Hepatitis Management

HIV Management titis Management THE NEW YORK COURSE

Update on Sexually Transmitted Infections

Jeanne Marrazzo, MD, MPH

Division of Infectious Diseases University of Alabama at Birmingham School of Medicine Birmingham, Alabama

Outline

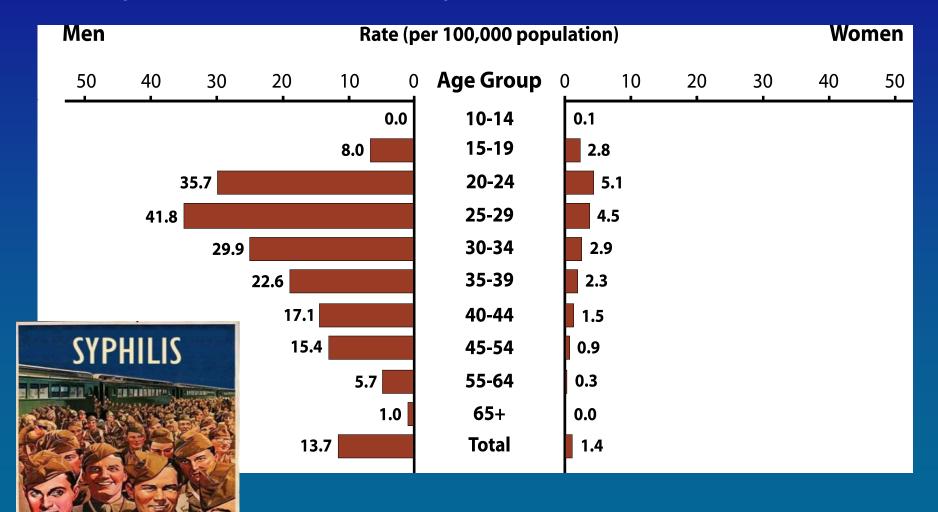
ATTACK
OF THE SYPHILIS
CURSED OF THIS, WATCH OUT!

STATING
SYPHILIS - YOU - AND YOU - AND MAYBE YOU TOO

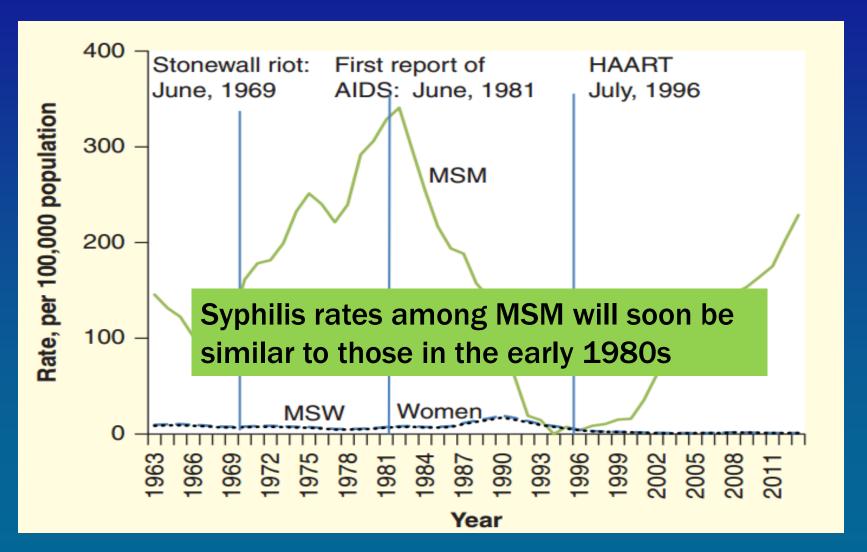
TO BE THE THIS DIRECTORY OF THE STATE OF TH

- Syphilis in all its splendor
 - Postexposure prophylaxis: a desperate measure?
- Gonorrhea treatment: few and no new options
- Chlamydia: reappearance of LGV proctitis?
- ► Vaccinate: HBV/HAV, HPV, meningococcus
- Screen: all relevant anatomic sites

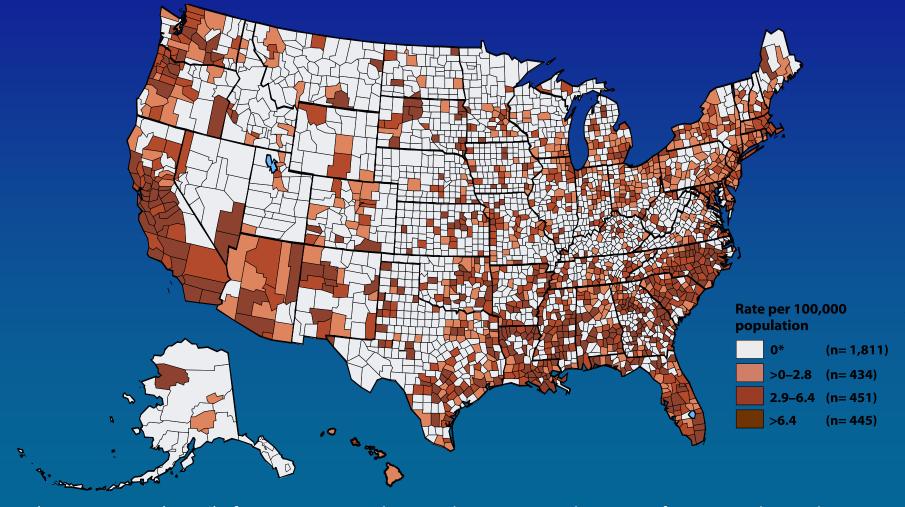
Primary and Secondary Syphilis — Rates of Reported Cases by Age Group and Sex, United States, 2015



