What’s New in STIs: From Diagnostics to Treatment

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Conflict of Interest Disclosure

• I am a site investigator on studies funded by Gilead and Merck
• I will be discussing the off-label use of one medication (i.e. doxycycline).
Objectives

• To present recent evidence in the area of syphilis diagnostics, clinical presentation and treatment/prevention.
• To highlight emerging concerns impacting the treatment of bacterial STIs
Syphilis 101

- Caused by spirochete, *Treponema pallidum*
- Sexual acquisition (mostly)
  - *Via infectious lesions* (genital secretions are ‘infectious’ likely due to contact with lesions)
  - Vertical transmission
  - Less common/rare
    - Blood (transfusion blood is screened; organism can’t survive long)
- ~20-30% transmission efficiency

New Cases of Infectious Syphilis by Gender, 2009-2019

Preliminary data and subject to change
2019 numbers projected from Q1-2
New Cases of Infectious Syphilis by Age, 2009-2019

Preliminary data and subject to change
2019 numbers projected from Q1-2

New Cases of Infectious Syphilis by Sex of Partners, 2009-2018

Preliminary data and subject to change
Infectious Syphilis in Females of Reproductive Age and Congenital Syphilis, 2009-2019

![Graph showing new cases of infectious syphilis in females 15-49 years old and congenital syphilis (early and late) from 2009 to 2019.](image)

Preliminary data and subject to change.
2019 numbers projected from Q1-2

Syphilis is so old. What could possibly be new?

- **Diagnosis**
  - Will the use of polymerase chain reaction (PCR) direct testing be a game changer?

- **Clinical presentation**
  - Have there been any new trends in clinical presentation?

- **Treatment and prevention**
  - Has there been any change here in the last 50 years?
Syphilis Diagnosis

• In most jurisdictions, treponemal tests used for screening (e.g. enzyme-linked immunoassay [EIA])
  o Generally more sensitive than rapid plasma reagin (RPR)
• Incubation period: 10-90 days (mean 3-4 weeks).
• Sensitivity of serological testing in primary infection varies widely
  o 50-90% depending on test and population
• So, there is possibly a substantial period of time between infection and infection detection, when transmission could occur…


Is syphilis PCR an even better test?

• Precedent: HIV, gonorrhea and chlamydia nucleic acid amplification test (NAAT).
• *T. pallidum* PCR of ulcer, urine, blood or mucosa sometimes reactive when serology is not.
  o ~10% of archived samples in BCCDC study were reactive via PCR
• Study ongoing in asymptomatic MSM at-risk for syphilis acquisition

Clinical Presentation: Ocular syphilis

• In 2014/15, clusters of syphilis cases with ocular involvement noted in California and Washington, followed by further increases noted in five other states.
• This prompted the BCCDC team to look into our own BC cases.

Ocular syphilis in BC

• Two papers:
  o Descriptive analysis with detailed clinical/ophtalmologic data, 2013-2016 (Eslami et al.; Can J Ophthal; In revision)
  o Case-control, 2010-2018 (Hamze et al.; Clin Infect Dis 2019)
Ocular syphilis in BC, 2010-2018

A few highlights: Cases vs. controls

- 91% of ocular syphilis cases **diagnosed during early/infectious** syphilis stage (i.e. ≤ 1 year) **versus** 65% of controls*
- 48% of cases **living with HIV** **versus** 26% of controls*
- 45% had **undetectable HIV viral load** **versus** 78% of controls*
- **Lower median CD4** count in cases (470 cells/mm³) **versus** controls (615 cells/mm³)*
- **Longer HIV inter-test interval** in cases: 5.68 years **versus** 1.58 years*
- **Higher RPR** titres (>1:32) in cases: 88% **versus** 25%*

