Management of STIs in HIV-Infected and At-Risk Patients

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*No commercial disclosures or conflicts of interest

Disclosures

• In the past 12 months, Dr. Hsu has had no relevant financial interests or other relationships with manufacturer(s) of product(s) or provider(s) of service(s) that will be discussed in this presentation

• This presentation will include discussion of pharmaceuticals or devices that have not been approved by the FDA

NEWS FLASH: May 23, 2019
Cepheid and Hologic have now received FDA approval for extragenital (oropharyngeal and rectal swab) gonorrhea and chlamydia NAAT

Objectives

• Discuss shifts in STI/HIV epidemiology
  – MSM
  – Women

• Review STI screening and treatment in HIV-infected and at-risk patients
  – Focus upon newer diagnostics
  – Focus upon STIs where treatment or follow-up in HIV-infected patients is different than HIV-non-infected patients
  – Review common problems: persistent urethritis and recurrent BV
Syphilis and Gonorrhea Over Time


Decreases in syphilis cases were due to BOTH behavior change AND to deaths occurring in HIV-syphilis co-infected individuals.

Trichomoniasis and HIV

- HIV-infected women
  - Prevalence of TV infection ranging up to 53% (Cu-Uvin 2002, Miller 2008)
  - Higher incidence of TV compared with HIV-uninfected women (Mullins 2013)
  - Associated with PID (Moodley 2002)
  - Treatment associated with significant decreases in genital tract viral load and vaginal HIV viral shedding (Kissinger 2009, Anderson 2012)
**Why Bother Screening?**
*Many Infections in MSM are Asymptomatic*

**Rectal Infections**
- Chlamydia: 86% (n=316)
- Gonorrhea: 84% (n=264)

**Urethral Infections**
- Chlamydia: 42% (n=315)
- Gonorrhea: 10% (n=364)

*Kent, CK et al, Clin Infect Dis July 2005*

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**Population-level Control of STIs**

Basic Reproductive Rate

\[ R_0 = T \cdot C \cdot D \]

Screening and **RAPID APPROPRIATE** treatment decrease D (duration) of carriage and therefore transmission

*Anderson & May, 1980s*

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**STI Screening in HIV+ Patients: FIRST VISIT**

- **All patients**
  - Ask about STD symptoms
  - Syphilis: serology
  - Chlamydia, Gonorrhea: NAAT
  - Hepatitis A/B/C status
- **Patients who report receptive anal sex**
  - Rectal gonorrhea
  - Rectal chlamydia
- **Patients who report receptive oral sex**
  - Pharyngeal gonorrhea

*CDC/HRSA/NIH/IDSA Recommendations*
**STI Screening in HIV+ Patients:**

**FIRST VISIT**

- **Women**
  - **Chlamydia:** routinely test all sexually active women especially those <25 years
  - **Gonorrhea:** routinely test all sexually active women especially those <25 years
  - **Trichomonas:** NAAT
  - **HPV:** start Pap smear screening within 1 year of sexual debut, but no later than age 21 years
  - **Pregnancy:** ask women of childbearing age if pregnancy suspected or missed periods

*Identify possible current pregnancy, interest in future pregnancy, or sexual activity without reliable contraception

CDC/HRSA/NIH/IDSA Recommendations

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**STI Screening in HIV+ Patients:**

**SUBSEQUENT VISITS**

- Periodic retesting for all sexually active patients
- Annually for all, more frequent (every 3-6 months) depending on risk:
  - Multiple or anonymous sex partners
  - Unprotected vaginal or anal intercourse with partner with negative or unknown HIV status
  - Sex or needle-sharing partner with above risks
  - "Life changes" associated with increased risk
  - Because re-infection rates are high, patients with chlamydia, gonorrhea, or trichomoniasis should be re-tested 3 months after treatment

CDC/HRSA/NIH/IDSA Recommendations

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**Re-screening for STIs in those previously infected, reaches those at HIGHEST STI RISK**
Results: Cases of Confirmed Chlamydia, Gonorrhea, and Infectious Syphilis, Massachusetts 2014-2016

OF 13-65 year olds in Massachusetts (N = 4,847,510):
 • 1% (49,142) were reported with bacterial STI
 • 0.1% (6,999) accounted for 28% of all reported bacterial STIs
 • 56% of high-volume repeaters sought care in >1 clinical system

HOW GOOD IS YOUR CLINIC AT CALLING PEOPLE BACK FOR THE 3 MONTH TEST OF REINFECTION?
EXPEDITE PARTNER THERAPY

Population-level Control of STIs

Basic Reproductive Rate

\[ R_0 = \text{Transmissibility} \cdot \text{No. of Sexual Contacts} \cdot \text{Duration of Infectiousness} \]

Screening and RAPID APPROPRIATE treatment decrease D (duration) of carriage and therefore transmission

But if sexual contacts are not treated, index cases may become re-infected!

