Learning Objectives

After attending this presentation, participants will be able to:

- Recognize clinical manifestations of syphilis and other common sexually transmitted infections (STIs)
- Diagnose and treat STIs appropriately
- Screen for STIs based on risk assessment and sexual history
- Prescribe preexposure prophylaxis (PrEP) to men who have sex with men (MSM) and who have syphilis and rectal gonorrhea (GC)

Outline of Talk

- Syphilis
  - Diagnostic updates, LP headaches
- GC Treatment
- STI prevention, including HPV vaccine
- PrEP & STIs
  - New challenges & opportunities
Rates of Primary & Secondary Syphilis (per 100,000) in the United States, 1941-2014

- Two-thirds of cases in MSM, many HIV+
- 7 times higher rates among African-Americans

Early Syphilis Incidence per 100,000 Among MSM by HIV Status, King County, WA 1997-2014

- In 2013, 2.3% of all HIV+ MSM were diagnosed with early syphilis
- Syphilis rate in HIV+ MSM was >9x higher than in HIV- MSM

Overview: Syphilis Issues

- Syphilis in HIV+ continues to increase: Importance of screening & recognition of clinical manifestations
- New syphilis serologic issues
  - Reversal of the screening and confirmatory test order
  - Titer responses
- Syphilis management dilemmas
  - How much penicillin
  - Use of azithromycin
  - When to LP
  - Neurosyphilis diagnosis and follow-up of treated cases
Clinical Challenges: Syphilis & HIV

- Even in cities with syphilis outbreaks, individual providers see few cases
- Syphilis manifestations are protean & easily misdiagnosed, particularly rash in HIV+ persons on HAART
- Need to maintain high degree of clinical suspicion and routinely perform RPR serologies in asymptomatic persons
- Follow titers for 6 – 12 months instead of 6 months for primary and secondary syphilis
- Titers may persist at higher levels than previously thought

Primary syphilis chancre

Titer 1:4, healing

Titer 1:8, inflamed due to empiric treatment with imiquimod

Cutaneous Manifestations of Secondary Syphilis

* May be widespread and florid or very subtle
* Involves palms & soles in 60%
* Usually not pruritic or vesicular
* Differential dx of rash in secondary syphilis:
  - Rash associated with ART, tinea versicolor, pityriasis rosea, generalized scabies, fixed drug eruption, erythema multiforme, psoriasis

- nunca
- nunca
Most syphilis is detected through serologic screening

<table>
<thead>
<tr>
<th>Treponemal tests* (i.e., EIA*, CLIA)</th>
<th>Non-treponemal tests (i.e., RPR, VDRL**)</th>
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<tbody>
<tr>
<td>Specific to T. Pallidum</td>
<td>Non-specific to T. Pallidum</td>
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<tr>
<td>Qualitative</td>
<td>Quantitative</td>
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<tr>
<td>Reactivity persists over lifetime</td>
<td>Reactivity declines with time</td>
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<tr>
<td>Treponemal tests* can be used for screening but if positive, need quantitative reflex RPR/VDRL for clinical management</td>
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<tr>
<td>Highly automated, no titers, less costly</td>
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<tr>
<td>False-positive EIA can occur, especially in low prevalence populations</td>
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*FDA approved treponemal tests: Captia, Trep-Check, Trep-Sure, Liaison

Latent Syphilis

Divided into two stages for treatment purposes

- Early latent syphilis: <1yr duration
  - Negative syphilis serology in the past year
  - Known contact to an early case of syphilis
  - Good history of typical signs/symptoms in the past year
  - 4-fold increase in titers in past year
  - Reactive serologies in person whose only exposure occurred in the past year
- Late latent syphilis: >1yr duration
- Latent syphilis of unknown duration


**“To LP or not to LP?”:**

CSF Exam in Latent Syphilis

- Neurologic or ophthalmic symptoms/signs
- Evidence of tertiary disease (aortitis, gumma)
- Treatment failure
- HIV infection with late latent or latent of unknown duration and neurologic symptoms
- CSF exam may be considered in HIV+ with syphilis of any stage and CD4 count ≤ 350 and RPR titer ≥ 1:32
- Normalization of serum RPR predicts normalization of CSF parameters

