objective

Perform a complete physical examination, including vital signs and thyroid, cardiac, pulmonary, and neurologic evaluation.

During actual panic attacks, patients may have an increased heart rate or respiratory rate.

A: Assessment

A partial differential diagnosis includes the following conditions:

- ◆ Allergic reactions
- ◆ Cardiac insufficiency, congestive heart failure, myocardial ischemia
- ◆ Hyperthyroidism
- ◆ Hypoglycemia
- ◆ Major depression with superimposed panic attack
- ◆ Medication effect
- ◆ Pheochromocytoma medication effect
- ◆ Phobia (phobia is a specific response to a specific stimulus, whereas a patient with panic attacks is unsure when they will recur and what will trigger them)
- ◆ Respiratory infection
- ◆ Pheochromocytoma
- ◆ Withdrawal from or intoxication with psychoactive substances (eg, caffeine, amphetamines, cocaine, hallucinogens, or medications)

P: Plan

Diagnostic Evaluation

Perform the following tests:

- ◆ Blood glucose; gamma-glutamyl transpeptidase (GGT) if symptoms are related to hunger or are consistent with rebound hypoglycemia
- ◆ Thyroid studies
- ◆ Arterial blood gases if the patient has persistent shortness of breath
- ◆ Electrocardiogram if chest pain is present

Treatment

Once other diagnoses have been ruled out, consider the following treatments:

Cognitive-behavioral therapy

Options include individual cognitive-behavioral therapy (CBT) interventions (refer to community-based support), a stress management group, relaxation therapy, visualization, and guided imagery. Emergency referrals may be needed.

Psychotherapy

Psychotherapy may be indicated if the patient is capable of forming an ongoing relationship with a therapist. If possible, refer to an HIV-experienced professional.

Pharmacotherapy

Patients with advanced HIV disease, like geriatric patients, may become more vulnerable to the central nervous system (CNS) effects of certain medications. Medications that affect the CNS should be started at low doses and should be titrated slowly. Similar precautions should apply to patients with liver dysfunction.

Some interactions occur between selective serotonin reuptake inhibitors (SSRIs), benzodiazepines, and HIV medications. Consult with an HIV expert or pharmacist before prescribing.

Treatment should be continued for at least 6 months beyond the resolution of symptoms.

Options

- ◆ SSRI-type antidepressants, including fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), citalopram (Celexa), and escitalopram (Lexapro) may be effective. Venlafaxine timed-release formulation (Effexor XR), at a dosage of 75-225 mg/d, has been approved for the treatment of generalized anxiety disorder. There is a risk of hypertension at the higher dosages of venlafaxine; monitor blood pressure.
- ◆ Tricyclic antidepressants may be used at low doses, including nortriptyline (Pamelor), 10-75 mg at bedtime; desipramine (Norpramin), 10-50 mg daily; amitriptyline (Elavil), 25-75 mg at bedtime; and imipramine (Tofranil), 25-75 mg at bedtime. Doses should be titrated slowly. Tricyclic antidepressants may reach higher blood concentrations when coadministered with certain protease inhibitors, including ritonavir (contained in Kaletra); consult with an HIV expert or pharmacist.
- ◆ Many patients will require initial short-term treatment with benzodiazepines, which are titrated downward as the antidepressant is titrated upward. Benzodiazepines should be used only for acute, short-term management, because of the risks of tolerance and physiologic dependence. These risks are more problematic in patients with a history of addiction. Note that protease inhibitors and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines.

If benzodiazepines are used, they should be started at low doses, and other CNS depressants should be avoided. Consult with a clinical pharmacist before prescribing.

- ◆ Note that midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors and with delavirdine and efavirenz.

Patient Education

- ◆ Behavioral interventions can help to reduce the frequency and severity of panic attacks. Patients should seek help from a therapist, an experienced source, or a friend.
- ◆ Some patients develop problems with sexual function because of the medications. Patients should report any problems to their prescribers.

References

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- ◆ New York State Department of Health AIDS Institute. *Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner*. 2001. Available online at www.hivguidelines.org/. Accessed February 7, 2006.
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Insomnia

Background

Insomnia is a common accompaniment to HIV infection, especially as the disease progresses and complications worsen. Once present, insomnia tends to be chronic, unlike the transient disturbances of sleep that are a normal part of life. Most insomnia related to HIV can be characterized by the amount, quality, or timing of sleep. Insomnia may cause progressive fatigue and diminished functioning.

S: Subjective

The patient may complain of the following:

- ◆ Difficulty initiating sleep
- ◆ Early-morning waking
- ◆ Mind-racing thoughts (eg, "I can't turn off my thoughts.")
- ◆ Difficulty maintaining sleep
- ◆ Nonrestorative sleep (ie, although the amount of sleep is adequate, the patient does not feel rested upon awakening)
- ◆ Nighttime restlessness

Take a history to include:

- ◆ Determine the patient's bedtime sleep habits; if possible, request additional history from a sleep partner.
- ◆ Try to quantify how long the patient actually sleeps each night.
- ◆ Ask about alcohol and recreational drug use, caffeine intake, and concurrent medications that may cause insomnia as an adverse effect (eg, efavirenz, corticosteroids, pseudoephedrine, and decongestants).
- ◆ Screen for depression and anxiety.
- ◆ Ask about nightmares, life stressors, and any over-the-counter medications or supplements used to promote sleep.
- ◆ Ask about shift work, exercise, nighttime reflux or heartburn, snoring, and periods of apnea (not breathing).
- ◆ Ask about collar size (size >16 or 16 1/2 is more often associated with sleep apnea).

O: Objective

Perform a general symptom-directed physical examination, including evaluation of body habitus, neurologic status, and mental status.

Polysomnography may be indicated when a physiologic cause is suspected or insomnia is severe.

A: Assessment

A partial differential diagnosis includes the following:

- ◆ Alcohol intake (interferes with sleep 2-4 hours after ingestion)
- ◆ Anxiety disorder
- ◆ Caffeine intake
- ◆ Cognitive impairment
- ◆ Disturbance of the sleep/wake cycle because of excessive time in bed
- ◆ Major depression (insomnia is a primary symptom)
- ◆ Medication adverse effects (eg, from steroids, efavirenz)
- ◆ Other identifiable sleep disorders (eg, obstructive sleep apnea, periodic leg movements)
- ◆ Pain
- ◆ Recreational drug use
- ◆ Transient insomnia related to acute stress

P: Plan

Treatment

The following options are available for treatment:

Behavioral strategies

- ◆ To correct deleterious sleep habits, patients should do the following:
 - ◆ Establish a bedtime routine.
 - ◆ Avoid stimuli before bedtime.
 - ◆ Avoid vigorous exercise within 3-4 hours of bedtime.
 - ◆ Reduce or eliminate daytime napping.
 - ◆ Avoid eating, reading, watching TV, or working in bed.

- ◆ Wake up at the same time each day regardless of total hours of sleep.
- ◆ Have a dark, quiet, comfortable environment conducive to sleep.
- ◆ If unable to fall sleep after 15-20 minutes, the patient should get up, go into another room for nonstimulating activity in dim light (such as reading), and not go back to bed until sleepy.
- ◆ The patient should discontinue use of caffeine, central nervous system stimulants, alcohol, and tobacco, with tapering if necessary to avoid withdrawal symptoms.
- ◆ Teach or refer the patient for relaxation techniques.

Pharmacotherapy

The following options are available:

- ◆ Antihistamines, such as diphenhydramine or hydroxyzine 25-50 mg at bedtime (be aware of anticholinergic adverse effects).
- ◆ Sedating antidepressants such as trazodone 25-50 mg at bedtime, or amitriptyline 10-50 mg at bedtime. Check for drug interactions with antiretroviral agents and other medications. Mirtazapine (Remeron) is a newer antidepressant with fewer drug interactions that may be used at low dosages (7.5-15 mg) for insomnia.
- ◆ Sedative hypnotics, such as triazolam (Halcion) 0.125-0.25 mg at bedtime as needed; temazepam (Restoril), 15 mg at bedtime; and newer agents such as zolpidem (Ambien), eszopiclone (Lunesta), zaleplon (Sonata). Because of addictive potential and problems such as amnesia and confusion, these should be used only for short-term management (5-7 days).
- ◆ Note that protease inhibitors and nonnucleoside reverse transcriptase inhibitors may raise blood concentrations of many benzodiazepines. If benzodiazepines are used, they should be started at low dosages, and other central nervous system depressants should be avoided. Consult with a clinical pharmacist before prescribing.
- ◆ Midazolam (Versed) and triazolam (Halcion) are contraindicated with all protease inhibitors and delavirdine and efavirenz.
- ◆ Consult with a skilled mental health clinician if problems persist or depression is suspected.

Patient Education

- ◆ Behavioral interventions can help to reduce insomnia.
- ◆ Patients should report new or worsening symptoms to their health care provider.

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Suicidal Ideation

Background

Transient suicidal thoughts are common in some people throughout the course of HIV disease and do not usually indicate significant risk of suicide. However, persistent suicidal thoughts with associated feelings of hopelessness and intent to die are very serious and must be assessed promptly and carefully. The risk of suicide is especially high for patients who are depressed and for those at pivotal points in the course of HIV infection.

Many events may trigger suicidal thoughts among persons with HIV. Such events may include learning about their positive HIV status, disclosing to family and friends, starting antiretroviral therapy, noticing the first symptoms, having a decrease in CD4 counts, undergoing a major illness or hospitalization, receiving an AIDS diagnosis, losing a job, experiencing major changes in lifestyle, requiring evaluation for dementia, and losing of a significant relationship. A suicide assessment must always be included in the psychiatric evaluation.

Risk factors for suicide attempts include the following:

- ◆ Abandonment by, or isolation from family, friends, or significant others
- ◆ Age, especially teen years or >45 years of age
- ◆ Recent or current illness
- ◆ Any acute change in health status
- ◆ Fear of HIV-associated dementia
- ◆ Financial difficulty
- ◆ Hopelessness
- ◆ Multiple losses or recent stressors
- ◆ Pain
- ◆ Perception of poor prognosis
- ◆ Perception of poor social support
- ◆ Previous suicide attempts
- ◆ Substance abuse, especially alcohol
- ◆ Relapse into drug use after significant recovery
- ◆ Severe anxiety, depression, or other mental health disorder
- ◆ Social isolation (eg, being single, divorced, or alone, or experiencing the death of a spouse)

- ◆ Stigmatization due to illness, sexual orientation, substance use history, or other factors

S: Subjective

The patient expresses or exhibits, or a personal care giver discloses the following:

- ◆ Active suicidal ideation with intent and plan, such as giving away significant personal belongings, saying goodbye, gathering the means (eg, gun, pills), writing a suicide note
- ◆ Passive withdrawal from therapy or medical care or decreased adherence (eg, stopping medications, missing appointments)
- ◆ A desire for HIV disease to progress more rapidly

History

Inquire about the following during the history:

- ◆ Previous suicide attempt(s)
- ◆ Friend or family member who has committed suicide
- ◆ Personal or family history of depression
- ◆ Previous episode of psychosis
- ◆ Presence of risk factors described above

Probe for other depressive symptoms and the immediacy of potential suicidal intent. Sample questions may include the following:

- ◆ “It sounds as if you're in great pain. Have you ever thought life is not worth living?”
- ◆ “Do you often think of death?”
- ◆ “Do you think about hurting yourself?”
- ◆ “How might you do that?”
- ◆ “Is this something you feel you might do?”

O: Objective

- ◆ Perform a mental status examination and suicide assessment.
- ◆ Look for signs of self-inflicted injuries such as wrist lacerations or neck burns.

A: Assessment

See chapter *Depression* for differential diagnosis of possible causes of depression and suicidality.

P: Plan

Evaluation

Evaluate the patient for depression, risk factors for suicide, and contributing psychiatric illnesses or situational stressors. Determine the immediacy of potential suicidal intent. If a mental health professional is available on site or can be summoned, an urgent consultation is often helpful in making these determinations.

Take the following actions as appropriate:

- ◆ If the patient exhibits active suicidal ideation with a plan, hospitalize the patient immediately, preferably in a psychiatric facility.
- ◆ If suicidal behavior is passive, refer for psychotherapy with an HIV-experienced mental health provider.
- ◆ Establish a contract with the patient not to inflict self-harm, to contact you or another specified clinician for help, or to go to hospital if suicidal ideations become active.
- ◆ Contact the patient between appointments. Enlist the help of significant others (if the patient agrees); invite them to accompany the patient on the next visit and see all of them together. Consider a support group or peer referral if available.
- ◆ Consider dispensing medications on a weekly basis for the purposes of:
 - ◆ Monitoring emotional status and treatment adherence
 - ◆ Preventing the availability of lethal doses of medications
- ◆ Perform appropriate follow-up. In consultation with a skilled mental health provider, be sure that the patient is receiving appropriate ongoing treatment for underlying or persisting psychiatric illness. Assess at each visit for adherence to mental health care and for reoccurrence of symptoms.

Patient Education

- ◆ Suicidal ideation and severe depression are not normal aspects of HIV infection, and usually can be treated effectively.
- ◆ Patients should report suicidal thoughts to their health care providers.
- ◆ Providers should inform patients about local suicide prevention resources, including suicide hotlines, emergency response (eg, 911), and local emergency departments.

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HIV-Associated Dementia and Minor Cognitive Motor Disorder

Background

The HIV virus is neurotropic and directly invades brain tissue shortly after infection. Accordingly, HIV may cause cognitive difficulties, including HIV-associated dementia (HAD), also called AIDS dementia complex (ADC). In the United States in past years, HAD was the most common neurologic complication of AIDS, affecting 40-60% of all AIDS patients. In recent years, the incidence of HAD has declined, probably because of the use of potent combination antiretroviral therapy (ART). Other HIV-related opportunistic infections of the central nervous system (CNS) (eg, toxoplasmosis, cytomegalovirus encephalitis) and malignancies (eg, lymphoma) have declined in frequency even more sharply than HAD. The fact that HAD has not declined as much as other HIV-related CNS disease suggests that the CNS may be an important reservoir for HIV and that current antiretroviral medications do not protect the CNS as well as they protect the rest of the body. The HIV viral load in the CNS is correlated with cognitive decline; however, it is not correlated with plasma viral load and cannot be estimated from plasma viral load.

The American Psychiatric Association describes dementia as “an organic mental disorder defined as a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning.” The clinical presentation of dementia varies. Patients may develop ambulation or gait problems, mania, panic, psychosis, social isolation, or anxiety. Dementia is progressive but with a variable course; some patients have a rapid progression, whereas others have a slow decline in function. Many patients with HIV-related neurocognitive impairments are acutely aware of their deterioration and may develop an adjustment disorder characterized by profound fear, anxiety, or depression.

Some HIV-infected patients may develop a milder form of cognitive disorder, called minor cognitive motor disorder (MCMD), which is not necessarily an early stage of dementia. The distinction between MCMD and dementia is important and may have a major psychological impact on the patient.

Manifestations of Dementia

Early manifestations of dementia may include the following:

- ◆ Decreased attention or concentration
- ◆ Reduced speed of information processing
- ◆ Psychomotor slowing
- ◆ Impaired executive functioning (eg, abstraction, divided attention, shifting cognitive sets)

Late manifestations may include:

- ◆ Visuospatial difficulties
- ◆ Language problems
- ◆ Apraxias

S: Subjective

The patient complains of, or a care giver reports, the following:

- ◆ Impairment in memory (short-term and long-term), abstract thinking, judgment, and higher cortical functioning
- ◆ Personality changes that interfere with relationships
- ◆ Inability to carry out normal social or occupational functions
- ◆ Some patients experience only minor forgetfulness and diminished visual or motor skills

History

Take a thorough history, including the following:

- ◆ Medications
- ◆ Approximate onset of symptoms
- ◆ Drug and alcohol use
- ◆ Symptoms of opportunistic infections
- ◆ Pain
- ◆ HIV history, including duration, opportunistic illnesses, and CD4 levels
- ◆ Common manifestations (see above)

0: Objective

Perform the following tests:

- ◆ Check temperature and other vital signs, and perform a thorough physical examination to determine potentially reversible causes such as opportunistic infections.
- ◆ Perform a thorough neurologic examination, including funduscopic exam. Check symmetry of brow wrinkling, eyelid closure, and pupil size. Perform Romberg and other tests to rule out focal neurologic deficits.
- ◆ Check gait by asking the patient to walk rapidly, turn, and stop. Ask the patient to walk on heels and tiptoes. Test steadiness of gait with eyes open and closed. Ask the patient to stand from a squatting position without assistance.
- ◆ Perform a complete minimental status examination. As a quick screen, ask the patient to write his or her name, date, and location; to spell "world" backwards; to perform memory-object recall of 3 objects after 5 minutes; and to make change from a dollar.

A: Assessment

Partial Differential Diagnosis

- ◆ Other CNS conditions, such as toxoplasmosis, fungal infection, *Mycobacterium avium* complex (MAC), lymphoma, cytomegalovirus ventriculitis or encephalitis, normal-pressure hydrocephalus, neurosyphilis, tuberculosis, or *Cryptococcus neoformans*. Many of these are treatable.
- ◆ Depression, which can present as cognitive impairment.
- ◆ Other medical causes, such as nutritional deficiencies (eg, vitamin B12), metabolic disorders (eg, hypothyroidism), toxins (eg, chronic alcohol use), or infections (eg, tertiary syphilis)
- ◆ Delirium, which is an acute manifestation of cognitive impairment with inability to maintain attention. Delirium can be due to many medical conditions, but is also commonly caused by medications, including those with anticholinergic adverse effects, such as amitriptyline (Elavil), promethazine (Phenergan), prochlorperazine (Compazine), and diphenhydramine (Benadryl). An anticholinergic delirium is characterized by visual or tactile hallucinations, confusion, and sometimes

agitation. Other medications that may cause delirium include prednisone, meperidine (Demerol), lithium (at toxic levels, which may occur in a stable patient with a serious opportunistic infection or dehydration), agonist-antagonist analgesics such as pentazocine (Talwin), and short-acting benzodiazepines such as midazolam (Versed) and triazolam (Halcion).

- ◆ Intoxication or withdrawal.

Mild Manifestations: HIV-Associated Minor Cognitive Motor Disorder

At least 2 of the following symptom should be present:

- ◆ Impaired attention, concentration, or memory
- ◆ Mental and psychomotor slowing
- ◆ Personality changes

Rule out other causes.

Severe Manifestations: HIV-Associated Dementia

Signs will include the following:

- ◆ Acquired cognitive abnormality in 2 or more domains, causing functional impairment
- ◆ Acquired abnormality in motor performance or behavior
- ◆ No clouding of consciousness or other confounding cause (eg, CNS infections, psychopathology, drug abuse)

Table 1 describes the states of HAD.

Table 1. Stages and Characteristics of HIV-Associated Dementia

Stage	Characteristics
Stage 0 (normal)	Normal mental and motor function
Stage 0.5 (subclinical)	Equivocal symptoms of cognitive or motor dysfunction; no impairment of work or activities of daily living (ADL)
Stage 1 (mild)	Evidence of intellectual or motor impairment, but able to perform most ADL
Stage 2 (moderate)	Unable to work, but can manage self-care
Stage 3 (severe)	Major intellectual incapacity or motor disability
Stage 4 (end-stage)	Nearly vegetative

Source: Bartlett JG, Gallant JE. 2005-2006 *Medical Management of HIV Infection*. Baltimore: Johns Hopkins University Division of Infectious Diseases; 2005. Available online at <http://hopkins-aids.edu/mmhw/order.html>.

P: Plan

- ◆ Check thyroid function, vitamin B12, folate, rapid plasma reagin (RPR), blood chemistries and electrolytes, liver function tests (LFTs), complete blood count (CBC), and testosterone level.
- ◆ Order computed tomography (CT) scan or magnetic resonance imaging (MRI). (Cortical atrophy, similar to that seen in Alzheimer dementia, may be visible in very late stages of HAD.) Rule out masses and space-occupying lesions.
- ◆ Check cerebrospinal fluid (CSF): In patients with HAD, the CSF will show increased protein and mononuclear pleocytosis. It may be valuable to check the HIV viral load in the CSF, because sometimes the CSF viral load is high regardless of the plasma viral load; this may explain the patient's central deficits.
- ◆ Perform an electroencephalogram (may show mild, nonspecific slowing).
- ◆ Refer the patient to a psychiatrist and neurologist for further evaluation and neuropsychological testing.

Treatment

Pharmacotherapy

ART may be helpful in treating MCMD and HAD and should be recommended for all patients, unless there are contraindications. The ability of particular antiretroviral drugs to penetrate the blood-brain barrier may be less important to treatment success than the overall potency of the regimen and the ability of the patient to adhere to it.

Studies from the 1980s showed that zidovudine monotherapy was beneficial in patients with HAD, so some clinicians include it in the ART regimen for anyone with neurocognitive impairment. Others suggest using at least 2 drugs that cross the blood-brain barrier (eg, zidovudine, stavudine, abacavir, lamivudine, and nevirapine). Efavirenz, didanosine, and lamivudine cross to a lesser degree. As a class, protease inhibitors (PIs) have poor blood-brain barrier penetration. Nevertheless, patients have shown neurocognitive improvement while taking PI-containing regimens, perhaps because of indirect effects on HIV activity in the CNS.

Treat depressive symptoms with low dosages of selective serotonin reuptake inhibitors (SSRIs) (see chapter *Depression* for details).

Antipsychotic medications may be useful in treating agitation and hallucinations, but patients with these conditions are often extremely sensitive to anticholinergic adverse effects and extrapyramidal symptoms. Newer neuroleptic or antipsychotic agents, such as olanzapine and risperidone, have lower rates of significant side effects compared with older drugs. The starting dosage of olanzapine is 2.5 mg orally at bedtime; that for risperidone is 0.5-1 mg orally at bedtime. Note that these drugs may interact with antiretroviral medications, especially ritonavir, and can cause weight gain and other metabolic adverse effects. Avoid benzodiazepines, which tend to increase confusion and decrease concentration. Consult with a knowledgeable psychiatrist or pharmacist.

Psychostimulants such as methylphenidate (Ritalin) and dextroamphetamine (Dexedrine) have been used to improve attention, concentration, and psychomotor function. Dosages of methylphenidate start at 5 mg for a test dose, then 2.5-5.0 mg twice daily, increasing by doses of 5 mg every other day until the desired effect is achieved. Usual dosages are in the range of 20-30 mg per day. Monitor blood pressure, heart rate, and symptoms of restlessness, agitation, nausea, and psychosis. No data are available regarding the use of atomoxetine (Strattera) to improve attention and concentration in patients with HAD.

Psychosocial interventions

For a patient who is knowledgeable about HIV, a dementia workup or diagnosis often precipitates a crisis, with an increased risk of suicide. Carefully screen for depression and suicidality, and treat these if they develop.

Behavioral management strategies may assist the patient with early manifestations of dementia to continue living with some degree of independence and safety in the home. Memory aids such as posted notes, calendars, alarmed pill-boxes, and other environmental cues may help.

It is critical to enlist the support of family members and significant others at an early stage of the illness. Because the disease is frightening and may be progressive, the patient and members of the support system need assistance in anticipating and planning for the future. Plans for assisted living or other in-home custodial care should be made early. Severe or late dementia causes fear, misunderstanding, and frustration for both the patient and care givers. All involved will require

help from visiting nurses, social workers, hospice workers, and physicians. Recommend the preparation of an advance directive for the patient with early manifestations of dementia.

Patient Education

- ◆ Patients should maintain their support system as much as possible.
- ◆ Refer patients to a support group or an HIV-experienced counselor who can respond to their fears and concerns.
- ◆ ART has helped some people with HAD. Patients who are candidates for ART, should find someone to help with their antiretroviral medications, if at all possible. Enlist family members or roommates to help the patient take the medications as scheduled. Educate them about adverse effects, and whom to call with problems and questions.
- ◆ Teach patients to use cues (eg, notes, calendars, alarms) to help themselves keep track of medicines, appointments, social events, and other important activities. Help them identify ways to make the house safer and to maintain as much functionality and dignity as possible.

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Correctional Settings

Background

Caring for the HIV-infected incarcerated patient is complex and challenging. For many of these patients, the prison health service provides their first opportunity for access to health care. HIV seroprevalence rates among inmates in the United States are 5 times higher than in the nonincarcerated population (CDC, 2001). Within the prison system in the United States, mortality due to AIDS has dropped dramatically since the advent of effective combination antiretroviral therapy (ART), with the number of AIDS-related deaths decreasing by 72% in state prisons between 1995 and 2002 (Maruschak, 2001).

Often, behaviors that lead to incarceration also put inmates at high risk for becoming infected with HIV, hepatitis C virus (HCV), and other infectious diseases. These risk factors may include unsafe substance use behaviors, such as sharing syringes and other injection equipment, and high-risk sexual practices, such as having multiple sex partners or unprotected sex. Many inmates also may have conditions that increase the risk of HIV transmission or acquisition, such as untreated sexually transmitted diseases (STDs).

Of the approximately 1.8 million inmates in the United States, 30–40% are infected with HCV. The incidence is 10 times higher among inmates than among noninmates and is 33% higher in women than in men (Nerenberg et al, 2002). Chronic hepatitis B virus (HBV) infection and tuberculosis are substantially more common in the incarcerated population than in the general public. The presence of any of these conditions should prompt HIV testing (Nicodemus and Paris, 2002).

Incarcerated Women

Women represent 5–10% of the prison population in the United States. The HIV epidemic in the United States increasingly affects women of color, and this trend is reflected in HIV rates among the incarcerated. Incarcerated women have higher HIV seroprevalence rates than incarcerated men (3% vs 1.9%). Several risk factors for HIV are present in abundance among female inmates, including the following:

- ◆ History of sex work, with increased frequency of forced, unprotected sex
- ◆ High rates of STDs
- ◆ High rates of mental illness
- ◆ History of injection drug use (IDU) and/or sex partners with IDU history
- ◆ Poverty

Among all women entering a correctional facility, 10% are pregnant (De Groot and Cu Uvin, 2005). These women should be offered HIV testing, and HIV-infected pregnant women should be offered ART immediately to prevent perinatal HIV transmission. Many incarcerated women will receive their first gynecologic care in prison. Because the incidence of cervical cancer is higher in women with HIV, referrals for colposcopy should be made for any HIV-infected woman with an abnormal Papanicolaou test.

Testing and Prevention

The correctional facility is an ideal location for identifying those already infected with HIV, HCV, and/or HBV, and for preventing infection among those at highest risk for these diseases. The corrections setting is often the first site at which an HIV-infected person interacts with the health care system, making it an important avenue for HIV testing. HIV testing policies in correctional facilities vary from state to state and among local, state, and federal penal institutions. Depending on the setting, policies may require testing of inmates upon entry, upon release, or both. Testing may be based on clinical indication or risk exposure during incarceration, and may be voluntary or mandatory (Bartlett et al, 2000). The U.S. Centers for Disease Control and Prevention (CDC) recommends routine counseling and testing in settings with an HIV prevalence of 1% or higher. In high-risk settings such as correctional facilities, routine, voluntary HIV testing has been shown to be cost-effective and clinically advantageous (Paltiel, 2005).

Testing and treatment of HIV-infected inmates prior to release is critical. Given the high HIV seroprevalence rates among inmates, the reentry of inmates into the community presents the danger of spreading HIV and other infectious diseases, and thus is a public health

- ◆ History of childhood sexual abuse and neglect

concern. Inmates need adequate HIV prevention counseling before release both to protect themselves and to decrease transmission of HIV to others in their communities (Gaiter, 1996).

Health care providers in correctional settings are in a key position to evaluate inmates for HIV risk factors, to offer HIV testing, and to educate and counsel this high-risk group about HIV. Inmates often are hesitant to be tested for HIV because of fear of a positive diagnosis and because of the potential stigma involved. Often, they lack accurate information about HIV, including awareness of behaviors that may have put them at risk and knowledge of means for protecting themselves from becoming infected.

The World Health Organization (WHO) has stated: “All inmates and correctional staff and officers should be provided with education concerning transmission, prevention, treatment, and management of HIV infection. For inmates, this information should be provided at intake and updated regularly thereafter” (see: <http://www.who.int/en/>). Risk reduction counseling addresses specific ways the inmate can reduce the risk of becoming infected with HIV. If already HIV infected, the goal of counseling is to reduce the risk of infecting others or becoming infected with a drug-resistant strain of HIV. Education should focus on the use of latex barriers with all sexual activity. Although condoms and dental dams are not available in most prisons and jails, the inmate should receive education regarding their proper use.

Inmates with a history of IDU should be educated that needle sharing conveys a high risk of transmitting HIV, HCV, and HBV. Substance abuse treatment should be provided when appropriate.

Recovery from addiction often is a chronic process and relapses are common. In addition to treatment, risk reduction strategies should include planning for support after release. For example, prior to release, inmates should be provided with information about needle exchange or clean needle access programs in their communities. These programs have proved to be quite effective in decreasing the rate of parenteral HIV transmission (CDC, 1999).

Antiretroviral Therapy in Correctional Facilities

In correctional facilities, as in any setting, a consideration of HIV treatment must begin with educating the patient about the risks and benefits of treatment and the need to fully adhere to the entire regimen, as well as with an assessment of the patient’s motivation to take ART.

Correctional facilities have two medical policies for dispensing medications. Each has advantages and disadvantages that can impact treatment adherence.

Directly Observed Therapy

Directly Observed Therapy (DOT) is the system in which the inmate goes directly to the medical unit or pharmacy for all medication doses. This system offers the advantage of more frequent interaction between the patient and the health care team, allowing for earlier identification of side effects and other issues. In general, patients have better medication adherence in this system, resulting in better control of HIV. For some inmates, however, the need for frequent visits to the medical unit or pharmacy may be a barrier to treatment, particularly if they are housed at a distance from the unit. Another disadvantage of DOT is the potential loss of confidentiality, as many inmates feel that the frequency of treatment and the large number of pills they must take will reveal clues that they are HIV infected. In addition, this system puts the inmate in a passive role in terms of medication treatment and does not foster self-sufficiency.

Keep on Person

Keep on Person (KOP) is the system that allows the inmates to keep their medications in their cells and take them independently. Monthly supplies are obtained at the medical unit or pharmacy. This system offers greater privacy and confidentiality regarding HIV status. It also allows the inmate to develop self-sufficiency in managing medications, which may facilitate improved adherence upon release. However, as the KOP system involves less interaction with medical staff, problems with adherence can be more difficult to identify (Ruby, 2000).

In a study comparing DOT in HIV-infected inmates with KOP in nonincarcerated HIV-infected patients receiving ART as part of a clinical trial, a higher percentage of DOT patients achieved undetectable viral loads compared with the KOP patients (85% vs 50%) over a 48-week period (Fischl, 2001).

Adherence

Adherence is one of the most important factors in determining success of ART. For the HIV-infected inmate starting ART, a number of issues can affect medication adherence. These include patient-related factors, factors related to systems of care (including the medication dispensing systems described above), and medication-related factors. The following are suggestions for supporting adherence to ART.

Patient-Related Factors

- ◆ Provide alcohol and substance abuse treatment prior to initiating ART. Without appropriate treatment during incarceration, linkages to supports, and follow-up treatment upon discharge, the inmate is at risk for returning to high-risk behaviors that may interfere with adherence to ART.
- ◆ Utilize mental health consultation to identify inmates with psychiatric needs. Treatment for underlying mental health disorders should precede or occur simultaneously with the initiation of ART to ensure successful adherence. Depression and other psychiatric illnesses are more prevalent among inmates than among the general population (Maruschak, 2001).
- ◆ Correct misconceptions about HIV and ART that are common among inmates and could affect adherence adversely. The inmate should be educated about the disease process and the role of the medications, along with the potential risks and benefits of taking ART.
- ◆ Encourage participation in peer support groups. These can be effective ways to foster self-esteem, empower inmates to come to terms with a positive diagnosis, allay fears and correct misconceptions about HIV disease, and aid adherence. Upon release, telephone hotlines may be available to provide follow-up support and linkages to community services. To the extent possible, family and friends should be included in the education process.
- ◆ Use teaching tools that are appropriate in terms of language and reading level. Illiteracy and low-level reading ability are common among inmates. Diagrams and videos may be more effective than reading-intensive material in some cases. Basic HIV education prior to initiation of ART should include:
 - ◆ How the medications work

- ◆ Consequences of nonadherence
- ◆ Names and dosages of all medications
- ◆ Potential side effects with strategies to manage them

Factors Related to Systems of Care

- ◆ Educate security staff about the importance of timely medication dosing, and communicate with other facilities in advance of a transfer; this can eliminate or limit missed doses.
- ◆ Schedule frequent follow-up medical visits in the early weeks after ART is initiated; these can make the difference in whether or not patients "stay the course."
- ◆ Consult with an HIV specialist, if possible. If a facility's medical provider lacks experience in treating patients with HIV, the results may be undertreatment of side effects, or ART prescribing errors. Because caring for HIV patients is complicated, HIV specialists can provide assurance that patients are receiving proper care. Of particular concern are patients whose current ART regimens are failing, those who are declining clinically, and those who are coinfecting with other infectious diseases such as tuberculosis, HCV, and HBV.

Medication-Related Factors

Any consideration of HIV treatment must begin with educating the patient about the risks and benefits of treatment and the need to fully adhere to the entire regimen, as well as with assessing the patient's motivation to take ART.

- ◆ *Aggressively monitor and treat side effects.* The most common barrier to adherence to ART is side effects from the medications. The inmate should be educated in advance about potential adverse events to observe and report. In the first weeks after starting a new ART regimen, patients should be assessed frequently for side effects. For treating gastrointestinal toxicities, antiemetics and antidiarrheals should be available on an as-needed basis. As with all patients on ART, inmates should have appropriate laboratory monitoring.
- ◆ *Be aware of food requirements.* Various food requirements must be considered carefully when administering ART. This can be especially challenging in the correctional environment,

particularly if the facility does not allow inmates to self-administer medications. Make arrangements with prison authorities to provide food when inmates are taking medications that require administration with food.

- ◆ *Avoid complex regimens and regimens with large pill burdens, if possible.* Simple regimens with few pills appear to help improve adherence.
- ◆ *Avoid drug-drug interactions.* Some antiretroviral medications have clinically significant interactions with other drugs (eg, methadone, oral contraceptives, cardiac medications, antacids). These interactions may cause failure of either the antiretroviral drug or the other medication, or may cause additional toxicity. Consult an HIV specialist or pharmacologist for information on drug interactions.
- ◆ The patient should be questioned about medication adherence at each appointment.
- ◆ ART regimens need to fit into each patient's schedule and lifestyle. This becomes a bigger issue when the inmate is close to release. Education about HIV management, including ART adherence, should begin well before the inmate is discharged back to the community. At the time of discharge from the correctional facility, all HIV-infected inmates should have a discharge plan that addresses:
 - ◆ Housing
 - ◆ Health insurance
 - ◆ 30-day supply of HIV medications
 - ◆ Follow-up appointments for medical care and, if necessary, psychiatric and substance abuse care

A number of HIV education resources for inmates and correctional health care providers are cited on Albany Medical College's Web site at <http://www.amc.edu/Patient/Services/HIV/HIVMedicine/index.html> (go to the section on correctional education).

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Karnofsky Performance Scale

Background

The Karnofsky Performance Scale is an assessment tool used to assist clinicians and caretakers in measuring a patient’s ability to carry out activities of daily living. It is important to assess a patient’s performance on a regular basis, especially as the effects of HIV progress.

Documentation of Karnofsky scores may be very helpful if a patient applies for disability benefits, and may be useful for some research applications.

Table 1. The Karnofsky Performance Scale

Description	Percent (%)
Normal; no complaints; no evidence of disease	100
Able to carry on normal activity; minor signs and symptoms of disease	90
Normal activity with effort; some signs and symptoms of disease	80
Cares for self; unable to carry on normal activity or do work	70
Requires occasional assistance, but is able to care for most personal needs	60
Requires considerable assistance and frequent medical care	50
Disabled; requires special care and assistance	40
Severely disabled; hospitalization indicated although death not imminent	30
Very sick; hospitalization necessary; requires active support treatment	20
Moribund; fatal processes progressing rapidly	10
Dead	0

Sulfa Desensitization

Background

Trimethoprim-sulfamethoxazole (TMP-SMX), also known as Septra, Bactrim, and cotrimoxazole, is a key antibiotic for prophylaxis and treatment of several HIV-related illnesses. It is the most effective prophylaxis and the first-line treatment for *Pneumocystis jiroveci pneumonia* (PCP). In addition, it is effective in preventing toxoplasmosis encephalitis in severely immunocompromised patients who have evidence of previous infection, and it is effective against certain bacterial infections. TMP-SMX also is quite inexpensive, which is a rarity in the world of HIV treatment. Because of its effectiveness and availability, it is used widely throughout the world. However, adverse reactions to TMP-SMX and other sulfa drugs occur in a high proportion of HIV-infected patients (roughly 25%), and such reactions may limit treatment.

Desensitization to TMP-SMX should be considered when there are no reasonable or available alternatives and the patient has not experienced severe reactions (eg, Stevens-Johnson syndrome) to sulfa drugs. Several methods of desensitizing patients with previous reactions to TMP-SMX have been tried. These methods vary in starting dosage and length of dosage escalation, but success rates are around 80% in most cases and may be higher in those patients with <200 CD4 cells/ μ L.

S: Subjective

The patient reports a previous adverse reaction to sulfa drugs, such as erythema, pruritus, or rash. The patient has no history of anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis, and no reaction involving vesiculation, desquamation, ulceration, exfoliative dermatitis, etc.

O: Objective

CD4 count <200 cells/ μ L, or other important indication for TMP-SMX.

A: Assessment

Reaction to sulfa, possibly reversible with desensitization protocol.

P: Plan

Begin 9- to 13-day desensitization protocol, starting with pediatric oral suspension, which contains 40 mg of TMP and 200 mg of SMX per 5 mL (1 teaspoon). Gradually increase the dosage according to the protocol.

If there is any question about the severity of a previous reaction, have the patient take the initial morning dose in the clinic so that the patient may be monitored for 3–4 hours before going home. (This assumes that emergency treatment, including IV access materials and IV fluids, antihistamines, and steroids, are readily available.)

Treat with an antihistamine medication 1 day before starting the desensitization regimen and continue daily until the dose escalation is completed.

More rapid desensitization protocols are available (see References below) for patients urgently needing treatment with TMP-SMX.

Desensitization Regimen

Use commercially available pediatric suspension (containing TMP 8 mg and SMX 40 mg per mL), followed by double-strength tablets, as follows:

Table 1. Sulfa Desensitization Regimen

Days	Dosage (TMP/SMX)	Volume or Tablet
1-3	8 mg/40 mg	1 mL
3-6	16 mg/80 mg	2 mL
5-9	40 mg/200 mg	5 mL
7-12	80 mg/400 mg	1/2 double-strength tablet (or 1 single-strength tablet)
9-10 and thereafter	160 mg/800 mg	1 double-strength tablet

In the event of mild reaction: If the patient experiences a mild reaction or itching, the same dosage should be given for an additional day. If the reaction diminishes, the patient may advance to the next dosage; if the reaction worsens, the TMP-SMX should be discontinued. Antihistamines or antipyretics may be used to treat symptoms of mild reactions.

In case of severe reaction: the desensitization regimen should be discontinued.

Patient Education

For home desensitization regimen

Explain the benefits of using TMP-SMX. Be sure the patient understands and is able to follow instructions.

- ◆ Measure your dose carefully and take it each morning, followed by a glass (6-8 oz) of water. (The patient should do a demonstration, if possible, using the syringe that will be used for the actual measuring at home.)
- ◆ TMP-SMX can make you very ill unless you pay attention to any problems you have. It is extremely important that you check your temperature each afternoon. If your temperature is more than 100.5° F by mouth, stop taking the drug and contact your clinician. Note: If you have shaking chills, check your temperature as soon as the shaking stops, and contact the clinic. If you continue the medication despite a red rash and/or fever, serious illness or a life-threatening reaction may occur. Report any adverse event immediately.
- ◆ Stop the regimen and return to the clinic or emergency room immediately if you develop a red rash, blisters on your skin or in your mouth, or vomiting. Check your skin each evening, and any time you notice itching.

If you have mild itching or a faint rash, you can take diphenhydramine (Benadryl) 25-50 mg, every 4 hours as needed. If this persists, stay with the same dosage for an additional day; and call or go to the clinic if you have questions or concerns.

- ◆ Call or go to the clinic for alternate dosage instructions in the event of persistent itching without rash.

For all desensitized patients

- ◆ After desensitization is complete, continue to take the daily dosage. If the drug is stopped, the entire regimen may have to be repeated.

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Patient Education

Background

It has long been acknowledged that informed and empowered patients are better able to achieve healthy outcomes due to improved communication and development of trust with their care providers. HIV patient education provides patients with knowledge about HIV infection and tools to enable them to participate more actively in decisions regarding their medical care. Given the complexity and the rapid evolution of HIV information, patients should be given ample and multiple opportunities to receive this information and to learn of updates in our understanding of HIV care. Similarly, the clinical management of HIV patients should include educating the patient on the various aspects of living with HIV infection. This chapter will review the areas that should be addressed in patient education and discuss some strategies for integrating patient education into HIV care.

S: Subjective

A newly diagnosed patient presents to clinic after being referred from a testing center in the community. He received his positive HIV results more than a year ago, but it took him this long to seek care. He wasn't ready to hear that he was "going to die." Now, he is ready to consider facing his "terminal" illness. He received some information about HIV infection at the testing center, but that was several months ago.

O: Objective

See *Initial History*, *Initial Physical Examination*, and *Initial and Interim Laboratory* and *Other Tests* chapters.

A: Assessment/Plan

This patient will need extensive information and education about HIV infection in general, his individual health status and prognosis, and the support and care systems available to him. Below are some suggestions about specific areas to review with a new patient.

What Should Be Included in Patient Education?

Patient education should cover the following topics:

- ◆ What is HIV?
- ◆ How HIV is transmitted
- ◆ Prognosis/progression of HIV
- ◆ Interpretation of lab results
- ◆ Treatment information
 - ◆ Indications for treatment, goals of treatment
 - ◆ General information regarding the benefits of treatment
 - ◆ General information regarding potential side effects of treatment
 - ◆ Access to medication
 - ◆ Insurance information
- ◆ Treatment options
- ◆ Prevention for positives
- ◆ Support services and support groups available to the patient

Who Should Provide Patient Education?

In most clinics, various personnel may take on the responsibilities of providing health education to patients. They may include primary care providers, nurses, social workers, case managers, and pharmacists. Some clinics have designated health educators whose role is to provide this type of support for patients. Even when a formal health educator is available, a collaborative, multidisciplinary approach to patient education serves both patients and providers optimally. However, it is important to ensure that patient education messages are coordinated and that patients are receiving consistent information.

Patient education must be provided in a language and at a literacy level appropriate for the patient. Patient education should be conducted in the patient's primary language, if possible; otherwise, skilled medical interpreters should be involved.

How Should Patient Education Be Provided?

Rarely are patients able to absorb all of the necessary information in a single session. Attention and comprehension levels are optimal during the first 15–20 minutes of a visit, after which an individual's ability to absorb and retain information declines. Therefore, clinics should consider strategies to integrate these patient education messages throughout the course of patient care and to engage patients in this process. Support groups, case managers, and peer educators can be invaluable in this process of engagement.

It is also important to keep the medical information specific to the patient. Although there are some areas of education that should be considered for all patients (see above), patients should not be required to have a high level of understanding in each area. Patients should be given the opportunity to learn as much about an area as they would like and to retain the volume of information necessary to keep them healthy and safe. For example, in the area of “What is HIV?” there may be some patients who want to know details about the basic science and immunologic impact of HIV. With this information, these patients might then want to take the lead in making treatment and care decisions for themselves, in consultation with their care providers. Other patients, however, would feel overwhelmed by this volume of information and involvement and may be best engaged in participating in their care by knowing how HIV is transmitted, how to keep themselves healthy, and how to access more information if they want it. Some patients would prefer for their care providers to “just tell them what to do” rather than take the lead in their own treatment decisions.

There are a number of Web sites that provide HIV information for patients (see *Web-Based Resources* chapter). Many patients may prefer this form of self-education. Encourage patients to bring any information they discover to clinic for further discussion. Reminding patients that they can be teachers as well as students can be a useful strategy for engaging patients in this process. In addition, patients may learn of novel tools and information sources that could be useful to others.

The following are some useful suggestions that providers can convey to their patients:

- ◆ Define your goals for each visit; please let your provider know your concerns and what you hope to learn in the course of the visit.
- ◆ Write down questions and concerns as they arise, and take that list with you to your appointments.
- ◆ Meet all the members of your care team and learn their areas of expertise and what they might be able to offer you.
- ◆ Ask about support groups and other peer groups that might be able to provide support/education.
- ◆ Review brochures and/or Web sites that provide additional information.
- ◆ Ask supportive friends or family members to accompany you to clinic visits. They may be able to obtain information that is helpful for their role in supporting your health or reminding you of information discussed at visits.

Web-Based Resources

Background

The care and management of HIV-infected patients is a rapidly evolving field. Keeping up to date with clinical information about HIV care has in the past required attendance at national and international conferences. With the increasing availability of the Internet, clinicians and patients are able to access the most current advances through Web coverage, without requiring travel or time away from work.

The challenge of using Internet resources is in determining which Web sites are accurate and current. Check for dates of authorship, the credentials of the site sponsors and authors, and how well supported any recommendations or analysis may be. Be aware of any possible commercial bias. Finally, it is important to remember that information on these sites does not replace clinical judgment or consultation with HIV experts.

Listed below are a selection of useful and accurate Internet sites. Many of these Web sites also link out to additional information resources, and many allow users to subscribe to receive updates via email. Many providers find it helpful to review sites geared toward patients, in order to maintain familiarity with patients' concerns and patient-based information resources.

Web-Based Resources for Providers

◆ AIDS Education and Training Centers

National Resource Center

<http://www.aidsetc.org>

Clinical training resources, including curricula, self-study, and slide sets, including slides for all national guidelines. Online home for the Clinical Manual for Management of the HIV-Infected Adult.

◆ AIDSInfo

<http://aidsinfo.nih.gov>

Official repository for HIV/AIDS information from the U.S. Public Health Service. Content includes HIV/AIDS treatment guidelines, national clinical trial information, drug and vaccine overviews, and fact sheets for patients.

◆ Aidsmap

<http://www.aidsmap.org>

London-based HIV/AIDS news and treatment information site. Patient information written at both lower and higher literacy levels. International focus.

◆ Clinical Care Options for HIV

<http://clinicaloptions.com>

CME materials related to HIV/AIDS including conference reviews.

◆ HIV InSite

<http://hivinsite.ucsf.edu>

Major HIV/AIDS portal from the University of California San Francisco. Includes HIV InSite Knowledge Base, updated ARV information, including an interactions database, global country profiles, and links out to other useful sites.

◆ HIV Resistance Web

<http://hivresistanceweb.com>

Information on resistance mutations to antiretroviral medications.

◆ HIV Web Study

<http://hivwebstudy.org>

Northwest AETC, University of Washington. Dozens of online clinical cases featuring downloadable tables, charts, and images.

- ◆ **HIVandHepatitis.com**
<http://www.hivandhepatitis.com/>
Clinical information on HIV and hepatitis B and hepatitis C viruses, including conferences reviews.
- ◆ **International Training and Education Center on HIV**
<http://go2itech.org>
The international AETC. Web site features extensive database of international HIV/AIDS training materials.
- ◆ **International AIDS Society-USA**
<http://iasusa.org>
ARV resistance mutations charts and “Cases on the Web” online CME courses.
- ◆ **Johns Hopkins AIDS Service**
<http://www.hopkins-aids.edu/>
Major clinical information site that includes expert Q&A, the popular Pocket Guide to Adult HIV/AIDS Treatment, and the online and PDA-based POC-IT HIV Guide.
- ◆ **Medscape HIV/AIDS Topic Area**
<http://www.medscape.com/hiv-home?src=pdown>
Continuing Medical Education (CME) materials related to HIV/AIDS, including conference coverage, news, and special features.
- ◆ **National HIV/AIDS Clinicians’ Consultation Center**
<http://www.ucsf.edu/hivcntr>
An AIDS Education and Training Centers clinical resource for health care professionals, with contact information for the Warmline, PEPLINE, and Perinatal HIV Hotline.
- ◆ **VA National HIV/AIDS Program**
<http://www.hiv.va.gov/>
Comprehensive information portal for patients and providers.
- ◆ **Women, Children, and HIV**
<http://www.womenchildrenhiv.org/>
Expert-selected, evidence-based information on prevention of mother-to-child transmission of HIV, care of women and children with HIV, and related topics.

Web-Based Resources for Patients and the Community

- ◆ **AIDS.org**
<http://www.aids.org/>
Online home of AIDS Treatment News.
- ◆ **AIDS InfoNet**
<http://www.aidsinfonet.org/>
Comprehensive collection of fact sheets on clinical topics, available in English and Spanish, in print-friendly and downloadable formats. Regularly updated.
- ◆ **AIDSmeds**
<http://aidsmeds.com>
Information regarding HIV-related medications for patients, including drug interactions calculator.
- ◆ **AIDS Project Los Angeles**
<http://www.apla.org/>
Fact sheets, newsletters, and program information. Some information in Spanish.
- ◆ **The Body**
<http://thebody.com>
Major HIV information resource geared toward patients and the community.
- ◆ **Gay Men’s Health Crisis**
<http://www.gmhc.org/>
Patient and program information from one of the oldest community organizations. Some information in Spanish.
- ◆ **Project Inform**
<http://projectinform.org>
Comprehensive information and advocacy information geared toward individuals infected and affected by HIV.
- ◆ **San Francisco AIDS Foundation**
<http://www.sfaf.org/>
AIDS 101, BETA treatment newsletter, and prevention and program information. Some information in Spanish.
- ◆ **Test Positive Aware Network (TPAN)**
<http://www.tpan.com/index.shtml>
Chicago-based community organization with newsletter, drug guide, and service information.
- ◆ **VA National HIV/AIDS Program**
<http://www.hiv.va.gov/>
Comprehensive information portal for patients and providers.

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<i>Drug</i>	<i>FDA Adult Dose</i>	<i>Dosage Forms</i>	<i>Alternative or Adjusted Dose</i>	<i>Diet</i>	<i>Special Considerations</i>	<i>Adverse Effects</i>
Single Tablet Regimen						
EFV/FTC/TDF Atripla [®]	1 tablet QHS	- Efavirenz (EFV) 600mg + - Emtricitabine (FTC) 200mg + - Tenofovir (TDF) 300mg		Empty stomach recommended	Do not use if renal function is impaired (must adjust individual components)	Refer to individual agents
Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTI)						
Abacavir Ziagen [®] (ABC)	300mg BID - or - 600 mg Daily	300mg tablet 20mg/mL oral solution		With or without food	Abacavir Hypersensitivity DO NOT RECHALLENGE If hypersensitivity suspected No Renal Dosing Adjustments	Hypersensitivity reaction Symptoms may include: Fever, Rash, Nausea, Vomiting, Malaise or Fatigue, Respiratory Difficulties*
Didanosine Videx-EC [®] (ddl)	Didanosine-EC: 400mg Daily <i>If weight <60 kg:</i> 250mg Daily	125mg, 200mg, 250mg, 400mg EC capsules <i>(check package insert for other formulations)</i>	Didanosine + Tenofovir: <i>If weight > 60 kg:</i> - ddl-EC 250mg Daily + TDF 300mg Daily; <u>together with or without food</u> <i>If weight <60 kg:</i> - Appropriate dose not established, probably ddl <250 mg/day	Empty stomach with water Videx-EC capsule formulation should not be crushed, but swallowed whole	Numerous formulations with different dosing requirements exist – use caution!! - Dose adjust for impaired renal function	Peripheral neuropathy, Pancreatitis, Nausea, Diarrhea*
Emtricitabine Emtriva [®] (FTC)	200mg daily	200mg capsule		With or without food	Dose adjust for impaired renal function	Generally well tolerated; Headaches, Fatigue, Nausea*
Lamivudine Epivir [®] (3TC)	150mg BID - or - 300mg daily	150mg, 300mg tablet 10mg/mL oral solution		With or without food	Dose adjust for impaired renal function	Generally well tolerated; Headaches, Fatigue, Nausea*
Stavudine Zerit [®] (d4T)	40mg BID <i>If weight <60 kg:</i> 30mg BID	15mg, 20mg, 30mg, 40mg capsule 1mg/ml for oral solution		With or without food	- Dose adjust for impaired renal function - Co-administration with zidovudine not recommended	Peripheral neuropathy, Pancreatitis, Altered liver function, Lipoatrophy, Hyperlipidemia, Ascending paresis (rare)*
Tenofovir DF Viread [®] (TDF)	300mg Daily	300mg tablet	Didanosine + Tenofovir <i>If weight >60 kg:</i> - ddl-EC 250mg Daily + TDF 300mg Daily; <u>together with or without food</u> <i>If weight <60 kg:</i> - Appropriate dose not established, probably ddl <250mg/day Atazanavir + Tenofovir - ATV 300mg Daily + RTV 100mg Daily + TDF 300mg Daily	With or without food	Dose adjust for impaired renal function	Generally well tolerated; Nausea, Upset stomach, Vomiting, Fanconi Syndrome (rare)*
Zidovudine Retrovir [®] (AZT)	300mg BID - or - 200mg TID	100mg capsule 300mg tablet 10mg/mL oral syrup		With or without food (suggest with food)	- Dose adjust for impaired renal function - Co-administration with stavudine not recommended	Anemia, Neutropenia, Headaches, Nausea, Body aches, Insomnia*
* Class Adverse Reaction: lactic acidosis with hepatic steatosis (rare, but potentially life threatening reaction with use of NRTIs)						
NRTI Fixed Dose Combinations						
AZT/3TC Combivir [®]	1 tablet BID	- Zidovudine (AZT) 300mg + - Lamivudine (3TC) 150mg		With or without food (suggest with food)	DO NOT use if renal function is impaired (must adjust individual components)	Refer to individual agents*
ABC/3TC Epzicom [®]	1 tablet Daily	- Abacavir (ABC) 600mg + - Lamivudine (3TC) 300mg		With or without food	Abacavir hypersensitivity (see abacavir) DO NOT use if renal function is impaired (must adjust 3TC dose)	Refer to individual agents* Headaches, Fatigue, Nausea DO NOT RECHALLENGE!
ABC/AZT/3TC Trizivir [®]	1 tablet BID	- Abacavir (ABC) 300mg + - Zidovudine (AZT) 300mg + - Lamivudine (3TC) 150mg		With or without food (suggest with food)	Abacavir hypersensitivity (see abacavir) DO NOT use if CrCl < 50mL/min (adjust individual components) DO NOT use in hepatic dysfunction	Refer to individual agents* DO NOT RECHALLENGE!
FTC/TDF Truvada [®]	1 tablet Daily	- Emtricitabine (FTC) 200mg + - Tenofovir (TDF) 300mg		With or without food	DO NOT use if renal function is impaired (must adjust individual components)	Refer to individual agents*

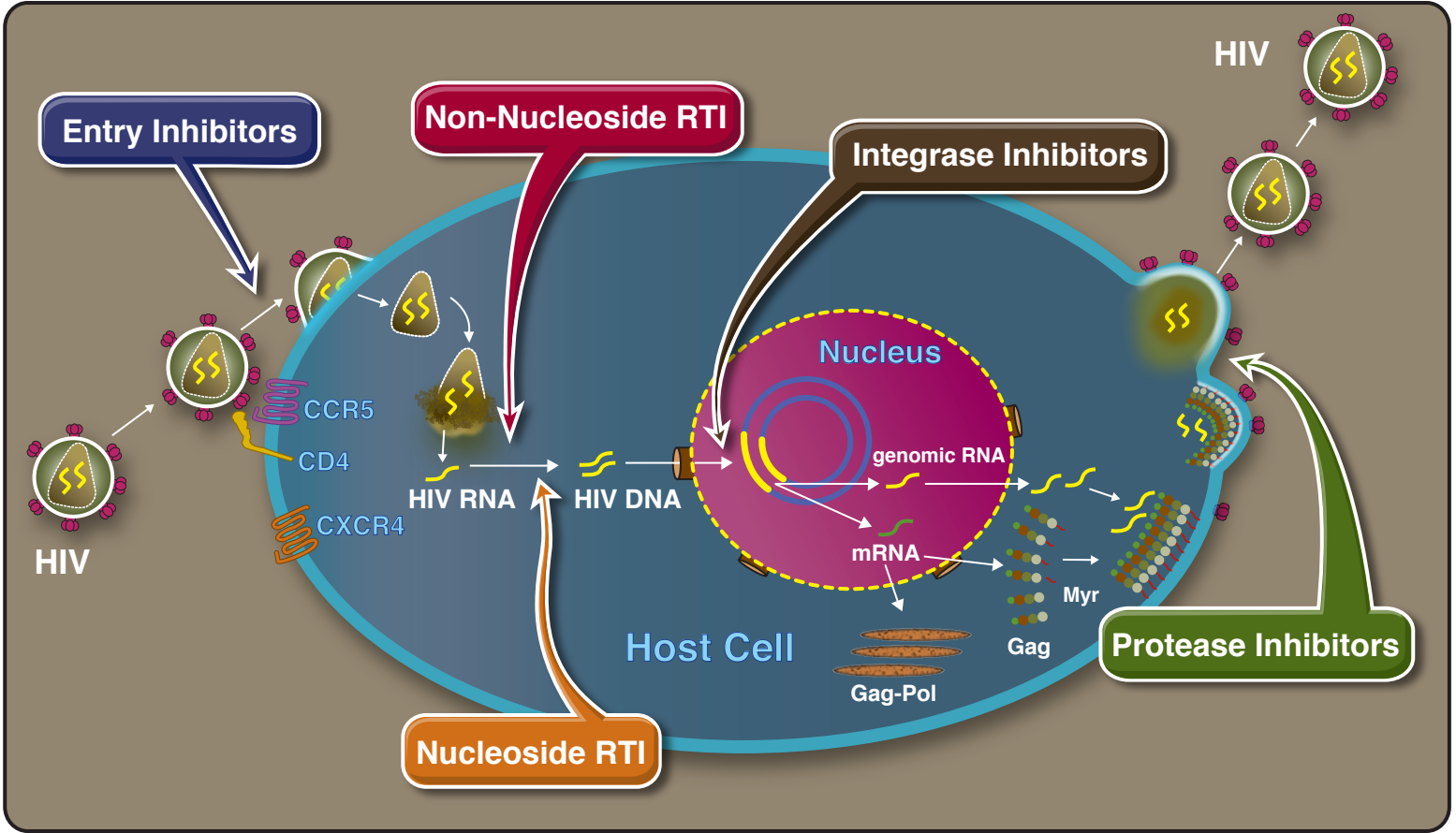
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<i>Drug</i>	<i>FDA Adult Dose</i>	<i>Dosage Forms</i>	<i>Alternative or Adjusted Dose</i>	<i>Diet</i>	<i>Special Considerations</i>	<i>Adverse Effects</i>
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)						
Delavirdine Rescriptor® (DLV)	• 400mg TID • 600mg BID	• 100mg, 200mg tablet		With or without food (Do not take with antacids)	• Older agent; not commonly used	Rash, Headache, Altered liver function
Efavirenz Sustiva® (EFV)	600mg PO QHS	• 600mg tablet • 50mg, 100mg, 200mg capsule	Dosage adjustment: EFV standard dose + • ATV 300mg Daily + RTV 100mg Daily • FPV 700mg BID + RTV 100mg BID • FPV 1,400mg Daily + RTV 300mg Daily (not recommended for tx exp pts) • LPVr 600mg/150mg (3 tabs) BID • IDV 800mg BID + RTV 100-200mg BID	Empty stomach recommended Avoid taking with high-fat meals – food may increase side effects	• Minimize alcohol intake • False + cannabinoid test	Rash, CNS effects x 2-3 weeks (Abnormal dreams, Dizziness, Impaired concentration, Insomnia, Drowsiness), Altered liver function
Etravirine Intence® (ETR)	200mg BID	• 100mg tablet	Do not co-administer etravirine with the following ARVs: • TPV/RTV, FPV/RTV, ATV/RTV • Protease inhibitors administered without RTV • NNRTIs	Take following a meal (empty stomach ↓'s absorption)	• Indicated for tx-experienced patients with resistant HIV-1, including K103N mutation • Caution is warranted when co-administered with 3A4, 2C9, and 2C19 substrates (drug levels may be altered) • Dose adjustment not required for renal dysfunction, mild/moderate hepatic dysfunction, or Hep B or C co-infection	Rash (most common in weeks 2-4, typically resolved x 1-2 weeks), Nausea
Nevirapine Viramune® (NVP)	200mg Daily x first 14 days, then 200mg BID	• 200mg tablet • 10mg/ml oral suspension	Dosage adjustment: NVP standard dose + • ATV 300mg Daily + RTV 100mg Daily • FPV 700mg BID + RTV 100mg BID • FPV 1,400mg Daily + RTV 300mg Daily (not recommended for tx exp pts) • IDV 800mg BID + RTV 100-200mg BID • LPVr 600mg/150mg (3 tabs) BID	With or without food <i>(with food if with RTV)</i>		Rash, Hepatitis, Hepatic necrosis (50% with rash) – especially in women with a baseline CD4 >250 or in men with a baseline CD4 >400
Fusion Inhibitors						
Enfuvirtide Fuzeon® (T-20)	Administered dose: 90mg/mL SQ BID (108mg vial diluted with 1.1 mL sterile water)	• Available as kit containing 60 doses w/ syringes, diluent & alcohol pads • Also available as biojector device			• Rotate injection sites • Store at controlled room temperature (59–86° F) • Visit www.fuzeon.com for ordering information	Injection site reaction: Pain/discomfort, induration, Erythema, Nodules Other: Diarrhea, Nausea, Vomiting, Fatigue, Insomnia, Nerve pain & Bruising with biojector device
CCR5 Receptor Antagonist						
Maraviroc Selzentry® (MVC)	300mg BID <i>(See alternative or adjusted dose)</i>	• 150mg, 300mg tablets	When given with strong CYP3A inhibitors (with or w/o a CYP3A inducer) including PIs (except tipranavir/ritonavir), delavirdine: • 150mg BID With NRTIs, tipranavir/ritonavir, nevirapine: • 300mg BID When given with CYP3A inducers (w/o a strong CYP3A inhibitor) including efavirenz: • 600mg BID	With or without food	• Only indicated in tx-experienced pts with CCR5-tropic-HIV-1, with evidence of viral replication and HIV-1 strains resistant to multiple ARV agents	Hepatotoxicity, Systemic allergic reaction prior to hepatotoxicity, Cough, Pyrexia, URI, Rash, Musculoskeletal Symptoms, Abdominal Pain, Dizziness
Integrase Inhibitors						
Raltegravir Isentress® (RAL)	400mg BID	• 400mg tablet		With or without food	• Indicated for tx-experienced pts with evidence of viral replications and HIV-1 strains resistant to multiple ARV agents • Caution in patients with an increased risk of myopathy or rhabdomyolysis.	Nausea, Headache, Diarrhea, Pyrexia

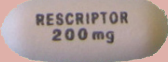
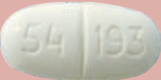
FDA Approved Antiretrovirals for the treatment of HIV Infection
Revised April 2008

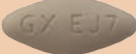
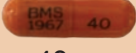
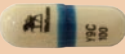
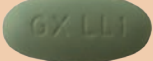
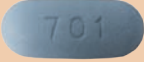
<i>Drug</i>	<i>FDA Adult Dose</i>	<i>Dosage Forms</i>	<i>Alternative or Adjusted Dose</i>	<i>Diet</i>	<i>Special Considerations</i>	<i>Adverse Effects</i>
Protease Inhibitors (PI)						
Atazanavir Reyataz [®] (ATV)	<u>Un-boosted:</u> 400mg Daily <u>Boosted:</u> 300mg Daily + RTV 100mg Daily	100mg, 150mg, 200mg, 300mg capsule	Use boosted dose of Atazanavir when used with Efavirenz, Nevirapine, or Tenofovir: - ATV 300mg Daily + RTV 100mg Daily Do not take with antacids, H2 blockers or proton pump inhibitors without consulting the prescribing information.	Take with a <u>light meal</u> for better absorption.	In PI-experienced patients, the combination of Atazanavir + Ritonavir should be used - Dose adjust for hepatic impairment	Generally well tolerated; Diarrhea, Nausea, Abdominal discomfort, Rash, Hyperbilirubinemia ⁺⁺
Darunavir Prezista [™] (DRV)	<u>Boosted only:</u> DRV 600mg BID + RTV 100mg BID	300mg tablet	DRV requires RTV boosting	Take with food for enhanced absorption	Caution in patients with known sulfonamide allergy	Diarrhea, Nausea, Headache, Rash, and Cold Symptoms ⁺⁺
Fosamprenavir Lexiva [®] (f-APV)	<u>Un-boosted:</u> 1400mg BID <u>Boosted:</u> - 700mg BID + RTV 100mg BID - 1400mg QD + RTV 100mg-200mg QD	700mg tablet	When combining with Efavirenz or Nevirapine: - f-APV 1400mg Daily + RTV 300mg Daily (not recommended for tx exp pts) - f-APV 700mg BID + RTV 100mg BID	May be taken with or without food (with food if with RTV)	- Caution in patients with known sulfonamide allergy - Dose adjust for hepatic impairment	Rash, Diarrhea, Nausea, Headache ⁺⁺
Indinavir Crixivan [®] (IDV)	<u>Un-boosted:</u> 800mg Q8H <u>Boosted:</u> 800mg BID + RTV 100-200mg BID	100mg, 200mg, 333mg, 400mg capsule	Dosage adjustment of Indinavir when used with NNRTIs (except DLV): - IDV 1000mg Q8H - IDV 800mg BID + RTV 100-200mg BID	Un-boosted IDV: Empty stomach <u>or</u> low fat snack Ritonavir boosted IDV: take <u>with food</u>	- If intolerable, take with light, non-fat snack - Drink at least 1.5 liters of fluids daily - No grapefruit juice (decreased IDV level)	Nausea, Vomiting, Kidney stone formation, Heartburn, Hyperbilirubinemia ⁺⁺
Lopinavir/ Ritonavir Kaletra [®] (LPVr)	This combination is boosted (contains RTV)	- Lopinavir 200mg/Ritonavir 50mg tablet - LPV 80mg/RTV 20mg per ml oral solution	Can be given 2 tabs BID or 4 tabs Daily Dosage adjustment of LPVr when used with NNRTIs (except DLV): LPVr 600mg/150mg (3 tabs) BID	With or without food	- RTV has multiple drug interactions via CYP450 and P-glycoprotein - Refrigerate oral solution	Diarrhea, Nausea, Headache, Asthenia (lack of strength) ⁺⁺
Nelfinavir Viracept [®] (NFV)	1250mg BID 750mg TID	250mg, 625mg tablet 50mg/1g scoop, powder for solution		Take <u>with food</u> for enhanced absorption	Important to provide <u>anti-diarrheal</u> agent	Diarrhea, Nausea, Vomiting, Abdominal pain ⁺⁺
Ritonavir Norvir [®] (RTV)	Ritonavir is primarily used in low doses to boost drug levels of other protease inhibitors	100mg capsule 80mg/mL oral solution	- Numerous combinations use ritonavir for pharmacokinetic enhancement - Most use 100-200mg RTV Daily	Take <u>with food</u> for enhanced absorption	- Refrigerate capsules. May store at room temperature up to 30d. DO NOT refrigerate oral solution (may crystallize) - Multiple drug interactions via CYP450 and P-glycoprotein	Diarrhea, Nausea, Headache, Numbness around the mouth, Altered taste, Asthenia ⁺⁺
Saquinavir Invirase [®] (SQV)	<u>Boosted only:</u> 1000mg BID + RTV 100mg BID	200mg hard gel capsule 500mg tablet	SQV requires RTV boosting	Take <u>with food</u> for enhanced absorption	Store at room temperature	Diarrhea, Nausea, Headache ⁺⁺
Tipranavir Aptivus [®] (TPV)	<u>Boosted only:</u> 500mg BID + RTV 200mg BID	250mg soft gel capsule	Separate Videx EC from TPV/RTV by at least 2 hours	Take <u>with food</u> for enhanced absorption DO NOT take with antacids	- Caution in patients with known sulfonamide allergy - Contraindicated in patients with moderate to severe hepatotoxicity - Refrigerate capsules – may store at room temp up to 60 days	Diarrhea, Nausea, Vomiting, Stomach cramps, Rash, Intracranial Hemorrhage ⁺⁺

⁺⁺ **PI Class Effects & Adverse Reactions:** CYP3A4 inhibition, hepatotoxicity, hyperlipidemia (all PIs except ATV), insulin resistance/diabetes mellitus, fat maldistribution, osteonecrosis, increased bleeding episodes in hemophilic pts.



For specific and detailed information regarding dosing recommendations, drug-drug interactions and adverse effects, see the guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents at <http://aidsinfo.nih.gov>

Drug Name	Pill	Dose	Adverse Effects
Entry Inhibitors			
Enfuvirtide (ENV) Fuzeon®	 90 mg/ml	Administered dose: 90 mg/mL subcutaneously (SQ) 2 times a day (108 mg vial diluted with 1.1 mL sterile water) • Store at controlled room temperature	Injection site reaction: pain/discomfort, induration, erythema, nodule Other: diarrhea, nausea, vomiting Fatigue, Insomnia
Maraviroc (MVC) Selzentry®	 150 mg 300 mg	1 x 300 mg tablet 2 times a day (With NRTIs, tipranavir/ritonavir, nevirapine, and weak CYP3A inhibitors or CYP3A inducers) 1 x 150 mg tablet 2 times a day (When given with strong CYP3A inhibitors with or without CYP3A inducers) 2 x 300 mg tablet 2 times a day (With CYP3A inducers including efa-	Liver toxicity, cough, fever, upper respiratory infection, rash, musculoskeletal symptoms, stomach pain, dizziness Other: Use with caution in those with liver disease or at risk for cardiovascular events
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)			
Delavirdine (DLV) Rescriptor®	 200 mg	2 x 200 mg tablets 3 times a day • May be taken with or without food	Rash, headache, altered liver function
Efavirenz (EFV) Sustiva®	 200 mg 600 mg	1 x 600 mg tablet once daily at bedtime 3 x 200 mg capsules once daily at bedtime • Empty stomach recommended	Rash, altered liver function, dizziness, insomnia, impaired concentration, drowsiness
Etravirine (ETR) Intelence®	 100 mg	2 x 100 mg tablet 2 times a day • Take with food	Nausea, headache, rash, Stevens-Johnson syndrome, hypersensitivity reaction, erythema
Nevirapine (NVP) Viramune®	 200 mg	1 x 200 mg tablet 2 times a day (start with 200 mg tablet once daily x 14 days) • May be taken with or without food	Rash, headache, altered liver function

Drug Name	Pill	Dose	Adverse Effects
Nucleos(t)ide Reverse Transcriptase Inhibitors (NRTI)			
Abacavir (ABC) Ziagen®	 300 mg	1 x 300 mg tablet 2 times a day 2 x 300 mg tablets once daily • May be taken with or without food	Hypersensitivity reaction symptoms may include: fever, rash, nausea, vomiting, malaise or fatigue, respiratory difficulties
Didanosine (ddI) Videx®	 250 mg  400 mg	1 x 400 mg capsule once daily • Reduce dose for weight < 60 Kg • Take on an <u>empty stomach</u> Note: When combined with tenofovir, reduce didanosine to 250 mg once daily, may be taken with food.	Peripheral neuropathy, pancreatitis, nausea, diarrhea
Emtricitabine (FTC) Emtriva®	 200 mg	1 x 200 mg capsule once daily • May be taken with or without food	Headaches, fatigue, nausea
Lamivudine (3TC) Epivir®	 150 mg  300 mg	1 x 150 mg tablet 2 times a day 1 x 300 mg tablet once daily • May be taken with or without food	Headaches, fatigue, nausea
Stavudine (d4T) Zerit®	 30 mg  40 mg	1 x 40 mg capsule 2 times a day • Reduce dose for weight < 60 Kg 1 x 30 mg capsule 2 times a day • May be taken with or without food	Peripheral neuropathy, altered liver function
Tenofovir DF (TDF) Viread®	 300 mg	1 x 300 mg tablet once daily • May be taken with or without food	Renal insufficiency (rare), nausea, upset stomach
Zidovudine (ZDV, AZT) Retrovir®	 100 mg  300 mg	1 x 300 mg tablet 2 times a day • May be taken with or without food	Anemia, neutropenia, headaches, nausea, body aches, insomnia
Combination NRTIs			
Abacavir + Lamivudine Epzicom®	 ABC 600 mg/3TC 300 mg	1 tablet once daily • May be taken with or without food	Hypersensitivity reaction (as above), headaches, fatigue, nausea DO NOT RECHALLENGE!
Abacavir + Lamivudine + Zidovudine Trizivir®	 ABC 300 mg/3TC 150 mg/ AZT 300 mg	1 tablet 2 times a day • May be taken with or without food	Hypersensitivity reaction (as above), refer to adverse effects listed for individual agents DO NOT RECHALLENGE!
Zidovudine + Lamivudine Combivir®	 AZT 300 mg/3TC 150 mg	1 tablet 2 times a day • May be taken with or without food	Refer to adverse effects listed for individual agents
Tenofovir + Emtricitabine Truvada®	 TDF 300 mg/FTC 200 mg	1 tablet once daily • May be taken with or without food	Refer to adverse effects listed for individual agents
Combination NRTIs + NNRTI			
Tenofovir + Emtricitabine + Efavirenz Atripla®	 TDF 300 mg/FTC 200 mg/ EFV 600 mg	1 tablet once daily at bedtime • Empty stomach recommended	Refer to adverse effects listed for individual agents
Integrase Inhibitors			
Raltegravir (RAL) Isentress®	 400 mg	1 tablet 2 times a day • May be taken with or without food	Nausea, headache, fever, diarrhea Unclear if related: myopathy or rhabdomyolysis

Drug Name	Pill	Dose	Adverse Effects
Protease Inhibitors (PI)			
Atazanavir (ATV) Reyataz®	 150 mg 200 mg 300 mg	2 x 200 mg capsules once daily 1 x 300 mg capsule with ritonavir 100 mg capsule once daily. Note: Use ritonavir boosted dose when combined with efavirenz, nevirapine, or tenofovir • Take with <u>light meal</u> • Consult Reyataz prescribing information for use with antacids, H2-blockers and proton pump inhibitors.	Diarrhea, nausea, rash, abdominal discomfort, increased bilirubin (jaundice)
Darunavir (DRV) Prezista®	 400 mg 600 mg	Always use with ritonavir 1 x 600 mg tablet 2 times a day with ritonavir 1 x 100 mg capsule 2 times a day 2 x 400 mg tablet once a day with ritonavir 1 x 100 mg capsule once a day • Take <u>with food</u>	Diarrhea, nausea, headache, rash ¹
Fosamprenavir (FPV) Lexiva®	 700 mg	PI-naïve patients: 2 x 700 mg tablets 2 times a day 2 x 700 mg tablets once daily with 1 or 2 x 100 mg ritonavir capsules once daily Note: Use ritonavir boosted dose when combined with efavirenz or nevirapine, use ritonavir 300 mg once daily when combined with NNRTIs. 1 x 700 mg tablet 2 times a day with ritonavir 1 x 100 mg capsule 2 times a day PI-experienced patients: 1 x 700 mg tablet 2 times a day with 1 x 100 mg ritonavir capsule 2 times a day • May be taken with or without food	Diarrhea, nausea, headache, rash ¹
Indinavir (IDV) Crixivan®	 400 mg	2 x 400 mg capsules 2 times a day with ritonavir 100-200 mg capsule(s) 2 times a day • Take <u>with food</u> • Drink at least 1.5 liters of fluid per day	Nausea, vomiting, kidney stones, heartburn, increased bilirubin (jaundice)
Lopinavir/ Ritonavir (LPV/r) Kaletra®	 LPV 200 mg/RTV 50 mg	PI-naïve patients: 2 tablets 2 times a day 4 tablets once daily PI-experienced patients: 2 tablets 2 times a day Once daily not recommended Note: Use 3 tablets 2 times a day when used with nevirapine or efavirenz	Diarrhea, nausea, asthenia (lack of strength), headache
Nelfinavir (NFV) Viracept®	 250 mg 625 mg	2 x 625 mg tablets 2 times a day 5 x 250 mg tablets 2 times a day 3 x 250 mg tablets 3 times a day • Always take <u>with food</u>	Diarrhea, nausea, vomiting, abdominal pain
Ritonavir (RTV) Norvir®	 100 mg	Ritonavir is primarily used in low doses to boost drug levels of other protease inhibitors • Keep refrigerated	Diarrhea, nausea, headache
Saquinavir (SQV) Invirase®	 200 mg 500 mg	Always take at same time with ritonavir 2 x 500 mg tablets 2 times a day with ritonavir 100 mg capsule 2 times a day 5 x 200 mg capsules 2 times a day with ritonavir 100 mg capsule 2 times a day • Always take <u>with food</u>	Diarrhea, nausea, headache
Tipranavir (TPV) Aptivus®	 250 mg	Always use with ritonavir PI-experienced patients: 2 x 250 mg capsules 2 times a day with ritonavir 2 x 100 mg capsules 2 times a day • Take <u>with food</u>	Diarrhea, nausea, vomiting, stomach cramps, rash ¹ , intracranial hemorrhage ²

Class Adverse Reactions: hepatotoxicity, insulin resistance/diabetes mellitus, fat maldistribution, osteonecrosis, hyperlipidemia

¹ Caution in patients with known sulfonamide allergy

² Increased bleeding episodes in hemophiliac patients



Recreational Drugs and HIV Antiretrovirals

A Guide to
Interactions for
Clinicians

2009



Recreational Drugs and HIV Antiretrovirals – A Guide to Interactions for Clinicians

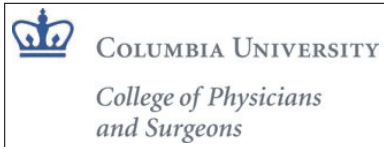
**Prepared by: Antonio Urbina, MD, John Faragon, PharmD, BCPS, AAHIVE,
Christine Kubin, PharmD and Audrey Castillo, MPH.**

This clinical support tool is sponsored by the New York/New Jersey AIDS Education Training Center (NY/NJ AETC). The NY/NJ AETC is funded by the Health Resources and Services Administration (HRSA) and is part of the National AIDS Education Training Center Program, a network of federally funded regional and national centers that conduct targeted multidisciplinary HIV/AIDS education and training programs for health care providers.

