Intersection of Clinical and Public Health Practice: STI Management in the HIV-Infected Person

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Disclosures & Off-Label Uses

DISCLOSURES

- None

OFF- LABEL USES

- NAATs for extragenital gonorrhea and chlamydia testing
Primary Care Guidelines for the Management of Persons Infected With HIV: 2013 Update by the HIV Medicine Association of the Infectious Diseases Society of America

At the end of this presentation, participants should be able to:

- Recognize critical components of the history and physical examination of HIV-infected patients that impact STI screening and management
- Describe recommended approaches to screen for syphilis, gonorrhea, chlamydia, trichomoniasis, and herpes
- Identify appropriate antimicrobial treatment regimens for gonorrhea
- Formulate an approach to preventing HPV infections among HIV-infected persons
A 30 year old man who was recently diagnosed with HIV (CD4 650 cells/mm³, HIV RNA 55,000 copies/ml) presents for his first clinic appointment. He is asymptomatic.

Which of the following screening tests should be performed at initiation of care and how often should the screening test be repeated thereafter?

A. NAATs test for rectal chlamydia at initiation and yearly thereafter
B. NAATs test for pharyngeal gonorrhea at initiation and yearly thereafter
C. Serological screening test for syphilis at initiation and yearly thereafter
D. All of the above
E. None of the above
Probability of Asymptomatic STIs

- Urethra
- Rectum
- Pharynx
- Urethra
- Rectum
- Cervix
- Any Herpes

Men
Women

Risk Assessment: The H&P

- Screening for all STIs is risk-based, so accurate information is critical
  - Obtain a sexual history in an open non-judgmental manner
- A sexual history should include:
  - Current and past sexual practices (number of partners, gender of partners, **exposure sites**, condom and contraceptive use, past STD history, etc.)
  - Use of drugs (ETOH, poppers, methamphetamines, etc.) with sex
  - Risks and status of partners
    - *Do you have oral sex? Do you use a condom when you have oral sex?*
    - *versus*
    - *The last time you put your mouth on your partner’s penis, did you use a condom? Do you use a condom most times you do that?*
- A physical examination should include:
  - Pelvic examination in women
  - Anogenital examination in both men and women
  - Careful skin/mucus membrane examination
Screening
Chlamydia, gonorrhea, trichomoniasis, syphilis & herpes
## What is the best specimen type to screen for genital gonorrhea and chlamydia?

### WOMEN
- **A vaginal swab** for NAATs testing is preferred
- Endocervical swabs and urine are acceptable alternate specimen types for NAATs testing
- Endocervical swabs are the only acceptable specimen type for gonorrhea cultures

### MEN
- **First-catch urine** for NAATs testing is preferred
- Urethral swabs are acceptable alternate specimen types for NAATs testing
- Urethral swabs are the only acceptable specimen type for gonorrhea cultures

*MMWR Recomm Rep. 2011;60(1):18*
Why screen for extragenital gonorrhea (GC) and chlamydia (CT) infections?

- The majority of cases of pharyngeal and rectal GC and CT are asymptomatic
- Up to 65% of cases of GC and 50% of cases of CT among MSM may be missed if genital-only testing were performed.  
  
  *Sex Transm Dis. 2008;35(10):845*  
  *Clin Infect Dis. 2005;41(1):67*

- In women, 10% of CT and 31% of GC infections would have been missed if extragenital testing were not done  
  
  *Sex Transm Dis. 2011;38(9):783*

- Rectal and pharyngeal infections are of public health significance  
  
  *Clin Infect Dis. 2009;49(12):1793*
Extragenital GC & CT diagnostics

- Sensitivity of culture <50% to detect rectal and pharyngeal GC vs. >90% sensitivity for NAATs (this can vary by NAAT type)
  
  *Sex Transm Infect.* 2009;85(3):182-6

- The CDC recommends that NAATs be used to detect these extragenital infections
  
  *MMWR Recomm Rep.* 2011;60(1):18

- Although none of the NAATs are FDA cleared to use with extragenital specimens, most large laboratories have established performance specifications to validate the tests and satisfy compliance with Clinical Laboratory Improvement Amendments
GC & CT screening recommendations

- Annual chlamydia screening for all women aged ≤25 years, for all sexually active MSM, and for high-risk women aged >25 years is recommended.

- Annual screening for gonorrhea is recommended for all sexually active MSM, and targeted screening is recommended for high-risk women (e.g., women with previous gonorrhea infection, other STIs, new or multiple sex partners, and inconsistent condom use; those who engage in commercial sex work and drug use; women in certain demographic groups; and those living in communities with a high prevalence of disease).