Syphilis rates among MSM: a timeline

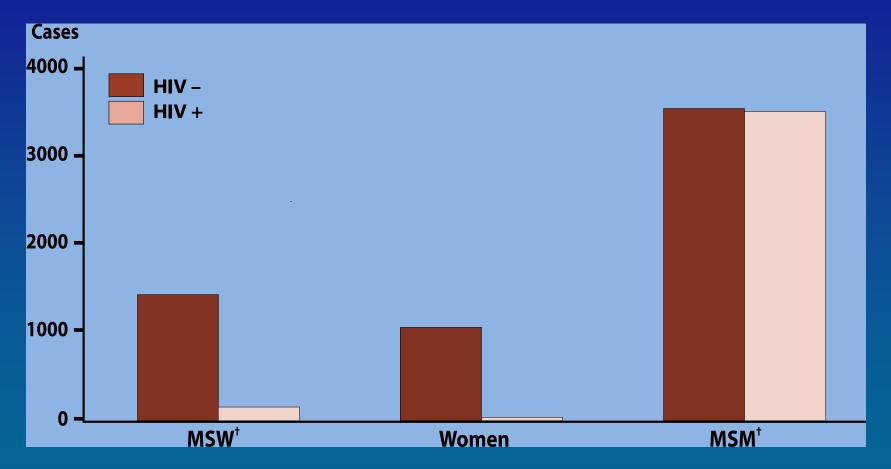


Primary and Secondary Syphilis — Rates of Reported Cases by County, United States, 2015



^{*} In 2015, 1,811 (57.7%) of 3,141 counties in the United States reported no cases of primary and secondary syphilis. Refer to the NCHHSTP Atlas for further county-level rate information: https://www.cdc.gov/nchhstp/atlas/.

Primary and Secondary Syphilis — Reported Cases by Sex, Sexual Behavior, and HIV Status, 31 States*, 2015



^{* 31} states were able to classify ≥70% of reported cases of primary and secondary syphilis as MSW †, MSM †, or women and ≥70% of cases as HIV-positive or HIV-negative during 2015.

[†] MSM = men who have sex with men; MSW = men who have sex with women only.

Ocular Syphilis — Eight Jurisdictions, United States, 2014–2015

Sara E. Oliver, MD^{1,2}; Mark Aubin³; Leah Atwell, MPH⁴; James Matthias, MPH^{4,5}; Anna Cope, PhD^{5,6}; Victoria Mobley, MD⁶; Alexandra Goode, MSc⁷; Sydney Minnerly, MA⁸; Juliet Stoltey, MD⁹; Heidi M. Bauer, MD⁹; Robin R. Hennessy, MPH^{5,10}; Dawne DiOrio, MPA^{5,11}; Robyn Neblett Fanfair, MD¹²; Thomas A. Peterman, MD⁵; Lauri Markowitz, MD²

► 388 cases MMWR 11/4/16

- ► Most among MSM with HIV
 - A few among HIV-negative persons, including heterosexual men and women
- ► Several resulted in significant sequelae, including blindness
- ▶ All should be reported within 24 h of diagnosis to Public Health

TABLE 1. Suspected ocular syphilis and total syphilis cases — eight jurisdictions, United States, 2014–2015

Jurisdiction	Suspected ocular syphilis		Total surveillance syphilis cases		% surveillance syphilis cases with suspected ocular syphilis	
	2014	2015	2014	2015	2014	2015
California*	48	60	6,238	7,824	0.77	0.77
Florida	10	32	6,030	7,154	0.17	0.45
Indiana†	_	8	· –	714	_	1.10
Maryland	10	17	1,524	1,779	0.66	0.96
New York City	14	12	5,798	6,116	0.24	0.20
North Carolina	21	42	1,799	2,435	1.20	1.70
Texas	27	16	7,337	8,400	0.37	0.19
Washington	27	44	857	1,125	3.20	3.90
Total	157	231	29,583	35,547	0.53	0.65

^{*} California does not include syphilis reports from San Francisco or Los Angeles.

[†] Indiana reviewed data from 2015 only.