Disclaimer: Neither the AIDS Education and Training Centers nor HRSA condone or recommend the use of illicit drugs in any context. The data in this guide are intended for use by clinicians and other health care providers to provide advice that may reduce harm to patients who use these substances in conjunction with antiretroviral agents.

The data in this guide are a compilation of information obtained from published and anecdotal studies through November 2009.

*** PLEASE REFER TO PAGE 10 OF THIS GUIDE FOR IMPORTANT HARM REDUCTION THAT SHOULD BE SHARED WITH PATIENTS.**



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GENERAL

PHARMACOKINETICS

ALCOHOL
Confusion, disorientation, incoordination, loss of balance and judgement, respiratory depression, stupor, coma

Metabolized by alcohol dehydrogenase and aldehyde dehydrogenase; alcohol may induce CYP2E1 and CYP3A

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

No known interactions specific to this combination

NRTIs

abacavir (ABC, Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
* emtricitabine (FTC, Emtriva)
Epzicom (3TC/ABC)
lamivudine (3TC, EpiVir)
stavudine (d4T, Zerit)
tenofovir (TDF, Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Increases abacavir AUC ~40% (decreased abacavir metabolism by alcohol dehydrogenase)

Increased risk of pancreatitis

*** SEE INDIVIDUAL COMPONENTS**

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

No known interactions specific to this combination. Caution with amprenavir and fosamprenavir oral solution as increased risk of propylene glycol toxicity possible.

CCR5 Inhibitor

Maraviroc (Selzentry)

No known interactions specific to this combination

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

AMPHETAMINES (Crystal)

Paranoia, anxiety, depression, hallucinations, tachycardia, hypertension, stroke, myocardial infarction, hyperthermia, rhabdomyolysis, diarrhea, erectile dysfunction, teeth grinding

Metabolized by hydroxylation and deamination via CYP2D6 pathway; CYP2D6 inhibitors may increase amphetamine levels (try to avoid)

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

No known interactions specific to this combination

NRTIs

abacavir (ABC, Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, EpiVir)
stavudine (d4T, Zerit)
tenofovir (TDF, Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

*** SEE INDIVIDUAL COMPONENTS**

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

Use of full dose ritonavir or low dose ritonavir for boosting other protease inhibitors has the potential to increase amphetamine levels in the blood.

No known interactions specific to this combination. Refer to comments for this drug class in general

Increases amphetamine blood levels 2-3 times

CCR5 Inhibitor

Maraviroc (Selzentry)

No known interactions specific to this combination

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

AMYL NITRITE (amyl nitrate, poppers)

Reduces glutathione levels; inhaling the fumes acts as a vasodilator (hypotension, tachycardia, headaches), skin flushing

GENERAL

PHARMACOKINETICS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intencele)

NRTIs

abacavir (ABC, Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddl, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF, Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

KNOWN DRUG INTERACTIONS

No known interactions specific to this combination

* SEE INDIVIDUAL COMPONENTS

No known interactions

No known interactions specific to this combination

No known interactions specific to this combination

BENZODIAZEPINES

CNS depression, drowsiness, memory loss, impaired coordination

Most agents extensively metabolized in the liver by the CYP3A4 system; lorazepam, oxazepam, and temazepam metabolized by conjugation via glucuronidation.

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intencele)

NRTIs

abacavir (ABC, Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddl, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF, Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

KNOWN DRUG INTERACTIONS

Likely inhibits benzodiazepine metabolism through CYP3A4 inhibition and increases risk of adverse effects; concomitant use should be avoided

No known interactions specific to this combination

Diazepam drug levels may be increased by etravirine; a decrease in diazepam dosage may be needed

* SEE INDIVIDUAL COMPONENTS

Likely to interfere with metabolism and increase AUC of benzodiazepines; use of PIs with benzodiazepines should be avoided due to increased risk of sedation and respiratory depression;

midazolam and triazolam specifically contraindicated with all PIs. DHHS guidelines recommend that parenteral midazolam can be used with caution as a single dose if given in a monitored situation for procedural sedation.

No known interactions specific to this combination. Refer to comments for this drug class in general

Decreases therapeutic effect of lorazepam, oxazepam, and temazepam (monitor for withdrawal)

No known interactions specific to this combination

No known interactions specific to this combination

COCAINE (coke, blow)

Increases rate of HIV viral replication in vitro, hypertension, cardiac dysrhythmias, myocardial infarction, seizures, depression, anxiety

GENERAL

PHARMACOKINETICS

Mainly metabolized by nonspecific tissue and plasma esterases; some cocaine metabolism (~10%) via CYP3A4

NNRTIs KNOWN DRUG INTERACTIONS

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

No known interactions specific to this combination

NRTIs

abacavir (ABC, Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF, Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

SEE INDIVIDUAL COMPONENTS

No known interactions

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

No known interactions specific to this combination

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

ECSTASY (X, MDMA)

Tachycardia, hypertension, hyperthermia, dehydration, dry mouth, tense jaw, teeth grinding, depression

CYP2D6 demethylation important in metabolism; 2D6 inhibitors are likely to increase ecstasy levels

NNRTIs KNOWN DRUG INTERACTIONS

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

No known interactions specific to this combination

NRTIs

abacavir (ABC, Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF, Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

SEE INDIVIDUAL COMPONENTS

Increase levels of ecstasy

No known interactions specific to this combination. Refer to comments for this drug class in general

Increases risk of kidney stones due to dehydration

Potential to increase ecstasy levels

Increases ecstasy levels 5-10 times (AVOID)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

No known interactions specific to this combination

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

Erectile Dysfunction Agents

(sildenafil (Viagra), tadalafil (Cialis), vardenafil (Levitra))

Hypotension, tachycardia, arrhythmias (cardiac arrest and death),
headache, flushing, rhinitis, dyspepsia, nausea, and visual effects (e.g.
light sensitivity, changes in color vision), priapism

GENERAL

PHARMACOKINETICS

Metabolized in the liver via CYP3A4

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intencele)

NRTIs

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

Potential to significantly increase sildenafil, tadalafil, and vardenafil concentrations. Use sildenafil at reduced doses of 25 mg every 48 hours, tadalafil at reduced doses of 10 mg every 72 hours, vardenafil at reduced doses of no more than 2.5 mg every 72 hours and monitor closely for adverse effects.
No known interactions specific to this combination.

Bravirine has been shown to decrease sildenafil concentrations, though may be used together without sildenafil dosage adjustment. Sildenafil dosage may need to be adjusted based upon clinical effect. Similar interactions are also predicted with tadalafil and vardenafil.

* SEE INDIVIDUAL COMPONENTS

Potential to significantly increase sildenafil, tadalafil, and vardenafil concentrations. Use sildenafil at reduced doses of 25 mg every 48 hours, tadalafil at reduced doses of 10 mg every 72 hours, vardenafil at reduced doses of no more than 2.5 mg every 72 hours and monitor closely for adverse effects.

No known interactions specific to this combination. Refer to comments for this drug class in general

Increases sildenafil AUC ~340% and vardenafil AUC 16-fold. May increase tadalafil concentrations. Refer to comments for this drug class in general. Monitor closely for adverse effects.

Increases sildenafil AUC 1000%, tadalafil AUC 124%, and vardenafil AUC 49-fold and half-life 5-6 fold. Refer to comments for this drug class in general. Monitor closely for adverse effects.

Increases sildenafil AUC ~210%. May increase tadalafil and vardenafil concentrations. Refer to comments for this drug class in general. Monitor closely for adverse effects.

No known interactions specific to this combination

No known interactions specific to this combination

GHB
(gamma-hydroxy-butyrate, grievous bodily harm, liquid X)
Seizures, bradycardia, severe respiratory depression, hypotension, vomiting coma, death

GENERAL

PHARMACOKINETICS

Utilizes CYP2D6 pathway for metabolism

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

No known interactions specific to this combination

NRTIs

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddl, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, EpiVir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

*SEE INDIVIDUAL COMPONENTS

PIs potentially increase drug levels of GHB

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

No known interactions specific to this combination.
Refer to comments for this drug class in general

CCR5 Inhibitor

Maraviroc (Selzentry)

No known interactions specific to this combination

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

HEROIN (smack, brown junk, China White)
Dreamlike state of warmth and well-being with small doses; CNS depression, drowsiness, respiratory depression, constricted pupils, nausea/vomiting with excessive doses

Utilizes CYP3A4 pathway for metabolism

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

No known interactions specific to this combination

NRTIs

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddl, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, EpiVir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

*SEE INDIVIDUAL COMPONENTS

Possible decrease in heroin levels

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

No known interactions specific to this combination. Refer to comments for this drug class in general

Reduces heroin levels by 50%

CCR5 Inhibitor

Maraviroc (Selzentry)

No known interactions specific to this combination

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

KETAMINE (K, Special K)

GENERAL Paranoia, anxiety, mania, hallucinations, "K-hole" (semi-catatonic stupor). Elevated levels may cause tachycardia, hypertension, respiratory depression

PHARMACOKINETICS

Undergoes N-demethylation and hydroxylation (possibly mediated by CYP3A4); possible weak inhibitor of CYP2D1 and CYP3A4

KNOWN DRUG INTERACTIONS

NNRTI's

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

NRTI's

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddl, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

*SEE INDIVIDUAL COMPONENTS

Likely increase the effect of ketamine (more sedation, increased heart rate and blood pressure). Effects last longer

No known interactions specific to this combination. Refer to comments for this drug class in general

Combination may increase risk of drug induced hepatitis

No known interactions specific to this combination

No known interactions specific to this combination

LSD (acid)

Paranoia, visual and auditory hallucinations

KNOWN DRUG INTERACTIONS

NNRTI's

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intelence)

NRTI's

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddl, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

*SEE INDIVIDUAL COMPONENTS

No known interactions

No known interactions specific to this combination

No known interactions specific to this combination

MARIJUANA (Tetrahydrocannabinol;THC)

Tachycardia, loss of inhibitions, dry mouth, visual hallucinations

GENERAL

PHARMACOKINETICS

Metabolized in the liver to active metabolite (11-hydroxy THC) via CYP3A4, 2C9, and 2C6; inhibitors/inducers of CYP3A4 may interfere with THC metabolism

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intencele)

NRTIs

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

* SEE INDIVIDUAL COMPONENTS

Potential to increase THC levels

No known interactions specific to this combination.

Refer to comments for this drug class in general

In one study, concentrations of atazanavir were reduced up to 60% in patients using marijuana. Study did not differentiate whether atazanavir was boosted with ritonavir or not.

No known interactions specific to this combination

No known interactions specific to this combination

METHADONE

Generalized CNS depression

Primarily utilizes CYP3A4 pathway for metabolism; inhibitor of CYP2D6 and CYP3A4

KNOWN DRUG INTERACTIONS

NNRTIs

delavirdine (Rescriptor)
efavirenz (Sustiva)
nevirapine (Viramune)
etravirine (Intencele)

NRTIs

abacavir (ABC,Ziagen)
* Atripla (EFV/TDF/FTC)
* Combivir (AZT/3TC)
didanosine (ddI, Videx)
emtricitabine (FTC, Emtriva)
* Epzicom (3TC/ABC)
lamivudine (3TC, Epivir)
stavudine (d4T, Zerit)
tenofovir (TDF,Viread)
* Trizivir (AZT/3TC/ABC)
* Truvada (FTC/TDF)
zidovudine (AZT, ZDV, Retrovir)

Protease Inhibitors

amprenavir (Agenerase)
fosamprenavir (Lexiva)
atazanavir (Reyataz)
darunavir (Prezista)
indinavir (Crixivan)
lopinavir/ritonavir (Kaletra)
nelfinavir (Viracept)
ritonavir (Norvir)
saquinavir (Fortovase, Invirase)
tipranavir (Aptivus)

CCR5 Inhibitor

Maraviroc (Selzentry)

Integrase Inhibitor

Raltegravir (Isentress)

No known interactions specific to this combination

Decreases methadone AUC significantly (~60%); titrate methadone dose to effect

Decreases methadone AUC significantly (~40-50%); titrate methadone dose to effect

Bravirine and methadone may be used together without dosage adjustments; monitor as needed

Increases methadone clearance ~22% (an increase in methadone dose may be required in some patients)

Decreases didanosine AUC ~41-60% (consider didanosine tablet form dose increase or switch to enteric-coated formulation which may not be affected to the same degree)

Decreases stavudine AUC ~23%

Increases zidovudine AUC ~40% (increases

AUC ~29% during chronic treatment)

Interaction highly variable and patients should be evaluated on an individual basis

Decreases methadone levels ~13-30%; monitor for withdrawal and consider methadone dose increase if needed

Decreases methadone AUC ~16-36% (may require methadone dose increase)

Decreases methadone AUC ~26-53% (may require methadone dose increase)

Decreases methadone AUC ~47% (may require methadone dose increase)

Decreases methadone AUC ~37% (may require methadone dose increase)

Decrease methadone AUC by ~50% (may require methadone dosage increase)

No known interactions specific to this combination

PATIENT INFORMATION TO REDUCE HARM

ALCOHOL

If you take ddl, do not drink alcohol. Try to avoid alcohol or use modestly.

AMYL NITRITE (amyl nitrate, poppers)

Do not use with sildenafil (Viagra), vardenafil (Levitra) or tadalafil (Cialis). Heart problems, glaucoma, or anemia make poppers more dangerous.

COCAINE (coke, blow)

Don't get so high you forget to stick to your antiretroviral regimen. Avoid cocaine if you have heart or liver problems, or high blood pressure

Erectile Dysfunction Agents

Do not mix with amyl or butyl nitrates (poppers). Combination can cause sudden drop in blood pressure leading to fainting or heart attack.

GHB

Start with half-teaspoon, wait half-hour before taking more. Do not mix with alcohol, tranquilizers, pain-killers, or allergy medications. Do not use if you are alone. The dose you used last week can kill you this week.

KETAMINE (K, Special K)

Start with 1/3 or 1/2 of usual dose. Wait a half-hour before doing more. Always use with a friend, never alone.

AMPHETAMINES (Crystal)

Avoid use if you have heart or liver problems, or high blood pressure. Recent reports of transmitted HIV resistance in patients using methamphetamine and practicing unsafe sex.

BENZODIAZEPINES

Any changes to your methadone regimen or HIV medications should be reported to both providers to ensure potential interactions are identified.

ECSTASY (X, MDMA)

Start with 1/4 or 1/2 tablet. Drink plenty of water.

HEROIN (smack, brown junk, China, White)

Start with normal dose and increase only if you experience less of a hit and less buzz. Safe injecting. Do not mix with other recreational drugs.

METHADONE

Any changes to your methadone regimen or HIV medications should be reported to both providers to ensure potential interactions are identified.

RESOURCES

The National AETC Program also includes the following services:

National HIV/AIDS Clinicians Consultation Center: 1-800-933-3413

Offering treating clinicians current HIV clinical and drug information and individualized, expert case consultation.

Post-Exposure Prophylaxis 24 hour hotline: 1-888-HIV-4911

Providing consultation for occupational exposures.

Perinatal Hotline: 1-888-448-8765

Providing consultation for perinatal exposure and treatment.

AETC HIV/AIDS National Resource Center: <http://www.aidsetc.org/>

Providing resources (including curricula and lecture slide sets) on HIV disease treatment, education and data.

**FOR FURTHER INFORMATION,
PLEASE VISIT ONE OF THE FOLLOWING WEBSITES:**

NY/NJ AIDS Education and Training Center
www.nynjaetc.org

U.S. DHHS AIDS Info
aidsinfo.nih.gov

NYSDOH AIDS Institute Clinical Resources
www.hivguidelines.org

Substance Abuse and Mental Health Services Administration
www.samhsa.gov

Addiction Technology Transfer Center
www.nattc.org

Harm Reduction Coalition
www.harmreduction.org

Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

December 1, 2009

Developed by the DHHS Panel on
Antiretroviral Guidelines for Adults
and Adolescents – A Working Group of the
Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:

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It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the **AIDSinfo Web site** (<http://aidsinfo.nih.gov>).

What's New in the Document?

The following key changes were made to update the November 3, 2008, version of the guidelines. Significant updates are highlighted throughout the document.

New Section

Based on interests and requests from HIV practitioners, a new section entitled “[Considerations in Managing Patients with HIV-2 Infection](#)” has been added to the guidelines. This new section briefly reviews the current knowledge on the epidemiology and diagnosis of HIV-2 infection and the role of antiretroviral therapy in the management of patients with HIV-2 mono-infection and HIV-1/HIV-2 coinfection.

Key Updates

Drug Resistance Testing

In this revision, the Panel provides more specific recommendations on when to use genotypic versus phenotypic testing to guide therapy in treatment-experienced patients with viremia while on treatment.

- Genotypic testing is recommended as the preferred resistance testing to guide therapy in patients with suboptimal virologic responses or virologic failure while on first or second regimens (**AIII**).
- Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors (**BIII**).

Initiation of Antiretroviral Therapy

In this updated version of the guidelines, the Panel recommends earlier initiation of antiretroviral therapy with the following specific recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with CD4 count < 350 cells/mm³ (**AI**).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (**AI**), HIV-associated nephropathy (**AII**), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (**AIII**).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm³. The Panel was divided on the strength of this recommendation: 55% of Panel members for strong recommendation (A) and 45% for moderate recommendation (B) (**A/B-II**).
- For patients with CD4 counts > 500 cells/mm³, 50% of Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment as optional (C) in this setting (**B/C-III**).

Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (**AIII**). Patients may choose to postpone therapy, and providers may elect to defer therapy, based on clinical and/or psychosocial factors on a case-by-case basis.

What to Start in Antiretroviral-Naïve Patients

- Increasing clinical trial data in the past few years have allowed for better distinction between the virologic efficacy and safety of different combination regimens. Instead of providing recommendations for individual antiretroviral components to use to make up a combination, the Panel now defines what regimens are recommended in treatment-naïve patients.
- Regimens are classified as “Preferred,” “Alternative,” “Acceptable,” “Regimens that may be acceptable but more definitive data are needed,” and “Regimens to be used with caution.”
- The following changes were made in the recommendations:
 - “Raltegravir + tenofovir/emtricitabine” has been added as a “Preferred” regimen based on the results of a Phase III randomized controlled trial (**AI**).
 - Four regimens are now listed as “Preferred” regimens for treatment-naïve patients. They are:

- efavirenz/tenofovir/emtricitabine;
 - ritonavir-boosted atazanavir + tenofovir/emtricitabine;
 - ritonavir-boosted darunavir + tenofovir/emtricitabine; and
 - raltegravir + tenofovir/emtricitabine.
- Lopinavir/ritonavir-based regimens are now listed as “Alternative” **(BI)** instead of “Preferred” regimens, except in pregnant women, where twice-daily lopinavir/ritonavir + zidovudine/lamivudine remains a “Preferred” regimen **(AI)**.

Additional Updates

The following sections and their relevant tables have been substantially updated:

- What Not to Use
- Management of Treatment-Experienced Patients
- Treatment Simplification
- Hepatitis C Coinfection
- Antiretroviral-Associated Adverse Effects
- Antiretroviral Drug Interactions
- Preventing Secondary Transmission of HIV

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DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents Panel Roster

These Guidelines were developed by the Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (a Working Group of the Office of AIDS Research Advisory Council).

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Updated December 1, 2009

Introduction (Updated November 3, 2008)

Antiretroviral therapy for treatment of human immunodeficiency virus type 1 (HIV-1) infection has improved steadily since the advent of potent combination therapy in 1996. New drugs have been approved that offer new mechanisms of action, improvements in potency and activity even against multi-drug-resistant viruses, dosing convenience, and tolerability.

The Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents (the Panel) is a working group of the Office of AIDS Research Advisory Council (OARAC). The primary goal of the Panel is to provide recommendations for HIV care practitioners based on current knowledge of antiretroviral drugs used to treat adults and adolescents with HIV infection in the United States. The Panel reviews new evidence and updates recommendations when needed. The primary areas of attention have included baseline assessment, treatment goals, indications for initiation of antiretroviral therapy, choice of the initial regimen in treatment-naïve patients, drugs or combinations to be avoided, management of adverse effects and drug interactions, management of treatment failure, and special considerations in specific patient populations.

These guidelines generally represent the state of knowledge regarding the use of antiretroviral agents. However, as the science rapidly evolves, the availability of new agents and new clinical data may rapidly change therapeutic options and preferences. (Information included in these guidelines may not represent FDA approval or approved labeling for the particular products or indications in question. Specifically, the terms “safe” and “effective” may not be synonymous with the FDA-defined legal standards for product approval.) The guidelines, therefore, are updated frequently by the Panel and are available as a “living document” on the *AIDSinfo* Web site (<http://www.aidsinfo.nih.gov>). However, these guidelines cannot always keep pace with the rapid evolution of new data in this field, and the guidelines cannot provide guidance for all patients. Therefore, clinicians need to exercise good judgment in management decisions tailored to unique patient circumstances.

GUIDELINES DEVELOPMENT PROCESS

An outline of the composition of the Panel and guidelines process can be found in Table 1.

Table 1. Outline of the Guidelines Development Process (Updated November 3, 2008)

Page 1 of 2

Topic	Comment
Goal of the guidelines	Provide guidance to HIV care practitioners on the optimal use of antiretroviral agents for the treatment of HIV infection in adults and adolescents in the United States.
Panel members	The Panel is composed of more than 30 voting members who have expertise in HIV care and research. The U.S. government representatives include at least one representative from each of the following DHHS agencies: Centers for Disease Control and Prevention (CDC), Food and Drug Administration (FDA), Health Resource Services Administration (HRSA), and National Institutes of Health (NIH). These members are appointed by their respective agencies. Approximately two thirds of the Panel members are nongovernmental scientific members. There are 4–5 community members. Members who do not represent U.S. government agencies are selected after an open announcement to call for nominations. Each member serves on the Panel for a 4-year term, with an option to be reappointed for an additional term. A list of the current members can be found on Page vi of this document.
Financial disclosure	All members of the Panel submit a written financial disclosure annually reporting any association with manufacturers of antiretroviral drugs or diagnostics used for management of HIV infections. A list of the latest disclosures can be found in Appendix A of this document.
Users of the guidelines	HIV treatment providers

Topic	Comment
Developer	Panel on Antiretroviral Guidelines for Adults and Adolescents—a working group of the OARAC
Funding source	Office of AIDS Research, NIH
Evidence collection	The recommendations generally are based on studies published in peer-reviewed journals. On some occasions, particularly when new information may affect patient safety, unpublished data presented at major conferences or prepared by the FDA and/or manufacturers as warnings to the public may be used as evidence to revise the guidelines.
Recommendation grading	As described in Table 2
Method of synthesizing data	Each section of the guidelines is assigned to a working group with expertise in the area of interest. The members synthesize the available data and propose a recommendation to the Panel. All proposals are discussed at monthly teleconferences and then are voted on by the Panel members before being endorsed as official recommendations.
Other guidelines	These guidelines focus on treatment for adults and adolescents. Separate guidelines outline the use of antiretroviral therapy for such populations as pregnant women, children, and those who experience occupational or non-occupational exposure to HIV. These guidelines are also available on the AIDSinfo Web site (http://www.aidsinfo.nih.gov). There is a brief discussion of the management of women of reproductive age and pregnant women in this document. For a more detailed and up-to-date discussion on this and other special populations, the Panel defers to the designated expertise offered by panels that have developed those guidelines.
Update plan	The Panel meets monthly by teleconference to review data that may warrant modification of the guidelines. Updates may be prompted by new drug approvals (or new indications, dosing formulations, or frequency), new significant safety or efficacy data, or other information that may have a significant impact on the clinical care of patients. For cases in which significant new data become available that may affect patient safety, a warning announcement with the Panel's recommendations may be made on the AIDSinfo Web site until appropriate changes can be made in the guidelines document. Updated guidelines are available on the AIDSinfo Web site (http://www.aidsinfo.nih.gov).
Public comments	After release of an update on the AIDSinfo Web site, the public is given a 2-week period to submit comments to the Panel. These comments are reviewed, and a determination is made as to whether revisions are indicated. The public is also able to submit comments to the Panel at any time at contactus@aidinfo.nih.gov .

Basis for Recommendations

Recommendations in these guidelines are based upon scientific evidence and expert opinion. Each recommended statement is rated with a letter of **A**, **B**, or **C** that represents the strength of the recommendation and with a numeral **I**, **II**, or **III** that represents the quality of the evidence (see Table 2 below).

Table 2. Rating Scheme for Recommendations (Updated November 3, 2008)

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement B: Moderate recommendation for the statement C: Optional recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes III: Expert opinion

HIV Expertise in Clinical Care

Multiple studies have demonstrated that better outcomes are achieved in HIV-infected outpatients cared for by a clinician with HIV expertise [1-6], which reflects the complexity of HIV infection and its treatment. Thus, appropriate training and experience, as well as ongoing continuing medical education (CME), are important components for optimal care. Primary care providers without HIV experience, such as those who provide service in rural or underserved areas, should identify experts in the region who will provide consultation when needed.

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Baseline Evaluation (November 3, 2008)

Each HIV-infected patient entering into care should have a complete medical history, physical examination, laboratory evaluation, and counseling regarding the implications of HIV infection. The purpose is to confirm the presence of HIV infection, obtain appropriate baseline historical and laboratory data, assure patient understanding about HIV infection, and initiate care as recommended by the HIV primary care guidelines and by the opportunistic treatment and prevention guidelines [1-2]. Baseline information then is used to define management goals and plans.

The following laboratory tests should be performed for a new patient during initial patient visits:

- HIV antibody testing (if prior documentation is not available or if HIV RNA is undetectable) **(AI)**;
- CD4 T-cell count **(AI)**;
- Plasma HIV RNA (viral load) **(AI)**;
- Complete blood count, chemistry profile, transaminase levels, BUN and creatinine, urinalysis, screening test for syphilis (e.g., RPR, VDRL, or treponema EIA), tuberculin skin test (TST) or interferon- γ release assay (IGRA) (unless there is a history of prior tuberculosis or positive TST or IGRA), anti-*Toxoplasma gondii* IgG, hepatitis A, B, and C serologies, and Pap smear in women **(AIII)**;
- Fasting blood glucose and serum lipids if the patient is considered at risk of cardiovascular disease and for baseline evaluation prior to initiation of combination antiretroviral therapy **(AIII)**; and
- For patients who have pretreatment HIV RNA >1,000 copies/mL, genotypic resistance testing when the patient enters into care, regardless of whether therapy will be initiated immediately **(AIII)**. For patients who have HIV RNA levels of 500–1,000 copies/mL, resistance testing also may be considered, even though amplification may not always be successful **(BII)**. If therapy is deferred, repeat testing at the time of antiretroviral initiation should be considered **(CIII)**. (See [Drug Resistance Testing](#) section.)

In addition:

- Testing for *Chlamydia trachomatis* and *Neisseria gonorrhoeae* is encouraged to identify both recent high-risk sexual behavior and the need for sexually transmitted disease (STD) therapy **(BII)**; and
- Chest x-ray in the presence of pulmonary symptoms or with a positive TST or IGRA test **(BIII)**.

Patients living with HIV infection must often cope with multiple social, psychiatric, and medical issues that are best addressed through a multidisciplinary approach to the disease. The evaluation also must include assessment of substance abuse, economic factors (e.g., unstable housing), social support, mental illness, comorbidities, high-risk behaviors, and other factors that are known to impair the ability to adhere to treatment and to promote HIV transmission. Once evaluated, these factors should be managed accordingly.

Lastly, education about HIV risk behaviors and effective strategies to prevent HIV transmission to others should be provided at each patient clinic visit. (See [Preventing Secondary Transmission of HIV](#) section.)

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Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy

(Updated December 1, 2009)

A number of laboratory tests are important for initial evaluation of an HIV-1-infected patient upon entry into care, during follow-up if therapy is not yet initiated, and prior to and after initiation or switch of therapy to assess virologic and immunologic efficacy of antiretroviral therapy as well as to monitor for laboratory abnormalities that may be associated with antiretroviral drugs. [Table 3](#) outlines the Panel's recommendations for the frequency of testing. As noted in the table, some of the tests may be repeated more frequently if clinically indicated.

Two surrogate markers are used routinely to assess the immune function and level of HIV viremia: CD4 T-cell count and plasma HIV RNA (viral load). Resistance testing should be used to guide selection of an antiretroviral regimen in both treatment-naïve and treatment-experienced patients; a viral tropism assay should be performed prior to initiation of a CCR5 antagonist; and HLA-B*5701 testing should be performed prior to initiation of abacavir. The rationale and utility of these laboratory tests are discussed below.

Table 3. Laboratory Monitoring Schedule for Patients Prior to and After Initiation of Antiretroviral Therapy (Updated December 1, 2009)

Abbreviations: ABC = abacavir; ART = antiretroviral therapy; EFV = efavirenz; HIVAN = HIV-associated nephropathy; TDF = tenofovir; ZDV = zidovudine

	Entry into care	Follow-up before ART	ART initiation or switch ¹	2–8 weeks post-ART initiation or switch	Every 3–6 months	Every 6 months	Every 12 months	Treatment failure	Clinically indicated
CD4 T-cell count	√	every 3–6 months	√		√ ²			√	√
HIV RNA	√	every 3–6 months	√	√ ³	√ ²			√	√
Resistance testing	√		√ ⁴					√	√
HLA-B*5701 testing			√ (if considering ABC)						
Tropism testing			√ (if considering a CCR5 antagonist)					√ (if considering a CCR5 antagonist)	√
Hepatitis B serology ⁵	√		√ (may repeat if not immune and if HBsAg was (-) at baseline)					√	√
Basic chemistry ⁶	√	every 6–12 months	√	√	√				√
ALT, AST, T. bilirubin, D. bilirubin	√	every 6–12 months	√	√	√				√
CBC with differential	√	every 3–6 months	√	√ (if on ZDV)	√				√
Fasting lipid profile	√	if normal, annually	√	√ (consider after starting new ART)		√ (if borderline or abnormal at last measurement)	√ (if normal at last measurement)		√
Fasting glucose	√	if normal, annually	√		√ (if borderline or abnormal at last measurement)	√ (if normal at last measurement)			√
Urinalysis ⁷	√		√			√ (patients with HIVAN)	√ (if on TDF)		√
Pregnancy test			√ (if starting EFV)						√

¹Antiretroviral switch may be for treatment failure, adverse effects, or simplification.

²For adherent patients with suppressed viral load and stable clinical and immunologic status for >2–3 years, some experts may extend the interval for CD4 count and HIV RNA monitoring to every 6 months.

³If HIV RNA is detectable at 2–8 weeks, repeat every 4–8 weeks until suppression to less than level of detection, then every 3–6 months.

⁴For treatment-naïve patients, if resistance testing was performed at entry into care, repeat testing is optional; for patients with viral suppression who are switching therapy for toxicity or convenience, resistance testing will not be possible and therefore is not necessary.

⁵If HBsAg is positive at baseline or prior to initiation of antiretroviral therapy, tenofovir + (emtricitabine or lamivudine) should be used as part of antiretroviral regimen to treat both HBV and HIV infections. If HBsAb is negative at baseline, Hepatitis B vaccine series should be administered.

⁶Serum Na, K, HCO₃, Cl, BUN, creatinine, glucose (preferably fasting); some experts suggest monitoring phosphorus while on tenofovir; determination of renal function should include estimation of creatinine clearance using Cockcroft and Gault equation or estimation of glomerular filtration rate based on MDRD equation.

⁷For patients with renal disease, consult “Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients: Recommendations of the HIV Medicine Association of the Infectious Diseases Society of America” [1].

CD4+ T-CELL COUNT

The CD4+ T-cell count (or CD4 count) serves as the major clinical indicator of immune function in patients who have HIV infection. It is one of the key factors in deciding whether to initiate antiretroviral therapy and chemoprophylaxis for opportunistic infections, and is the strongest predictor of subsequent disease progression and survival according to clinical trials and cohort studies [2-3]. A significant change (2 standard deviations) between two tests is approximately a 30% change in the absolute count or an increase or decrease in CD4 percentage by 3 percentage points.

- **Use of CD4 Count for Initial Assessment.** The CD4 count is one of the most important factors in the decision to initiate antiretroviral therapy and/or prophylaxis for opportunistic infections. All patients should have a baseline CD4 count at entry into care **(AI)**. Recommendations for initiation of antiretroviral therapy based on CD4 count are found in the [Initiating Antiretroviral Therapy](#) section of these guidelines.
- **Use of CD4 Count for Monitoring Therapeutic Response.** An adequate CD4 response for most patients on therapy is defined as an increase in CD4 count in the range of 50–150 cells/mm³ per year, generally with an accelerated response in the first 3 months. Subsequent increases in patients with good virologic control show an average increase of approximately 50–100 cells/mm³ per year for the subsequent years until a steady state level is reached [4]. Some patients who initiate therapy with a severely depleted CD4 count may have a blunted increase in their count despite virologic suppression.

Frequency of CD4 Count Monitoring – In general, CD4 counts should be monitored every 3–4 months to (1) determine when to start antiretroviral therapy in patients not being treated; (2) assess immunologic response to antiretroviral therapy; and (3) assess the need for initiation or discontinuation of prophylaxis for opportunistic infections **(AI)**. For those patients who are adherent to therapy with sustained viral suppression and stable clinical status for more than 2–3 years, the frequency of CD4 count monitoring may be extended to every 6 months **(BIII)**.

Factors that affect absolute CD4 count – The absolute CD4 count is a calculated value based on the total white blood cell (WBC) count and the percentages of total and CD4+ T lymphocytes. This absolute number may fluctuate among individuals or may be influenced by factors that may affect the total WBC and lymphocyte percentages, such as use of bone marrow-suppressive medications or the presence of acute infections. Splenectomy [5-6] or coinfection with HTLV-1 [7] may cause misleadingly elevated absolute CD4 counts. Alpha-interferon, on the other hand, may reduce the absolute CD4 number without changing the CD4 percentage [8]. In all these cases, CD4 percentage remains stable and may be a more appropriate parameter to assess the patient's immune function.

PLASMA HIV RNA TESTING

Plasma HIV RNA (viral load) should be measured in all patients at baseline and on a regular basis thereafter, especially in patients who are on treatment, because viral load is the most important indicator of response to antiretroviral therapy **(AI)**. Analysis of 18 trials that included more than 5,000 participants with viral load monitoring showed a significant association between a decrease in plasma viremia and improved clinical outcome [9]. Thus, viral load testing serves as a surrogate marker for treatment response [10] and can be useful in predicting clinical progression [11-12]. The minimal change in viral load considered to be statistically significant (2 standard deviations) is a threefold, or a 0.5 log₁₀ copies/mL change. One key goal of therapy is suppression of viral load to below the limits of detection (below 40–75 copies/mL by most commercially available assays). For most individuals who are adherent to their antiretroviral regimens and who do not harbor resistance mutations to the prescribed drugs, viral suppression is generally achieved in 12–24 weeks, even though it may take a longer time in some patients. Recommendations for the frequency of viral load monitoring are summarized below.

- **At Initiation or Change in Therapy.** Plasma viral load should be measured before initiation of therapy and preferably within 2–4 weeks, and not more than 8 weeks, after treatment initiation or after treatment modification **(BI)**. Repeat viral load measurement should be performed at 4–8-week intervals until the level falls below the assay's limit of detection **(BII)**.
- **In Patients Who Have Viral Suppression but Therapy Was Modified Due to Drug Toxicity or Regimen Simplification.** Viral load measurement should be performed within 2–8 weeks after changing therapy. The purpose

of viral load monitoring at this point is to confirm potency of the new regimen **(BII)**.

- **In Patients on a Stable Antiretroviral Regimen.** Viral load should be repeated every 3–4 months or as clinically indicated **(BII)**. In adherent patients who have suppressed viral loads for more than 2–3 years and who are at stable clinical and immunologic status, some clinicians may extend the interval to every 6 months **(BIII)**.

Monitoring in Patients with Suboptimal Response. In addition to viral load monitoring, a number of additional factors, such as adherence to prescribed medications, altered pharmacology, or drug interactions, should be assessed. Patients who fail to achieve viral suppression should undergo resistance testing to aid in the selection of an alternative regimen, as discussed in the [Drug Resistance Testing](#) and [Management of the Treatment-Experienced Patient](#) sections **(AI)**.

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DRUG RESISTANCE TESTING (Updated December 1, 2009)

Panel's Recommendations:

- HIV drug resistance testing is recommended for persons with HIV infection when they enter into care regardless of whether therapy will be initiated immediately or deferred (AIII). If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered (CIII). HIV drug resistance testing should be performed to assist in the selection of active drugs when changing antiretroviral regimens in patients with virologic failure and HIV RNA levels >1,000 copies/mL (AI). In persons with >500 but <1000 copies/mL, testing may be unsuccessful but should still be considered (BII).
- Drug resistance testing should also be performed when managing suboptimal viral load reduction (AII).
- Drug resistance testing in the setting of virologic failure should be performed while the patient is taking prescribed antiretroviral drugs, or, if not possible, within 4 weeks after discontinuing therapy (AII).
- Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).
- Genotypic testing is recommended as the preferred resistance testing to guide therapy in antiretroviral naïve patients and in patients with suboptimal virologic responses or virologic failure while on first or second regimens (AIII).
- Addition of phenotypic testing to genotypic testing is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors (BIII).

Genotypic and Phenotypic Resistance Assays

Genotypic and phenotypic resistance assays are used to assess viral strains and inform selection of treatment strategies. Standard assays provide information on resistance to nucleoside and non-nucleoside reverse transcriptase and protease inhibitors. Testing to evaluate integrase and fusion inhibitor resistance can also be performed through some commercial laboratories. No commercial assays are currently available for assessing resistance to CCR5 antagonists.

Genotypic Assays

Genotypic assays detect drug resistance mutations present in relevant viral genes. Most genotypic assays involve sequencing of the reverse transcriptase and protease genes to detect mutations that are known to confer drug resistance. A genotypic assay that assesses mutations in the integrase gene is also commercially available. Genotypic assays can be performed rapidly with results available within 1–2 weeks of sample collection. Interpretation of test results requires knowledge of the mutations that different antiretroviral drugs select for and of the potential for cross resistance to other drugs conferred by certain mutations. The International AIDS Society-USA (IAS-USA) maintains a list of updated significant resistance-associated mutations in the reverse transcriptase, protease, integrase, and envelope genes (see http://www.iasusa.org/resistance_mutations) [1]. The Stanford University HIV Drug Resistance Database (<http://hivdb.stanford.edu>) also provides helpful guidance for interpreting genotypic resistance test results. Various techniques are now available to assist the provider in interpreting genotypic test results [2–5]. Clinical trials have demonstrated the benefit of consultation with specialists in HIV drug resistance in improving virologic outcomes [6]. Clinicians are thus encouraged to consult a specialist to facilitate interpretation of genotypic test results and the design of an optimal new regimen.

Phenotypic Assays

Phenotypic assays measure the ability of a virus to grow in different concentrations of antiretroviral drugs. Reverse transcriptase and protease gene sequences and, more recently, integrase and envelope sequences derived from patient plasma HIV RNA are inserted into the backbone of a laboratory clone of HIV or used to generate pseudotyped viruses that express the patient-derived HIV genes of interest. Replication of these viruses at different drug concentrations is monitored by expression of a reporter gene and is compared with replication of a reference HIV strain. The drug concentration that inhibits 50% of viral replication (i.e., the median inhibitory concentration [IC]₅₀) is calculated, and the ratio of the IC₅₀ of test and reference viruses is reported as the fold increase in IC₅₀ (i.e., fold resistance).

Automated phenotypic assays are commercially available with results reported in 2–3 weeks. However, phenotypic assays cost more to perform than genotypic assays. In addition, interpretation of phenotypic assay results is complicated by incomplete information regarding the specific resistance level (i.e., fold increase in IC_{50}) that is associated with drug failure, although clinically significant fold increase cutoffs are now available for some drugs [7-11]. Again, consultation with a specialist can be helpful for interpreting test results.

Further limitations of both genotypic and phenotypic assays include lack of uniform quality assurance for all available assays, relatively high cost, and insensitivity for minor viral species. Despite being present, drug-resistant viruses constituting less than 10%–20% of the circulating virus population will probably not be detected by available assays. This limitation is important because after drugs exerting selective pressure on drug-resistant populations are discontinued, a wild-type virus often re-emerges as the predominant population in the plasma. This results in a decrease of the proportion of virus with resistance mutations to below the 10%–20% threshold [12-14]. For some drugs, this reversion to predominantly wild-type virus can occur in the first 4–6 weeks after drugs are stopped. Prospective clinical studies have shown that, despite this plasma reversion, reinstitution of the same antiretroviral agents (or those sharing similar resistance pathways) is usually associated with early drug failure, and the virus present at failure is derived from previously archived resistant virus [15]. Therefore, resistance testing is of greatest value when performed before or within 4 weeks after drugs are discontinued **(AII)**. Because detectable resistant virus may persist in the plasma of some patients for longer periods of time, resistance testing beyond 4 to 6 weeks after discontinuation may still reveal mutations. However, the absence of detectable resistance in such patients must be interpreted with caution in designing subsequent antiretroviral regimens.

Use of Resistance Assays in Clinical Practice (Table 4)

No definitive prospective data exist to support using one type of resistance assay over another (i.e., genotypic vs. phenotypic) in different clinical situations. In most situations genotypic testing is preferred because of the faster turnaround time, lower cost, and enhanced sensitivity for detecting mixtures of wild-type and resistant virus. However, for patients with a complex treatment history, results derived from both assays might provide critical and complementary information to guide regimen changes.

Use of Resistance Assays in Determining Initial Treatment

Transmission of drug-resistant HIV strains is well documented and associated with suboptimal virologic response to initial antiretroviral therapy [16-19]. The likelihood that a patient will acquire drug-resistant virus is related to the prevalence of drug resistance in persons engaging in high-risk behaviors in the community. In the United States and Europe, recent studies suggest the risk that transmitted virus will be resistant to at least one antiretroviral drug is in the range of 6%–16% [20-25], with 3%–5% of transmitted viruses exhibiting resistance to drugs from more than one class [24, 26]. If the decision is made to initiate therapy in a person with acute HIV infection, resistance testing at baseline will provide guidance in selecting a regimen to optimize virologic response. Therefore, resistance testing in this situation is recommended **(AIII)** using a genotypic assay. In the absence of therapy, resistant viruses may decline over time to less than the detection limit of standard resistance tests but may still increase the risk of treatment failure when therapy is eventually initiated. Therefore, if the decision is made to defer therapy, resistance testing during acute HIV infection should still be performed **(AIII)**. In this situation, the genotypic resistance test result might be kept on record for several years before it becomes clinically useful. Because it is possible for a patient to acquire drug-resistant virus (i.e., superinfection) between entry into care and initiation of antiretroviral therapy, repeat resistance testing at the time treatment is started should be considered **(CIII)**.

Performing drug resistance testing before initiation of antiretroviral therapy in patients with chronic HIV infection is less straightforward. The rate at which transmitted resistance-associated mutations revert to wild-type virus has not been completely delineated, but mutations present at the time of HIV transmission are more stable than those selected under drug pressure, and it is often possible to detect resistance-associated mutations in viruses that were transmitted several years earlier [27-29]. No prospective trial has addressed whether drug resistance testing prior to initiation of therapy confers benefit in this population. However, data from several, but not all, studies suggest suboptimal virologic responses in persons with baseline mutations [16-19, 30-32]. In addition, a cost-effectiveness analysis of early genotypic resistance testing suggests that baseline testing in this population should be performed [33]. Therefore, resistance testing in chronically infected persons at the time of entry into HIV care is recommended **(AIII)**. Genotypic

testing is generally preferred in this situation because of lower cost, more rapid turnaround time, ability to detect mixtures of wild-type and resistant virus, and the relative ease of interpretation **(AIII)**. If therapy is deferred, repeat testing just prior to initiation of antiretroviral therapy should be considered because the patient may have possibly acquired drug-resistant virus (i.e., superinfection) **(CIII)**.

Presently, drug resistance testing in antiretroviral-naïve persons involves genotypic testing for mutations in the reverse transcriptase and protease genes. As the use of integrase inhibitors increases, it is possible that genotypic testing for resistance to this class of drugs will become clinically useful when an integrase inhibitor is being considered as part of an initial regimen.

Use of Resistance Assays in the Event of Virologic Failure

Resistance assays are useful in guiding decisions for patients experiencing virologic failure while on antiretroviral therapy. Several prospective studies assessed the utility of resistance testing in guiding antiretroviral drug selection in patients with virologic failure. These studies involved genotypic assays, phenotypic assays, or both [6, 34-40]. In general, these studies found that early virologic response to salvage regimens was improved when results of resistance testing were available to guide changes in therapy, compared with responses observed when changes in therapy were guided only by clinical judgment. Additionally, one observational study demonstrated improved survival in patients with detectable HIV plasma RNA when drug resistance testing was performed [41]. Thus, resistance testing appears to be a useful tool in selecting active drugs when changing antiretroviral regimens for virologic failure in persons with HIV RNA >1,000 copies/mL **(AI)**. (See [Management of the Treatment-Experienced Patient](#).) In persons with >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered **(BII)**.

Resistance testing also can help guide treatment decisions for patients with suboptimal viral load reduction **(AII)**. Virologic failure in the setting of combination antiretroviral therapy is, for certain patients, associated with resistance to only one component of the regimen [42-44]. In that situation, substituting individual drugs in a failing regimen might be possible, although this concept will require clinical validation. (See [Management of the Treatment-Experienced Patient](#).)

Genotypic testing is generally preferred for virologic failure or suboptimal viral load reduction in persons failing their first or second antiretroviral drug regimen because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus **(AIII)**. Addition of phenotypic testing to genotypic testing, is generally preferred for persons with known or suspected complex drug resistance mutation patterns, particularly to protease inhibitors **(BIII)**.

The clinical utility of resistance testing for integrase and fusion inhibitor resistance is limited at present because of lack of availability of second-line drugs within these classes; that is, there is no need to test for cross resistance to other drugs. However, in patients failing integrase- or fusion inhibitor-based regimens, testing for integrase or fusion inhibitor resistance may be helpful to determine whether to include drugs from these classes in subsequent regimens **(CIII)**. A coreceptor tropism assay should be performed whenever the use of a CCR5 antagonist is being considered **(AII)**. (See section on [Coreceptor Tropism Assays](#).)

Use of Resistance Assays in Pregnant Patients

In pregnant women, the goal of antiretroviral therapy is to maximally reduce plasma HIV RNA to provide appropriate maternal therapy and prevent mother-to-child transmission of HIV. Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy **(AIII)** and for those entering pregnancy with detectable HIV RNA levels while on therapy **(AII)**. Phenotypic testing may provide additional information in those found to have complex drug resistance mutation patterns, particularly to protease inhibitors **(BIII)**. Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy while results of resistance testing are pending. Once the results are available, the antiretroviral regimen can be changed as needed.

Table 4. Recommendations for Using Drug Resistance Assays (Updated December 1, 2009)

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Clinical Setting/Recommendation	Rationale
Drug resistance assay recommended	
In acute HIV infection: Drug resistance testing is recommended regardless of whether treatment is initiated immediately or deferred (AIII). A genotypic assay is generally preferred (AIII). If treatment is deferred, repeat resistance testing should be considered at the time antiretroviral therapy is initiated (CIII). A genotypic assay is generally preferred (AIII).	If treatment is to be initiated immediately, drug resistance testing will determine whether drug-resistant virus was transmitted. Test results will help in the design of initial regimens or, if therapy was initiated prior to results, change regimens. Genotypic testing is preferable to phenotypic testing because of lower cost, faster turnaround time, and greater sensitivity for detecting mixtures of wild-type and resistant virus. If treatment is deferred, testing should still be performed because of the greater likelihood that transmitted resistance-associated mutations will be detected earlier in the course of HIV infection. Results of resistance testing may be important when treatment is initiated. Repeat testing at the time antiretroviral therapy is initiated should be considered because the patient may have acquired a drug-resistant virus (i.e., superinfection).
In treatment-naïve patients with chronic HIV infection: Drug resistance testing is recommended at the time of entry into HIV care, regardless of whether therapy is initiated immediately or deferred (AIII). A genotypic assay is generally preferred (AIII). If therapy is deferred, repeat resistance testing should be considered at the time antiretroviral therapy is initiated (CIII). A genotypic assay is generally preferred (AIII).	Transmitted HIV with baseline resistance to at least one drug is seen in 6%–16% of patients, and suboptimal virologic responses may be seen in patients with baseline resistant mutations. Some drug resistance mutations can remain detectable for years in untreated chronically infected patients. Repeat testing prior to initiation of antiretroviral therapy should be considered because the patient may have acquired a drug-resistant virus (i.e., a superinfection). Genotypic testing is preferred for the reasons noted previously.
In patients with virologic failure: Drug resistance testing is recommended in persons on combination antiretroviral therapy with HIV RNA levels >1,000 copies/mL (AI). In persons with HIV RNA levels >500 but <1,000 copies/mL, testing may be unsuccessful but should still be considered (BII). A genotypic assay is generally preferred in those experiencing virologic failure on their first or second regimens (AIII). Addition of phenotypic assay to genotypic assay is generally preferred for those with known or suspected complex drug resistance patterns, particularly to protease inhibitors (BIII).	Testing can help determine the role of resistance in drug failure and maximize the clinician's ability to select active drugs for the new regimen. Drug resistance testing should be performed while the patient is taking prescribed antiretroviral drugs or, if not possible, within 4 weeks after discontinuing therapy. Genotypic testing is generally preferred for the reasons noted previously. Phenotypic testing can provide useful additional information for those with complex drug resistance mutation patterns, particularly to protease inhibitors.

Clinical Setting/Recommendation	Rationale
Drug resistance assay recommended (continued)	
In patients with suboptimal suppression of viral load: Drug resistance testing is recommended in persons with suboptimal suppression of viral load after initiation of antiretroviral therapy (AII).	Testing can help determine the role of resistance and thus assist in identifying the number of active drugs available for a new regimen.
In HIV-infected pregnant women: Genotypic resistance testing is recommended for all pregnant women prior to initiation of antiretroviral therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AI).	The goal of antiretroviral therapy in HIV-infected pregnant women is to achieve maximal viral suppression for treatment of maternal HIV infection and for prevention of perinatal HIV transmission. Genotypic resistance testing will assist the clinician in selecting the optimal regimen for the patient.
Drug resistance assay not usually recommended	
After therapy discontinued: Drug resistance testing is not usually recommended after discontinuation (>4 weeks) of antiretroviral drugs (BIII).	Drug resistance mutations might become minor species in the absence of selective drug pressure, and available assays might not detect minor drug-resistant species. If testing is performed in this setting, the detection of drug resistance may be of value; however, the absence of resistance does not rule out the presence of minor drug-resistant species.
In patients with low HIV RNA levels: Drug resistance testing is not usually recommended in persons with a plasma viral load <500 copies/mL (AIII).	Resistance assays cannot be consistently performed given low HIV RNA levels.

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HLA-B*5701 SCREENING (Updated December 1, 2007)

Panel's Recommendations:

- **The Panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen, to reduce the risk of hypersensitivity reaction (AI).**
- **HLA-B*5701-positive patients should not be prescribed abacavir (AI).**
- **The positive status should be recorded as an abacavir allergy in the patient's medical record (AII).**
- **When HLA-B*5701 screening is not readily available, it remains reasonable to initiate abacavir with appropriate clinical counseling and monitoring for any signs of hypersensitivity reaction (CIII).**

The abacavir hypersensitivity reaction (ABC HSR) is a multiorgan clinical syndrome typically seen within the initial 6 weeks of abacavir treatment. This reaction has been reported in 5%–8% of patients participating in clinical trials when using clinical criteria for the diagnosis, and it is the major reason for early discontinuation of abacavir. (See [Table 12](#).) Discontinuing abacavir usually promptly reverses HSR, whereas subsequent rechallenge can cause a rapid, severe, and even life-threatening recurrence.

Studies that evaluated demographic risk factors for ABC HSR have shown racial background as a risk factor, with white patients generally having a higher risk (5%–8%) than black patients (2%–3%). Several groups reported a highly significant association between ABC HSR and the presence of the MHC class I allele HLA-B*5701 [1, 2]. An abacavir skin patch test (ABC SPT) was developed as a research tool to immunologically confirm ABC HSR, because the clinical criteria used for ABC HSR are overly sensitive and may lead to false-positive ABC HSR diagnoses [3]. A positive ABC SPT is an abacavir-specific delayed hypersensitivity reaction that results in redness and swelling at the skin site of application. All ABC SPT–positive patients studied were also positive for the HLA-B*5701 allele [4]. The ABC SPT could be falsely negative for some patients with ABC HSR. It is not recommended to be used as a clinical tool at this point. The PREDICT-1 study randomized patients before starting abacavir either to be prospectively screened for HLA-B*5701 (in which HLA-B*5701–positive patients were not offered abacavir) or to standard of care at the time of the study (i.e., no screening, with all patients receiving abacavir) [5]. The overall HLA-B*5701 prevalence in this predominately white population was 5.6%. In this cohort, screening for HLA-B*5701 eliminated immunologic ABC HSR (defined as ABC SPT positive) compared with standard of care (0% vs. 2.7%), yielding a 100% negative predictive value with respect to SPT as well as significantly decreasing the rate of clinically suspected ABC HSR (3.4% vs. 7.8%). The

SHAPE study corroborated the low rate of immunologically validated ABC HSR in black patients and confirmed the utility of HLA-B*5701 screening for the risk for ABC HSR (100% sensitivity in black and white populations) [6].

On the basis of the results of these studies, the Panel recommends screening for HLA-B*5701 before starting patients on an abacavir-containing regimen **(AI)**. HLA-B*5701–positive patients should not be prescribed abacavir **(AI)**, and the positive status should be recorded as an abacavir allergy in the patient’s medical record **(AII)**. HLA-B*5701 testing needs to be performed only once in a patient’s lifetime, so efforts to carefully record and maintain the result and to educate the patient about its implications are important. The specificity of the HLA-B*5701 test in predicting ABC HSR is lower than the sensitivity (i.e., 33%–50% of HLA-B*5701 positive patients would likely not develop confirmed ABC HSR if exposed to ABC). HLA-B*5701 should not be used as a substitute for clinical judgment or pharmacovigilance, because a negative HLA-B*5701 result does not absolutely rule out the possibility of some form of ABC HSR. When HLA-B*5701 screening is not readily available, it remains reasonable to initiate ABC with appropriate clinical counseling and monitoring for any signs of ABC HSR **(CIII)**.

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CORECEPTOR TROPISM ASSAYS (Updated November 3, 2008)

Panel’s Recommendations:

- **Coreceptor tropism assay should be performed whenever the use of a CCR5 inhibitor is being considered (AII).**
- **Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on a CCR5 inhibitor (BIII).**

HIV enters cells by a complex process that involves the sequential attachment to the CD4 receptor followed by binding to either the CCR5 or CXCR4 molecules and fusion of the viral and cellular membranes [1]. The CCR5 inhibitors (i.e., maraviroc, vicriviroc) prevent HIV entry into target cells by binding to the CCR5 receptor [2]. Phenotypic and, to a lesser degree, genotypic assays have been developed that can determine the coreceptor tropism (i.e., CCR5, CXCR4, or both) of the patient’s dominant virus population. One assay (*Trofile*, Monogram Biosciences, Inc., South San Francisco, CA) was used to screen patients who were participating in studies that formed the basis of approval for maraviroc, the only CCR5 inhibitor currently available. Other assays are under development and are currently used primarily for research purposes or in clinical situations in which the *Trofile* assay is not readily available.

Background

The vast majority of patients harbor a CCR5-utilizing virus (R5 virus) during acute/recent infection, which suggests that the R5 variant is preferentially transmitted compared with the CXCR4 (X4) variant. Viruses in many untreated patients eventually exhibit a shift in coreceptor tropism from CCR5 to either CXCR4 or both CCR5 and CXCR4 (i.e., dual- or mixed-tropic; D/M-tropic). This shift is temporally associated with a more rapid decline in CD4 T-cell counts [3, 4], although whether this shift is a cause or a consequence of progressive immunodeficiency remains undetermined [1].

Antiretroviral-treated patients who have extensive drug-resistance are more likely to harbor detectable X4- or D/M-tropic variants than untreated patients who have comparable CD4 T-cell counts [5]. The prevalence of X4- or D/M-tropic variants increases to more than 50% in treated patients who have CD4 T-cell counts <100 cells/mm³ [5, 6].

Phenotypic Assays

There are now at least two high-throughput phenotypic assays that can quantify the coreceptor characteristics of plasma-derived virus. Both involve the generation of laboratory viruses that express patient-derived envelope proteins (i.e., gp120 and gp41). These pseudoviruses are either replication-competent (*Phenoscript* assay, VIRalliance, Paris, France) or replication-defective (*Trofile* assay, Monogram Biosciences, Inc.) [7, 8]. These pseudoviruses then are used to infect target cell lines that express either CCR5 or CXCR4. In the *Trofile* assay, the coreceptor tropism of the patient-derived virus is confirmed by testing the susceptibility of the virus to specific CCR5 or CXCR4 inhibitors *in vitro*. The *Trofile* assay takes about 2 weeks to perform and requires a plasma HIV RNA level $\geq 1,000$ copies/mL.

The performance characteristics of these assays have evolved. Most, if not all, patients enrolled in premarketing clinical trials of maraviroc and other CCR5 inhibitors were screened with an earlier, less-sensitive version of the *Trofile* assay [7]. This earlier assay failed to routinely detect low levels of CXCR4-utilizing variants. As a consequence, some patients enrolled in these clinical trials harbored low, undetectable levels of CXCR4-utilizing viruses at baseline and exhibited rapid virologic failure after initiation of a CCR5 inhibitor [9]. This assay has since been revised and is now able to detect lower levels of CXCR4-utilizing viruses. *In vitro*, the assay can detect CXCR4-utilizing clones with 100% sensitivity when those clones make up 0.3% of the population; per <http://www.trofileassay.com> [10]. Although this more sensitive assay has had limited use in prospective clinical trials, it is now the only one that is commercially available. For unclear reasons, a minority of samples cannot be successfully phenotyped with either generation of the *Trofile* assay.

Genotypic Assays

These assays are under investigation [11, 12] but are not commercially available.

Use of Coreceptor Tropism Assays in Clinical Practice

Coreceptor tropism assays should be used whenever the use of a CCR5 inhibitor is being considered **(AII)**. Coreceptor tropism testing might also be considered for patients who exhibit virologic failure on maraviroc (or any CCR5 inhibitor) **(BIII)**.

Other potential clinical uses for the tropism assay are for prognostic purposes or for assessment of tropism prior to starting antiretroviral therapy, in case a CCR5 inhibitor is required later (e.g., in a regimen change for toxicity). Currently, there are not sufficient data to support these uses.

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Treatment Goals (Updated December 1, 2009)

Eradication of HIV infection cannot be achieved with available antiretroviral regimens. This is chiefly because the pool of latently infected CD4 T-cells is established during the earliest stages of acute HIV infection [1] and persists with a long half-life, even with prolonged suppression of plasma viremia [2-5]. The primary goals driving the decision to initiate antiretroviral therapy therefore are to:

- maximally and durably suppress plasma HIV viral load,
- reduce HIV-associated morbidity and prolong survival,
- improve quality of life,
- restore and preserve immunologic function, and
- prevent HIV transmission.

Adoption of treatment strategies recommended in these guidelines has reduced HIV-related morbidity and mortality [6-8] and has reduced vertical transmission [9-10]. HIV suppression with antiretroviral therapy may also decrease inflammation and immune activation thought to contribute to higher rates of cardiovascular and other comorbidities reported in HIV-infected cohorts (see [Initiating Antiretroviral Therapy](#) section). Maximal and durable suppression of plasma viremia delays or prevents the selection of drug resistance mutations, preserves CD4 T-cell numbers, and confers substantial clinical benefits, all of which are important treatment goals [11].

Achieving maximal viral suppression in initial therapy requires the use of antiretroviral regimens with at least two, and preferably three, active drugs from multiple drug classes. Baseline resistance testing should guide the specific regimen design. When maximal initial suppression is not achieved or is lost, changing to a new regimen with at least two active drugs is required (see [Management of Patients with Antiretroviral Treatment Failure](#) section). The increasing number of drugs and drug classes makes viral suppression below detection limits the goal in all patients, even those with primary or acquired drug resistance.

Viral load reduction to below limits of assay detection in a treatment-naïve patient usually occurs within the first 12–24 weeks of therapy. Predictors of virologic success include:

- high potency of antiretroviral regimen,
- excellent adherence to treatment regimen [12],
- low baseline viremia [13],
- higher baseline CD4 T-cell count (>200 cells/mm³), [14] and
- rapid reduction of viremia in response to treatment [13, 15].

Successful outcomes are usually observed although adherence difficulties may lower the success rate in clinical practice to below the 90% rate commonly seen in clinical trials [16].

STRATEGIES TO ACHIEVE TREATMENT GOALS

Achieving treatment goals requires a balance of sometimes competing considerations, outlined below. Providers and patients must work together to define individualized strategies to achieve treatment goals.

Selection of Initial Combination Regimen

Several preferred and alternative antiretroviral regimens are recommended for use. (See [What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient](#).) Many of these regimens have comparable efficacy but vary to some degree in dosing frequency, pill burden, drug interactions, and potential side effects. A regimen should be tailored to each patient to enhance adherence and thus improve outcome of care. Individual tailoring is based on such considerations as expected side effects, convenience, comorbidities, interactions with concomitant medications, and results of pretreatment genotypic drug resistance testing.

Pretreatment Drug Resistance Testing

Current studies suggest a prevalence of HIV drug resistance of 6%–16% in antiretroviral treatment-naïve patients [17-20], and some studies suggest that the presence of transmitted drug-resistant viruses may lead to suboptimal virologic responses [21]. Therefore, pretreatment genotypic resistance testing should be used in guiding selection of the most optimal initial antiretroviral regimen. (See [Drug Resistance Testing](#) section.)

Improving Adherence

Suboptimal adherence may result in reduced treatment response. Incomplete adherence can result from complex medication regimens; patient factors, such as active substance abuse and depression; and health system issues, including interruptions in medication access and inadequate treatment education and support. Conditions that promote adherence should be maximized prior to and after initiation of antiretroviral therapy. (See [Adherence to Antiretroviral Therapy](#) section.)

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Initiating Antiretroviral Therapy in Treatment-Naïve Patients

(Updated December 1, 2009)

Panel's Recommendations:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm³ (AI).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (AI), HIV-associated nephropathy (AII), and hepatitis B virus (HBV) coinfection when treatment of HBV is indicated (AIII).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm³. The Panel was divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) (A/B-II).
- For patients with CD4 counts >500 cells/mm³, the Panel was evenly divided: 50% favor starting antiretroviral therapy at this stage of HIV disease (B); 50% view initiating therapy at this stage as optional (C) (B/C-III).
- Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence (AIII). Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = data from randomized controlled trials; II = data from well-designed nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = expert opinion

The primary goal of antiretroviral therapy is to reduce HIV-associated morbidity and mortality. This is best accomplished by using antiretroviral therapy to maximally inhibit HIV replication, as measured by consistent plasma HIV RNA (viral load) values below the level of detection using commercially available assays. Additional benefits of antiretroviral therapy, supported by accumulating evidence, are reduction in HIV-associated inflammation and its associated complications and reduction in HIV transmission.

Over the past 20 years, the Panel has made several changes to the recommendations on when to start therapy based on prevailing clinical trial and cohort data and therapeutic options available at the time of each revision. The standard procedure for the Panel is to only make recommendations in agreement with two-thirds of the Panel members. This has not been possible for the **When to Start** recommendations in this updated version of the guidelines. Accordingly, the breakdown of votes is presented for recommendations supported by less than two-thirds of Panel members.

Randomized controlled trials provide evidence supporting the benefit of antiretroviral therapy in patients with CD4 counts of 350 cells/mm³ or less. However, such evidence showing benefit for patients with higher CD4 cell counts is not yet available. Based on cumulative observational cohort data demonstrating benefits of antiretroviral therapy in reducing AIDS- and non-AIDS-associated morbidity and mortality, the Panel now recommends antiretroviral therapy for patients with CD4 count between 350 and 500 cells/mm³ (A-B/II). For patients with CD4 count >500 cells/mm³, Panel members are evenly divided: 50% favor starting antiretroviral therapy at earlier stages of HIV disease (BIII); 50% view initiating therapy at this stage as optional (CIII).

Panel members favoring earlier initiation of therapy base their recommendation on several recent developments: (1) report from at least one recent cohort study demonstrating survival benefit with initiation of antiretroviral therapy at CD4 count >500 cells/mm³; (2) growing awareness that untreated HIV infection may be associated with development of many non-AIDS-defining diseases, including cardiovascular disease, kidney disease, liver disease, and malignancy; (3) availability of antiretroviral regimens that are more effective, more convenient, and better tolerated than antiretroviral combinations no longer in use; and (4) increasing evidence that effective antiretroviral therapy reduces HIV transmission (BIII).

The other 50% of the Panel members feel that current evidence does not definitively demonstrate clear benefit of antiretroviral therapy in all patients with CD4 count >500 cells/mm³. They also feel that risks of short- or long-term drug-related complications, nonadherence to lifelong therapy in asymptomatic patients, and potential for development of drug resistance may offset possible benefits of earlier initiation of therapy. Thus, pending more definitive supporting evidence, these panel members recommend that therapy in this setting should be optional and considered on a case-by-case basis **(CIII)**.

The known benefits, risks, and limitations of antiretroviral therapy, as well as the strength of the recommendations according to CD4 count levels, are discussed below.

BENEFITS OF ANTIRETROVIRAL THERAPY

Earlier studies definitively showed that potent combination antiretroviral therapy improves survival and reduces AIDS-related complications in patients with advanced HIV disease. There is now increasing evidence demonstrating the benefits of viral suppression and immunologic responses on reducing mortality and non-AIDS-related complications in patients with higher pretreatment CD4 counts. The following is a focused discussion of the rationale that forms the basis for the Panel's recommendation favoring earlier treatment.

Reduction in Mortality and/or AIDS-Related Morbidity

Patients with a history of an AIDS-defining illness or CD4 count <350 cells/mm³

HIV-infected patients with CD4 counts <200 cells/mm³ are at higher risk of opportunistic diseases, non-AIDS morbidity, and death. Randomized controlled trials in patients with CD4 counts <200 cells/mm³ and/or a history of an AIDS-defining condition provide strong evidence that antiretroviral therapy improves survival and delays disease progression in these patients [1-3]. Long-term data from multiple observational cohort studies evaluating earlier antiretroviral therapy (>200 cells/mm³) compared with later treatment (<200 cells/mm³) have also provided strong support for these findings [4-8].

Few large, randomized controlled trials address when to start therapy in patients with CD4 counts >200 cells/mm³. CIPRA HT-001 is a randomized clinical trial conducted in Haiti. Study participants were randomized to start antiretroviral therapy at CD4 count of 200–350 cells/mm³ or to defer treatment until their CD4 count dropped below 200 cells/mm³ or they developed an AIDS-defining condition. In an interim analysis of the study, a higher mortality rate (hazard ratio [HR] = 4.0, $p = 0.0011$) and greater incident tuberculosis (HR = 2.0, $p = 0.0125$) were observed among patients who deferred therapy compared with participants who began antiretroviral therapy with CD4 counts of 200 to 350 cells/mm³ [9]. This evidence led to the study Data Safety Monitoring Board's recommendation to terminate the trial before completion.

The SMART study was a multi-national trial enrolling more than 5,400 participants with CD4 counts >350 cells/mm³. Participants were randomized to continuous antiretroviral therapy or to treatment interruption until CD4 count dropped below 250 cells/mm³. In a subgroup analysis involving the 249 study participants who were treatment naïve at enrollment, a trend of lower risk of serious AIDS- and non-AIDS-related events was seen in those who initiated therapy immediately compared with those who deferred therapy until CD4 count dropped to <250 cells/mm³ ($p = 0.06$) [10].

Collectively, these studies support the Panel's recommendation that antiretroviral therapy should be initiated in patients with a history of an AIDS-defining illness or with a CD4 count <350 cells/mm³ **(AI)**.

Patients with a CD4 count between 350 and 500 cells/mm³

There are no randomized trials using current combination regimens in patients with CD4 counts >350 cells/mm³ to provide data that directly address the question of when to start therapy in these patients. Data from the ART Cohort Collaboration (ART-CC), which included 61,798 patient-years of follow-up, showed a declining risk of AIDS or death for up to 5 years in subjects starting therapy with a CD4 count ≥ 350 cells/mm³ compared with subjects starting

between 200 and 349 cells/mm³ [11]. A more recent rigorous analysis of this cohort found that deferring therapy until the 251 to 350 cells/mm³ range was associated with a higher rate of progression to AIDS and death compared with initiating therapy in the 351 to 450 cells/mm³ range (risk ratio: 1.28, 95% CI: 1.04 to 1.57) [6].

In a collaboration of North American cohort studies (NA-ACCORD) that evaluated patients regardless of whether they had started therapy, the 6,278 patients who deferred therapy until CD4 count <350 cells/mm³ had an increased risk of death compared with 2,084 patients who initiated therapy with CD4 count between 351 and 500 cells/mm³ (risk ratio: 1.69, 95% CI: 1.26 to 2.26) after adjustment for other factors that differed between these two groups [12].

When interpreting both of these cohort studies it is important to note that although the relative risk of a mortality event is evident, the overall number of events was small. In these cohort studies, the relative risks determined could have been influenced by unmeasured confounders that cannot be adjusted for in the analysis. The findings from these observational cohort studies point to potential harm if therapy is deferred until CD4 count falls below 350 cells/mm³. Based on these findings, combined with emerging biologic evidence regarding potential damage to end organs from inflammation associated with untreated HIV replication and the potential reduction in HIV transmission with treatment (see below), the Panel recommends antiretroviral therapy in patients with CD4 counts between 350 and 500 cells/mm³. The Panel was divided on the strength of this recommendation: 55% voted for strong recommendation (A) and 45% voted for moderate recommendation (B) **(A/B-II)**.

Patients with a CD4 count >500 cells/mm³

The NA-ACCORD study also observed patients who started treatment at CD4 count >500 cells/mm³ or after the CD4 count dropped below this threshold. The adjusted mortality rates were significantly higher among the 6,935 patients who deferred therapy until CD4 count fell below 500 cells/mm³ compared with rates in the 2,200 patients who started therapy while CD4 count was above 500 cells/mm³ (risk ratio: 1.94, 95% CI: 1.37 to 2.79) [12]. Although large and generally representative of care in the United States, the study has several limitations, including the small number of deaths and the potential for unmeasured confounders that might have influenced outcomes independent of antiretroviral therapy.