- Anorectal screening for gonorrhea chlamydia should be performed on the basis of report of receptive anal intercourse. A test for pharyngeal gonorrhea should be considered if the patient reports a history of receptive oral sex. Testing for oropharyngeal chlamydia is not routinely recommended because its prevalence is generally low.

- More frequent STI screening (i.e., at 3- to 6-month intervals) is indicated for MSM who have multiple or anonymous partners. In addition, MSM who have sex in conjunction with illicit drug use (particularly methamphetamine use) or whose sex partners participate in these activities should be screened more frequently.
Screening for trichomoniasis

For sexually active women who are HIV-positive, screening for trichomoniasis at entry into care with subsequent screening performed at least annually is recommended based on the reported prevalence of *T. vaginalis*, the effect of treatment at reducing vaginal HIV shedding, and the potential complications of upper-genital-tract infections among women who are left untreated

- 85% of women with trichomoniasis are asymptomatic
- Prevalence of trichomoniasis **increases with age** and lifetime number of sexual partners among African American women

Diagnostics

- Wet mount sensitivity is estimated at 51-65% (time-dependent)
- Culture sensitivity is 75-95%
- The rapid antigen test is 82-95% sensitive
- The APTIMA *Trichomonas vaginalis* Assay (Hologic Gen-Probe, San Diego, CA) was FDA-cleared in 2011 for use with urine, endocervical and vaginal swabs and Thin Prep Pap; it is 95-100% sensitive
- No FDA-cleared NAATs for men; some laboratories have verified the performance characteristics of NAATs through a validation process for male urine specimens or penile meatal swabs.

**Clin Infect Dis. 2007 Nov 15;45(10):1319-26**
**MMWR Recomm Rep. 2011 ;60(1):18**
**APHL: Laboratory Diagnosis of Trichomonas, August 2013**
Retesting to detect repeat infections

- Reinfection with GC, CT and trichomoniasis is common in both men and women
  
  *Sex Transm Inf. 2007;83:304-9*  
  *Sex Transm Dis. 2009; 36:478-89*

- All persons treated for GC, CT, and all women treated for trichomoniasis should be re-tested in three months because of high reinfection rates regardless of whether their partner(s) was/were treated
  
  *MMWR Recomm Rep. 2011 ;60(1):18*
Screening for syphilis: Serological tests

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<tr>
<th>Clinical stages of syphilis</th>
<th>Primary</th>
<th>Secondary</th>
<th>Latent (asymptomatic)</th>
<th>Tertiary</th>
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<tr>
<td>Primary lesion</td>
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<td>Secondary lesion</td>
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<th>Serological Tests For Syphilis</th>
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<td><strong>Non-treponemal Tests</strong></td>
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<td>Complement fixation tests</td>
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<td>- Wasserman reaction</td>
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<td>Flocculation Tests</td>
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<td>- Rapid Plasma Reagin (RPR)</td>
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www.cdc.gov
Screening for syphilis: Serological algorithms

Traditional Algorithm
- RPR/VDRL
  - No further testing
  - Treponemal Test

Reverse Sequence Algorithm
- Treponemal Immunoassay (EIA/CIA)
  - No further testing
  - RPR/VDRL
    - No further testing
    - Confirmatory Treponemal Test
Screening for syphilis: Interpretation of RSA

CIA

CIA (+)

RPR titer (Quantitative)

RPR (+)

Syphilis

RPR (-)

FTA

FTA (+)

Syphilis

FTA (-)

Syphilis Unlikely

CIA (-)

No serological evidence of infection with Treponema pallidum. Incubating or early primary syphilis cannot be excluded.

Report

Report

Evaluate clinically, determine if treated for syphilis in the past, assess risk of infection, and administer therapy according to CDC’s STD Treatment Guidelines if not previously treated.

Report

Syphilis positive:
  a) early syphilis
  b) past treated syphilis
  c) past untreated syphilis

Report

Syphilis unlikely. Clinician may repeat testing in several weeks if patient is at risk for syphilis.
There was a 34% increase in overall syphilis diagnoses from 2010 to 2011 and a 29% increase among MSM.
20% had repeat syphilis

Cooley LA, Pearl ML, Flynn C et al. Low Viral Suppression and High HIV Diagnosis Rate Among Men Who Have Sex with Men (MSM) with Syphilis — Baltimore, Maryland. Poster session presented at: Conference on Retroviruses and Opportunistic Infections; 2014 March 3-6; Boston, MA.
Time Between Two Most Recent Syphilis Diagnoses Among MSM in Baltimore City and Baltimore County with Repeat Syphilis (n = 92)