MMWR Nov 4, 2016

TABLE 2. Demographic characteristics of patients with suspected ocular syphilis — eight jurisdictions, United States, 2014–2015

Characteristic	No.	(%)
Total	388	(100.0)
Male	362	(93.3)
Known MSM (among 362 males)	249	(68.8)
Race		
White	217	(55.9)
Black	81	(20.9)
Hispanic	48	(12.4)
Asian	13	(3.4)
Native Hawaiian/Pacific Islander	1	(0.3)
Other/Unknown	28	(7.2)
HIV-positive	198	(51.0)

Abbreviations: HIV = human immunodeficiency virus; MSM = men who have sex with men.

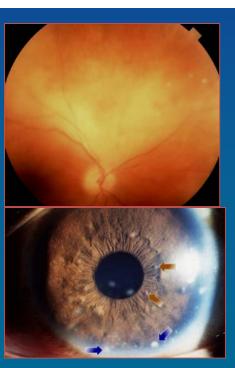


TABLE 3. Clinical characteristics, laboratory results and diagnoses for syphilis and suspected ocular syphilis — eight jurisdictions, United States, 2014–2015

Characteristic	No.	(%)
Total	388	(100.0)
Stage of syphilis		
Primary	8	(2.1)
Secondary	101	(26.0)
Early latent	79	(20.4)
Late or latent of unknown duration	193	(49.7)
Unknown	7	(1.8)
Additional symptoms of neurosyphilis	87	(22.4)
Reported ocular symptoms (among 326 wit	th symptoms)	
Blurry vision	210	(64.4)
Vision loss	107	(32.8)
Eye pain or red eye	46	(14.1)
Eye exam	158	(40.7)
Diagnosis (among 158 with documented ey	/e exam)*	
Uveitis	72	(45.6)
Retinitis	20	(12.7)
Optic neuritis	18	(11.4)
Retinal detachment	6	(3.8)
CSF analysis performed	188	(48.5)
CSF VDRL (among 174 with a documented i	result)	
Reactive	122	(70.1)
Nonreactive	52	(29.9)
Treatment		
Aqueous penicillin G IV	230	(59.3)
Other treatment	146	(37.6)
No/Unknown treatment	12	(3.1)

Abbreviations: CSF = cerebrospinal fluid; IV = intravenous; VDRL = Venereal Disease Research Laboratory test.

^{*} Can be included in multiple categories.

LP in HIV & Syphilis: Key Points

- Routine LP in HIV not recommended; base on history & examination
- CSF VDRL is insensitive (false negatives 30%-70%)
- Consider abnormality of any CSF parameter evidence for CNS involvement if serology is +, exam consistent, or known exposure
 - 1 WBC (usually lymphocytes; not specific; >5 typical, but some authors have used >20 to account for HIV-related pleiocytosis)
 - ↑ Protein
 - + VDRL
 - + FTA/TPPA: very sensitive; not specific (helpful if negative)

Syphilis Treatment

- Penicillin preferred for all stages
- Early syphilis (primary, secondary, early latent)
 - BZN PCN (L-A) single dose IM 2.4 million units
 - Do not use other injectable PCN formulations
 - Do not use azithromycin (resistance; treatment failure)
- Late latent
 - BZN PCN (L-A) IM 2.4 million units weekly x 3 doses (7.2 million u total)
- Alternatives: doxycycline, ceftriaxone



MAJOR ARTICLE





Single Dose Versus 3 Doses of Intramuscular Benzathine Penicillin for Early Syphilis in HIV: A Randomized Clinical Trial

Roberto Andrade, Maria C. Rodriguez-Barradas, 1.2 Kosuke Yasukawa, Erick Villarreal, Michael Ross, 4 and Jose A. Serpa

¹Section of Infectious Diseases, Department of Medicine, Baylor College of Medicine, and ²Section of Infectious Diseases, Department of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; ³Department of Medicine, Alpert Medical School, Brown University, Providence, Rhode Island; and ⁴Department of Family Medicine and Community Health, University of Minnesota Medical School, Minneapolis

- Open-label randomized trial enrolling 64 participants; mean CD4 388
- Serologic treatment success 12 mos.
 - 28 of 35 (80%) in single-dose regimen
 - 27 of 29 (93%) in 3-dose regimen
 - Per-protocol analysis: 93% vs 100%;
 absolute difference 7% (95% C.I. -7%,
 22%); P = 0.49
 - Not modified by CD4 count, RPR titer, syphilis stage
- Not powered to demonstrate non-inferiority

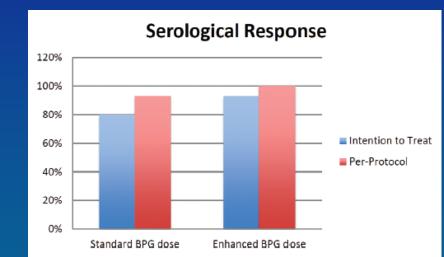


Figure 2. Intention-to-treat and per-protocol analyses of the comparison between a single dose vs 3 doses of 2.4 million units of intramuscular benzathine penicillin G (BPG) for early syphilis in human immunodeficiency virus-infected individuals. Abbreviation: BPG, benzathine penicillin G.



