

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-aids-clinical-society.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 immunosorbent 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-naive 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 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 ultrasensitive 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 dapson, 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, ≥38.5°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 fundoscopic 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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