In contrast, analysis of the ART-CC cohort failed to identify a benefit for patients initiating antiretroviral therapy with CD4 counts above 450 cells/mm³. This analysis also did not identify a harmful effect of this strategy [6]. Deferral of therapy to the 351–450 cells/mm³ range was associated with a similar rate of progression to AIDS/death compared with initiation of therapy in the 451–550 cells/mm³ range (risk ratio: 0.99, 95% CI: 0.76 to 1.29). This study also found that the proportion of patients with CD4 counts between 451 and 550 cells/mm³ who would progress to AIDS or death before having a CD4 count below 450 cells/mm³ was low (1.6%; 95% CI: 1.1 to 2.1%).

Based on these data, along with a better understanding of the pathogenesis of HIV infection and the growing awareness that untreated HIV infection increases the risk of many non-AIDS-defining diseases (see below), 50% of Panel members favor initiation of antiretroviral therapy in HIV-infected persons with a CD4 count above 500 cells/mm³ **(BIII)**.

The other 50% of the Panel members are reluctant to broadly recommend starting antiretroviral therapy at higher CD4 cell counts and consider that therapy should be optional at this stage of HIV disease **(CIII)**. In making this recommendation, the Panel members note that the amount of data supporting initiation of therapy decreases as the CD4 count increases above 350–500 cells/mm³, and concerns remain over the unknown overall benefit and long-term risks with earlier treatment.

When discussing starting antiretrovirals at higher CD4 cell counts (>500 cells/mm³), clinicians should inform patients that data on the clinical benefit of starting treatment at such levels is not conclusive. There is a need for further ongoing research (both with randomized clinical trials and cohort studies) to assess the short- and long-term clinical and public health benefits, and cost-effectiveness of starting therapy at higher CD4 counts. Such research findings will provide guidance for future recommendations by the Panel.

Effects of Antiretroviral Therapy on HIV-Related Morbidity

HIV-related morbidity and mortality derive not only from immune deficiency but also from direct effects of HIV on specific end organs and the indirect effects of HIV-associated inflammation on these organs. In general, the available data demonstrate that:

- Untreated HIV infection may have detrimental effects at all stages of infection.
- Treatment is beneficial even when initiated later in infection. However, later therapy may not repair damage associated with viral replication during early stages of infection.
- Earlier treatment may prevent the damage associated with HIV replication during early stages of infection.

Clinical studies have demonstrated that sustaining viral suppression and maintaining higher CD4 count, mostly as a result of effective combination antiretroviral therapy, delay or prevent some non-AIDS-defining complications, such as HIV-associated kidney disease. Sustained viral suppression and immune recovery may also delay or prevent other disorders, such as liver disease, cardiovascular disease, and malignancies, as discussed below.

HIV-associated Nephropathy (HIVAN)

HIVAN is the most common cause of chronic kidney disease in HIV-infected individuals that may lead to end-stage kidney disease [13]. HIVAN is seen almost exclusively in black patients and can occur at any CD4 count. Ongoing viral replication appears to be directly involved in renal injury [14]. HIVAN is extremely uncommon in virologically suppressed patients [15]. Antiretroviral therapy in patients with HIVAN has been associated with both preserved renal function and prolonged survival [16-18], and therefore should be started in these patients **(AII)**.

Co-infection with hepatitis B virus (HBV) and/or hepatitis C virus (HCV)

HIV infection is associated with more rapid progression of viral hepatitis-related liver disease, including cirrhosis, end-stage liver disease, hepatocellular carcinoma, and fatal hepatic failure [19-20]. Although the mechanisms of accelerated liver disease in HIV-infected patients have not been fully elucidated, HIV-related immunodeficiency and a direct interaction of HIV with hepatic stellate and Kupffer cells have been implicated [21-24]. Antiretroviral therapy may attenuate liver disease progression in persons coinfecting with HBV and/or HCV by preserving or restoring immune function and reducing HIV-related immune activation and inflammation [25-27]. Antiretroviral drugs active against both HIV and HBV (e.g., tenofovir, lamivudine, emtricitabine) may also prevent the development of significant liver disease by directly suppressing HBV replication [28-29]. Although antiretroviral drugs do not directly inhibit HCV replication, HCV treatment outcomes may be improved if HIV replication is controlled or if CD4 counts are increased [30]. The presence of chronic viral hepatitis increases the risk of antiretroviral therapy-induced liver injury; however, the majority of coinfecting persons do not develop clinically significant liver injury, particularly those receiving recommended antiretroviral regimens [31-33]. Some studies suggest that the rate of hepatotoxicity is greater in persons with more advanced HIV disease. Nevirapine toxicity is a notable exception: the hypersensitivity reaction and associated hepatotoxicity to this drug are more frequent in patients with higher CD4 cell counts [34]. Collectively, these data suggest earlier treatment of HIV infection in persons coinfecting with HBV, and possibly HCV **(CIII)**, may reduce the risk of liver disease progression. Furthermore, antiretroviral therapy including drugs active against both HIV and HBV should be started in all patients coinfecting with HBV who are also going to receive HBV treatment **(AIII)**.

Cardiovascular disease

Cardiovascular disease is a major cause of mortality among HIV-infected patients, accounting for a third of serious non-AIDS conditions and at least 10% of deaths among HIV-infected patients [35-36]. There are studies that link exposure to specific antiretroviral drugs to a higher risk of cardiovascular disease [37-38]. Certain HIV treatment regimens are associated with a more atherogenic lipid profile as assessed by lipoprotein particle size analysis among HIV-infected men compared with uninfected controls [39]. Untreated HIV infection may also be associated with an increased risk of cardiovascular disease. In some cross-sectional studies, patients with HIV have higher levels of markers of inflammation and endothelial dysfunction than HIV-uninfected controls [40-42]. In two randomized trials,

markers of inflammation and coagulation increased following treatment interruption [43-44]. One study suggests that antiretroviral treatment may improve endothelial function [45].

In the SMART study, the risk of cardiovascular events was greater in participants randomized to CD4-guided treatment interruption compared with participants who received continuous antiretroviral therapy [46]. In other studies, antiretroviral therapy resulted in marked improvement in parameters associated with cardiovascular diseases, including markers of inflammation (e.g., interleukin 6 [IL-6] and high sensitivity C-reactive protein [hsCRP]) and endothelial dysfunction [41, 45]. There is also a modest association between lower CD4 count while on therapy and short-term risk of cardiovascular disease [7, 47-48]. However, in at least one of these cohorts (the CASCADE study), the link between CD4 count and fatal cardiovascular events was no longer statistically significant when adjusting for plasma HIV RNA level. Collectively, the data linking viremia and endothelial dysfunction and inflammation, the increased risk of cardiovascular events with treatment interruption, and the association between cardiovascular disease and CD4 cell depletion suggest that early control of HIV replication with antiretroviral therapy can be used as a strategy to reduce cardiovascular disease risk **(BIII)**.

Malignancies

Several population-based analyses suggest increased incidence of non-AIDS-associated malignancies during chronic HIV infection. The incidence of non-AIDS malignancy in HIV-infected subjects is higher than in matched HIV-uninfected controls [49]. Large cohort studies of mostly patients receiving antiretroviral treatment have reported a consistent link between low CD4 counts (<350 – 500 cells/mm³) and the risk of AIDS- and/or non-AIDS-defining malignancy [7, 47, 50-53]. The ANRS C04 demonstrated a statistically significant relative risk of all cancers evaluated (except for anal carcinoma) in patients with CD4 counts <500 cells/mm³ compared with patients with current CD4 counts >500 cells/mm³ and a protective effect of antiretroviral therapy for HIV-associated malignancies [50]. This potential effect of HIV-associated immunodeficiency is particularly striking with regard to cancers associated with chronic viral infections (e.g., HBV, HCV, HPV, EBV, HHV-8) [54-55]. Cumulative HIV viremia itself may also be associated with the risk of non-Hodgkin lymphoma and other AIDS-defining malignancies, independent of other factors [53, 56]. Together this evidence suggests that initiating antiretroviral therapy to suppress HIV replication and maintain CD4 counts at above 350 – 500 cells/mm³ may reduce the risk of both AIDS-defining and non-AIDS-defining malignancy **(CIII)**.

Neurocognitive decline

Early in the HIV epidemic, HIV was identified in brain tissue [57] and assumed to be the cause of AIDS dementia complex [58]. The improvement of AIDS dementia complex symptoms with the use of antiretroviral therapy supported this assumption [59-60]. The CASCADE observational cohort reported a dramatic decline in the incidence of HIV-associated dementia from 6.49 per 1,000 person-years (before 1997) to 0.66 per 1,000 person-years (2003–2006), after the widespread use of potent antiretroviral therapy [61]. In this cohort, having a current CD4 count >350 cells/mm³ was associated with the lowest risk of developing HIV-associated dementia. HIV infection has also been associated with a number of less severe neurologic complications, including changes in neuropsychological ability, speed of processing, and everyday functioning [62]. Such syndromes also were predicted by a lower pretherapy CD4 nadir and/or by CD4 count while on therapy [63-64]. Additional clinical data are needed to determine the relative roles of ongoing HIV replication and potential neurotoxicity of antiretroviral agents in the development of neurocognitive dysfunction. Whether early initiation of therapy will prevent HIV-associated neurocognitive dysfunction remains unclear. However, the neurological complications that may accompany uncontrolled HIV replication and CD4 depletion suggest a potential benefit of earlier initiation of antiretroviral therapy **(CIII)**.

Age and treatment-related immune reconstitution

The CD4 cell response to therapy is an important predictor of short-term and long-term morbidity and mortality. Treatment initiation at an older age is consistently associated with a less robust CD4 count response; starting therapy at a younger age may result in better immunologic and perhaps clinical outcomes [65-67] **(CIII)**.

T-cell activation and inflammation

Early untreated HIV infection is associated with sustained high-level inflammation and T-cell activation [68-70]. The degree of T-cell activation during untreated disease is associated with risk of subsequent disease progression, independent of other factors such as plasma HIV RNA levels and the peripheral CD4 T-cell count [71-72]. Antiretroviral therapy results in a rapid, but often incomplete, decrease in most markers of HIV-associated immune activation [73-77]. Persistent T-cell activation and/or T-cell dysfunction is particularly evident among patients who delay therapy until later stage disease (CD4 count <350 cells/mm³) [74, 77-78]. The degree of persistent inflammation during treatment, as represented by the levels of IL-6, may be independently associated with risk of death [44]. Collectively, these observations support earlier use of antiretroviral therapy for at least two reasons. First, treatment decreases the level of inflammation and T-cell activation, which may be associated with reduced short-term risk of AIDS- and non-AIDS-related morbidity and mortality [44, 79-80]. Second, because it appears that the degree of residual inflammation and/or T-cell dysfunction during antiretroviral therapy is higher in patients with lower CD4 cell nadirs [74, 77-78], earlier treatment may result in less residual immunological perturbations on therapy, and hence less risk for AIDS- and non-AIDS-related complications **(CIII)**.

Prevention of HIV Transmission

Prevention of Mother-to-Child Transmission

Effective antiretroviral therapy reduces transmission of HIV. The most dramatic and well-established example of this effect is the use of antiretroviral therapy in pregnant women to prevent mother-to-child transmission of HIV. Effective suppression of HIV replication, as reflected in plasma HIV RNA, is a key determinant in reducing perinatal transmission. In the United States, the use of combination antiretroviral therapy during pregnancy has reduced the HIV transmission rate from approximately 20–30% to $<2\%$ [81]. Thus, antiretroviral therapy is recommended for all HIV-infected pregnant women, both for maternal health and to prevent HIV transmission from mother to child **(AI)**. For detailed recommendations, see [Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission](#) [82].

Prevention of Sexual Transmission

Emerging evidence supports the concept of "treatment as prevention" of sexual transmission of HIV. Lower plasma HIV RNA levels are associated with decreases in the concentration of the virus in genital secretions [83-84]. Studies of HIV serodiscordant heterosexual couples have demonstrated a relationship between the level of plasma viremia and HIV transmission risk: when plasma HIV RNA levels are lower, transmission events are less common [85-89]. These investigations, as well as other observational studies and modeling analyses demonstrating a decreased rate of HIV transmission among serodiscordant heterosexual couples following the introduction of antiretroviral therapy, suggest that suppression of viremia in treatment-adherent patients with no concomitant sexually transmitted infections substantially reduces the risk of HIV transmission [88-93]. Based on these studies, the use of effective antiretroviral therapy regardless of CD4 count is likely to reduce transmission to the uninfected sexual partner **(BII)**.

POTENTIAL LIMITATIONS OF EARLIER INITIATION OF THERAPY

Although there are benefits associated with earlier initiation of antiretroviral therapy, there are also potential limitations to this approach. Concerns about long-term toxicity and the development of antiretroviral resistance have served as a rationale for the deferral of HIV therapy. Earlier initiation of antiretroviral therapy at higher CD4 counts (e.g., >500 cells/mm³) results in greater cumulative time on therapy. Assuming treatment for many decades after initiation, the additional therapy represents a small percentage of the total time on treatment for most patients.

Although newer antiretroviral regimens are generally better tolerated, more convenient, and more potent than older regimens, there are fewer longer term safety data for the newer agents. Analyses supporting antiretroviral initiation at CD4 counts above 350/mm³ (e.g., NA-ACCORD and ART-CC) were conducted with cohorts largely treated with regimens less commonly used in clinical practice. These studies reported on clinical endpoints of death and/or AIDS

disease progression but lacked information on drug toxicities, resistance, or adherence. Therefore, in considering earlier initiation of therapy, concerns for some adverse consequences of antiretroviral therapy remain.

Antiretroviral Drug Toxicities and Quality of Life

Earlier initiation of antiretroviral therapy extends exposure to antiretroviral agents by several years. The D:A:D study found an increased incidence of cardiovascular disease associated with cumulative exposure to some drugs within the NRTI and PI classes [38, 94]. In the SMART study, continuous exposure to antiretroviral treatment has been associated with significantly greater loss of bone density compared with interruption or deferral of antiretroviral therapy [46]. There may be unknown complications related to cumulative use of antiretroviral drugs for many decades. A list of known antiretroviral-associated toxicities along with prevention and management strategies can be found in the [Adverse Effects of Antiretroviral Agents](#) section.

Although antiretroviral therapy frequently improves quality of life among symptomatic patients, it may also be associated with reduced quality of life in some patients, especially those who are asymptomatic at initiation of therapy. Although better tolerated and easier to administer than older drugs, most antiretroviral drugs now used in first line regimens can cause side effects that reduce quality of life. Efavirenz, for example, can cause neurocognitive or psychiatric side effects, and all the protease inhibitors have been associated with gastrointestinal side effects. Furthermore, some patients may find that the inconvenience of taking medication every day outweighs the overall benefit and might choose to delay therapy whenever possible.

Drug Resistance

Very early treatment initiation may lead to an earlier onset of drug resistance selection in nonadherent patients. The consequent harm is loss of important drugs or drug classes and risk of transmission of drug-resistant HIV. Some asymptomatic patients may be less motivated to remain adherent to their HIV treatment regimen if treatment is initiated far in advance of an immediate risk of HIV-associated morbidity and mortality. The greater convenience and potency of current antiretroviral regimens facilitate adherence and reduce the risk of antiretroviral resistance. One study suggests that the risk of drug resistance at the time of virologic failure is lower among patients who initiated treatment at higher CD4 counts [95]. Treatment adherence is key to viral suppression and should be stressed prior to initiation of therapy and during follow-up visits.

Nonadherence to Antiretroviral Therapy

At any CD4 count, adherence to therapy is essential to achieve viral suppression and prevent emergence of resistance mutations. Several behavioral and social factors associated with lower adherence have been identified, such as untreated major psychiatric disorders, active substance abuse, social circumstances, patients' concerns about side effects, and poor adherence to clinic visits. Clinicians should identify areas where additional intervention is needed to improve adherence both before and after initiation of therapy. Some strategies to improve adherence are discussed in the [Adherence](#) section.

Cost

Although antiretroviral therapy adds to the annual cost of treatment, several modeling studies support the cost-effectiveness of HIV therapy initiated soon after diagnosis [96-98]. Studies have reported that the annual cost of care is 2½ times higher for patients with CD4 counts <50 cells/mm³ compared with patients with CD4 counts >350 cells/mm³ [99]. A large proportion of the health care expenditure in patients with advanced infection is from nonantiretroviral drugs and hospitalization. However, no cost comparisons have been reported between those starting antiretroviral therapy with a CD4 count between 350 and 500 cells/mm³ versus >500 cells/mm³.

SUMMARY

In earlier versions of these treatment guidelines, concerns about long-term toxicity, reduced quality of life, and the potential for drug resistance served as key reasons to defer HIV therapy for as long as possible. Inherent in this

argument was the assumption that the harm associated with viral replication was less than the harm associated with the toxicities of antiretroviral drugs in patients with higher CD4 count. There is now more evidence that untreated HIV infection has negative consequences on health at all stages of disease. Also, the drug combinations now available are better tolerated than previous regimens, leading to greater efficacy and improved adherence [100]. The current guidelines therefore emphasize avoiding adverse consequences of untreated HIV infection while managing potential drug toxicity.

RECOMMENDATIONS

Based on the cumulative weight of evidence described above, the Panel recommends that:

- Antiretroviral therapy should be initiated in all patients with a history of an AIDS-defining illness, or with CD4 count of < 350 cells/mm³ (**AI**).
- Antiretroviral therapy should also be initiated, regardless of CD4 count, in patients with the following conditions: pregnancy (**AI**), HIV associated nephropathy (**AII**), hepatitis B virus (HBV) co-infection when treatment of HBV is indicated (**AIII**).
- Antiretroviral therapy is recommended for patients with CD4 counts between 350 and 500 cells/mm³. The Panel was divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation (A) and 45% voted for moderate recommendation (B) (**A/B-II**).
- For patients with CD4 counts > 500 cells/mm³, 50% of the Panel members favor starting antiretroviral therapy (B); the other 50% of members view treatment is optional (C) in this setting (**B/C-III**).
- Patients initiating antiretroviral therapy should be willing and able to commit to lifelong treatment, and should understand the benefits and risks of therapy and the importance of adherence (**AIII**).
- Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

Conditions Favoring More Rapid Initiation of Therapy

Deferring antiretroviral therapy may be appropriate in some cases. However, several conditions increase the urgency for therapy, including:

- Pregnancy (**AI**)
- AIDS-defining conditions (**AI**)
- Acute opportunistic infections (see discussion below)
- Lower CD4 counts (e.g., < 200 cells/mm³) (**AI**)
- Rapidly declining CD4 counts (e.g., > 100 cells/mm³ decrease per year) (**AIII**)
- Higher viral loads (e.g., $> 100,000$ copies/ml) (**BII**)
- HIV-associated nephropathy (**AII**)
- HBV coinfection when treatment for HBV is indicated (**AIII**)

Acute opportunistic infections

In patients with opportunistic conditions for which there is no effective therapy (e.g., cryptosporidiosis, microsporidiosis, progressive multifocal leukoencephalopathy) but for which antiretroviral therapy may improve outcomes by improving immune responses, the benefits of antiretroviral therapy outweigh any increased risk, and therefore treatment should be started as soon as possible (**AIII**).

In the setting of opportunistic infections, such as cryptococcal meningitis or non-tuberculous mycobacterial infections, for which immediate therapy may increase the risk of immune reconstitution inflammatory syndrome (IRIS), a short delay may be warranted before initiating antiretroviral treatment [101-102] (**CIII**).

In the setting of other opportunistic infections, such as *Pneumocystis jiroveci* pneumonia (PCP), early initiation of antiretroviral therapy is associated with increased survival, and therapy should not be delayed [3] (**AI**).

In patients with tuberculosis with low CD4⁺ T-cell counts, initiating antiretroviral therapy within the first 2 months of treatment for tuberculosis appears to confer a significant survival advantage [103-104]. Clinicians should refer to [Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents](#) [105] for more detailed discussion on when to initiate antiretroviral therapy in the setting of a specific opportunistic infection.

Conditions Where Deferral of Therapy Might be Considered

Some patients and their clinicians may decide to defer therapy for a period of time based on clinical or personal circumstances. The degree to which these factors might argue for deferral of therapy depends on the CD4 count and viral load. Although deferring therapy for the reasons discussed below may be reasonable for patients with high CD4 counts (e.g., >500 cells/mm³), deferral for patients with much lower CD4 counts (e.g., <200 cells/mm³) should be considered only in rare situations and should be undertaken with close clinical follow-up. A brief delay in initiating therapy may be considered to allow a patient more time to prepare for lifelong treatment.

When there are significant barriers to adherence

Deferring treatment for patients with higher CD4 counts who are at risk of poor adherence may be prudent while the barriers are being addressed. However, potential predictors of poor adherence may be overridden when more urgent antiretroviral therapy is indicated (see above).

Several methodologies exist to help providers assess adherence. When the most feasible measure of adherence is self-report, this assessment should be completed at each clinic visit, using one of the available reliable and valid instruments [106-107]. If other objective measures are available (e.g., pharmacy refill data, pill count), these methods should also be implemented as therapy begins [108-110]. Continuous assessment and counseling make it possible for the clinician to intervene early to address barriers to adherence occurring at any point during treatment.

Presence of comorbidities that complicate or prohibit antiretroviral therapy

Deferral of antiretroviral therapy may be considered when either the treatment or manifestations of other medical conditions could complicate the treatment of HIV infection or vice versa. Examples include patients:

- requiring surgery that might result in an extended interruption of antiretroviral therapy
- taking medications that have clinically significant drug interactions with antiretroviral agents and for whom alternative therapy is not available.

In each of these cases, it is assumed that the situation is temporary and that antiretroviral therapy will be initiated after the conflicting condition has resolved.

There are some less common situations in which antiretroviral therapy may not be indicated at any time while CD4 counts remain high. In particular, such situations include patients with a poor prognosis due to a concomitant medical condition who would not be expected to derive survival or quality-of-life benefits from antiretroviral therapy. Examples include patients with incurable non-HIV-related malignancies or end-stage liver disease who are not being considered for liver transplantation. The decision to forego antiretroviral therapy in such patients may be easier in those with higher CD4 counts; they are likely asymptomatic for HIV, and their survival is unlikely to be prolonged by antiretroviral therapy. However, it should be noted that antiretroviral therapy may improve outcomes, including survival, in patients with some HIV-associated malignancies (e.g., lymphoma or Kaposi's sarcoma) and in patients with liver disease due to chronic HBV or HCV.

Elite HIV controllers or long-term nonprogressors

A small subset of antiretroviral-untreated HIV-infected persons (~3%–5%) are able to maintain normal CD4 cell counts for many years (long-term nonprogressors), while an even smaller subset (~1%) are able to maintain suppressed viral loads for years (elite controllers). It is possible that such patients would not benefit from antiretroviral therapy. However, some nonprogressors have high viral loads, while some elite controllers progress clinically or

immunologically [111-112]. Although therapy may be theoretically beneficial for patients in either group, clinical data supporting therapy for nonprogressors and elite controllers are lacking.

THE NEED FOR EARLY DIAGNOSIS OF HIV

Fundamental to the earlier initiation of therapy recommended in these guidelines is the assumption that patients will be identified early in the course of HIV infection, making earlier initiation of therapy an option. Unfortunately, most HIV-infected patients are not diagnosed until they are at much later stages of disease [113-116]. Despite the 2006 CDC recommendations for routine, opt-out HIV screening in the health care setting [117] regardless of perceived risk of infection, the median CD4 count for newly diagnosed patients remains in the ~200 cells/mm³ range. (The exception is pregnant women diagnosed during prenatal care, who have a much higher median initial CD4 count.) Delay in HIV diagnosis is more often seen in nonwhites, injection drug users, and older patients; a substantial proportion of these individuals develop AIDS-defining illnesses within 1 year of diagnosis [114-116]. Therefore, for the current treatment guidelines to have maximum impact, routine HIV screening per current CDC recommendations is essential. It is critical that all newly diagnosed patients be educated about HIV disease and linked to care for full evaluation, follow-up, and management. Once in care, focused effort is required to retain patients in the health care system.

CONCLUSION

These revised recommendations are based on increasing evidence that supports earlier initiation of antiretroviral therapy than was advocated in previous guidelines. The strength of the recommendations varies with the quality and availability of existing evidence. The Panel members are divided regarding the strength of recommendations for starting therapy in patients with higher CD4 cell counts as discussed above. The Panel will continue to monitor and assess the results of ongoing and planned randomized clinical trials and observational studies, which will provide the Panel with additional guidance to form future recommendations.

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What to Start: Initial Combination Regimens for the Antiretroviral-Naïve Patient (Updated December 1, 2009)

Panel's Recommendations:

- The Panel recommends initiating antiretroviral therapy in treatment naïve patients with 1 of the following 3 types of regimen:
 - NNRTI + 2 NRTI
 - PI (preferably boosted with ritonavir) + 2 NRTI
 - INSTI + 2 NRTI
- The Panel recommends the following as preferred regimens for treatment naïve patients:
 - Efavirenz + tenofovir + emtricitabine (AI)
 - Ritonavir-boosted atazanavir + tenofovir + emtricitabine (AI)
 - Ritonavir-boosted darunavir + tenofovir + emtricitabine (AI)
 - Raltegravir + tenofovir + emtricitabine (AI)
- A list of Panel recommended alternative and acceptable regimens can be found in [Table 5a](#).
- Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions.
- Based on individual patient characteristics and needs, in some instances, an alternative regimen may actually be a preferred regimen for a patient.

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor

There are more than 20 approved antiretroviral drugs in 6 mechanistic classes with which to design combination regimens. These 6 classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase strand transfer inhibitors (INSTI). The most extensively studied combination regimens for treatment-naïve patients that provide durable viral suppression generally consist of two NRTIs plus either one NNRTI or a PI (with or without ritonavir boosting). In July 2009, a regimen consisting of raltegravir was approved for treatment-naïve patients, making the combination of an INSTI + 2 NRTIs an additional option.

In the current guidelines, the Panel refines its recommendations for the selection of regimens for use in antiretroviral-naïve persons. This reflects a change from previous versions of the guidelines where a list of preferred or alternative choices within each drug class was provided to allow clinicians to construct the regimen by combining drugs from each list. We now provide recommendations for preferred, alternative, and acceptable regimens as well as regimens that may be acceptable but more definitive data are needed and regimens to be used with caution ([Tables 5a, 5b](#)).

Potential advantages and disadvantages of the components recommended as initial therapy for treatment-naïve patients are listed in [Table 6](#) to guide prescribers in choosing the regimen best suited for an individual patient. A list of agents or components not recommended for initial treatment can be found in [Table 7](#). Some agents or components that are not recommended for use because of lack of potency or potential serious safety concerns are listed in [Table 8](#).

CONSIDERATIONS WHEN SELECTING A FIRST ANTIRETROVIRAL REGIMEN FOR TREATMENT-NAÏVE PATIENTS

Data Used for Making Recommendations

In its deliberations, the Panel reviews clinical trial data published in peer-reviewed journals and data prepared by manufacturers for FDA review. In selected cases, data presented in abstract format in major scientific meetings also

are reviewed. The first criteria for selection are published data from a randomized, prospective clinical trial with an adequate sample size that demonstrate durable viral suppression and immunologic enhancement (as evidenced by increase in CD4 T-cell count). Few of these trials include clinical endpoints, such as development of AIDS-defining illness or death. Thus, assessment of regimen efficacy and potency is primarily based on surrogate marker endpoints (HIV RNA and CD4 responses). The Panel reviewed data from randomized clinical trials to arrive at preferred versus alternative ratings in [Table 5a](#). “Preferred regimens” are those studied in randomized controlled trials and shown to have optimal and durable virologic efficacy, have favorable tolerability and toxicity profiles, and are easy to use. “Alternative regimens” are those regimens that are effective but have potential disadvantages when compared to preferred regimens. On the basis of individual patient characteristics and needs, a regimen listed as an alternative regimen may actually be the preferred regimen in certain situations. Some regimens are now classified as “Acceptable Regimens” because of less virologic activity, lack of efficacy data from large clinical trials, or greater toxicities when compared to the preferred or alternative regimens.

[Table 5b](#) includes other regimens that maybe acceptable but definitive data from randomized trials are not yet published. Lastly, Table 5b includes several regimens shown to be efficacious in some studies; however, the Panel recommends using them with caution because of some safety or efficacy concerns.

Factors to Consider When Selecting an Initial Regimen

Regimen selection should be individualized and should be based on a number of factors, including:

- comorbid conditions (e.g., cardiovascular disease, chemical dependency, liver disease, psychiatric disease, renal diseases, or tuberculosis);
- potential adverse drug effects;
- potential drug interactions with other medications;
- pregnancy or pregnancy potential;
- results of genotypic drug resistance testing;
- gender and pretreatment CD4 T-cell count if considering nevirapine;
- HLA-B*5701 testing if considering abacavir;
- [coreceptor tropism assay if considering maraviroc](#);
- patient adherence potential; and
- convenience (e.g., pill burden, dosing frequency, and food and fluid considerations).

Considerations for Therapies

A listing of characteristics (i.e., dosing, pharmacokinetics, and common adverse effects) of individual antiretroviral agents can be found in [Appendix B, Tables 1–6](#). Additionally, [Appendix B, Table 7](#) provides clinicians with antiretroviral dosing recommendations for patients who have renal or hepatic insufficiency.

Recommended regimens use combinations of two NRTIs with an NNRTI, PI (preferably boosted with ritonavir), [or an INSTI, namely raltegravir](#). In many clinical trials, NNRTI-, PI-, and [INSTI](#)-based regimens result in suppression of HIV RNA levels and CD4 T-cell increases in a large majority of patients [1-6]. Some comparative data are available (see below).

[Tables 5a and 5b](#) include the Panel’s recommendations for initial therapy.

Table 5a. Antiretroviral Regimens Recommended for Treatment-Naïve Patients
(Updated December 1, 2009)

Patients naïve to antiretroviral therapy should be started on one of the following three types of combination regimens:

- NNRTI + 2 NRTIs; or
- PI (preferably boosted with ritonavir) + 2 NRTIs; or
- INSTI + 2 NRTIs.

Selection of a regimen should be individualized based on virologic efficacy, toxicity, pill burden, dosing frequency, drug-drug interaction potential, resistance testing results, and comorbid conditions. Refer to [Table 6](#) for a list of advantages and disadvantages, and [Appendix B, Tables 1–6](#) for dosing information for individual antiretroviral agents listed below. The regimens in each category are listed in alphabetical order.

Preferred Regimens (Regimens with optimal and durable efficacy, favorable tolerability and toxicity profile, and ease of use) The preferred regimens for non-pregnant patients are arranged by order of FDA approval of components other than nucleosides, thus, by duration of clinical experience.	
NNRTI-based Regimen • EFV/TDF/FTC¹ (AI) PI-based Regimens (in alphabetical order) • ATV/r + TDF/FTC¹ (AI) • DRV/r (once daily) + TDF/FTC¹ (AI) INSTI-based Regimen • RAL + TDF/FTC¹ (AI) Preferred Regimen² for Pregnant Women • LPV/r (twice daily) + ZDV/3TC¹ (AI)	Comments EFV should not be used during the first trimester of pregnancy or in women trying to conceive or not using effective and consistent contraception. ATV/r should not be used in patients who require >20mg omeprazole equivalent per day. Refer to Table 14a for dosing recommendations regarding interactions between ATV/r and acid-lowering agents.
Alternative Regimens (Regimens that are effective and tolerable but have potential disadvantages compared with preferred regimens. An alternative regimen may be the preferred regimen for some patients.)	
NNRTI-based Regimens (in alphabetical order) • EFV + (ABC or ZDV)/3TC¹ (BI) • NVP + ZDV/3TC¹ (BI) PI-based Regimens (in alphabetical order) • ATV/r + (ABC or ZDV)/3TC¹ (BI) • FPV/r (once or twice daily) + either [(ABC or ZDV)/3TC¹] or TDF/FTC¹ (BI) • LPV/r (once or twice daily) + either [(ABC or ZDV)/3TC¹] or TDF/FTC¹ (BI) • SQV/r + TDF/FTC¹ (BI)	Comments NVP: • Should not be used in patients with moderate to severe hepatic impairment (Child-Pugh B or C)³ • Should not be used in women with pre-ARV CD4 >250 cells/mm³ or men with pre-ARV CD4 >400 cells/mm³ ABC: • Should not be used in patients who test positive for HLA-B*5701 • Use with caution in patients with high risk of cardiovascular disease or with pretreatment HIV-RNA >100,000 copies/mL (see text) Once-daily LPV/r is not recommended in pregnant women.
Acceptable Regimens (Regimens that may be selected for some patients but are less satisfactory than preferred or alternative regimens.)	
NNRTI-based Regimen • EFV + ddI + (3TC or FTC) (CI) PI-based Regimen • ATV + (ABC or ZDV)/3TC¹ (CI)	Comments EFV + ddI + FTC or 3TC has only been studied in small clinical trials. ATV/r is generally preferred over ATV. Unboosted ATV may be used when ritonavir boosting is not possible.

¹3TC may substitute for FTC or vice versa.

²For more detailed recommendations on antiretroviral use in an HIV-infected pregnant woman, refer to “[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#),” at <http://aidsinfo.nih.gov/guidelines>.

³Refer to [Appendix B, Table 7](#) for the criteria for Child-Pugh classification.

Abbreviations:

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, NRTI = nucleos(t)ide reverse transcriptase inhibitor, PI = protease inhibitor

ABC = abacavir, ATV = atazanavir, 3TC = lamivudine, ddI = didanosine, DRV = darunavir, EFV = efavirenz, FPV = fosamprenavir, FTC = emtricitabine, LPV = lopinavir, NVP = nevirapine, RAL = raltegravir, r = low dose ritonavir, SQV = saquinavir, TDF = tenofovir, ZDV = zidovudine

The following combinations in the recommended list above are available as fixed-dose combination formulations: ABC/3TC, EFV/TDF/FTC, LPV/r, TDF/FTC, and ZDV/3TC.

Table 5b. Antiretroviral Regimens that May be Acceptable and Regimens to be Used with Caution (Updated December 1, 2009)

Regimens that may be acceptable but more definitive data are needed	
CCR5-Antagonist-based Regimen - MVC + ZDV/3TC¹ (CIII) INSTI-based Regimen - RAL + (ABC or ZDV)/3TC¹ (CIII) PI-based Regimen (DRV/r or SQV/r) + (ABC or ZDV)/3TC¹ (CIII)	Comment With MVC, tropism testing required before treatment. Only patients found to have CCR-5 tropic-only virus (i.e., absence of CXCR4 tropic virus) are candidates for MVC.
Regimens to be Used with Caution (Regimens that have demonstrated virologic efficacy in some studies, but have safety, resistance, or efficacy concerns.)	
NNRTI-based Regimens - NVP + ABC/3TC¹ (CIII) - NVP + TDF/FTC¹ (CIII) PI-based Regimen - FPV + [(ABC or ZDV)/3TC¹ or TDF/FTC¹] (CIII)	Comments Use NVP and ABC together with caution because both can cause hypersensitivity reactions within first few weeks after initiation of therapy. Early virologic failure with high rates of resistance has been reported in some patients receiving NVP + TDF + (3TC or FTC). Larger clinical trials are currently in progress. FPV/r is generally preferred over unboosted FPV. Virologic failure with unboosted FPV-based regimen may select mutations that confer cross resistance to DRV.

¹3TC may be substituted with FTC or vice versa.

Abbreviations:

INSTI = integrase strand transfer inhibitor, NNRTI = non-nucleoside reverse transcriptase inhibitor, PI = protease inhibitor

ABC = abacavir, 3TC = lamivudine, DRV = darunavir, FPV = fosamprenavir, FTC = emtricitabine, MVC = maraviroc, NVP = nevirapine, RAL = raltegravir, r = low dose ritonavir, SQV = saquinavir, TDF = tenofovir, ZDV = zidovudine

NNRTI- Versus PI- Versus INSTI-Based Regimens

Efavirenz-based regimens were superior to indinavir- and nelfinavir-based regimens in earlier comparative studies [3, 7]. Neither indinavir nor nelfinavir is recommended now as part of initial therapy. The A1424-034 study demonstrated comparable virologic and immunologic responses with atazanavir- and efavirenz-based regimens [5]. The ACTG A5142 study showed better virologic responses with an efavirenz-based regimen compared with a lopinavir/ritonavir-based regimen, but better CD4 cell responses and less resistance after virologic failure with lopinavir/ritonavir plus two NRTIs [4]. A smaller randomized trial in Mexico, which compared the same agents in treatment-naïve participants who had CD4 cell counts <200/mm³, also suggested a virologic advantage among efavirenz recipients [8].

PI-based regimens generally are associated with more gastrointestinal symptoms and lipid abnormalities, whereas efavirenz-based regimens are associated with more rash and central nervous system adverse effects. Both kinds of regimens may be associated with hepatic transaminase elevations [9].

Drug resistance to most PIs requires multiple mutations in the HIV protease gene, and it seldom develops after early virologic failure [10], especially when ritonavir boosting is used. Resistance to efavirenz or nevirapine, however, is conferred by a single mutation in the reverse transcriptase gene, and it develops rapidly after virologic failure [10]. An estimated 7% of HIV-infected patients in the United States are infected with NNRTI-resistant viruses [11]. Because of the concern for primary resistance in the treatment-naïve population, genotypic testing results should be used to guide the selection of the initial antiretroviral regimen (see [Drug Resistance Testing](#) section). In terms of convenience, the coformulated tablet of tenofovir, emtricitabine, and efavirenz allows for once-daily dosing with a single tablet. Most PI-based regimens include ritonavir, may be dosed once or twice daily, and generally require more pills in the regimen, although the pill burden associated with PI-based regimens has decreased when compared to earlier years. Drug-drug

interactions are important with both kinds of regimens, but more clinically significant interactions are seen with ritonavir-boosted regimens.

Another option for initial therapy is the combination of tenofovir, emtricitabine, and the INSTI raltegravir [6]. This combination has shown similar virologic efficacy as a combination of tenofovir, emtricitabine, and efavirenz up to 96 weeks [12] and is generally well tolerated. There are no clinical trial data comparing INSTI-based with PI-based regimens. Raltegravir requires twice-daily dosing, has a low genetic barrier for selection of resistance mutations, and has had relatively limited use with other dual-NRTI combinations.

The discussions below focus on the rationale for the Panel's recommendations, based on the efficacy, safety, and other characteristics of different agents within the individual drug classes.

NNRTI-BASED REGIMENS (1 NNRTI + 2 NRTIs)

Summary: NNRTI-Based Regimens

Four NNRTIs (delavirdine, efavirenz, etravirine, and nevirapine) are currently FDA approved.

NNRTI-based regimens have demonstrated virologic potency and durability. The major disadvantages of currently available NNRTIs involve prevalence of NNRTI-resistant viral strains in treatment-naïve patients [11, 13-15] and the low genetic barrier of NNRTIs for development of resistance. Resistance testing should be performed for treatment-naïve patients to guide therapy selection (see [Drug Resistance Testing](#) section). The first three approved NNRTIs (i.e., efavirenz, nevirapine, delavirdine) require only a single mutation to confer resistance, and cross resistance affecting these three NNRTIs is common. Etravirine, an NNRTI approved for treatment-experienced patients, has *in vitro* activity against some viruses with mutations that confer resistance to delavirdine, efavirenz, and nevirapine [16].

On the basis of clinical trial results and safety data, the Panel recommends either efavirenz or nevirapine as the NNRTI for initial antiretroviral therapy. In most instances, efavirenz should be the preferred choice based on its potency and tolerability (as discussed below). Efavirenz should not be used in pregnant women (especially during the first trimester) or in women of childbearing potential who are planning to conceive or who are sexually active with men and not using effective and consistent contraception.

Nevirapine may be used as an alternative to efavirenz for the initial NNRTI-based regimen in women with pretreatment CD4 counts ≤ 250 cells/mm³ or in men with pretreatment CD4 counts ≤ 400 cells/mm³ (**BI**). (See discussion below.)

Among these four agents, delavirdine is dosed three times daily, has the least supportive clinical trial data, and appears to have the least antiviral activity. As such, it is not recommended as part of an initial regimen (**BIII**). Etravirine has not been studied in large, randomized trials in treatment-naïve participants. Thus, it cannot currently be recommended as part of initial therapy (**BIII**).

Following is a more detailed discussion of preferred and alternative NNRTI-based regimens for initial therapy.

Efavirenz as Preferred NNRTI

Large randomized, controlled trials and cohort studies of treatment-naïve patients have demonstrated potent viral suppression in efavirenz-treated patients; a substantial proportion of these patients had HIV RNA < 50 copies/mL during up to 7 years of follow-up [1-2, 17]. Studies that compared efavirenz-based regimens with other regimens have demonstrated the combination of efavirenz with two NRTIs was superior virologically to some PI-based regimens, including indinavir [3], lopinavir/ritonavir [4], and nelfinavir [7], and to triple-NRTI-based regimens [18-19]. Efavirenz-based regimens also had comparable activities to nevirapine- [20-21], atazanavir-, [5], and **raltegravir-based regimens [6]**.

The ACTG 5142 study randomized patients to receive two NRTIs together with either efavirenz or lopinavir/ritonavir (or an NRTI-sparing regimen of efavirenz and lopinavir/ritonavir) [4]. The dual-NRTI and efavirenz regimen was associated with a significantly better virologic response than the dual-NRTI and lopinavir/ritonavir regimen at 96

weeks, whereas the dual-NRTI with lopinavir/ritonavir regimen was associated with a significantly better CD4 cell response and less drug resistance after virologic failure.

The 2NN trial compared efavirenz and nevirapine, both given with stavudine and lamivudine, in treatment-naïve patients. Virologic responses were similar for both drugs, although nevirapine was associated with greater toxicity and did not meet criteria for noninferiority compared with efavirenz [20].

Two major limitations of efavirenz are its central nervous system adverse effects, which usually resolve over a few weeks, and its potential teratogenic effects. In animal reproductive studies, efavirenz caused major congenital anomalies in the central nervous system in nonhuman primates at drug exposure levels similar to those achieved in humans [22]. Several cases of neural tube defects in human newborns, when mothers were exposed to efavirenz during the first trimester of pregnancy, have been reported in the literature and to the Antiretroviral Pregnancy Registry [23-24]. Therefore, efavirenz is not recommended in pregnant women during the first trimester of pregnancy or in women with high pregnancy potential (women who are of childbearing potential who are trying to conceive or who are sexually active with men and are not using effective and consistent contraception) **(AIII)**.

Studies that use efavirenz and dual-NRTI combinations (abacavir, didanosine, stavudine, tenofovir, or zidovudine together with emtricitabine or lamivudine) show durable virologic activity, although there may be differences among the various combinations chosen (see [Dual NRTI Options](#) section). A single tablet coformulated with tenofovir, emtricitabine, and efavirenz provides one-tablet, once-daily dosing and is currently the preferred NNRTI-based regimen **(AI)**.

Nevirapine as Alternative NNRTI (BI)

In the 2NN trial, 70% of participants in the efavirenz arm and 65.4% in the twice-daily nevirapine arm had virologic suppression (defined as HIV RNA <50 copies/mL) at 48 weeks. This difference did not reach criteria necessary to demonstrate noninferiority of nevirapine [20]. Two deaths were attributed to nevirapine use. One resulted from fulminant hepatitis and one from staphylococcal sepsis as a complication of Stevens-Johnson syndrome.

In a randomized controlled trial, presented in abstract form, nevirapine was found to be noninferior to boosted atazanavir when combined with tenofovir/emtricitabine [25]. This study enrolled only women and men with <250 and <400 CD4 cell counts/mm³, respectively, the threshold recommended to reduce the incidence of hepatic toxicity (see below). Three smaller studies (n <100) have suggested more virologic failures than would be expected in treatment-naïve participants who receive nevirapine plus tenofovir and either lamivudine or emtricitabine [26-28]. Pending published results from randomized trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

Serious hepatic events have been observed when nevirapine was initiated in treatment-naïve patients. These events generally occur within the first few weeks of treatment. In addition to experiencing elevated serum transaminases, approximately half of the patients also develop skin rash, with or without fever or flu-like symptoms. Women with higher CD4 counts appear to be at highest risk [29-30]. A 12-fold higher incidence of symptomatic hepatic events was seen in women (including pregnant women) with CD4 counts >250 cells/mm³ at the time of nevirapine initiation when compared with women with CD4 counts ≤250 cells/mm³ (11.0% vs. 0.9%). An increased risk was also seen in men with pretreatment CD4 counts >400 cells/mm³ when compared with men with pretreatment CD4 counts ≤400 cells/mm³ (6.3% vs. 1.2%). Most of these patients had no identifiable underlying hepatic abnormalities. In some cases, hepatic injuries continued to progress despite discontinuation of nevirapine [30-31]. Symptomatic hepatic events have not been reported with single doses of nevirapine given to mothers or infants for prevention of perinatal HIV infection.

On the basis of the safety data described, the Panel recommends that nevirapine may be used as an alternative to efavirenz as initial therapy for women with pretreatment CD4 counts ≤250 cells/mm³ or in men with CD4 counts ≤400 cells/mm³ **(BI)**. Patients who experience CD4 count increases to levels above these thresholds as a result of nevirapine-containing therapy can safely continue therapy without an increased risk of adverse hepatic events [32].

At the initiation of nevirapine, a 14-day lead-in period at a dosage of 200mg once daily should be instituted before increasing to the maintenance dosage of 200mg twice daily. Some experts recommend monitoring serum transaminases

at baseline, prior to and 2 weeks after dose escalation, then monthly for the first 18 weeks. Clinical and laboratory parameters should be assessed at each visit. More detailed recommendations on the management of nevirapine-associated hepatic events can be found in [Table 12](#).

PI-BASED REGIMENS (RITONAVIR-BOOSTED OR UNBOOSTED PI + 2 NRTIs)

Summary: PI-Based Regimens

PI-based regimens have demonstrated virologic potency, durability, and high barriers to resistance. In patients who experience virologic failure during their first PI-based regimen, few or no PI mutations are detected at failure. Each PI has its own virologic potency, adverse effect profile, and pharmacokinetic properties. The characteristics, advantages, and disadvantages of each PI can be found in [Table 6](#) and [Appendix B, Table 3](#). In selecting a boosted PI-based regimen for a treatment-naïve patient, clinicians should consider factors such as dosing frequency, food requirements, pill burden, daily ritonavir dose, drug interaction potential, baseline hepatic function, toxicity profile of the individual PI, and pregnancy status. (See “[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#)” for specific recommendations in pregnancy.)

A number of metabolic abnormalities, including dyslipidemia and insulin resistance, have been associated with PI use. The currently available PIs differ in their propensity to cause these metabolic complications, which are also dependent on the dose of ritonavir used as a pharmacokinetic boosting agent. These complications may result in adverse long-term consequences, such as increased cardiovascular events. In an analysis from the D:A:D study, cumulative use of lopinavir/ritonavir or indinavir was associated with an increased risk of myocardial infarction, coronary heart disease, and stroke [33]. In another observational analysis from a French cohort, use of amprenavir or fosamprenavir (with or without ritonavir), or use of lopinavir/ritonavir, was associated with a higher rate of myocardial infarction [34]. It should be noted that in both studies, there were too few patients receiving ritonavir-boosted atazanavir or darunavir to be included in the analysis.

The potent inhibitory effect of ritonavir on the cytochrome P450 3A4 isoenzyme has allowed the addition of low-dose ritonavir to other PIs (with the exception of nelfinavir) as a pharmacokinetic booster to increase drug exposure and prolong plasma half-lives of the active PI. This allows for reduced dosing frequency and/or pill burden, which may improve overall adherence to the regimen. The increased trough concentration (C_{min}) may improve the antiretroviral activity of the active PI, which can be beneficial when the patient harbors HIV strains with reduced susceptibility to the PI [35-37], and also may contribute to the lower risk of resistance upon virologic failure compared to unboosted PIs. The drawbacks associated with this strategy are the potential for increased risk of hyperlipidemia and a greater potential of drug-drug interactions from the addition of ritonavir. In patients without pre-existing PI resistance, there is growing support for the use of once-daily boosted PI regimens that use only 100mg per day of ritonavir, because they tend to cause fewer gastrointestinal side effects and less metabolic toxicity than regimens that use ritonavir at a dose of 200mg per day. In the case of ritonavir-boosted darunavir (800/100mg once daily) and atazanavir (300/100mg once daily), there are large head-to-head trials demonstrating noninferiority or superiority compared with lopinavir/ritonavir, with less gastrointestinal and lipid toxicity.

The Panel uses the following criteria to distinguish between preferred versus alternative PIs in treatment-naïve subjects: (1) demonstrated superior or noninferior virologic efficacy when compared with at least one other PI-based regimen, with at least published 48-week data; (2) ritonavir-boosted PI with no more than 100mg of ritonavir per day; (3) once-daily dosing; (4) low pill count; and (5) good tolerability. Using these criteria, the Panel recommends atazanavir + ritonavir (once daily) (AI) and darunavir + ritonavir (once daily) (AI) as preferred PIs.

Preferred PI Components (in alphabetical order, by active PI component)

Ritonavir-Boosted Atazanavir (AI). Ritonavir boosting of atazanavir, given as two pills once daily, enhances the concentrations of atazanavir and improves virologic activity compared with unboosted atazanavir in a clinical trial [38].

The CASTLE study compared once-daily atazanavir/ritonavir with twice-daily lopinavir/ritonavir, each in combination with tenofovir/emtricitabine, in 883 antiretroviral-naïve participants. In this open-label, noninferiority study, analysis at 48 weeks [39] and at 96 weeks [40] showed similar virologic and CD4 T-cell count responses of the two regimens. More hyperbilirubinemia and less gastrointestinal toxicity were seen in the ritonavir-boosted atazanavir arm. This study supports the designation of boosted atazanavir in combination with tenofovir/emtricitabine as a preferred regimen.

The main adverse effect associated with atazanavir/ritonavir is indirect hyperbilirubinemia, with or without jaundice or scleral icterus, but without concomitant hepatic transaminase elevations. Several cases of nephrolithiasis have been reported in patients who received ritonavir-boosted or unboosted atazanavir [41]. Atazanavir/ritonavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H₂ antagonists, and particularly proton pump inhibitors, may impair absorption of atazanavir. [Table 14a](#) provides recommendations for how to use ritonavir-boosted atazanavir with these agents.

Ritonavir-Boosted Darunavir (AI). The ARTEMIS study compared darunavir/ritonavir (800/100mg once daily, three pills per day) with lopinavir/ritonavir (once or twice daily), both in combination with tenofovir/emtricitabine, in a randomized, open-label, noninferiority trial. The study enrolled 689 treatment-naïve participants who had a median CD4 count of 225 cells/mm³ and a median plasma HIV RNA level of 4.85 log₁₀copies/mL. At 48 weeks, darunavir/ritonavir was noninferior to lopinavir/ritonavir (p<0.001). The virologic response rates were lower in the lopinavir/ritonavir arm among those participants whose baseline HIV RNA levels were >100,000 copies/mL (p<0.05). Grades 2 to 4 adverse events, primarily diarrhea, were seen more frequently in lopinavir/ritonavir recipients (p<0.01) [42]. At 96 weeks, virologic response to darunavir/ritonavir was superior to response to lopinavir/ritonavir (p=0.012) [43].

Alternative PI Components (in alphabetical order, by active PI component)

Ritonavir-Boosted Fosamprenavir (once or twice daily) (BI). Ritonavir-boosted fosamprenavir is recommended as an alternative PI. The KLEAN trial compared twice-daily ritonavir-boosted fosamprenavir with lopinavir/ritonavir, each in combination with abacavir and lamivudine, in treatment-naïve patients. At weeks 48 and 144, similar percentages of subjects achieved viral loads of <400 copies/mL [44–45]. Clinical and laboratory adverse events did not differ between the regimens. In this study of treatment-naïve participants, twice-daily ritonavir-boosted fosamprenavir was noninferior to twice-daily lopinavir/ritonavir. Metabolic adverse effects occurred at similar frequencies with boosted fosamprenavir as with lopinavir/ritonavir in the KLEAN study. Based on the above criteria for preferred PIs, which favor once-daily regimens with no more than 100mg/day of ritonavir, twice-daily fosamprenavir is now considered an alternative choice.

In a study comparing once-daily ritonavir-boosted fosamprenavir (1,400 mg with ritonavir 200mg once daily) with nelfinavir [46], similar virologic efficacy was reported in both arms. A comparative trial of once-daily ritonavir-boosted fosamprenavir (1,400/100mg) with once-daily ritonavir-boosted atazanavir, both in combination with tenofovir/emtricitabine, was conducted in 106 antiretroviral-naïve participants [47]. Similar virologic and CD4 T-cell benefits were seen with both regimens. The small sample size of this study precludes the assessment of superior or noninferior virologic efficacy required for a preferred PI. Collectively, fosamprenavir/ritonavir regimens, with once- or twice-daily dosing, are recommended as alternatives.

Lopinavir/Ritonavir (coformulated) (BI). Lopinavir/ritonavir is the only available coformulated boosted PI. In PI-naïve patients, it can be given once or twice daily. However, the need for 200mg/day of ritonavir, and the higher rate of gastrointestinal side effects and hyperlipidemia when compared with boosted PIs using ritonavir 100mg/day, make it an alternative rather than preferred PI for PI-naïve patients. Several clinical trials show that regimens containing twice-daily lopinavir/ritonavir with two NRTIs have virologic activity in treatment-naïve patients. Early studies showed that lopinavir/ritonavir was superior to nelfinavir in maintaining undetectable viral loads [48]. A 7-year follow-up study of lopinavir/ritonavir and two NRTIs showed sustained virologic suppression in patients who were maintained on the originally assigned regimen [49]. Results of clinical trials that compared lopinavir/ritonavir with ritonavir-boosted atazanavir, darunavir, fosamprenavir, or saquinavir are discussed in the respective sections of this document. The ACTG 5142 study showed that the regimen of twice-daily lopinavir/ritonavir plus two NRTIs was associated with decreased virologic efficacy when compared with efavirenz plus two NRTIs. However, the CD4 T-cell

count response was greater with lopinavir/ritonavir, and there was less drug resistance associated with virologic failure [4].

Several trials have evaluated different formulations and dosages of lopinavir/ritonavir administered once or twice daily [42, 50-52]. In the largest trial that compared once-daily with twice-daily lopinavir/ritonavir, both in combination with tenofovir and emtricitabine, 664 treatment-naïve participants were randomized to receive once- or twice-daily soft-gel capsules or once- or twice-daily tablets for 8 weeks; at Week 8, all participants received the tablet formulation and maintained their same randomized dosing schedule [53]. At week 48, 77% of once-daily and 76% of twice-daily lopinavir/ritonavir recipients achieved viral loads <50 copies/mL. Rates of moderate to severe drug-related diarrhea were similar between the two groups. In addition to diarrhea, major adverse effects of lopinavir/ritonavir include insulin resistance and hyperlipidemia, especially hypertriglyceridemia; these require pharmacologic management in some patients. In the D:A:D and French observational cohorts, cumulative use of lopinavir/ritonavir was associated with a slightly increased risk of myocardial infarction [33-34]. Once-daily lopinavir/ritonavir should not be used in patients who have HIV mutations associated with PI resistance, because higher lopinavir trough levels may be required to suppress resistant virus. Lopinavir/ritonavir given twice daily is the preferred PI for use in pregnant women [54]. Once-daily dosing should not be used in this situation, especially during the third trimester, when lopinavir levels are expected to decline. For more detailed information regarding antiretroviral drug choices and related issues in pregnancy, see [“Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States”](#) [54].

Ritonavir-Boosted Saquinavir (BI). The GEMINI study compared saquinavir/ritonavir (1,000/100mg twice daily) with lopinavir/ritonavir, both given twice daily, in combination with tenofovir/emtricitabine given once daily, in 337 treatment-naïve participants who were monitored over 48 weeks. Similar levels of viral suppression (64.7% vs. 63.5%) and increases in CD4 counts were seen in both arms [55]. Triglyceride levels were significantly higher in the lopinavir/ritonavir arm. The higher pill burden (6 pills per day), need for twice-daily dosing, and use of 200mg of ritonavir make ritonavir-boosted saquinavir an alternative PI for treatment-naïve patients.

Acceptable PI-Based Component

Atazanavir (BI). Unboosted atazanavir is given once daily and has fewer adverse effects on lipid profiles than other available PIs. Three studies compared atazanavir-based combination regimens to either nelfinavir- or efavirenz-based regimens. These studies established similar virologic efficacy among atazanavir 400mg once daily and both comparator treatment groups in antiretroviral-naïve patients after 48 weeks of therapy [5, 38, 56-57]. The ACTG 5175 trial compared three regimens in treatment-naïve patients. The Data Safety Monitoring Board for this trial recommended that participants be unblinded and switched to alternative therapy if they were randomized to a regimen that consisted of atazanavir + enteric-coated didanosine + emtricitabine because of an inferior virologic response when compared with the other two arms—once-daily efavirenz plus either zidovudine/lamivudine (twice daily) or tenofovir/emtricitabine (once daily) [58]. If unboosted atazanavir is prescribed for a treatment-naïve patient, clinicians should consider using an alternative dual-NRTI backbone other than didanosine + emtricitabine (or lamivudine).

Unboosted atazanavir may be chosen as initial therapy for patients when a once-daily regimen without ritonavir is desired and in patients who have underlying risk factors with which hyperlipidemia may be particularly undesirable. Atazanavir should not be used without ritonavir if tenofovir or efavirenz are used concomitantly because these two agents have been shown to lower the concentrations of atazanavir. Atazanavir requires acidic gastric pH for dissolution. Thus, concomitant use of drugs that raise gastric pH, such as antacids, H₂ antagonists, and proton pump inhibitors, may significantly impair its absorption. Proton pump inhibitors should not be used in patients who are taking unboosted atazanavir. H₂ antagonists and antacids should be used with caution and with careful dose separation. (See [Tables 13 and 14a.](#))

PI Component to be Used with Caution

Fosamprenavir (twice daily) (BI). In a study comparing unboosted fosamprenavir given twice daily with nelfinavir, more participants who were randomized to fosamprenavir achieved viral suppression at 48 weeks than those who were assigned to nelfinavir, and greater differences were seen in those who had pretreatment viral loads >100,000 copies/mL [59]. However, virologic failure on unboosted fosamprenavir may select for resistance mutations that confer cross

resistance to darunavir [60-61], a PI with an important role in management of treatment-experienced patients. As such, ritonavir-boosted fosamprenavir is preferred over unboosted fosamprenavir, and the unboosted strategy should be used with caution.

INSTI-BASED REGIMEN (INSTI + 2 NRTIs)

Raltegravir is an INSTI that was first approved for use in combination antiretroviral regimens for treatment-experienced patients with HIV strains resistant to multiple antiretroviral drugs. It is now approved by the FDA for use in treatment-naïve patients, based on results of STARTMRK, a Phase III study that compared raltegravir (400mg twice daily) to efavirenz (600mg once daily), each in combination with tenofovir/emtricitabine, in treatment-naïve subjects. This multinational double-blind, placebo-controlled study enrolled 563 subjects with plasma HIV-1 RNA levels >5,000 copies/mL. At week 48, similar numbers of subjects achieved HIV-1 RNA levels <50 copies/mL in both groups (86.1% and 81.9% for raltegravir and efavirenz, respectively, $p < 0.001$ for noninferiority). CD4 cell counts rose by $189/\text{mm}^3$ in the raltegravir group versus $163/\text{mm}^3$ in the efavirenz group. Serious adverse events occurred at a similar frequency in both groups [6]. At 96 weeks, virologic and immunologic responses remained similar in both groups with no new safety concerns identified [12]. Based on these data, the Panel recommends raltegravir + tenofovir + emtricitabine (or lamivudine) as a preferred regimen for treatment-naïve patients **(AI)**.

Comparisons of raltegravir-based regimens with other regimens in treatment-naïve subjects have not yet been reported, and there is less experience with raltegravir than with efavirenz or boosted PIs for initial therapy. In addition, raltegravir has to be administered twice daily, a potential disadvantage when compared with some other regimens. Raltegravir, like efavirenz, has a lower genetic barrier to resistance than ritonavir-boosted PIs, and resistance mutations were observed at approximately the same frequency in the comparative trial. Its use with other dual NRTIs (such as abacavir/lamivudine or zidovudine/lamivudine) may be acceptable, but more definitive data for these regimens are needed **(CIII)**.

DUAL-NRTI OPTIONS AS PART OF INITIAL COMBINATION THERAPY

Summary: Dual-NRTI Components

Dual NRTIs are commonly used in combination with an NNRTI, a PI (usually boosted with ritonavir), or an INSTI. Most dual-NRTI combinations used in clinical practice consist of a primary NRTI plus lamivudine or emtricitabine. Both lamivudine and emtricitabine have few adverse effects and may select for the M184V resistance mutation, which confers high-level resistance to both drugs; a modest decrease in susceptibility to didanosine and abacavir; and improved susceptibility to zidovudine, stavudine, and tenofovir [62].

All NRTIs except didanosine can be taken without food restrictions. Adherence may be additionally improved with once-daily dosing (available for all NRTIs except stavudine and zidovudine) and with fixed-dosage combination products, such as abacavir/lamivudine, tenofovir/emtricitabine (with or without efavirenz), or zidovudine/lamivudine.

The Panel's recommendations on specific dual-NRTI options are made on the basis of virologic potency and durability, short- and long-term toxicities, the propensity to select for resistance mutations, and dosing convenience.

Preferred Dual-NRTI

Tenofovir/Emtricitabine (coformulated) (AI). Tenofovir is a nucleotide analog with potent activity against both HIV and hepatitis B virus (HBV) and with a long intracellular half-life that allows for once-daily dosing. The fixed-dose combinations of tenofovir/emtricitabine and tenofovir/emtricitabine/efavirenz are both administered as one tablet once daily and are designed to improve adherence.

Tenofovir, when used with either lamivudine or emtricitabine as part of an efavirenz-based regimen in treatment-naïve patients, demonstrated potent virologic suppression [17] and was superior to zidovudine/lamivudine in virologic efficacy at up to 144 weeks [63]. In the 934 study, more participants in the zidovudine/lamivudine arm developed loss

of limb fat as assessed by DEXA scans and anemia at 96 and 144 weeks compared with the tenofovir/emtricitabine arm [63]. Emergence of the M184V mutation was less frequent than with zidovudine/lamivudine, and no participant had developed the K65R mutation after 144 weeks of therapy, in contrast to other studies in which tenofovir was combined with lamivudine. Tenofovir with emtricitabine or lamivudine has been studied in combination with several different boosted PIs **and raltegravir** in randomized clinical trials; all such trials demonstrate good virologic benefit [6, 39, 42, 47, 51].

Tenofovir/emtricitabine was compared with abacavir/lamivudine in the ACTG 5202 study [64] and the HEAT trial [65]. Preliminary data from the ACTG trial suggest potential inferior virologic responses in participants randomized to abacavir/lamivudine who had a pretreatment HIV-RNA >100,000 copies/mL. This was not confirmed by the results from HEAT. (See the abacavir/lamivudine section below for more detailed discussion.)

One randomized controlled trial, presented in abstract form, found nevirapine to be noninferior to boosted atazanavir when combined with tenofovir/emtricitabine [25]. Three small studies (n <100) have suggested more virologic failures than would be expected in treatment-naïve participants who receive nevirapine plus tenofovir and either lamivudine or emtricitabine [26-28]. Pending published results from randomized trials, clinicians should closely monitor virologic responses if using this combination **(CIII)**.

Renal impairment, manifested by increases in serum creatinine, glycosuria, hypophosphatemia, and acute tubular necrosis, has been reported with tenofovir use [66-67]. Risk factors may include advanced HIV disease, greater treatment experience, and pre-existing renal impairment [68]. Renal function, urinalysis, and electrolytes should be monitored in patients who are on tenofovir. In patients who have some degree of pre-existing renal insufficiency (creatinine clearance [CrCl] <50 mL/min), tenofovir dosage adjustment is required (see [Appendix B, Table 7](#) for dosage recommendations). However, because no safety and efficacy data that use the dosage adjustment guidelines for renal dysfunction are available, the use of alternative NRTIs (especially abacavir) may be preferred over dose-adjusted tenofovir in this setting.

Tenofovir concentrations can be increased by some PIs, and studies have suggested a greater risk of renal dysfunction when tenofovir is used in PI-based regimens [66, 69-72]. Tenofovir has been used in combination with PIs without renal toxicity in several clinical trials that involved patients who had CrCl >50–60 mL/min.

Tenofovir plus either emtricitabine or lamivudine is the preferred NRTI combination, especially for patients coinfecting with both HIV and HBV because these drugs have activity against both viruses. The use of a single HBV-active NRTI (e.g., lamivudine or emtricitabine) can lead to HBV resistance and is not recommended. (See [Hepatitis B \(HBV\)/HIV Coinfection](#).)

Alternative Dual NRTIs (in alphabetical order)

Abacavir/Lamivudine (coformulated) for Patients Who Test Negative for HLA-B*5701 (BI). Abacavir has the potential for serious hypersensitivity reactions (HSRs). Clinically suspected HSRs have been observed in 5%–8% of patients who start this drug. The risk of this reaction is highly associated with the presence of the HLA-B*5701 allele (see [HLA-B*5701 Screening](#) section) [73-74]. Whenever possible, HLA-B*5701 testing should precede the use of abacavir. Abacavir should not be given to patients who test positive for HLA-B*5701, and based on test results, abacavir hypersensitivity should be noted on the patient's allergy list. Those who test negative are less likely to experience HSR, but they should be counseled about the symptoms of the reaction.

In a comparative trial of abacavir/lamivudine and zidovudine/lamivudine (both given twice daily and combined with efavirenz), participants from both arms achieved similar virologic responses. The abacavir-treated participants experienced a greater CD4 T-cell increase at 48 weeks [75]. The fixed-dose combination of abacavir/lamivudine allows for one-pill, once-daily dosing.

The ACTG 5202 study, a randomized controlled trial in more than 1,800 participants, evaluated the efficacy and safety of abacavir/lamivudine versus tenofovir/emtricitabine when used in combination with either efavirenz or ritonavir-boosted atazanavir. Treatment randomization was stratified based on a screening HIV RNA of <100,000 copies/mL or ≥100,000 copies/mL. An independent Data Safety Monitoring Board recommended early termination

of the $\geq 100,000$ copies/mL stratification group because of a significantly shorter time to study-defined virologic failure in the abacavir/lamivudine arm compared with the $\geq$ tenofovir/emtricitabine arm [64]. Participants who had HIV RNA levels $<100,000$ copies/mL at study screening remain randomized and on study. In another study (HEAT), 688 participants received abacavir/lamivudine or tenofovir/emtricitabine in combination with once-daily lopinavir/ritonavir. A subgroup analysis according to baseline HIV RNA of $<100,000$ copies/mL or $\geq 100,000$ copies/mL yielded similar percentages of participants with HIV RNA <50 copies/mL at 96 weeks for the two regimens (63% vs. 58% for those who had $<100,000$ copies/mL and 56% vs. 58% for those who had $>100,000$ copies/mL, respectively) [65].

There have been concerns regarding the potential cardiovascular risks of abacavir-containing regimens. The D:A:D study, a large, multinational, observational cohort, found that recent (within 6 months) or current use of abacavir predicted an increased risk of MI (relative risk [RR] 1.9; 95% CI, 1.5–2.6) [76]. The heightened risk of MI was accentuated in participants who had pre-existing cardiac risk factors. In a subsequent analysis from the same study, such an association was not seen with recent use of tenofovir (RR 1.14; 95% CI, 0.85–1.52) [33]. Several additional studies have addressed the possible association between abacavir use and cardiovascular risk [34, 76–81], and some have explored possible biologic mechanisms underlying such an association [82–83]. In a pooled analysis of 52 clinical trials involving more than 9,500 participants who received abacavir, no increase risk of MI was found [84]. Thus, no consensus has been reached yet, either on the association or a possible mechanism. Channeling bias may sometimes interfere with the causal evaluation of medication effects due to the differential allocation of medications to patient groups with varying risk factors for disease outcomes [85]. It is possible that channeling bias may, in part, account for some of the differences observed among the reported studies. However, pending additional data, abacavir/lamivudine should be used with caution in individuals who have plasma HIV RNA levels $\geq 100,000$ copies/mL as well as in persons at higher risk of cardiovascular disease. However, the combination of abacavir/lamivudine remains a good alternative dual-NRTI option for some treatment-naïve patients.

Zidovudine/Lamivudine (coformulated) (BI). The dual-NRTI combination of zidovudine/lamivudine has extensive durability, safety, and tolerability experience [3, 5, 7, 18, 86–88]. A fixed-dose combination of zidovudine/lamivudine is available for one-tablet, twice-daily dosing. Selection of the lamivudine-associated M184V mutation has been associated with increased susceptibility to zidovudine. In a comparative trial of abacavir/lamivudine versus zidovudine/lamivudine (both given twice daily and combined with efavirenz), even though virologic responses were similar in both arms, the CD4 T-cell count increase was greater in the abacavir/lamivudine–treated patients than in the zidovudine/lamivudine–treated patients [75].

Bone marrow suppression, manifested by macrocytic anemia and/or neutropenia, is seen in some patients. Zidovudine also is associated with gastrointestinal toxicity, fatigue, and possibly mitochondrial toxicity, including lactic acidosis/hepatic steatosis and lipoatrophy. In the 934 study, participants who took zidovudine had significantly less limb fat at 96 and 144 weeks than those who took tenofovir, and there was a significant loss of fat among zidovudine recipients between 48, 96, and 144 weeks [63]. In ACTG 5142, limb fat was lowest in patients treated with stavudine, but those treated with zidovudine had significantly less limb fat than those treated with tenofovir [9]. Primarily because of its greater toxicity compared with tenofovir/emtricitabine, zidovudine/lamivudine is now considered an alternative rather than a preferred dual-NRTI option (BI).

Zidovudine/lamivudine remains the preferred option in pregnant women. This dual NRTI has the most pharmacokinetic, safety, and efficacy data for both mother and newborn. For more detailed information regarding antiretroviral drug choices and related issues in pregnancy, see “[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#)” [54], available at <http://aidsinfo.nih.gov>.

Acceptable Dual NRTI

Didanosine + (Emtricitabine or Lamivudine) (CI). The FTC-301A trial tested didanosine + emtricitabine with efavirenz in treatment-naïve patients and demonstrated potent virologic suppression (78% of patients achieved HIV RNA <50 copies/mL at 48 weeks) [89]. The GESIDA 3903 study compared didanosine/lamivudine with zidovudine/lamivudine, and both were given with food and were combined with efavirenz [90]. At 48 weeks, virologic

response for didanosine/lamivudine was noninferior to zidovudine/lamivudine, with 70% and 63% of the participants, respectively, achieving HIV RNA <50 copies/ml.

The ACTG 5175 trial compared three regimens in treatment-naïve patients. The Data Safety Monitoring Board for this trial recommended that participants be unblinded and switched to alternative therapy if they were randomized to a regimen that consisted of atazanavir + enteric-coated didanosine + emtricitabine because of an inferior virologic response when compared with the other two arms (once-daily efavirenz plus either zidovudine/lamivudine twice daily, or tenofovir/emtricitabine once daily) [58]. Alternative PIs should be considered if didanosine + (emtricitabine or lamivudine) are used. Didanosine use also is associated with an increased risk of pancreatitis, peripheral neuropathy, other mitochondria-associated toxicities, and possibly noncirrhotic portal hypertension [91]. In the D:A:D study of MI risk, the use of didanosine within the previous 6 months was associated with an increased risk of MI (RR 1.5; 95% CI, 1.1–2.1), when compared with the use of other NRTIs [76]. This increase in cardiovascular risk was not seen in the SMART study [92].

Based on the limited clinical trial experience with the use of didanosine + lamivudine (or emtricitabine) with another antiretroviral drug other than efavirenz, the unfavorable results from ACTG 5175, and the many side effects associated with didanosine, the Panel considers it an acceptable but inferior option, and only to be used with efavirenz (CI).

NRTIs and Hepatitis B. Three of the current NRTIs—emtricitabine, lamivudine, and tenofovir—have activity against HBV. Most coinfecting patients should use coformulated tenofovir/emtricitabine (or tenofovir + lamivudine) as their nucleoside backbone to provide additional activity against HBV and to avoid lamivudine/emtricitabine resistance. It is important to note that patients who have HBV/HIV coinfection may be at risk of acute exacerbation of hepatitis after initiation or upon discontinuation of these drugs [93–95]. Thus, these patients should be monitored closely for clinical or chemical hepatitis if these drugs are initiated or discontinued. (See [Hepatitis B \(HBV\)/HIV Coinfection](#) and [Initiating Antiretroviral Therapy](#) sections.)

ALL-NRTI REGIMENS

A triple-NRTI combination regimen has some potential advantages: fewer drug-drug interactions, low pill burden, availability of a fixed-dose combination (e.g., zidovudine/lamivudine/abacavir), and the ability to spare patients from potential adverse effects seen with PIs and NNRTIs. However, several clinical trials that studied triple-NRTI regimens have shown suboptimal virologic activity [18–19, 96–99], and current PI- and NNRTI-based regimens have improved convenience and tolerability compared with older regimens.

Abacavir/Lamivudine/Zidovudine (coformulated). Abacavir/lamivudine/zidovudine is the only triple-NRTI combination for which randomized, controlled trials are available. Abacavir/lamivudine/zidovudine demonstrated comparable antiretroviral activity to indinavir-based [87–88] and nelfinavir-based regimens [99] but was inferior virologically to an efavirenz-based regimen [18]. This combination is **generally not recommended (BI)** and should be used only when a preferred, an alternative, or an acceptable NNRTI-, PI-, or INSTI- based regimen is less desirable because of concerns about toxicities, drug interactions, or regimen complexity.

Zidovudine/Lamivudine + Tenofovir. The DART study demonstrated that the combination of zidovudine/lamivudine + tenofovir has antiviral activity [100]; however, comparative data with standard regimens are not available and therefore this combination **cannot be recommended** in routine clinical practice (BIII).

Zidovudine + Lamivudine + Abacavir + Tenofovir. A quadruple-NRTI regimen of zidovudine + lamivudine + abacavir + tenofovir first showed comparable virologic responses to an efavirenz-based regimen in a small pilot study [101]. A larger study randomized 322 subjects to receive tenofovir/emtricitabine combined with efavirenz, atazanavir/ritonavir, or a quadruple-NRTI regimen with zidovudine and abacavir. Although the threshold of noninferiority for the protocol-defined virologic response was satisfied by the quadruple-NRTI regimen, the proportion of patients reaching HIV RNA ≤50 copies/ml was significantly lower with the quadruple-NRTI regimen and the rate of serious toxicity was twice as high as that observed with the efavirenz-based regimen [102]. Thus, this regimen **cannot be recommended** at this time (BI).