RESEARCH ARTICLE

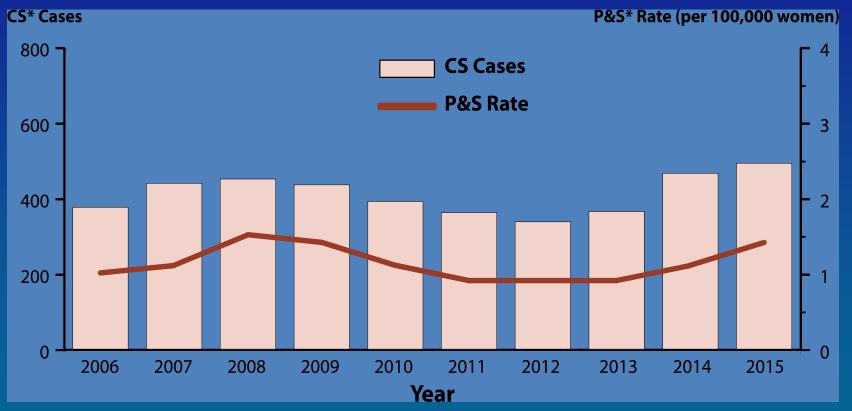
Open Access

A systematic review of syphilis serological treatment outcomes in HIV-infected and HIV-uninfected persons: rethinking the significance of serological non-responsiveness and the serofast state after therapy

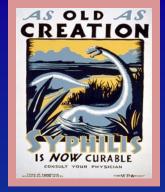
Arlene C. Seña^{1*†}, Xiao-Hui Zhang^{2†}, Trudy Li³, He-Ping Zheng², Bin Yang², Li-Gang Yang², Juan C. Salazar⁴, Myron S. Cohen¹, M. Anthony Moody^{5,6}, Justin D. Radolf^{4,7} and Joseph D. Tucker¹

- Identified 1,693 reports in the literature, reviewed 20 studies that met selection criteria.
- Median proportion of patients with serological nonresponse was 12.1% overall (interquartile range, 4.9–25.6)
- Serofast proportion estimated from 2 studies, which ranged from 35.2%–44.4
 %. Serological cure primarily associated with younger age, higher baseline nontreponemal titers, and earlier syphilis stage
- Relationship between serological cure and HIV status inconsistent; among HIV-infected patients, CD4 count and HIV viral load not associated with serologic cure

Congenital Syphilis — Reported Cases by Year of Birth and Rates of Primary and Secondary Syphilis Among Women, United States, 2006–2015



Increase in Incidence of Congenital Syphilis — United States, 2012–2014



Key points

- We are in the middle of an impressive resurgent epidemic of STI, especially syphilis, in MSM
 - Considerable number of neurologic syndromes, including auditory, facial nerve palsy, visual abnormalities
- Among these infected MSM, at least half are coinfected with HIV
- Infection is occurring nationwide, across race/ethnicities
- Congenital syphilis events are still occurring
- Early syphilis PREDICTS HIV acquisition in those not already infected with HIV

A Vicious Cycle: STDs predict future HIV Risk

Rectal GC or CT



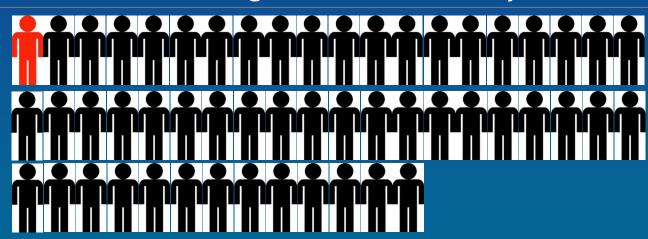
1 in 15 MSM were diagnosed with HIV within 1 year.*

Primary or secondary syphilis



1 in 18 MSM were diagnosed with HIV within 1 year. **

No rectal STD or syphilis infection



1 in 53 MSM were diagnosed with HIV within 1 year.*

*STD Clinic Patients, New York City. Pathela, CID 2013:57;

**Matched STD/HIV Surveillance Data, New York City. Pathela, CID 2015:61

Syphilis Predicts HIV Incidence Among Men and Transgender Women Who Have Sex With Men in a Preexposure Prophylaxis Trial

Marc M. Solomon,^{1,2} Kenneth H. Mayer,^{4,5} David V. Glidden,² Albert Y. Liu,³ Vanessa M. McMahan,¹ Juan V. Guanira,⁶ Suwat Chariyalertsak,⁷ Telmo Fernandez,⁸ and Robert M. Grant^{1,2}; for the iPrEx Study Team^a

- Of 2499 men, 360 (14.4%) RPR+ at screening; 333 (92.5%) confirmed
- Syphilis incidence during trial: 7.3 cases/100 p-y
 - No difference between study arms
- ► HIV incidence varied by incident syphilis
 - 2.8 cases /100 p-y for none vs 8.0
 - Hazard ratio 2.6 (95% CI, 1.6–4.4; P <.001)

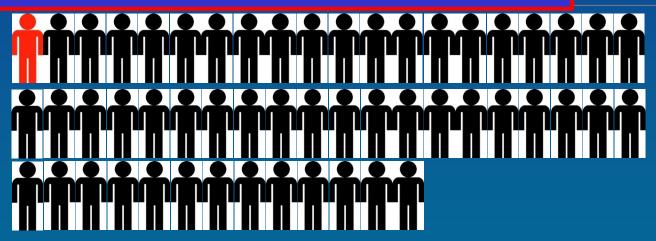
A Vicious Cycle: STDs predict future HIV Risk

Rectal GC or CT

Primary or secondary syphilis

No rectal STD or syphilis infection

So what do we do while we wait for a vaccine?