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**Syphilis Treatment**

Primary, Secondary & Early Latent

Recommended regimen for adults:
- Benzathine penicillin G 2.4 million units IM, single dose
- No enhanced efficacy of additional doses of benzathine PCN, amoxicillin or other antibiotics

Alternatives (non-pregnant penicillin-allergic adults):
- Doxycycline 100 mg po bid x 2 weeks
- Tetracycline 500 mg po qid x 2 weeks
- Ceftriaxone 1 g IV or IM qd x 10-14 d
- Azithromycin 2 g po in a single dose (use with caution and not in MSM or pregnant women)

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**Case**

- Latino MSM seen in Oral Medicine clinic, complaining of sore tongue
- Thought to be HIV- by history (5 yrs since last HIV-negative test)
- Labs: HIV+, CD4 125
- 2nd visit at Urgent Care clinic, noted to have punched out lesion on palm
- What is your differential diagnosis?
- What testing should be done?
Differential Diagnosis

- Hand foot mouth disease
- Erythema multiforme
- Behcet’s
- Secondary syphilis
- Aphthous ulcer
- Histoplasmosis

Summary of Case

- VDRL 1:128, MHA-TP + (took 3 visits before syphilis was considered)
- Stage: secondary syphilis in HIV+ man with low CD4
- LP not mandatory, but some experts would recommend
  - Higher risk of relapse with low CD4
  - However, pt had no neurologic signs/symptoms
  - Serologic follow-up required; LP if titers don’t decline

Ocular syphilis case

29 HIV+ MSM (lost to follow up, not on ARVs, CD4 214, VL 41K in 2011) presented with:
- Progressive vision loss: L eye > R eye; sx began 3 months earlier w/ L eye, now progressive; floaters; L paracentral scotoma.
- Bilateral hands and feet paresthesias, skin on palms/soles peeled off; arthralgias
- Resolved diffuse, pururitic rash on torso
- 40 # weight loss, weakness now bed bound x 7 weeks, 6 weeks of diarrhea
- “OH YEAH, my husband, who is also here to see you today, has similar symptoms.”
Ocular syphilis findings

- Tachycardic, cachectic (BMI 14.9) with scattered raised purple nodules, palmar and plantar erythema
- Ocular: Conjunctiva moderately injected. Fundi can't be visualized 2/2 fogging of lens. Visual acuity: sees colors and basic shapes only.
- Neuro: A0x3, CN2-12 intact. Notable LUE weakness, unable to stand 2/2 weakness. Reflexes intact. + paresthesias of BL UE/LE

Ophthalmology Exam:
- Chronic bilateral anterior uveitis, intermediate uveitis and panuveitis.
- Focal R retinal detachment on R, L nasal and temporal retinal detachment
- Posterior synechiae in both eyes with iris bombe

Ocular syphilis lab findings

- Seru RPR: 1:1024 (T pallidum IgG Reactive)
- LP: WBC 318 (30% PMN, 58% L, 12% M) Glucose 13, protein 124.
- PCR: T. pallidum
- CSF VDRL: 1:4 (+), FTA: Reactive
- HIV labs: CD4 64 (8%), VL 107,800

Hospital course

- IV PCN G for 2 week course; Jarisch-Herxheimer reaction
- Initiated elvitegravir/cobicistat/emtricitabine, sulfamethoxazole/trimethoprim, azithromycin,
- Ocular drops: prednisilone, atropine, erythromycin Post Hospitalization Follow Up:
  - CD4: 134 (11%) & HIV VL <40
  - Rash resolved; 12 kilogram weight gain
  - Subjective significant improvement in vision
  - Ophtho: improved visual acuity & decreased inflammation

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- Ophtho: improved visual acuity & decreased inflammation
Ocular syphilis

- 5 cases of ocular syphilis in King County: 4 HIV+, all MSM
  - All presented with vision loss; + RPR, LP studies consistent with neurosyphilis
  - All treated with aqueous crystalline PCN G or procaine PCN G and probenecid
  - Several other cases have been identified in San Francisco, CA

30 years of epidemiologic data show synergistic relationship between HSV-2 & HIV

- HSV reactivation increases HIV susceptibility & infectiousness
  (as well as potentially accelerating HIV disease progression)