OTHER TREATMENT OPTION UNDER INVESTIGATION: INSUFFICIENT DATA TO RECOMMEND

Maraviroc-Based Regimen. The MERIT study compared the CCR5 antagonist maraviroc with efavirenz, both in combination with zidovudine/lamivudine, in a randomized, double-blind trial in treatment-naïve participants [103]. Only participants who had CCR5 virus and no evidence of resistance to any drugs used in the study were enrolled (n = 633). At 48 weeks, virologic suppression (defined as HIV RNA <400 copies/mL) was seen in 75.3% of maraviroc recipients and in 78.9% of efavirenz recipients, and HIV RNA <50 copies/mL was observed in 65.2% of maraviroc recipients and in 69.2% of efavirenz recipients. The HIV RNA <50 copies/mL results did not meet the criteria set by the investigators to demonstrate noninferiority for maraviroc in this study. CD4 count increased by an average of 170 cells/mm³ in the maraviroc arm and by an average of 143 cells/mm³ in the efavirenz arm. Through 48 weeks, more participants discontinued maraviroc because of lack of efficacy (11.9% vs. 4.2%), whereas fewer participants discontinued maraviroc because of toxicity (4.2% vs. 13.6%). Follow-up results at 96 weeks demonstrated durable responses [104]. Based on the results, the U.S. FDA recently approved maraviroc for use in regimens for treatment-naïve patients. Our guidelines will provide further recommendations regarding maraviroc-based regimens in the next revision.

Table 6. Advantages and Disadvantages of Antiretroviral Components Recommended as Initial Antiretroviral Therapy (Updated December 1, 2009)

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ARV Class	ARV Agent(s)	Advantages	Disadvantages
NNRTI (in alphabetical order)		NNRTI Class Advantages: - Saves PIs and RAL for future use - Long half-lives	NNRTI Class Disadvantages: - Low genetic barrier to resistance (single mutation confers resistance for efavirenz, nevirapine, and delavirdine): greater risk of resistance at the time of failure or treatment interruption - Potential for cross resistance - Skin rash - Potential for CYP450 drug interactions (see Tables 13, 14b, and 15b) - Transmitted resistance to NNRTIs more common than resistance to PIs
	Efavirenz (EFV)	- Virologic responses equivalent or superior to all comparators to date - Lowest pill burden; once-daily dosing - Fixed-dose combination with tenofovir + emtricitabine	- Neuropsychiatric side effects - Teratogenic in nonhuman primates, and several cases of neural tube defect reported in infants of women with first-trimester exposure. EFV is contraindicated in first trimester of pregnancy; avoid use in women with pregnancy potential.
	Nevirapine (NVP)	- No food effect - Fewer lipid effects than EFV	- Higher incidence of rash than with other NNRTIs, including rare but serious hypersensitivity reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis) - Higher incidence of hepatotoxicity than with other NNRTIs, including serious and even fatal cases of hepatic necrosis - Contraindicated in patients with moderate or severe (Child Pugh B or C) hepatic impairment - Treatment-naïve patients with high pre-NVP CD4 counts (>250 cells/mm³ for females, >400 cells/mm³ for males) are at higher risk of symptomatic hepatic events. NVP not recommended in these patients unless benefit clearly outweighs risk. - Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials - Fewer clinical trial data than with EFV
PI (in alphabetical order)		PI Class Advantages: - Save NNRTIs for future use - Higher genetic barrier to resistance - PI resistance uncommon with failure (boosted PIs)	PI Class Disadvantages: - Metabolic complications (e.g., dyslipidemia, insulin resistance, hepatotoxicity) - Gastrointestinal adverse effects - CYP3A4 inhibitors and substrates: potential for drug interactions (more pronounced with RTV-based regimens) (See Tables 13–14a.)
	Atazanavir (unboosted) (ATV)	- Fewer adverse effects on lipids than other PI - Once-daily dosing - Low pill burden (two pills per day) - Good GI tolerability - Signature mutation (I50L) not associated with broad PI cross resistance	- Indirect hyperbilirubinemia sometimes leading to jaundice or scleral icterus - PR interval prolongation: generally inconsequential unless combined with another drug with similar effect - Cannot be co-administered with TDF, EFV, or NVP (see ATV/r) - Nephrolithiasis - Skin rash - Food requirement - Absorption depends on food and low gastric pH (See Table 14a for detailed information regarding interactions with H2 antagonists, antacids, and proton pump inhibitors [PPIs].)
	Atazanavir/ritonavir (ATV/r)	- RTV boosting: higher trough ATV concentration and greater antiviral effect - Once-daily dosing - Lowest pill burden (two pills per day)	- More adverse effects on lipids than unboosted ATV - More hyperbilirubinemia and jaundice than unboosted ATV - Food requirement - Absorption depends on food and low gastric pH (See Table 14a for interactions with H2 antagonists, antacids, and PPIs.) - RTV boosting required with TDF and EFV. With EFV, use ATV 400mg and RTV 100mg once daily (PI-naïve patients only). - Should not be coadministered with NVP

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	Darunavir/ritonavir (DRV/r)	Once-daily dosing	- Skin rash - Food requirement
	Fosamprenavir (unboosted) (FPV)	No food effect	- Skin rash - Potential for PI resistance with failure, including emergence of mutations that can cause DRV cross resistance
	Fosamprenavir/ritonavir (FPV/r)	- Twice-daily dosing resulted in efficacy comparable to LPV/r - RTV boosting: higher trough amprenavir concentration and greater antiviral effect - Once-daily dosing possible with RTV 100mg or 200mg daily - No food effect	- Skin rash - Hyperlipidemia - Once-daily dosing results in lower amprenavir concentrations than twice-daily dosing - For FPV 1,400mg + RTV 200mg: Requires 200mg of ritonavir and no coformulation - Fewer data on FPV 1,400mg + RTV 100mg dose than with DRV/r and ATV/r
	Lopinavir/ritonavir (LPV/r)	- Coformulated - Once- or twice-daily dosing in treatment-naïve patients - No food requirement - Recommended PI in pregnant women (twice daily only) - Greater CD4 T-cell count increase than with EFV-based regimens	- Requires 200mg per day of ritonavir - Lower drug exposure in pregnant women—may need dose increase in third trimester - Once-daily dosing not recommended in pregnant women - Once-daily dosing: lower trough concentration than twice-daily dosing - Possible higher risk of myocardial infarction associated with cumulative use of LPV/r - PR and QT interval prolongation have been reported. Use with caution in patients at risk of cardiac conduction abnormalities or receiving other drugs with similar effect.
	Saquinavir + ritonavir (SQV/r)	- Efficacy similar to LPV/r with less hyperlipidemia - Alternative PI in pregnant women	- Highest pill burden among available PI regimens (6 pills per day) - Requires 200mg of ritonavir - Food requirement
INSTI	Raltegravir (RAL)	- Virologic response noninferior to EFV - Fewer drug-related adverse events and lipid changes than EFV - No food effect - Fewer drug-drug interactions than PI- or NNRTI-based regimens	- Less long-term experience in treatment-naïve patients than with boosted PI- or NNRTI-based regimens - Twice-daily dosing - Lower genetic barrier to resistance than with boosted PI-based regimens - No data with NRTIs other than TDF/FTC in treatment-naïve patients
Dual NRTIs		Dual-NRTI Class Advantage: Established backbone of combination antiretroviral therapy	Dual-NRTI Class Disadvantage: Rare but serious cases of lactic acidosis with hepatic steatosis reported (d4T>ddI=ZDV>TDF=ABC=3TC=FTC)
Dual-NRTI pairs (in alphabetical order)	Abacavir + lamivudine (ABC/3TC)	- Virologic response noninferior to ZDV/3TC - Better CD4 T-cell count response than with ZDV/3TC - Once-daily dosing - Coformulation - No food effect - No cumulative TAM-mediated resistance	- Potential for abacavir hypersensitivity reaction (HSR) in patients with HLA-B*5701 - Potential for increased cardiovascular events, especially in patients with cardiovascular risk factors - Inferior virologic responses when compared with TDF/FTC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study.
	Didanosine + (lamivudine or emtricitabine) (ddI + [3TC or FTC])	- Once-daily dosing - No cumulative TAM-mediated resistance	- Peripheral neuropathy, pancreatitis - Reports of noncirrhotic portal hypertension - Food effect; must be taken on an empty stomach - Requires dosing separation from some PIs - Increase in toxicities when used with ribavirin, tenofovir, stavudine, or hydroxyurea - Preliminary data showed inferior virologic responses of ATV/ddI/FTC when compared with EFV/ZDV/3TC or EFV/TDF/FTC—combination of ATV/ddI/FTC should be avoided.

ARV Class	ARV Agent(s)	Advantages	Disadvantages
	Tenofovir/emtricitabine (or lamivudine) (TDF/FTC or TDF + 3TC)	• Better virologic responses than with ZDV/3TC • Better virologic responses than with ABC/3TC in patients with baseline HIV RNA >100,000 copies/mL in ACTG 5202 study; however, this was not seen in the HEAT study. • Once-daily dosing • No food effect • Coformulated (TDF/FTC) and (EFV/TDF/FTC) • No cumulative TAM-mediated resistance	• Potential for renal impairment • Early virologic failure of NVP + TDF + (FTC or 3TC) in small clinical trials • Potential for decrease in bone mineral density
	Zidovudine/lamivudine (ZDV/3TC)	• Coformulated (ZDV/3TC and ZDV/3TC/ABC) • No food effect (although better tolerated with food) • Preferred 2 NRTI in pregnant women	• Bone marrow suppression, especially anemia and neutropenia • Gastrointestinal intolerance, headache • Mitochondrial toxicity, including lipoatrophy, lactic acidosis, hepatic steatosis • Inferior to TDF/FTC in combination with EFV • Diminished CD4 T-cell responses compared with ABC/3TC

Table 7. Antiretroviral Components Not Recommended as Initial Therapy
(Updated December 1, 2009)

Antiretroviral drugs or components (in alphabetical order)	Reasons for <u>not</u> recommending as initial therapy
Abacavir/lamivudine/zidovudine (coformulated) as triple-NRTI combination regimen (BI)	• Inferior virologic efficacy
Abacavir + lamivudine + zidovudine + tenofovir as quadruple NRTI combination (BI)	• Inferior virologic efficacy
Abacavir + didanosine (BIII)	• Insufficient data in treatment-naïve patients
Abacavir + tenofovir (BIII)	• Insufficient data in treatment-naïve patients
Darunavir (unboosted)	• Use without ritonavir has not been studied
Delavirdine (BII)	• Inferior virologic efficacy • Inconvenient (three times daily) dosing
Didanosine + tenofovir (BII)	• High rate of early virologic failure • Rapid selection of resistance mutations • Potential for immunologic nonresponse/CD4 decline
Enfuvirtide (BIII)	• No clinical trial experience in treatment-naïve patients • Requires twice-daily subcutaneous injections
Etravirine (BIII)	• Insufficient data in treatment-naïve patients
Indinavir (unboosted) (BIII)	• Inconvenient dosing (three times daily with meal restrictions) • Fluid requirement
Indinavir (ritonavir-boosted) (BIII)	• High incidence of nephrolithiasis
Nelfinavir (BI)	• Inferior virologic efficacy • High incidence of diarrhea
Ritonavir as sole PI (BIII)	• High pill burden • Gastrointestinal intolerance
Saquinavir (unboosted) (BI)	• Inferior virologic efficacy
Stavudine + lamivudine (BI)	• Significant toxicities including lipoatrophy, peripheral neuropathy, and hyperlactatemia, including symptomatic and life-threatening lactic acidosis, hepatic steatosis, and pancreatitis
Tipranavir (ritonavir-boosted) (BI)	• Inferior virologic efficacy

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What Not to Use (Updated December 1, 2009)

Some antiretroviral regimens or components are not generally recommended because of suboptimal antiviral potency, unacceptable toxicities, or pharmacologic concerns. These are summarized below.

ANTIRETROVIRAL REGIMENS NOT RECOMMENDED

Monotherapy with NRTI. Single-NRTI therapy does not demonstrate potent and sustained antiviral activity and **should not be used (AII)**. For prevention of mother-to-child transmission, zidovudine monotherapy might be considered in certain unusual circumstances in women with HIV RNA < 1,000 copies/mL, although the use of a potent combination regimen is generally preferred. (See “[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#)” [1], available at <http://aidsinfo.nih.gov>.)

Single-drug treatment regimens with a ritonavir-boosted PI, either lopinavir [2], atazanavir [3], or **darunavir** [4-5] are under investigation with mixed results, and **cannot be recommended** outside of a clinical trial at this time.

Dual-NRTI regimens. These regimens **are not recommended** because they have not demonstrated potent and sustained antiviral activity compared with triple-drug combination regimens [6] **(AI)**.

Triple-NRTI regimens. In general, triple-NRTI regimens other than abacavir/lamivudine/zidovudine **(BI)** and possibly zidovudine/lamivudine + tenofovir **(BII)** **should not be used** because of suboptimal virologic activity [7-9] or lack of data **(AI)**.

ANTIRETROVIRAL COMPONENTS NOT RECOMMENDED

Atazanavir + indinavir. Both of these PIs can cause grade 3 to 4 hyperbilirubinemia and jaundice. Additive adverse effects may be possible when these agents are used concomitantly. Therefore, these two PIs **are not recommended** for combined use **(AIII)**.

Didanosine + stavudine. The combined use of didanosine and stavudine as a dual-NRTI backbone can result in a high incidence of toxicities, particularly peripheral neuropathy, pancreatitis, and lactic acidosis [10-13]. This combination has been implicated in several deaths of HIV-infected pregnant women secondary to severe lactic acidosis with or without hepatic steatosis and pancreatitis [14]. Therefore, the combined use of didanosine and stavudine **is not recommended (AII)**.

Two-NNRTI combinations. In the 2NN trial, treatment-naïve participants were randomized to receive once- or twice-daily nevirapine versus efavirenz versus efavirenz plus nevirapine, all combined with stavudine and lamivudine [15]. A higher frequency of clinical adverse events that led to treatment discontinuation was reported in participants randomized to the two-NNRTI arm. Both efavirenz and nevirapine may induce metabolism of etravirine, which leads to reduction in etravirine drug exposure [16]. Based on these findings, the Panel **does not recommend using two NNRTIs in combination in any regimen (AI)**.

Efavirenz in first trimester of pregnancy and in women with significant childbearing potential. Efavirenz use was associated with significant teratogenic effects in nonhuman primates at drug exposures similar to those representing human exposure. Several cases of congenital anomalies have been reported after early human gestational exposure to efavirenz [17-18]. Efavirenz **should be avoided** in pregnancy, particularly during the first trimester, and in women of childbearing potential who are trying to conceive or who are not using effective and consistent contraception **(AIII)**. If no other antiretroviral options are available for the woman who is pregnant or at risk of becoming pregnant, the provider should consult with a clinician who has expertise in both HIV infection and pregnancy. (See “[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](#)” [1], available at <http://aidsinfo.nih.gov>.)

Emtricitabine + lamivudine. Both of these drugs have similar resistance profiles and have minimal additive antiviral activity. Inhibition of intracellular phosphorylation may occur *in vivo*, as seen with other dual-cytidine analog combinations [19]. These two agents **should not be used** as a dual-NRTI combination **(AIII)**.

Etravirine + unboosted PI. Etravirine may induce the metabolism and significantly reduce the drug exposure of unboosted PIs. Appropriate doses of the PIs have not been established [16] **(AII)**.

Etravirine + ritonavir-boosted atazanavir or fosamprenavir. Etravirine may alter the concentrations of these PIs. Appropriate doses of the PIs have not been established [16] **(AII)**.

Etravirine + ritonavir-boosted tipranavir. Ritonavir-boosted tipranavir significantly reduces etravirine concentrations. These drugs **should not be coadministered** [16] **(AII)**.

Nevirapine initiated in treatment-naïve women with CD4 counts >250 cells/mm³ or in treatment-naïve men with CD4 counts >400 cells/mm³. Greater risk of symptomatic hepatic events, including serious and life-threatening events, have been observed in these patient groups. Nevirapine **should not be initiated** in these patients **(BI)** unless the benefit clearly outweighs the risk [20-22]. Patients who experience CD4 count increases to levels above these thresholds as a result of antiretroviral therapy can be safely switched to nevirapine [23].

Unboosted darunavir, saquinavir, or tipranavir. The virologic benefit of these PIs has been demonstrated only when they were used with concomitant ritonavir. Therefore, use of these agents as part of a combination regimen **without ritonavir is not recommended (AII)**.

Stavudine + zidovudine. These two NRTIs **should not be used** in combination because of antagonism demonstrated *in vitro* [24] and *in vivo* [25] **(AII)**.

Table 8. Antiretroviral Regimens or Components That Should Not Be Offered At Any Time
(Updated January 29, 2008)

	Rationale	Exception
Antiretroviral Regimens <u>Not</u> Recommended		
Monotherapy with NRTI (AII)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception ¹
Dual-NRTI regimens (AI)	• Rapid development of resistance • Inferior antiretroviral activity when compared with combination of three or more antiretrovirals	• No exception ²
Triple-NRTI regimens (AI) except for abacavir/zidovudine/lamivudine (BI) or possibly tenofovir + zidovudine/lamivudine (BII)	• High rate of early virologic nonresponse seen when triple-NRTI combinations, including ABC/TDF/3TC or TDF/ddI/3TC, were used as initial regimen in treatment-naïve patients • Other triple-NRTI regimens have not been evaluated	• Abacavir/zidovudine/lamivudine (BI), and possibly tenofovir + zidovudine/lamivudine (BII), in selected patients in whom other combinations are not desirable
Antiretroviral Components <u>Not</u> Recommended as Part of an Antiretroviral Regimen		
Atazanavir + indinavir (AIII)	• Potential additive hyperbilirubinemia	• No exception
Didanosine + stavudine (AII)	• High incidence of toxicities: peripheral neuropathy, pancreatitis, and hyperlactatemia • Reports of serious, even fatal, cases of lactic acidosis with hepatic steatosis with or without pancreatitis in pregnant women	• When no other antiretroviral options are available and potential benefits outweigh the risks (BIII)
2-NNRTI combination (AI)	• When EFV combined with NVP, higher incidence of clinical adverse events seen when compared to either EFV- or NVP-based regimen. • Both EFV and NVP may induce metabolism and may lead to reductions in efavirenz (ETR) exposure; thus, they should not be used in combination with ETR.	• No exception
Efavirenz in first trimester of pregnancy or in women with significant child-bearing potential (AIII)	• Teratogenic in nonhuman primates	• When no other antiretroviral options are available and potential benefits outweigh the risks (BIII)
Emtricitabine + lamivudine (AIII)	• Similar resistance profiles • No potential benefit	• No exception
Etravirine + unboosted PI (AII)	• Etravirine may induce metabolism of these PIs, appropriate doses not yet established	• No exception
Etravirine + ritonavir-boosted atazanavir or fosamprenavir (AII)	• Etravirine may alter the concentrations of these PIs; appropriate doses not yet established	• No exception
Etravirine + ritonavir-boosted tipranavir (AII)	• Etravirine concentration may be significantly reduced by ritonavir-boosted tipranavir	• No exception
Nevirapine in treatment-naïve women with CD4 >250 or men with CD4 >400 (BI)	• High incidence of symptomatic hepatotoxicity	• If no other antiretroviral option available; if used, patients should be closely monitored
Stavudine + zidovudine (AII)	• Antagonistic effect on HIV-1	• No exception
Unboosted darunavir, saquinavir, or tipranavir (AII)	• Inadequate bioavailability	• No exception

¹ When constructing an antiretroviral regimen for an HIV-infected pregnant woman, consult “[Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV Transmission in the United States](http://www.aidsinfo.nih.gov)” [1] at <http://www.aidsinfo.nih.gov>.

² When considering an antiretroviral regimen to use in post-exposure prophylaxis, consult “Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis” in *CDC MMWR Recommendations and Reports*. September 30, 2005/54 (RR 09); 1–17 and “Management of Possible Sexual, Injection-Drug-Use, or Other Non-occupational Exposure to HIV, Including Considerations Related to Antiretroviral Therapy” in *CDC MMWR Recommendations and Reports*. January 21, 2005/54 (RR 02); 1–19.

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Management of the Treatment-Experienced Patient

Panel's Recommendations:

- In treatment-experienced patients with suppressed viremia, assess adherence frequently and simplify the regimen when feasible. Change individual antiretroviral drugs to reduce or manage toxicity, as needed.
- Evaluation of antiretroviral treatment failure in a patient should include an assessment of the severity of HIV disease of the patient; the antiretroviral treatment history, including the duration, drugs used, antiretroviral potency and response, adherence history, and drug intolerance/toxicity; the use of concomitant medications with consideration of adverse drug interactions with antiretrovirals; HIV RNA and CD4 T-cell count trends over time; and the results of prior drug resistance testing.
- Optimal virologic response to treatment is maximal virologic suppression (e.g., HIV RNA level <400 copies/mL after 24 weeks, <50 copies/mL after 48 weeks). Persistent low-level viremia (e.g., HIV RNA 50–200 copies/mL) does not necessarily indicate virologic failure or a reason to change treatment.
- Drug resistance testing should be obtained (AI) while the patient is taking the failing antiretroviral regimen (or, if not possible, within 4 weeks of treatment discontinuation).
- The goal of treatment for patients with prior drug exposure and drug resistance is to re-establish maximal virologic suppression, with HIV RNA suppressed to below the limit of detection of a sensitive assay (e.g., <50 copies/mL) (AI).
- The patient's treatment history and the past and current resistance test results should be used to identify fully active agents to design a new regimen (AII). A fully active agent is one that is likely to have antiretroviral activity on the basis of the patient's treatment history, susceptibility on drug resistance testing, and mechanistic class. Assessing and managing a patient who has antiretroviral experience, who exhibits drug resistance, and who is experiencing treatment failure is complex and expert advice is critical and should be sought. Adding at least two (preferably three) fully active agents to an optimized background antiretroviral regimen can provide significant antiretroviral activity (AII).
- Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 response despite virologic suppression.
- For immunologic failure, current medications, untreated coinfection, and serious medical conditions should be assessed.
- There is no consensus for when and how to treat immunologic failure. The immunomodulator interleukin-2 has not demonstrated clinical benefits in randomized trials and is not recommended (AI).
- For some highly treatment experienced patients, maximal virologic suppression is not possible. In this case, antiretroviral therapy should be continued with regimens designed to minimize toxicity, preserve CD4 cell counts, and avoid clinical progression. In this scenario, expert advice is essential and should be sought.

THE TREATMENT-EXPERIENCED PATIENT (Updated December 1, 2009)

Most HIV-infected patients benefit from antiretroviral treatment. In clinical trials and in clinical practice using effective combination regimens, a majority of study participants maintain virologic suppression for at least 3 to 7 years [1-5]. Given our current understanding of viral dynamics during treatment, it is expected that most first-line antiretroviral regimens should be able to suppress virus indefinitely, assuming that the optimal regimen is selected and assuming that the patient can adhere to that regimen indefinitely.

In a patient with virologic suppression on antiretroviral therapy, adherence to antiretroviral drugs should be assessed on an ongoing basis (see [Adherence](#) section). In such patients, antiretroviral regimens should be simplified as much as possible to ensure maximal adherence (see [Regimen Simplification](#) section). The use of newer formulations or coformulations of antiretroviral drugs reduces dosing frequency and pill counts. Changing antiretroviral drugs to reduce or manage toxicity also is reasonable.

However, antiretroviral treatment failure is not uncommon, and it increases the risk of HIV disease progression; therefore, it should be addressed aggressively.

MANAGEMENT OF PATIENTS WITH ANTIRETROVIRAL TREATMENT FAILURE **(December 1, 2009)**

Definitions and Causes of Antiretroviral Treatment Failure

Antiretroviral treatment failure can be defined as a suboptimal response to therapy. Treatment failure is often associated with virologic failure, immunologic failure, and/or clinical progression. Many factors are associated with an increased risk of treatment failure, including:

- Baseline patient factors, such as:
 - starting therapy in earlier years, when less potent regimens or less well tolerated antiretroviral drugs were used,
 - higher pretreatment or baseline HIV RNA level (depending on the specific regimen used),
 - lower pretreatment or nadir CD4 T-cell count,
 - prior AIDS diagnosis,
 - comorbidities (e.g., depression, active substance abuse),
 - presence of drug-resistant virus, and
 - prior treatment failure, with development of drug resistance or cross resistance;
- incomplete medication adherence and missed clinic appointments;
- drug side effects and toxicities;
- suboptimal pharmacokinetics (variable absorption, metabolism, or, theoretically, penetration into reservoirs; food/fasting requirements, adverse drug-drug interactions with concomitant medications);
- suboptimal potency of the antiretroviral regimen;
- **provider experience**, and/or
- other or unknown reasons.

Data from some patient cohorts suggest that suboptimal adherence and toxicity accounted for 28%–40% of treatment failure and regimen discontinuations [6-7]. Treatment failure in an individual patient can occur for multiple reasons.

Assessment of Antiretroviral Treatment Failure and Changing Therapy

In general, the cause of treatment failure should be explored by reviewing the medical history and performing a physical examination to assess for signs of clinical progression.

A medical history review should include:

- change in HIV RNA and CD4 T-cell count over time,
- occurrence of HIV-related clinical events,
- antiretroviral treatment history,
- results of prior resistance testing (if any),
- medication-taking behavior (including adherence to recommended drug doses, dosing frequency, and food/fasting requirements),
- tolerability of the medications,
- concomitant medications (with consideration of adverse drug-drug interactions), and
- comorbidities (including substance abuse).

In many cases the cause(s) of treatment failure will be readily apparent. In some cases, no obvious cause may be identified.

Initial Assessment of Treatment Failure

In conducting the assessment of treatment failure, it is important to distinguish among the reasons for treatment failure, because the approaches to subsequent therapy will differ. The following assessments should be undertaken initially:

- **Adherence.** Assess the patient's adherence to the regimen. For incomplete adherence, identify and address the underlying cause(s) of nonadherence (e.g., [difficulties accessing or tolerating medications](#), depression, active substance abuse) and simplify the regimen if possible (e.g., decrease pill count or dosing frequency) (**AIII**). (See [Adherence](#) section.)
- **Medication Intolerance.** Assess the patient's tolerance of the current regimen and the severity and duration of side effects (e.g., the limited duration of gastrointestinal symptoms with some regimens). Management strategies for intolerance in the absence of drug resistance may include:
 - using symptomatic treatment (e.g., antiemetics, antidiarrheals);
 - changing one drug to another within the same drug class, if needed (e.g., change to tenofovir or abacavir for zidovudine-related gastrointestinal symptoms or anemia; change to nevirapine for efavirenz-related central nervous system symptoms) (**AII**);
 - changing from one drug class to another (e.g., from an NNRTI to a PI, from enfuvirtide to raltegravir) if necessary and no drug resistance is suspected (**AI**).
- **Pharmacokinetic Issues.** Review food/fasting requirements for each medication. Review recent history of gastrointestinal symptoms (such as vomiting or diarrhea) to assess the likelihood of short-term malabsorption. Review concomitant medications and dietary supplements for possible adverse drug-drug interactions (consult [Drug Interactions](#) section and tables for common interactions) and make appropriate substitutions for antiretroviral agents and/or concomitant medications, if possible (**AIII**). (See also [Exposure-Response Relationship and Therapeutic Drug Monitoring](#).)
- **Suspected Drug Resistance.** Obtain resistance testing while the patient is taking the failing regimen or within 4 weeks after regimen discontinuation (**AII**). (See [Drug Resistance Testing](#).)

Further Assessment of Treatment Failure

When adherence, tolerability, and pharmacokinetic causes of treatment failure have been considered and addressed, make further assessments for virologic failure, immunologic failure, and clinical progression.

Virologic suppression is best defined as a maximal inhibition of viral replication *in vivo*, as evidenced by a sustained reduction in plasma HIV RNA level below the assay limit of detection (e.g., <50 copies/mL). Virologic failure is best understood in the context of virologic success; that is, virologic failure is defined as the inability to achieve or maintain suppression of viral replication to levels below the limit of detection (e.g., <50 copies/mL) and may manifest as any of the following:

- **Incomplete virologic response:** For example, two consecutive plasma HIV RNA >400 copies/mL after 24 weeks or above the limit of assay detection (e.g., >50 copies/mL) by 48 weeks on an antiretroviral regimen. Baseline HIV RNA may affect the time course of response, and some patients will take longer than others to suppress HIV RNA levels. The timing, pattern, and/or slope of HIV RNA decrease may predict ultimate virologic response [8]. For example, most patients with an adequate virologic response at 24 weeks had at least a 1 log₁₀ decrease in HIV RNA copies/mL at 1–4 weeks after starting therapy [9–11].
- **Virologic rebound:** After virologic suppression, repeated detection of HIV RNA above the assay limit of detection (e.g., >50 copies/mL).

Assessment of Virologic Failure. There is no consensus on the optimal time to change therapy for virologic failure. The most aggressive approach would be to change for any repeated, detectable viremia (e.g., two consecutive HIV RNA >50 copies/mL after suppression to <50 copies/mL in a patient taking the regimen). Other approaches allow detectable viremia up to an arbitrary level (e.g., 1,000–5,000 copies/mL). However, ongoing viral replication in the presence of antiretroviral drugs promotes the selection of drug resistance mutations [12] and may limit future treatment options. Isolated episodes of viremia "blips" (e.g., single levels of 51–1,000 copies/mL) may simply represent laboratory variation [13] and usually are not associated with subsequent virologic failure. However, rebound to higher viral load levels or more frequent episodes of viremia increase the risk of virologic failure [14–15].

When assessing virologic failure, the clinician should evaluate the degree of drug resistance and consider the patient's prior treatment history and prior resistance test results **(AII)**. Drug resistance tends to be cumulative for a given individual; thus, all prior treatment history and resistance test results should be taken into account.

Management of Virologic Failure. Ideally, a new antiretroviral regimen should contain at least two, and preferably three, fully active drugs on the basis of drug history, resistance testing, or new mechanistic class **(AII)** [16–24]. Some antiretroviral drugs (e.g., NRTIs) may contribute partial antiretroviral activity to an antiretroviral regimen, despite drug resistance [25], while others (e.g., enfuvirtide, non-nucleoside reverse transcriptase inhibitors, raltegravir) likely do not provide partial activity [25–27]. Because of the potential for drug-class cross resistance that reduces drug activity, using a "new" drug that a patient has not yet taken may not mean that the drug is fully active. Archived drug resistance mutations may not be detected by standard drug resistance tests. Drug potency and viral susceptibility are more important than the number of drugs prescribed. Early studies of treatment-experienced patients identified factors associated with better virologic responses to subsequent regimens [28–29]. These factors included lower HIV RNA and/or higher CD4 cell count at the time of therapy change, using a new (i.e., not yet taken) class of antiretroviral drugs, and using ritonavir-boosted PIs in PI-experienced patients.

More recent clinical trials illustrate effective therapeutic strategies for treatment-experienced patients [17–18, 20–21, 30]. In these studies, patients received an optimized background antiretroviral regimen based on drug treatment history and resistance testing (genotype and phenotype) and then were randomized to add on a new active antiretroviral agent or placebo. Patients who received more active drugs had a better and more prolonged virologic response than those with fewer active drugs in the regimen. Higher genotypic and/or phenotypic susceptibility scores (indicating a greater number of active agents) were associated with better virologic responses [20–21].

These studies illustrate and support the strategy of conducting resistance testing while a treatment-experienced patient is taking a failing regimen, designing a new regimen based on the treatment history and resistance testing results, and selecting active antiretroviral drugs for the new treatment regimen. Active antiretroviral drugs include those with activity against drug-resistant viral strains, including newer members of existing classes (the NNRTI etravirine, the PIs darunavir and tipranavir) and drugs with new mechanisms of action (the fusion inhibitor enfuvirtide, the CCR5 inhibitor maraviroc, and the integrase inhibitor raltegravir).

Clinical Scenarios in Management of Patients with Antiretroviral Treatment Failure.

- **Prior treatment with low-level viremia (50–1,000 copies/mL).** Assess adherence. Consider variability in HIV RNA assays. Patients with isolated increases in HIV RNA ("blips") do not require a change in treatment [13] **(AII)**. Some HIV RNA assays are associated with more frequent "blips" [31] and results should be interpreted with caution. It is not clear how to manage patients with persistent low-level viremia; many experts would not change therapy and would follow the patient closely **(CII)**.
- **Prior treatment with detectable viremia (e.g., HIV RNA >1,000 copies/mL) and no resistance identified.** Consider the timing of the drug resistance test (e.g., Was the patient off antiretroviral medications for >4 weeks and/or nonadherent?). Consider resuming the same regimen or starting a new regimen and then repeating genotypic testing early (e.g., in 2–4 weeks) to determine whether a resistant viral strain emerges **(CIII)**. Consider pharmacokinetic enhancement (ritonavir boosting for an unboosted PI such as atazanavir, fosamprenavir) **(BII)**.

- **Prior treatment and drug resistance.** The goals in this situation are to re-suppress HIV RNA levels maximally (e.g., to <50 copies/mL) and to prevent further selection of resistance mutations. With virologic failure, consider changing the treatment regimen sooner, rather than later, to minimize continued selection of resistance mutations. Discontinuing an NNRTI in a patient with ongoing viremia and evidence of NNRTI resistance to decrease the risk of selecting additional NNRTI-resistance mutations is particularly important, because newer NNRTIs with activity against some NNRTI-resistant strains are available (e.g., etravirine). **Similarly, consideration should be given to discontinuing enfuvirtide or raltegravir in a failing regimen to decrease selection of additional drug mutations.** A new regimen should include at least two, and preferably three, fully active agents (**AII**).
- **Extensive prior treatment and drug resistance.** The goal is to re-suppress the HIV RNA levels maximally (e.g., to <50 copies/mL). With the availability of multiple new antiretroviral drugs, including some with new mechanisms of action, this goal is now possible in many patients, including those with extensive treatment experience and drug resistance. In some cases, however, viral suppression may be difficult to achieve. If maximal virologic suppression cannot be achieved, the goals are to preserve immunologic function and to prevent clinical progression (even with ongoing viremia). Even partial virologic suppression of HIV RNA >0.5 log₁₀ copies/mL from baseline correlates with clinical benefits [32]; however, this must be balanced with the ongoing risk of accumulating additional resistance mutations.
- **Extensive prior treatment and highly drug resistant HIV.** There exists a subset of patients who have developed resistance to all or most currently available regimens, and designing a regimen with two or three fully active drugs is not possible. Many of these patients received newer agents in suboptimal regimens (i.e., did not have access to more than one or two of the drugs at the time they became available) or have been unable to adhere to any regimen. There is no consensus on how to optimize the management of these patients. It is reasonable to observe a patient on the same regimen, rather than changing the regimen, depending on the stage of HIV disease (**BII**). There is evidence from cohort studies that continuing therapy, even in the presence of viremia and the absence of CD4 T-cell count increases, decreases the risk of disease progression [33]. Other cohort studies suggest continued immunologic and clinical benefits if the HIV RNA level is maintained <10,000–20,000 copies/mL [34–35]. In general, adding a single, fully active antiretroviral drug in a new regimen is not recommended because of the risk of development of rapid resistance (**BII**). However, in patients with a high likelihood of clinical progression (e.g., CD4 T-cell count <100/mm³) and limited drug options, adding a single drug may reduce the risk of immediate clinical progression, because even transient decreases in HIV RNA and/or transient increases in CD4 T-cell counts have been associated with clinical benefits (**CI**). Weighing the risks (e.g., selection of drug resistance) and benefits (e.g., antiretroviral activity) of using a single active drug in the heavily treatment experienced patient is complicated, and consultation with an expert is advised. Patients with ongoing viremia and with an insufficient number of approved treatment options to construct a fully suppressive regimen may be candidates for single-patient access of investigational new drug(s) (IND), as specified in FDA regulations: <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm163982.htm>). Access requires ineligibility or inability to participate in ongoing study protocols, agreement from the sponsor to supply the investigational drug, and local institutional review board approval.
- **Discontinuing antiretroviral therapy.** Discontinuing or briefly interrupting therapy (even with ongoing viremia) may lead to a rapid increase in HIV RNA and a decrease in the CD4 T-cell count and increases the risk of clinical progression [36–37]. Therefore, this strategy is not recommended (**AII**). See **Discontinuation or Interruption of Antiretroviral Therapy** section.
- **Prior treatment and suspected drug resistance, now presenting to care in need of therapy and with limited information (i.e., incomplete or absence of medical records or previous resistance data).** This is a common scenario. Every effort should be made to obtain medical records and prior drug resistance testing results; however, this is not always possible. One strategy is to restart the most recent antiretroviral regimen and assess drug resistance in 2–4 weeks to help guide the choice of the next regimen.

Immunologic failure can be defined as a failure to achieve and maintain an adequate CD4 T-cell response despite virologic suppression. There is no specific definition for immunologic failure, although some studies have focused on patients who fail to increase CD4 T-cell counts above a specific threshold (e.g., >350 or 500 cells/mm³) over a specific period of time (e.g., 4–7 years). Others have focused on an inability to increase CD4 T-cell counts above pre-therapy

levels by a certain threshold (e.g., >50 or 100 cells/mm^3) over a given time period. The former approach may be preferable because of data linking these thresholds with the risk of non-AIDS clinical events [38].

The proportion of patients experiencing immunologic failure depends on how failure is defined, the observation period, and the CD4 T-cell count when treatment was started. In the longest study conducted to date, the percentage of patients with suppressed viremia who reached a CD4 T-cell count $>500 \text{ cells/mm}^3$ through 6 years of treatment was 42% (starting treatment with a CD4 $<200 \text{ cells/mm}^3$), 66% (starting with CD4 $200\text{--}350 \text{ cells/mm}^3$), and 85% (starting with CD4 $>350 \text{ cells/mm}^3$) [39]; increases in CD4 T-cell counts in treatment-naïve patients with initial antiretroviral regimens are approximately 150 cells/mm^3 over the first year [40]. A CD4 T-cell count plateau may occur after 4–6 years of treatment with suppressed viremia [39, 41–44].

A persistently low CD4 T-cell count while on suppressive antiretroviral therapy is associated with a small, but appreciable, risk of AIDS- and non-AIDS-related morbidity and mortality [45–46]. For example, in the FIRST study [47], a low CD4 T-cell count on therapy was associated with an increased risk of AIDS-related complications (adjusted hazard ratio of 0.57 for CD4 T-cell count 100 cells/mm^3 higher). Similarly, a low CD4 T-cell count was associated with an increased risk of non-AIDS events, including cardiovascular, hepatic, renal, and cancer events. Other studies support these associations [48–50].

Factors associated with poor CD4 T-cell response:

- CD4 count $<200/\text{mm}^3$ when starting ART;
- Older age;
- Coinfection (e.g., HCV, HIV-2, HTLV-1, HTLV-2);
- Medications, both antiretrovirals (zidovudine [51], tenofovir + didanosine [52–54]) and other medications;
- Persistent immune activation;
- Loss of regenerative potential of the immune system; and
- Other medical conditions

Assessment of Immunologic Failure. CD4 T-cell count should be confirmed by repeat testing. Concomitant medications should be reviewed carefully, with a focus on those known to decrease white blood cells or, specifically, CD4 T-cells (e.g., interferon, cancer chemotherapy, prednisone, zidovudine, combination of tenofovir and didanosine), and consideration should be given to substituting or discontinuing these drugs, if possible. Untreated coinfections (e.g., HIV-2, HTLV-1, HTLV-2) and serious medical conditions (e.g., malignancy) also should be considered. In many cases, no obvious cause for immunologic failure can be identified.

Management of Immunologic Failure. There is no consensus on when or how to treat immunologic failure. Given the risk of clinical events, it is reasonable to focus on patients with CD4 T-cell counts $<200/\text{mm}^3$. Patients with higher CD4 T-cell counts have a low risk of clinical events. It is not clear that immunologic failure in the setting of virologic suppression should prompt a change in the antiretroviral drug regimen. Because ongoing viral replication occurs in some patients with suppressed HIV RNA levels, some have suggested adding a drug to an existing regimen. However, this strategy does not result in clear virologic or immunologic benefit [55]. Others suggest changing the regimen to a more suppressive regimen or from an NNRTI-based regimen to a PI-based regimen, based on some evidence that suggests improved CD4 T-cell count responses. These two strategies, however, have not been completely tested.

An immune-based therapy, interleukin-2, demonstrated CD4 T-cell count increases but no clinical benefit in two large randomized studies [56] and therefore is not recommended (AI). Other immune-based therapies (e.g., growth hormone, cyclosporine, interleukin-7) are currently under investigation. Currently, immune-based therapies should not be used unless it is in the context of a clinical trial (BIII).

Clinical progression can be defined as the occurrence or recurrence of HIV-related events (after at least 3 months on an antiretroviral regimen), excluding immune reconstitution syndromes [57–58]. In one earlier study using older combination regimens, clinical progression (a new AIDS event or death) occurred in 7% of treated patients with virologic suppression, 9% of treated patients with virologic rebound, and 20% of treated patients who never achieved virologic suppression in 2.5 years [59].

Management of Clinical Progression. Identify and consider treatment for potential HIV-related illnesses. Consider the possibility of immune reconstitution syndrome (IRS) [57-58], which typically occurs within the first 3 months after starting effective antiretroviral therapy. IRS may respond better to anti-inflammatory treatment(s) and treatment of the specific opportunistic infection than to changing antiretroviral therapy. Clinical progression may not warrant a change in therapy in the setting of suppressed viremia and adequate immunologic response (**BIII**).

Relationship Among Virologic Failure, Immunologic Failure, and Clinical Progression

Some patients demonstrate discordant responses in virologic, immunologic, and clinical parameters [60]. In addition, virologic failure, immunologic failure, and clinical progression have distinct time courses and may occur independently or simultaneously. In general, virologic failure occurs first, followed by immunologic failure, and finally by clinical progression. These events may be separated by months to years [61].

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REGIMEN SIMPLIFICATION (Updated December 1, 2009)

Regimen simplification can be defined broadly as a change in established effective therapy to reduce pill burden and dosing frequency, to enhance tolerability, or to decrease specific food and fluid requirements. Many patients on suppressive antiretroviral therapy may be considered candidates for this strategy, especially if (1) they are receiving treatments that are no longer recommended as preferred or alternative choices for initial therapy; (2) they were prescribed a regimen in the setting of treatment failure at a time when there was an incomplete understanding of resistance or drug-drug interaction data; or (3) they were prescribed a regimen prior to the availability of newer options or formulations that might be easier to administer and/or more tolerable.

This section will review situations in which clinicians might consider simplifying treatment in a patient with virologic suppression. Importantly, this section will not be considering changes in treatment for reducing ongoing adverse effects. Regimens used in simplification strategies generally should be those that have proven high efficacy in

treatment-naïve patients (see [What to Start](#) section) or that would be predicted to be highly active for a given patient based on their past treatment history and resistance profile.

Rationale

The major rationales behind regimen simplification are to improve the patient's quality of life, improve medication adherence, avoid long-term toxicities, and reduce the risk of virologic failure. Systematic reviews in the non-HIV literature have shown that adherence is inversely related to the number of daily doses [1]. Some prospective studies in HIV-infected individuals have shown that those on regimens with reduced dosing frequency have higher levels of adherence [2-3]. Patient satisfaction with regimens that contain fewer pills and reduced dosing frequency is also higher [4].

Candidates for Regimen Simplification

Unlike antiretroviral agents developed earlier in the HIV epidemic, many antiretroviral medications that have been approved in recent years have sufficiently long half-lives to allow for once-daily dosing, and most also do not have dietary restrictions. Patients who receive regimens initiated earlier in the era of potent combination antiretroviral therapy with drugs that involve a large pill burden and/or frequent dosing requirements are often good candidates for regimen simplification.

Patients without suspected drug-resistant virus. Patients on first (or modified) treatment regimens without a history of treatment failure are ideal candidates for regimen simplification. These patients are less likely to harbor drug-resistant virus, especially if a pretreatment genotype did not detect drug resistance. Prospective clinical studies have demonstrated that the likelihood of treatment failure after simplification is relatively low, and indeed may be lower than in patients who do not simplify treatment [5]. However, some patients may have unrecognized drug-resistant HIV, either acquired at the time of infection or as a consequence of prior treatment, such as those who were treated with presumably nonsuppressive mono- or dual-NRTI regimens before the widespread availability of HIV RNA monitoring and resistance testing.

Patients with documented or suspected drug resistance. Treatment simplification may also be appropriate for selected individuals whose virus is suppressed after having had documented or suspected drug resistance. Often, these patients are on regimens selected at a time when management of drug resistance, understanding of potentially adverse drug-drug interactions, and understanding of treatment options were relatively limited. Additional patients for whom to consider regimen simplification are those on two ritonavir-boosted PIs. Despite success of this treatment in suppressing viral replication, these patients may be on regimens that are cumbersome and associated with potential long-term adverse events. The ability to simplify regimens in this setting often reflects the availability of recently approved agents that have activity against drug-resistant virus and that are easier to take without sacrificing antiviral activity. Specific situations in which drug simplification could be considered in treatment-experienced patients with viral drug resistance are outlined below. Simplifying regimens in patients who have extensive prior treatment histories is complicated. In these cases, designing a new regimen should be done after a thorough review of treatment history, treatment responses and tolerance, and resistance test results. Expert consultation should be considered whenever possible.

Types of Treatment Simplification

Within-Class Simplifications. Within-class substitutions offer the advantage of not exposing patients to still-unused drug classes, which potentially preserves other classes for future regimens. In general, within-class substitutions use a newer agent; coformulated drugs; a formulation that has a lower pill burden, has a lower dosing frequency; or would be less likely to cause toxicity.

- **NRTI Substitutions** (e.g., changing from zidovudine or stavudine to tenofovir or abacavir): This may be considered for a patient who has no history of viral resistance on an NRTI-containing regimen. Other NRTIs may be substituted to create a regimen with lower dosing frequency (e.g., once daily) that takes advantage of coformulated agents and potentially avoids some long-term toxicities (e.g., pancreatitis, peripheral neuropathy, lipoatrophy).
- **Switching of NNRTIs** (e.g., from nevirapine to efavirenz): This may be considered to reduce dosing frequency or to take advantage of coformulated agents.

- **Switching of PIs:** This switch can be from one PI to another PI, to the same PI at a lower dosing frequency or, in the case of atazanavir, to administration without ritonavir boosting [6]. (Unboosted atazanavir is presently not a preferred PI component. It is not recommended if the patient is taking tenofovir or if the patient has HIV with reduced susceptibility to atazanavir. Unboosted atazanavir must be taken with caution when the patient requires acid-reducing agents.) Such changes can reduce dosing frequency, pill count, drug-drug or drug-food interactions, or dyslipidemia or can take advantage of coformulation. These switches can be done with relative ease in those patients without PI-resistant virus, but the switches are not recommended in patients who have a history of documented or suspected PI resistance because of a lack of convincing data in that setting.

Out-of-Class Substitutions. The most common out-of-class substitutions for regimen simplification involve a change from a PI-based to an NNRTI-based regimen. One important study in this regard was the NEFA trial, which evaluated substitution of a PI-based regimen in virologically suppressed patients with nevirapine, efavirenz, or abacavir [7]. Although the baseline regimens in the study are no longer in widespread use, the NEFA findings are still relevant, and provide information about the risks and benefits of switching treatment in patients with virologic suppression. In this study, 460 patients on stable, PI-based regimens with virologic suppression (<200 copies/mL for the previous 6 months) were switched to their randomized treatment arms. After 36 months of follow-up, virologic failure occurred more frequently in patients switched to abacavir than in those switched to efavirenz or nevirapine. The increased risk of treatment failure was particularly high in those who had previous suboptimal treatment with mono- and dual-NRTI therapy. This emphasizes the need to consider the potential for drug-resistant virus prior to attempting simplification [8].

Newer agents that target different sites in the HIV life cycle, such as raltegravir and maraviroc, also offer opportunities for out-of-class substitutions, particularly in those patients who have a history of virus resistant to older HIV drugs. However, results of substitution studies involving these agents are limited. Switching patients who are suppressed on a lopinavir/ritonavir-based regimen to a raltegravir-based regimen has been reported to be associated with increased risk of virologic rebound in patients with more extensive prior treatment history, therefore should be done with caution [9].

One situation in which substitution of novel agents has been increasingly described is for the use of newer agents to replace enfuvirtide. Because enfuvirtide requires twice-daily injections, causes injection-site reactions, and is more expensive than other available antiretroviral agents, patients who are virologically suppressed on enfuvirtide-containing regimens may wish to substitute it with an active oral agent. Because the majority of patients on enfuvirtide have highly drug-resistant virus, substitution must be with another fully active agent. Data from one randomized trial and one observational study suggest that raltegravir can safely substitute for enfuvirtide in patients not previously treated with integrase inhibitors [10-11]. Although this strategy generally maintains virologic suppression and is well tolerated, clinicians should be aware that any drug substitution may introduce unanticipated adverse effects or drug-drug interactions. Another study reported continued viral suppression with an enfuvirtide to raltegravir switch but raised concern about decreased levels of the concurrent boosted PI after the switch (darunavir or tipranavir) [12]. In one report, four patients experienced depression after substituting different antiretroviral drugs with raltegravir, which highlights that substitution of new drugs in a suppressive regimen may introduce unexpected adverse effects, even with treatments that are generally well tolerated [13]. Use of novel combinations of antiretrovirals for which there are limited drug interaction data is also a concern, as illustrated by a report of liver toxicity after raltegravir was substituted for enfuvirtide in three patients who received ritonavir-boosted tipranavir [14]. Although a similar substitution can be considered with etravirine or maraviroc, this strategy can be limited by the inability to perform testing to assess etravirine resistance or viral tropism in virologically suppressed patients. No data are currently available using maraviroc in this setting. In the etravirine early access program, switching from enfuvirtide to etravirine showed promise in maintaining viral suppression at 24 weeks, but only 37 subjects were included in this report [15].

Reducing the number of active drugs in a regimen. This approach to treatment simplification involves switching a patient from a suppressive regimen to fewer active drugs. Early studies of this approach were associated with a higher risk of treatment failure than continuation of standard treatment with two NRTIs plus a PI [16]. More recently, studies have evaluated the use of a ritonavir-boosted PI as monotherapy after virologic suppression with a two-NRTI + boosted-PI regimen [17-18]. The major motivations for this approach are a reduction in NRTI-related toxicity and a lower cost. In the largest of these studies [18], low-level viremia was more common in those on maintenance ritonavir-boosted lopinavir alone than on a three-drug combination regimen. Viral suppression was achieved by resuming the NRTIs. Studies of darunavir/ritonavir monotherapy, both as once- or twice-daily dosing, have reported mixed results [19-20]. In aggregate,

boosted-PI monotherapy as initial [21] or as simplification treatment has been somewhat less effective in achieving complete virologic suppression and avoiding resistance. Therefore, this strategy cannot be recommended currently.

Monitoring After Treatment Simplification

After treatment simplification, patients should be evaluated in 2–6 weeks to assess tolerance and to undergo laboratory monitoring, including HIV RNA, CD4 cell count, and markers of renal and liver function. Assessment of fasting cholesterol subsets and triglycerides should be performed within 3 months after the switch. In the absence of any specific complaints, laboratory abnormalities, or viral rebound at that visit, patients may resume regularly scheduled clinical and laboratory monitoring.

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EXPOSURE-RESPONSE RELATIONSHIP AND THERAPEUTIC DRUG MONITORING (TDM) FOR ANTIRETROVIRAL AGENTS (Updated November 3, 2008)

Panel's Recommendation:

- ***Therapeutic drug monitoring (TDM) for antiretroviral agents is not recommended for routine use in the management of the HIV-infected adult (CIII).***

Knowledge of the relationship between systemic exposure (or concentration) and drug responses (beneficial and/or adverse) is key to selection of a dose for a drug, to understanding the variability in the response of patients to a drug, and to design strategies to optimize response and tolerability.

Therapeutic drug monitoring (TDM) is a strategy applied to certain antiarrhythmics, anticonvulsants, antineoplastics, and antibiotics that utilizes drug concentrations to design regimens that are safe and that will achieve a desired therapeutic outcome. The key characteristic of a drug that is a candidate for TDM is knowledge of the exposure-response relationship and a therapeutic range of concentrations. The therapeutic range is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

Current antiretroviral agents meet most of the characteristics of agents that can be considered candidates for a TDM strategy [1]. The rationale for TDM in managing antiretroviral therapy arises because of the following:

- data showing that considerable interpatient variability in drug concentrations exists among patients who take the same dose;
- data indicating that relationships exist between the concentration of drug in the body and anti-HIV effect—and, in some cases, toxicities; and
- data from small prospective studies demonstrating that TDM improved virologic response and/or decreased the incidence of concentration-related drug toxicities [2, 3].

However, TDM for antiretroviral agents is not recommended for routine use in the management of the HIV-infected adult (CIII).

There are multiple factors that limit the routine use of TDM in adults [4, 5]. They include the following:

- lack of large prospective studies demonstrating that TDM improves clinical and virologic outcomes. This is the most important limiting factor for the implementation of TDM at present;
- lack of established therapeutic range of concentrations associated with achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions;
- inpatient variability in antiretroviral drug concentrations; and
- lack of widespread availability of laboratories that perform quantitation of antiretroviral drug concentrations under rigorous quality assurance/quality control standards, and the shortage of experts to assist with interpretation of antiretroviral concentration data and application of such data to revise patients' dosing regimens.

TDM with Different Antiretroviral Classes

PIs and NNRTIs. Data that describe relationships between antiretroviral agents and treatment response have been reviewed in various publications [4-7]. Although there are limitations and unanswered questions, the consensus among U.S. and European clinical pharmacologists is that the data provide a framework for the potential implementation of TDM for PIs and NNRTIs. This is because exposure-response data exist for these agents. Information on relationships between concentrations and drug-associated toxicities are sparse. Clinicians who use TDM as a strategy to manage either antiretroviral response or toxicities should consult the most current data on the proposed therapeutic concentration range. Exposure-response data for darunavir and etravirine are accumulating but are not sufficient for a recommendation at this time.

CCR5 Antagonists. Trough maraviroc concentrations have been shown to be an important predictor of virologic success in studies conducted in treatment-experienced persons [8, 9]. Clinical experience in the use of TDM for maraviroc, however, is very limited. Nonetheless, as with PIs and NNRTIs, the exposure-response data provide a framework for TDM, and that information is presented in these guidelines ([Table 9](#)).

Integrase Inhibitors. Exposure-response data for raltegravir are accumulating but are not sufficient for a recommendation at this time.

NRTIs. Relationships between plasma concentrations of NRTIs and their intracellular pharmacologically active moieties have not yet been established. Therefore, monitoring of plasma or intracellular NRTI concentrations for an individual patient largely remains a research tool. Measurement of plasma concentrations, however, is routinely used for studies of drug-drug interactions.

Scenarios for Use of TDM. There are multiple scenarios in which both data and expert opinion indicate that information on the concentration of an antiretroviral agent may be useful in patient management. Consultation with a clinical pharmacologist may be advisable. These scenarios include the following:

- **with clinically significant drug-drug or drug-food interactions** that may result in reduced efficacy or increased dose-related toxicities;
- **with changes in pathophysiologic states** that may impair gastrointestinal, hepatic, or renal function, thereby potentially altering drug absorption, distribution, metabolism, or elimination;
- **in pregnant women**, who may be at risk for virologic failure as a result of changes in their pharmacokinetic parameters during the later stage of pregnancy, which may result in plasma concentrations lower than those achieved in the earlier stages of pregnancy and in the nonpregnant patient;
- **in treatment-experienced persons** who may have viral isolates with reduced susceptibility to antiretroviral agents;
- **with use of alternative dosing regimens** in which safety and efficacy have not been established in clinical trials;
- **with concentration-dependent, drug-associated toxicities;** and
- **with lack of expected virologic response** in medication-adherent persons.

TDM in different patient populations

- **Patients who have drug-susceptible virus.** [Table 9](#) presents a synthesis of recommendations [2-7] for minimum target trough PI and NNRTI concentrations in persons with drug-susceptible virus.
- **Treatment-experienced patients.** Fewer data are available to formulate suggestions for minimum target trough concentrations in treatment-experienced patients who have viral isolates with reduced susceptibility to these agents. Concentration recommendations for tipranavir and maraviroc were derived only from studies in treatment-experienced persons. It is likely that use of PIs and NNRTIs in the setting of reduced viral susceptibility may require higher trough concentrations than those needed for wild-type virus. The inhibitory quotient (IQ), which is the ratio of antiretroviral drug concentration to a measure of susceptibility (genotype or phenotype) of the patient's strain of HIV to that drug, may additionally improve prediction of virologic response—as has been shown, for example, with darunavir in treatment-experienced persons [10].

Monitoring Drug Concentrations. There are several challenges and considerations for implementation of TDM in the clinical setting. Use of TDM to monitor drug concentrations in a patient requires multiple steps:

- quantification of the concentration of the drug, usually in plasma or serum;
- determination of the patient's pharmacokinetic characteristics;
- integration of information on patient adherence;
- interpretation of the concentrations; and
- adjustment of the drug dose to achieve concentrations within the therapeutic range, if necessary.

Guidelines for the collection of blood samples and other practical suggestions can be found in a position paper by the Adult AIDS Clinical Trials Group Pharmacology Committee [4].

A final caveat to the use of measured drug concentrations in patient management is a general one—drug concentration information cannot be used alone; it must be integrated with other clinical and patient information. In addition, as knowledge of associations between antiretroviral concentrations and virologic response continues to accumulate, clinicians who employ a TDM strategy for patient management should consult the most current literature.

Table 9. Suggested Minimum Target Trough Concentrations [2-9]
(Updated November 3, 2008)

Drug	Concentration (ng/mL)
Fosamprenavir	400 (measured as amprenavir concentration)
Atazanavir	150
Indinavir	100
Lopinavir	1,000
Nelfinavir ¹	800
Saquinavir	100–250
Efavirenz	1,000
Nevirapine	3,000
Recommendations applicable only to treatment-experienced persons who have resistant HIV-1 strains	
Maraviroc	>50
Tipranavir	20,500

¹Measurable active (M8) metabolite

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DISCONTINUATION OR INTERRUPTION OF ANTIRETROVIRAL THERAPY

(Updated November 3, 2008)

Discontinuation of antiretroviral therapy may result in viral rebound, immune decompensation, and clinical progression. Unplanned interruption of antiretroviral therapy may become necessary because of severe drug toxicity, intervening illness, surgery that precludes oral therapy, or antiretroviral medication nonavailability. Planned treatment discontinuations have been proposed by some in situations such as: in patients who achieve viral suppression aiming to enhance adherence; reduce inconvenience, long-term toxicities, and costs for patients; or in extensively-treated patients who experience treatment failure due to resistant HIV, to allow reversion to wild-type virus. Potential risks and benefits of interruption vary according to a number of factors, including the clinical and immunologic status of the patient, the reason for the interruption, the type and duration of the interruption, and the presence or absence of resistant HIV at the time of interruption. Below are brief discussions on what is currently known about the risks and benefits of treatment interruption in some of these circumstances.

Short-Term Therapy Interruptions

Reasons for short-term interruption (days to weeks) of antiretroviral therapy vary and may include drug toxicity; intercurrent illnesses that preclude oral intake, such as gastroenteritis or pancreatitis; surgical procedures; or nonavailability of drugs. Stopping antiretroviral drugs for a short time (i.e., <1 to 2 days) due to medical/surgical procedures can usually be done by holding all drugs in the regimen. Recommendations for some other scenarios are listed below:

Unanticipated Need for Short-Term Interruption:

- **When a patient experiences a severe or life-threatening toxicity or unexpected inability to take oral medications** – all components of the drug regimen should be stopped simultaneously, regardless of drug half-life.

Planned Short Term Interruption (>2–3 days):

- **When all regimen components have similar half-lives and do not require food for proper absorption** – all drugs may be given with a sip of water, if allowed; otherwise, should be stopped simultaneously or. All discontinued regimen components should be restarted simultaneously.
- **When all regimen components have similar half-lives and require food for adequate absorption, and the patient is required not to take anything by mouth for a sustained period of time** – temporary discontinuation of all drug components is indicated. The regimen should be restarted as soon as the patient can resume oral intake.
- **When the antiretroviral regimen contains drugs with differing half-lives** – stopping all drugs simultaneously may result in functional monotherapy with the drug with the longest half-life (typically an NNRTI). Options in this circumstance are discussed below. (See [Discontinuation of efavirenz, etravirine, or nevirapine.](#))

Interruption of Therapy After Pregnancy

During pregnancy, HIV-infected pregnant women who otherwise do not meet current CD4 count or clinical criteria for starting treatment may initiate antiretroviral therapy primarily for the purpose of preventing mother-to-child HIV transmission. After delivery, these women may desire to stop therapy. Discontinuation recommendations are in the current guidelines for pregnant women [1] and in the [HIV-Infected Women](#) section.

Planned Long-Term Therapy Interruptions

Planned therapy interruptions have been contemplated in various scenarios, listed below. Research is ongoing in several of the scenarios. None of the therapy interruptions can be recommended at this time outside of controlled clinical trials (AI).

- **In patients who initiated therapy during acute HIV infection and achieved virologic suppression**—the optimal duration of treatment and the consequences of treatment interruption are not known at this time. (See [Acute HIV Infection](#) section.)
- **In patients who have had exposure to multiple antiretroviral agents, have experienced antiretroviral treatment failure, and have few treatment options available because of extensive resistance mutations**—interruption is **not** recommended unless it is done in a clinical trial setting (AI). Several clinical trials largely yielding negative results, but some with conflicting results have been conducted to better understand the role of treatment interruption in these patients [2-5]. The largest of these studies showed negative clinical impact of treatment interruption in these patients [2]. The Panel notes that partial virologic suppression from combination therapy has been associated with clinical benefit [6]; therefore, interruption of therapy is not recommended.
- **In patients on antiretroviral therapy who have maintained a CD4 count above the level currently recommended for treatment initiation and irrespective of whether their baseline CD4 count was either above or below that recommended threshold**—interruption is also **not recommended** unless it is done in a clinical trial setting (BI). (See discussion below highlighting potential adverse outcomes seen in some treatment interruption trials.)

Temporary treatment interruption to reduce inconvenience, potential long-term toxicity, and/or overall treatment cost has been considered as a strategy for patients on antiretroviral therapy who have maintained CD4 counts above those currently recommended for initiating therapy. Several clinical trials have been designed to determine the safety of such interruptions, in which reinitiation is triggered by predetermined CD4 count thresholds. In these trials, various CD4 count levels have been set to guide both treatment interruption and reinitiation. Two separate, randomized clinical trials of CD4 count-guided treatment interruption have been reported. In the SMART study, the largest of such trials with over 5,000 subjects, interrupting treatment with CD4 counts >350 cells/mm³ and reinitiating when <250 cells/mm³ was associated with an increased risk of disease progression and death compared with the trial arm of continuous antiretroviral therapy [7]. In the TRIVACAN study, the same CD4 count thresholds were used for stopping and restarting treatment [8]. This study also showed that interruption was an inferior strategy; the interventions in both trials were stopped early because of these findings. Data from the DART trial reported a two-fold increase in rates of WHO stage 4 events/deaths in the 12-week ART cycling group among African patients achieving a CD4 count >300 /mm³ compared to the continuous ART group [9]. Observational data from the EuroSIDA cohort noted a 2-fold increase in risk of death after a treatment interruption of ≥ 3 months. Factors linked to increased risk of death or progression included lower CD4 counts, higher viral loads, and a prior history of AIDS [10]. Other studies have reported no major safety concerns [11-13], but these studies had smaller sample

sizes. Results have been reported from several small observational studies evaluating treatment interruption in patients doing well with nadir CD4 counts $>350/\text{mm}^3$, but further studies are needed to determine the safety of treatment interruption in this population [14, 15]. There is concern that CD4 counts <500 cells/ mm^3 are associated with a range of non-AIDS clinical events (e.g., cancer, heart, liver, and kidney disease) [7, 16, 17].

Planned long-term therapy interruption strategies **cannot** be recommended at this time outside of controlled clinical trials **(BI)** based on available data and a range of ongoing concerns.

If therapy has to be discontinued, patients should be counseled about the need for close clinical and laboratory monitoring. They should also be aware of the risks of viral rebound, acute retroviral syndrome, increased risk for HIV transmission, decline of CD4 count, HIV disease progression or death, development of minor HIV-associated manifestations such as oral thrush, development of serious non-AIDS complications, development of drug resistance, and the need for chemoprophylaxis against opportunistic infections depending on the CD4 count. Treatment interruptions often result in rapid reductions in CD4 counts.

Prior to any planned treatment interruption, a number of antiretroviral-specific issues should be taken into consideration. These include:

- **Discontinuation of efavirenz, etravirine, or nevirapine.** The optimal interval between stopping efavirenz, etravirine, or nevirapine and other antiretroviral drugs is not known. The duration of detectable levels of efavirenz or nevirapine after discontinuation ranges from less than 1 week to more than 3 weeks [18, 19]. Simultaneously stopping all drugs in a regimen containing these agents may result in functional monotherapy with the NNRTIs, because their half-lives are much longer than other agents. This may increase the risk of selection of NNRTI-resistant mutations. It is further complicated by evidence that certain host genetic polymorphisms may result in slower rates of clearance. Such polymorphisms may be more common among specific ethnic groups, such as African Americans and Hispanics [19, 20]. Some experts recommend stopping the NNRTI but continuing the other antiretroviral drugs for a period of time. The optimal time sequence for staggered component discontinuation has not been determined. A study in South Africa demonstrated that giving four or seven days of zidovudine + lamivudine after a single dose of nevirapine reduced the risk of postnatal nevirapine resistance from 60% to 10%–12% [21]. Use of nucleosides with a longer half-life such as tenofovir plus emtricitabine has also been shown to decrease nevirapine resistance after single dose treatment [22]. The findings may however differ in patients on chronic nevirapine treatment. An alternative strategy is to substitute a PI for the NNRTI and to continue the PI with dual NRTIs for a period of time. In a post-study analysis of the patients who interrupted therapy in the SMART trial, patients who were switched from NNRTI to a PI based regimen prior to interruption had a lower rate of NNRTI-resistant mutation after interruption and a greater chance of re-suppression of HIV-RNA after restarting therapy than those who stopped all the drugs simultaneously or stopping the NNRTI before the 2-NRTI [23]. The optimal duration needed to continue the PI-based regimen after stopping the NNRTI is not known. Given the potential of prolonged detectable NNRTI concentrations for more than 3 weeks, some suggest that the PI-based regimen may need to be continued for up to 4 weeks. Further research to determine the best approach to discontinuing NNRTIs is needed. Clinical data on etravirine and treatment interruption is lacking but its long half-life of approximately 40 hours suggests that stopping etravirine needs to be done carefully using the same suggestions for nevirapine and efavirenz for the time being.
- **Discontinuation and reintroduction of nevirapine.** Because nevirapine is an inducer of the drug-metabolizing hepatic enzymes, administration of full therapeutic doses of nevirapine without a 2-week, low-dose escalation phase will result in excess plasma drug levels and potentially increase the risk for toxicity. Therefore, in a patient who has interrupted treatment with nevirapine for more than 2 weeks, nevirapine should be reintroduced with a dose escalation period of 200mg once daily for 14 days, then a 200mg twice-daily regimen **(AII)**.
- **Discontinuation of emtricitabine, lamivudine, or tenofovir in patients with hepatitis B coinfection.** Patients with hepatitis B coinfection (hepatitis B surface antigen or HBeAg positive) and receiving one or a combination of these NRTIs may experience an exacerbation of hepatitis upon drug discontinuation [24, 25]. (See [Hepatitis B \(HBV\)/HIV Coinfection](#) section.)

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Considerations for Antiretroviral Use in Special Patient Populations

ACUTE HIV INFECTION (Updated January 29, 2008)

Panel's Recommendations:

- *Whether treatment of acute HIV infection results in long-term virologic, immunologic, or clinical benefit is unknown; treatment should be considered optional at this time (CIII).*
- *Therapy should also be considered optional for patients in whom HIV seroconversion has occurred within the previous 6 months (CIII).*
- *If the clinician and patient elect to treat acute HIV infection with antiretroviral therapy, treatment should be implemented with the goal of suppressing plasma HIV RNA to below detectable levels (AIII).*
- *For patients with acute HIV infection in whom therapy is initiated, testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described for patients with established, chronic HIV infection (AII).*
- *If the decision is made to initiate therapy in a person with acute HIV infection, genotypic resistance testing at baseline will likely optimize virologic response; this strategy is therefore recommended (AIII). If therapy is deferred, genotypic resistance testing should still be performed, because the result may be useful in optimizing the virologic response when therapy is ultimately initiated (AIII).*
- *Since clinically significant resistance to PIs is less common than resistance to NNRTIs in treatment-naïve persons who harbor drug-resistant virus, consideration should be given to using a PI-based regimen if therapy is initiated before drug resistance test results are available (BIII).*

This section focuses on diagnosis and treatment of acute HIV-1 infection.

An estimated 40%–90% of patients acutely infected with HIV will experience symptoms of acute retroviral syndrome characterized by fever, lymphadenopathy, pharyngitis, skin rash, myalgias/arthritis, and other symptoms [1-6]. However, acute HIV infection is often not recognized by primary care clinicians because of the similarity of the symptoms to those of influenza, infectious mononucleosis, or other illnesses. Additionally, acute infection can occur asymptomatically. [Table 10](#) provides guidance to practitioners on the recognition, diagnosis, and management of acute HIV infection.

Diagnosis of Acute HIV Infection

Health care providers should maintain a high level of suspicion of acute HIV infection in patients who have a compatible clinical syndrome and who report recent high-risk behavior [7]. However, in some settings, patients may not always disclose or admit to high risk behaviors, or might not perceive their behaviors as high-risk. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high risk behaviors.

When acute retroviral syndrome is suspected, a plasma HIV RNA test should be used in conjunction with an HIV antibody test to diagnose acute infection (**BII**). Acute HIV infection is often defined by detectable HIV RNA in plasma in the setting of a negative or indeterminate HIV antibody test. A low-positive HIV RNA level (<10,000 copies/mL) may represent a false-positive test, since values in acute infection are generally very high (>100,000 copies/mL) [5, 6]. A qualitative HIV RNA test can also be used in this setting. Patients diagnosed with acute HIV infection on the basis of either a quantitative or a qualitative HIV RNA test should have confirmatory serologic testing performed at a subsequent time point (**AI**). ([Table 10](#))

Data from the United States and Europe demonstrate that transmitted virus may be resistant to at least one antiretroviral drug in 6%–16% of patients. If the decision is made to initiate therapy in a person with acute HIV infection, resistance

testing at baseline will likely optimize virologic response; this strategy is therefore recommended **(AIII)**. (See [Drug Resistance Testing](#) section.) If therapy is deferred, resistance testing should still be performed because the result may be useful in optimizing the virologic response when therapy is ultimately initiated **(AIII)**.

Treatment for Acute HIV Infection

Clinical trials information regarding treatment of acute HIV infection is limited. Ongoing trials are addressing the question of the long-term benefit of potent treatment regimens initiated during acute infection. Potential benefits and risks of treating acute infection are as follows:

- **Potential Benefits of Treating Acute Infection.** Preliminary data indicate that treatment of acute HIV infection with combination antiretroviral therapy has a beneficial effect on laboratory markers of disease progression [8–12]. Theoretically, early intervention could decrease the severity of acute disease; alter the initial viral setpoint, which can affect disease-progression rates; reduce the rate of viral mutation as a result of suppression of viral replication; preserve immune function; and reduce the risk for viral transmission. Additionally, although data are limited and the clinical relevance is unclear, the profound loss of gastrointestinal lymphoid tissue that occurs during the first weeks of infection may be mitigated by the early initiation of antiretroviral therapy [13, 14].
- **Potential Risks of Treating Acute HIV Infection.** The potential disadvantages of initiating therapy include exposure to antiretroviral therapy without a known clinical benefit, which could result in drug toxicities, development of antiretroviral drug resistance, the need for continuous therapy with strict adherence, and adverse effect on quality of life.

The above risk and benefit considerations are similar to those for initiating therapy in the chronically infected asymptomatic patient with high CD4 T-cell count. The health care provider and the patient should be fully aware that the rationale for therapy for acute HIV infection is based on theoretical considerations, and the potential benefits should be weighed against the potential risks. For these reasons, treatment of acute HIV infection should be considered optional at this time **(CIII)**. Providers should consider enrolling patients with acute HIV infection in a clinical trial to evaluate the natural history of acute HIV and to determine the role of antiretroviral therapy in this setting. Information regarding such trials can be obtained at www.clinicaltrials.gov or from local HIV treatment experts.

Treatment of Recent but Nonacute HIV Infection or Infection of Undetermined Duration

Besides patients with acute HIV infection, experienced clinicians also recommend consideration of therapy for patients in whom seroconversion has occurred within the previous 6 months **(CIII)**. Although the initial burst of viremia among infected adults usually resolves in 2 months, rationale for treatment during the 2- to 6-month period after infection is based on the probability that virus replication in lymphoid tissue is still not maximally contained by the immune system during this time [15].

Treatment Regimen for Acute or Recent HIV Infection

If the clinician and patient have made the decision to use antiretroviral therapy for acute or recent HIV infection, treatment should be implemented in an attempt to suppress plasma HIV RNA levels to below detectable levels **(AIII)**. Data are insufficient to draw firm conclusions regarding specific drug recommendations to use in acute HIV infection. Potential combinations of agents should be those used in established infection ([Table 6](#)). However, since clinically significant resistance to PIs is less common than resistance to NNRTIs in treatment-naïve persons who harbor drug resistant virus, consideration should be given to using a PI-based regimen if therapy is initiated before drug resistance test results are available **(BIII)**.

Patient Follow-up

Testing for plasma HIV RNA levels and CD4 count and toxicity monitoring should be performed as described in [Laboratory Testing for Initial Assessment and Monitoring While on Antiretroviral Therapy](#) (i.e., HIV RNA on initiation of therapy, after 2–8 weeks, then every 4–8 weeks until viral suppression, then every 3–4 months thereafter) **(AII)**.

Duration of Therapy for Acute or Recent HIV Infection

The optimal duration of therapy for patients with acute or recent HIV infection is unknown, but ongoing clinical trials may provide relevant data regarding these concerns. Difficulties inherent in determining the optimal duration and therapy composition for acute or recent infection (and the potential need for lifelong treatment) should be considered when first counseling the patient regarding therapy.