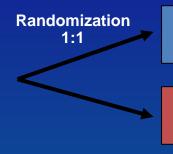
1 in 53 MSM were diagnosed with HIV within 1 year.*



On-Demand Post-Exposure Prophylaxis With Doxycycline for MSM: Follow on to IPERGAY

Open-Label Study (n = 232)

HIV-negative high-risk MSM enrolled in the open-label IPERGAY extension study No contraindication to doxycycline



On Demand PEP doxycycline 200 mg (~24 hours after sex, up to 72 hours)

No PEP

Visits: baseline and every 2 months
Serologic assays for HIV and syphilis
PCR assays for chlamydia and gonorrhea
Urine, anal, and throat samples collected

- Baseline characteristics:
 - Median age: 38-39 years
 - White: 95%
 - History of PEP use in IPERGAY: 19%.
 - Use of psychoactive drugs (ecstasy, crack, cocaine, crystal, speed,

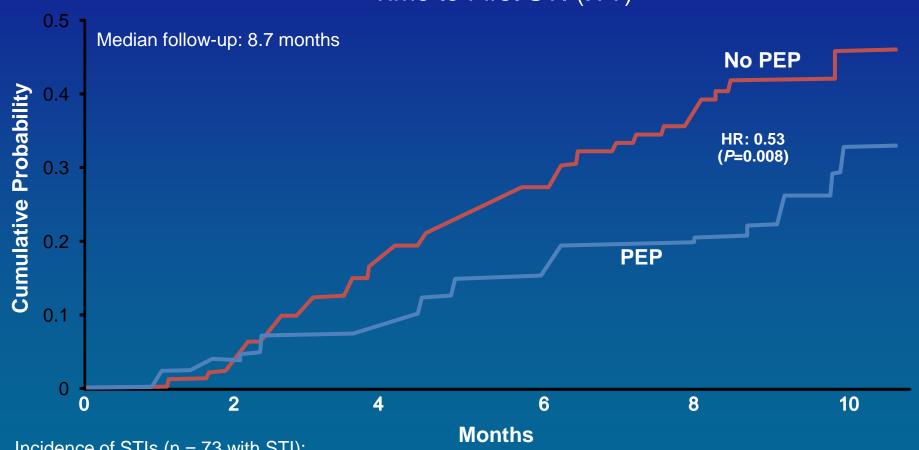
GHB/GBL): 42%

- Circumcised: 21%
- Prior gonorrhea, chlamydia, syphilis infection: 16%
- Number of sexual acts in prior 4 weeks: 10



Time to First STI With On-Demand PEP With Doxycycline for MSM

Time to First STI (ITT)



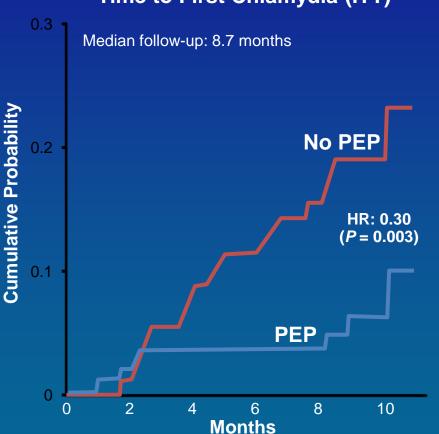
Incidence of STIs (n = 73 with STI): No PEP (n = 45): 70/100 person-years. PEP (n = 28): 38/100 person-years).

Molina J-M, et al. 24th CROI. Seattle, 2017 Abstract 91LB.



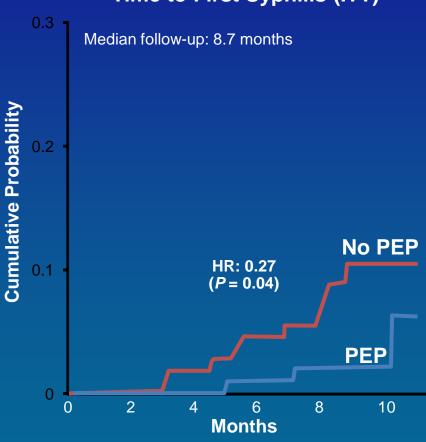
Time to First Chlamydia and Syphilis with On-Demand PEP With Doxycycline for MSM





Incidence of chlamydia (n = 28): No PEP (n = 21): 29/100 person-years. PEP (n = 7): 9/100 person-years).