CDC EPT guidelines

“PDPT can prevent reinfection of index case and has been associated with a higher likelihood of partner notification...”

www.cdc.gov/STD/EPT
Syphilis, Trichomoniasis, and the Triple Dip

STI DIAGNOSTIC TESTING

Syphilis Serology

**Non-treponemal:** VDRL & RPR
- Antibody to cardiolipin-lecithin-cholesterol antigen; not specific to *T. pallidum*
- Quantitative: titer measured
- Used to follow treatment response (always use same test)

**Treponemal:** TP-PA, FTA-ABS, EIA/CIA
- Qualitative
- Confirmatory

Syphilis Screening Paradigm

**EMERGENT NEW...**

Treponemal tests (e.g., EIA, CIA, MBIA)
- SPECIFIC TO TP
- QUALITATIVE
- REACTIVITY PERSISTS OVER LIFETIME
- REACTIVITY DECLINES WITH TIME

Non-treponemal tests (e.g., RPR, VDRL)
- NON-SPECIFIC ANTIBODY TO LIPOIDAL ANTIGENS
- QUANTITATIVE
- REACTIVITY DECLINES WITH TIME
Why switch to EIA/CIA?

180 tests per hour, no manual pipetting

Newer Treponemal Screening Tests

- Enzyme immunoassays (EIA)
  - Trep-Sure IgM/IgG, CAPTIA Syphilis G (Trinity Biotech)
    - wild type treponemal antigens
- Chemiluminescence immunoassays (CIA)
  - LIAISON IgM/IgG (Diasorin) – recombinant TpN17
- Microbead immunoassays (MBIA)
  - BioPlex 2200 Syphilis IgM and IgG (BioRad) – recombinant TpN15, TpN17, TpN47
  - AtheNA Multi-Lyte T. pallidum IgG (Zeus Scientific) – recombinant T. pallidum antigen p17kDa

Sena et al., CID 2010
Park et al., CID 2018

CDC Recommendations

- All reactive EIA/CIAs should be reflexed to a quantitative non-treponemal test (e.g. RPR, VDRL)
  - Confirm reactive EIA/CIA
  - Detect active infection
- Discordant specimens (e.g. EIA+/RPR-) should be confirmed with a 2nd treponemal test
- Confirmatory treponemal test should ideally be similarly sensitive and more specific than EIA/CIA
  - TP-PA recommended
  - FTA-ABS test not recommended (lower specificity than other treponemal tests and probably lower sensitivity; also requires trained personnel and a dedicated fluorescence microscope)
- Results of all 3 tests (EIA, RPR, TP-PA) should be reported simultaneously to provider

Radolf JD et al. MMWR, 2011
Park et al., CID 2018
Causes of False Positive Syphilis Testing

- Non-treponemal tests
  - Viral infections
    - Infectious mononucleosis
    - Hepatitis
    - Varicella
    - Measles
    - Lymphoma
    - TB
  - Malignancies
  - Malaria
  - Endocarditis
  - Connective tissue disease
  - Pregnancy
  - Abuse of injection drugs

- Treponemal tests
  - Other spirochetal illnesses (e.g., Lyme, leptospirosis, rat-bite fever, relapsing fever, yaws, pinta)
  - But note, VDRL is non-reactive in Lyme!!

AAP Red Book, 2015

Trichomoniasis: Diagnosis

Nucleic Acid Amplification Tests (Vaginal swab +/- other samples)
- AmpliVue (Quidel)
- APTIMA (Hologic)
- MAX, ProbeTec ET (BD)
- Solana (Quidel)
- Xpert (Cepheid)

Sens/Spec: 88-100%, 97-99.9%

Point-of-care tests
- OSOM trichomonas rapid antigen test (Genzyme)
- Affirm VP III (BD)