Table 10. Identifying, Diagnosing, and Managing Acute HIV-1 Infection (Updated January 29, 2008)

- **Suspecting acute HIV infection:** Signs or symptoms of acute HIV infection with recent (within 2-6 weeks) high HIV risk exposure*
 - Signs/symptoms/laboratory findings may include but are not limited to one or more of the following: fever, lymphadenopathy, skin rash, myalgia/arthralgia, headache, diarrhea, oral ulcers, leucopenia, thrombocytopenia, transaminase elevation
 - High risk exposures include sexual contact with a person infected with HIV or at risk of HIV, sharing of injection drug use paraphernalia, or contact of potentially infectious blood with mucous membranes or breaks in skin*
- **Differential diagnosis:** EBV- and non-EBV (e.g., CMV)-related infectious mononucleosis syndromes, influenza, viral hepatitis, streptococcal infection, syphilis
- **Evaluation/diagnosis of acute/primary HIV infection**
 - HIV antibody EIA (rapid test if available)
 - Reactive EIA must be followed by Western blot
 - Negative EIA or reactive EIA with negative or indeterminate Western blot should be followed by a virologic test**
 - Positive virologic test in this setting is consistent with acute HIV infection
 - Positive quantitative or qualitative HIV RNA test should be confirmed with subsequent documentation of seroconversion
- **Patient management:**
 - Treatment of acute HIV infection is considered optional (CIII).
 - Enrollment in clinical trial should be considered.

* In some settings, behaviors conducive to acquisition of HIV infection might not be ascertained, or might not be perceived as “high-risk” by the health care provider or the patient or both. Thus, symptoms and signs consistent with acute retroviral syndrome should motivate consideration of this diagnosis even in the absence of reported high risk behaviors.

** p24 antigen or HIV RNA assay. P24 antigen is less sensitive but more specific than HIV RNA tests; HIV RNA tests are generally preferred. HIV RNA tests include quantitative bDNA or RT-PCR, or qualitative transcription-mediated amplification (APTIMA, GenProbe).

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HIV-INFECTED ADOLESCENTS (Updated November 3, 2008)

Older children and adolescents now make up the largest percentage of HIV-infected children cared for at U.S. sites. The CDC estimates that 15% of the 35,314 new HIV diagnoses reported among the 33 states that participated in confidential, name-based HIV infection reporting in 2006 were among youth aged 13–24 years old [1]. Recent trends in HIV prevalence among 13–19 year olds reveal racial minority youth to be more disproportionately affected than analogous disparities seen in adults [2]. HIV-infected adolescents represent a heterogeneous group in terms of sociodemographics, mode of HIV infection, sexual and substance abuse history, clinical and immunologic status, psychosocial development, and readiness to adhere to medications. Many of these factors may influence decisions concerning when to start and what antiretroviral medications should be used.

Most adolescents have behavioral acquisition of their HIV infection. Many of them have recent acquisition of infection and may not yet know their HIV infection status. Thus, many youths are in an early stage of HIV infection, which makes them ideal candidates for early interventions, such as prevention counseling, linkage, and engagement to care. A recent study conducted by the Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN) that enrolled HIV-infected adolescents and young adults who presented for care identified primary genotypic resistance mutations to antiretroviral medications in up to 18% of the evaluable sample of recently infected youth, as determined by the detuned antibody testing assay strategy that defined recent infection as occurring within 180 days of testing [3]. In addition, a limited but increasing number of HIV-infected adolescents are long-term survivors of HIV infection acquired perinatally or through blood products as infants. Such adolescents are usually heavily treatment-experienced and may have a unique clinical course that differs from that of adolescents infected later in life [4]. If they harbor resistant virus, optimal antiretroviral regimens should be based on the same guiding principles as for heavily treatment-experienced adults.

Antiretroviral Therapy Considerations in Adolescents

Adult guidelines for antiretroviral therapy are usually appropriate for postpubertal adolescents, because HIV-infected adolescents who were infected sexually or through injection drug use during adolescence follow a clinical course that is more similar to that of adults than to that of children.

Dosage of medications for HIV infection and opportunistic infections should be prescribed according to Tanner staging of puberty and not solely on the basis of age [5, 6]. Adolescents in early puberty (i.e., Tanner Stages I and II) should be administered doses on pediatric schedules, whereas those in late puberty (i.e., Tanner Stage V) should follow adult dosing schedules. However, Tanner stage and age are not necessarily directly predictive of drug pharmacokinetics. Because

puberty may be delayed in perinatally HIV-infected children [7], continued use of pediatric doses in puberty-delayed adolescents can result in medication doses that are higher than the usual adult doses. Because data are not available to predict optimal medication doses for each antiretroviral medication for this group of children, issues such as toxicity, pill or liquid volume burden, adherence, and virologic and immunologic parameters should be considered in determining when to transition from pediatric to adult doses. Youth who are in their growth spurt period (i.e., Tanner Stage III in females and Tanner Stage IV in males) and who are using adult or pediatric dosing guidelines and those adolescents whose doses have been transitioned from pediatric to adult doses should be closely monitored for medication efficacy and toxicity. Therapeutic drug monitoring can be considered in selected circumstances to help guide therapy decisions under this context. Pharmacokinetic studies of drugs in youth are needed to better define appropriate dosing. For a more detailed discussion, see [Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection](#) [8].

Adherence Concerns in Adolescents

HIV-infected adolescents have specific adherence problems. Comprehensive systems of care are required to serve both the medical and psychosocial needs of HIV-infected adolescents, who are frequently inexperienced with health care systems and who lack health insurance. Many HIV-infected adolescents face challenges in adhering to medical regimens for reasons that include:

- denial and fear of their HIV infection;
- misinformation;
- distrust of the medical establishment;
- fear and lack of belief in the effectiveness of medications;
- low self-esteem;
- unstructured and chaotic lifestyles;
- lack of familial and social support; and
- unavailable or inconsistent access to care or health insurance and incumbent risks of inadvertent parental disclosure of the youth's HIV infection status if parental health insurance is used.

Treatment regimens for adolescents must balance the goal of prescribing a maximally potent antiretroviral regimen with realistic assessment of existing and potential support systems to facilitate adherence. Adolescents benefit from reminder systems (e.g., beepers, timers, and pill boxes) that are stylish and do not call attention to themselves. It is important to make medication adherence as user friendly and as little stigmatizing as possible for the older child or adolescent. The concrete thought processes of adolescents make it difficult for them to take medications when they are asymptomatic, particularly if the medications have side effects. Adherence to complex regimens is particularly challenging at a time of life when adolescents do not want to be different from their peers. Directly observed therapy, although considered impractical for all adolescents, might be important for selected HIV-infected adolescents [9-13].

Difficult Adherence Problems

Because adolescence is a period that is characterized by rapid changes in physical maturation, cognitive processes, and life style, predicting long-term adherence in an adolescent can be very challenging. The ability of youth to adhere to therapy needs to be included as part of therapeutic decision making concerning the risks and benefits of starting treatment. Erratic adherence may result in the loss of future regimens because of the development of resistance mutations. Clinicians who care for HIV-infected adolescents frequently manage youth in whom therapy is needed but in whom significant concerns exist regarding the ability to adhere to therapy. In these cases, alternative considerations to initiation of therapy can be the following: (1) a short-term deferral of treatment until adherence is more likely or while it is aggressively addressed; (2) an adherence testing period in which a placebo (e.g., vitamin pill) is administered; and (3) the avoidance of any regimens with low genetic resistance barriers. Such decisions are ideally individualized to each patient and should be taken carefully in context with the clinical status. For a more detailed discussion on specific therapy and adherence issues for HIV-infected adolescents, see [Guidelines for Use of Antiretroviral Agents in Pediatric HIV Infection](#) [8].

Special Considerations in Adolescents

Sexually transmitted infections (STIs), in particular human papilloma virus (HPV), should also be addressed among every adolescent. For a more detailed discussion on STIs, see the most recent CDC guidelines [14] and the pediatric opportunistic infection treatment guidelines on HPV among HIV-infected adolescents [15]. Family planning counseling, including a discussion of the risks of perinatal HIV transmission and methods to reduce them, should be provided to all youth. Gynecologic care is especially important to provide for the HIV-infected female adolescent. Contraception, including the interaction of specific antiretroviral drugs on hormonal contraception, and the potential for pregnancy also may alter choices of antiretroviral therapy. As an example, efavirenz should be used with caution in females of childbearing age and should only be prescribed after intensive counseling and education about the potential effects on the fetus, the need for close monitoring—including periodic pregnancy testing—and a commitment on the part of the teen to use effective contraception. For a more detailed discussion, see [HIV-Infected Women](#) [16].

Transitioning Care

Given the lifelong infection with HIV and the need for treatment through several stages of growth and development, HIV care programs and providers need flexibility to appropriately transition care for HIV-infected children, adolescents, and young adults. A successful transition requires an awareness of some fundamental differences between many adolescent and adult HIV care models. In most adolescent HIV clinics, care is more “teen-centered” and multidisciplinary, with primary care being highly integrated into HIV care. Teen services, such as sexual and reproductive health, substance use treatment, mental health, treatment education, and adherence counseling are all found in one clinic setting. In contrast, many adult HIV clinics may rely more on referral of the patient to separate subspecialty care settings, such as gynecology. Transitioning the care of an emerging young adult includes considerations of areas such as medical insurance, independence, autonomy, decisional capacity, confidentiality, and consent. Also, adult clinic settings tend to be larger and can easily intimidate younger, less motivated patients. As an additional complication to this transition, HIV-infected adolescents belong to two epidemiologically distinct subgroups: (1) those who acquired their infection perinatally—who would likely have more disease burden history, complications, and chronicity; less functional autonomy; greater need for antiretroviral treatment; and higher mortality risk; and (2) those who are behaviorally infected. Thus, these subgroups have unique biomedical and psychosocial considerations.

To maximize the likelihood of a successful transition, facilitators to successful transitioning are best implemented early on. These include the following: (1) optimizing provider communication between adolescent and adult clinics; (2) addressing patient/family resistance caused by knowledge deficits, stigma or disclosure concerns, and differences in practice styles; (3) preparing youth for life skills development, including counseling them on the appropriate utilization of a primary care provider and appointment management, the importance of prompt symptom recognition and reporting, and of the importance of self-efficacy with medication management, insurance, and entitlements; (4) identifying an optimal clinic model for a given setting (i.e., simultaneous transition of mental health and/or case management versus a gradual phase-in); (5) implementing ongoing evaluation to measure the success of a selected model; (6) engaging in regular multidisciplinary case conferences between adult and adolescent care providers; (7) implementing interventions that may be associated with improved outcomes, such as support groups and mental health consultation; and (8) incorporating a family planning component into clinical care. Attention to these key areas will likely improve adherence to appointments and avert the potential for a youth to “fall through the cracks”, as it is commonly referred to in adolescent medicine.

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HIV AND ILLICIT DRUG USERS (IDUs) (Updated November 3, 2008)

Treatment Challenges of HIV-Infected IDUs and Other Illicit Substance Users

Injection drug use is the second-most common mode of HIV transmission in the United States. In addition, non-injection illicit drug use may facilitate sexual transmission of HIV. Injection and non-injection illicit drugs include the following: heroin, cocaine, marijuana, and club drugs (i.e., methamphetamine, ketamine, gamma-hydroxybutyrate [GHB], and amyl nitrate). The most commonly used illicit drugs associated with HIV infection are heroin and cocaine; however, the use of club drugs has increased substantially in the past several years and is common among those who have HIV infection or who are at risk for HIV infection. Methamphetamine and amyl nitrate (i.e., poppers) have been the most strongly associated with high-risk sexual behavior in men who have sex with men (MSM), and the association is less consistent with the other club drugs [1].

All illicit drugs have been associated with depression and anxiety, either as part of the withdrawal process or as a consequence of repeated use. This is particularly relevant in the treatment of HIV infection, as depression is one of the strongest predictors of poor adherence and poor treatment outcomes [2]. Although treatment of HIV disease in this population can be successful, IDUs who have HIV disease present special treatment challenges. These may include the following: (1) an array of complicating comorbid medical and mental health conditions, (2) limited access to HIV

care, (3) inadequate adherence to therapy, (4) medication side effects and toxicities, (5) the need for substance abuse treatment, and (6) drug interactions that can complicate HIV treatment [3].

Underlying health problems among IDUs result in increased morbidity and mortality, either independent of or accentuated by HIV disease. Many of these problems are the consequence of prior exposures to infectious pathogens and from nonsterile needle and syringe use. Such problems can include hepatitis B or C virus infection, tuberculosis, skin and soft tissue infections, recurrent bacterial pneumonia, endocarditis, and neurologic and renal disease. Furthermore, the high prevalence of underlying mental health illness in this population, which antedates and/or is exacerbated by illicit substance use, results in both morbidity and difficulties in providing clinical care and treatment [4-6]. Successful HIV therapy for IDUs often rests upon acquiring familiarity with and providing care for these comorbid conditions.

IDUs have less access to HIV care and are less likely to receive antiretroviral therapy than other populations [7, 8]. Factors associated with low rates of antiretroviral therapy use among IDU have included active drug use, younger age, female gender, suboptimal health care, lack of access to illicit drug treatment programs, recent incarceration, and lack of expertise among health care providers [7, 8]. The typically unstable chaotic life patterns of many IDU, the powerful pull of addictive substances; and common misperceptions about the dangers, impact, and benefits of antiretroviral therapy all contribute to decreased adherence [9]. The chronic and relapsing nature of substance abuse as a biologic and medical disease, compounded by the high rate of mental illness, additionally complicates the relationship between health care workers and IDU. The first step in provision of care and treatment for these individuals is the recognition of the existence of a substance abuse problem. Whereas this is often open and obvious, patients may hide such behaviors from clinicians. Assessment of the patient for the presence of substance abuse should be part of routine medical history taking and should be done in a clinical, straightforward, and nonjudgmental manner.

Treatment Efficacy in HIV-Infected Illicit Drug Use Populations

Although IDUs are underrepresented in HIV therapy clinical trials, available data indicate that—when they are not actively using drugs—efficacy of antiretroviral therapy in the IDU is similar to that seen in other populations [10]. Furthermore, therapeutic failure in this population generally correlates with the degree that drug use disrupts daily activities rather than with drug use *per se* [11]. Providers need to remain attentive to the possible impact these factors have upon the patient before and during prescription of antiretroviral therapy. Although many IDUs can sufficiently control their drug use over long enough periods of time to benefit from care, substance abuse treatment is often necessary for successful HIV management.

Close collaboration with substance abuse treatment programs and proper support and attention to this population's special multidisciplinary needs are critical components of successful HIV treatment. Essential to this end are accommodating and flexible, community-based HIV care sites that are characterized by familiarity with and nonjudgmental expertise in management of drug users' wide array of needs and in development of effective strategies to promote medication adherence [5, 6], including, if available, the use of adherence support mechanisms, such as modified directly observed therapy, which has shown promise in this population [12].

Antiretroviral Agents and Illicit Drugs: Toxicities and Interactions

IDUs are more likely to experience an increased frequency of side effects and toxicities of antiretroviral therapy. Although not systematically studied, this is likely because underlying hepatic, renal, neurologic, psychiatric, gastrointestinal, and hematologic diseases are highly prevalent among IDUs. Selection of antiretroviral agents in this population should be made with consideration of these comorbid conditions and risks.

Methadone and Antiretroviral Therapy. Methadone, an orally administered, long-acting opiate agonist, is the most common pharmacologic treatment for opiate addiction. Its use is associated with decreased heroin addiction, decreased needle sharing, and improved quality of life. Because of its opiate-induced effects on gastric emptying and the metabolism of cytochrome P450 isoenzymes 3A4 and 2D6, pharmacologic effects and interactions with antiretroviral agents may commonly occur. These may diminish the effectiveness of either or both therapies by causing opiate withdrawal or overdose, increased methadone toxicity, and/or decreased antiretroviral efficacy.

Methadone and NRTIs

Most of the currently available antiretroviral agents have been examined in terms of potential significant pharmacokinetic interactions with methadone. (See [Table 14c](#).) No NRTIs appear to have a clinically significant effect on methadone metabolism. Abacavir may increase methadone clearance, but the clinical significance is unknown [13]. Conversely, methadone is known to increase the area under the curve of zidovudine by 40% [14], with a possible increase in zidovudine related side effects. Methadone decreases didanosine levels when didanosine is in the tablet formulation [15] but not when in the EC formulation. Recent data indicate a lack of significant interaction between methadone and lamivudine or tenofovir [16, 17].

Methadone and NNRTIs

Pharmacokinetic interactions between NNRTIs and methadone are well described and clinically problematic [18, 19]. (See [Table 14b](#).) Both efavirenz and nevirapine, potent inducers of CYP450 enzymes, have been associated with significant decreases in methadone levels, which results in the potential for opiate withdrawal. It is necessary to inform patients and substance abuse treatment facilities of the likelihood of this interaction if either drug is prescribed to those receiving methadone. The clinical effect is usually seen after 7 days of coadministration and may be managed by increasing the methadone dosage, usually in 5-mg to 10-mg increments daily until the desired effect is achieved. Delavirdine, a CYP450 isoenzyme inhibitor, increases methadone levels moderately but is not likely to be of clinical significance [20]. Etravirine does not affect methadone level [21].

Methadone and PIs

Limited information indicates that PI levels are generally not affected by methadone. However, many PIs have significant effects on methadone metabolism. Lopinavir and nelfinavir administration result in a significant decrease in methadone levels [22], although opiate withdrawal is less likely to occur with nelfinavir use. This is likely because of lack of effect on free rather than total methadone levels. Lopinavir/ritonavir-associated significant reductions in methadone levels and opiate withdrawal symptoms are the result of the lopinavir, not the ritonavir, component [23]. There is no pharmacokinetic interaction between atazanavir and methadone [24], and saquinavir does not significantly affect free unbound methadone levels [25]. [Table 14a](#) provides updated information regarding interactions between PIs and methadone.

Buprenorphine and Antiretroviral Drugs. Buprenorphine, a partial μ -opiate agonist, is administered sublingually and is coformulated with naloxone. It is being increasingly used for opiate abuse treatment. The lower risk of respiratory depression and overdose compared with methadone allows it to be prescribed by physicians for the treatment of opiate dependency. This flexible treatment setting could be of significant value to opiate-addicted HIV-infected patients who require antiretroviral therapy, as it enables one physician or program to provide both medical and substance abuse services.

Limited information is currently available about interactions between buprenorphine and antiretroviral agents [26]. Findings from available studies show a more favorable drug interaction profile than that of methadone. In contrast to methadone, buprenorphine does not appear to increase zidovudine levels. Buprenorphine concentration is significantly reduced when administered with efavirenz, but opioid withdrawal has not been observed [27]. Buprenorphine/naloxone has also been studied in combination with several protease inhibitors (nelfinavir, lopinavir/ritonavir, and ritonavir). Findings from these studies indicate pharmacokinetic interactions that result in altered buprenorphine exposure, but these have not been of clinical significance [28]. In a small case series, over-sedation and probable opioid excess occurred in patients who received buprenorphine/naloxone with ritonavir-boosted atazanavir [29]. A recent formal pharmacokinetic study suggested, but did not confirm, these findings [30]. Nevertheless, when atazanavir and buprenorphine/naloxone are coadministered, patients should be monitored carefully for opioid excess.

Methylenedioxymethamphetamine (MDMA), GHB, ketamine, and methamphetamine all have the potential to interact with antiretroviral agents as all are cleared, at least in part, by the cytochrome P450 system. Overdoses secondary to interactions between the party drugs (i.e., MDMA or GHB) and PI-based antiretroviral therapy have been reported [31].

Summary

It is usually possible over time to support most active drug users, such that acceptable adherence levels with antiretroviral agents can be achieved [32, 33] Providers must work to combine all available resources to stabilize an

active drug user to prepare them for antiretroviral therapy. This should include identification of concurrent medical and psychiatric illnesses, drug treatment, needle and syringe exchange, and harm reduction strategies. A history of drug use alone is insufficient reason to withhold antiretroviral therapy, as those with a history of prior drug use have adherence rates similar to non-drug users.

Important considerations in the selection of successful regimens and the provision of appropriate patient monitoring in this population include supportive clinical sites; linkage to substance abuse treatment; and awareness of the interactions between illicit drugs and antiretroviral agents, including the increased risk for side effects and toxicities. Simple regimens should be considered to enhance medication adherence. Preference should be given to antiretroviral agents that have a lower risk for hepatic and neuropsychiatric side effects, simple dosing schedules, and minimal interaction with methadone.

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HIV-INFECTED WOMEN (Updated November 3, 2008)

Panel's Recommendations:

- *When initiating antiretroviral therapy for HIV-infected women, the indications for initiation of therapy and the goals of treatment are the same as for other adults and adolescents (AI).*
- *Women taking antiretroviral agents that have drug interactions with oral contraceptives should use an additional or alternative contraceptive method for prevention of unintended pregnancy (AIII).*
- *In pregnant women, an additional goal of therapy is prevention of mother-to-child transmission (PMTCT), with a goal of maximal viral suppression to reduce the risk of transmission of HIV to the fetus and newborn (AI).*
- *Genotypic resistance testing is recommended for all HIV-infected patients, including pregnant women, prior to initiation of therapy (AIII) and for those entering pregnancy with detectable HIV RNA levels while on therapy (AII).*
- *Selection of an antiretroviral combination in pregnant women should take into account known safety, efficacy, and pharmacokinetic data of each agent during pregnancy (AIII).*
- *Efavirenz should be avoided in a pregnant woman during the first trimester or in a woman who desires to become pregnant or who does not or cannot use effective and consistent contraception (AIII).*
- *Clinicians should consult the most current Public Health Service guidelines when designing a regimen for a pregnant patient (AIII).*

This section provides a brief discussion of some unique considerations and basic principles to follow when caring for HIV-infected women in general and for pregnant HIV-infected women. Clinicians who provide care for pregnant women should consult the latest guidelines of the [Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#) for in-depth discussion and management assistance [1].

Gender Considerations in Antiretroviral Therapy

Adverse Effects:

- ***Nevirapine-associated hepatotoxicity:*** Nevirapine has been associated with an increased risk of symptomatic, potentially fatal, and often rash-associated liver toxicity among antiretroviral-naïve individuals. These complications generally occur early in the course of treatment, and women with higher CD4 T-cell counts appear to be at greatest risk [2-5]. A meta-analysis of nevirapine-related clinical trials and observational studies found that a CD4 T cell count >250 cells/mm³ at the time of nevirapine initiation was associated with a 9.8-fold increase in symptomatic hepatic events compared with lower CD4 T-cell counts in women [2]. Thus, it is generally recommended that nevirapine should not be prescribed to antiretroviral-naïve women who have CD4 T-cell counts >250 cells/mm³ unless there is no other alternative and the benefit from the therapy outweighs the risk of hepatotoxicity (AI).
- ***Lactic acidosis:*** There appears to be a female predominance in the increased incidence of symptomatic and even fatal lactic acidosis associated with prolonged exposure to nucleoside analogues, particularly with stavudine and/or didanosine [6]. Although deaths as a result of lactic acidosis have been reported in HIV-infected pregnant women, it is unclear whether pregnancy increases the incidence of this disorder. However, because pregnancy itself can mimic some of the early symptoms of lactic acidosis and because pregnancy can also be associated with other significant disorders of liver metabolism (such as acute fatty liver of pregnancy and HELLP [hemolysis, elevated liver enzymes, and low platelet count] syndrome), early signs and symptoms of lactic acidosis related to antiretroviral use may be missed. Women receiving antiretroviral therapy should be warned about the signs and symptoms of lactic acidosis, and levels of liver enzymes and electrolytes should be monitored on a periodic basis [6].
- ***Metabolic complications:*** A few studies have compared women with men in terms of metabolic complications associated with antiretroviral therapy use. HIV-infected women are more likely to experience increases in central fat with antiretroviral therapy and are less likely to have triglyceride elevations on treatment [7, 8]. Women have an increased risk of osteopenia/osteoporosis, particularly after menopause, and this risk may be exacerbated by HIV and antiretroviral therapy [9, 10]. At the present time, none of these differences require a change in recommendations regarding treatment or therapeutic monitoring.

Drug Interactions: Several PIs and NNRTIs have drug interactions with oral contraceptives. Interactions include either a decrease or an increase in blood levels of ethinyl estradiol and/or norethindrone levels (See [Tables 14a and b](#)), which potentially decrease contraceptive efficacy or increase estrogen- or progestin-related adverse effects (e.g., thromboembolic risk). In general, women who are on any of these antiretroviral agents should use an alternative or additional method of contraception (**AIII**). Although there is minimal information about drug interactions with use of newer combined hormonal contraceptive methods (e.g., transdermal patch, vaginal ring), an additional or alternative contraceptive method should also be considered on the basis of established drug interactions between antiretroviral agents and oral contraceptives. There are limited data on drug interactions between antiretroviral agents and progestin-only contraceptive methods; however, recent data have found no significant changes in antiretroviral drug concentrations of nelfinavir, nevirapine, or efavirenz when used with depot medroxyprogesterone acetate (DMPA), and there is no evidence of reduced DMPA effectiveness [11-13].

Women of Childbearing Potential

All women of childbearing potential should be offered preconception counseling and care as a component of routine primary medical care. Discussion should include special considerations with antiretroviral therapy use when trying to conceive and during pregnancy. (See [Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#).) Antiretroviral regimen selection should account for the possibility of planned or unplanned pregnancy. The most vulnerable period in fetal organogenesis is early in gestation, often before pregnancy is recognized. Sexual activity, reproductive plans, and use of effective contraception to prevent unintended pregnancy should be discussed with the patient. As part of the evaluation for initiating therapy, women should be counseled about the potential teratogenic risk of efavirenz-containing regimens, should pregnancy occur. These regimens should be avoided in women who are trying to conceive or who are not using effective and consistent contraception. Counseling should be provided on an ongoing basis.

Pregnant Women

The decision to use any antiretroviral drug during pregnancy should be made by the woman after counseling and discussion with her clinician regarding the benefits versus risks to her, her fetus, and the newborn. Her decision should be respected; coercive and punitive policies undermine provider-patient trust and could discourage women from seeking prenatal care and adopting health care behaviors that optimize personal, fetal, and neonatal well-being.

Prevention of Mother-to-Child Transmission (PMTCT). Antiretroviral therapy is recommended in all pregnant women, regardless of virologic, immunologic, or clinical parameters, for the purpose of PMTCT (**AI**). Both reduction of HIV RNA levels and use of antiretroviral therapy appear to have an independent effect on reduction of perinatal transmission [14-16]. The goal with antiretroviral therapy in pregnancy, as in nonpregnant individuals, is to achieve maximal and sustained suppression of HIV RNA levels.

Genotypic resistance testing is recommended for all pregnant women prior to initiation of therapy (**AIII**) and for those entering pregnancy with detectable HIV RNA levels while on therapy (**AII**). Optimal prevention of perinatal transmission may require initiation of antiretroviral therapy before results of resistance testing are available, in which case therapy should be modified if the result demonstrates the presence of significant mutation(s) that may confer resistance to the prescribed antiretroviral regimen.

Long-term follow-up is recommended for all infants born to women who have received antiretroviral drugs during pregnancy, regardless of the infant's HIV status.

Regimen Considerations. Pregnancy should not preclude the use of optimal therapeutic regimens. However, recommendations regarding the choice of antiretroviral drugs for treatment of HIV-infected pregnant women are subject to unique considerations, which may result in different specific recommendations regarding timing of initiation and choice of drugs. These considerations include the following:

- potential changes in pharmacokinetics, and thus dosing requirements, which result from physiologic changes associated with pregnancy,
- potential adverse effects of antiretroviral drugs in pregnant women,

- effect on the risk for perinatal HIV transmission, and
- potential short- and long-term effects of the antiretroviral drug on the fetus and newborn, all of which are unknown for many antiretroviral drugs.

Clinicians should review “[Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#)” [1] for a detailed discussion of drug choices. Combination drug regimens are considered the standard of care for therapy, both for the treatment of HIV infection and for PMTCT. Zidovudine by intravenous infusion to the mother during labor and orally to the neonate for 6 weeks is recommended irrespective of antenatal regimen chosen.

There are some specific differences in treatment recommendations in pregnancy based on the above considerations:

- Zidovudine should be included in the antenatal antiretroviral regimen unless there is severe toxicity, there is documented resistance, or the woman is receiving a stavudine-containing regimen. Stavudine and zidovudine coadministration is contraindicated because of virologic antagonism. However, women well-controlled on a non-zidovudine-containing regimen have a very low risk of perinatal transmission, and substitution or addition of zidovudine may compromise adherence. Therefore, it is reasonable to continue a non-zidovudine-containing regimen as long as it is fully suppressive. Although controversial, the use of zidovudine alone might be an appropriate option for pregnant women who have CD4 T-cell counts >350 cells/mm³ and HIV RNA levels $<1,000$ on no treatment and who wish to restrict exposure of their fetus to antiretroviral drugs during pregnancy while still reducing the risk of HIV transmission to their infants. In this situation, time-limited use of zidovudine during the second and third trimesters of pregnancy is less likely to induce the development of resistance than it is in women with higher pre-treatment viral loads.
- Efavirenz-containing regimens should be avoided in the first trimester, because significant teratogenic effects were seen in primate studies at drug exposures similar to those achieved during human exposure **(AIII)**. In addition, several cases of neural tube defects have now been reported after early human gestational exposure to efavirenz [17, 18]. Efavirenz may be considered for use after the first trimester if indicated because of toxicity, resistance, or drug interaction concerns (e.g., need for anti-tuberculosis therapy).
- Nevirapine has been associated with hepatic failure and death among a small number of pregnant patients [19]. Although there is no evidence that pregnancy additionally increases risk, pregnant women may receive combination antiretroviral regimens at higher CD4 T-cell counts for PMTCT, even if they would not otherwise meet indications for treatment. In antiretroviral-naïve pregnant women who have CD4 T-cell counts >250 cells/mm³, nevirapine should not be initiated as a component of a combination regimen unless the benefit clearly outweighs the risk **(AII)**. Pregnant patients on chronic nevirapine prior to pregnancy are probably at a much lower risk for this toxicity. If nevirapine is used, close clinical and laboratory monitoring, particularly during the first 18 weeks of treatment, is advised, and nevirapine should be stopped immediately in all women who develop signs or symptoms of hepatitis. The use of single-dose nevirapine for prevention of perinatal transmission has not been associated with hepatotoxicity.
- Several small studies show that optimal levels of several PIs may not be achieved in pregnancy, especially in the third trimester, although the clinical relevance of this is unknown [20-22]. Once-daily lopinavir/ritonavir dosing is not recommended in pregnancy, because there are no data to address adequacy of blood levels with this dosing regimen **(BII)**.
- There are minimal data on the use of newer agents, such as enfurvitide, etravirine, maraviroc, or raltegravir, in pregnancy.

Clinicians who are treating HIV-infected pregnant women are strongly encouraged to report cases of prenatal exposure to antiretroviral drugs (either administered alone or in combinations) to the **Antiretroviral Pregnancy Registry** (<http://www.apregistry.com/>). The registry collects observational, nonexperimental data regarding antiretroviral exposure during pregnancy for the purpose of assessing potential teratogenicity. For more information regarding selection and use of antiretroviral therapy during pregnancy, please refer to “[Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States](#)” [1].

Lastly, women should be counseled regarding the avoidance of breastfeeding. Continued clinical, immunologic, and virologic follow-up should be done as recommended for nonpregnant adults and adolescents.

Discontinuation of Antiretroviral Therapy Postpartum

For women who began antiretroviral therapy with a nadir CD4 T-cell count >350 cells/mm³ for PMTCT, the decision on whether to continue therapy after delivery should take into account current recommendations for initiation of antiretroviral therapy, current and nadir CD4 T-cell counts and trajectory, HIV RNA levels, and patient preference. A recent study from the Women and Infants Transmission Study (WITS) of women who were antiretroviral-naïve prior to pregnancy and had CD4 T-cell counts >350 /mm³ [23] found no significant differences in CD4 T-cell count, viral load, or disease progression among those who did or did not continue antiretroviral treatment after delivery through 12 months postpartum. In most cases, when drugs are discontinued postnatally, all drugs should be stopped simultaneously. However, if therapy includes an NNRTI, stopping all regimen components simultaneously may result in functional monotherapy because of the long half-life of the NNRTI, which may increase risk of resistance. Nevirapine resistance mutations have been identified postpartum in women taking nevirapine-containing combination regimens only for PMTCT. In one study, nevirapine resistance was identified in 16% of women despite continuation of the nucleoside backbone for 5 days after stopping nevirapine [24]. The current recommendation in women receiving NNRTI-based regimens is to continue the dual NRTI backbone for a short period of time after stopping the NNRTI to decrease the risk of NNRTI resistance. However, the optimal interval between stopping an NNRTI and the other antiretroviral drugs is unknown. An alternative strategy is to substitute the NNRTI with a PI for a period of time while continuing the NRTIs, then to discontinue all the drugs at the same time. Additional research is needed to assess appropriate strategies for stopping NNRTI-containing combination regimens after delivery in situations when ongoing maternal treatment is not indicated, as well as to assess the effect of limited-duration, fully suppressive antiretroviral prophylaxis in pregnancy on future treatment efficacy. (See [Discontinuation or Interruption of Antiretroviral Therapy](#) section.)

In HIV and hepatitis B virus (HBV) coinfecting pregnant women who are receiving antiretroviral therapy only for perinatal prophylaxis and who are stopping therapy after delivery, careful clinical and laboratory monitoring for HBV flare should be performed postpartum when antiretroviral agents active against HBV are discontinued. However, if treatment for HBV is indicated, a full combination regimen for both HIV and HBV infection should be continued. (See [Initiating Antiretroviral Therapy](#) section.)

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CONSIDERATIONS IN MANAGING PATIENTS WITH HIV-2 INFECTION

(New, December 1, 2009)

HIV-2 infection is endemic in West Africa, and although the virus has had only limited spread outside this area, it should be considered in persons of West African origin or those who have had sexual contact or shared needles with persons of West African origin. The prevalence of HIV-2 infection is also disproportionately high in countries with strong socioeconomic ties to West Africa (e.g., France; Spain; Portugal; and former Portuguese colonies such as Brazil, Angola, Mozambique, and parts of India near Goa).

The clinical course of HIV-2 infection is generally characterized by a longer asymptomatic stage, lower plasma HIV-2 viral loads, and lower mortality rates compared with HIV-1 infection [1-2]. However, HIV-2 infection can progress to AIDS, and thus antiretroviral therapy may become necessary during the course of infection. Concomitant HIV-1 and HIV-2 infection may occur and should be considered in patients from a high prevalence area. In the appropriate epidemiologic setting, HIV-2 infection should be suspected in patients with clinical conditions suggestive of HIV infection but with atypical serologic results (e.g., a positive screening assay with an indeterminate HIV-1 Western blot [3]). The possibility of HIV-2 infection should also be considered in the appropriate epidemiologic setting in patients with serologically confirmed HIV infection but low or undetectable viral loads, or in those with declining CD4 cell counts despite apparent virologic suppression on antiretroviral therapy.

The Multispot HIV-1/HIV-2 Rapid Test (Bio-Rad Laboratories) is FDA approved for differentiating HIV-1 from HIV-2 infection. Commercially available HIV-1 viral load assays do not reliably detect or quantify HIV-2, and there are no HIV-2 commercial viral load assays currently available [4-5]. Most studies reporting HIV-2 viral loads use “in-house” assays that are not widely available, making it difficult to monitor virologic response in the clinical setting. In addition, there are no available validated HIV-2 genotypic or phenotypic antiretroviral resistance assays.

To date, there have been no randomized trials addressing the question of when to start antiretroviral therapy or the choice of initial or second-line therapy for HIV-2 infection [6]; thus, the optimal treatment strategy has not been

defined. HIV-2 appears intrinsically resistant to NNRTIs [7] and to enfuvirtide [8]. *In vitro* data suggest HIV-2 is sensitive to the currently available NRTIs, although with a lower barrier to resistance than HIV-1 [9-10]. Variable sensitivity among PIs has been reported, with lopinavir, saquinavir, and darunavir having greater activities than other approved PIs [11-12]. The integrase inhibitor, raltegravir, [13] and the CCR5 antagonist, maraviroc, appear active against some HIV-2 isolates, although there are no approved assays to determine HIV-2 coreceptor tropism and HIV-2 is known to utilize multiple minor coreceptors in addition to CCR5 and CXCR4 [14]. Several small studies suggest poor responses among HIV-2 infected individuals treated with some antiretroviral regimens, including dual-NRTI regimens, regimens containing two NRTIs + NNRTI, and some unboosted PI-based regimens including nelfinavir or indinavir plus zidovudine and lamivudine [6, 15-17]. There are conflicting clinical data on the utility of triple-NRTI regimens [18-19]. In general, boosted PI-containing regimens have resulted in more favorable virologic and immunologic responses [19]. One small study suggested satisfactory responses to lopinavir/ritonavir-containing regimens in 17 of 29 (59%) of antiretroviral-naïve subjects [20].

Resistance-associated mutations develop commonly in HIV-2 patients on therapy [15, 19, 21] and genotypic algorithms used to predict drug resistance in HIV-1 may not be applicable to HIV-2 [10, 19]. CD4 cell recovery on therapy may be poor [22], suggesting that more reliable methods for monitoring disease progression and treatment efficacy in HIV-2 infection are needed.

Until more definitive data are available in a treatment-naïve patient with HIV-2 mono-infection or with HIV-1/HIV-2 dual infection who requires treatment, clinicians should initiate a boosted PI-based regimen. Monitoring of treatment response in such patients is problematic because of the lack of a commercially available HIV-2 viral load assay; however, clinical and CD4 count improvement can be used to assess treatment response.

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Antiretroviral Considerations in Patients with Coinfections

HEPATITIS B (HBV)/HIV COINFECTION (Updated December 1, 2007)

It is not clear that treatment of HBV improves the course of HIV infection, nor is there evidence that treatment of HIV alters the natural history of chronic HBV. However, several liver-associated complications that are ascribed to flares in HBV activity or to toxicity of antiretroviral agents can affect the treatment of HIV in patients with HBV coinfection. These include the following:

- Emtricitabine, lamivudine, and tenofovir have activity against both HIV and HBV. Discontinuation of these drugs may potentially cause serious hepatocellular damage resulting from reactivation of HBV [1-3];
- Lamivudine-resistant HBV is observed in approximately 40% of patients after 2 years of lamivudine monotherapy for chronic HBV and in approximately 90% after 4 years when it is used as the only active drug for HBV in coinfecting patients [4, 5];
- Entecavir has activity against HIV, and its use in patients with dual infection has been associated with selection of the M184V mutation that confers resistance to lamivudine and emtricitabine [6, 7]. Therefore, entecavir should be used only with a fully suppressive antiretroviral regimen in HIV/HBV-coinfecting patients.
- Immune reconstitution can be associated with elevation in transaminases, possibly because HBV is primarily an immune-mediated disease [8]; and
- Many antiretroviral drugs can cause increases in transaminase levels. The rate and magnitude of these increases are higher with HBV coinfection [9, 10]. The etiology and consequences of these changes in liver function tests are unclear, because continuation of therapy may be accompanied by resolution of the changes. Nevertheless, some experts suspend the implicated agent(s) when the ALT is increased to 5–10 times the upper limit of normal. However, in HIV/HBV-coinfecting persons, increases in transaminase levels can herald HBeAg seroconversion, so the cause of the elevations should be investigated prior to the decision to discontinue medications. HBeAg seroconversion can be evaluated by checking HBeAg and anti-HBe as well as HBV DNA levels.

Treatment Recommendations for HBV/HIV Coinfecting Patients

- All patients with HBV should be advised to abstain from alcohol; should receive hepatitis A vaccine if found not to be immune at baseline (i.e., absence of hepatitis A total or IgG antibody); should be advised on methods to prevent HBV transmission (which do not differ from those to prevent HIV transmission); and should be evaluated for the severity of HBV infection.
- **If neither HIV nor HBV infection requires treatment:** Monitor the progression of both infections. If treatment becomes necessary for either infection, follow the guidelines listed in the scenarios below.
- **If treatment is needed for HIV but not for HBV:** The combination of tenofovir and emtricitabine or tenofovir and lamivudine should be used as the NRTI backbone of an antiretroviral regimen, which will result in treatment of both infections. To avoid development of HBV-resistant mutants, none of these agents should be used as the only agent with anti-HBV activity in an antiretroviral regimen.
- **If treatment for HBV is needed:** Patients who need treatment for HBV infection should also be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against both viruses: for example, tenofovir plus either emtricitabine or lamivudine. The use of lamivudine, emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk for resistance. If tenofovir cannot be used, another agent with anti-HBV activity should be used in combination with lamivudine or emtricitabine for treatment of HBV infection. Management of HIV should be continued with a combination regimen to provide maximal suppression.
- **Treating only HBV:** In instances when HIV treatment is not an option or is not desirable, pegylated interferon-alpha may be used for the treatment of HBV infection, as it does not lead to the emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10mg dose; however, there is a theoretical risk for development of HIV resistance, as it has anti-HIV activity at higher doses and is related to tenofovir. Because of

the risk for HIV drug resistance, the use of emtricitabine, lamivudine, tenofovir, or entecavir without a full combination antiretroviral regimen should be avoided.

- **Need to discontinue emtricitabine, lamivudine, or tenofovir:** Monitor clinical course with frequent liver function tests and consider the use of interferon, adefovir dipivoxil, or telbivudine to prevent flares, especially in patients with marginal hepatic reserve.

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HEPATITIS C (HCV)/HIV COINFECTION (Updated December 1, 2009)

Long-term studies of patients with chronic HCV infection show that approximately 33% of the patients progress to cirrhosis at a median time of less than 20 years [1-2]. This rate of progression increases with older age, alcoholism, male sex, and HIV infection [3-6]. A meta-analysis demonstrated that the rate of progression to cirrhosis for persons coinfecting with HCV/HIV was about three times higher compared with the rate for HCV mono-infected patients [5]. This accelerated rate is magnified in patients with low CD4 counts. Chronic HCV infection also complicates HIV treatment due to the increased frequency of antiretroviral-associated hepatotoxicity [7]. Multiple studies have shown poor prognosis for HCV/HIV coinfection in the era of combination antiretroviral therapy. It is unclear if HCV infection accelerates the rate of HIV progression [8-9] or if the accelerated rate primarily reflects the impact of injection drug use, which is strongly linked to HCV infection [10-11]. Although whether antiretroviral therapy reduces the attributable morbidity/mortality from untreated HCV is unknown, the presence of chronic HCV infection influences the treatment of HIV with antiretroviral therapy as discussed below.

Assessment of HCV/HIV Coinfection Prior to Antiretroviral Therapy

- Prior to initiation of antiretroviral therapy, HIV-infected patients should be screened for HCV infection with sensitive immunoassays licensed for detection of antibody to HCV in blood. To confirm the presence of chronic infection, HCV-seropositive persons should be tested for HCV RNA using a qualitative or quantitative assay [12].
- Patients with HCV/HIV coinfection should be advised to avoid alcohol consumption, use appropriate precautions to prevent transmission of both viruses to others, and should be given hepatitis A and B vaccine if susceptible.
- All patients with HCV/HIV coinfection should be evaluated for HCV therapy. HCV treatment is recommended according to standard guidelines with strong preference for treating patients with higher CD4 counts. For patients with lower CD4 counts (<200 cell/mm³), it may be preferable to initiate antiretroviral therapy and delay HCV therapy until CD4 counts increase as a result of HIV treatment [12-15].

- Concurrent treatment of both HIV and HCV is feasible but may be complicated by pill burden, drug toxicities, and drug interactions. Some notable considerations include:
 - Didanosine should not be given with ribavirin because of the potential for drug-drug interactions leading to life-threatening didanosine-associated mitochondrial toxicity including hepatomegaly/steatosis, pancreatitis, and lactic acidosis [16].
 - Zidovudine combined with ribavirin should be avoided when possible because the higher rates of anemia associated with the combination make ribavirin dose reduction necessary [17].
 - Abacavir has been associated with decreased response to peginterferon plus ribavirin in some, but not all, retrospective studies; current evidence is insufficient to recommend avoiding this combination [18-20].
 - Growth factors (e.g., filgrastim and erythropoietin) may be required to manage interferon-associated neutropenia and ribavirin-associated anemia; zidovudine may increase the need for adjuvant growth factors due to increased bone marrow suppression [17].

Antiretroviral Therapy in HCV/HIV Coinfection

- **Hepatotoxicity:** Drug-induced liver injury (DILI) following antiretroviral therapy is more common in HIV/HCV coinfection. The greatest risk for DILI may be observed in coinfecting persons with advanced liver disease (e.g., cirrhosis or end-stage liver disease) [21]. Eradication of HCV infection may decrease the likelihood of antiretroviral-associated DILI [22].
 - Given the substantial heterogeneity in patient populations and drug regimens, comparison of DILI incidence rates for individual antiretroviral agents across clinical trials is difficult. In such studies, the highest incidence rates of grade 3 or 4 elevations in liver enzyme levels have been observed during therapy with regimens that include stavudine (with or without didanosine), nevirapine, full-dose ritonavir (600mg twice daily), or tipranavir (boosted by low-dose ritonavir) [23]. Also, due to the potential for concurrent fatty liver disease (steatosis), the use of stavudine or didanosine should be limited [24].
 - Patients should be monitored by following alanine and aspartate aminotransferase levels at 1 month and then every 3 months following initiation of antiretroviral therapy. Mild to moderate fluctuations in liver enzyme levels are typical in persons with chronic HCV infection. In the absence of signs and/or symptoms of liver disease these fluctuations do not require interruption of antiretroviral therapy. Significant elevation in liver enzyme levels (>5 times the upper limit of the laboratory reference range) should prompt careful evaluation for signs and symptoms of liver insufficiency and for alternative causes of liver injury (e.g., acute viral hepatitis A or B infection, hepatobiliary disease, or alcoholic hepatitis); short-term antiretroviral interruption may be required [25].
- **When to start antiretroviral therapy:** The rate of liver disease (fibrosis) progression is accelerated by HIV/HCV coinfection, particularly in persons with low CD4 cell counts ($\leq 350/\text{mm}^3$). Data derived largely from retrospective cohort studies regarding the effect of antiretroviral therapy on the natural history of HCV disease are inconsistent [6, 26-27]. However, antiretroviral therapy may slow the progression of liver disease by preserving or restoring immune function and reducing HIV-related immune activation and inflammation [28-30]. Thus, for most coinfecting patients including those with cirrhosis, the potential benefits of antiretroviral therapy outweigh concerns regarding DILI.
 - Antiretroviral therapy should be started in HCV/HIV-coinfecting persons in accordance with the Panel's recommendation for initiating antiretroviral therapy in treatment-naïve patients.
- **What to start and what not to use:** Initial combination regimens for the antiretroviral-naïve patient with HCV/HIV are the same as for persons without HCV infection. HCV infection does not significantly alter the virologic or immunologic response to effective antiretroviral therapy [31]. Special considerations for antiretroviral therapy in persons with HCV/HIV coinfection include:
 - Patients receiving or considering therapy with ribavirin should avoid didanosine, stavudine, and zidovudine.

- o Antiretroviral agents with the greatest risk of DILI should be used with caution.
- o Cirrhotic patients should be carefully assessed for signs of liver decompensation according to the Child-Turcotte-Pugh classification system because hepatically metabolized antiretroviral drugs may require dose modification or avoidance in patients with Child-Pugh class B and C disease (see [Appendix B, Table 7](#)).

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MYCOBACTERIUM TUBERCULOSIS DISEASE OR LATENT TUBERCULOSIS INFECTION WITH HIV COINFECTION (Updated January 29, 2008)

Panel's Recommendations:

- **The treatment of active tuberculosis (TB) disease in patients with HIV infection should follow the same principles for persons without HIV infection (AI).**
- **Presence of active TB requires immediate initiation of treatment (AI).**
- **The optimal timing of initiation of antiretroviral therapy in patients with active TB disease is not known. In antiretroviral-naïve patients, delay of antiretroviral therapy for 2 to 8 weeks after initiation of TB treatment may allow for easier identification of causes of adverse drug reactions, and may reduce the risk of Immune Reconstitution Inflammatory Syndrome (IRIS or a “paradoxical reaction”) once antiretroviral therapy is initiated. However, delay may increase the risk of HIV-related complications and mortality, particularly in those with very low CD4 cell counts (BII).**
- **Directly observed therapy of TB treatment is strongly recommended for HIV-infected patients with active TB disease (AII).**
- **Despite pharmacokinetic drug interactions, a rifamycin should be included in regimens for patients receiving antiretroviral therapy, with dosage adjustment as necessary (AII).**
- **Where available, rifabutin is the preferred rifamycin in HIV-infected patients with active TB disease due to its lower risk of substantial interactions with antiretroviral therapy (AII).**
- **Rifampin/rifabutin-based regimens should be given at least three times weekly in HIV-infected patients with active disease and CD4 count <100 cells/mm³; twice weekly is acceptable if CD4 count >100 cells/mm³ (AII).**
- **Once-weekly rifapentine is not recommended in the treatment of active TB disease in HIV-infected patients (AI).**
- **The optimal management of IRIS is unknown; TB treatment and antiretroviral therapy should be continued, along with use of non-steroidal anti-inflammatory agents for milder cases and consideration of the use of high dose corticosteroids for 1 to 4 weeks in severe cases, with the length of treatment and taper based on control of symptoms (BIII).**
- **Immune restoration as a result of antiretroviral therapy may be associated with conversion from a negative to a positive tuberculin skin test (TST) or IFN- γ release assay (IGRA) in response to M.TB-specific proteins; repeat TST or IGRA is recommended in previously TST-negative or IGRA-negative individuals after initiation of antiretroviral therapy when the CD4 cell count exceeds 200 cells/mm³ (BII).**
- **HIV-infected individuals found to have latent TB infection (LTBI), defined as ≥ 5 mm skin test induration or positive IGRA with no prior treatment for LTBI and after appropriate evaluation to rule out active TB disease and no prior treatment of LTBI, should commence treatment with isoniazid (with pyridoxine) for 6 to 9 months (AI).**

HIV infection significantly increases the risk of progression from latent to active tuberculosis (TB) disease. In HIV-negative individuals with latent TB infection (LTBI), the lifetime risk of developing active TB disease is 5%–10%, whereas in people living with HIV with latent TB, the risk is 10% *per year* [1]. The CD4 T-cell count influences both the frequency and clinical expression of active TB disease [2, 3]. Active TB also negatively affects HIV disease. It may be associated with a higher HIV viral load and more rapid progression of HIV disease [1, 2]. Important issues with respect to the use of antiretroviral therapy in patients with active TB disease are 1) the sequencing of treatments, 2) the value of directly observed therapy, 3) potential for significant pharmacokinetic drug interactions with rifamycins, 4) the additive toxicities including high rates of hepatotoxicity and neuropathy associated with drugs used for each condition, 5) development of Immune Reconstitution Inflammatory Syndrome (IRIS) with TB after initiation of antiretroviral therapy, 6) the effect of antiretroviral therapy on results of tuberculin skin testing, and 7) the need for integration of HIV and TB care and therapy.

Terminology: In this section, the terms “HIV infected with active TB disease” and “HIV/TB disease” are used synonymously to designate HIV-infected patients with active TB disease in need of TB treatment. The term “HIV/TB coinfection” may cause confusion because it can refer to either active TB or LTBI in the presence of HIV infection.

Sequencing of Treatments

The treatment of active TB disease should follow the general principles for TB treatment in persons without HIV (**AI**). Below are two scenarios for sequencing the treatment of HIV-infected patients with active TB disease:

- **Patients Currently Receiving Antiretroviral Therapy.** Patients receiving antiretroviral therapy at the time of initiation of TB treatment will require assessment of the antiretroviral therapy regimen in order to adjust the doses to permit use of the optimal TB regimen with particular attention to pharmacokinetic interactions with rifamycins (discussed below).
- **Patients Not Receiving Antiretroviral Therapy at the Time of Active TB Diagnosis.** Active pulmonary or extrapulmonary TB disease requires prompt initiation of TB treatment. However, a delay in initiation of antiretroviral therapy for 2 to 8 weeks permits easier assessment of signs and symptoms related to adverse drug reactions and may reduce the risk of IRIS. Starting antiretroviral therapy within a few days or weeks after initiating TB treatment increases the risk of IRIS compared to waiting for longer periods of time [4]. However, in patients with CD4 counts <200 cells/mm³, starting antiretroviral therapy within a few days or weeks of initiating TB treatment may reduce the risk of the development of opportunistic infections (OIs) and other HIV-related complications and may improve survival [5]. The optimal timing of initiation of antiretroviral therapy after starting TB treatment is not known. Although these guidelines and the OI Treatment and Prevention Guidelines [6] from the NIH, CDC, and HIVMA/IDSA recommend a delay of antiretroviral therapy for 2 to 8 weeks (**BII**), the timing chosen for an individual patient depends on clinical judgment, taking into account factors such as immunologic and clinical parameters and the availability of health care.

Some experts base the timing of initiation of antiretroviral therapy in patients with active TB disease on CD4 cell counts at the start of TB treatment, as shown below:

- CD4 <100 cells/mm³: start antiretroviral therapy after 2 weeks of TB treatment
- CD4 = 100–200 cells/mm³: start antiretroviral therapy after 8 weeks of TB treatment
- CD4 = 200–350 cells/mm³: start antiretroviral therapy after 8 weeks of TB treatment*
- CD4 >350 cells/mm³: start ART after 8 to 24 weeks or after end of TB treatment*

* On case-by-case basis in clinician’s judgment.

It is important to carefully monitor patients in whom initiation of antiretroviral therapy is deferred through regular clinical and CD4 cell count assessments during TB treatment in order to promptly initiate antiretroviral therapy if there is evidence of HIV disease progression or of a drop in CD4 cell count. Individuals with CD4 cell counts <200 cells/mm³ should be placed on PCP prophylaxis, regardless of timing of initiation of antiretroviral therapy.

Treatment of TB

Treatment of drug-susceptible active TB disease in HIV-infected individuals should include the standard short-course regimen outlined in treatment guidelines, which consists of isoniazid (INH), rifampin (RIF) or rifabutin (RFB), pyrazinamide (PZA), and ethambutol (EMB) or streptomycin (SM) given for 2 months, followed by INH + RIF for 4 to

7 months [6, 7] **(AI)**. Special attention should be given to the potential of drug-drug interactions with rifamycin as discussed below. A minimum of thrice weekly treatment with rifamycin-containing TB treatment regimens is recommended for patients with a CD4 cell count <100 cells/mm³ **(AII)**. Once- or twice-weekly dosing has been associated with increased rates of development of rifamycin resistance in patients with advanced HIV, and once-weekly rifapentine is not recommended **(AI)** [7-9].

Directly Observed Therapy (DOT)

DOT of TB treatment, in a manner supportive of the patients' needs is strongly recommended for patients with HIV/TB disease **(AII)**. In general, daily or thrice weekly DOT is recommended for the first 2 months and then three times weekly DOT for the continuation phase of 4 to 7 months **(BII)**.

Anti-Tuberculosis/Antiretroviral Drug Toxicities and Interactions

Almost all antiretroviral drugs are associated with the potential for hepatotoxicity. INH, RIF, and PZA may also cause drug-induced hepatitis. These first-line TB drugs should be used for treatment of active TB disease, if possible, even with coadministration of other potentially hepatotoxic drugs or in the presence of baseline liver disease **(AIII)**. Patients receiving drugs with potential hepatotoxicity should have frequent monitoring for clinical symptoms and signs of hepatitis and laboratory monitoring for hepatotoxicity, including serum aminotransferases, bilirubin, and alkaline phosphatase.

Rifamycins are essential drugs for the treatment of active TB disease. However, they are associated with significant drug interactions with PIs, NNRTIs, maraviroc, and raltegravir, because of their effects as inducers of the hepatic cytochrome P450 and UGT1A1 enzymes. Despite these interactions, a rifamycin should be included in the TB treatment regimen in patients receiving antiretroviral therapy [6, 10] **(AII)**. Rifampin is the most potent inducer of hepatic enzymes, and results in significant decreases in exposure to ritonavir-boosted or unboosted PIs, with resultant risk of antiretroviral treatment failure. Coadministration of rifampin and nevirapine or efavirenz is associated with lower NNRTI drug exposures and greater variability in plasma NNRTI drug levels. However, some clinical and pharmacologic data suggest that comparable virologic, immunologic, and clinical outcomes are achieved with either efavirenz [11, 12] or nevirapine [13, 14] in standard doses in combination with rifampin-containing regimens. Some experts recommend consideration of dose escalation of efavirenz in patients who weigh more than 60 kg; other experts suggest that no dosage adjustment is necessary ([Table 14b](#)). One large, observational study from South Africa evaluated virologic responses at 6 months in patients treated with an NNRTI-based regimen with or without TB treatment that contained rifampin. Among the nevirapine-treated patients, the rate of virologic failure was higher among those with TB compared with those without TB [16.3% vs. 8.3%; adjusted odd ratio, 2.1 (95% CI, 1.2–3.4)]. No difference in virologic response was seen when comparing TB vs. non-TB patients who were started on efavirenz-based regimens [15]. Rifabutin has fewer and less severe drug interactions with antiretroviral therapy drugs and is preferred in patients with HIV/TB disease when used in combination with appropriate dose adjustments, according to [Tables 14a and 14b](#). In the case of an antiretroviral therapy-experienced patient in whom NNRTI-based regimens are not an option and for whom rifabutin is not available, consultation with an HIV expert is recommended.

IRIS with TB: Clinical Disease

Some patients while on treatment for active TB will develop IRIS, which is characterized by findings such as fever, new or worsening lymphadenopathy, worsening of pulmonary infiltrates, and pleural effusion. These reactions may occur in the absence of HIV infection and in the absence of antiretroviral therapy, but are more common after initiation of antiretroviral therapy in patients with active TB disease as a consequence of immune reconstitution. IRIS has been reported in 8%–43% of patients with HIV/TB disease, and may contribute to the higher mortality from antiretroviral therapy in the first year of treatment. Predictors of IRIS include CD4 cell count <50 cells/mm³, severe TB disease with high pathogen burden, and interval between initiation of TB and HIV treatment of less than 30 days [4, 13, 16–19]. Most IRIS in HIV/TB disease occurs within three months of the start of TB treatment. Delaying the start of antiretroviral therapy for 2 to 8 weeks may reduce the incidence and severity of IRIS but must be weighed against the potential benefit of earlier antiretroviral therapy in improving immune function and preventing progression of HIV disease. In mild to moderate cases of IRIS, treatment of TB and HIV should be continued and nonsteroidal anti-inflammatory agents may be used to alleviate specific symptoms **(AII)**. In severe cases of IRIS high-dose prednisone (1mg/kg for 1 to 4 weeks followed by tapering doses, with the duration and timing of tapering based on

the control of symptoms) has been associated with clinical improvement [19-21] **(BIII)**, and additional measures, such as surgical decompression, also may be required.

Immune Reconstitution with Antiretroviral Therapy: Conversion to Positive TST and/or IGRA Test

Immune reconstitution with antiretroviral therapy may result in unmasking LTBI (i.e., conversion of a previously negative TST to a positive TST or a positive interferon-gamma [IFN- γ] release assay [IGRA] for *M.TB*-specific proteins). A positive IGRA, similar to a positive TST, is indicative of LTBI in the absence of evidence of active TB disease [22]. Because treatment for LTBI is indicated in the absence of evidence of active TB disease, clinicians should be aware of this phenomenon. In individuals with a negative TST or IGRA and advanced HIV disease (i.e., CD4 count <200 cells/mm³), TST or IGRA should be repeated after they have started antiretroviral therapy and their CD4 count has increased to above 200 cells/mm³ [23] **(BII)**.

A TST or IGRA should also be performed prior to the initiation of antiretroviral therapy regardless of the CD4 count. Individuals found to have LTBI by IGRA or TST—defined as >5 mm skin test induration without evidence of active TB disease and after appropriate evaluation for active TB disease—should commence treatment as recommended by the guidelines for treatment and prevention of OIs in HIV-infected patients [6]. Caution should be taken regarding use of rifamycins with certain antiretroviral drugs (see above).

A more complete discussion of the use of IGRAs and the diagnosis and treatment of TB disease and LTBI in patients with HIV infection will be available in “[The Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents—2009: Recommendations from the NIH, the CDC, and the HIVMA/IDSA](#)” [6].

Integration of TB and HIV Care

Due to the complexities described above, optimal management of HIV-infected individuals with active TB disease requires close collaboration between TB and HIV clinicians, health care institutions, and public health programs.

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Limitations to Treatment Safety and Efficacy

ADHERENCE TO ANTIRETROVIRAL THERAPY (Updated November 3, 2008)

Adherence to antiretroviral therapy has been strongly correlated with HIV viral suppression, reduced rates of resistance, an increase in survival, *and* improved quality of life [1, 2]. Because HIV treatment is a lifelong endeavor, and because many patients will initiate therapy when they are generally in good health, feel well, and demonstrate no obvious signs or symptoms of HIV disease, adherence poses a special challenge and requires commitment from the patient and the health care team. Adherence remains a challenging and complicated topic; the guidance put forth in this document provides a basis to guide clinicians in their approach.

Predictors of Adherence

Adherence is related to characteristics of the patient, the regimen, the clinical setting, and the strength of the provider/patient relationship [3]. The information given and the patient's understanding about HIV disease and the specific regimen to be taken is critical. A number of factors have been associated with poor adherence, including the following:

- low levels of literacy [4];
- certain age-related challenges (e.g., vision loss, cognitive impairment) [5];
- psychosocial issues (e.g., depression, homelessness, lower social support, stressful life events, dementia, or psychosis) [6];
- active (but not history of) substance abuse, particularly for patients who have experienced recent relapse;
- stigma [7];
- difficulty with medication taking (e.g., trouble swallowing pills, daily schedule issues);
- complex regimens (e.g., pill burden, dosing frequency, food requirements);
- adverse drug effects; and
- treatment fatigue.

Adherence studies in the early era of combination therapy with unboosted PIs found that taking 95% or more of doses was required for full viral suppression [8]. More recent adherence studies that utilized boosted PIs and NNRTIs suggest that boosted PIs and efavirenz may be more forgiving of lapses in adherence because of their longer half-lives [9, 10]. Nonetheless, clinicians should encourage patients to adhere as closely as possible to the prescribed doses for all antiretroviral regimens.

Measurement of Adherence

There is no gold standard for the assessment of adherence [1], but there are many validated tools and strategies to choose from. Although patient self-report of adherence predictably overestimates adherence by as much as 20% [11], this measure still is associated with viral load responses [12]. Thus, a patient's report of suboptimal adherence is a strong indicator of nonadherence and should be taken seriously.

When ascertained in a simple, nonjudgmental, routine, and structured format that normalizes less-than-perfect adherence and minimizes socially desirable responses, patient self-report remains the most useful method for the assessment and longitudinal monitoring of a patient's adherence in the clinical setting. A survey of all doses during the past 3 days or the past week accurately reflects longitudinal adherence and is the most practical and readily available tool for adherence assessments in clinical trials and in clinical practice [1]. Other strategies may also be effective. One study found that asking patients to rate their adherence on a six-point scale during 1 month was more accurate than asking them how often they miss doses or asking about the percentage of doses taken during the previous 3 or 7 days [13]. Pharmacy records and pill counts can also be used as an adjunct to simply asking the patient [14]. Other methods of assessing adherence include the use of electronic measurement devices (e.g., bottle caps, dispensing systems). However, these methods may not be feasible in some clinical settings.

Interventions to Improve Adherence

Prior to writing the first prescriptions, the clinician should assess the patient's readiness to take medication; factors that might limit adherence (e.g., psychiatric illness, active drug use, etc) that may require additional support; understanding of the disease and the regimen; social support; housing; work and home situation; and daily schedules. Patients should understand that the first regimen is usually the best chance for a simple regimen with long-term treatment success and prevention of drug resistance. Resources should be identified to assist in achievement of good adherence that is individualized to each patient's schedule, competing psychosocial needs, learning needs, and literacy level.

Individualizing treatment with involvement of the patient in decision making is the cornerstone of any treatment plan [14]. The first principle of successful treatment is negotiation of an understandable plan to which the patient can commit [15, 16]. Establishing a trusting relationship over time and maintaining good communication will help to improve adherence and long-term outcomes. With the patient who is not critically ill, several office visits and the patience of clinicians are generally required before therapy can be started.

There is a growing menu of possible interventions that have demonstrated efficacy in improving adherence to antiretroviral therapy. For example, a meta-analysis of 19 randomized controlled trials of antiretroviral adherence interventions found that intervention participants were 1.5 times as likely to report 95% adherence and 1.25 times as likely to achieve an undetectable viral load compared with participants in comparison conditions [17]. Interventions that have been successful include those focused on the patient and those that work to improve the tolerability of the regimen. Successful support interventions of different modalities have included the following: adherence support groups, peer adherence counselors, behavioral interventions, cognitive-behavioral and reminder strategies, and use of community-based case managers and peer educators. Health care team members, such as nurses, nurse practitioners, pharmacists, medication managers, and social workers, have integral roles in successful adherence programs [18-21]. It is also important to address the competing needs of a patient, including active substance use, depression, and housing issues, to reduce the risk of nonadherence.

A number of advances during the past several years have dramatically simplified many regimens, particularly for treatment-naïve patients. Prescribing regimens that are simple to take, have a low pill burden and frequency of dosing, have no food requirements, and have low incidence and severity of adverse effects will facilitate adherence. Current treatment recommendations take regimen simplicity as well as efficacy into account.

Adherence assessment and counseling should be done at each clinical encounter and should be the responsibility of the entire health care team. Directly observed therapy (DOT) has been shown to be effective in provision of antiretroviral therapy to active drug users [22]. In resource-limited settings, the use of community-based DOT has been very successful, and programs have replicated this intervention with success in the United States [23]. Although DOT is labor intensive and programmatically complex, modification of traditional DOT methodologies may be feasible and can be adapted in a variety of clinical settings, in which DOT is given a few days each week [24].

Conclusion

There has been significant progress made regarding determinants, measurements, and interventions to improve adherence to antiretroviral therapies. Given the various assessment strategies and potential interventions available, the challenge for the treatment team is to select the techniques that provide the best fit for their treatment setting, resources, and patient population. The complexity of this topic and the importance of adherence encourage clinicians to continue to seek novel, patient-centered ways to prevent nonadherence and to tailor adherence interventions. Early detection of nonadherence and prompt intervention can greatly reduce the development of viral resistance and the likelihood of virologic failure.

Table 11. Strategies to Improve Adherence to Antiretroviral Therapy

Strategies	Examples
Utilize a multidisciplinary team approach Provide an accessible, trusting healthcare team	• Nurses, social workers, pharmacists, and medications managers
Establish a trusting relationship with the patient	
Establish readiness to start ART	
Identify potential barriers to adherence prior to starting ART	• Psychosocial issues • Active substance abuse or at high risk for relapse • Low literacy level • Busy daily schedule and/or travel away from home • Lack of disclosure of HIV diagnosis • Skepticism about ART • Lack of prescription drug coverage
Provide resources for the patient	• Referrals for mental health and/or substance abuse treatment • Resources to obtain prescription drug coverage • Pillboxes
Involve the patient in ARV regimen selection	For each option, review potential side effects, dosing frequency, pill burden, storage requirements, food requirements, and consequences of nonadherence
Assess adherence at every clinic visit	• Simple checklist patient can complete in the waiting room • Assessment also by other members of the healthcare team • Ask the patient open-ended questions (e.g., <i>In the last three days, please tell me how you took your medicines?</i>)
Identify the type of nonadherence	• Failure to fill the prescription(s) • Failure to take the right dose(s) at the right time(s) • Nonadherence to food requirements
Identify reasons for nonadherence	• Adverse effects from medications • Complexity of regimen – pill burden, dosing frequency, etc. • Difficulty swallowing large pills • Forgetfulness • Failure to understand dosing instructions • Inadequate understanding of drug resistance and its relationship to adherence • Pill fatigue • Reassess other potential barriers listed above
Assess and simplify regimen, if possible	

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ADVERSE EFFECTS OF ANTIRETROVIRAL AGENTS (Updated December 1, 2009)

Adverse effects have been reported with all antiretroviral drugs and are among the most common reasons for switching or discontinuing therapy as well as for medication nonadherence [1]. Rates of treatment-limiting adverse events in treatment-naïve patients enrolled in randomized trials appear to be declining with newer antiretroviral regimens and are generally now less than 10%. In the Swiss Cohort study, the presence of laboratory adverse events was associated with higher rates of mortality during 6 years of follow-up, highlighting the importance of adverse events in overall patient management [2]. Whereas some common adverse effects were identified during premarketing clinical trials, other less frequent toxicities (e.g., lactic acidosis with hepatic steatosis and progressive ascending neuromuscular weakness

syndrome) and longer term complications (e.g., dyslipidemia and fat maldistribution) were not recognized until after the drugs had been in use for years. In rare cases, some drug-related events may result in significant morbidity and even mortality.

Several factors may predispose individuals to certain antiretroviral-associated adverse events. For example, women seem to have a higher propensity of developing Stevens-Johnson syndrome and symptomatic hepatic events from nevirapine (especially treatment-naïve women with CD4 counts greater than 250 cells/mm³) [3-5]. Women have also been observed to suffer higher rates of lactic acidosis from NRTIs [6-8]. Other factors may also contribute to the development of adverse events: concomitant use of medications with overlapping and additive toxicities; comorbid conditions that may increase the risk of or exacerbate adverse effects (e.g., alcoholism [9] or coinfection with viral hepatitis, which may increase risk of hepatotoxicity [10-12]); drug-drug interactions that may lead to an increase in dose-related toxicities (e.g., concomitant use of ribavirin with didanosine, which may increase didanosine-associated toxicities) [13-15]; or genetic factors predisposing patients to abacavir hypersensitivity reaction [16-17].

Although the therapeutic goals of antiretroviral therapy include achieving and maintaining viral suppression and improving patient immune function, an overarching goal should be to select a regimen that is not only effective but is also safe. This requires taking into account an individual patient's underlying conditions, concomitant medications, and history of drug intolerance.

Information on adverse events is outlined in multiple tables in the guidelines:

[Appendix B, Tables 1–6](#) summarize common adverse effects of individual antiretroviral agents. [Table 12](#) provides clinicians with a list of antiretroviral-associated adverse events, common causative agents, estimated frequency of occurrence, timing of symptoms, clinical manifestations, potential preventive measures, and suggested management strategies.

Table 12. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations
 (Updated December 1, 2009)

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Bleeding events	TPV/r: Reports of intracranial hemorrhage (ICH) PIs: ↑ bleeding in hemophiliac patients	<u>Median time to ICH event:</u> 525 days on TPV/r therapy <u>Hemophiliac patients:</u> ↑ spontaneous bleeding tendency (in joints, muscles, and soft tissues) and hematuria	<u>For ICH:</u> 24 reported cases with TPV/r use, including 12 fatalities [18] <u>For hemophilia:</u> frequency unknown	<u>For ICH:</u> • CNS lesions • Head trauma • Recent neurosurgery • Coagulopathy • Hypertension • Alcohol abuse • Receiving anticoagulant or anti-platelet agents including vitamin E <u>For hemophiliac patients:</u> PI use	Avoid vitamin E supplements, particularly with the oral solution formulation of TPV <u>For ICH:</u> Avoid using TPV/r in patients at risk of ICH <u>For hemophiliac patients:</u> • Consider using a non-PI-based regimen • Monitor for spontaneous bleeding	<u>For ICH:</u> • Discontinue TPV/r • Manage ICH with supportive care <u>For hemophiliac patients:</u> May require increased use of factor VIII products
Bone marrow suppression	ZDV	<u>Onset:</u> Few weeks to months <u>Laboratory abnormalities:</u> • Anemia (usually macrocytic) • Neutropenia <u>Symptoms:</u> • Fatigue because of anemia • Potential for increased bacterial infections because of neutropenia	<u>Severe anemia (Hgb <7 g/dL):</u> 1.1%–4% <u>Severe neutropenia (ANC <500 cells/mm³):</u> 1.8%–8%	• Advanced HIV • High dose • Pre-existing anemia or neutropenia • Concomitant use of bone marrow suppressants (e.g., cotrimoxazole, ganciclovir, valganciclovir) or drugs that cause hemolytic anemia (e.g., ribavirin) or neutropenia (e.g., alpha interferon)	• Avoid use in patients at risk • Avoid other bone marrow suppressants if possible • Monitor CBC with differential after the first few weeks, then at least every 3 months (more frequently in at-risk patients)	• Switch to another NRTI if possible • Discontinue concomitant bone marrow suppressant if possible; otherwise, <u>For neutropenia:</u> • Identify and treat other causes • Consider treatment with filgrastim <u>For anemia:</u> • Identify and treat other causes of anemia (if present) • Blood transfusion if indicated • Consider erythropoietin therapy
Cardiovascular effects (including myocardial infarction [MI]) and cerebrovascular accidents (CVA)	<u>MI and CVA:</u> associated with PI but not NNRTI use in cohort study <u>MI only:</u> association between recent ABC and ddI use found in observational cohort; association not seen in randomized studies of ABC (see What to Start text)	<u>Onset:</u> Months to years after beginning of therapy <u>Presentation:</u> Coronary artery disease or CVA	3–6 per 1,000 patient-years <u>CVA:</u> ~1 per 1,000 patient-years	• Smoking • Age • Hyperlipidemia • Hypertension • Diabetes mellitus • Family history of premature coronary artery disease • Personal history of coronary artery disease	• Assess cardiac disease risk factors • Monitor and identify patients with hyperlipidemia or hyperglycemia • Consider regimen with fewer adverse lipid effects • Recommend life style modifications to reduce risk factors (e.g., smoking cessation, diet, physical activity)	• Prevent or manage other cardiovascular risk factors (e.g., hyperlipidemia, hypertension, insulin resistance/diabetes mellitus) with early diagnosis, lifestyle modifications, and medication • Modify lifestyle risk factors (smoking, diet, physical activity) • Switch to agents with less propensity for increasing cardiovascular risk factors, especially in patients at greatest risk of CVD

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Central nervous system effects	EFV	<u>Onset:</u> Within first doses <u>Symptoms:</u> • May include one or more of the following: drowsiness, somnolence, insomnia, abnormal dreams, dizziness, impaired concentration and attention span, depression, hallucination, exacerbation of psychiatric disorders, psychosis, suicidal ideation • Most symptoms subside or diminish after 2–4 week	>50% of patients may have some symptoms	- History of psychiatric illness - Concomitant use of medication with neuropsychiatric effects - History of injection drug use - Higher plasma EFV concentrations in people with G→T polymorphism at position 516 (516G → T) of CYP2B6 [19]	- Take at bedtime or 2–3 hours before bedtime - Take on an empty stomach to reduce drug concentration and CNS effects - Restrict risky activities (e.g., operating heavy machinery) during first 2–4 weeks of therapy	- Symptoms usually diminish or disappear within 2–4 weeks - Consider switching to alternative agent if symptoms persist and cause significant impairment in daily function or exacerbation of psychiatric illness
Gastrointestinal (GI) intolerance	All PIs, ZDV, ddI	<u>Onset:</u> Within first doses <u>Symptoms:</u> • Nausea, vomiting, abdominal pain with all listed agents • Diarrhea, most commonly seen with NFV, some RTV-boosted PIs, and buffered formulations of ddI	Varies with different agents	All patients	- Taking with food may reduce symptoms (ddI and unboosted IDV are recommended on empty stomach) - Some patients may require antiemetics or antidiarrheals pre-emptively to reduce symptoms	- Rule out other causes such as pancreatitis or infectious gastroenteritis - Symptoms may spontaneously resolve or become tolerable with time; if not, consider, <u>For nausea and vomiting:</u> - Antiemetic prior to dosing - Switch to less emetogenic ARV <u>For diarrhea:</u> - Bulk-forming agents (e.g., psyllium products) - Antimotility agents (e.g., loperamide, diphenoxylate/atropine) - Calcium tablets - Pancreatic enzymes - L-glutamate may reduce diarrhea, especially when associated with NFV or LPV/r <u>For severe GI symptoms:</u> Rehydration and electrolyte replacement as indicated
Hypersensitivity with hepatic failure	NVP	<u>Onset:</u> Greatest risk within first 6 weeks of therapy; can occur through 18 weeks <u>Symptoms:</u> • Abrupt onset of flu-like symptoms (nausea, vomiting, myalgia, malaise, fatigue), abdominal pain, jaundice, or fever with or without skin rash • May progress to fulminant hepatic failure particularly in those with rash • Rhabdomyolysis may accompany hepatic failure • Approximately 1/2 of the cases have accompanying skin rash, some presenting as part of DRESS syndrome (drug rash with eosinophilia and systemic symptoms)	<u>Symptomatic hepatic events:</u> 4% overall (2.5%–11% from different trials) <u>In women:</u> 11% with pre-NVP CD4 >250 cells/mm³ vs. 0.9% with CD4 <250 cells/mm³ <u>In men:</u> 6.3% with pre-NVP CD4 >400 cells/mm³ vs. 2.3% with CD4 <400 cells/mm³	- Treatment-naïve patients with higher CD4 count at initiation (>250 cells/mm³ in women and >400 cells/mm³ in men) - Women (risk is 3 times higher than in men) - HIV(-) individuals when NVP is used for post-exposure prophylaxis - Possibly, high NVP concentrations	2-week dose escalation may reduce incidence; follow instructions for dose escalation - Avoid initiation of NVP in women with CD4 >250 cells/mm³ or men with CD4 >400 cells/mm³ - Do not use NVP in HIV(-) individuals for post-exposure prophylaxis - Counsel patients on signs and symptoms of hypersensitivity and hepatitis; instruct them to stop NVP and seek medical attention if signs and symptoms of hepatitis, severe skin rash, or hypersensitivity reactions appear - Monitor ALT and AST (every 2 weeks x first month, then monthly x 3 months, then every 3 months) - Obtain AST and ALT in patients with rash	- Discontinue ARVs, including NVP - Discontinue all other hepatotoxic agents if possible - Rule out other causes of hepatitis - Manage with aggressive supportive care as indicated - Hepatic injury may progress despite treatment discontinuation. Careful monitoring should continue until symptom resolution. Do not rechallenge patient with NVP. - Use other NNRTIs (e.g., EFV, ETR, DLV) with caution; it is unknown if they can be safely used in patients who experienced significant hepatic event from NVP.