Time to First Syphilis (ITT)



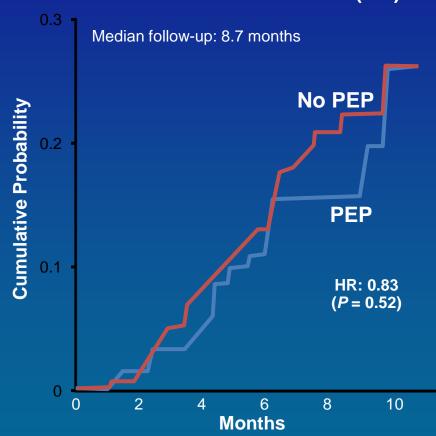
Incidence of syphilis (n = 13): No PEP (n = 10): 13/100 person-years. PEP (n = 3): 4/100 person-years).



Time to First Gonorrhea with On-Demand PEP With Doxycycline for MSM

- No effect on gonorrhea incidence
- Number sites of gonorrhea infection (PEP vs no PEP)
 - Anus: 11 vs 19
 - Throat: 15 vs 12
 - Urine: 1 vs 7

Time to First Gonorrhea (ITT)



Incidence of gonorrhea (n = 47): No PEP (n = 25): 35/100 person-years. PEP (n = 22): 29/100 person-years).

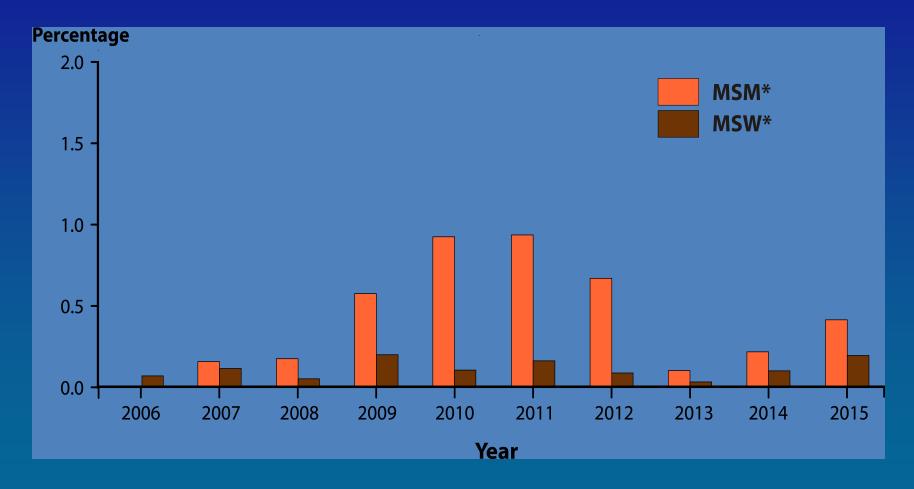


Conclusions

- ▶ PEP reduced overall incidence of bacterial STI by 47% in MSM on PrEP (8.7 months of follow-up)
- No effect on gonorrhea, but strong reduction in chlamydia and syphilis
- No evidence of sexual risk compensation
- Analysis of antibiotic resistance is pending
- Long-term benefit of PEP is not yet known
- Antibiotic prophylaxis for STIs still not recommended
- More research is needed



N. gonorrhoeae — Percentage of Urethral Isolates with Elevated Ceftriaxone MICs (≥0.125 µg/ml) by Reported Sex of Sex Partner, Gonococcal Isolate Surveillance Project, 2006–2015



^{*} MSM = Gay, bisexual, and other men who have sex with men (collectively referred to as MSM); MSW = Men who have sex with women only.

2015 CDC STD Treatment Guidelines: Gonorrhea

Urogenital & pharyngeal infection:

Ceftriaxone 250 mg injection x 1

PLUS:

Azithromycin 2 g orally x 1

Doxycycline removed as second agent: >25% isolates are resistant

- If CTX not available & urogenital infection
 - Cefixime 400 mg + azithromycin 1 g
- If severe cephalosporin allergy
 - Gentamicin 240 mg IM + azithromycin 1 g

Cluster of Lymphogranuloma Venereum Cases Among Men Who Have Sex with Men — Michigan, August 2015–April 2016

Alex de Voux, PhD^{1, 2}; James B. Kent, MS³;
Kathryn Macomber, MPH³; Karen Krzanowski, MA, MPH⁴;
Dawn Jackson⁴; Tayneata Starr⁴; Sandra Johnson⁴;
Deborah Richmond, MSN⁵; Lawrence R. Crane, MD⁵;
Jonathan Cohn, MD⁵; Christopher Finch⁵; Jevon McFadden, MD⁶;
Allan Pillay, PhD²; Cheng Chen, PhD²; Laurie Anderson²;
Ellen N. Kersh, PhD²

BOX. Case definition of lymphogranuloma venereum (LGV) included in Michigan Health Alert Network sent out on October 22, 2015

Suspected case

- A clinically compatible illness in a person with one or more signs or symptoms compatible with LGV (proctocolitis, inguinal/femoral lymphadenopathy, or genital or rectal ulcers), and
- A sexual partner of a person meeting the probable or confirmed case definition.