OSOM Sens/Spec: 67-100%, 92-100%
Affirm VP Sens/Spec: 89-93%, ~100%

Saline Wet Mount
- Motile trichomons
- pH >4.5
- Whiff test may be +

Sens/Spec: 36-70%, ~100%

Culture
- Diamond's
- InPouch TV, BioMed Diagnostics

Sens/Spec: 75-95%, 100%

Miller & Nyirjesy, Curr Infect Dis Rep 2011
Schwebke, JCM 2011
APHL, Advances in Laboratory Detection of T. vaginalis (Updated) 2016
Newer Testing Options for Trich

- Microscopy is inferior to new options, including
  - Rapid antigen testing (OSOM)
  - Nucleic acid amplification testing
    - APTIMA TMA Trichomonas vaginalis assay
    - BD ProbeTec TV Q Amplified DNA assay
    - May use same specimen types as used with gc/chl NAATs (i.e. vaginal swab, endocervical swab, urine)

Table 3. Differences in test sensitivity stratified by the presence or absence of vaginal symptoms.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sens</th>
<th>Spec</th>
</tr>
</thead>
<tbody>
<tr>
<td>APTIMA TMA</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>OSOM</td>
<td>90%</td>
<td>100%</td>
</tr>
<tr>
<td>Culture</td>
<td>83%</td>
<td>100%</td>
</tr>
<tr>
<td>Wet prep</td>
<td>56%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Slide courtesy of Marrazzo, IDSA 2011

Proportion of CT and GC infections MISSED among 3398 asymptomatic MSM if screening only urine/urethral sites, San Francisco, 2008-2009

Marcus et al, STD Oct 2011; 38: 922-4

Chlamydia and Gonorrhea
Nucleic Acid Amplification Testing

NEWS FLASH: May 23, 2019
Cepheid and Hologic have now received FDA approval for extragenital (oropharyngeal and rectal swab) gonorrhea and chlamydia NAAT preferred testing method over culture
Don’t forget the q3mth “triple dip” for at-risk MSM

- HIV/Syphilis/ HepC* Serologies
- Pharyngeal GC NAAT**
- Urine GC/CT NAAT
- Rectal GC/CT NAAT**

*In HIV-coinfected individuals, screen Hep C at least annually
**Off-label use - not FDA-approved for testing at extragenital sites, but many reference labs have validated the assay for use

STI TREATMENT AND FOLLOW-UP

Treatment of STI in HIV-infected persons

- CDC STD Treatment Guidelines highlight specific regimens for HIV-infected persons when appropriate

- In general, treatment guidelines are similar between HIV-infected and non-infected patients
  - Bacterial STIs: no treatment differences
  - Viral/protozoan STIs: treat with higher doses and/or longer

www.cdc.gov/std/treatment
Have you consulted on a case of ocular syphilis within the past year?

1. Yes 24%
2. No 76%

Ocular Syphilis

Manifestations:
- Conjunctivitis, scleritis, and episcleritis
- Uveitis: anterior and/or posterior
- Elevated intraocular pressure
- Chorioretinitis, retinitis
- Vasculitis

Symptoms:
- Redness
- Eye pain
- Floaters
- Flashing lights
- Visual acuity loss
- Blindness

Diagnosis:
- Ophthalmologic exam
- Serologies: RPR (if negative, rule out prozone, VDRL, treponemal tests
- Lumbar puncture

Ocular Syphilis Specimen Protocol:

- CDC study of strain types associated with ocular syphilis
- U. of Washington lab to do strain typing
- Specimens: Need to be pre-antibiotic (untreated syphilis- ocular manifestations)
  - Whole blood 3 ml purple top (EDTA) tube
  - Primary lesions and moist Secondary Lesions (squeeze/swab lesion with sterile Dacron swab- place swab in freezer tube)
  - CSF 2-3 ml
  - Ocular fluid (aqueous or vitreous)
  - Freeze specimens immediately at -80°C
    (-20C to -70C OK if -80C not available)
    Specimens need to be shipped on dry ice
- CDC contact for detailed instructions
  - Google "CDC Ocular Syphilis" for latest information
**Syphilis: Evaluation of CNS in the HIV-Infected Patient**

- CNS invasion occurs in early syphilis regardless of HIV or neurologic symptoms (protein, pleocytosis)
  - Clinical significance unknown (HIV+/-)
  - Clinical and CSF consistent with neurosyphilis associated with RPR ≥ 1:32 and/or CD4 ≤ 350
    - Criteria likely sensitive, but non-specific (many negative LPs)
    - Unless neurologic symptoms present, CSF exam has not been associated with improved clinical outcomes