- 26% had a repeat diagnosis in 12 months or less
- 40% had a repeat diagnosis >1 - 2 yr
- 21% had a repeat diagnosis >2 - 3 yr
- 12% had a repeat diagnosis >3 - 4 yr
- 1% had a repeat diagnosis >4 - 5 yr

Cooley LA, Pearl ML, Flynn C et al. Low Viral Suppression and High HIV Diagnosis Rate Among Men Who Have Sex with Men (MSM) with Syphilis — Baltimore, Maryland. Poster session presented at: Conference on Retroviruses and Opportunistic Infections; 2014 March 3-6; Boston, MA.
A higher proportion of MSM with repeat syphilis are HIV-infected.
Every 3-month screenings among sexually active MSM at high risk for infection is very high-yield and cost efficient. Contact tracing is high-yield but costly. Screening in jails also appeared to be cost efficient.


Mathematical models suggest that changes in behaviors and condom use, particularly short-term ones (and even long-term ones if they were only modest) would not impact syphilis rates and that frequent screening among very high risk individuals is probably what would have the most impact.

Gray RT, et al. STD 2011;38: 1151-1158

About 30% of high-risk MSM were not rescreened in the 6 months following therapy for syphilis.

Marcus JL, et al. STD 2011; 38:24-29
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.
Screening tests for HSV

- Use Glycoprotein G-based type-specific assays (gG1 & gG2)
  - If gG2 is positive, patient has genital herpes
  - If gG1 is positive, patient either has oral herpes or genital herpes
  - Do NOT use crude antigen-based serological assays
  - Do NOT use IgM serological assays

REMEMBER:
- Antibodies may be negative in early primary infection
- The specificity of these tests is high but not perfect. As such, if the pre-test probability of having herpes is low, a positive test result has a high likelihood of being a false positive

CID 2002; 35 (S2): S173-S182
Routine screening for HSV is not recommended. Counseling infected persons and their sex partners may help reduce the risk of HSV sexual and perinatal transmission.

Type-specific HSV serologic assays may be performed in the following patients:

- Patients with recurrent genital symptoms, or atypical symptoms in whom HSV cultures have been negative
- Patients who have been given a clinical diagnosis of genital herpes without laboratory confirmation
- Patients who have a partner with genital herpes
- Consider in persons presenting for an STD evaluation, persons HIV+, and MSM
Case 1

A 30 year old man who was recently diagnosed with HIV (CD4 650 cells/mm³, HIV RNA 55,000 copies/ml) presents for his first clinic appointment. He is asymptomatic.

Which of the following screening tests should be performed at initiation of care and how often should the screening test be repeated thereafter?

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MANAGEMENT

Gonorrhea and Syphilis Therapy & HPV Prevention
A 24 year old HIV-infected woman presents with endocervical discharge. Gram’s stain of endocervical fluid reveals intracellular Gram-negative diplococci. Swab specimen for nucleic acid amplification testing (NAAT) for gonorrhea and chlamydia is obtained. The patient is treated with single dose cefixime 400 mg orally and azithromycin 1g orally.

The patient returns 1 week later with persistent symptoms. She denies intervening sexual exposures. Results of NAATs obtained 1 week earlier confirm the diagnosis of gonorrhea. Gram’s stain at current visit still demonstrates intracellular Gram-negative diplococci.

In addition to obtaining a specimen for culture, what do the most current CDC STD Treatment Guidelines recommend for therapy?
Case II

A. Azithromycin 2 g oral
B. Cefixime 800 mg oral + azithromycin 1 g oral
C. Ceftriaxone 250 mg IM + azithromycin 1 g oral
D. Ceftriaxone 250 mg IM + azithromycin 2 g oral
E. Ciprofloxacin 500 mg oral

*IM=intramuscular
Updated CDC GC treatment recommendations

- **First-Line**
  - Ceftriaxone 250 mg IM X1 + Azithromycin 1g PO X 1 or Doxycycline 100mg PO BID X 7 days
  - Azithromycin is preferred over doxycycline but both are acceptable
  - Use dual therapy even if *C. trachomatis* is ruled out

- **Alternate**
  - Cefixime 400mg PO X1 + Azithromycin 1g PO X1 or Doxycycline 100mg PO BID X 7 days
  - Azithromycin 2g PO X 1 (single therapy single dose)
    - Azithromycin 2g PO X1 is the only regimen currently available to treat a patient who has an allergy to cephalosporins

*MMWR 2012 ;61(31):590-4*
**Treatment failure with alternate regimens**

- Culture relevant clinical sites and perform antimicrobial susceptibility testing using disk diffusion, E-test, or agar dilution.
- Treat with intramuscular ceftriaxone 250 mg + azithromycin 2g orally as a single dose.
- Evaluate sex partners from the preceding 60 days with culture from all exposed sites and treat with above enhanced regimen.
- The laboratory should retain the isolate for possible further testing.