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Hepatotoxicity (clinical hepatitis or asymptomatic serum transaminase elevation)	All NNRTIs; all PIs; most NRTIs; maraviroc	<u>Onset:</u> • NNRTIs: for NVP, 2/3 of patients within first 12 weeks • NRTIs: over months to years • PIs: generally after weeks to months <u>Symptoms/findings:</u> <u>NNRTIs:</u> • Asymptomatic to nonspecific symptoms (e.g., anorexia, weight loss, or fatigue) • Approximately 1/2 of patients with NVP-associated symptomatic hepatic events present with skin rash. <u>NRTIs:</u> • ZDV, ddI, d4T: may have greater risk of hepatotoxicity associated with lactic acidosis with microvesicular or macrovesicular hepatic steatosis because of mitochondrial toxicity • ddI: prolonged exposure associated with noncirrhotic portal hypertension with esophageal varices [20] • 3TC, FTC, or TDF: HBV-coinfected patients may develop severe hepatic flare when these drugs are initiated, withdrawn, or when resistance develops <u>PIs:</u> • Clinical hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with TPV/r and also with other PIs to varying degrees. • May be asymptomatic, some with anorexia, weight loss, jaundice, etc.	Varies with different agents	• HBV or HCV coinfection • Alcoholism • Concomitant hepatotoxic drugs, particularly rifampin • Elevated ALT and/or AST at baseline • For NVP-associated hepatic events: female with pre-NVP CD4 >250 cells/mm³ or male with pre-NVP CD4 >400 cells/mm³ • Higher drug concentrations for PIs, particularly TPV • Underlying liver disease • Hepatitis B or C infection	<u>NVP</u> • Monitor liver-associated enzymes at baseline, at 2 and 4 weeks, then monthly for first 3 months; then every 3 months <u>TPV/RTV</u> • Contraindicated in patients with moderate to severe hepatic insufficiency; follow other patients frequently during treatment <u>Other agents</u> • Monitor liver-associated enzymes at least every 3–4 months or more frequently in at-risk patients	• Rule out other causes of hepatotoxicity (alcoholism; viral hepatitis; chronic HBV with 3TC, FTC, or TDF initiation or withdrawal; HBV resistance, etc.) <u>For symptomatic patients:</u> • Discontinue all ARVs and other potential hepatotoxic agents • After symptoms subside and serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) <u>For asymptomatic patients:</u> • If ALT >5–10x ULN, some may consider discontinuing ARVs, others may continue therapy with close monitoring unless direct bilirubin is also elevated • After serum transaminases return to normal, construct a new ARV regimen without the potential offending agent(s) • Refer to information regarding NVP-associated symptomatic hepatic events and NRTI-associated lactic acidosis with hepatic steatosis in this table

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Hyperlipidemia	All PIs (except unboosted ATV); d4T; EFV > NVP	<u>Onset:</u> Weeks to months after beginning of therapy <u>Presentation:</u> <u>All PIs (except unboosted ATV):</u> • ↑ in LDL, total cholesterol (TC), and triglycerides (TG) • ↑ HDL seen with ATV, DRV, FPV, LPV, SQV when boosted with RTV <u>LPV/r and FPV/r:</u> Disproportionate ↑ in TG compared with either DRV/r or ATV/r [21-23] <u>EFV and to a lesser extent NVP:</u> • ↑ LDL and TC • Slight ↑ TG • ↑ HDL <u>d4T and ZDV:</u> ↑ LDL, TC, and TG	Varies with different agents <u>Swiss Cohort:</u> ↑ TC and TG; 1.7–2.3x higher in patients receiving (non-ATV) PI	• Underlying hyperlipidemia • Risk based on ARV therapy <u>PI:</u> • All RTV-boosted PIs may ↑ LDL and TG • ATV/r may produce less of an ↑ in LDL and TG <u>NNRTI:</u> EFV > NVP [24] <u>NRTI:</u> d4T > ZDV > ABC > TDF [25-26]	• Assess cardiac disease risk factors • Use PIs and NNRTIs with less adverse effect on lipids, and non-d4T-based regimen • Monitor fasting lipid profile at baseline, at 3–6 months after starting new regimen, then annually or more frequently if indicated (in high-risk patients or in patients with abnormal baseline levels)	• Lifestyle modifications (e.g., diet, exercise, smoking cessation) • Switch to agents with less propensity for causing hyperlipidemia <u>Pharmacologic Management:</u> • Per HIVMA/ACTG guidelines [27] and National Cholesterol Education Program ATP III guidelines [28] • For potential interactions between ARV and lipid-lowering agents, refer to Tables 14a and 14b
Hypersensitivity reaction (HSR)	ABC	<u>Onset of first reaction:</u> Median onset is 9 days; approximately 90% of reactions occur within the first 6 weeks <u>Onset of rechallenge reactions:</u> Within hours of rechallenge dose <u>Usually >2–3 acute symptoms seen with HSR:</u> • (In descending frequency) high fever, diffuse skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms (pharyngitis, dyspnea/tachypnea) • With continuation of ABC, symptoms may worsen to include hypotension, respiratory distress, vascular collapse <u>Rechallenge reactions:</u> Generally greater intensity than first reaction, can mimic anaphylaxis	Clinically suspected ≈ 8% in clinical trial (2%–9%); 5% in retrospective analysis; significantly reduced with pre-treatment HLA-B*5701 screening [16]	• HLA-B*5701, HLA-DR7, HLA-DQ3 • In one study, higher incidence of grade 3 or 4 HSR with 600mg once-daily dose than with 300mg twice-daily dose (5% vs. 2%)	• HLA-B*5701 screening prior to initiation of ABC • ABC should not be started if HLA B*5701 (+) • Indicate allergy to ABC in medical records of patients tested (+) for HLA-B*5701 • Educate patients about potential signs and symptoms of HSR and to report symptoms promptly • Provide patients with wallet card with warning information • Note multiple names for products containing ABC (Ziagen, Epzicom or Kivexa, Trizivir)	• Discontinue ABC and switch to another NRTI • Rule out other causes of symptoms (e.g., intercurrent illnesses such as viral syndromes and other causes of skin rash) • Most signs and symptoms resolve 48 hours after discontinuation of ABC <u>More severe cases:</u> • Manage with symptomatic support (antipyretic, fluid resuscitation, pressure support if necessary) • Do not rechallenge patients with ABC after suspected HSR, even in patients who are (-) for HLA-B*5701. There are cases of hypersensitivity in HLA-B*5701(-) patients.

Table 12. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations

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Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Insulin resistance/diabetes mellitus (DM)	Thymidine analogs (ZDV, d4T); some PIs linked to insulin resistance and diabetes mellitus (but unclear if a class effect)	<u>Onset:</u> Weeks to months after beginning of therapy <u>Presentation:</u> Polyuria, polydipsia, polyphagia, fatigue, weakness; exacerbation of hyperglycemia in patients with underlying DM	3%–5% of patients developed diabetes in some series; D:A:D cohort incidence rate of 5.72 per 1,000 person-years of follow-up (95% CI: 5.31–6.13) [29] Incidence of DM in HIV (+) women in WHIS (2.5–2.9 per 100 person-years) [30] and associated with NRTIs	•Family history of DM	•Use non-thymidine analog-containing regimens or NNRTIs •Fasting blood glucose 1–3 months after starting new regimen, then at least every 3–6 months	•Diet and exercise •Consider switching to non-thymidine analog-containing ART •Consider using NNRTI if feasible •Pharmacotherapeutic management per American Diabetic Association and American Association of Clinical Endocrinologists guidelines [31–32]
Lactic acidosis/hepatic steatosis +/- pancreatitis (severe mitochondrial toxicities)	NRTIs, especially d4T, ddI, ZDV	<u>Onset:</u> Generally months after initiation of NRTIs <u>Symptoms:</u> •Insidious onset with nonspecific GI prodrome (nausea, anorexia, abdominal pain, vomiting), weight loss, and fatigue •Subsequent symptoms may be rapidly progressive, with tachycardia, tachypnea, hyperventilation, jaundice, muscular weakness, mental status changes, or respiratory distress •Some may present with multi-organ failure (e.g., hepatic failure, acute pancreatitis, encephalopathy, and respiratory failure) •Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L <u>Laboratory findings:</u> •Increased lactate (often >5 mmol/L) •Low arterial pH (as low as <7.0) •Low serum bicarbonate •Increased anion gap •Elevated serum transaminases, prothrombin time, bilirubin •Low serum albumin •Increased serum amylase and lipase in patients with pancreatitis •Histologic findings of the liver: microvesicular or macrovesicular steatosis	Rare Depends on regimen and patient gender <u>U.S.:</u> <1 case per 1,000 patient-years <u>South Africa:</u> 16.1 cases per 1,000 patient-years in females and 1.2 cases per 1,000 patient-years in males [33]	•d4T + ddI •d4T, ZDV, ddI (d4T most frequently implicated) •Long duration of NRTI use •Female sex •Obesity •Pregnancy (especially with d4T + ddI) •ddI + hydroxyurea or ribavirin	•Routine monitoring of lactic acid is not recommended •Consider obtaining lactate levels in patients with low serum bicarbonate or high anion gap and with symptoms consistent with lactic acidosis •Employ appropriate phlebotomy technique for obtaining lactate level	•For mild cases, switch offending drugs to safer alternatives •For severe lactic acidosis, discontinue all ARVs if this syndrome is highly suspected (diagnosis is established by clinical correlations, drug history, and lactate level) •Symptomatic support with fluid hydration •Some patients may require IV bicarbonate infusion, hemodialysis or hemofiltration, parenteral nutrition, or mechanical ventilation •IV thiamine and/or riboflavin, which rapidly resolved hyperlactatemia in some case reports Note: •Interpretation of high lactate level should be done in the context of clinical findings •The implication of asymptomatic hyperlactatemia is unknown at this point <u>ARV treatment options:</u> •Use NRTIs with less propensity for mitochondrial toxicity (e.g., ABC, TDF, 3TC, FTC) •Recommend close monitoring of serum lactate after restarting NRTIs •Consider NRTI-sparing regimens

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Lipodystrophy	Lipoatrophy: NRTIs (d4T > ZDV > TDF, ABC, 3TC, FTC), especially when combined with EFV [34] Lipo-hypertrophy: PI- or NNRTI-based regimens and with thymidine analogs (e.g., d4T, ZDV)	Onset: Gradual (i.e., months after initiation of therapy) Symptoms: •Lipoatrophy: peripheral fat loss manifested as facial thinning and as thinning of extremities and buttocks (d4T) •Lipohypertrophy: increase in abdominal girth, breast size, and dorsocervical fat pad (buffalo hump)	High; exact frequency uncertain and dependent on regimen; increases with duration on offending agents	Both lipoatrophy and lipohypertrophy: Low baseline body mass index	Lipoatrophy: Avoid thymidine analogs (especially when combined with EFV), or switch from ZDV or d4T to ABC or TDF Lipohypertrophy: Pretreatment diet/exercise program may reduce incidence and extent	Lipoatrophy: •Switch from thymidine analogs to TDF or ABC, which may slow or halt progression but may not fully reverse effects •Injectable poly-L-lactic acid or other injectable fillers for treatment of facial lipoatrophy Lipohypertrophy: •Liposuction for dorsocervical fat pad enlargement (recurrence common) •Diet/exercise •Recombinant human growth hormone and GH-releasing hormone analogue under investigation •Improvement in visceral fat seen in patients on LPV/r switched to ATV/r [35]
Nephrolithiasis/urolithiasis/crystalluria	IDV, ATV, FPV	Onset: Any time after beginning of therapy, especially at times of reduced fluid intake Laboratory abnormalities: Pyuria, hematuria, crystalluria; rarely, rise in serum creatinine and acute renal failure Symptoms: Flank pain and/or abdominal pain (can be severe), dysuria, urinary frequency	IDV: 12.4% of nephrolithiasis reported in clinical trials (4.7%–34.4% in different trials) ATV and FPV: rare; case reports only	•History of nephrolithiasis •Patients unable to maintain adequate fluid intake •High peak IDV concentration (↑ATV levels not found to correlate with risk) •↑ duration of exposure •Hot climate	•Drink at least 1.5–2 liters of noncaffeinated fluid (preferably water) per day •Increase fluid intake at first sign of darkened urine •Monitor urinalysis and serum creatinine every 3–6 months	•Increase hydration •Control pain •If possible, switch to alternative agent •May require stent placement
Nephrotoxicity	IDV, TDF	Onset: IDV: months after therapy TDF: weeks to months after therapy Laboratory and other findings: IDV: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy TDF: ↑ serum creatinine, proteinuria, hypophosphatemia, glycosuria, hypokalemia, non-anion gap metabolic acidosis Symptoms: IDV: asymptomatic; rarely progresses to end-stage renal disease TDF: asymptomatic to signs of nephrogenic diabetes insipidus, interstitial nephritis, acute renal failure, or Fanconi syndrome with weakness and myalgias	Severe toxicity rare	IDV and TDF: •History of renal disease; elevated creatinine at baseline •Concomitant use of nephrotoxic drugs TDF: •Advanced age, low body weight, low CD4 count, prior adefovir renal toxicities	•Avoid use of other nephrotoxic drugs •Hydrate adequately if on IDV therapy •Monitor serum creatinine, urinalysis, serum potassium, and phosphorus in at-risk patients • Do not use in patients with prior history of adefovir-associated nephrotoxicity	•Stop offending agent, generally reversible •Supportive care •Electrolyte replacement as indicated

Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Neuromuscular weakness syndrome (ascending)	d4T is ARV most frequently implicated	<u>Onset:</u> Months after initiation of ARV; then dramatic motor weakness occurring within days to weeks <u>Symptoms:</u> • Very rapidly progressive ascending demyelinating polyneuropathy, may mimic Guillain-Barré syndrome • Some patients may develop respiratory paralysis requiring mechanical ventilation • Resulted in deaths in some patients <u>Laboratory findings may include:</u> • Lactic acidosis reported in some cases • Markedly increased creatine phosphokinase	Rare	Prolonged d4T use (found in 61 of 69 cases [88%] in one report) [36]	• Early recognition and discontinuation of ARVs may avoid further progression	• Discontinue ARVs • Supportive care, including mechanical ventilation if needed (as in cases of lactic acidosis listed previously) • Other measures attempted with variable success include plasmapheresis, high-dose corticosteroids, intravenous immunoglobulin, carnitine, acetylcarnitine • Recovery often takes months and ranges from complete recovery to substantial residual deficits; symptoms may be irreversible in some patients • Do not rechallenge patient with offending agent
Osteonecrosis	Linked to older PIs, but unclear whether caused by ARVs or by HIV	<u>Clinical presentation (generally similar to non-HIV-infected population):</u> • Insidious in onset, with subtle symptoms of mild to moderate periarticular pain • 85% of cases involving one or both femoral heads, but other bones may also be affected • Pain may be triggered by weight bearing or movement	<u>Symptomatic osteonecrosis:</u> 0.08%–1.33% <u>Asymptomatic osteonecrosis:</u> 4% from MRI reports	• Diabetes • Advanced HIV disease • Prior steroid use • Older age • Alcohol use • Hyperlipidemia • Role of ARVs and osteonecrosis is still controversial	• Risk reduction (e.g., limit steroid and alcohol use) • For asymptomatic cases with <15% bony head involvement, follow with MRI every 3–6 months x 1 yr, then every 6 months x 1 yr, then annually to assess for disease progression	<u>Conservative management:</u> • ↓ weight bearing on affected joint • Remove or reduce risk factors • Analgesics as needed <u>Surgical Intervention:</u> • Core decompression +/- bone grafting for early stages of disease • Total joint arthroplasty for more severe and debilitating disease
Osteopenia (defined as DEXA scan t-score of 1–2.5 SD from normal) or osteoporosis (t-score >2.5 SD from normal)	Some evidence for bone loss after starting variety of ARVs; association with TDF or d4T; similar rate of bone loss with EFV (-2.3%) or LPV/r (-2.5%) based regimens over 96-week period [37]	<u>Onset:</u> Months to years after starting ART <u>Symptoms:</u> Generally asymptomatic, bone pain, increased risk of fractures	Wide range depending on methodology and patient population; rate appears much higher than seen in the general population: 20%–54% for osteopenia and 2%–27% for osteoporosis. [38]	<u>General:</u> • Low body weight, history of significant weight loss • Female • White, Southeast Asian • Older age • Alcohol use, smoking, caffeine • Hypogonadism • Hyperthyroidism • Corticosteroids • Vit D deficiency <u>HIV:</u> • Low CD4 count • Duration of HIV • Lipotrophy • Increased lactic acid levels • TDF exposure	• Consider assessment of bone mineral density with DEXA scan (baseline and follow-up if abnormal; proper interval in setting of HIV(+) not determined) [39] • Weight-bearing exercise • Calcium and vitamin D supplementation • Hormone replacement	• Switch from potentially contributing ARVs (i.e., d4T or TDF) and stop other contributing drugs • Follow National Osteoporosis Foundation Guidelines [40] and/or IDSA Guidelines [41] • Increase exercise, improve diet, decrease alcohol and tobacco use, increase calcium and vitamin D supplementation • Bisphosphonate (e.g., once-weekly alendronate) • Judicious hormone replacement • Intranasal calcitonin

Table 12. Antiretroviral Therapy-Associated Adverse Effects and Management Recommendations
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Adverse Effects	Associated ARVs	Onset/Clinical Manifestation	Estimated Frequency	Risk Factors	Prevention/Monitoring	Management
Pancreatitis	ddI alone; ddI + d4T, hydroxyurea (HU), ribavirin (RBV), or TDF. rare reports with LPV/r	<u>Onset:</u> Usually weeks to months <u>Laboratory abnormalities:</u> Increased serum amylase and lipase <u>Symptoms:</u> Postprandial abdominal pain, nausea, vomiting	<u>ddI alone:</u> 1%–7% <u>ddI with HU:</u> ↑ 4–5 times <u>ddI with d4T, TDF, or ribavirin:</u> ↑ frequency	• High intracellular and/or serum ddI concentrations • History of pancreatitis • Alcoholism • Hypertriglyceridemia • Concomitant use of ddI with d4T, HU, or RBV • Use of ddI + TDF without ddI dose reduction	• Do not use ddI in patients with history of pancreatitis • Avoid concomitant use of ddI with d4T, TDF, HU, or RBV • Reduce ddI dose when used with TDF • Monitoring of amylase/lipase in asymptomatic patients is generally not recommended • Treat hypertriglyceridemia	• Discontinue offending agent(s) • Manage symptoms of pancreatitis (bowel rest, IV hydration, pain control, then gradual resumption of oral intake) • Parenteral nutrition may be necessary in patients with recurrent symptoms upon resumption of oral intake
Peripheral neuropathy	ddI, d4T	<u>Onset:</u> Weeks to months after initiation of therapy (may be sooner in patients with pre-existing neuropathy) <u>Symptoms:</u> • Begins with numbness and paresthesia of toes and feet • May progress to painful neuropathy of feet and calves • Upper extremities less frequently involved • Can be debilitating for some patients • May be irreversible despite discontinuation of offending agent(s)	<u>ddI:</u> 12%–34% in clinical trials <u>d4T:</u> 52% in monotherapy trial Incidence increases with prolonged exposure	• Pre-existing peripheral neuropathy • Combined use of these NRTIs or concomitant use of other drugs that may cause neuropathy • Advanced HIV disease • High dose or concomitant use of drugs that may increase ddI intracellular activities (e.g., HU, TDF, or RBV)	• Avoid using these agents in at-risk patients, if possible • Avoid combined use of these agents • Ask patient about possible symptoms at each encounter	• Discontinue offending agent if alternative is available; may halt further progression, but symptoms may be irreversible • Substitute alternative ART without potential for neuropathy <u>Pharmacologic management (with variable successes):</u> • Gabapentin (most experience), tricyclic antidepressants, lamotrigine, carbamazepine (potential for CYP interactions), topiramate • Tramadol • Narcotic analgesics • Topical capsaicin • Topical lidocaine
Stevens-Johnson syndrome (SJS)/toxic epidermal necrosis (TEN)	NVP > DLV, EFV, ETR Also reported with APV, FPV, ABC, DRV, ZDV, ddI, IDV, LPV/r, ATV	<u>Onset:</u> First few days to weeks after initiation of therapy but can occur later <u>Symptoms:</u> • Skin eruption with mucosal ulcerations (may involve orolingival mucosa, conjunctiva, anogenital area) • Can rapidly evolve with blister or bullae formation • May eventually evolve to epidermal detachment and/or necrosis • For NVP, may occur with hepatic toxicity • Systemic symptoms (e.g., fever, tachycardia, malaise, myalgia, arthralgia) may be present <u>Complications:</u> • Decreased oral intake and fluid depletion • Bacterial or fungal superinfection • Multi-organ failure	<u>NVP:</u> 0.3%–1% <u>DLV, EFV:</u> 0.1% <u>ETR:</u> approximately <0.1% <u>ABC, FPV, ddI, ZDV, IDV, LPV/r, ATV, DRV:</u> 1–2 case reports	<u>NVP:</u> • Female • Black, Asian, Hispanic	• Educate patients to report symptoms as soon as they appear	• Discontinue all ARVs and any other possible agent(s) (e.g., cotrimoxazole) <u>Aggressive symptomatic support may include:</u> • Intensive care support • Aggressive local wound care (e.g., in a burn unit) • Intravenous hydration • Parenteral nutrition, if needed • Pain management • Antipyretics • Empiric broad-spectrum antimicrobial therapy if superinfection is suspected <u>Controversial management strategies:</u> • Corticosteroids • Intravenous immunoglobulin Note: • Do not rechallenge patient with offending agent. • It is unknown whether patients who experienced SJS while on one NNRTI are more susceptible to SJS from another NNRTI. Most experts would suggest avoiding use of this class unless no other options are available.

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DRUG INTERACTIONS (Updated November 3, 2008)

Potential drug-drug and/or drug-food interactions should be taken into consideration when selecting an antiretroviral regimen. A thorough review of current medications can help in designing a regimen that minimizes undesirable interactions. Moreover, review of drug interaction potential should be undertaken when any new drug, including over-the-counter agents, is added to an existing antiretroviral combination. [Tables 13–15b](#) list significant drug interactions with different antiretroviral agents and suggested recommendations on contraindications, dose modifications, and alternative agents.

PI and NNRTI Drug Interactions

Most drug interactions with antiretrovirals are mediated through inhibition or induction of hepatic drug metabolism [1]. All PIs and NNRTIs are metabolized in the liver by the CYP 450 system, particularly by the CYP3A4 isoenzyme. The list of drugs that may have significant interactions with PIs or NNRTIs is extensive and is continuously expanding.

Some examples of these drugs include medications that are commonly prescribed in HIV patients for non-HIV medical conditions, such as lipid-lowering agents (e.g., statins), benzodiazepines, calcium channel blockers, immunosuppressants (e.g., cyclosporine and tacrolimus), anticonvulsants, rifamycins, erectile dysfunction agents (e.g., sildenafil), ergot derivatives, azole antifungals, macrolides, oral contraceptives, and methadone. Herbal products, such as St. John's wort, can also cause negative interactions.

All PIs are substrates of CYP3A4, so their metabolic rates may be altered in the presence of CYP inducers or inhibitors. Some PIs may also be inducers or inhibitors of other CYP isoenzymes and of P-glycoprotein or other transporters. Tipranavir, for example, is a potent inducer of P-glycoprotein. The net effect of tipranavir/ritonavir on CYP3A *in vivo* appears to be enzyme inhibition. Thus, concentrations of drugs that are substrates for only CYP3A are likely to be increased if given with tipranavir/ritonavir. The net effect of tipranavir/ritonavir on a drug that is a substrate for both CYP3A and P-glycoprotein cannot be confidently predicted; significant decreases in saquinavir, amprenavir, and lopinavir concentrations have been observed *in vivo* when given with tipranavir/ritonavir.

The NNRTIs are also substrates of CYP3A4 and can act as an inducer (nevirapine), an inhibitor (delavirdine), or a mixed inducer and inhibitor (efavirenz). Etravirine is a substrate of CYPs 3A4, 2C9, and 2C19. It is also an inducer of CYP3A4 and an inhibitor of 2C9 and 2C19. Thus, these antiretroviral agents can interact with each other in multiple ways and with other drugs commonly prescribed for other concomitant diseases.

The use of a CYP3A4 substrate that has a narrow margin of safety in the presence of a potent CYP3A4 inhibitor may lead to markedly prolonged elimination half-life ($t_{1/2}$) and toxic drug accumulation. Avoidance of concomitant use or dose reduction of the affected drug, with close monitoring for dose-related toxicities, may be warranted.

The inhibitory effect of ritonavir, however, can be beneficial when added to a PI, such as atazanavir, fosamprenavir, or indinavir [2]. The PIs darunavir, lopinavir, saquinavir, and tipranavir require coadministration with ritonavir. Lower-than-therapeutic doses of ritonavir are commonly used in clinical practice as a pharmacokinetic enhancer to increase the trough concentration (C_{min}) and prolong the half-life of the active PIs [3]. The higher C_{min} allows for a greater C_{min} : IC_{50} ratio, which reduces the chance for development of drug resistance as a result of suboptimal drug exposure; the longer half-life allows for less frequent dosing, which may enhance medication adherence.

Coadministration of PIs or NNRTIs with a potent CYP3A4 inducer, on the other hand, may lead to suboptimal drug concentrations and reduced therapeutic effects of the antiretroviral agents. These drug combinations should be avoided if alternative agents can be used. If this is not possible, close monitoring of plasma HIV RNA, with or without antiretroviral dosage adjustment and therapeutic drug monitoring (TDM), may be warranted. For example, the rifamycins (i.e., rifampin and, to a lesser extent, rifabutin) are CYP3A4 inducers that can significantly reduce plasma concentrations of most PIs and NNRTIs [4, 5]. As rifabutin is a less potent inducer, it is generally considered a reasonable alternative to rifampin for the treatment of TB when it is used with a PI- or NNRTI-based regimen, despite wider experience with rifampin use [6]. [Tables 14a and 14b](#) lists dosage recommendations for concomitant use of rifamycins and other CYP3A4 inducers with PIs and NNRTIs.

NRTI Drug Interactions

Unlike PIs and NNRTIs, NRTIs do not undergo hepatic transformation through the CYP metabolic pathway. Some, however, do have other routes of hepatic metabolism. Significant pharmacodynamic interactions of NRTIs and other drugs have been reported. They include increases in intracellular drug levels and toxicities when didanosine is used in combination with hydroxyurea [7, 8] or ribavirin [9]; additive bone marrow suppressive effects of zidovudine and ganciclovir [10]; and antagonism of intracellular phosphorylation with the combination of zidovudine and stavudine [11]. Pharmacokinetic interactions have also been reported. However, the mechanisms of some of these interactions are still unclear. Examples of such interactions include increases of didanosine concentration in the presence of oral ganciclovir or tenofovir [12, 13] and decreases in atazanavir concentration when atazanavir is coadministered with tenofovir [14, 15]. [Table 14c](#) lists significant interactions with NRTIs.

CCR5 Antagonist Drug Interaction

Maraviroc, the first FDA-approved CCR5 antagonist, is a substrate of CYP3A enzymes and P-glycoprotein. As a consequence, the concentrations of maraviroc can be significantly increased in the presence of strong CYP3A inhibitors (such as ritonavir and other PIs, except for ritonavir-boosted tipranavir) and are reduced when used with CYP3A inducers, such as efavirenz or rifampin. Dose adjustment is necessary when used in combination with these agents (See [Appendix, Table 6](#) for dosage recommendations.). Maraviroc is neither an inducer nor an inhibitor of the CYP3A system. It does not alter the pharmacokinetics of the drugs evaluated in interaction studies to date.

Fusion Inhibitor Drug Interaction

The fusion inhibitor enfuvirtide is a 36–amino acid peptide that does not enter human cells. It is expected to undergo catabolism to its constituent amino acids with subsequent recycling of the amino acids in the body pool. No clinically significant drug-drug interaction has been identified with enfuvirtide to date.

Integrase Inhibitor Drug Interaction

Raltegravir, an HIV integrase strand transfer inhibitor, is primarily eliminated by glucuronidation that is mediated by the UDP-glucuronosyltransferase (UGT1A1) enzymes. Strong inducers of UGT1A1 enzymes (e.g., rifampin) can significantly reduce the concentration of raltegravir. The significance of this interaction is unknown; thus, this combination should be used with caution or an alternative therapy should be considered. Other inducers of UGT1A1, such as efavirenz, tipranavir/ritonavir, or rifabutin, can also reduce raltegravir concentration. A pharmacokinetic interaction should be considered if optimal virologic response is not achieved when these drugs are used in combination.

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Table 13. Drugs That Should Not Be Used With PI, NNRTI, or CCR5 Antagonist Antiretrovirals
(Updated December 1, 2009)

Drug Categories										
Antiretrovirals ^{1,2}	Cardiac Agents	Lipid-Lowering Agents	Anti-mycobacterials	Gastro-intestinal Drugs	Neuro-leptics	Psycho-tropics	Ergot Alkaloids (vasoconstrictors)	Herbs	Antiretrovirals	Others
Atazanavir (+/- ritonavir) (ATV +/- RTV)	none	simvastatin lovastatin	rifampin rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	dihydroergotamine (D.H.E. 45) ergotamine ⁷ (various forms) ergonovine methylethergonovine	St. John's wort	ETR IDV NVP	fluticasone irinotecan proton pump inhibitors (with unboosted ATV)
Darunavir/ ritonavir (DRV/r)	none	simvastatin lovastatin	rifampin rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	none	carbamazepine phenobarbital phenytoin fluticasone ⁸
Fosamprenavir (+/- ritonavir) (FPV +/- RTV)	none	simvastatin lovastatin	rifampin rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	ETR	fluticasone oral contraceptives
Indinavir (+/- ritonavir) (IDV +/- RTV)	amiodarone	simvastatin lovastatin	rifampin rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	ATV	
Lopinavir/ ritonavir (LPV/r)	flecainide propafenone	simvastatin lovastatin	rifampin ⁴ rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	none	fluticasone ⁸
Nelfinavir (NFV)	amiodarone quinidine	simvastatin lovastatin	rifampin rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	ETR	none
Ritonavir (RTV)	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	none	voriconazole (with RTV ≥400mg BID) fluticasone alfuzosin
Saquinavir/ ritonavir (SQV/r)	none	simvastatin lovastatin	rifampin ⁴ rifapentine	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort garlic supplements	none	fluticasone ⁸
Tipranavir/ ritonavir (TPV/r)	amiodarone flecainide propafenone quinidine	simvastatin lovastatin	rifampin rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	ETR	fluticasone ⁸
Efavirenz (EFV)	none	none	rifapentine ³	cisapride ⁵	pimozide	midazolam ⁶ triazolam	as above	St. John's wort	other NNRTIs	none
Etravirine (ETV)	none	none	rifabutin (if used with ritonavir- boosted PI) rifampin rifapentine ³	none	none	none	none	St. John's wort	unboosted PIs, ATV/r, FPV/r, or TPV/r; other NNRTIs	carbamazepine phenobarbital phenytoin
Nevirapine (NVP)	none	none	rifapentine ³	none	none	none	none	St. John's wort	ATV +/- RTV other NNRTIs	none
Maraviroc (MVC)	none	none	rifapentine ³	none	none	none	none	St. John's wort	none	none

¹ Delavirdine is not included in this table. Refer to the FDA package insert for information regarding delavirdine drug interactions.

² Certain listed drugs are contraindicated based on theoretical considerations. Thus, drugs with narrow therapeutic indices and suspected metabolic involvement with CYP450 3A, 2D6, or unknown pathways are included in this table. Actual interactions may or may not occur in patients.

³ HIV patients treated with rifapentine have a higher rate of TB relapse than those treated with other rifamycin-based regimens; an alternative agent is recommended.

⁴ A high rate of grade 4 serum transaminase elevation was seen when a higher dose of ritonavir was added to lopinavir/ritonavir or saquinavir or when double-dose lopinavir/ritonavir was used with rifampin to compensate for rifampin's induction effect, so these dosing strategies should not be used.

⁵ The manufacturer of cisapride has a limited-access protocol for patients who meet specific clinical eligibility criteria.

⁶ Contraindicated with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.

⁷ This is likely a class effect.

⁸ Concomitant use of fluticasone and ritonavir results in significantly reduced serum cortisol concentrations. Coadministration of fluticasone and ritonavir or any ritonavir-boosted PI regimen is not recommended unless potential benefit outweighs risk of systemic corticosteroid adverse effects. Fluticasone should be used with caution, and alternatives should be considered, if given with an unboosted PI regimen.

Suggested Alternatives to:

Lovastatin, simvastatin: Pravastatin and fluvastatin have the least potential for drug-drug interactions (except for pravastatin with darunavir/ritonavir, see [Table 14a](#)); atorvastatin and rosuvastatin - use with caution, start with the lowest possible dose and titrate based on tolerance and lipid-lowering efficacy.

Rifampin: Rifabutin (with dosage adjustment - see [Tables 14a and 14b](#))

Midazolam, triazolam: temazepam, lorazepam, oxazepam

Table 14a. Drug Interactions Between Protease Inhibitors (PIs) and Other Drugs

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(Updated December 1, 2009)

This table provides information relating to pharmacokinetic interactions between PIs and non-antiretroviral drugs. When information is available, interactions with boosted and unboosted PIs are listed separately. For interactions among antiretroviral agents and for dosing recommendations, refer to [Table 15a](#).

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Acid Reducers			
Antacids	ATV +/- RTV	↓ ATV expected when given simultaneously	Give ATV at least 2 hrs before or 1 hr after antacids or buffered medications.
	FPV	APV AUC ↓ 18%; no significant change in APV C _{min}	FPV can be given simultaneously or separated at least 2 hrs before or 1 hr after antacids.
	TPV/r	TPV AUC ↓ 27%	Give TPV at least 2 hrs before or 1 hr after antacids.
H₂ receptor antagonists	RTV-boosted PIs		
	ATV/r	↓ ATV	H ₂ receptor antagonist dose should not exceed a dose equivalent to famotidine 40mg BID in treatment-naïve patients or 20mg BID in treatment-experienced patients. Administer ATV 300mg + RTV 100mg simultaneously with and/or ≥10 hours after the H ₂ receptor antagonist. If using TDF and H ₂ receptor antagonist in treatment-experienced patients, use ATV 400mg + RTV 100mg.
	DRV/r, LPV/r	No significant effect	
	PIs without RTV		
	ATV	↓ ATV	H ₂ receptor antagonist single dose should not exceed a dose equivalent of famotidine 20mg or total daily dose equivalent of famotidine 20mg BID in treatment-naïve patients. Give ATV at least 2 hours before and at least 10 hours after the H ₂ receptor antagonist.
	FPV	APV AUC ↓ 30%; no significant change in APV C _{min}	Give separately if coadministration is necessary. Consider boosting with RTV.
Proton pump inhibitors (PPIs)	ATV	↓ ATV	PPIs are not recommended in patients receiving unboosted ATV. In these patients, consider alternative acid-reducing agents, ritonavir boosting, or alternative PIs.
	ATV/r	↓ ATV	PPIs should not exceed a dose equivalent to omeprazole 20mg daily in PI-naïve patients. PPIs should be administered at least 12 hrs prior to ATV/r. PPIs are not recommended in PI-experienced patients.
	DRV/r, TPV/r	↓ omeprazole PI: no significant effect	May need to increase omeprazole dose with TPV/r.
	FPV +/- RTV, IDV, LPV/r	No significant effect	
	NFV	NFV AUC ↓ 36%; M8 AUC ↓ 92%	Do not coadminister PPIs and NFV.
	SQV/r	SQV AUC ↑ 82%	Monitor for SQV toxicities.
Antifungals			
Fluconazole	RTV-boosted PIs		
	ATV/r	No significant effect	
	SQV/r	No data with RTV boosting SQV (1,200mg TID) AUC ↑ 50%	
	TPV/r	TPV AUC ↑ 50%	Fluconazole >200mg daily is not recommended.
	PIs without RTV		
	IDV	No significant effect	
Itraconazole	RTV-boosted PIs		
	ATV/r, DRV/r, FPV/r, IDV/r, TPV/r	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments. High doses (>200 mg/day) are not recommended unless dosing is guided by drug levels.
	LPV/r	↑ itraconazole	Consider not exceeding 200mg itraconazole daily or monitor itraconazole level.
	SQV/r	Bidirectional interaction has been observed	Dose not established, but decreased itraconazole dosage may be warranted. Consider monitoring itraconazole level.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Itraconazole (continued)	PIs without RTV		
	ATV, FPV, NFV	↑ itraconazole possible ↑ PI possible	Consider monitoring itraconazole level to guide dosage adjustments.
	IDV	↑ IDV With IDV 600mg Q8h + itraconazole 200mg BID: IDV AUC similar to IDV 800mg Q8h	Dose: IDV 600mg Q8h (without ritonavir); do not exceed 200mg itraconazole BID. IDV dosage when used with ritonavir and itraconazole has not been established.
Ketoconazole	RTV-boosted PIs		
	ATV/r, FPV/r, IDV/r	↑ ketoconazole expected	Use with caution. Do not exceed 200mg ketoconazole daily.
	DRV/r	ketoconazole AUC ↑ 212% DRV AUC ↑ 42%	
	LPV/r	ketoconazole AUC ↑ 204% LPV Cmin ↓ 25%	
	SQV/r	SQV (unboosted) AUC ↑ 190%	Potential for bidirectional interaction between ketoconazole and IDV/r, SQV/r, and TPV/r.
	PIs without RTV		
	ATV, NFV	ATV: no significant change NFV AUC ↑ 35%	No dosage adjustment necessary.
	FPV	No data with FPV APV AUC ↑ 31% ketoconazole AUC ↑ 44%	Consider ketoconazole dose reduction if dose is >400mg/day. Presumably similar interaction as seen with APV.
	IDV	IDV AUC ↑ 68%	Dose: IDV 600mg Q8h IDV/r dosage when used with ketoconazole has not been established.
Posaconazole	ATV/r	ATV AUC ↑ 146%	Monitor for adverse effects of ATV.
	ATV	ATV AUC ↑ 268%	Monitor for adverse effects of ATV.
Voriconazole	RTV-boosted PIs		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	voriconazole AUC ↓ 82% with RTV 400mg BID voriconazole AUC ↓ 39% with RTV 100mg BID	Concomitant use of voriconazole and RTV 100mg once daily or BID is not recommended unless benefit outweighs risk. Consider monitoring voriconazole level. Administration of voriconazole and RTV 400mg BID or higher is contraindicated.
	PIs without RTV		
	ATV, FPV, NFV	↑ voriconazole possible ↑ PI possible	Monitor for toxicities.
	IDV	No significant effect	No dose adjustment
Anticonvulsants			
Carbamazepine	RTV-boosted PIs		
	ATV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	↑ carbamazepine possible TPV/r ↑ carbamazepine AUC 26% May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.
	DRV/r	carbamazepine AUC ↑ 45% DRV: no significant change	Monitor anticonvulsant level and adjust dose accordingly.
	PIs without RTV		
	ATV, FPV, NFV, IDV	May ↓ PI levels substantially ↓ IDV	Monitor anticonvulsant level and virologic response. Consider alternative anticonvulsant; RTV boosting for ATV, FPV, and IDV; and/or monitoring PI level.
Lamotrigine	LPV/r	lamotrigine AUC ↓ 50% LPV: no significant change	Titrate lamotrigine dose to effect. A similar interaction is possible with other RTV-boosted PIs.
Phenobarbital	All PIs	May ↓ PI levels substantially	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.
Phenytoin	RTV-boosted PIs		
	ATV/r, DRV/r, IDV/r, SQV/r, TPV/r	↓ phenytoin possible ↓ PI possible	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response.
	FPV/r	phenytoin AUC ↓ 22% APV AUC ↑ 20%	Monitor phenytoin level and adjust dose accordingly. No change in FPV/r dose recommended.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Phenytoin (continued)	LPV/r	phenytoin AUC ↓ 31% LPV/r AUC ↓ 33%	Consider alternative anticonvulsant or monitor levels of both drugs and assess virologic response. Do not coadminister with LPV/r once daily.
	PIs without RTV		
	ATV, FPV, NFV, IDV	NFV ↓ phenytoin AUC 30% May ↓ PI levels substantially	Consider alternative anticonvulsant; RTV boosting for ATV, FPV, and IDV; and/or monitoring PI level. Monitor anticonvulsant level and virologic response.
Valproic acid (VPA)	LPV/r	↓VPA possible LPV AUC ↑ 75%	Monitor VPA levels and response. Monitor for LPV-related toxicities.
Anti-mycobacterials			
Clarithromycin (Clar)	ATV ± RTV	clarithromycin AUC ↑ 94%	May cause QTc prolongation. Reduce clarithromycin dose by 50%. Consider alternative therapy.
	DRV/r IDV +/- RTV LPV/r SQV/r TPV/r	DRV/r ↑ Clar AUC 57%; IDV ↑ Clar AUC 53%; LPV/r ↑ Clar expected; RTV 500mg BID ↑ Clar 77%; SQV unboosted ↑ Clar 45%; Clar ↑ unboosted SQV 177%; TPV/r ↑ Clar 19% and ↓ active metabolite 97%; Clar ↑ TPV 66%	Monitor for clarithromycin-related toxicities. Reduce clarithromycin dose by 50% in patients with CrCl 30–60mL/min. Reduce clarithromycin dose by 75% in patients with CrCl <30mL/min.
	FPV	APV AUC ↑ 18%	No dose adjustment
	RTV-boosted PIs		
Rifabutin	ATV +/- RTV	rifabutin (150mg daily) AUC ↑ 110% and metabolite AUC ↑ 2,101% compared with rifabutin 300mg daily alone	Rifabutin 150mg every other day or 3x/week Acquired rifamycin resistance has been reported in patients with inadequate rifabutin levels while on 150mg twice weekly and RTV-boosted PIs. Rifabutin 150mg three times weekly in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated tuberculosis. Pharmacokinetic data reported in this table are results from healthy volunteer studies. Therapeutic drug monitoring for rifabutin is recommended.
	DRV/r	rifabutin (150mg every other day) and metabolite AUC ↑ 55% compared with rifabutin 300mg daily alone	
	FPV/r	rifabutin (150mg every other day) and metabolite AUC↑ 64% compared with rifabutin 300mg daily alone	
	IDV/r	↑ rifabutin expected	
	LPV/r	rifabutin (150mg once daily) and metabolite AUC ↑ 473% compared with rifabutin 300mg daily alone	
	SQV/r	↑ rifabutin with unboosted SQV	
	TPV/r	rifabutin (150mg x 1 dose) and metabolite AUC ↑ 333%	
	PIs without RTV		
	FPV	↑ rifabutin AUC expected	Rifabutin 150mg daily or 300mg 3x/week
	IDV	rifabutin AUC ↑ 204% IDV AUC ↓ 32%	Rifabutin 150mg daily or 300mg 3x/week + IDV 1,000mg q8h or consider RTV boosting
	NFV	rifabutin AUC ↑ 207% NFV (750mg Q8H) AUC ↓ 32%	Rifabutin 150mg daily or 300mg 3x/week
	Rifampin	All PIs	↓ PI >75% approximately
Benzodiazepines			
Alprazolam Diazepam	All PIs	↑ benzodiazepine possible RTV 200mg BID x 2 days ↑ alprazolam half-life 200% and AUC 248%	Consider alternative benzodiazepines such as lorazepam, oxazepam, or temazepam.
Lorazepam Oxazepam Temazepam	All PIs	No data	Metabolism of these benzodiazepines via non-CYP450 pathways decreases interaction potential compared with other benzodiazepines.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
Midazolam	All PIs	↑ midazolam expected SQV/r ↑ midazolam (oral) AUC 1,144% and Cmax 327%	Do not coadminister oral midazolam and PIs. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	All PIs	↑ triazolam expected RTV 200mg BID ↑ triazolam half-life 1,200% and AUC 2,000%	Do not coadminister triazolam and PIs.
Cardiac Medications			
Bosentan	All RTV-boosted PIs	LPV/r ↑ bosentan 48-fold (Day 4) and 5-fold (Day 10)	In patients on RTV >10 days: start bosentan at 62.5mg once daily or every other day. In patients on bosentan who require RTV: discontinue bosentan ≥36 hours prior to initiation of RTV and restart 10 days after initiating RTV at 62.5mg once daily or every other day.
Digoxin	RTV, SQV/r	RTV 200mg BID ↑ digoxin AUC 29% and half-life 43% SQV/r ↑ digoxin AUC 49%	Monitor digoxin levels. Digoxin dose may need to be decreased.
Dihydropyridine calcium channel blockers (CCB)	All PIs	↑ dihydropyridine possible IDV/r ↑ amlodipine AUC 90%	Use with caution. Titrate CCB dose and monitor closely. ECG monitoring is recommended when used with ATV.
Diltiazem	ATV +/- RTV	diltiazem AUC ↑ 125%	Decrease diltiazem dose by 50%. ECG monitoring is recommended.
	DRV/r, FPV +/- RTV, IDV +/- RTV, LPV/r, NFV, SQV/r, TPV/r	↑ diltiazem possible IDV/r ↑ diltiazem AUC 26%	Use with caution. Adjust diltiazem according to clinical response and toxicities.
Herbal Products			
St. John's wort	All PIs	↓ PI expected	Do not coadminister.
Hormonal Contraceptives			
Hormonal contraceptives	RTV-boosted PIs		
	ATV/r	↓ ethinyl estradiol ↑ norgestimate	Oral contraceptive should contain at least 35mcg of ethinyl estradiol. Oral contraceptives containing progestins other than norethindrone or norgestimate have not been studied.
	DRV/r	ethinyl estradiol AUC ↓ 44% norethindrone AUC ↓ 14%	Use alternative or additional method.
	FPV/r	ethinyl estradiol AUC ↓ 37% norethindrone AUC ↓ 34%	Use alternative or additional method.
	LPV/r	ethinyl estradiol AUC ↓ 42% norethindrone AUC ↓ 17%	Use alternative or additional method.
	SQV/r	↓ ethinyl estradiol	Use alternative or additional method.
	TPV/r	ethinyl estradiol AUC ↓ 48% norethindrone: no significant change	Use alternative or additional method.
	PIs without RTV		
	ATV	ethinyl estradiol AUC ↑ 48% norethindrone AUC ↑ 110%	Oral contraceptive should contain no more than 30mcg of ethinyl estradiol or use alternate method. Oral contraceptives containing less than 25mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate have not been studied.
	FPV	With APV: ↑ ethinyl estradiol and ↑ norethindrone; ↓ APV 20%	Use alternative method.
	IDV	ethinyl estradiol AUC ↑ 25% norethindrone AUC ↑ 26%	No dose adjustment
	NFV	ethinyl estradiol AUC ↓ 47% norethindrone AUC ↓ 18%	Use alternative or additional method.

Concomitant Drug	Protease Inhibitor (PI)	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
HMG-CoA Reductase Inhibitors			
Atorvastatin	All PIs	↑ atorvastatin; DRV/r + atorvastatin 10mg similar to atorvastatin 40mg alone; FPV +/- RTV ↑ atorvastatin AUC 130%–153%; LPV/r ↑ atorvastatin AUC 488%; NFV ↑ atorvastatin AUC 74%; SQV/r ↑ atorvastatin AUC 79%; TPV/r ↑ atorvastatin AUC 836%	Use lowest possible starting dose with careful monitoring for toxicities or consider other HMG-CoA reductase inhibitors with less potential for interaction.
Lovastatin	All PIs	Significant ↑ lovastatin expected	Contraindicated – do not coadminister.
Pravastatin	DRV/r	pravastatin AUC ↑ 81%	Use lowest possible starting dose with careful monitoring.
	LPV/r	pravastatin AUC ↑ 33%	No dose adjustment necessary
	NFV, SQV/r	pravastatin AUC ↓ 47%–50%	No dose adjustment necessary
Rosuvastatin	ATV/r	rosuvastatin AUC ↑ 213% and Cmax ↑ 600%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	DRV/r, IDV +/- RTV, NFV, SQV/r	↑ rosuvastatin possible	
	FPV +/- RTV	No significant change	No dosage adjustment necessary
	LPV/r	rosuvastatin AUC ↑ 108% and Cmax ↑ 366%	Use lowest possible starting dose with careful monitoring or consider other HMG-CoA reductase inhibitors with less potential for interaction.
	TPV/r	rosuvastatin AUC ↑ 26% and Cmax ↑ 123%	
Simvastatin	All PIs	Significant ↑ simvastatin level NFV ↑ simvastatin AUC 505% SQV/r 400mg/400mg BID ↑ simvastatin AUC 3,059%	Contraindicated – do not coadminister.
Methadone			
Methadone	RTV-boosted PIs		
	ATV/r, DRV/r, FPV/r, IDV/r, LPV/r, SQV/r, TPV/r	↓ methadone levels ATV/r, DRV/r, FPV/r ↓ R-methadone AUC 16%–18%; LPV/r ↓ methadone AUC 26%–53%; SQV/r 1,000/100mg BID ↓ R-methadone AUC 19%; TPV/r ↓ R-methadone AUC 48%	Opiate withdrawal unlikely but may occur. No adjustment in methadone usually required but monitor for opiate withdrawal and increase methadone dose as clinically indicated. (R-methadone is the active form of methadone.)
	PIs without RTV		
	ATV, IDV	No significant effect	
	FPV	No data with FPV With APV: R-methadone Cmin ↓ 21%, AUC no significant change	Monitor and titrate methadone as clinically indicated. The interaction with FPV is presumed to be similar.
	NFV	NFV ↓ methadone AUC 40%	Opiate withdrawal rarely occurs. Monitor and titrate dose as clinically indicated. May require ↑ methadone dose.
Phosphodiesterase Type 5 Inhibitors			
Sildenafil	All PIs	DRV/r + sildenafil 25mg similar to sildenafil 100mg alone; IDV ↑ sildenafil AUC 340%; RTV 500mg BID ↑ sildenafil AUC 1,000%; SQV unboosted ↑ sildenafil AUC 210%	Sildenafil For treatment of erectile dysfunction: start with 25mg every 48 hours and monitor for adverse effects of sildenafil For treatment of pulmonary arterial hypertension: contraindicated
Tadalafil	All PIs	RTV 200mg BID ↑ tadalafil AUC 124%; TPV/r (1 st dose) ↑ tadalafil AUC 133%; TPV/r steady state: no significant effect	Tadalafil: start with 5mg dose and do not exceed a single dose of 10mg every 72 hours. Monitor for adverse effects of tadalafil.
Vardenafil	All PIs	IDV ↑ vardenafil AUC 16-fold; RTV 600mg BID ↑ vardenafil AUC 49-fold	Vardenafil: start with 2.5mg every 72 hours and monitor for adverse effects of vardenafil.

Drug-Specific Interactions

Protease Inhibitor (PI)	Concomitant Drug Class/Name	Effect on PI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comments
All PIs	Dexamethasone	↓ PI levels possible	
DRV/r	Paroxetine Sertraline	paroxetine AUC ↓ 39% sertraline AUC ↓ 49%	Monitor closely for antidepressant response. Titrate SSRI dose based on clinical assessment.
FPV/r	Paroxetine	paroxetine AUC ↓ 55%	Monitor closely for antidepressant response. Titrate paroxetine dose based on clinical assessment.
IDV	Grapefruit juice Vitamin C >1 g/day	↓ IDV ↓ IDV	Monitor for virologic responses.
LPV/r	Bupropion	bupropion AUC ↓ 57%	Titrate bupropion based on clinical response.
RTV	Salmeterol	↑ salmeterol	Coadministration is not recommended.
	Trazodone	RTV 200mg BID ↑ trazodone AUC 240%	Use lowest dose of trazodone and monitor for CNS and cardiovascular adverse effects.
TPV/r	Bupropion	bupropion AUC ↓ 46%	Titrate bupropion based on clinical response.

Abbreviations: APV = amprenavir (FPV is a prodrug of APV), ATV = atazanavir, ATV/r = atazanavir + ritonavir, DRV/r = darunavir + ritonavir, FPV = fosamprenavir (FPV is a prodrug of APV), FPV/r = fosamprenavir + ritonavir, IDV = indinavir, IDV/r = indinavir + ritonavir, LPV/r = lopinavir + ritonavir, NFV = nelfinavir, RTV = ritonavir, SQV/r = saquinavir + ritonavir, TPV/r = tipranavir + ritonavir.

Table 14b. Drug Interactions Between NNRTIs* and Other Drugs (Updated December 1, 2009)

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*Delavirdine is not included in this table. Please refer to the FDA package insert for information regarding delavirdine drug interactions.

This table provides information relating to pharmacokinetic interactions between NNRTIs and non-antiretroviral drugs. For interactions among antiretroviral agents and for dosing recommendations, refer to [Table 15b](#).

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Fluconazole	EFV	No significant effect	
	ETR	↑ ETR possible	No dosage adjustment necessary
	NVP	NVP AUC ↑ 110%	Increased risk of hepatotoxicity possible with this combination. Monitor NVP toxicity or use alternative antiretroviral agent.
Itraconazole	EFV	itraconazole and OH-itraconazole AUC, C _{max} , and C _{min} ↓ 35%–44%	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
	ETR	↓ itraconazole possible ↑ ETR possible	Dose adjustments for itraconazole may be necessary. Monitor itraconazole level.
	NVP	↓ itraconazole possible ↑ NVP possible	Consider monitoring NNRTI and itraconazole levels.
Ketoconazole	EFV	↓ ketoconazole possible	
	ETR	↓ ketoconazole possible ↑ ETR possible	Dose adjustment for ketoconazole may be necessary depending on other coadministered drugs.
	NVP	ketoconazole AUC ↓ 72% ↑ NVP 15%–30%	Coadministration not recommended.
Posaconazole	EFV	posaconazole AUC ↓ 50%	Consider alternative antifungal if possible or consider monitoring posaconazole level if available.
	ETR	↑ ETR possible	No dosage adjustment necessary
Voriconazole	EFV	voriconazole AUC ↓ 77% EFV AUC ↑ 44%	Contraindicated at standard doses. Dose: voriconazole 400mg BID, EFV 300mg daily
	ETR	↑ voriconazole possible ↑ ETR possible	Dose adjustments for voriconazole may be necessary depending on other coadministered drugs. Monitor voriconazole level.
	NVP	↓ voriconazole possible ↑ NVP possible	Monitor for toxicity and antifungal outcome and/or voriconazole level.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	EFV	carbamazepine + EFV: carbamazepine AUC ↓ 27% and EFV AUC ↓ 36% phenytoin + EFV: ↓ EFV and ↓ phenytoin possible	Monitor anticonvulsant and EFV levels, or if possible, use alternative anticonvulsant.
	ETR	↓ anticonvulsant and ETR possible	Do not coadminister. Consider alternative anticonvulsants.
	NVP	↓ anticonvulsant and NVP possible	Monitor anticonvulsant and NVP levels and virologic responses.
Anti-mycobacterials			
Clarithromycin	EFV	clarithromycin AUC ↓ 39%	Monitor for efficacy or consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	ETR	clarithromycin AUC ↓ 39% OH-clarithromycin AUC ↑ 21% ETR AUC ↑ 42%	Consider alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
	NVP	Clarithromycin AUC ↓ 31% OH-clarithromycin AUC ↑ 42%	Monitor for efficacy or use alternative agent, such as azithromycin, for MAC prophylaxis and treatment.
Rifabutin	EFV	Rifabutin ↓ 38%	Dose: rifabutin 450–600mg once daily or 600mg 3x/week if EFV is not coadministered with a PI.
	ETR	rifabutin and metabolite AUC ↓ 17% ETR AUC ↓ 37%	Dose: rifabutin 300mg once daily if ETR is not coadministered with a RTV-boosted PI. If ETR is coadministered with a RTV-boosted PI, rifabutin should not be coadministered.
	NVP	rifabutin AUC ↑ 17% and metabolite AUC ↑ 24% NVP C _{min} ↓ 16%	No dosage adjustment necessary. Use with caution.
Rifampin	EFV	EFV AUC ↓ 26%	Maintain EFV dose at 600mg once daily and monitor for virologic response. Some clinicians suggest EFV 800mg dose in patients >60kg.
	ETR	Significant ↓ ETR possible	Do not coadminister.
	NVP	NVP ↓ 20%–58%	Do not coadminister.

Concomitant Drug Class/Name	NNRTI	Effect on NNRTI or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Benzodiazepines			
Alprazolam	EFV, ETR, NVP	No data	Monitor for therapeutic efficacy of alprazolam.
Diazepam	ETR	↑ diazepam possible	Decreased dose of diazepam may be necessary.
Lorazepam	EFV	lorazepam Cmax ↑ 16%, AUC no significant effect	No dosage adjustment necessary
Midazolam	EFV	Significant↑ midazolam expected	Do not coadminister with oral midazolam. Parenteral midazolam can be used with caution as a single dose and can be given in a monitored situation for procedural sedation.
Triazolam	EFV	Significant ↑ triazolam expected	Do not coadminister.
Cardiac Medications			
Dihydropyridine Calcium channel blockers (CCBs)	EFV, NVP	↓ CCBs possible	Titrate CCB dose based on clinical response.
Diltiazem	EFV	diltiazem AUC ↓ 69%	Titrate diltiazem dose based on clinical response.
	NVP	↓ diltiazem possible	
Herbal Products			
St. John’s wort	EFV, ETR, NVP	↓ NNRTI	Do not coadminister.
Hormonal Contraceptives			
Hormonal contraceptives	EFV	ethinyl estradiol AUC ↑ 37%	Clinical significance unknown
	ETR	ethinyl estradiol AUC ↑ 22% norethindrone: no significant effect	No dosage adjustment necessary
	NVP	ethinyl estradiol AUC ↓ 20% norethindrone AUC ↓ 19%	Use alternative or additional methods.
		depomedroxyprogesterone acetate: no significant change	No dosage adjustment necessary
HMG-CoA Reductase Inhibitors			
Atorvastatin	EFV, ETR, NVP	atorvastatin AUC ↓ 32%–43% with EFV, ETR	Adjust atorvastatin according to lipid responses, not to exceed the maximum recommended dose.
Fluvastatin	ETR	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.
Lovastatin Simvastatin	EFV	simvastatin AUC ↓ 68%	Adjust simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	ETR	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
	NVP	↓ lovastatin possible ↓ simvastatin possible	Adjust lovastatin or simvastatin dose according to lipid responses, not to exceed the maximum recommended dose. If used with RTV-boosted PI, simvastatin and lovastatin should be avoided.
Pravastatin Rosuvastatin	EFV	pravastatin AUC ↓ 44% rosuvastatin: no data	Adjust statin dose according to lipid responses, not to exceed the maximum recommended dose.
	ETR	No significant effect expected	No dosage adjustment necessary
Methadone			
Methadone	EFV	methadone AUC ↓ 52%	Potential for opiate withdrawal; increased methadone dose often necessary.
	ETR	No significant effect	No dosage adjustment necessary
	NVP	↓ methadone NVP: no significant effect	Opiate withdrawal common; increased methadone dose often necessary.
Oral Anticoagulant			
Warfarin	EFV, NVP	↑ or ↓ warfarin possible	Monitor INR and adjust warfarin accordingly.
	ETR	↑ warfarin possible	Monitor INR and adjust warfarin dose accordingly.

Abbreviations: DLV = delavirdine, EFV = efavirenz, ETR = etravirine, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine, CBZ = carbamazepine.

Drug-Specific Interactions

NNRTI	Concomitant Drug Class/Name	Effect on NNRTI or Concomitant Drug Concentrations	Dosage Recommendations and Clinical Comment
EFV	Sertraline	sertraline AUC ↓ 39%	Titrate sertraline dose based on clinical response.
	Bupropion	bupropion AUC ↓ 55%	Titrate bupropion dose based on clinical response.
ETR	Dexamethasone	↓ ETR	Use systemic dexamethasone with caution or consider alternative corticosteroid for long-term use.
	Sildenafil	sildenafil AUC ↓ 57%	May need to increase sildenafil dose based on clinical effect.

Abbreviations: DLV = delavirdine, EFV = efavirenz, ETR = etravirine, NNRTI = non-nucleoside reverse transcriptase inhibitor, NVP = nevirapine

Table 14c. Drug Interactions Between NRTIs and Other Drugs (including antiretroviral agents)
(Updated December 1, 2009)

Concomitant Drug Class/Name	NRTI	Effect on NRTI or Concomitant Drug Concentrations	Clinical Comment
Antivirals			
Ganciclovir (GCV) Valganciclovir	ddI	ddI AUC ↑ 50%–111% GCV AUC ↓ 21% when ddI administered 2 hours prior to oral GCV No change in IV GCV concentrations	Appropriate doses for combination of ddI and GCV have not been established. Monitor for ddI-associated toxicities.
	TDF	No data	Serum concentrations of these drugs and/or TDF may be increased. Monitor for dose-related toxicities.
	ZDV	No significant pharmacokinetic effects	Potential increase in hematologic toxicities
Ribavirin	ddI	↑ intracellular ddI	Contraindicated—do not coadminister. Fatal hepatic failure and other ddI-related toxicities have been reported with coadministration.
	ZDV	Ribavirin inhibits phosphorylation of ZDV	Avoid coadministration if possible or closely monitor virologic response and hematologic toxicities.
Integrase Inhibitor			
Raltegravir (RAL)	TDF	RAL AUC ↑ 49%, Cmax ↑ 64%	No dosage adjustment necessary.
Methadone			
Methadone	ABC	↓ methadone	Monitor for opiate withdrawal and titrate methadone as clinically indicated. May need to increase methadone dose.
	d4T	↓ d4T	No dosage adjustment necessary
	ZDV	ZDV AUC ↑ 43%	Monitor for ZDV-related adverse effects.
NRTIs			
Didanosine (ddI)	d4T	No significant effect	Avoid coadministration. Peripheral neuropathy, lactic acidosis, and pancreatitis seen with this combination.
	TDF	ddI-EC AUC and Cmax ↑ 48%–60%	Avoid coadministration if possible. <u>Dose if CrCl >60mL/min</u> ≥60kg: ddI-EC 250mg/day <60kg: ddI-EC 200mg/day Monitor for ddI-associated toxicity.
Other			
Allopurinol	ddI	ddI AUC ↑ 113% ddI AUC ↑ 312% with renal impairment	Contraindicated—do not coadminister. Potential for increased didanosine-associated toxicities.
PIs			
Atazanavir (ATV)	ddI	With ddI-EC + ATV (with food): ddI AUC ↓ 34%; ATV no change	Administer ATV with food 2 hours before or 1 hour after didanosine.
	TDF	ATV AUC ↓ 25% and Cmin ↓ 23%–40% (higher Cmin with RTV than without) TDF AUC ↑ 24%–37%	<u>Dose:</u> ATV/r 300/100mg daily coadministered with TDF 300mg daily. Avoid concomitant use without ritonavir. Monitor for TDF-associated toxicity.
	ZDV	ZDV Cmin ↓ 30%, no change in AUC	Clinical significance unknown
Darunavir/ritonavir (DRV/r)	TDF	TDF AUC ↑ 22%, Cmax ↑ 24%, and Cmin ↑ 37%	Clinical significance unknown. Monitor for TDF toxicity.
Lopinavir/ritonavir (LPV/r)	TDF	LPV/r AUC ↓ 15% TDF AUC ↑ 34%	Clinical significance unknown. Monitor for TDF toxicity.
Tipranavir/ritonavir (TPV/r)	ABC	ABC ↓ 35%–44% with TPV/r 1,250/100mg BID	Appropriate doses for this combination have not been established.
	ddI	ddI-EC ↓ 10% and TPV Cmin ↓ 34% with TPV/r 1,250/100mg BID	Separate doses by at least 2 hours.
	ZDV	ZDV AUC ↓ 31%–43% and Cmax ↓ 46%–51% with TPV/r 1,250/100mg BID	Appropriate doses for this combination have not been established.

Abbreviations: ABC = abacavir, ddI = didanosine, d4T = stavudine, TDF = tenofovir, ZDV = zidovudine.

Table 14d. Drug Interactions Between CCR5 Antagonist and Other Drugs**(Updated December 1, 2009)**

This table provides information relating to pharmacokinetic interactions between maraviroc and non-antiretroviral drugs. For interactions among antiretroviral agents and for dosing recommendations, please refer to [Table 15b](#).

Concomitant Drug Class/Name	CCR5 Antagonist	Effect on CCR5 Antagonist or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Antifungals			
Itraconazole	MVC	↑ MVC possible	<u>Dose:</u> MVC 150mg BID
Ketoconazole	MVC	MVC AUC ↑ 400%	<u>Dose:</u> MVC 150mg BID
Voriconazole	MVC	↑ MVC possible	Consider dose reduction to MVC 150mg BID.
Anticonvulsants			
Carbamazepine Phenobarbital Phenytoin	MVC	↓ MVC possible	<u>If used without a strong CYP3A inhibitor:</u> MVC 600mg BID or use alternative antiepileptic agent.
Anti-mycobacterials			
Clarithromycin	MVC	↑ MVC possible	<u>Dose:</u> MVC 150mg BID
Rifabutin	MVC	↓ MVC possible	<u>If used without a strong CYP3A inducer or inhibitor:</u> MVC 300mg BID. <u>If used with a strong CYP3A inhibitor:</u> MVC 150mg BID.
Rifampin	MVC	MVC AUC ↓ 64%	Coadministration is not recommended. If coadministration is necessary use MVC 600mg BID. If coadministered with a strong CYP3A inhibitor use MVC 300mg BID.
Herbal Products			
St. John's wort	MVC	↓ MVC possible	Coadministration is not recommended.
Hormonal Contraceptives			
Hormonal Contraceptives	MVC	No significant effect on ethinyl estradiol or levonorgestrel	Safe to use in combination

Abbreviation: MVC = maraviroc.

Table 14e. Drug Interactions Between Integrase Inhibitor and Other Drugs

Concomitant Drug Class/Name	Integrase Inhibitor	Effect on Integrase Inhibitor or Concomitant Drug Concentrations	Dosing Recommendations and Clinical Comment
Acid Reducers			
Omeprazole	RAL	RAL AUC ↑ 212%, C _{max} ↑ 315%, and C _{min} ↑ 46%	No dosage adjustment recommended.
Anti-mycobacterials			
Rifampin	RAL	RAL AUC ↓ 40% and C _{min} ↓ 61% with RAL 400mg Rifampin with RAL 800mg BID compared with RAL 400mg BID alone: RAL AUC ↑ 27% and C _{min} ↓ 53%	<u>Dose:</u> RAL 800mg BID Monitor closely for virologic response.

Abbreviation: RAL = raltegravir

Table 15a. Interactions Among Protease Inhibitors (Updated December 1, 2009)

Drug Affected	Atazanavir	Fosamprenavir	Lopinavir/ Ritonavir	Nelfinavir	Ritonavir	Saquinavir	Tipranavir
Protease Inhibitors							
Darunavir (DRV)	<u>Dose:</u> ATV 300mg once daily + DRV 600mg BID + RTV 100mg BID	No data	Should not be coadministered because doses are not established	No data	<u>Dose:</u> (DRV 600mg + RTV 100mg) BID or (DRV 800mg + RTV 100mg) once daily	Should not be coadministered because doses are not established	No data
Fosamprenavir (FPV)	<u>Dose:</u> Insufficient data	•	Should not be coadministered because doses are not established	See FPV + NFV cell	<u>Dose:</u> (FPV 1,400mg + RTV 100mg or 200mg) once daily; or (FPV 700mg + RTV 100mg) BID	<u>Dose:</u> Insufficient data	Should not be coadministered because doses are not established
Indinavir (IDV)	Should not be coadministered because of potential for additive hyperbilirubinemia	<u>Dose:</u> Not established	<u>Dose:</u> IDV 600mg BID + LPV/r 400/100mg BID	<u>Dose:</u> Limited data for IDV 1,200mg BID + NFV 1,250mg BID	<u>Dose:</u> IDV 800mg BID + RTV 100–200mg BID	<u>Dose:</u> Insufficient data	Should not be coadministered because doses are not established
Lopinavir/ Ritonavir (LPV/r)	<u>Dose:</u> ATV 300mg once daily + LPV/r 400/100mg BID	See LPV/r + FPV cell	•	See LPV/r + NFV cell	Lopinavir is coformulated with ritonavir as Kaletra	See LPV/r + SQV cell	Should not be coadministered because doses are not established
Nelfinavir (NFV)	No data	<u>Dose:</u> Insufficient data	<u>Dose:</u> No data with LPV/r tablets	•	See NFV + RTV cell	See NFV+SQV cell	Should not be coadministered because doses are not established
Ritonavir (RTV)	<u>Dose:</u> (ATV 300mg + RTV 100mg) once daily	See RTV + FPV cell	Lopinavir is coformulated with ritonavir as Kaletra.	<u>Dose:</u> Not established	•	<u>Dose:</u> (SQV 1,000mg + RTV 100mg) BID	<u>Dose:</u> (TPV 500mg + RTV 200mg) BID
Saquinavir (SQV)	<u>Dose:</u> Insufficient data	<u>Dose:</u> Insufficient data	<u>Dose:</u> SQV 1,000mg BID + LPV/r 400/100mg BID	<u>Dose:</u> SQV 1200mg BID + NFV 1,250mg BID	See SQV + RTV cell	•	Should not be coadministered because doses are not established

Table 15b. Interactions Between NNRTIs*, Maraviroc, Raltegravir, and PIs (Updated December 1, 2009)

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*Delavirdine is not included in this table. Refer to the FDA package insert for information regarding delavirdine drug interactions.