**Indications for LP**

1. Serologic evidence of syphilis + neurologic symptoms
   - Includes isolated ophthalmic syphilis (e.g. uveitis, neuroretinitis, optic neuritis)
2. Lack of 4-fold decline serologic decline in non-specific treponemal testing by ...
   - 6-12 mths after tx for early syphilis (1st, 2nd, early latent)
   - 12-24 mths after tx for late latent syphilis
   - In 13 HIV-infected individuals without 4-fold decline, followed median of 287 days after tx, 4 (31%) had CSF abnormalities consistent with axon neurosyphilis – thus recommendation to tap these individuals (Ohanem et al., CID 2009)
   - However, titers may decline more slowly in HIV-infected (Ohanem et al., STI 2007), so clinicians “may elect” to follow for full 12 mths for early or 24 mths for late latent before labeling as treatment failures
3. ≤ 350 CD4 cell count & ≥ 1:32 RPR titer increases likelihood of identifying those with neurosyphilis, BUT ...
   - 2/3 studies included those with neuro sx who already warranted LP (Libois et al., STD 2007; Marra et al., JID 2004), 3rd study which included also HIV+ patients was retrospective (Ohanem et al., CID 2009), none of the 3 studies addressed long-term benefits of LP
   - Again, unless neuro sx present, no association was seen with improved clinical outcomes

18 yo HIV-infected MSM well-controlled on ART, with rash of secondary syphilis. What treatment regimen do you recommend?

1. **2.4 MU IM benzathine pen G**
   - x 1 dose
   - 44%

2. **2.4 MU IM benzathine pen G**
   - x 3 doses
   - 53%

3. Other
   - 3%
**SYPHILIS - TREATMENT**

**PENICILLIN**

Primary, secondary, and early latent syphilis

Benzathine PCN 2.4 million units IM x 1 dose

(Jarisch-Herxheimer reaction can occur during tx of secondary syphilis)

PCN allergy – If compliance can’t be assured, desensitize, treat with PCN

(instructions in 2010 STD Treatment guidelines)

– Doxycycline or tetracycline for 14 days

– Ceftriaxone 1 g daily for 10-14 days

– Azithromycin 2 g, one dose (but failures/resistance reported – therefore do not use with MSM or pregnant women)

Late latent disease

Benzathine PCN 2.4 million units IM once a week x 3 doses

Neurologic/ocular syphilis

LP, ophthalmic exam, and formal ophthalmologic eval indicated if related clinical symptoms exist (cognitive dysfunction, motor or sensory deficits, ophthalmic or auditory symptoms, cranial nerve palsies, or meningitis)

Aqueous crystalline penicillin G 18–24 million units per day for 10–14 days

Consider benzathine PCN 2.4 million units IM once a week for up to 3 weeks as chaser

Follow titers q3 mths for a year

**SYPHILIS – FOLLOW-UP IN HIV+**

• Quantitative non-treponemal serologic tests should be repeated MORE FREQUENTLY
  
  – 3, 6, 9, 12, and 24 months after primary and secondary syphilis
  
  – 6, 12, 18, and 24 months after latent syphilis

• Neurosyphilis - LP should be repeated q5mths if CSF pleocytosis was present initially, until cell count normalizes
  
  – If not decreased after 6 mths or if CSF not normal after 2 yrs, re-tx should be considered
  
  – Changes in CSF-VDRL or CSF protein occur more slowly, persistent abnormalities may be less clinically important

• Re-treat for syphilis (and re-consider neurosyphilis) if
  
  – Titer fails to decline at least 4-fold within 6-12 months of tx for early syphilis, or 12-24 months of tx for late syphilis
  
  – New signs or symptoms of syphilis appear

**Treatment: First Clinical HSV Episode**

• Acyclovir 400 mg PO tid
• Acyclovir 200 mg PO 5x per day
• Valacyclovir* 1 g PO bid
• Famciclovir** 250 mg PO tid

  for 7-10 days or until clinical resolution

*Not licensed for pre-pubertal

**Not licensed for <18 yrs
### Treatment: Episodic Recurrent HSV
- Acyclovir 400 mg PO tid
- Acyclovir 800 mg PO bid
- Valacyclovir* 1 g PO qd bid
- Famciclovir** 425 mg PO bid