Probable case, either or both of the following:

- A patient meeting the suspected case definition, in whom other causes of LGV-like symptoms (e.g., syphilis, gonorrhea, and herpes simplex virus) have been ruled out, and a positive *Chlamydia trachomatis* from culture or nucleic acid amplification test (NAAT) from a body site associated with symptoms.
- Sexual partner of a person meeting the probable or confirmed case definition and a positive C. trachomatis from culture or NAAT.

Confirmed case

 A probable case with laboratory confirmation for C. trachomatis genotypes L1, L2, or L3 by genetic analysis (LGV-specific polymerase chain reaction or sequencing).



- 38 cases reported to CDC
- All in HIV+ MSM
- Median CD4 483
- Suspect in severe or persistent proctitis, especially if lymphadenopathy is present
- Treat with doxycyline 100 mg bid x3 weeks
- Report to local health department

"STI" Immunizations in HIV

- ► Hepatitis A/B
- ► Either 9vHPV or 4vHPV vaccination through age 26 years if not vaccinated previously
- ► Meningococcal vaccine
 - MenACWY-D (Menactra) or MenACWY-CRM (Menveo)

TABLE 1. Evidence of increased risk for meningococcal disease among HIV-infected persons compared with HIV-uninfected persons — seven study populations, 1996–2013

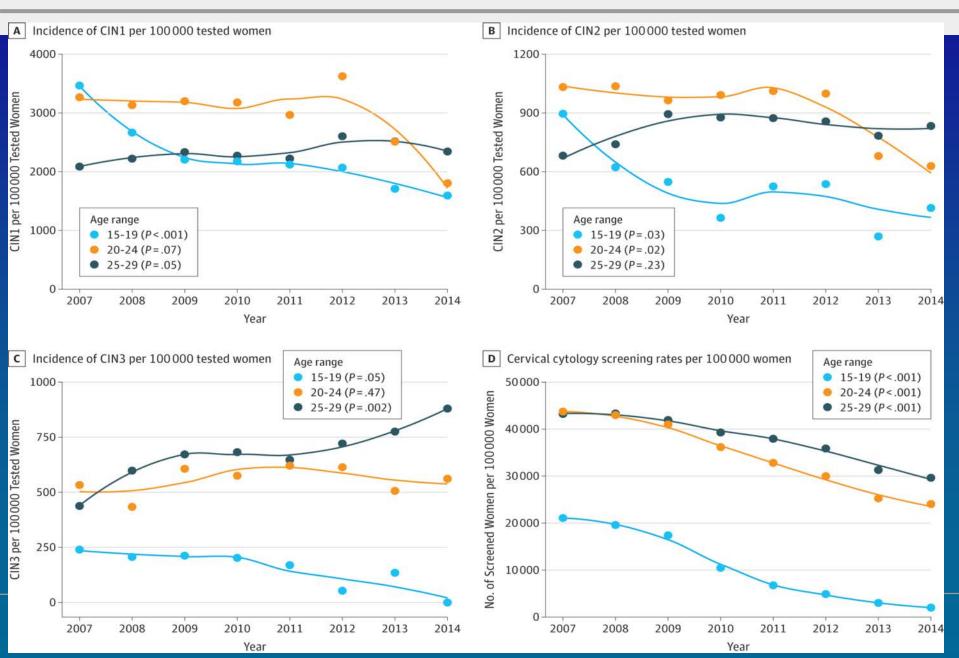
Period	Study site		No. of cases*	Increase in meningococcal disease rate among HIV-infected compared with HIV-uninfected persons	
renou	Study site	Age group	No. or cases	niv-unimiected persons	Serogroups
1996-1999	Australia†	All ages	60	5-fold	B, C
1990-2000	London [§]	All ages	2,900	14-fold	B, C
1988-1993	Atlanta, Georgia [¶]	18-45 years	132	24-fold	B, C, Y
2003-2007	South Africa**	All ages	504	11-fold	A, B, C, W, Y
2000-2008	United States ABCs ^{††}	25-64 years	491	13-fold	B, C, W, Y
2000-2011	New York City ⁶⁵	15-64 years	265	10-fold	C, Y
2011-2013	United Kingdom ^{¶¶}	All ages	2,353	5-fold	A, B, C, W, Y

Abbreviations: ABCs = Active Bacterial Core surveillance; HIV = human immunodeficiency virus.

Recommendations for Use of Meningococcal Conjugate Vaccines in HIV-Infected Persons — Advisory Committee on Immunization Practices, 2016

From: Population-Based Incidence Rates of Cervical Intraepithelial Neoplasia in the Human Papillomavirus Vaccine Era

JAMA Oncol. Published online September 29, 2016. doi:10.1001/jamaoncol.2016.3609



STD Screening for MSM

HIV
 Syphilis
 Urethral GC and CT
 Rectal GC and CT (if RAI)
 Pharyngeal GC (if oral sex)
 HSV-2 serology (consider)
 Hepatitis B (HBsAg, freq not specified)
 Hepatitis C (HIV+ MSM, at least annually)

Anal Cancer in HIV+ MSM: Data insufficient to recommend routine screening, some centers perform anal Pap and HRA

* At least annually, more frequent (3-6 months) if at high risk (multiple/anonymous partners, drug use, high-risk partners) & at relevant anatomic sites

CDC 2015 STD Treatment Guidelines

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Serologic Screening for Genital Herpes Infection US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

IMPORTANCE Genital herpes is a prevalent sexually transmitted infection in the United States, occurring in almost 1 in 6 persons aged 14 to 49 years. Infection is caused by 2 subtypes of the herpes simplex virus (HSV), HSV-1 and HSV-2. Antiviral medications may provide symptomatic relief from outbreaks but do not cure HSV infection. Neonatal herpes infection, while uncommon, can result in substantial morbidity and mortality.