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Atazanavir (ATV)	Exposure	With unboosted ATV ATV: AUC ↓ 74% EFV: no significant change With (ATV 300mg + RTV 100mg) once daily with food ATV concentrations similar to unboosted ATV without EFV	With unboosted ATV ETR: AUC ↑ 50%, Cmax ↑ 47%, and Cmin ↑ 58% ATV: AUC ↓ 17% and Cmin ↓ 47% With (ATV 300mg + RTV 100mg) once daily ETR: AUC, Cmax, and Cmin ↑ approximately 30% ATV: AUC ↓ 14% and Cmin ↓ 38%	With (ATV 300mg + RTV 100mg) once daily ATV: AUC ↓ 42% and Cmin ↓ 72% NVP: AUC ↑ 25%	With unboosted ATV MVC: AUC ↑ 257% With (ATV 300mg + RTV 100mg) once daily MVC: AUC ↑ 388%	With unboosted ATV RAL: AUC ↑ 72% With (ATV 300mg + RTV 100mg) once daily RAL: AUC ↑ 41%
	Dose	Do not coadminister with unboosted ATV. <u>In treatment-naïve patients</u> (ATV 400mg + RTV 100mg) once daily Do not coadminister in treatment-experienced patients.	Do not coadminister with ATV +/- RTV.	Do not coadminister with ATV +/- RTV.	MVC 150mg BID with ATV +/- RTV	Standard
Darunavir (DRV)	Exposure	With (DRV 300mg + RTV 100mg) BID DRV: AUC ↓ 13%, Cmin ↓ 31% EFV: AUC ↑ 21%	ETR 100mg BID with (DRV 600mg + RTV 100mg) BID DRV: no significant change ETR: AUC ↓ 37%, Cmin ↓ 49%	With (DRV 400mg + RTV 100mg BID) DRV: AUC ↑ 24%† NVP: AUC ↑ 27% and Cmin ↑ 47%	With (DRV 600mg + RTV 100mg) BID MVC: AUC ↑ 305% With (DRV 600mg + RTV 100mg) BID + ETR MVC: AUC ↑ 210%	With (DRV 600mg + RTV 100mg) BID RAL: AUC ↓ 29% and Cmin ↑ 38%
	Dose	Clinical significance unknown. Use standard doses and monitor closely. Consider monitoring levels.	Standard Despite decreased ETR, safety and efficacy established with this combination in a clinical trial	Standard	MVC 150mg BID	Standard
Efavirenz (EFV)	Exposure		↓ ETR possible	NVP: no significant change EFV: AUC ↓ 22%	MVC: AUC ↓ 45%	EFV: AUC ↓ 36%
	Dose		Do not coadminister.	Do not coadminister.	MVC: 600mg BID	Standard
Etravirine (ETR)	Exposure	↓ ETR possible		↓ ETR possible	MVC: AUC ↓ 53%, Cmax ↓ 60%	ETR: Cmin ↓ 17% RAL: Cmin ↓ 34%
	Dose	Do not coadminister.		Do not coadminister.	MVC 600mg BID	Standard
Fosamprenavir (FPV)	Exposure	With (FPV 1,400mg + RTV 200mg) once daily APV: Cmin ↓ 36%	With (FPV 700mg + RTV 100mg) BID APV: AUC ↑ 69%, Cmin ↑ 77%	With unboosted FPV 1,400mg BID APV: AUC ↓ 33% NVP: AUC ↑ 29% With (FPV 1,400mg + RTV 100mg) BID NVP: Cmin ↑ 19%	Unknown; ↑ MVC possible	No data
	Dose	(FPV 1,400mg + RTV 300mg) once daily; or (FPV 700mg + RTV 100mg) BID EFV standard	Do not coadminister with FPV +/- RTV.	(FPV 700mg + RTV 100mg) BID NVP standard	MVC 150mg BID	No data
Indinavir (IDV)	Exposure	IDV: ↓ 31%	IDV: ↓	IDV: ↓ 31% NVP: no effect	Unknown; ↑ MVC possible	No data
	Dose	IDV 1,000mg q8h or (IDV 800mg + RTV 100–200mg) BID EFV standard	Do not coadminister.	IDV 1,000mg q8h, or (IDV 800mg + RTV 100–200mg) BID NVP standard	MVC 150mg BID	No data

		Efavirenz	Etravirine	Nevirapine	Maraviroc	Raltegravir
Lopinavir/ Ritonavir (LPV/r)	Exposure	With LPV/r tablets 500/125mg BID† + EFV 600mg LPV levels similar to LPV/r 400/100mg BID without EFV	With LPV/r tablets ETR: levels ↓ 30%–45% (comparable to the decrease with DRV/r) LPV: levels ↓ 13%–20%.	With LPV/r capsules LPV: AUC ↓ 27% and Cmin ↓ 51%	MVC: AUC ↑ 295% With LPV/r + EFV MVC: AUC ↑ 153%	No data
	Dose	LPV/r tablets 500/125mg‡ BID; LPV/r oral solution 533/133mg BID EFV standard	Standard	LPV/r tablets 500/125mg‡ BID; LPV/r oral solution 533/133mg BID NVP standard	MVC 150mg BID	No data
Nelfinavir (NFV)	Exposure	NFV: AUC ↑ 20%	No data	NFV: Cmin ↓ 32% NVP: no significant effect	Unknown, possibly ↑ MVC concentration	No data
	Dose	Standard	Do not coadminister.	Standard	MVC 150mg BID	No data
Nevirapine (NVP)	Exposure	NVP: no significant change EFV: AUC ↓ 22%	↓ ETR possible		No significant change	No data
	Dose	Do not coadminister.	Do not coadminister.	•	Without PI MVC 300mg BID With PI (except TPV/r) MVC 150mg BID	No data
Raltegravir (RAL)	Exposure	RAL: AUC ↓ 36%	ETR: Cmin ↑ 17% RAL: Cmin ↓ 34%	No data	RAL: AUC ↓ 37% MVC: AUC ↓ 21%	•
	Dose	Standard	Standard	No data	Standard	
Ritonavir (RTV)	Exposure				With RTV 100 mg BID MVC: AUC ↑ 161%	With RTV 100mg BID RAL: AUC ↓ 16%
	Dose	Refer to information for boosted PI	Refer to information for boosted PI	Refer to information for boosted PI	MVC 150mg BID	Standard
Saquinavir (SQV)	Exposure	With SQV 1,200mg TID SQV: AUC ↓ 62% EFV: AUC ↓ 12%	With (SQV 1,000mg + RTV 100mg) BID SQV: AUC unchanged ETR: AUC ↓ 33%, Cmin ↓ 29% Reduced ETR levels similar to reduction with DRV/r	With SQV 600mg TID SQV: AUC ↓ 38% NVP: no significant change	With (SQV 1,000mg + RTV 100mg) BID MVC: AUC ↑ 877% With (SQV 1,000mg + RTV 100mg) BID + EFV MVC: AUC ↑ 400%	No data
	Dose	(SQV 1,000mg + RTV 100mg) BID	(SQV 1,000mg + RTV 100mg) BID	(SQV 1,000mg + RTV 100mg) BID	MVC 150mg BID	No data
Tipranavir (TPV)	Exposure	With (TPV 500mg + RTV 100mg) BID TPV: AUC ↓ 31%, Cmin ↓ 42% EFV: no significant change With (TPV 750mg + RTV 200mg) BID: TPV: no significant change EFV: no significant change	With (TPV 500mg + RTV 200mg) BID ETR: AUC ↓ 76%, Cmin ↓ 82% TPV: AUC ↑ 18%, Cmin ↑ 24%	With (TPV 250mg + RTV 200mg) BID and with (TPV 750mg + RTV 100mg) BID NVP: no significant change TPV: no data	With (TPV 500mg + RTV 200mg) BID MVC: no significant change in AUC TPV: no data	With (TPV 500mg + RTV 200mg) BID RAL: AUC ↓ 24%
	Dose	Standard	Do not coadminister.	Standard	MVC 300mg BID	Standard

† Based on between-study comparison.

‡ Use a combination of two LPV/r 200mg/50mg tablets + one LPV/r 100mg/25mg tablet to make a total dose of LPV/r 500mg/150mg.

Preventing Secondary Transmission of HIV

(Updated December 1, 2009)

PREVENTION COUNSELING

Interventions to prevent transmission of HIV are key components of the management of HIV infection, yet multiple studies show that prevention is frequently neglected in clinical practice. Each patient encounter provides opportunities to reinforce HIV prevention messages—messages that patients often look to their providers to deliver, but may fail to receive [1-2]. Despite the challenges to providing effective prevention interventions in a busy practice setting, multiple approaches are available, including formal guidance from CDC for incorporating HIV prevention into medical care settings [3]. Such interventions have been demonstrated to be effective in changing sexual risk behavior [4-6] and can reinforce self-directed behavior change early in diagnosis [7].

The CDC has identified prevention interventions for HIV-infected people that meet stringent criteria for efficacy and scientific rigor (CDC, 2009) and three that demonstrated efficacy in treatment settings (Options, Partnership for Health, and Positive Choices). The interventions are available through CDC trainings and materials, delivered as brief messages by providers or via laptop computer, and are readily implemented into busy clinics (<http://www.cdc.gov/hiv/topics/research/prs/index.htm>).

Evidence also exists regarding the efficacy of interventions to reduce injection drug use risk behavior. These include both behavioral interventions [8-10] and opiate substitution treatment with methadone [11-12].

There is evidence of increases in HIV risk behaviors among infected persons coinciding with the availability of potent combination antiretroviral therapy. In some cohorts the rate of reported risk behaviors almost doubled compared with rates in the era prior to such therapies [7]. A meta-analysis of studies of HIV risk behaviors demonstrates that the prevalence of unprotected sex acts was increased in those who believed that receiving antiretroviral therapy or having a suppressed viral load protects against transmitting HIV [13]. Attitudinal shifts away from safer sexual practices since the availability of potent antiretroviral therapy underscore the role for provider-initiated HIV prevention counseling. With wider recognition of the concept that effective treatment may decrease the probability of transmission, it is particularly important for providers to help patients understand that a sustained viral load below the limits of detection will dramatically reduce but does not absolutely assure the absence of virus in the genital and blood compartments, and hence the inability to transmit virus to others [13-14].

Additionally, given the role of sexually transmitted infections (STIs) as facilitators of HIV transmission, an essential adjunct to prevention counseling is the routine screening and symptom directed testing for STIs, as recommended by CDC [3].

ANTIRETROVIRAL THERAPY AS PREVENTION

Antiretroviral therapy does have a role in preventing HIV transmission. Lower levels of plasma RNA have been associated with decreases in the concentration of virus in genital secretions [15-16]. Observational studies have demonstrated a decreased rate of HIV transmission among serodiscordant heterosexual couples following antiretroviral-induced viral suppression, in the absence of concomitant STIs. Multiple studies have demonstrated a direct correlation between HIV inoculum size (i.e., viral load) and probability of transmission [17-18]. Although some data suggest that the risk of heterosexual HIV transmission is low when an individual's viral load is <40 copies/ml, these data are contingent upon several assumptions, including: 1) completely suppressed viremia; 2) complete adherence to an effective antiretroviral regimen; and 3) the absence of a concomitant STI. The reduction of the viral load in the genital compartment notwithstanding, there is not yet published evidence from randomized clinical trials that antiretroviral therapy confirms the reduction or elimination of risk of HIV sexual transmission. Detection of HIV RNA in the genital secretions has been documented in individuals with controlled plasma HIV RNA [19-20]. Moreover, it is critical that any biological reduction in infectivity not be offset by increases in risk behavior (i.e., risk compensation).

SUMMARY

In summary, consistent and effective use of antiretroviral therapy, resulting in a sustained reduction in viral load, in conjunction with consistent condom usage, safer sexual and drug use practices, and detection and treatment of STIs are essential tools for prevention of sexual and blood-borne transmission of HIV. Given these important considerations, medical visits provide a vital

opportunity to reinforce HIV prevention messages, discuss sexual- and drug-related risk behaviors, diagnose and treat intercurrent STIs, and develop open communication between provider and patient.

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Conclusion

The Panel has carefully reviewed recent results from clinical trials in HIV therapy and considered how they inform appropriate care guidelines. The Panel appreciates that HIV care is highly complex and rapidly evolving. Guidelines are never fixed and must always be individualized. Where possible, the Panel has based recommendations on the best evidence from prospective trials with defined endpoints. When such evidence does not yet exist, the panel attempted to reflect reasonable options in its conclusions.

HIV care requires, as always, partnerships and open communication. The provider can make recommendations most likely to lead to positive outcomes only if the patient's own point of view and social context are well known. Guidelines are only a starting point for medical decision making. They can identify some of the boundaries of high-quality care, but cannot substitute for sound judgment.

As further research is conducted and reported, guidelines will be modified. The Panel anticipates continued progress in the simplicity of regimens, improved potency and barrier to resistance, and reduced toxicity. The Panel hopes the guidelines are useful and is committed to their continued adjustment and improvement.

Appendix A: Financial Disclosure for Members of the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – February 2009

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Abbreviations: C = Co-Chair; ES = Executive Secretary; M = Member; N/A = not applicable

Appendix B, Table 1. Characteristics of Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

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(Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in renal or hepatic insufficiency, see Appendix, Table 7	Elimination	Serum/ Intracellular Half-lives	Adverse Events
Abacavir (ABC)/ Ziagen Also available as: Trizivir ABC with ZDV+3TC Epzicom ABC with 3TC	Ziagen 300mg tablets or 20mg/mL oral solution Trizivir ABC 300mg + ZDV 300mg + 3TC 150mg Epzicom ABC 600mg + 3TC 300mg	Ziagen 300mg BID or 600mg once daily Take without regard to meals Trizivir 1 tablet BID Epzicom 1 tablet once daily	Metabolized by alcohol dehydrogenase and glucuronyl transferase Renal excretion of metabolites 82% Dosage adjustment for ABC is recommended in patients with hepatic insufficiency (see Appendix, Table 7)	1.5 hrs/ 12–26 hrs	- Hypersensitivity reaction symptoms may include fever, rash, nausea, vomiting, malaise or fatigue, or respiratory symptoms such as sore throat, cough, or shortness of breath. - Some cohort studies suggest increased risk of MI with recent or current use of ABC, but this is not substantiated in other studies.
Didanosine (ddI)/ Videx EC, generic didanosine enteric coated (dose same as Videx EC)	Videx EC 125, 200, 250, 400mg capsules Buffered tablets (non-EC) no longer available Videx 10mg/mL oral solution	Body weight $\geq$ 60kg: 400mg once daily*; with TDF , 250mg once daily Body weight < 60kg: 250mg once daily*; with TDF , 200mg once daily Take 1/2 hour before or 2 hours after a meal *Preferred dosing with oral solution is BID (total daily dose divided into 2 doses)	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (see Appendix, Table 7)	1.5 hrs/ >20 hrs	- Pancreatitis - Peripheral neuropathy - Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) - Potential association with noncirrhotic portal hypertension
Emtricitabine (FTC)/ Emtriva Also available as: Atripla FTC with EFV+TDF Truvada FTC with TDF	Emtriva 200mg hard gelatin capsule or 10mg/mL oral solution Atripla FTC 200mg + EFV 600mg + TDF 300mg Truvada FTC 200mg + TDF 300mg	Emtriva 200mg capsule once daily or 240mg (24 mL) oral solution once daily Take without regard to meals Atripla 1 tablet at or before bedtime Take on an empty stomach to reduce side effects Truvada 1 tablet once daily	Renal excretion 86% Dosage adjustment in renal insufficiency recommended (see Appendix, Table 7)	10 hrs/ >20 hrs	- Minimal toxicity - Hyperpigmentation/skin discoloration - Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue FTC.

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in renal or hepatic insufficiency, see Appendix, Table 7	Elimination	Serum/ Intracellular Half-lives	Adverse Events
Lamivudine (3TC)/ Epivir Also available as: <u>Combivir</u> 3TC with ZDV <u>Epzicom</u> 3TC with ABC <u>Trizivir</u> 3TC with ZDV+ABC	<u>Epivir</u> 150, 300mg tablets or 10mg/mL oral solution <u>Combivir</u> 3TC 150mg + ZDV 300mg <u>Epzicom</u> 3TC 300mg + ABC 600mg <u>Trizivir</u> 3TC 150mg + ZDV 300mg + ABC 300mg	<u>Epivir</u> 150mg BID or 300mg once daily Take without regard to meals <u>Combivir</u> 1 tablet BID <u>Epzicom</u> 1 tablet once daily <u>Trizivir</u> 1 tablet BID	Renal excretion 70% Dosage adjustment in renal insufficiency recommended (see Appendix, Table 7)	5–7 hrs/ 18–22 hrs	- Minimal toxicity - Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue 3TC.
Stavudine (d4T)/ Zerit	<u>Zerit</u> 15, 20, 30, 40mg capsules or 1mg/mL oral solution	Body weight ≥ 60 kg: 40mg BID Body weight < 60 kg: 30mg BID* Take without regard to meals *WHO recommends 30mg BID dosing regardless of body weight.	Renal excretion 50% Dosage adjustment in renal insufficiency recommended (see Appendix, Table 7)	1.0 hr/ 7.5 hrs	- Peripheral neuropathy - Lipoatrophy - Pancreatitis - Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity) - Hyperlipidemia - Rapidly progressive ascending neuromuscular weakness (rare)
Tenofovir Disoproxil Fumarate (TDF)/ Viread Also available as: <u>Atripla</u> TDF with EFV+FTC <u>Truvada</u> TDF with FTC	<u>Viread</u> 300mg tablet <u>Atripla</u> TDF 300mg + EFV 600mg + FTC 200mg <u>Truvada</u> TDF 300mg + FTC 200mg	<u>Viread</u> 1 tablet once daily Take without regard to meals <u>Atripla</u> 1 tablet at or before bedtime Take on an empty stomach to reduce side effects <u>Truvada</u> 1 tablet once daily	Renal excretion Dosage adjustment in renal insufficiency recommended (see Appendix, Table 7)	17 hrs/ >60 hrs	- Asthenia, headache, diarrhea, nausea, vomiting, and flatulence - Renal insufficiency, Fanconi syndrome - Osteomalacia - Potential for decrease in bone mineral density - Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue TDF.
Zidovudine (AZT, ZDV)/ Retrovir, generic zidovudine Also available as: <u>Combivir</u> ZDV with 3TC <u>Trizivir</u> ZDV with 3TC+ABC	<u>Retrovir</u> 100mg capsules, 300mg tablets, 10mg/mL intravenous solution, 10mg/mL oral solution <u>Combivir</u> ZDV 300mg + 3TC 150mg <u>Trizivir</u> ZDV 300mg + 3TC 150mg + ABC 300mg	<u>Retrovir</u> 300mg BID or 200mg TID Take without regard to meals <u>Combivir</u> 1 tablet BID <u>Trizivir</u> 1 tablet BID	Metabolized to AZT glucuronide (GAZT) Renal excretion of GAZT Dosage adjustment in renal insufficiency recommended (see Appendix, Table 7)	1.1 hrs/ 7 hrs	- Bone marrow suppression: macrocytic anemia or neutropenia - Gastrointestinal intolerance, headache, insomnia, asthenia - Nail pigmentation - Lactic acidosis with hepatic steatosis (rare but potentially life-threatening toxicity)

Appendix B, Table 2. Characteristics of Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) (Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in renal or hepatic insufficiency, see Appendix, Table 7	Elimination	Serum Half-life	Adverse Events
Delavirdine (DLV)/ Rescriptor	100, 200mg tablets	400mg TID; four 100mg tablets can be dispersed in >3 oz. of water to produce slurry; 200mg tablets should be taken as intact tablets Take without regard to meals Separate dose from antacids by 1 hour	CYP3A4 substrate and inhibitor; 51% excreted in urine (<5% unchanged) and 44% in feces	5.8 hrs	• Rash* • Increased transaminase levels • Headaches
Efavirenz (EFV)/ Sustiva Also available as:	50, 200mg capsules or 600mg tablets	600mg once daily at or before bedtime Take on an empty stomach to reduce side effects	Metabolized by CYPs 2B6 and 3A4 CYP3A4 mixed inducer/inhibitor (more an inducer than an inhibitor)	40–55 hrs	• Rash* • Central nervous system symptoms† • Increased transaminase levels • False-positive results reported with some cannabinoid and benzodiazepine screening assays • Teratogenic in nonhuman primate and potentially teratogenic in humans
<u>Atripla</u> EFV with FTC + TDF	<u>Atripla</u> EFV 600mg + FTC 200mg + TDF 300mg	<u>Atripla</u> 1 tablet once daily at or before bedtime			
Etravirine (ETR)/ Intelence	100mg tablets	200mg BID Take following a meal	CYP3A4, 2C9, and 2C19 substrate 3A4 inducer; 2C9 and 2C19 inhibitor	41 +/- 20 hrs	• Rash * • Hypersensitivity reactions have been reported, characterized by rash, constitutional findings, and sometimes organ dysfunction, including hepatic failure • Nausea
Nevirapine (NVP)/ Viramune	200mg tablets or 50mg/5 mL oral suspension	200mg once daily for 14 days (lead-in period); thereafter, 200mg BID Take without regard to meals Repeat lead-in period if therapy is discontinued for >7 days In patients who develop mild to moderate rash without constitutional symptoms, continue lead-in period until rash resolves but no longer than 28 days total.	CYP450 substrate and 3A inducer; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in feces	25–30 hrs	• Rash, including Stevens-Johnson syndrome* • Symptomatic hepatitis, including fatal hepatic necrosis, has been reported‡

* During clinical trials, NNRTI was discontinued because of rash among 7% of NVP-treated, 4.3% of DLV-treated, 1.7% of EFV-treated, and 2% of ETR-treated patients. Rare cases of Stevens-Johnson syndrome have been reported with all NNRTIs; the highest incidence was seen with NVP.

† Adverse events can include dizziness, somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, impaired concentration, amnesia, agitation, depersonalization, hallucinations, and euphoria. Overall frequency of any of these symptoms associated with use of efavirenz was 52% compared with 26% among controls subjects; 2.6% of those persons on EFV discontinued the drug because of these symptoms. Symptoms usually subside spontaneously after 2–4 weeks.

‡ Symptomatic, sometimes serious, and even fatal hepatic events (accompanied by rash in approximately 50% of cases) occur at significantly higher frequency in treatment-naïve female patients with pre-NVP CD4 counts >250 cells/mm³ or in treatment-naïve male patients with pre-NVP CD4 counts >400 cells/mm³. NVP should not be initiated in these patients unless the benefit clearly outweighs the risk. This toxicity has not been observed when NVP is given as single doses to mothers or infants for prevention of mother-to-child transmission of HIV.

Appendix B, Table 3. Characteristics of Protease Inhibitors (PIs) (Updated December 1, 2009)

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Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Elimination	Serum Half-life	Storage	Adverse Events
Atazanavir (ATV)/ Reyataz	100, 150, 200, 300mg capsules	ARV-naïve pts: 400mg once daily or (ATV 300mg + RTV 100mg) once daily With TDF or for ARV-experienced pts: (ATV 300mg + RTV 100mg) once daily With EFV in treatment-naïve pts: (ATV 400mg + RTV 100mg) once daily (For dosing recommendations with H2 antagonists and PPIs, refer to Table 14a) Take with food	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (see Appendix, Table 7)	7 hrs	Room temperature (up to 25°C or 77°F)	• Indirect hyperbilirubinemia • Prolonged PR interval—first degree symptomatic AV block in some pts • Use with caution in pts with underlying conduction defects or on concomitant medications that can cause PR prolongation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • Nephrolithiasis
Darunavir (DRV)/ Prezista	75, 150, 400, 600mg tablets	ARV-naïve pts: (DRV 800mg + RTV 100mg) once daily ARV-experienced pts: (DRV 600mg + RTV 100mg) BID Unboosted DRV is not recommended Take with food	CYP3A4 inhibitor and substrate	15 hrs (when combined with RTV)	Room temperature (up to 25°C or 77°F)	• Skin rash (10%)—DRV has a sulfonamide moiety; Stevens-Johnson syndrome and erythema multiforme have been reported • Hepatotoxicity • Diarrhea, nausea • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Fosamprenavir (FPV)/ Lexiva (a prodrug of amprenavir)	700mg tablet or 50mg/mL oral suspension	ARV-naïve pts: • FPV 1,400mg BID or • (FPV 1,400mg + RTV 100–200mg) once daily or • (FPV 700mg + RTV 100mg) BID PI-experienced pts (once-daily dosing not recommended): • (FPV 700mg + RTV 100mg) BID With EFV: • (FPV 700mg + RTV 100mg) BID or • (FPV 1,400mg + RTV 300mg) once daily Take without regard to meals	Amprenavir is a CYP3A4 substrate, inhibitor, and inducer Dosage adjustment in hepatic insufficiency recommended (see Appendix, Table 7)	7.7 hrs (amprenavir)	Room temperature (up to 25°C or 77°F)	• Skin rash (19%) • Diarrhea, nausea, vomiting • Headache • Hyperlipidemia • Transaminase elevation • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • Nephrolithiasis
Indinavir (IDV)/ Crixivan	200, 333, 400mg capsules	800mg every 8 hrs Take 1 hour before or 2 hours after meals; may take with skim milk or low-fat meal With RTV: (IDV 800mg + RTV 100–200mg) BID Take without regard to meals	CYP3A4 inhibitor and substrate Dosage adjustment in hepatic insufficiency recommended (see Appendix, Table 7)	1.5–2 hrs	Room temperature (15°–30°C/ 59°–86°F) Protect from moisture	• Nephrolithiasis • GI intolerance, nausea • Indirect hyperbilirubinemia • Hyperlipidemia • Headache, asthenia, blurred vision, dizziness, rash, metallic taste, thrombocytopenia, alopecia, and hemolytic anemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Elimination	Serum Half-life	Storage	Adverse Events
Lopinavir + Ritonavir (LPV/r)/ Kaletra	Tablets: (LPV 200mg + RTV 50mg) or (LPV 100mg + RTV 25mg) Oral solution: Each 5 mL contains (LPV 400mg + RTV 100mg) Oral solution contains 42% alcohol	LPV/r 400mg/100mg BID or LPV/r 800mg/200mg once daily Once-daily dosing is only recommended for PI-naïve pts and not for pregnant women or pts receiving EFV, NVP, FPV, or NFV With EFV or NVP (PI-naïve or PI-experienced pts): LPV/r 500mg/125mg tablets BID (use a combination of two LPV/r 200mg/50mg tablets + one LPV/r 100mg/25mg tablet to make a total dose of LPV/r 500mg/125mg.) or LPV/r 533mg/133mg oral solution BID Tablet: take without regard to meals Oral solution: take with food	CYP3A4 inhibitor and substrate	5–6 hrs	Oral tablet is stable at room temperature. Oral solution is stable at 2°–8°C until date on label and is stable when stored at room temperature (up to 25°C or 77°F) for 2 months.	• GI intolerance, nausea, vomiting, diarrhea • Asthenia • Hyperlipidemia (especially hypertriglyceridemia) • Elevated serum transaminases • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • PR interval prolongation • QT interval prolongation and torsade de pointes
Nelfinavir (NFV)/ Viracept	250, 625mg tablets 50mg/g oral powder	1,250mg BID or 750mg TID Take with food	CYP2C19 and 3A4 substrate—metabolized to active M8 metabolite; CYP 3A4 inhibitor	3.5–5 hrs	Room temperature (15°–30°C/59°–86°F)	• Diarrhea • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia • Serum transaminase elevation
Ritonavir (RTV)/ Norvir	100mg capsules 80mg/mL oral solution	As pharmacokinetic booster for other PIs: 100–400mg per day in 1–2 divided doses (refer to other PIs for specific dosing recommendations) Take with food if possible; this may improve tolerability	CYP3A4 >2D6 substrate; potent 3A4, 2D6 inhibitor	3–5 hrs	Refrigerate capsules Capsules can be left at room temperature (up to 25°C or 77°F) for up to 30 days. Oral solution should not be refrigerated.	• GI intolerance, nausea, vomiting, diarrhea • Paresthesias—circumoral and extremities • Hyperlipidemia (especially hypertriglyceridemia) • Hepatitis • Asthenia • Taste perversion • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia
Saquinavir tablets and hard gel capsules (SQV)/ Invirase	500mg tablets or 200mg hard gel capsules	(SQV 1,000mg + RTV 100mg) BID Unboosted SQV is not recommended. Take within 2 hours after a meal	CYP3A4 inhibitor and substrate	1–2 hrs	Room temperature (15°–30°C/59°–86°F)	• GI intolerance, nausea, and diarrhea • Headache • Elevated transaminase enzymes • Hyperlipidemia • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Elimination	Serum Half-life	Storage	Adverse Events
Tipranavir (TPV)/ Aptivus	250mg capsules or 100mg/mL oral solution	(TPV 500mg + RTV 200mg) PO BID Unboosted TPV is not recommended. Take without regard to meals	Cytochrome P450 3A4 inducer and substrate Net effect when combined with RTV (CYP 3A4, 2D6 inhibitor)	6 hrs after single dose of TPV/r	Refrigerate capsules Capsules can be stored at room temperature (25°C or 77°F) for up to 60 days. Oral solution should not be refrigerated or frozen and should be used within 60 days after opening the bottle.	• Hepatotoxicity—clinical hepatitis, (including hepatic decompensation and hepatitis-associated fatalities) has been reported; monitor closely, especially in pts with underlying liver diseases. • Skin rash—TPV has a sulfonamide moiety; use with caution in pts with known sulfonamide allergy. • Rare cases of fatal and nonfatal intracranial hemorrhages have been reported. Most pts had underlying comorbidity, such as brain lesion, head trauma, recent neurosurgery, coagulopathy, hypertension, or alcoholism or were on medication with increased risk of bleeding. • Hyperlipidemia (especially hypertriglyceridemia) • Hyperglycemia • Fat maldistribution • Possible increased bleeding episodes in pts with hemophilia

Appendix B, Table 4. Characteristics of Integrase Inhibitors (Updated December 1, 2009)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Serum half-life	Route of Metabolism	Adverse Events
Raltegravir (RAL)/ Isentress	400mg tablets	400mg BID With rifampin: 800mg BID Take without regard to meals	~9 hrs	UGT1A1-mediated glucuronidation	• Nausea • Headache • Diarrhea • Pyrexia • CPK elevation

Appendix B, Table 5. Characteristics of Fusion Inhibitors (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations	Serum half-life	Elimination	Storage	Adverse Events
Enfuvirtide (T20)/ Fuzeon	• Injectable—supplied as lyophilized powder • Each vial contains 108mg of T20; reconstitute with 1.1mL of sterile water for injection for delivery of approximately 90mg/1mL	90mg (1mL) subcutaneously BID	3.8 hrs	Expected to undergo catabolism to its constituent amino acids, with subsequent recycling of the amino acids in the body pool	Store at room temperature (up to 25°C or 77°F). Reconstituted solution should be stored under refrigeration at 2°C–8°C (36°F–46°F) and used within 24 hours.	• Local injection site reactions in almost 100% of patients (pain, erythema, induration, nodules and cysts, pruritus, ecchymosis) • Increased bacterial pneumonia • Hypersensitivity reaction (<1%)—symptoms may include rash, fever, nausea, vomiting, chills, rigors, hypotension, or elevated serum transaminases; rechallenge is not recommended

Appendix B, Table 6. Characteristics of CCR5 Antagonists (Updated January 29, 2008)

Generic Name (abbreviation)/ Trade Name	Formulation	Dosing Recommendations For dosage adjustment in hepatic insufficiency, see Appendix, Table 7	Serum Half-life	Elimination	Adverse Events
Maraviroc (MVC)/ Selzentry	150, 300mg tablets	• 150mg BID when given with strong CYP3A inhibitors (with or without CYP3A inducers) including PIs (except TPV/r) • 300mg BID when given with NRTIs, T-20, TPV/r, NVP, and other drugs that are not strong CYP3A inhibitors or inducers • 600mg BID when given with CYP3A inducers, including EFV, ETR, etc. (without a CYP3A inhibitor) Take without regard to meals	14–18 hrs	CYP3A4 substrate	• Abdominal pain • Cough • Dizziness • Musculoskeletal symptoms • Pyrexia • Rash • Upper respiratory tract infections • Hepatotoxicity • Orthostatic hypotension

Appendix B, Table 7. Antiretroviral Dosing Recommendations in Patients with Renal or Hepatic Insufficiency (Updated December 1, 2009)

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See reference section following tables for creatinine clearance (CrCl) calculation formulas and criteria for Child-Pugh classification.

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Nucleoside Reverse Transcriptase Inhibitors – Note: Use of fixed-dose combination NRTI (+/- NNRTI) of Atripla, Combivir, Trizivir, or Epzicom is not recommended in patients with CrCl <50 mL/min. Use of Truvada is not recommended in patients with CrCl <30 mL/min.			
Abacavir (ABC)/ Ziagen	300mg PO BID	No dosage adjustment necessary	Child-Pugh Score Dose 5–6 200mg BID (use oral solution) > 6 Contraindicated
Didanosine enteric coated (ddI)/ Videx EC	Body weight ≥60 kg: 400mg PO once daily Body weight <60 kg: 250mg PO once daily	Dose (once daily) CrCl (mL/min) ≥60 kg <60 kg 30–59 200mg 125mg 10–29 125mg 125mg <10, HD, CAPD 125mg use oral solution	No dosage adjustment necessary
Didanosine oral solution (ddI)/ Videx	Body weight ≥60 kg: 200mg PO BID or 400mg PO once daily Body weight <60 kg: 250mg PO once daily or 125mg PO BID	Dose (once daily) CrCl (mL/min) ≥60 kg <60 kg 30–59 200mg 150mg 10–29 150mg 100mg <10, HD, CAPD 100mg 75mg	No dosage adjustment necessary
Emtricitabine (FTC)/ Emtriva	200mg oral capsule PO once daily or 240mg (24mL) oral solution PO once daily	Dose CrCl (mL/min) Capsule Solution 30–49 200mg q48h 120mg q24h 15–29 200mg q72h 80mg q24h <15 or HD 200mg q96h 60mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Lamivudine (3TC)/ Epivir	300mg PO once daily or 150mg PO BID	CrCl (mL/min) Dose 30–49 150mg q24h 15–29 1 x 150mg, then 100mg q24h 4–14* 1 x 150mg, then 50mg q24h <5 or HD 1 x 50mg, then 25 mg q24h Take dose after HD session on dialysis days	No dosage adjustment necessary
Stavudine (D4T)/ Zerit	Body weight ≥ 60 kg: 40mg PO BID Body weight <60 kg: 30mg PO BID	Dose CrCl (mL/min) ≥60 kg <60 kg 26–50 20mg q12h 15mg q12h 10–25 or HD 20mg q24h 15 mg q24h Take dose after HD session on dialysis days	No dosage recommendation
Tenofovir (TDF)/ Viread	300mg PO once daily	CrCl (mL/min) Dose 30–49 300mg q48h 10–29 300mg twice weekly <10 not on HD no recommendation HD 300mg q7d Take dose after HD session on dialysis days	No dosage adjustment necessary
Emtricitabine (FTC) + Tenofovir (TDF) / Truvada	1 tablet PO once daily	CrCl (mL/min) Dose 30–49 1 tablet q48h <30 or HD not recommended	No dosage recommendation
Zidovudine (AZT, ZDV)/ Retrovir	300mg PO BID	CrCl (mL/min) Dose < 15 or HD 100mg TID or 300mg once daily	No dosage recommendation

* Error corrected January 15, 2010

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Non-Nucleoside Reverse Transcriptase Inhibitors			
Delavirdine (DLV)/ Rescriptor	400mg PO TID	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV)/ Sustiva	600mg PO at or before bedtime	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Efavirenz (EFV) + Emtricitabine (FTC) + Tenofovir (TDF) / Atripla	1 tablet PO once daily	Atripla not recommended if CrCl <50 mL/min	
Etravirine (ETR)/ Intelence	200mg PO BID	No dosage adjustment necessary	Child-Pugh Class A or B: no dosage adjustment Child-Pugh Class C: no dosage recommendation
Nevirapine (NVP)/ Viramune	200mg PO BID	HD patients: Some suggest additional 200mg after dialysis; however, pharmacokinetic data for this strategy are not available.	Child-Pugh Class B or C: contraindicated
Protease Inhibitors			
Atazanavir (ATV)/ Reyataz	400mg PO once daily or (ATV 300mg + RTV 100mg) PO once daily	No dosage adjustment for patients with renal dysfunction not requiring hemodialysis <u>Treatment-naïve patients on hemodialysis:</u> (ATV 300mg + RTV 100mg) once daily <u>Treatment-experienced patients on hemodialysis:</u> ATV or RTV-boosted ATV not recommended	Child-Pugh Score Dose 7–9 300mg once daily >9 not recommended RTV boosting is not recommended in patients with hepatic impairment (Child-Pugh Score ≥7).
Darunavir (DRV)/ Prezista	(DRV 800mg + RTV 100mg) PO once daily (ARV-naïve pts) or (DRV 600mg + RTV 100mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: no dosage adjustment Severe hepatic impairment: not recommended
Fosamprenavir (FPV)/ Lexiva	1,400mg PO BID or (FPV 1,400mg + RTV 100– 200mg) PO once daily or (FPV 700mg + RTV 100mg) PO BID	No dosage adjustment necessary	Child-Pugh Score Dose PI naïve only: 5–9 700mg BID 10–15 350mg BID PI naïve or PI experienced: 5–6 700mg BID + RTV 100mg once daily 7–8 450mg BID + RTV 100mg once daily 10–15 300mg BID + RTV 100mg once daily
Indinavir (IDV)/ Crixivan	800mg PO q8h	No dosage adjustment necessary	Mild to moderate hepatic insufficiency because of cirrhosis: 600mg q8h
Lopinavir/ritonavir (LPV/r) Kaletra	400/100mg PO BID or 800/200mg PO once daily (only for ARV-naïve patients)	No dosage adjustment necessary	No dosage recommendation; use with caution in patients with hepatic impairment
Nelfinavir (NFV)/ Viracept	1,250mg PO BID	No dosage adjustment necessary	Mild hepatic impairment: no dosage adjustment Moderate to severe hepatic impairment: do not use
Ritonavir (RTV)/ Norvir	<u>As a PI-boosting agent:</u> 100–400mg per day	No dosage adjustment necessary	Refer to recommendations for the primary PI
Saquinavir (SQV)/ Invirase	(SQV 1,000mg + RTV 100mg) PO BID	No dosage adjustment necessary	Mild to moderate hepatic impairment: use with caution Severe hepatic impairment: contraindicated
Tipranavir (TPV)/ Aptivus	(TPV 500mg + RTV 200mg) PO BID	No dosage adjustment necessary	Child-Pugh Class A: use with caution Child-Pugh Class B or C: contraindicated

Abbreviations: CAPD = chronic ambulatory peritoneal dialysis, HD = hemodialysis

Antiretrovirals Generic Name (abbreviation)/ Trade Name	Daily Dose	Dosing in Renal Insufficiency	Dosing in Hepatic Impairment
Fusion Inhibitors			
Enfuvirtide (T20)/ Fuzeon	90mg subcutaneous BID	No dosage adjustment necessary	No dosage recommendation
CCR5 Antagonists			
Maraviroc (MVC)/ Selzentry	The recommended dose differs based on concomitant medications because of drug interactions. See Appendix B, Table 6 for detailed dosing information.	No dosage recommendation; use with caution. Patients with CrCL <50 mL/min should receive MVC and CYP3A inhibitor only if potential benefits outweigh the risk.	No dosage recommendations. Concentrations will likely be increased in patients with hepatic impairment.
Integrase Inhibitors			
Raltegravir (RAL)/ Isentress	400mg BID	No dosage adjustment necessary	Mild to moderate hepatic insufficiency: no dosage adjustment necessary Severe hepatic insufficiency: no recommendation

Creatinine Clearance Calculation	
Male: $\frac{(140 - \text{age in yrs}) \times \text{weight (kg)}}{72 \times \text{S.Cr.}}$	Female: $\frac{(140 - \text{age in yrs}) \times \text{weight (kg)} \times 0.85}{72 \times \text{S.Cr.}}$

Child-Pugh Score			
Component	Points Scored		
	1	2	3
Encephalopathy*	None	Grade 1–2	Grade 3–4
Ascites	None	Mild or controlled by diuretics	Moderate or refractory despite diuretics
Albumin	>3.5 g/dL	2.8–3.5 g/dL	<2.8 g/dL
Total bilirubin or	<2 mg/dL (<34 μmol/L)	2–3 mg/dL (34 μmol/L to 50 μmol/L)	>3 mg/dL (>50 μmol/L)
Modified total bilirubin†	<4 mg/dL	4–7 mg/dL	>7 mg/dL
Prothrombin time (seconds prolonged) or	<4	4–6	>6
International normalized ratio (INR)	<1.7	1.7–2.3	>2.3

* Encephalopathy Grades

Grade 1: Mild confusion, anxiety, restlessness, fine tremor, slowed coordination

Grade 2: Drowsiness, disorientation, asterixis

Grade 3: Somnolent but rousable, marked confusion, incomprehensible speech, incontinence, hyperventilation

Grade 4: Coma, decerebrate posturing, flaccidity

† Modified total bilirubin used to score patients who have Gilbert's syndrome or who are taking indinavir or atazanavir

Child-Pugh Classification	Total Score*
Class A	5–6 points
Class B	7–9 points
Class C	>9 points

* Sum of points for each component

Primary Care Guidelines for the Management of Persons Infected with Human Immunodeficiency Virus: 2009 Update by the HIV Medicine Association of the Infectious Diseases Society of America

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Evidence-based guidelines for the management of persons infected with human immunodeficiency virus (HIV) were prepared by an expert panel of the HIV Medicine Association of the Infectious Diseases Society of America. These updated guidelines replace those published in 2004. The guidelines are intended for use by health care providers who care for HIV-infected patients or patients who may be at risk for acquiring HIV infection. Since 2004, new antiretroviral drugs and classes have become available, and the prognosis of persons with HIV infection continues to improve. However, with fewer complications and increased survival, HIV-infected persons are increasingly developing common health problems that also affect the general population. Some of these conditions may be related to HIV infection itself and its treatment. HIV-infected persons should be managed and monitored for all relevant age- and gender-specific health problems. New information based on publications from the period 2003–2008 has been incorporated into this document.

SUMMARY OF CHANGES

These updated guidelines replace those published in 2004 [1]. The following general changes have been made to the document since the previous publication:

- Formatting changes have been incorporated to help readers easily identify the recommendations. Each

section begins with a specific question and is followed by numbered recommendations and a brief evidence-based summary.

- Tables on immunizations and routine health care maintenance issues have been added.
- Many other human immunodeficiency virus (HIV)–related guidelines have been updated, as have our recommendations that are based on other revised guidelines.

Specific changes and/or additions are as follows:

- There is an expanded list of diagnostic HIV tests.
- All HIV-infected patients should have a genotypic

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This guideline might be updated periodically. To be sure you have the most recent version, check the Web site of the journal (<http://www.journals.uchicago.edu/page/cid/IDSAguidelines.html>).

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It is important to realize that guidelines cannot always account for individual variation among patients. They are not intended to supplant physician judgment with respect to particular patients or special clinical situations. The Infectious Diseases Society of America considers adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in the light of each patient's individual circumstances.

resistance test performed at baseline regardless of whether antiretroviral therapy will be initiated (A-III).

- Patients who are seronegative for varicella zoster virus (VZV) or who do not give a history of chickenpox or shingles should receive postexposure prophylaxis with VZV immune globulin (VariZIG) as soon as possible (within 96 h) after exposure to a person with chickenpox or shingles (A-III).
- Varicella primary vaccination may be considered for HIV-infected VZV-seronegative persons aged >8 years with CD4 cell counts >200 cells/mm³ (C-III) and in HIV-infected children aged 1–8 years with CD4 cell percentages ≥15% (B-II).
- Among patients with syphilis, cerebrospinal (CSF) examination should be performed for persons with neurologic or ocular signs or symptoms, active tertiary syphilis, and syphilis treatment failure. CSF examination is also recommended for HIV-infected persons with late-latent syphilis, including those with syphilis of unknown duration (A-II).
- HLA-B*5701 testing should be performed prior to initiating abacavir therapy to reduce the risk of a hypersensitivity reaction (A-I). Patients who are positive for the HLA B*5701 haplotype should not be treated with abacavir (A-II).
- Baseline urinalysis and calculated creatinine clearance should be considered, especially in black patients, because of an increased risk of HIV-associated nephropathy (B-II).
- Urinalysis and calculated creatinine clearance should also be performed prior to initiating treatment with drugs such as tenofovir or indinavir, which have the potential for nephrotoxicity (B-II).
- Tropism testing should be performed before initiation of treatment with a CCR5-antagonist antiretroviral drug (A-II).
- For women aged 40–49 years, providers should periodically perform individualized assessment of risk for breast cancer and inform the patient of the potential benefits and risks of screening mammography (B-II).
- The routine use of hormone replacement therapy has been associated with a slightly increased risk of breast cancer, cardiovascular disease, and thromboembolic disease and is not currently recommended (A-I). However, hormone replacement therapy may be considered in women who experience severe menopausal symptoms (eg, vasomotor symptoms or vaginal dryness) but should generally be used only for a limited period of time and at the lowest effective doses (B-II).
- Emphasis should be placed on the importance of adherence to care rather than focusing solely on adherence to medications (B-II).

INTRODUCTION

It has been >25 years since the first case of AIDS was identified. There have been dramatic changes in the management of HIV infection since the introduction of potent antiretroviral therapy in 1996. There has also been a significant decrease in morbidity

and mortality among persons living with HIV infection, resulting from improved access to care, prophylaxis against opportunistic infections, and antiretroviral therapy. A working group of clinical scientists was chosen by the HIV Medicine Association (HIVMA) of the Infectious Diseases Society of America (IDSA) to develop guidelines addressing the primary care of HIV-infected persons. The purpose of these guidelines is to assist health care providers in their management of HIV-infected persons. Because of the improved survival among people living with HIV infection, it is imperative that, in addition to screening for conditions related to HIV infection and its management, all such persons should receive other recommended preventive health interventions as determined on the basis of their age and gender.

These guidelines discuss the following topics: (1) transmission of HIV infection; (2) HIV diagnosis; (3) risk screening; (4) management, with special sections concerning women and children; and (5) adherence to care. It is not our intent to duplicate the extensive guidelines endorsed by the United States (US) Public Health Service, the Department of Health and Human Services, the Centers for Disease Control and Prevention (CDC), IDSA, or other accredited organizations. We have referred to these guidelines where applicable, so that this document may also serve as a “guide to the guidelines” (table 1). The following clinical questions are addressed:

- I. What is the optimal way to diagnose HIV infection?
- II. What risk-screening measures and interventions are appropriate for HIV-infected patients?
- III. What initial evaluation and laboratory testing should be performed for HIV-infected patients?
- IV. How is HIV disease staged?
- V. What is the schedule-of-care evaluation for HIV-infected patients?
- VI. What are the special considerations for women?
- VII. What are the special considerations for mother-to-child transmission and children?
- VIII. What are the long-term metabolic complications associated with antiretroviral therapy?
- IX. How can patient adherence to HIV care be optimized?

Modes of HIV Transmission

The modes of transmission of HIV—sexual contact, exposure to infected blood through sharing of injection drug use paraphernalia or receipt of contaminated blood products, and perinatal transmission—were clarified early in the AIDS epidemic. In the United States, their relative importance is reflected by the frequency of risk behaviors among reported persons with HIV/AIDS. These data, which include information on HIV-infected persons with and without AIDS, were available from

Table 1. Guidelines from Various Sources Regarding Aspects of Care of Human Immunodeficiency Virus (HIV)–Infected Persons

Topic	Title	URL	Issuing agency	Reference
Antiretroviral therapy for adults and adolescents	Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents	http://aidsinfo.nih.gov/guidelines	US Department of Health and Human Services	[2]
Antiretroviral therapy for pediatric patients	Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection	http://aidsinfo.nih.gov/guidelines	NIH	[3]
Antiretroviral therapy for pregnant women	Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1 Infected women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States	http://aidsinfo.nih.gov/guidelines	US Public Health Service Task Force	[4]
Chronic Kidney Disease	Guidelines for the Management of Chronic Kidney Disease in HIV-Infected Patients	http://www.journals.uchicago.edu/doi/abs/10.1086/430257	HIVMA of IDSA	[5]
Diabetes	Clinical Practice Recommendations	http://care.diabetesjournals.org/content/vol31/Supplement_1/index.shtml	American Diabetes Association	[6]
Hepatitis	Management of Chronic Hepatitis B	http://www.easl.ch/PDF/cpg/EASL_HBV_CPGs.pdf	European Association For The Study Of The Liver	[7]
Hepatitis	Care of HIV Patients with Chronic Hepatitis B	...	HIV-Hepatitis B Virus International Panel	[8]
Hepatitis	Care of HIV Patients with Chronic Hepatitis C	...	Hepatitis C virus-HIV International Panel	[9]
Hepatitis	Guidelines for the Clinical Management and Treatment of Chronic Hepatitis B and C Coinfection In HIV-Infected Adults	http://www.european-aidsclinicalociety.org/guidelinespdf/3_Treatment_chronic_hepatitis_coinfection.pdf	European AIDS Clinical Society	[10]
HIV testing and counseling	Revised Guidelines for HIV Testing	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5514a1.htm	CDC	[11]
Hyperlipidemia in HIV	Guidelines for the Evaluation and Management of Dyslipidemia in HIV-Infected Adults Receiving Antiretroviral Therapy	http://www.journals.uchicago.edu/doi/abs/10.1086/378131	HIVMA/IDSA; Adult AIDS Clinical Trials Group	[12]
Immunization Schedules	Child and Adolescent Immunization Schedule	http://www.cdc.gov/vaccines/recs/schedules/	CDC	
Immunizations	Practice Guidelines for Quality Standards for Immunization	http://www.cdc.gov/vaccines/pubs/ACIP-list.htm#comp	Advisory Committee on Immunization Practices	[13, 14]

Table 1. (Continued.)

Topic	Title	URL	Issuing agency	Reference
Mental health	Mental Health Care for People with HIV Infection: Clinical Guidelines for the Primary Care Practitioner	http://www.hivguidelines.org/Content.aspx?PageID=261	New York State Department of Health AIDS Institute	[15]
Metabolic complications in HIV	Management of Metabolic Complications Associated with Antiretroviral Therapy for HIV-1 Infection	http://www.iasusa.org/pub/Schambelan%20et%20al-JAIDS-11.1.02.pdf	International AIDS Society USA Panel	[16]
Occupational exposures	Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5011a1.htm	US Public Health Service	[17]
Opportunistic infections	Guidelines for Treating Opportunistic Infections among HIV-Infected Adults and Adolescents	http://aidsinfo.nih.gov/guidelines	U.S. Public Health Service; HIVMA/IDSA; CDC	[18]
Opportunistic infections in children	Guidelines for Prevention and Treatment of Opportunistic Infections among HIV-Exposed and HIV-Infected Children	http://aidsinfo.nih.gov/guidelines	US Public Health Service; HIVMA/IDSA, CDC, Pediatric Infections Diseases Society	[19]
Pediatric HIV	Red Book: 2009 Report of the Committee of Infectious Diseases	http://aapredbook.aappublications.org/	American Academy of Pediatrics	[20]
Resistance testing	Antiretroviral Drug Resistance Testing in Adults Infected with Human Immunodeficiency Virus Type 1	http://www.iasusa.org/pub/	International AIDS Society USA Panel	[21]
Risk assessment	Incorporating HIV Prevention into the Medical Care of Persons Living with HIV	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5212a1.htm	CDC, Health Resources and Services Administration, NIH, HIVMA/IDSA	[22]
Sexually transmitted diseases	Sexually Transmitted Diseases Treatment Guidelines 2006	http://www.cdc.gov/std/treatment/2006/rr5511.pdf	CDC	[23]

NOTE. CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV-1, HIV type 1; HIVMA, HIV Medicine Association; IDSA, Infectious Diseases Society of America; NIH, National Institutes of Health.

33 US states for persons who received a diagnosis of HIV/AIDS in 2006.

In 2006, male-to-male sexual contact was the most frequently reported risk factor for HIV exposure among adult and adolescent males, accounting for 67% of reported HIV/AIDS cases in men. The second most frequently reported risk factor among men was high-risk heterosexual contact, accounting for 16% of cases, followed by injection drug use (12% of cases). An additional 5% of cases were diagnosed among men who re-

ported both male-to-male sexual contact and injection drug use [24].

Twenty-six percent of cases of HIV/AIDS reported among adults and adolescents in 2006 occurred in women. High-risk heterosexual contact accounted for 80% of cases in women, and injection drug use accounted for 19% of cases [24].

The epidemic continues to affect racial and ethnic minorities disproportionately. In the United States in 2006, 49% of HIV/AIDS cases occurred in black persons, and 18% occurred in

Hispanic persons. Among men, these percentages were 43% and 20%, respectively, and among women, they were 65% and 15%, respectively [24].

Studies have yielded estimates of the probability of HIV transmission by various routes in adults and adolescents. Per-act probabilities of transmission would be expected to vary considerably, depending on factors such as plasma HIV RNA level in the index case, presence of sexually transmitted diseases (STDs) (defined as chlamydia, gonorrhea, herpes simplex virus infection, human papillomavirus infection, and/or syphilis) in the index case or the partner, and the quantity of blood transferred via needlestick. Nevertheless, the overall probability of becoming infected by transfusion with contaminated blood or blood products has been estimated to be 95 in 100, by perinatal transmission from mother to child in the absence of antiretroviral therapy has been estimated to be 1 in 4, by needle sharing has been estimated to be 1 in 150, and by occupational needlestick exposure has been estimated to be 1 in 300. The risk of infection by male-to-male receptive anal intercourse has been estimated to be between 1 in 10 and 1 in 1600, by male-to-female vaginal intercourse has been estimated to be 1 in 200 to 1 in 2000, and by female-to-male vaginal intercourse has been estimated to be between 1 in 700 and 1 in 3000 [25].

The prevention of mother-to-child transmission of HIV has been highly successful over the past decade. The ACTG 076 study, published in 1994 [26], rapidly changed practice in well-resourced settings. In the decade after 1994, as the availability of antiretroviral drugs and access to effective treatment for pregnant women increased, the percentage of infants born to HIV-infected mothers who were perinatally infected with HIV decreased substantially in the United States and Europe, from 25% to <2%. In addition to specific perinatal prophylaxis, the availability of safe infant formula feeding to replace breastfeeding and of selective utilization of cesarean delivery has made perinatal transmission a rare event in developed countries [27, 28]. Given that the CDC estimates that 7000 HIV-positive women give birth every year in the United States, clinicians must remain vigilant in the diagnosis and treatment of HIV-infected pregnant women for this success to continue.

PRACTICE GUIDELINES

“Practice guidelines are systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, clinical flexibility, clarity, multidisciplinary process, review of evidence, and documentation” [29, p. 8].

METHODS

Panel Composition

A panel of experts composed of specialists in internal medicine, pediatrics, infectious diseases, obstetrics, and gynecology prepared these guidelines.

Literature Review and Analysis

For the 2009 update, the Expert Panel completed a review and analysis of literature on the management of persons with HIV published since 2000 and reviewed the older literature as well. Computerized literature searches of PubMed (for articles from January 2000 to December 2008) were performed. Data published after December 2008 were also considered in the final preparation of the manuscript. Only English language literature was reviewed.

Process Overview

In evaluating the evidence regarding the management of persons with HIV infection, the Panel followed a process used in the development of other IDSA guidelines. The process included a systematic weighting of the quality of the evidence and the grade of recommendation [30] (table 2).

Consensus Development on the Basis of Evidence

The Panel met on several occasions via teleconference and worked via e-mail communications to complete the work of these guidelines. The purpose of the teleconferences was to discuss the questions to be addressed, make writing assignments, and discuss recommendations. All members of the panel participated in the preparation and review of the draft guidelines. Feedback from external peer reviewers was obtained. These guidelines were reviewed and cleared by the CDC and the IDSA Standards and Practice Guidelines Committee (SPGC) and the boards of the HIVMA and the IDSA prior to dissemination.

Guidelines and Conflict of Interest

All members of the Expert Panel complied with the IDSA policy on conflicts of interest, which requires disclosure of any financial or other interest that might be construed as constituting an actual, potential, or apparent conflict. Members of the Expert Panel were provided with the IDSA's conflict of interest disclosure statement and asked to identify ties to companies developing products that might be affected by promulgation of the guidelines. Information was requested regarding employment, consultancies, stock ownership, honoraria, research funding, expert testimony, and membership on company advisory committees. The Panel made decisions on a case-by-case

Table 2. Definition of Quality of Evidence and Strength of Recommendation

Assessment	Type of evidence
Strength of recommendation	
Grade A	Good evidence to support a recommendation for use
Grade B	Moderate evidence to support a recommendation for use
Grade C	Poor evidence to support a recommendation
Quality of evidence	
Level I	Evidence from at least 1 properly designed randomized, controlled trial
Level II	Evidence from at least 1 well-designed clinical trial, without randomization; from cohort or case-controlled analytic studies (preferably from >1 center); from multiple time series; or from dramatic results of uncontrolled experiments
Level III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

NOTE. Adapted from the Canadian Task Force on the Periodic Health Examination [30].

basis as to whether an individual's role should be limited as a result of a conflict. No limiting conflicts were identified.

Revision Dates

At annual intervals, the Expert Panel chair, the SPGC liaison advisor, and the chair of the SPGC will determine the need for revisions to the guidelines on the basis of an examination of current literature. If necessary, the entire Panel will be reconvened to discuss potential changes. When appropriate, the Panel will recommend revision of the guidelines to the SPGC and will submit revision to the boards of the HIVMA and IDSA for review and approval.

RECOMMENDATION FOR THE MANAGEMENT OF PERSONS INFECTED WITH HIV

I. WHAT IS THE OPTIMAL WAY TO DIAGNOSE HIV INFECTION?

Recommendation

1. HIV type 1 (HIV-1) infection should be diagnosed by a rapid HIV test or a conventional enzyme-linked immunoabsorbent assay (ELISA) and confirmed by Western blot or indirect immunofluorescence assay (A-I).

Evidence Summary

HIV infection is typically diagnosed by means of serologic tests that demonstrate the presence of antibodies to HIV. A positive or reactive screening test result is confirmed by Western blot or indirect immunofluorescence assay. Several rapid tests for HIV (Clearview HIV 1/2 STAT-PAK Assay and Clearview Complete HIV1/2, Inverness Medical Innovations; Multispot HIV-1/HIV-2 Rapid Test, Bio-Rad Laboratories; OraQuick Advance Rapid HIV-1/2 Antibody Test, OraSure Technologies; Reveal

G3 Rapid HIV-1 Antibody Test, MedMira; Uni-Gold Recombigen HIV Test, Trinity BioTech) have been approved for detection of HIV antibodies by the US Food and Drug Administration (FDA). Several of these tests can be performed on whole blood specimens obtained by fingerstick or venipuncture, all of them can be performed on plasma specimens, and all but the Oraquick test can be performed on serum specimens. The OraQuick test can be performed on oral fluid specimens. The OraQuick test is not approved for use on children aged <13 years. Clinicians should review the package inserts to understand the limitations of the test being used.

Some authorities recommend that a positive oral rapid test result be routinely confirmed with a whole blood rapid test because of the potential for a higher frequency of false-positive results with the oral rapid test [31].

Specimens reactive on screening tests are interpreted to be "preliminary positive" and must be confirmed by Western blot or indirect immunofluorescence assay, even if a subsequent conventional screening test is not reactive [32]. If such confirmatory testing results are negative or indeterminate, follow-up testing should be performed on a blood specimen collected 4 weeks after the initial reactive HIV test result. In limited circumstances, action may be indicated on the basis of the preliminary positive results of screening tests. For example, a physician may elect to withhold postexposure antiretroviral prophylaxis from a person who is exposed to HIV but has a positive screening test result for HIV infection, suggesting prior established infection. On the other hand, pregnant women with preliminary positive HIV test results should receive antiretroviral prophylaxis while in labor with a recommended short-course regimen to prevent perinatal transmission prior to confirmation of results [4].

Persons reporting risk behaviors associated with HIV infec-

tion, those exhibiting symptoms or signs suggestive of HIV infection, and those with tuberculosis or seeking treatment for STDs should be advised to be tested. The CDC recommends that all persons aged 13–64 years in health care settings be screened for HIV infection [11]. The CDC sponsors a web site (<http://www.hivtest.org/>) that provides locations of all HIV testing locations in the country and specifies whether tests are offered free of charge. Providers should be aware of state and local laws or regulations regarding informed consent. Persons with known high-risk behaviors should be tested at least annually. All women should be screened for HIV infection during each pregnancy because of the availability of treatment to reduce the likelihood of mother-to-child transmission and to maintain the health of the mother. HIV testing in the third trimester is recommended for women who are at ongoing risk for HIV infection, even if they have negative test results earlier in pregnancy. Rapid HIV testing should be offered during labor to women of unknown or undocumented HIV serostatus. All infants exposed to HIV in utero should be tested according to CDC and American Academy of Pediatrics (AAP) guidelines [33]. Because of passive transfer of maternal antibodies, infants require diagnostic virologic assays, such as HIV DNA polymerase chain reaction (PCR) or RNA PCR tests, for diagnosis of HIV infection [34]. Testing should be offered to anyone who has been sexually assaulted. Persons potentially exposed to HIV via an occupational exposure should follow the Updated US Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis (HBV, hepatitis B virus; HCV, hepatitis C virus) [17].

Infection with HIV type 2 (HIV-2), a virus that shares ~60% of its genetic sequences with HIV-1, has been documented in <200 persons in the United States (CDC, unpublished data). Most of these persons are immigrants from or are epidemiologically linked to West Africa, where HIV-2 infection is common. HIV-2 infection should be suspected in persons of West African origin who have clinical conditions suggestive of HIV infection but have atypical serologic test results, usually involving the presence of viral bands but the absence of envelope gp41, gp120, and gp160 on Western blot. The Multispot rapid test is FDA approved for differentiating HIV-1 from HIV-2 infection, but, because no serologic tests are approved for confirmation of HIV-2 infection, providers should consult their state health departments for assistance in the diagnosis of such cases.

HIV-seronegative persons perceived to be at risk should be counseled regarding the risk of acquiring HIV infection. Because of the delayed appearance of HIV antibodies in recently infected persons, high-risk activity within the past 3 months should prompt repeated serologic testing at 6, 12, and 24 weeks. Symptoms and signs of acute retroviral syndrome (fever, mal-

aise, pharyngitis, aseptic meningitis, lymphadenopathy, or rash) in a person reporting recent high-risk behavior should prompt testing for plasma HIV RNA in addition to HIV antibody testing. Quantitative plasma HIV RNA (viral load) tests are not approved by the FDA for HIV diagnosis and, if performed, require confirmation by subsequent serologic testing to document seroconversion. Recently, a qualitative HIV-1 RNA test (Aptima HIV-1 Qualitative Assay; GenProbe) was approved for use in the diagnosis of HIV infection; a positive result in this test can be considered to be confirmatory.

HIV-infected persons should be counseled regarding the nature of their infection and the risk of transmission of HIV to others, in addition to being referred for support services and medical treatment. More details concerning counseling and testing can be found in the CDC's counseling and testing guidelines [11].

II. WHAT RISK-SCREENING MEASURES ARE APPROPRIATE FOR HIV-INFECTED PATIENTS?

Recommendations

2. Persistent high-risk behavior has implications for the health of the patient as well as for the risk of transmission of HIV infection to others. Therefore, each visit of an HIV-infected person to any health care provider should include screening for high-risk behavior (A-II).
3. Patients should also be asked about symptoms related to STDs at each visit (A-I).

Evidence Summary

Screening for high-risk behavior can be accomplished by a brief series of questions administered by questionnaire in the patient waiting room by the health care provider or by other personnel in the health care setting; an example of such a questionnaire is included in Incorporating HIV Prevention into the Medical Care of Persons Living with HIV: Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America [22] (table 3). The presence of STDs indicates recent high risk behavior, despite what the patient may report. STDs constitute a health problem for the patient and increase the risk of HIV transmission to others and, in the case of the pregnant women, to the infant (table 4). Additional details concerning risk screening of HIV-infected persons can be found in the recommendations from the CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of IDSA [22].

BEHAVIORAL INTERVENTION

Recommendations

Table 3. Examples of Screening Strategies to Elicit Patient-Reported Risk for Human Immunodeficiency Virus (HIV) Transmission

Open-ended question by clinician, similar to 1 of the following
“What are you doing now that you think may be a risk for transmitting HIV to a partner?”
“Tell me about the people you’ve had sex with recently.”
“Tell me about your sex life.”
Screening questions (checklist) for use with a self-administered questionnaire; computer-, audio-, or video-assisted questionnaire; or a face-to-face interview ^a
“Since your last checkup here,” or, if first visit, “Since you found out you were infected with HIV,”
“Have you been sexually active; that is, have you had vaginal, anal, or oral sex with a partner?”
If yes, “Have you had vaginal or anal intercourse without a condom with anyone?”
If yes,
“Were any of these people HIV-negative, or are you unsure about their HIV status?”
“Have you had oral sex with someone?”
If yes (for a male patient), “Did you ejaculate into your partner’s mouth?”
“Have you had a genital sore or discharge, discomfort when you urinate, or anal burning or itching?”
“Have you been diagnosed or treated for an STD, or do you know if any of your sex partners have been diagnosed or treated for an STD?”
“Have you shared drug-injection equipment (needles, syringes, cotton, cooker, water) with others?”
If yes, “Were any of these people HIV negative, or are you unsure about their HIV status?”

NOTE. Adapted from [22]. STD, sexually transmitted disease.

^a This checklist can be administered by the patient or clinician and should take 4 min. A positive response to any of the screening questions should cue the clinician to have a more in-depth discussion to ensure that specific risks are clearly understood.

4. General messages regarding risk reduction should be provided at all health care encounters, regardless of risk behaviors reported by the patient or perceived risk on the part of the health care provider. Such messages can be delivered by the provider, by others in the health care setting, or by educational materials (eg, pamphlets, posters, and videos) in the health care setting (A-III).

5. Tailored messages are critical for patients who report persistent high-risk behavior or who have symptoms or signs of STDs. In nearly all situations, the provider should offer brief counseling; in general, persons exhibiting risk behavior should also be referred to programs capable of offering more extensive intervention programs (A-I).

Evidence Summary

More details concerning behavioral intervention in the health care setting, including criteria for referrals and information about making referrals, can be found in the HIV prevention guidelines [22].

III. WHAT INITIAL EVALUATION AND LABORATORY TESTING SHOULD BE PERFORMED FOR HIV-INFECTED PATIENTS?

Recommendations

6. A comprehensive present and past medical history, physical examination, medication/social/family history, and review of systems, including HIV-related information, should be obtained for all patients upon initiation of care (A-III).

7. Providers should assess the presence of depression and domestic violence by means of direct questions or validated screening tools (B-III).

Evidence Summary

History and Physical Examination

History of present illness. Providers should inquire about the date of diagnosis of HIV infection and, if possible, the approximate date of infection, which can sometimes be determined on the basis of prior negative test results, occurrence of symptoms suggestive of the acute retroviral infection, or timing

Table 4. Examples of Screening Strategies to Detect Asymptomatic Sexually Transmitted or Blood-Borne Infections

First visit

All patients

- Serologic test for syphilis (ie, nontreponemal test, such as RPR or VDRL)
- Consider urine-based (first-void specimen) NAAT for gonorrhea
- Consider urine-based (first-void specimen) NAAT for *Chlamydia* species
- Serologic tests for hepatitis B and C (if hepatitis B negative, vaccinate)

Women

- Examination of vaginal secretions for *Trichomonas* species
- Cervical specimen for NAAT for *Chlamydia* species for all sexually active women aged <25 years and other women at increased risk

Patients reporting receptive anal sex

- Culture of rectal sample for *Neisseria gonorrhoeae*
- Culture of rectal sample for *Chlamydia* species

Patients reporting receptive oral sex: culture of pharyngeal sample for *N. gonorrhoeae*

Subsequent visits

All sexually active patients: screening tests for STDs should be repeated at least annually

Asymptomatic persons at higher risk

- More frequent periodic screening (eg, at 3-month to 6-month intervals) if any of the following factors are present
 - Multiple or anonymous sex partners
 - Past history of any STD
 - Identification of other behaviors associated with transmission of HIV and other STDs
 - Sex or needle-sharing partner(s) with any of the above-mentioned risks
 - Developmental changes in life that may lead to behavioral change with increased risky behavior (e.g., dissolution of a relationship)
 - High prevalence of STDs in the area or in the patient population
-

NOTE. Adapted from [22]. NAAT, nucleic acid amplification test; RPR, rapid plasma reagin; STD, sexually transmitted disease; VDRL, Venereal Disease Research Laboratory.

of high-risk activities. It is critical to obtain a thorough medication history for patients who have already received antiretroviral therapy. Such a history should include not only the drug combinations taken, but also response to each regimen, including CD4 cell count and viral load, duration of treatment, reasons for treatment changes, drug toxicities, adherence, and prior drug resistance test results. Patients should be asked whether they can recall both the lowest CD4 cell count and highest HIV load that they have ever had. Every effort should be made to obtain medical records from previous health care providers.

Past medical history. Patients should be asked about any prior HIV-associated complications and comorbidities, including opportunistic infections, malignancies, and cardiovascular disease history and risk. Providers should inquire about chronic medical conditions, such as peripheral neuropathy, gastrointestinal disease, chronic viral hepatitis, hyperlipidemia, diabetes mellitus, or renal insufficiency, that might affect the choice of therapy or response to therapy. Other past medical conditions that may have implications for HIV-infected patients include a history of chickenpox or shingles; tuberculosis or tuberculosis

exposure, including results of tuberculin skin tests (TSTs); STDs; and gynecologic problems. It is important that the history also include questions about where the patient has traveled and lived. For example, patients reporting travel in areas of endemicity for histoplasmosis (Ohio and Mississippi River valleys) or coccidioidomycosis (southwestern deserts) may be at risk for reactivation disease, even after moving to areas in which these infections are not endemic. The status of adult immunizations, including tetanus toxoid, pneumococcal vaccine, and hepatitis A and B vaccines, should be elicited. A full birth history and review of maternal history and risk factors should be available for all children.

Medications and allergies. Patients should be asked about any medications they take, including prescription and over-the-counter drugs, methadone, and dietary or herbal supplements, some of which have been shown to interact with antiretroviral drugs. A discussion of allergies should include questions about hypersensitivity reactions to prior therapies, including sulfonamides, nonnucleoside reverse-transcriptase inhibitors, and abacavir.

Social and family histories. The social history should in-

clude a discussion of the use of tobacco, alcohol, heroin, and recreational drugs, including marijuana, cocaine, 3,4-methylenedioxymethamphetamine (ie, "ecstasy"), ketamine, and methamphetamine. Active injection drug users should be asked about their drug-use practices, the source of their needles, and whether they share needles.

It is critical to obtain a sexual history in an open, nonjudgmental manner, asking about past and current practices. Risk reduction counseling can be introduced during this discussion. Counseling should focus on reduction of risk of HIV transmission to others, "superinfection," and infection with other sexually transmitted pathogens. Patients should also be asked about their partners, sexual practices (including condom and contraceptive use), and whether their partner(s) have been informed of their HIV serostatus. Laws vary from state to state regarding the obligation of health care providers to notify sex partners, and clinicians should be aware of laws in their own jurisdiction.

Patients should also be specifically asked whom they have informed of their HIV status, how they have been coping with the diagnosis of HIV infection, and what kinds of support they have been receiving. It is important to know about the patient's family, living situation, and work environment and how they have been affected by the diagnosis of HIV infection. Other pertinent information includes housing issues, employment, and plans for having children.

Family medical history has become more important because HIV-infected patients are living longer and are at increased risk for age- and gender-specific conditions in addition to treatment-related complications. Patients should be asked about family history of conditions that might predispose them to malignancies, neurologic diseases, and atherosclerotic disease (eg, hypertension, diabetes mellitus, hyperlipidemia) and whether there is a history of myocardial infarction in a first-degree relative before the age of 55 years in male relatives and before the age of 65 years in female relatives.

Review of systems. The review of systems should be comprehensive and include questioning about common HIV-related symptoms, including fever, night sweats, weight loss, headaches, visual changes, oral thrush or ulceration, swallowing difficulties, respiratory symptoms, diarrhea, skin rashes or lesions, and changes in neurological function or mental status. Patients should be questioned about how their current weight compares with baseline, along with a dietary assessment. For women, a menstrual history should be obtained. In the course of taking a complete history, the provider can begin to assess the patient's level of awareness about HIV infection and treatment, to evaluate his or her educational needs, and to determine what other supports might be necessary.

Depression and domestic violence screening. Depression is

common among HIV-infected patients, and the review of systems should include questions focusing on changes in mood, libido, sleeping patterns, appetite, concentration, and memory [15]. As part of the initial evaluation and at periodic intervals thereafter, providers should assess the presence of depression and domestic violence by means of direct questions or validated screening tools. Women with HIV infection have high rates of adult sexual and physical abuse and of childhood sexual abuse. The prevalence of depression among those with HIV infection is twice as high among women, compared with men, and is more prevalent in the setting of violence or victimization.

Physical examination. A complete physical examination should be performed at the initial encounter. Vital signs should be obtained. Abnormal measurements should be followed up. Special attention should be paid to examination of the skin, looking for evidence of seborrheic dermatitis, Kaposi sarcoma, folliculitis, fungal infections, psoriasis, and prurigo nodularis. The height and weight for all patients should be measured, and for children aged <3 years, head circumference should be measured and plotted against standard growth curves. The overall body habitus should be assessed, especially in patients receiving antiretroviral therapy who may have drug-related lipodystrophy, with evidence of fat accumulation (eg, increased dorso-cervical fat pad, gynecomastia, or abdominal protuberance from visceral fat) and/or lipoatrophy (eg, loss of subcutaneous fat in the face, extremities, or buttocks). Funduscopic examination should be performed by an ophthalmologist in patients with advanced HIV disease (CD4 cell count, <50 cells/mm³). Patients with advanced disease or ocular symptoms should be referred to an ophthalmologist for a dilated examination to look for evidence of cytomegalovirus (CMV) retinitis and other ocular manifestations of HIV infection. HIV-infected infants and young children usually require referral to an ophthalmologist because of the difficulty in performing an adequate funduscopy in patients of this age group. The oropharynx should be carefully examined for evidence of candidiasis, oral hairy leukoplakia, mucosal Kaposi sarcoma, aphthous ulceration, and periodontal disease. Although persistent generalized lymphadenopathy is common among HIV-infected patients, it does not correlate with prognosis or disease progression. A comprehensive cardiopulmonary examination should be performed, including examination for evidence of peripheral vascular disease. Localized lymphadenopathy or hepatomegaly or splenomegaly may be a sign of infection or malignancy and should be evaluated further. It is important to perform a careful anogenital examination for evidence of rectal cancer, prostate cancer in men, and STDs, including condylomata and herpes simplex infection. Examination of HIV-infected women should include careful palpation of the breasts and a pelvic examination. The pelvic examination should include visual inspection

of the vulva and perineum for evidence of genital ulcers, warts, or other lesions. Speculum examination is used to assess the presence of abnormal vaginal discharge or vaginal or cervical lesions. Bimanual and rectovaginal examinations assess the presence of cervical, uterine, adnexal, and rectal tenderness or masses. The neurological examination should include a general assessment of cognitive function, as well as motor and sensory testing. Developmental assessment is important in infants and children. Patients in whom cognitive dysfunction is suspected may benefit from formal neuropsychological testing.

BASELINE LABORATORY EVALUATION

A number of initial laboratory studies are indicated for patients presenting with HIV infection (table 5). The tests are used for determining HIV disease status, assessing baseline organ function, and screening for coinfections and comorbidities.