*MMWR 2012;61(31):590-4*
What about patients with penicillin or cephalosporin allergies?

- The cross reactivity between penicillins and cephalosporins has been found to be low (<2.5%).
  - The risk is highest with first generation cephalosporins
  - The risk of penicillin cross-reactivity between most second-generation and all third- and fourth- generation cephalosporins is negligible
- If severe allergy to PCN or cephalosporins treat with azithromycin 2g PO x 1
- Oral PID treatment in that setting is more complicated

*Clinical and Experimental Allergy. 2001; 31: 438-443*
Recent randomized trial of:

- Injectable gentamicin (5mg/kg) + oral azithromycin (2g)
  - 100% effectiveness
- Oral gemifloxacin (320mg) + oral azithromycin (2g)
  - 99.5% effectiveness

Many trial participants reported adverse effects from the drugs, mostly gastrointestinal issues.
Suspected Treatment Failure: Evaluating and treating sex partners

- If you suspect treatment failure, assure treatment for both patient and sex partner(s)

- In Maryland, local health departments can help assure that sex partners of patients with suspected treatment failure get treated
All Maryland providers are obligated by law to report all gonococcal infections and treatment information to local or State health officials.

For information on disease reporting, go to: http://phpa.dhmh.maryland.gov/SitePages/what-to-report.aspx
A 32 year old HIV-infected gay man presents for a routine follow-up appointment. He is doing well on his cART regimen. He has a history of several sexually transmitted infections. He has been monogamous with his current partner for the last three months. A sample is obtained for anorectal cytology and the results demonstrate ASC-US (atypical squamous cell-undetermined significance). Which of the following interventions is most appropriate at this time?

A. Perform HPV type-specific testing  
B. Repeat cytology in 3 to 6 months  
C. Repeat cytology in one year  
D. Refer for high-resolution anoscopy
MSM, women with a history of receptive anal intercourse or abnormal cervical Pap test results, and all HIV-infected persons with genital warts should have anal Pap tests (*weak recommendation, moderate quality evidence*).

- If anal cytologic screening (i.e., anal Pap smears) is performed and indicates abnormal findings, then high-resolution anoscopy should be performed with biopsy of abnormal areas and appropriate therapy based on biopsy results.

HPV vaccination: Although efficacy data in HIV-infected patients are lacking, the ACIP has recommended that vaccination be given to all HIV-infected males (quadrivalent vaccine only) and females in a 3-dose series at 11 or 12 years of age, and for those 13–26 years of age if not previously vaccinated.

- One small trial in HIV-infected boys and girls found the vaccine to be safe and immunogenic as did a study in HIV-infected men.

*JAIDS* 2010; 55:197–204

*J Infect Dis* 2010; 202:1246–53
A 30 year old HIV-infected man presents with a rash covering his abdomen and proximal extremities and low grade fevers. He denies headaches and his neurological examination is normal. His RPR is reactive at a titer of 1:2056 and his FTA-ABS is reactive.

Which of the following treatment regimens is most appropriate?

A. Azithromycin 2g orally  
B. Doxycycline 100mg orally twice daily for 14 days  
C. Benzathine PCN G 2.4 MU IM X1  
D. Benzathine PCN G 2.4 MU IM X3
579 HIV-infected participants with early syphilis from 7 hospitals in Taiwan between 2007 and 2012.

- BPG 2.4 MU X1 (N=302) vs. BPG 2.4 MU X3 (N=277)
- 70.9% serological responses in BPG X1 group vs. 76.7% in BPG X3 group
Resources in Maryland

Maryland Department of Health and Mental Hygiene
Prevention and Health Promotion Administration

- Center for Sexually Transmitted Infection Prevention
  - [http://phpa.dhmh.maryland.gov/OIDPCS/CSTIP/SitePages/cstip-for-healthcare-providers.aspx](http://phpa.dhmh.maryland.gov/OIDPCS/CSTIP/SitePages/cstip-for-healthcare-providers.aspx)

- Disease Reporting in Maryland
  - [http://phpa.dhmh.maryland.gov/SitePages/reportable-diseases.aspx](http://phpa.dhmh.maryland.gov/SitePages/reportable-diseases.aspx)
National Resources

- HIVMA Guidelines
  - http://www.idsociety.org/Organism/#ManagementofHIVInfectedPersons

- CDC 2010 STD Treatment Guidelines

- HRSA Performance Measures