HSV-2 increases HIV susceptibility

- **Epidemiologic Data**
  - Prevalent HSV-2 infection increase HIV acquisition 2-3 fold
  - Higher risk of HIV acquisition with incident HSV-2 (RR ~6)

- **Biologic Plausibility**
  - HSV-2 causes macro- & microscopic ulcerations
  - HSV-2 reactivation is frequent: 20% of days HSV PCR+ in HIV-negative persons (Mark JID 2009)
  - Persistent genital submucosal inflammation for weeks in spite of clinical response to acyclovir (Zha Science 2009)
Protean manifestations of Genital Herpes in HIV-negative persons

- Asymptomatic deep vulvar lesion
- Primary anogenital HSV-1 in gay man
- HSV-2 fissure mis-diagnosed as candida
- Recurrent gluteal HSV-2

HSV-2 & HIV: Increased infectiousness & HIV disease progression

- ACV plus mono or dual NRTIs reduced mortality (Ionniadis JID 1998)
- HSV-2 reactivation among HIV positive persons is high (PCR+ >30% of days)
- Extensive, long-lasting lesions if CD4 <200
- Increased plasma & genital HIV during asymptomatic HSV reactivation
- Mechanisms: HSV proteins upregulate HIV replication & pro-inflammatory cytokines

Summary of HIV/HSV Intervention Trials

- Suppressive ACV 400 mg bid did not prevent HSV-2 acquisition; likely because of persistent inflammation (Celum Lancet 2007, Watson Jones NEJM 2007)
- Acyclovir 400 mg bid did not prevent HIV transmission in spite of significantly reduced GUD & plasma HIV levels (Celum NEJM 2010)
- Acyclovir 400 mg bid modestly slowed progression of HIV disease in HIV/HSV-2 + persons with CD4>250 (Lingappa Lancet 2010)
- Need a genital herpes vaccine!
  - Progress in therapeutic HSV vaccines
  - Need prophylactic HSV vaccine candidates
What is old with a new twist: Gonorrhea

- Antibiotic resistance and treatment issues
- Diagnostic testing: urine-based NAAT work well, but don’t identify antibiotic resistance
  - Obtain culture if suspicious
- Routine annual screening of sites exposed (urethra, pharynx, rectum); more if risky
- Re-testing after treatment

2015 CDC STD Treatment Guidelines: Uncomplicated Gonorrhea Infection

**Recommended:**
- Ceftriaxone 250 mg injection x 1
- Azithromycin 1g orally x 1

**Alternatives:**
- Cefixime 400mg orally plus Azithromycin
  *Also for heterosexual expedited partner therapy. NOT for MSM or pharyngeal GC.
  Doxycycline removed as second agent

Gonorrhea – Treatment Issues

- Limited options in cephalosporin-allergic patients:
  - Spectinomycin is no longer manufactured
  - CDC recommends desensitization
  - Could be a special case to consider azithromycin, but
    - Requires 2 grams; GI tolerance issues
    - Resistance to azithro is increasing and treatment failures have been seen
  - If fluoroquinolones are the only option, obtain culture if possible prior to treatment to document FQ sensitivity; if not possible, obtain test-of-cure (3-5 days if culture, 3 weeks if NAAT)
PrEP & STIs

- Do STIs modulate the efficacy of PrEP?
- Can PrEP reduce the incidence of STIs?
- Are STIs helpful as a marker of recent risk for targeting PrEP?
- Are incident STIs useful as a marker of ‘risk compensation’?
- Can PrEP programs reduce STI burden through screening & treatment?

Do STIs modulate efficacy of PrEP?

- Similar PrEP efficacy among persons with STIs from RCTs
  - Syphilis incidence of 7.3/100 p-yr in iPrEx and no difference in PrEP among those with syphilis or not (Solomon CID 2014)
  - No difference in PrEP efficacy among those with STIs in Partners PrEP (Jumane AIDS 2013), including BV
- High PrEP effectiveness from open label PrEP projects
  - PROUD in UK: 73% with baseline STI & 86% effectiveness of PrEP (McCormack Lancet 2015)
  - US MSM PrEP Demo study: 90/100 p-yr STI incidence & 0.43/100 p-yr HIV incidence (Liu JAMA Int Med 2015)