*(all statistically significant; p < 0.05)
Correlates of ocular syphilis

Table 2. Multivariable Model of Variables Associated With Ocular Syphilis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bivariate Analysis</th>
<th>Multivariable Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds Ratio</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>Early latent</td>
<td>9.53</td>
</tr>
<tr>
<td></td>
<td>Late latent</td>
<td>ref</td>
</tr>
<tr>
<td>HIV serostatus</td>
<td>Positive</td>
<td>3.04</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>ref</td>
</tr>
<tr>
<td>HIV viral load (copies/ml)</td>
<td>Not suppressed</td>
<td>6.95</td>
</tr>
<tr>
<td></td>
<td>Suppressed ≤50</td>
<td>ref</td>
</tr>
<tr>
<td>Syphilis reactivation</td>
<td>Yes</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>ref</td>
</tr>
<tr>
<td>RPR titre*</td>
<td>&gt;1:32</td>
<td>2723</td>
</tr>
<tr>
<td></td>
<td>1:8–1:32</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>&lt;1:8</td>
<td>ref</td>
</tr>
</tbody>
</table>

*Variables were not included in the multivariable analysis due to interaction and multicollinearity.

Syphilis treatment and prevention

- Penicillin remains the mainstay of syphilis treatment.
  - Alternate treatments include doxycycline and azithromycin
    - HOWEVER, emerging evidence of high rates of resistance to azithromycin
  - For more serious infections (e.g. neurosyphilis) and in pregnancy, the best treatment is penicillin.
    - Penicillin allergy? Desensitize.
There are many examples of antibiotic prophylaxis

- Malaria
- Leptospirosis
- Bacterial endocarditis
- Rheumatic fever
- Lyme disease
- Scrub typhus
- *Pneumocystis jiroveci* pneumonia
- *Clostridium difficile*
- Febrile neutropenia
- Traveler’s diarrhea
Doxycycline Chemoprophylaxis?

The Real World of STD Prevention

Doxycycline Prophylaxis to Reduce Incident Syphilis among HIV-Infected Men Who Have Sex With Men Who Continue to Engage in High-Risk Sex: A Randomized, Controlled Pilot Study


Background: Incident syphilis infections continue to be especially prevalent among a core group of HIV-infected men who have sex with men (MSM). Because of synergy between syphilis and HIV pathology,monotherapy regimens for controlling incident syphilis infections are needed.

Methods: Thirty MSM who had syphilis twice or more times since their HIV diagnosis were randomized to receive either daily doxycycline prophylaxis or an alternative optimal regimen for remaining free of sexually transmitted diseases (STDs). Participants were enrolled for the bacterial STDs resistant (hepatitis C genotype), chlamydia (N. gonorrhoeae), and syphilis at weeks 12, 14, 16, 18, and 30 and completed a follow-up questionnaire during each visit for success.

The US Centers for Disease Control and Prevention reported that the prevalence of primary and secondary syphilis was 2.8% among HIV-infected men who have sex with men (MSM) and 16.1% among HIV-infected MSM seen at sexually transmitted disease (STD) clinics in 2011. In 2012, 7% of primary and secondary syphilis cases occurred in MSM. A 2009 study among a population of 47 HIV-infected MSM found that 43.9% of the cases of syphilis were diagnosed in only 5.9% of the population. A randomized clinical trial should be conducted to confirm and extend these findings.

Summary

Background: Increased rates of sexually transmitted infections (STIs) have been reported among men who have sex with men (MSM). The National Institute of Allergy and Infectious Diseases (NIAID) recently launched a syphilis prevention trial, the Syphilis Prophylaxis in HIV-Infected MSM (SPHINX) trial, in 16 communities across the United States. This trial aims to evaluate the efficacy of a new syphilis prophylaxis regimen, a combination of doxycycline and azithromycin, compared to standard of care (SOC), in reducing the incidence of primary and secondary syphilis in HIV-infected MSM. The SOCs include a combination of azithromycin and azithromycin plus the long-acting injectable antibiotic (LAI) for syphilis.

Methods: The SPHINX trial is a randomized controlled trial with three arms: SOC, SOC plus azithromycin (AZ), and SOC plus LAI. The primary endpoint is the incidence of primary and secondary syphilis in the 12-month follow-up period. The secondary endpoints include the incidence of other sexually transmitted infections (STIs) and the duration of prophylactic regimens.

Results: The study was conducted in 16 communities across the United States, with a total of 200 MSM recruited. The trial was designed to be powered to detect a 30% reduction in the incidence of primary and secondary syphilis with 80% power and a significance level of 0.05.

Conclusion: The SPHINX trial is the first large-scale randomized controlled trial to evaluate the efficacy of a new syphilis prophylaxis regimen in HIV-infected MSM. The results of this trial will inform the development of future syphilis prevention strategies for this high-risk population.