OBJECTIVE To update the 2005 US Preventive Services Task Force (USPSTF) recommendation on screening for genital herpes.

EVIDENCE REVIEW The USPSTF reviewed the evidence on the accuracy, benefits, and harms of serologic screening for HSV-2 infection in asymptomatic persons, including those who are pregnant, as well as the effectiveness and harms of preventive medications and behavioral counseling interventions to reduce future symptomatic episodes and transmission to others.

FINDINGS Based on the natural history of HSV infection, its epidemiology, and the available evidence on the accuracy of serologic screening tests, the USPSTF concluded that the harms outweigh the benefits of serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant.

CONCLUSIONS AND RECOMMENDATION The USPSTF recommends against routine serologic screening for genital HSV infection in asymptomatic adolescents and adults, including those who are pregnant. (D recommendation)

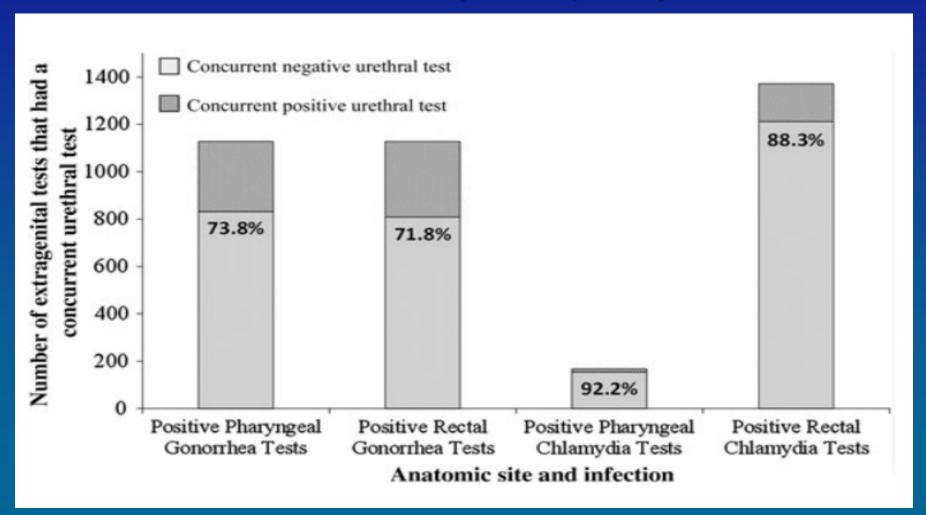
JAMA. 2016;316(23):2525-2530. doi:10.1001/jama.2016.16776

- Editorial page 2493
- Author Audio Interview
- CME Quiz at jamanetworkcme.com and CME Questions page 2546

Author/Group Information: The US Preventive Services Task Force (USPSTF) members are listed at the end of this article.

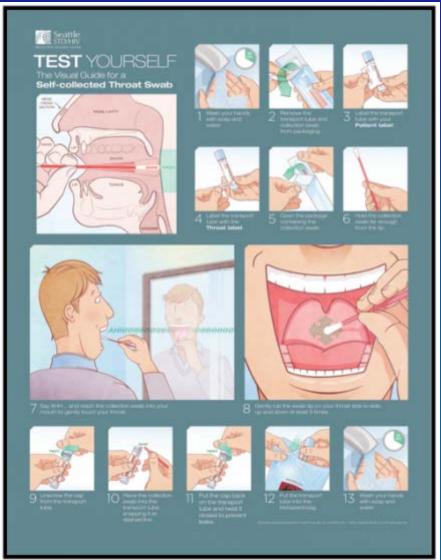
Corresponding Author: Kirsten Bibbins-Domingo, PhD, MD, MAS (chair@uspstf.net).

High proportion of Extragenital CT/GC associated with negative urine test, STD Surveillance Network (n=21,994)



UW PTC STI Self-Testing Program





Take-Home Messages

- Screen, appropriately!
- Rescreen for chlamydial and gonococcal infections 3 to 6 months after initial +
- Be aware of antibiotic-resistant GC
- Syphilis: it's not going away. Recognize neuroinvasive disease
- Hepatitis C
- Sexual health
 - Vaccinate for HPV
 - Continue Pap screening
 - Prevention messages

Wrap It Up Alaska Condoms



HIV Management Hepatitis Management THE NEW YORK COURSE