STIs occur in persons using PrEP

PROUD Study, UK
N=544
STIs in the 12 months prior to enrollment

But the population who needs PrEP has high STI rates — and STI rates have been rising in countries prior to PrEP (McCormack, Lancet 2016)
STIs occur in persons using PrEP

Kaiser-Permanente, San Francisco, USA
N=657
12-month cumulative STI percentages

- STI rates were high, but no HIV occurred, in one large PrEP program from the US (Volk, Clin Infect Dis 2015)

STIs in IPERGAY:
Placebo-controlled & open label phases

<table>
<thead>
<tr>
<th>STI</th>
<th>Double-Blind</th>
<th>Open-Label</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Median FU: 9.3 months</td>
<td>Median FU: 18.4 months</td>
</tr>
<tr>
<td></td>
<td>Nb Pt (%)</td>
<td>Nb Cases</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>81 (20)</td>
<td>114</td>
</tr>
<tr>
<td>Gonorrhea</td>
<td>88 (22)</td>
<td>123</td>
</tr>
<tr>
<td>Syphilis</td>
<td>39 (10)</td>
<td>45</td>
</tr>
<tr>
<td>HCV</td>
<td>5 (1)</td>
<td>5</td>
</tr>
<tr>
<td>All STIs</td>
<td>147 (37)</td>
<td>287</td>
</tr>
</tbody>
</table>

Incidence rate of first STI:
35.2 vs 40.6 per 100 PY in the double-blinded and OLE phases (Molina AIDS 2016)

Can PrEP reduce incidence of STIs?

- Tenofovir has in vitro anti-HSV-2 activity; EC_{90} is high so likely need high adherence to see effect (Andrei Cell Host Microbe 2011)
- Partners PrEP: Oral PrEP reduced HSV-2 acquisition by 31%
  - 35% efficacy in the subset with known HSV-2+ partners (Celum Annals Int Med 2014)
- iPrEx: No reduction in HSV-2 (Marcus PLoS One 2014)
- Given limited interventions for primary prevention of HSV-2, efficacy against HSV-2 provides additional benefit to PrEP
Lower NNT by targeting MSM with syphilis for PrEP

Can PrEP programs reduce STIs?
- Probably yes, given quarterly visits for PrEP refills & 3-6 month STI testing
- Opportunity for earlier treatment & STI partner notification

Summary: STIs & oral PrEP
- No evidence that STIs reduce efficacy of oral PrEP
- Modest reduction in HSV-2 with oral PrEP in heterosexual African HIV serodiscordant couples
  - Adds to substantial HIV protection
- STIs are prevalent in those who benefit from PrEP
  - Useful for PrEP targeting
  - Incident STIs increase risk of HIV; reaching ‘right’ population
- STI screening & treatment are key in PrEP delivery
STD Screening

• Remember: If don't ask, [often] won't tell
• Corollary: If don't look [i.e., screen], won't find STIs

STD Screening for MSM

- HIV blood oral, anal
- Syphilis blood any
- HSV-2 blood any
- GC/CT urethra or urine oral, anal
- GC/CT rectum receptive anal
- GC pharynx receptive oral

FREQUENCY: At initial visit then annually (more frequently if warranted based on risk)

Clinical Indications for HPV DNA Testing

Proven to be clinically useful for:
- Triage of ASCUS Pap smears in women >20 years of age
- Adjunct screening in women age 30 and over

NO proven benefit for:
- Deciding whether or not to vaccinate
- STD screening
- Triage of LSIL in adults or higher grade lesions
- Testing of adolescents <21 years of age
- Evaluation of sex partners
- Evaluation of genital warts
### HPV Vaccine

- HPV immunization for females aged 9-26 years, boys 11-21, unvaccinated MSM and HIV+ through age 26
  - Vaccine consists of synthesized L1 capsid proteins that self-assemble into virus-like particles
  - Bivalent (16, 18) –66% of all cervical cancers
  - Tetravalent (6/11/16/18) –66% of all cervical cancers
  - Nonovalent –additional 5 HPV types account for 15% of cervical cancers

### PrEP and STDs: Challenges & opportunities

“Nothing will ever be attempted if all possible objections must first be overcome”

Samuel Johnson (1709-1784)
SUGGESTED READINGS