HIV DISEASE TESTS

SEROLOGICAL ASSAYS FOR HIV

Recommendation

8. Patients who have no documentation of their HIV serostatus or who were tested anonymously should have an HIV serologic test performed upon initiation of care (A-III).

Evidence Summary

Serologic testing is especially important in patients who are asymptomatic and have a normal CD4 cell count and undetectable or very low viral load. In addition, patients may present to care with misinformation regarding previous test results or may be malingering to obtain other subsidized services that may be available for those infected with HIV. Although HIV

Table 5. Recommended Laboratory Studies for Patients Presenting with Human Immunodeficiency Virus (HIV) Infection

Test	Comment(s)
HIV-disease tests	
CD4 cell count and percentage	...
Coreceptor tropism assay	Recommended prior to prescribing a CCR5 entry inhibitor
HIV resistance testing	Genotype determination is preferred in antiretroviral-naïve patients
Plasma HIV RNA level (viral load)	...
Serologic testing for HIV	...
Safety Laboratory Tests	
Complete blood cell count with differential	...
Fasting lipid profile	...
Glucose-6-phosphate dehydrogenase	Screen for deficiency in appropriate racial or ethnic groups
HLA B*5701	Recommend prior to prescribing abacavir
Serum chemistry	...
Alanine aminotransferase, aspartate aminotransferase, bilirubin levels	...
Albumin level	...
Alkaline phosphatase level	...
Electrolytes, blood urea nitrogen, creatinine levels	...
Fasting blood glucose level	...
Urinalysis: RBC, WBC, proteinuria, sediment levels	...
Coinfection and comorbidity laboratory tests	
Chest radiography	For patients with positive tuberculosis test result; consider in patients with underlying lung disease for use as comparison in evaluation of future respiratory illness
CMV and other herpesvirus screening	CMV screening for patients at low risk for CMV infection; varicella zoster virus screening for those who deny history of chickenpox or shingles; HSV-2 screening is recommended by some experts
Cytology: Pap test	Cervical; consider anal if indicated
Screening for other STDs	...
Screening for syphilis	...
Serologic testing for <i>Toxoplasma gondii</i>	...
Serum testosterone level	In males with fatigue, weight loss, loss of libido, erectile dysfunction, or depression or who have evidence of reduced bone mineral density
Tuberculosis screening	...
Viral hepatitis screening	Hepatitis B surface antigen, antibody to hepatitis B surface antigen or to hepatitis B core antigen, antibody to hepatitis C virus, total hepatitis A antibody

NOTE. CMV, cytomegalovirus; HSV-2, herpes simplex virus type 2; RBC, red blood cell; STD, sexually transmitted disease; WBC, white blood cell.

serologic testing (ELISA or HIV rapid test with confirmatory Western blot) is extremely accurate and specific, false-positive ELISA or rapid test results may rarely occur. However, the Western blot will yield negative results in those cases. The ELISA and rapid tests may yield false-positive results for patients who have autoimmune disorders or who are pregnant.

CD4 AND CD8 T CELL LYMPHOCYTES AND PERCENTAGES

Recommendations

9. A CD4 cell count with percentage should be obtained upon initiation of care (A-I).

10. It is important that the provider and patient be aware of the substantial variation in CD4 cell counts, especially during acute illness. Some experts recommend obtaining 2 baseline measurements before decisions are made to initiate therapy (C-III).

11. Measurement of the CD8 cell count and the ratio of CD4 cells to CD8 cells should not be used in clinical decision making (B-III).

Evidence Summary

The CD4 cell count is used to stage HIV disease, to help establish the risk of specific HIV-associated complications, to determine the need for prophylaxis against opportunistic infections, and to determine the need for and response to antiretroviral therapy. CD4 cell counts may be affected by a variety of medications and intercurrent illnesses, so caution should be applied when interpreting CD4 cell counts during these situations. Although the absolute CD4 cell count is the number most often used in clinical practice, the CD4 cell percentage can also be used to assess immune function and is somewhat less variable than the absolute count. Total CD4 cell counts of 200 and 500 cells/mm³ generally correspond to CD4 cell percentages of 14% and 29%, respectively. In children aged <5 years, CD4 percentage is preferred for monitoring immune status due to more variability of the absolute count with age [19].

PLASMA HIV RNA LEVELS

Recommendation

12. A quantitative HIV RNA determination (viral load) should be obtained upon initiation of care (A-I).

Evidence Summary

Viral load testing is used to assess prognosis, to help determine the need for antiretroviral therapy, to define a baseline level so that the response to therapy can be measured, and to monitor response to therapy. Several HIV load assays have been approved by the FDA for clinical use: (1) HIV RNA PCR (Amplicor HIV-1 Monitor, version 1.5; Roche Laboratories); (2) Real Time HIV RNA PCR (RealTime HIV-1 Assay, Abbott

Laboratories; Cobas AmpliPrep/Cobas Taqman HIV-1 Test, Roche Diagnostics); (3) nucleic acid amplification test for HIV RNA (NucliSens, HIV-1 QT; bioMérieux); and (4) single amplification nucleic acid probe assay (VERSANT HIV-1 RNA 3.0 assay; Bayer). Thresholds for detection range from 200–400 copies/mL for standard assays to 20–80 copies/mL for ultra-sensitive assays. HIV load should be measured during the initial evaluation of the untreated patient. Ideally, patients should be monitored using the same HIV load assay throughout their care. Clinicians should be aware of changes in the type of assay used and the associated variability. The HIV load may be transiently increased by vaccinations and intercurrent illnesses.

HIV RESISTANCE TESTING

Recommendations

13. Because drug-resistant virus can be transmitted from one person to another, all patients should be assessed for transmitted drug resistance with an HIV genotype test upon initiation of care (A-III). If therapy is deferred, repeat testing at the time of antiretroviral therapy initiation should be considered because of the potential for superinfection (C-III).

14. The results of a baseline resistance assay may be useful in guiding therapy, even if treatment is deferred for many years (B-III).

15. Resistance testing is also indicated for patients who are experiencing virologic failure, to guide modification of antiretroviral therapy (A-II).

Evidence Summary

All patients should be tested for transmitted drug resistance at the time of initiation of care, regardless of whether antiretroviral therapy will be initiated [2, 21]. This test has become especially important in newly infected patients, with the increasing frequency of viral resistance in the community. In addition, patients who have previously received antiretroviral therapy and do not have documentation of resistance testing available or are currently receiving a failing regimen should undergo resistance testing. All infants and children should undergo resistance testing prior to initiating therapy. Resistance tests are most useful when performed during acute or early infection. With time, resistant mutants may “back mutate” to wild-type virus and may not be detected by standard genotype assays. However, replacement of mutant virus by wild-type virus can take years, which is one reason why baseline HIV genotype testing is now recommended for all patients. In patients with chronic HIV infection, a negative result may underestimate the true extent of virologic resistance, because the resistant virus, although persistent, is present at levels too low for detection by standard resistance assays.

CORECEPTOR TROPISM ASSAY

Recommendation

16. Tropism testing should be performed prior to the initiation of a CCR5 antagonist antiretroviral drug (A-II).

Evidence Summary

The recent availability of maraviroc, a CCR5 antagonist, has introduced the need for coreceptor tropism testing to determine which patients are appropriate candidates for therapy with this class of drugs [2]. The test currently recommended is the Trofile ES assay (Monogram Biosciences). CCR5 inhibitors should not be used in patients infected with X4- or dual/mixed-tropic virus. Some of the initial safety concerns about the possibility of more rapid progression of disease attributable to selection of X4-tropic virus have been allayed by recent data demonstrating no decrease in CD4 cell count despite selection of X4 virus when maraviroc was given to patients with dual/mixed-tropic virus [35]. However, the use of a CCR5 inhibitor in this population could increase the risk of virologic failure and resistance to the other drugs in the antiretroviral regimen. Tropism screening may fail to detect X4 virus present at low levels, and patients may experience treatment failure with CCR5 inhibitors because of the presence of pre-existing X4 virus not detected by the tropism assay. However, the currently available tropism assay (Trofile ES) is more sensitive at detecting low-level X4- or dual/mixed-tropic virus than was the original assay (Trofile).

At the present time, tropism testing is recommended for patients who are being considered for treatment with a CCR5 inhibitor. It is unclear whether tropism should be assessed prior to initiation of antiretroviral therapy with regimens that do not include a CCR5 inhibitor. The argument in favor of pretreatment screening is that, without it, a CCR5 inhibitor could not be substituted for another agent in a suppressive regimen, because the tropism assay can only be performed in patients with detectable viremia. However, tropism screening of all patients would be expensive, and a pretreatment assay demonstrating R5-tropic virus would not provide complete assurance that no tropism shifts had occurred prior to use of a CCR5 antagonist.

SAFETY LABORATORY TESTS

COMPLETE BLOOD COUNT AND CHEMISTRY PANEL

Recommendation

17. A complete blood count with differential white blood cell count and chemistry panel should be obtained upon initiation of care (A-III).

Evidence Summary

Anemia, leukopenia, and thrombocytopenia are common among HIV-infected persons. The complete blood count is also used to calculate the total CD4 lymphocyte count. A chemistry panel is an important tool to assess renal and hepatic function, as well as the patient's nutritional status. A fasting glucose level test is recommended to screen for glucose intolerance and diabetes, especially because of the increased prevalence in this population [36]. In infants and younger children, fasting blood studies are more problematic because of required feeding schedules, and clinicians may only obtain fasting levels when non-fasting levels are abnormal. Please see section VIII for further discussion of glucose abnormalities. The complete blood count and the chemistry panel also provide baseline information that is necessary before the initiation of therapeutic agents that may have myelosuppressive, nephrotoxic, or hepatotoxic effects or that require dosage adjustment for patients with renal or hepatic dysfunction.

GLUCOSE-6-PHOSPHATE DEHYDROGENASE (G6PD)

Recommendation

18. Qualitative screening for G6PD deficiency is recommended upon entry into care or before starting therapy with an oxidant drug in patients with a predisposing racial or ethnic background (B-III).

Evidence Summary

G6PD deficiency is a genetic condition that may result in hemolysis after exposure to oxidant drugs. The drugs most commonly used to treat HIV-infected patients that can lead to hemolysis in the presence of G6PD deficiency are dapsone, primaquine, and sulfonamides. Although there are many variants of G6PD deficiency, the most common variants are GdA–, which is found in 10%–15% of black men and women, and Gdmed, which is found predominantly in men from the Mediterranean, India, and Southeast Asia [37]. The hemolysis associated with Gdmed can be life-threatening, whereas patients with the GdA– variant have milder, more self-limited hemolysis that may not preclude the use of oxidant drugs.

FASTING LIPID PROFILE

Recommendation

19. Because many antiretroviral drugs, HIV infection itself, and host factors are associated with increased cholesterol and triglyceride levels, a fasting lipid profile should be obtained upon initiation of care (B-III).

Evidence Summary

Follow-up testing and response to therapy should be performed in accordance with current National Cholesterol Education Pro-

gram Guidelines [12, 16, 38]. Please see section VIII for further discussions regarding dyslipidemia.

HLA B*5701 SCREENING

Recommendations

20. HLA-B*5701 testing should be performed prior to initiating abacavir therapy (A-I).

21. Patients who are positive for the HLA B*5701 haplotype are at higher risk for hypersensitivity reaction and should not be treated with abacavir (A-II).

Evidence Summary

Screening for the HLA B*5701 haplotype is recommended to identify patients who are at high risk for the abacavir hypersensitivity reaction [2]. A negative test result does not rule out the possibility of a hypersensitivity reaction but makes it much less likely. Patients who have negative test results should still be counseled about a hypersensitivity reaction before being treated with abacavir. If HLA B*5701 screening is not available or a patient declines testing, it is reasonable to initiate abacavir with appropriate counseling and monitoring for symptoms or signs of a hypersensitivity reaction [2].

URINALYSIS AND CALCULATED CREATININE CLEARANCE

Recommendations

22. A baseline urinalysis and calculated creatinine clearance assay should be considered, especially in black HIV-infected patients and those with advanced disease or comorbid conditions, because of an increased risk of nephropathy (B-II).

23. Urinalysis and calculated creatinine clearance assay should also be performed prior to initiating drugs, such as tenofovir or indinavir, that have the potential for nephrotoxicity (B-II).

Evidence Summary

Kidney function is abnormal in up to 30% of HIV-infected patients, and HIV-associated nephropathy is a relatively common cause of end-stage renal disease in this population [5]. The glomerular filtration rate should be estimated to assist in prescribing antiretroviral agents and other commonly used medications that require renal dosing. Because studies of medications involved in renal failure have traditionally used the Cockcroft-Gault equation to calculate creatinine clearance, this equation is preferred, and medications should be dosed according to their package inserts regarding renal function. In addition, a screening urinalysis for proteinuria should be considered at initiation of care and annually thereafter, especially in patients who are at increased risk for developing proteinuric renal disease (eg, black persons, those with CD4 cell counts

<200 cells/mm³ or HIV RNA levels >4000 copies/mL, those with diabetes mellitus, hypertension, or HCV coinfection). Patients with proteinuria of grade $\geq 1+$ by dipstick analysis or reduced renal function (glomerular filtration rate, <60 mL/min per 1.73 m²) should be referred to a nephrologist for consultation and should undergo additional studies, including quantification of proteinuria, renal ultrasound, and potentially renal biopsy. Among patients who are at higher risk, biannual monitoring for renal function and urinary abnormalities is warranted for those receiving tenofovir or indinavir [5].

COINFECTION AND COMORBIDITY LABORATORY TESTS

TUBERCULOSIS SCREENING

Recommendations

24. Upon initiation of care, HIV-infected patients should be tested for *Mycobacterium tuberculosis* infection by either a TST applied on the volar surface of the forearm by the Mantoux (intradermal injection) method with an intermediate-strength purified protein derivative (0.1 mL containing 5 TU) or by an interferon- γ release assay (A-I). Those with positive test results should be treated for latent *M. tuberculosis* infection after acute tuberculosis has been excluded.

25. Repeat testing is recommended in patients with advanced HIV disease who initially had negative TST results but subsequently experienced an increase in the CD4 cell count to >200 cells/mm³ while receiving antiretroviral therapy and who, thus, may have restored sufficient immunocompetence to mount a positive reaction (A-III).

26. HIV-infected patients who are close contacts of persons with infectious tuberculosis should be treated for latent *M. tuberculosis* infection regardless of their TST results, age, or prior courses of tuberculosis treatment after the diagnosis of active tuberculosis has been excluded (A-II).

Evidence Summary

All HIV-infected patients should be tested for *M. tuberculosis* infection by TST upon initiation of care [2, 37]. For an HIV-infected person, induration of >5 mm is considered to be a positive result and should prompt chest radiography and other evaluation, as warranted, to rule out active tuberculosis [39]. Annual test should be considered for those who have negative results by TST but are at ongoing risk for exposure to tuberculosis. A TST should be performed any time there is concern of a recent exposure. Routine cutaneous anergy testing is no longer recommended because of lack of standardization of reagents, poor predictive value, and because prophylaxis provided to anergic persons has been shown to prevent few cases of tuberculosis [40]. Prior vaccination with bacillus Calmette-

Guérin may result in a positive TST result. This reaction may be to the vaccine itself or to latent *M. tuberculosis* infection. Therefore, evaluation to exclude active tuberculosis and consideration of therapy for latent infection is warranted. The QuantiFERON-TB Gold test, the QuantiFERON-TB Gold In-tube test (Cellestis Limited), and the T-SPOT TB test (Oxford Immunotech) are approved by the FDA as aids for detecting latent *M. tuberculosis* infection. Although the interferon- γ release assays have not been validated in the HIV-infected population, ongoing studies suggest that the interferon- γ release assays, compared with the TST, have more consistent and higher specificity (92%–97% vs 56%–95%), better correlation with surrogate measures of exposure to *M. tuberculosis*, and less cross reactivity due to *Bacillus Calmette-Guérin* vaccination or other nontuberculous mycobacteria exposure. Advanced immunosuppression may be associated with false negative results in all types of immunologically based tests used for detection of *M. tuberculosis* infection.

SEROLOGIC TESTING FOR *TOXOPLASMA GONDII*

Recommendations

27. All HIV-infected patients should be tested for prior exposure to *T. gondii* by measuring anti-*Toxoplasma* immunoglobulin (Ig) G upon initiation of care (B-III).

28. *Toxoplasma*-seronegative adults, representing 70%–90% of the US population, should be counseled on how to avoid new infection (B-III).

29. Serologic testing should be repeated for previously seronegative patients if the CD4 cell count decreases to 100 cells/mm³, especially if they are unable to receive prophylaxis against *Pneumocystis* pneumonia, which is active against toxoplasmosis (C-III).

Evidence Summary

If the anti-*Toxoplasma* IgG assay result is positive, the patient should be managed according to the published guidelines [18]. Although serologic tests for *Toxoplasma* can never be used to diagnose or exclude toxoplasmosis, a seronegative patient with a space-occupying lesion of the central nervous system is less likely to have toxoplasmosis than is a seropositive patient. HIV-infected pregnant women with a positive *Toxoplasma* serology result have an increased likelihood of maternal reactivation and congenital transmission. Infants born to women who are seropositive for *Toxoplasma* should be evaluated for congenital toxoplasmosis [19].

VIRAL HEPATITIS SCREENING AND VACCINATION RECOMMENDATIONS

Recommendations

30. HIV-infected patients should be screened for evidence of HBV infection upon initiation of care by detection of hepatitis B surface antigen (HBsAg), antibody to HBsAg, and antibody to hepatitis B total core antigen (A-III), and those who are susceptible to infection should be vaccinated against HBV (B-II). Sexual partners of persons who are positive for HBsAg should also be offered vaccination.

31. Patients who are negative for HBsAg and antibody to HBsAg but positive for hepatitis B total core antigen antibody should be screened for chronic HBV infection by determination of HBV load (HBV DNA PCR) (C-III).

32. HIV-infected patients should be screened for HCV infection upon initiation of care by a test for HCV antibody (B-III).

33. Positive HCV antibody test results should be confirmed by measurement of HCV RNA levels by PCR (A-II).

34. Infants born to HCV-positive women should be tested for HCV transmission (A-II).

35. Hepatitis A vaccination is recommended for all susceptible men who have sex with men (MSM), as well as others with indications for hepatitis A virus vaccine (eg, injection drug users, persons with chronic liver disease, or patients who are infected with hepatitis B and/or C) (A-II).

36. Hepatitis A vaccine may be considered for all other patients without prior exposure (negative anti-HAV test result) (C-III).

Evidence Summary

HBV vaccination should be administered to those persons who have a positive hepatitis B total core antigen antibody result with negative HBsAg and anti-HBsAg antibody results and who do not have detectable HBV DNA [41]. HCV RNA should also be measured in HCV-seronegative patients with a history of injection drug use or with unexplained increased serum transaminases, because ~6% of HIV- and HCV-coinfected persons do not develop HCV antibodies [22]. Pre vaccination screening for hepatitis A virus infection is cost-effective when there is a seroprevalence of >30% in the patient population.

The rate of mother-to-infant HCV transmission is increased among women who are coinfecting with HIV and is estimated to be 2.8-fold higher, according to multiple studies [42]. Infants can be tested for HCV RNA after 1–2 months of age or HCV antibody after 18 months of age. All infants born to HBsAg-positive women should receive hepatitis B immune globulin and hepatitis B immunization, preferably in the first 12 h of life. Routine hepatitis A and hepatitis B vaccination is recommended for all infants (<http://www.cdc.gov/vaccines/recs/schedules>).

HIV-infected persons who are coinfecting with HBV and/or HCV should be managed according to published guidelines [2, 7–10, 18].

SCREENING AND VACCINATION RECOMMENDATIONS FOR HERPESVIRUSES

Recommendations

37. Patients at lower risk of CMV infection (eg, populations other than MSM or injection drug users, both of which may be assumed to be CMV seropositive) should be tested for latent CMV infection with an anti-CMV IgG upon initiation of care (B-III).

38. Patients who do not have evidence of immunity to varicella should receive postexposure prophylaxis with VariZIG as soon as possible (but within 96 h) after exposure to a person with varicella or shingles (A-III).

39. Varicella primary vaccination may be considered in HIV-infected, VZV-seronegative persons aged >8 years with CD4 cell counts >200 cells/mm³ (C-III) and in HIV-infected children aged 1–8 years with CD4 cell percentages ≥15% (B-II).

Evidence Summary

Although the seroprevalence of CMV among HIV-infected persons is high, the identification of seronegativity would prompt the use of CMV-negative or leukocyte-reduced blood products when transfusions are needed, thus reducing the risk of iatrogenic infection [22, 43]. Persons who are seronegative for CMV should be reminded that CMV may be sexually transmitted and is yet another reason for the need to practice safer sex. It may also be valuable to determine anti-varicella IgG levels for the minority of patients who are unable to give a history of varicella or shingles. Limited data on the immunogenicity and safety of varicella vaccine among HIV-infected persons are available from a clinical trial involving children aged 1–8 years with a CD4 cell percentage of >15% and a CD4 cell count >200 cells/mm³ [44]. Data on the use of varicella vaccine in HIV-infected adolescents and adults are lacking. However, on the basis of expert opinion, the safety of varicella vaccine in HIV-infected persons aged >8 years with comparable levels of immune function is likely to be similar to that of children aged <8 years [45]. The Advisory Committee on Immunization Practices states that, after weighing the risk for severe disease from wild VZV and potential benefit of vaccination, varicella vaccination may be considered (2 doses administered 3 months apart) for HIV-infected persons with a CD4 cell count >200 cells/mm³ who do not have evidence of immunity to varicella [13, 14, 45]. Evidence of immunity to varicella includes any of the following: documentation of 2 doses of varicella vaccine, laboratory evidence of immunity or laboratory confirmation of disease, or verification of a history of varicella disease or herpes zoster by a health care provider. Persons without evidence of immunity who have contraindications to the vaccine and who are at risk of developing severe disease or complications should be offered VariZIG within 96 h after exposure [18, 45]. VariZIG can be obtained only under

a treatment investigational new drugs (contact FFF enterprises at 1-800-843-7477). VariZIG is not indicated for persons who received 2 doses of varicella vaccine and became immunocompromised later in life [13, 14, 18, 45]. Studies evaluating VZV vaccine for prevention of shingles in the adult HIV-infected population are in development, and no recommendations can be offered at this time. Serologic testing for other herpesvirus infections is not generally recommended because of its lack of diagnostic or therapeutic applications, although some experts advocate screening for herpes simplex virus type 2 [22].

SCREENING FOR SYPHILIS

Recommendations

40. All patients should be screened for syphilis upon initiation of care and periodically thereafter, depending on risk (A-II).

41. A lumbar puncture should always be performed for patients with serological test results reactive for syphilis and neurological or ocular symptoms or signs and in patients with late latent syphilis (>1 year duration) (A-II).

42. Patients who experience serologic treatment failure should also undergo lumbar puncture (B-III).

Evidence Summary

Serologic testing for syphilis should be performed at baseline and periodically thereafter depending on the patient's risk behavior or the presence of other new STDs [18, 22, 23]. Routine serologic screening for syphilis is recommended at least annually for sexually active HIV-infected persons, with more frequent screening (every 3–6 months) in those with multiple partners, a history of unprotected intercourse, a history of sex in conjunction with illicit drug use, methamphetamine use, or sexual partners who participate in such activities [18, 22, 23].

The standard approach to syphilis testing includes a nontreponemal test (eg, rapid plasma reagin or Venereal Disease Research Laboratory [VDRL] tests) followed by a treponemal test (eg, FTA-ABS, MHA-TP, or TPPA) if the first test is reactive. Some laboratories screen with an enzyme immunoassay that uses recombinant treponemal antigens, followed by a nontreponemal test titrated to endpoint dilution if reactive. Biologic false-positive rapid plasma reagin and VDRL test results are generally of low titer (ie, <1:8) and may be associated with a history of injection drug use. Expert opinion varies on the need for lumbar puncture in HIV-infected patients with syphilis. Some experts recommend CSF examination for all HIV-infected patients when the nontreponemal test result is positive at a high titer (ie, >1:32) or when the CD4 cell count is <350 cells/mm³, regardless of syphilis stage. The interpretation of CSF findings can be difficult because the CSF VDRL is insensitive for the diagnosis of neurosyphilis, and the mononuclear pleocytosis and increased CSF protein levels that are characteris-

tic of neurosyphilis may also be attributable to chronic HIV infection.

SCREENING FOR OTHER STDs (REFER TO SECTION II FOR INFORMATION ON ROUTINE STD SCREENING)

Recommendation

43. All patients should be initially screened with laboratory tests for syphilis, all women should be screened for trichomoniasis, and all women aged <25 years should be screened for chlamydial infection (A-II). All men and women should be screened for gonorrhea infection, and all men and women aged ≥25 years should be screened for chlamydial infection (B-II). All of these conditions should be screened for periodically thereafter, depending on reported behaviors, the presence of other STDs in the patient or their partner, and the prevalence of STDs in the community (B-III).

Evidence Summary

Bimanual examination should be performed to assess for cervical motion, uterine, or adnexal tenderness suggestive of pelvic inflammatory disease. Rectal testing for gonorrhea and *Chlamydia* infection should be performed on the basis of report of receptive anal intercourse, particularly among MSM. A test for pharyngeal gonorrhea infection should be considered if the patient reports a history of receptive oral sex in the past year (with use of culture, a test cleared by the FDA, or a test that has been locally verified in accordance with applicable statutes). Testing for oropharyngeal *Chlamydia* is not recommended. Periodic follow-up screening should be considered depending on the patient's reported risk behaviors. Women with concerning symptoms or signs and those whose partners have concerning symptoms or signs should be tested for STDs. Whenever a person has received a diagnosis of a specific STD for which there is curative treatment, their sexual contacts should be evaluated and presumptive treatment should be given.

SCREENING FOR ANOGENITAL HUMAN PAPILLOMAVIRUS (HPV)

Recommendation

44. HIV-infected men and women with HPV infection are at increased risk for anal dysplasia and cancer. MSM, women with a history of abnormal cervical Pap test results, and all HIV-infected persons with genital warts should be considered for anogenital HPV screening and anal Pap tests (C-III).

Evidence Summary

All HIV-infected women should have a cervical Pap test performed twice during the first year after diagnosis and, if the results of both Pap tests are normal, annually thereafter [18, 22]. See Gynecological Evaluation for Cervical Cancer Screen-

ing and Prevention for information regarding cervical cancer screening. Liquid-based cytology is the preferred approach for HPV testing [46]. The role of adjuvant HPV DNA testing has not been defined in the setting of HIV infection. HIV-infected women with HPV infection are at increased risk for cervical dysplasia and cancer. HIV-infected MSM with HPV infection are at increased risk for anal dysplasia and cancer. HPV-related anal dysplasia is seen at a lower frequency among heterosexual men. Anal cytologic screening (ie, anal Pap smears) in HIV-infected women and MSM is not considered to be the standard of care at this time but is being performed in some health care centers. Additional studies of screening and treatment protocols for anal dysplasia are in progress to clarify this issue [18]. Abnormal anal Pap smear findings should be further evaluated by high-resolution anoscopy with biopsy of abnormal areas and topical therapy of high-grade dysplastic lesions.

SERUM TESTOSTERONE LEVEL

Recommendation

45. Providers should consider obtaining morning serum total testosterone measurements in male patients who complain of fatigue, weight loss, loss of libido or erectile dysfunction, or depressive symptoms or who have evidence of reduced bone mineral density (C-III).

Evidence Summary

HIV-infected men, especially those with advanced disease, are at risk for hypogonadism. Whether antiretroviral therapy ameliorates or contributes to this condition is unclear. A total testosterone level that is below the lower limit of normal should be confirmed by repeat testing because of the variability of assays. Because testosterone circulates primarily while bound to plasma proteins, such as albumin and sex hormone-binding globulin, a determination of free testosterone with a reliable assay (such as equilibrium dialysis) may be needed if alterations in binding proteins are suspected. Alternatively, a free testosterone level can be estimated using a free androgen index (calculated as the total testosterone level divided by the sex hormone binding globulin level). Free testosterone assays available at most local laboratories that use analog methods have limited reliability.

Once the diagnosis of hypogonadism is established, further testing by measuring luteinizing hormone and follicular stimulating hormone should be considered to determine whether it is primary source (testicular failure) or central source (hypothalamic or pituitary dysfunction). If luteinizing hormone and/or follicular stimulating hormone levels are abnormal, further evaluation to establish the cause should be considered with specialty consultation as needed.

CHEST RADIOGRAPHY

Recommendation

46. A baseline chest radiograph should be obtained in all HIV-infected patients with a positive tuberculosis screening test result, to rule out active tuberculosis; it may also be useful in other patients who are likely to have pre-existing lung abnormalities (B-III).

Evidence Summary

HIV-infected patients are susceptible to a variety of pulmonary complications. Injection drug users are especially likely to have radiographic abnormalities that may be mistaken for infiltrates. A radiograph obtained at baseline in this patient population and in persons with a history of pulmonary disease may be useful for comparison in the evaluation of future respiratory complaints.

OTHER LABORATORY TESTS

Recommendation

47. Routine testing for cryptococcal infection by determination of serum cryptococcal antigen levels or for disseminated *Mycobacterium avium* complex infection by culture of blood for acid-fast bacilli is not recommended (B-II).

Evidence Summary

These tests are only appropriate for the diagnosis of symptomatic infection and should be reserved for patients with advanced immunodeficiency who have suggestive clinical findings. In patients with profound immunosuppression, testing for *M. avium* complex should be performed before initiating prophylaxis with macrolides.

Other tests that may be indicated, depending on the age and gender of the patient and/or symptoms, include electrocardiography, determination of thyroid-stimulating hormone, prostate-specific antigen, colonoscopy, bone density measurement, or mammography (see table 6 for specific recommendations). Patients with HIV infection may be at higher risk for developing age- and gender-specific malignancies; therefore, cancer screening should be considered annually.

IV. HOW IS HIV DISEASE STAGED?

Recommendation

48. Patients may be staged according to the CDC AIDS Surveillance Definition for epidemiologic and reporting purposes (C-III).

Evidence Summary

Adults. The most widely used system for staging HIV disease is the 1993 revision of the CDC's AIDS Surveillance Case Definition for Adolescents and Adults [47]. HIV disease is a con-

tinuous spectrum. These stages are used for defining resource requirements, especially those from governmental sources, and for surveillance. According to this system, individuals are assigned a stage according to a 3×3 matrix consisting of 3 CD4 cell count categories and 3 clinical categories (table 7). Although the list of AIDS-defining conditions is used in epidemiological research, including studies of prognosis, the 3×3 CDC staging system has not been validated for this purpose.

CD4 cell count categories are as follows: category 1, CD4 cell count >500 cells/mm³ or CD4 cell percentages $>29\%$; category 2, CD4 cell count 200–499 cells/mm³ or CD4 cell percentages 14%–28%; and category 3, CD4 cell count <200 cells/mm³ or CD4 cell percentages $<14\%$. Clinical category A is documented asymptomatic HIV infection, including persistent generalized lymphadenopathy, or acute HIV infection. Clinical category B is symptomatic disease, with conditions not listed in clinical category C, including those that are attributed to HIV infection or indicative of a defect in cell-mediated immunity or considered to have a clinical course or management that is complicated by HIV infection. Clinical category B includes conditions such as bacillary angiomatosis, persistent or recurrent thrush, poorly responsive vulvovaginal candidiasis, moderate to severe cervical dysplasia, constitutional symptoms (such as fever [temperature, $\geq 38.5^\circ\text{C}$] or diarrhea of >1 month duration or oral hairy leukoplakia), herpes zoster (>1 episode or >1 dermatome), idiopathic thrombocytopenic purpura, listeriosis, pelvic inflammatory disease, and peripheral neuropathy. Clinical category C consists of AIDS indicator conditions.

According to the 1993 case definition for AIDS, persons aged >13 years with stage A3, B3, C1, C2, or C3 infection have CDC-defined AIDS. Specifically, anyone with either an AIDS indicator condition or a CD4 cell count of <200 cells/mm³ has AIDS. Once a diagnosis of AIDS has been made, for surveillance purposes it is not negated by subsequent developments (eg, persons who receive a diagnosis of AIDS on the basis of a CD4 cell count of <200 cells/mm³ are still considered to have AIDS if their CD4 cell count subsequently increases to >200 cells/mm³ in response to antiretroviral therapy), although the relevance of the diagnosis may then be more historical than clinical.

Although reporting requirements for HIV infection vary somewhat from state to state, all states have implemented confidential HIV/AIDS case reporting. Accurate and complete reporting is important to ensure that adequate health and social resources are available, because the amount of federal AIDS funding received by a city or community is frequently based on the number of reported cases from that region.

Children. The CDC pediatric clinical and laboratory classification system [48] parallels the adult HIV case definition. There are age-specific differences in CD4 cell count that need

Table 6. Routine Health Care Maintenance in the Human Immunodeficiency Virus (HIV)-Infected Adult

Intervention	Recommendation	Comments
Blood pressure check	Perform annually in all patients	...
Digital prostate examination	Consider annually in all men	Controversial; testing at an earlier age may be advisable in men at higher risk of prostate cancer (eg, black patients and those with family history)
Ophthalmologic examination	Perform dilated examination every 6–12 months in patients with a CD4 cell count <50 cells/mL	Examination with tonometry is advised every 2–3 years in all patients aged ≥50 years
Depression screening	Perform annually in all patients	Use conventional mental health interview or standardized test
Fasting glucose	Perform every 6–12 months in all patients	Consider testing 1–3 months after starting or modifying antiretroviral therapy; hemoglobin A1c level should be obtained every 6 months in patients with diabetes mellitus
Fasting lipid profile	Perform every 6–12 months in all patients	Consider testing 1–3 months after starting or modifying antiretroviral therapy
Syphilis serology (RPR, VDRL)	Perform annually in patients at risk for STDs	More frequent testing may be indicated in patients at high risk for STDs
Gonorrhea and chlamydia testing	Perform annually in patients at risk for STDs	More frequent testing may be indicated in patients at high risk for STDs
Prostate-specific antigen	Discuss pros and cons with patient and consider annually in men aged ≥50 years	Controversial; testing at an earlier age may be advisable in men at higher risk of prostate cancer (eg, black patients and those with family history)
Tuberculin screening test	Perform annually in patients at risk for tuberculosis	No need to repeat in patients with prior positive purified protein derivative test; additional tuberculosis testing may be indicated depending on potential exposure
Colonoscopy	Perform at age 50 years and every 10 years thereafter in all patients	More frequent testing is indicated in patients with a history of adenomatous polyps; testing at an earlier age may be advised in patients with a strong family history of colon cancer
Mammography	Perform annually in all women age 50 years or older	Some authorities advise initiation of screening starting at age of 40 years based on an individual risk/benefit assessment
Cervical Pap smear	Perform annually in all women after 2 normal Pap tests documented during the first year after HIV diagnosis	More frequent testing is indicated in women with a history of atypical squamous cells of unknown significance or cervical dysplasia
Bone densitometry	Perform baseline examination in postmenopausal women aged ≥65 years and in younger postmenopausal women with 1 or more other risk factor(s) for premature bone loss; consider in persons aged ≥50 years, especially if they have ≥1 risk factor(s) for premature bone loss	Detection of premature bone loss requires periodic monitoring thereafter; risk factors for premature bone loss include white race, small body habitus, sedentary lifestyle, cigarette smoking, alcoholism, phenytoin therapy, corticosteroid therapy, hyperparathyroidism, vitamin D deficiency, thyroid disease, and hypogonadism
Abdominal ultrasonography	Perform once in men aged 65–75 years who have ever smoked	Screening test for abdominal aortic aneurysm
Patient education	Address regularly in all patients	Issues may include sexual behavior and drug counseling, dietary teaching, weight reduction, smoking cessation, and seat belt use

NOTE. For information on digital prostate examination, prostate-specific antigen, colonoscopy, and mammography, see United States Preventive Services Task Force (<http://www.ahrq.gov/clinic/USpstfix.htm>). RPR, rapid plasma reagin; STD, sexually transmitted disease; VDRL, Venereal Disease Research Laboratory.

Table 7. Centers for Disease Control and Prevention (CDC) Staging System for Classification of Human Immunodeficiency Virus–Infected Adults

CD4 cell count, cells/mm ³ (CD4 cell percentage)	CDC classification		
	A ^a	B ^b	C ^c
>500 (>29)	A1	B1	C1
200–500 (14–28)	A2	B2	C2
<200 (<14)	A3	B3	C3

NOTE. Adapted from [47].

^a Asymptomatic, persistent generalized lymphadenopathy, or acute human immunodeficiency virus infection.

^b Symptomatic (not A or C).

^c AIDS indicator condition.

to be accounted for when staging infants and young children (table 8).

V. WHAT IS THE SCHEDULE-OF-CARE EVALUATION FOR HIV-INFECTED PATIENTS?

ADULTS

Recommendations

49. Asymptomatic HIV-infected patients with normal CD4 cell counts and low viral loads should be monitored with repeat HIV-RNA load measurements and CD4 cell counts every 3–4 months (B-II).

50. CD4 cell counts should be monitored both to assess the efficacy of antiretroviral therapy and to determine the need for prophylaxis against opportunistic infections (A-I).

51. STD screening and tuberculosis screening tests should be repeated periodically depending on symptoms and signs, behavioral risk, and possible exposures (B-III).

52. Vaccinations for pneumococcal infection (A-II), influenza (A-III), varicella (B-III), and hepatitis A (A-II) and B (A-II) should be offered as indicated (table 9). The likelihood of a response to any vaccine is greatest in patients with higher CD4 cell counts or in patients receiving suppressive antiretroviral therapy.

Evidence Summary

The frequency of evaluation depends, in part, on the stage of HIV disease and, in part, on the rate at which it is progressing. Patients may need to be seen more frequently depending on their need for ancillary services, such as treatment adherence counseling, mental health services, HIV education, case management services, and others. Patients who are engaged in care are more likely to remain adherent to their medication and have improved health outcomes. See tables 6 and 9 for recommendations on routine immunizations and health maintenance evaluation. Complete blood count and chemistry pan-

els should be monitored on a regular basis to assess medication toxicity if the patient is given prophylaxis for opportunistic infections and/or antiretroviral therapy and to monitor potential comorbid conditions (eg, chronic renal disease or hepatitis). For example, when prescribing nevirapine, some experts recommend monitoring serum transaminase levels at baseline, prior to, and 2 weeks after dose escalation, then monthly for the first 18 weeks. Once antiretroviral therapy has been initiated, the response to therapy should be monitored 4–8 weeks later with a repeated viral load determination. After the viral load has become undetectable, laboratory tests can then be obtained at 3–4-month intervals, to monitor for drug toxicity and to assess response to therapy [2]. The CD4 cell count and viral load should not be measured within 2–3 weeks after an acute illness or immunization, if possible, because of the transient decrease in CD4 cell count and elevation in viral load that may occur. Serologic testing for viral hepatitis should be repeated if suspected exposure occurs or there are newly elevated transaminase levels in a patient who was not previously immune. Patients with a CD4 cell count <50 cells/mm³ should undergo regular dilated funduscopic examinations. All patients should have semiannual oral health examinations and regular screening for depression.

CHILDREN

Recommendation

53. Perinatally infected infants and HIV-infected children should have the following:

- CD4 cell counts and viral loads monitored no less often than every 3 months (B-III).
- Annual TB screening tests to diagnose latent tuberculosis infection; children with HIV infection are at high risk for tuberculosis (A-III).
- Childhood vaccinations should be administered according to Advisory Committee on Immunization Practices schedules for HIV-infected infants and children (A-II).

Table 8. Centers for Disease Control and Prevention Scheme for Defining Level of Immunosuppression in Human Immunodeficiency Virus–Infected Children

Category	CD4 cell count, cells/mm ³ (CD4 cell percentage), by age		
	0–12 months	1–5 years	≥6 years
Normal	>1500 (>25)	>1000 (>25)	>500 (>25)
Moderate	750–1499 (15–24)	500–999 (15–24)	200–499 (15–24)
Severe	<750 (<15)	<500 (<15)	<200 (<15)

Table 9. Routine Immunizations in Human Immunodeficiency Virus (HIV)–Infected Adults

Vaccine	Status	Dose and regimen	Comments
<i>Haemophilus influenzae</i> type B vaccine	Consider in selected settings; see comments	0.5 mL IM	Administer to asplenic patients and those with history of recurrent <i>Haemophilus</i> infection
Hepatitis A vaccine	Recommended in selected settings; see comments	1 mL IM with revaccination in 6–12 months for Havrix or 6–18 months for Vaqta; also available in combination with hepatitis B vaccine as Twinrix, administered as 3 or 4 dose	Hepatitis A vaccination is recommended for all susceptible men who have sex with men, as well as others with indications for hepatitis A virus vaccine (eg, injection drug users, persons with chronic liver disease or who are infected with hepatitis B and/or C).
Hepatitis B vaccine	Recommended in selected settings; see comments	Engerix B 20 µg or Recombivax HB 10 µg IM given at 0, 1, and 6 months; also available in combination with hepatitis A vaccine as Twinrix administered as 3 or 4 dose	Administer to patients without evidence of past or present hepatitis B infection. Vaccinated patients should be tested for HBsAg antibody response after the third dose; Higher dose (40 µg) booster or series may be considered for nonresponders.
Human papillomavirus vaccine	Ideally given prior to any sexual activity. Females aged 9–26 years but may consider in other groups as per text	Gardasil 0.5 mL IM for 3 dose series given at 0, 2, and 6 months	Safety and immunogenicity studies in those with HIV infection are ongoing.
Influenza vaccine	Inactivated influenza vaccine recommended; do not use live attenuated intranasal vaccine (FluMist)	0.5 mL IM annually	All patients especially important in patients at high risk for exposure to or morbidity from influenza.
Pneumococcal vaccine	Recommended	0.5 mL IM of the 23 polyvalent polysaccharide vaccine	Administer to patients with CD4 cell count >200 cells/mm ³ . Consider booster dose 5 years after initial immunization.
Polio vaccine	OPV contraindicated; IPV should be given if indicated	0.5 mL SC; 3 doses over 6–12 months for primary immunization	...
Tetanus toxoid	Same as for patient without HIV infection	Td, 0.5 mL IM; Tdap, 0.5–0.75 mL IM as per package insert	Substitute 1-time dose of Tdap vaccine at time of next booster, then Td every 10 years. Precautions with pregnancy. Td may be administered during 2nd or 3rd trimester or defer Td during pregnancy and administer Tdap postpartum
Varicella vaccine (primary)	Consider in selected settings: see comments	0.5 mL IM as 2 doses administered 3 months apart	Administer to HIV-infected persons with a CD4 cell count >200 cells/mm ³ who do not have evidence of immunity to varicella

NOTE. HBsAg, hepatitis B surface antigen; IM, intramuscular; IPV, inactivated polio vaccine; OPV, oral polio vaccine; SC, subcutaneous. Adapted from [14].

Evidence Summary

HIV-exposed newborns should be observed closely for symptoms and signs of HIV infection and comorbid conditions. HIV-exposed infants should be evaluated in the newborn nursery and have clinical visits at 2, 4, and 8 weeks and after that according to regular AAP guidelines for baby care. In non-breast-feeding infants, 2 negative virologic assay results (HIV-1 DNA or RNA detection or nucleic acid amplification test) at >2 and >4 weeks of age or 1 negative test result at 8 weeks can presumptively exclude HIV infection. In this scenario, trimethoprim-sulfamethoxazole prophylaxis can be avoided or discontinued if testing is performed early. A repeat PCR at 4 months should be performed to definitively exclude HIV infection. A positive HIV virologic test result should be repeated immediately. Infants determined to be infected with HIV should be started on antiretroviral therapy according to US Public Health Service guidelines [3]. Frequent clinical visits are required in this scenario, to assure that growth and development are on schedule, that appropriate adjustment of dosages occurs, and that the infant is tolerating the medications. Vaccination status should be reviewed at each visit. HIV-infected infants and children can safely receive most childhood vaccines, although effective response depends on the degree of immunosuppression. Varicella and the measles, mumps, and rubella vaccines should not be administered to severely immunocompromised children (ie, those with CD4 cell percentages <15%). All HIV-infected children should be vaccinated against *Pneumococcus* and receive yearly trivalent inactivated influenza vaccine. The appropriate use of combination antiretroviral drugs, with routine monitoring of adherence, immune status, and viral load, has become the standard of care for pediatric HIV-infected patients. Once the child is receiving a stable regimen, the frequency of laboratory testing is similar to that for adults.

VI. WHAT ARE THE SPECIAL CONSIDERATIONS FOR WOMEN?

Women with HIV infection have the same reproductive health needs and concerns as do women without HIV infection. In addition, they may have gynecologic problems that are associated epidemiologically with HIV infection because of common risk behaviors. Certain gynecologic problems may be more common or severe because of HIV-associated immunosuppression. Both the incidence and prevalence of gynecologic problems are high among HIV-infected women throughout their disease course [49].

As part of the initial assessment, a comprehensive gynecologic history should be obtained, including menstrual history; sexual practices; contraception history and current use; male or female condom use and consistency of use; previous STDs and other genital tract infections; prior abnormal Pap test results, including subsequent evaluation and treatment; history

of gynecologic conditions (eg, uterine fibroids, endometriosis, and infertility) or surgery; and current gynecologic symptoms (eg, abnormal vaginal discharge, abnormal vaginal bleeding, amenorrhea, and pelvic pain).

CONTRACEPTION AND PRECONCEPTION CARE

Recommendation

54. All HIV-infected women of childbearing age should be asked about their plans and desires regarding pregnancy upon initiation of care and routinely thereafter (A-III).

Evidence Summary

An in-depth discussion about childbearing is indicated if the patient expresses desire for future pregnancy, is not trying to conceive but is not using appropriate contraception, or expresses uncertainty about reproductive plans. The goal is to ensure informed decisions about contraception with prevention of unintended pregnancy and to offer preconception counseling if pregnancy is desired. Patients should explicitly be asked to communicate with their provider if their plans change, when they are ready to consider pregnancy, or when they have questions related to reproduction. In women who are at risk for pregnancy (ie, are trying to conceive or are not using effective and consistent contraception), providers should carefully review all medications and avoid drugs with potential reproductive toxicity. The time of greatest risk to the fetus is early in pregnancy, often before it has been recognized. Efavirenz has been associated with teratogenic effects in primate studies, and there are reports of significant central nervous system abnormalities in human infants exposed to efavirenz during the first trimester. Other medications sometimes used in HIV-infected women (eg, lithium, ribavirin, statins, and warfarin) are also potential teratogens.

Women who do not wish to become pregnant should be advised to use effective contraception. Condom use should be recommended with each sexual act, which provides dual protection against pregnancy, STDs, and potential superinfection with HIV. However, condoms are associated with higher rates of failure than other contraceptive methods, and women should be counseled about the greater effectiveness of using a second method of protection as well. Combined estrogen-progestin hormonal contraceptives (birth control pill, transdermal patch, and vaginal ring) have interactions with several antiretroviral drugs, which may decrease their effectiveness or increase the risk of adverse effects. Contraindications to combined hormonal methods, such as diabetes mellitus, hyperlipidemia, and chronic liver disease, may be more prevalent among HIV-infected women. Intrauterine device use in the context of HIV infection remains controversial and should be avoided in women at increased risk for other STDs; however, in low-risk

women, the benefits may outweigh the risks, and a levonorgestrel-releasing intrauterine device may have additional benefits in terms of reduction in menstrual blood loss. Spermicides have been associated with an increased risk of HIV seroconversion and are not recommended for the prevention of HIV transmission or acquisition.

Women who need or desire preconception counseling should be referred to a provider with expertise in this area. HIV-serodiscordant couples who desire pregnancy should be counseled about ways to minimize risk of transmission to the uninfected partner while trying to conceive. The use of home artificial insemination (vaginal insertion of ejaculate with a syringe) effectively avoids risk to an uninfected male partner, and consistent condom use in the relationship should be reinforced. When the man is HIV-infected and his female partner is uninfected, there is no current way to completely eliminate risk for the woman. In couples who wish to proceed after careful counseling, there are limited data to guide recommendations, but the following interventions may reduce risk of transmission: (1) each partner should be screened and treated for STDs to minimize genital tract HIV load; (2) semen analysis should be performed to exclude abnormalities that might preclude conception; (3) the male partner should be receiving effective antiretroviral therapy and have an undetectable HIV RNA level; (4) perieposure prophylaxis with antiretroviral drugs may be considered for the woman; and (5) the use of ovulation predictors should be considered to optimize timing of intercourse with unprotected sex limited to when conception is likely to occur. Alternatively, where possible, such couples should be referred to centers where assisted reproductive technology, including sperm washing, in vitro fertilization, and intracytoplasmic sperm injection, is available.

A pregnancy history in patients should include the number of pregnancies and outcomes (miscarriage, abortion, ectopic pregnancy, stillbirth, and preterm or term live birth), significant obstetrical complications, and number of living children and their HIV and general health status. Obstetrical issues, such as preconception counseling and care, antiretroviral management during pregnancy for maternal care, prevention of perinatal transmission, and decision-making about mode of delivery, are covered in detail in the US Public Health Service Perinatal HIV Guidelines [4]. HIV-infected women should be instructed to not breast-feed, to minimize the risk of viral transmission to their infant.

PREGNANCY TESTING

Recommendation

55. Pregnancy testing should be considered in the following situations (B-III):

- a. missed menses (unless using etonorgestrel implants or depot medroxyprogesterone acetate);
- b. irregular bleeding (unless using etonorgestrel implants or depot medroxyprogesterone acetate);
- c. new onset of irregular bleeding after prolonged amenorrhea while using etonorgestrel implants or depot medroxyprogesterone acetate;
- d. new onset pelvic pain;
- e. enlarged uterus or adnexal mass on examination;
- f. before institution of new medications with potential adverse effects for the pregnant woman or fetus;
- g. or at the patient's request.

Evidence Summary

Approximately 80% of HIV-infected women are of childbearing age. Because of issues related to perinatal HIV transmission, the potential impact of HIV and its treatment on mother, fetus, and pregnancy course, and the life-threatening nature of ectopic pregnancy, health care providers should question female patients about their interval menstrual history and sexual and contraceptive practices at each visit. Pregnancy tests can be performed on blood or urine, with the latter often available as rapid tests for use on site in clinics. Most available pregnancy tests yield positive results before the first missed menses with normal intrauterine pregnancy.

GYNECOLOGICAL EVALUATION FOR CERVICAL CANCER SCREENING AND PREVENTION

Recommendations

56. HIV-infected women should have a cervical Pap smear performed upon initiation of care, and this test should be repeated at 6 months and, if results are normal, annually thereafter (A-I).

57. Women with atypical squamous cells (both ASC-US [atypical squamous cells of unknown significance] and ASC-H [ASC cannot rule out high-grade squamous intraepithelial lesion or SIL]), atypical glandular cells, low-grade or high-grade squamous intraepithelial lesion, or squamous carcinoma noted by Pap testing should undergo colposcopy and directed biopsy, with further treatment as indicated by results of evaluation (A-II).

Evidence Summary

Abnormal cervical cytology is 10–11 times more common in HIV-infected women, compared with the general female population, and is associated with the presence of HPV infection and the degree of immune dysfunction. More frequent Pap smears should be considered in the following circumstances: if there is a previous history of an abnormal Pap smear; after treatment for cervical dysplasia; in women with symptomatic HIV infection; and in women with HPV infection. HIV-infected

women who have had a hysterectomy, particularly if they have had a history of abnormal cervical cytology before or at the time of the procedure, are at increased risk for squamous intraepithelial lesion on vaginal cytologic testing and should undergo regular screening with Pap smears [50]. Although the appropriate interval for screening has not been established, it is reasonable to follow guidelines similar to those for women who have not undergone a hysterectomy [46].

Pap smears should be reported according to the Bethesda System [51]. The results should include a statement on specimen adequacy and a general categorization (negative for intraepithelial lesion or malignancy, epithelial cell abnormality, or other). Specimens that are reported to be unsatisfactory for evaluation should be obtained again. The presence of epithelial cell abnormalities, including atypical squamous cells, squamous intraepithelial lesion, glandular cell abnormalities, and squamous cell carcinoma, warrants further evaluation. Newer Pap smear screening techniques that use liquid-based media appear to increase sensitivity, decrease the number of tests with inadequate sampling, and reduce but not eliminate false-negative results; they also offer the possibility of direct testing for HPV on collected specimens. The role of HPV testing as an adjunct to Pap testing in HIV-infected women has not been defined. However, recent evidence that the absence of oncogenic HPV is associated with a low incidence of squamous intraepithelial lesions over a 3-year period in HIV-infected women with a CD4 cell count >500 cells/mm³, comparable to that described in HIV-seronegative women, suggest that the same cervical cancer screening practices may be appropriate in both groups [52]. Consideration should be given to increasing the screening interval to 3 years if both Pap and HPV testing results are negative, which is now an option for HIV-negative women aged >30 years [53].

A preventive quadrivalent HPV vaccine is now available and recommended in a 3-dose schedule for females aged 13–26 years. This preparation is safe and highly effective in preventing infection with the HPV subtypes that are most often found in genital warts and that are responsible for ~70% of cervical cancers. There is no evidence that this vaccine has a therapeutic effect on pre-existing cervical dysplasia. Although immunosuppression is not a contraindication to HPV vaccine administration, safety and efficacy data in the context of HIV infection are lacking. There are studies evaluating the immunogenicity of the HPV vaccine in HIV-infected men and women and perinatally infected children. Depending on the immunogenicity rate, it may be reasonable to vaccinate perinatally HIV-infected adolescents who are not sexually active in addition to those adolescents and young adults who may be at additional risk of acquiring HPV infection.

BREAST CANCER SCREENING

Recommendations

58. Mammography should be performed annually in women aged >50 years (A-I).

59. In women aged 40–49 years, providers should perform individualized assessment of risk for breast cancer and inform them of the potential benefits and risks of screening mammography (B-II).

Evidence Summary

Breast cancer is the second leading cause of cancer-related death in women in the United States. It does not appear to be increased in prevalence among women with HIV infection, although unusual clinical presentations and rapid progression have been reported, suggesting that breast cancer may behave more aggressively in this setting [54, 55]. At present, screening mammography for HIV-infected women should follow standard guidelines [56, 57]. Mammography should be performed before the age of 40 years for women with a personal history of breast cancer, with a first-degree relative or multiple other relatives with a history of premenopausal breast cancer or breast and ovarian cancer, or with a persistent palpable mass or other suspicious finding on examination. Potential risks of mammography include false-positive or false-negative results (both may be more likely in younger women with denser breast tissue or hormonally-associated benign breast disease) and procedure-related discomfort; initial concerns about the risk of radiation exposure have been largely allayed by improvements in mammographic techniques and technology and clinical experience.

MENOPAUSE

Recommendations

60. Hormone replacement therapy, particularly if prolonged, has been associated with a small increased risk of breast cancer and cardiovascular and thromboembolic morbidity, and its routine use is not currently recommended (A-I).

61. Hormone replacement therapy may be considered in women who experience severe menopausal symptoms (eg, vasomotor symptoms and vaginal dryness) but should generally be used only for a limited period of time and at the lowest effective doses (B-II).

Evidence Summary

An increasing number of HIV-infected women are living past natural menopause or becoming infected at a later age, and some may undergo surgical menopause. In addition, there is evidence that HIV-infected women may be more likely to undergo premature physiologic menopause. Menopausal women

are at increased risk of premature bone loss (osteopenia and osteoporosis), which may be exacerbated by HIV infection and use of antiretroviral therapy; periodic bone density screening should be considered in this setting.

VII. WHAT ARE THE SPECIAL CONSIDERATIONS FOR MOTHER-TO-CHILD TRANSMISSION AND CHILDREN?

Recommendations

62. Pregnant women should be treated for HIV infection, regardless of their immunologic or virologic status, to prevent infection of their fetus (A-I).

63. Infants exposed to HIV in utero should receive antiretroviral postexposure prophylaxis and undergo HIV virologic diagnostic testing at 14–21 days of life, at 1–2 months of age, and at 4–6 months of age (A-II).

64. Any virologic test with a positive result should be repeated to confirm diagnosis (A-II).

65. HIV-infected infants should undergo HIV resistance testing (A-II) and, because of the rapid progression of disease, should initiate therapy in the first year of life regardless of CD4 cell count, RNA level, or clinical status (A-I).

66. HIV-infected infants and children should be managed by a specialist with knowledge of the unique therapeutic, pharmacologic, behavioral, and developmental issues associated with this disease (B-II).

Evidence Summary

Perinatal HIV infection is a preventable disease if pregnant women are identified through antenatal testing and receive antiretroviral therapy as outlined in the Public Health Service Task Force Recommendations for the Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States [4]. The transmission rate has been reported to be <1% in women who achieve undetectable HIV loads while receiving treatment. In addition to HIV infection, providers should screen pregnant women for other infections, including syphilis and HBV, HCV, and group B streptococcal infections, to determine whether to evaluate and/or treat the newborn. The rapid HIV antibody test should be offered to women with unknown serostatus who present in labor, so that antiretroviral therapy, if necessary, can be administered to the mother and infant. The use of postexposure prophylaxis instituted as soon as possible after birth, but certainly within 12 h, even without any maternal medication, can still significantly decrease HIV transmission [33].

Usually, HIV-infected neonates are asymptomatic, although a number of perinatal conditions may occur because of other maternal comorbidities. These include prematurity, fetal al-

cohol syndrome, opioid withdrawal, anemia, and other perinatal infections, including congenital syphilis, CMV, HBV, and HCV. Prior to discharge from the nursery, the infant should undergo a thorough medical evaluation. The infant's family should be advised about avoidance of breast-feeding and educated on antiretroviral prophylaxis with zidovudine and the need for medical follow-up [4]. A number of diagnostic issues set perinatal HIV infection apart from adult disease. Maternal IgG crosses the placenta, and term newborn infants may have positive serologic results because of maternal infection, independent of their infection status. In the case of HIV infection, maternally derived antibody can result in positive ELISA and Western blot assay results up to 18 months of age. Diagnosis of active HIV infection in the infant can be established by a PCR assay for HIV DNA or RNA. Infection is definitively ruled out if there are negative PCR assay results after 1 month and after 4 months of age [58]. Many experts confirm the absence of HIV-1 infection with a negative HIV-1 antibody assay result at 12–18 months of age. Any viral diagnostic test with a positive result should be immediately repeated.

After the diagnosis of perinatal HIV infection is made, the HIV RNA PCR assay is used to monitor the viral load. In general, perinatally HIV-infected infants have higher viral loads than do adults, and they can remain high throughout the first year. Infants are increasingly being born to highly treatment-experienced mothers who may have received multiple combination regimens in the past. The use of HIV resistance testing is recommended prior to initiating antiretroviral treatment in all treatment naive HIV-infected infants or children [3]. The long-term virologic or immunologic benefits of resistance testing in this setting need to be further assessed, but limited studies support this approach [59]. This assay should be obtained soon after diagnosis and prior to initiation of antiretroviral treatment (which should be initiated as early as possible during the first year of life to prevent progression of disease) [60].

There is no acute HIV syndrome recognized in vertically infected infants like that seen in adults or behaviorally-infected adolescents. *Pneumocystis pneumonia* was the presenting opportunistic infection in most infants before routine HIV prenatal testing programs were established and trimethoprim-sulfamethoxazole prophylaxis was introduced. Infants and children with undiagnosed HIV infection are more likely to present with common bacterial infections, chronic diarrhea with failure to thrive, or acute encephalopathy, rather than with the conditions defined in categories B or C that are seen in adults [20]. There are higher rates of serious bacterial infections, such as pneumococcal disease, herpes zoster, and tuberculosis [61]. Other common conditions in the young HIV-infected child include chronic lung and skin disease, asthma, and developmental delay. In the absence of pregnancy or newborn

HIV screening programs, up to 20% of perinatal infections present after 6 years of age and can cause diagnostic challenges, presenting with immune thrombocytopenic purpura, anemia, recurrent parotitis, chronic diarrhea, encephalopathy, or stroke. In the United States, the diagnosis of perinatal HIV infection is typically made within the first 6 months of age through routine screening of children born to known HIV-infected mothers. Unfortunately, HIV transmission attributable to sexual abuse is recognized in children, so children with signs and symptoms of HIV should be tested for HIV even if their initial testing result as an infant was negative.

There are age-specific differences in CD4 cell counts, with infants having higher normal absolute lymphocyte counts than adults. From birth through 12 months of age, the normal CD4 cell count is >1500 cells/mm³; for children aged 2–5 years, it is >1000 cells/mm³, and it decreases to adult ranges after 5 years of age. The normal CD4 cell percentage range for children and adults is similar. Periodic monitoring of CD4 cell counts in children is important to determine the need for opportunistic infection prophylaxis and to assess the response to antiretroviral therapy. The combination of age-adjusted CD4 cell count and HIV RNA level is the best predictor of progression of disease.

The advent of new classes of antiretroviral drugs and better monitoring tools has changed the epidemiology of pediatric HIV infection in developed countries from an acute fatal disease to a chronic treatable condition [62]. New challenges include the evolving care required for children with HIV infection who are surviving into adulthood and the translating of care and prevention advances in the United States to developing countries around the world [63].

The mean age of the US cohort of perinatally infected children is in the mid-teens, and many of these children have reached adulthood. As a result of increasing survival, many new challenges have emerged. Although more research is needed, several studies suggest that early disclosure of HIV serostatus to children promotes adjustment and trust and facilitates their involvement in self care [64]. The AAP guidelines strongly encourage disclosure to school-aged children [65]. Youth infected with HIV have to cope with many issues, including stigma, adherence issues, loss of family members, distortion of body image, and negotiation of sexual activity. In many studies, there are higher rates of cognitive, psychiatric, and behavioral problems in perinatally infected children [66]. Special attention needs to be paid to risk reduction counseling and secondary prevention in early adolescence. In a recent report of perinatally infected adolescent girls enrolled in the Long Term Outcome Study PACTG 219C, there were 36 pregnancies with known outcomes. All received antiretroviral therapy during pregnancy. Transmission occurred in only 1 case, for a mother-to-child transmission rate of 3.3% in this unique population [67].

The transition of care to adult providers should be a step-

wise process involving the health care team and the young patient. Adult providers need accurate records and should be aware of all previous therapy and past medical history. A 2002 consensus statement by the AAP emphasizes the importance of and illustrates the transition of youth with special health care needs, including HIV infection, to adult care. The goal is to “maximize lifelong functioning and potential through the provision of high-quality, developmentally appropriate health care services that continue uninterrupted” into adulthood [68, p. 1034]. Elements include a multidisciplinary team of professionals, youth involvement, and attention to the diverse needs of the adolescents that extend beyond medical care, including employment, independent living, and intimate relationships. Over time, youth need to learn to negotiate the health care system and assume increasing responsibility. Continued research on the most appropriate way to transition youth to adult providers is needed.

VIII. WHAT ARE THE LONG-TERM METABOLIC COMPLICATIONS ASSOCIATED WITH ANTIRETROVIRAL THERAPY?

The major abnormalities that complicate the management of HIV infection include body morphology changes (lipohypertrophy and lipoatrophy), serum lipid abnormalities, dysregulation of glucose metabolism, lactic acidemia, and bone disorders (reduced bone mineral density and avascular necrosis). Concern has been expressed about long-term cardiovascular morbidity in patients who experience increases in atherogenic serum lipids levels, glucose intolerance, and body fat distribution changes, but as of yet, this risk is not well defined. In general, it appears that the benefits of antiretroviral therapy used in accordance with published guidelines outweigh the risk of cardiovascular disease associated with long-term exposure [69, 70]. Guidelines have been developed to assist providers in the identification and management of lipid abnormalities and metabolic complications [12, 16].

Recommendations

67. Fasting glucose and lipid levels should be monitored prior to and within 4–6 weeks after starting antiretroviral therapy (A-III). Patients with diabetes mellitus should have a hemoglobin A1c level monitored every 6 months with a goal of $<7\%$, in accordance with the American Diabetes Association Guidelines. Patients with abnormal lipid levels should be managed according to the National Cholesterol Education Program Guidelines, with special consideration for persons with HIV infection.

68. There is no rationale for ordering lactic acid tests for asymptomatic patients at any time during HIV care (A-II).

69. Interruption of nucleoside reverse-transcriptase in-

hibitor (NRTI) therapy is recommended for symptomatic patients with a venous lactate level of >5 mmol/L (B-II).

70. Baseline bone densitometry measurement should be obtained in postmenopausal women aged ≥ 65 years and in younger postmenopausal women who have ≥ 1 risk factor for premature bone loss (B-III).

71. Routine screening for osteoporosis in HIV-infected patients without other risk factors for premature bone loss is not recommended at this time, on the basis of available data, but it should be considered in persons aged ≥ 50 years, especially if they have ≥ 1 risk factor for premature bone loss (B-III).

Evidence Summary

Insulin resistance has been associated with traditional risk factors, antiretroviral drugs, and possibly HIV infection itself. Diabetes mellitus is reported in 0.5%–6% of HIV-infected patients, but impaired glucose tolerance is considerably more common, occurring in 15%–20% of individuals. The Multi-center AIDS Cohort Study conducted during the period 1999–2003 indicated a 4-fold increased risk of diabetes mellitus in HIV-infected men receiving antiretroviral therapy [71]. A prospective study comparing glucose intolerance between HIV-infected pregnant women who were receiving protease inhibitor (PI)-based therapy and those not receiving PIs demonstrated that 38% of pregnant women developed impaired glucose tolerance and 9% had confirmed gestational diabetes mellitus, with no differences reported between those who received PIs and those who did not [72]. This is considerably higher than the expected normal percentages of 20%–25% and 2%–5% respectively, in the general obstetric population. HCV-infected patients are known to have an increased risk of insulin resistance and type 2 diabetes mellitus, and HIV- and HCV-coinfected patients have a 5-fold greater risk of developing hyperglycemia, compared with those with HIV infection alone.

The mechanisms behind insulin abnormalities in HIV-infected individuals are not fully defined. However, there is a known link between glucose intolerance and lipodystrophy in HIV infection, which is believed to be related to a failure of the pancreatic β cells to fully compensate for decrements in insulin sensitivity despite simultaneous reduction in insulin clearance. This mechanism may partially explain the association of insulin resistance and thymidine NRTIs. The association between PI use and insulin abnormalities was described in early studies. Indinavir is known to have the greatest effect on insulin sensitivity, presumably through inhibition of the insulin-regulated glucose transporter, GLUT-4, a molecule involved in insulin-mediated glucose uptake by cells. Other PIs have a modest impact, and the effect is usually temporary. This transient impairment of insulin sensitivity does not appear to have an important clinical implication, because $<5\%$ of individuals

treated with PIs experience clinical hyperglycemia. In most cases, blood glucose abnormalities can be effectively managed by lifestyle changes that include weight loss, increased exercise, and dietary modification. However, if therapeutic intervention is needed, insulin-sensitizing agents are preferred. Patients should be managed according to the American Diabetes Association guidelines [6]. The substitution of antiretroviral drugs that do promote insulin resistance with those that do not affect glucose metabolism may normalize blood glucose levels and prevent progression to diabetes mellitus, but the available evidence is inconclusive. There are no data suggesting that switching antiretroviral drugs is beneficial to patients who have impaired glucose tolerance associated with HIV infection itself or traditional risk factors.

Similar to the reports on insulin resistance, dyslipidemia has been associated with traditional risk factors, HIV infection itself, and antiretroviral drugs. It is recommended that all patients be assessed for coronary heart disease risk, and those with ≥ 2 risk factors should be further evaluated and managed according to the HIVMA and National Cholesterol Education Program guidelines [12, 38]. All patients should be encouraged to stop smoking regardless of cardiovascular risk, and hypertension and diabetes mellitus should be managed as appropriate.

Consideration should be given to switching antiretroviral therapy or using lipid-lowering therapy on an individualized basis [73, 74]. Although one should be aware of the potential for drug interactions and adverse effects from lipid-lowering therapy, its benefits may exceed the small but potential risk of virologic failure when antiretroviral therapy is modified. Results from the SMART trial indicated that patients in the CD4 cell-guided, intermittent treatment group were at increased risk for evidence of cardiac disease, and therefore, it is not recommended that antiretroviral therapy be stopped to improve lipid profiles [70].

Patient self-report of body shape changes may be sufficient for clinical practice screening for body morphology changes. Anthropometry (measurements of skin-fold thickness and circumference of the waist and hip) does not differentiate subcutaneous from visceral fat and requires training to perform. Although dual-energy X-ray absorptiometry has been used in research studies to evaluate regional body composition, it cannot distinguish subcutaneous from visceral fat but can compare limb fat with truncal fat. Computed tomography scanning at L4/5 can be used to assess visceral fat and quantitate subcutaneous fat. The body mass index assesses lean body mass but cannot determine fat distribution. None of these tools is currently recommended for clinical practice.

Poly lactic acid and calcium hydroxylapatite have been approved for treatment of facial lipoatrophy, but these interventions may provide only short-term benefit in some patients. Cosmetic surgery (eg, liposuction) may be warranted for dis-

figuring cases of lipohypertrophy. Modification of antiretroviral drug therapy (ie, substitution of another drug for stavudine or zidovudine in a patient with facial lipoatrophy) can partially reverse lipoatrophy.

The incidence of lactic acidosis in clinical practice has decreased because abacavir and tenofovir have largely replaced didanosine, stavudine, and zidovudine use in combination antiretroviral therapy. The clinical manifestations of hyperlactatemia without acidosis (normal arterial pH) are variable and nonspecific. Some patients may report fatigue, nausea, vomiting, abdominal pain, and/or diarrhea. Serum transaminase abnormalities are common, usually as a result of associated hepatic steatosis. Patients starting NRTI treatment should be made aware of the symptoms of lactic acidemia and asked to report them promptly to their health care provider. A serum venous lactate level should be determined in the case of unexplained symptoms. If the level is abnormal, the measurement should be repeated, and an arterial blood gas measurement should be performed. For patients with a serum venous lactate level of 2–5 mmol/L, close monitoring is advised. No intervention is necessary for patients with a level of <2 mmol/L. Lactic acidemia will generally resolve once treatment with the offending drug(s) is stopped [75, 76]. The safety of resuming NRTI treatment in this setting has not been clearly established but may be considered with non-thymidine analog NRTIs.

Baseline bone densitometry should be performed in postmenopausal women aged ≥ 65 years and in younger postmenopausal women with ≥ 1 additional risk factor(s) (other than being female and postmenopausal) for premature bone loss. Baseline bone densitometry should be considered in HIV-infected persons aged ≥ 50 years, especially if they have ≥ 1 risk factor(s) for premature bone loss. If the test demonstrates osteopenia or if the patient has a history of fragility or fracture, intervention with a bisphosphonate or other medical therapy should be considered. Bisphosphonates appear to be effective in improving bone density in small studies of HIV-infected patients, but the data are limited [77, 78]. A follow-up study 1 year later to monitor the response to therapy is advised. Patients should be reminded of the health benefits of regular exercise and adequate calcium and vitamin D intake. They should also be counseled about the risks of cigarette smoking and excessive alcohol consumption. Secondary causes of decreased bone density, such as hypogonadism and vitamin D deficiency, should be investigated and treated accordingly.

Routine radiographic monitoring for avascular necrosis in asymptomatic persons is not recommended, but for patients presenting with persistent hip pain who have normal standard radiologic studies, magnetic resonance imaging is the preferred method of diagnosis, and both sides should be imaged. Most patients with symptomatic avascular necrosis will ultimately require hip replacement.

IX. HOW CAN PATIENT ADHERENCE TO HIV CARE BE OPTIMIZED?

Recommendations

72. All HIV-infected patients should be provided timely access to routine and urgent primary medical care (B-II).

73. HIV care sites should make every effort to provide care in a way that is linguistically and culturally appropriate and competent (B-II).

74. HIV care sites should utilize a multidisciplinary model but identify a primary provider to each patient and support the development of trusting long-term patient-provider relationships (B-II).

75. All patients should be evaluated for depression and substance abuse, and if present, a management plan that addresses these problems should be developed and implemented in collaboration with appropriate providers (B-II).

Evidence Summary

The long-term effectiveness of antiretroviral therapy is dependent on durable suppression of viral replication. Unfortunately, not all patients achieve this goal [79, 80]. The primary reason for this failure, particularly among patients taking initial regimens, is suboptimal adherence to treatment regimens [81–83]. The Department of Health and Human Services Guidelines for Antiretroviral Therapy for Adults provides comprehensive recommendations for assisting patients with their efforts to consistently adhere to their antiretroviral regimen [2]. One of the most important predictors of adherence to medications is adherence with medical visits and engagement in care [79, 84]. Moreover, low adherence to visits and poor engagement in care has been found to be a predictor of higher mortality among those with HIV/AIDS. Specifically, patients with poor retention in care have been found to have ~50% higher mortality rate [85]. Thus, it is critically important that HIV providers and clinic sites have a strategy to effectively engage and retain patients in care.

The quality of the patient-provider relationship is often cited as one of the most important factors in a patient's engagement in care. Having a provider with whom the patient feels comfortable and can communicate effectively and frankly is key to developing this type of relationship [86, 87]. Devoting sufficient time to each patient to meet his or her needs is also quite important [88]. Ideally, the site should provide a setting in which provider accessibility and scheduling and a team approach to care make these goals achievable. A long waiting time from the call to schedule an initial appointment for HIV care until the date of the initial HIV medical visit has been shown to be one predictor of failure to engage in care [89]. Having an HIV team that includes a case manager has been frequently shown to enhance adherence to care and engagement [90].

Depression and substance abuse are highly prevalent in per-

sons living with HIV infection. These 2 comorbid conditions have been found to be tremendous barriers to consistent adherence to antiretroviral therapy and HIV care [91]. Treatment of depression can improve medication adherence, and thus, it is essential that patients with depression be identified and treated for the condition [92]. A variety of management strategies, including directly observed therapy, have been found to enable successful HIV treatment of active substance abusers [93].

As we seek to make each patient comfortable and promote his or her engagement in primary care, it is important to keep in mind that HIV/AIDS affects a diverse group of persons in terms of race/ethnicity, culture, gender, and lifestyle. Each patient should be treated as an individual, and HIV treatment sites should provide culturally competent and appropriate care to the community of patients being served. A broad range of components, from having staff of the same race, culture, or lifestyle to having art and reading material in the clinic that reflects the culture of the local community, may be useful in facilitating this goal [94–96].

PERFORMANCE MEASURES

HIV Performance Measures are in development through the American Medical Association–convened Physician Consortium for Performance Improvement, Health Resources and Services Administration, and the New York State AIDS Institute.

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