All for 5 – 10 days, OR
- Valacyclovir* 500 mg PO bid for 3 days, OR
- Acyclovir 800 mg PO tid for 2 days, OR
- Famciclovir** 1 g PO bid for 1 day
- Famciclovir** 500 mg PO x 1 dose then 250 mg PO bid x 2 days

Start during prodrome or within 1 day of lesion onset

*not licensed for pre-pubertal
**not licensed for <18 yrs

### Treatment: Daily Suppressive HSV Therapy
- Efficacious in decreasing clinical manifestations of HSV in HIV-infected persons
- Regimens for persons with HIV
  - Acyclovir 400 - 800 mg PO bid to tid
  - Valacyclovir* 500 mg PO bid
  - Famciclovir** 500 mg PO bid

Discuss need to continue therapy annually with patient

*not licensed for pre-pubertal
**not licensed for <18 yrs

### Trichomoniasis Treatment
- Recommended regimens
  - Metronidazole 2 g PO x 1 dose
  - Tindazol 2 g PO x 1 dose
- Alternative regimen
  - Metronidazole 500 mg PO bid x 7 days
- Pregnancy:
  - Metronidazole 2 g orally in a single dose
    - No evidence of teratogenicity (pregnancy category B)
    - Tindazol pregnancy category C, not recommended
- HIV-infected
  - Metronidazole 500 mg PO bid x 7 days
    - More effective than single-dose therapy

Pregnancy Category C. do NOT use!
Avoid EtOH x 72 hrs after tx
If breastfeeding, consult guidelines
Safe at all stages of pregnancy
Avoid EtOH x 24 hrs after tx
If breastfeeding, consult guidelines

2015 CDC STD Treatment Guidelines
Trichomonas Treatment in HIV

- 270 women enrolled (New Orleans, Houston, Jackson; HIV-infected, positive for TV by culture)
- Randomized to either MTZ 2 g PO x 1 or 500 mg PO bid x 7 days
- 255 women evaluated for test of cure (~1 mth)
- 152 women negative or didn’t return at TOC were eval. at ~3 mths

<table>
<thead>
<tr>
<th></th>
<th>TV+ rate overall, %</th>
<th>7-day dose, %</th>
<th>Single dose, %</th>
<th>RR (95% CI)</th>
<th>P</th>
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<tr>
<td>TOC visit (~1 mth)</td>
<td>12.5</td>
<td>8.5</td>
<td>16.8</td>
<td>0.50</td>
<td>0.045</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(0.25, 1.00)</td>
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<tr>
<td>3 month visit</td>
<td>17.8</td>
<td>11.0</td>
<td>24.1</td>
<td>0.46</td>
<td>0.03</td>
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<td></td>
<td>(0.21, 0.98)</td>
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Secondary analysis: lack of single dose treatment efficacy found only among women with asymptomatic BV

Kissinger et al., JAMA 2010

Conclusions

- STIs are on the increase
- Routine, FREQUENT STI screening and treatment in HIV-infected patients is critical for
  - individual patient benefit
  - reduction of HIV transmission and acquisition
  - reduction of circulating STI within this population
- Newer STI diagnostics include:
  - automated syphilis treponemal antibody testing
  - FDA-approved NAATs for trichomoniasis and M. genitalium
- STI treatment in HIV-infected patients only differs from non-HIV-infected patients for viral and protozoan STIs

MMWR

- Harmony with USPSTF screening guidelines on gonorrhea/chlamydia in adolescents
- New hepatitis C screening recommendations for HIV+ MSM
- New information on clinical management of transgender men and women
CDC STD Treatment Guidelines Development
- Evidence-based on principal outcomes of STD therapy
  1. Microbiologic eradication
  2. Alleviation of signs & sx
  3. Prevention of sequelae
  4. Prevention of transmission
- Recommended regimens preferred over alternative regimens
- Alphabetized unless there is a priority of choice
- Reviewed April 2013; published 2015
- www.cdc.gov/std/treatment
  - Pocket guides, teaching slides, charts, app
  Language in yellow highlighted boxes reflects changes between 2010 and 2015 guidelines

Want to know more about STDs?
There’s an app for that.

CDC STD Treatment Guidelines App for Apple and Android
Available now, FREE!
(accept no competitors)
Search “STD Treatment” in App store

STD Clinical Consultation Network
STDCCN – NEW!!!
- Provides STD clinical consultation services within 1-5 business days, depending on urgency, to healthcare providers nationally
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- Seven Self-Study Modules
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