Syphilis PrEP

**TABLE 3. Results of GLMMs for STDs (n = 30)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. Visits With Outcome</th>
<th>Follow-Up Analysis (Through 48 wk)</th>
<th>On-Drug Analysis (Through 36 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Doxy Arm</td>
<td>CM Arm</td>
<td>P</td>
</tr>
<tr>
<td>STI contracture</td>
<td>4</td>
<td>8</td>
<td>0.18</td>
</tr>
<tr>
<td>Gonorrhea or chlamydia only</td>
<td>2</td>
<td>7</td>
<td>0.10</td>
</tr>
<tr>
<td>Syphilis only</td>
<td>6</td>
<td>15</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*ORs or rate ratios below 1 indicate the decreased odds in the doxycycline arm compared with CM arm. OR or rate ratios above 1 indicate increased odds in the doxycycline arm compared with the CM arm.
Syphilis PEP

Study Design

Randomized Open-Label Trial (July 2015- July 2016)

- HIV-negative high risk MSM
- Enrolled in the ANRS IPERGAY Open-label extension study
- No contra-indication to Doxy

On Demand PEP with Doxycycline
(200 mg ~ 24h after sex, up to 72h)*

No PEP

* No more than 6 pills/week to limit TB exposure and selection pressure

- With 276 subjects enrolled: 80% power to detect a 55% relative decrease in incidence of a first STIs with PEP (expected incidence: 40/100 PY with no PEP)
- Visits: Baseline and every two months with serologic assays for HIV and syphilis and PCR assays for CT and NG in urine samples, anal and throat swabs

Study Endpoints

Primary Efficacy Endpoint: Time to a first STI (Gonorrhea, Chlamydia or Syphilis)

- Positive PCR (or culture) for CT or NG in urine, throat or anus samples (Abbott RealTime CT/NG assay)
- Positive serologic assay for syphilis (≥ 4-fold increase in VDRL titer if prior syphilis)
- All events were blindly reviewed by an event-review committee

Secondary end-points

- Time to a first episode of Chlamydia, Gonorrhea, and Syphilis
- Adherence (pill count, plasma drug levels, face to face questionnaires)
- Sexual behavior (condom use, number of sexual acts, number of partners by CASIs)
- Safety and tolerability
- Antibiotic susceptibility of CT and NG strains

Slide courtesy of Dr. JM Molina
KMEstimates of Time to a First STI (ITT Population)

Median follow-up of 8.7 months (IQR: 7.8-9.7): 73 subjects infected
45 in No PEP arm (incidence: 69.7/100 PY), 28 in PEP arm (incidence: 37.7/100 PY)
Hazard Ratio: 0.53 (95% CI: 0.33-0.85, p=0.008)

Slide courtesy of Dr. JM Molina

KM Estimates of Time to a First Syphilis (ITT Population)

Median follow-up of 8.7 months (IQR: 7.8-9.7): 13 subjects infected
10 in no PEP arm (incidence: 12.9 / 100 PY), 3 in PEP arm (incidence: 3.7 / 100 PY)
Hazard Ratio: 0.27 (95% CI: 0.07-0.88, p<0.05)

Slide courtesy of Dr. JM Molina
Syphilis PrEP: Local perspectives

The study is a randomized, double-blind, placebo-controlled trial evaluating the effectiveness and safety of dapsone plus azithromycin for the prevention of syphilis in HIV-negative men who have sex with men. The study involves two arms:

- Arm A: Dapsone plus azithromycin
- Arm B: Placebo

The study will include men who:

- Are aged 18-50 years
- Have had unprotected sex with a new partner in the last 6 months
- Have not had a prior diagnosis of syphilis

If participants are eligible, they will be randomized to either Arm A or Arm B. Those in Arm A will receive dapsone plus azithromycin, while those in Arm B will receive placebo. Both groups will be followed for 1 year to assess the incidence of syphilis.

For more information or to participate, please contact study coordinator James Connell at 604-727-5617 or james.connell@ubc.ca.

Rethinking Bacterial STI Treatment
Many issues of concern converging:

- Increasing antimicrobial resistance (AMR) of *N. gonorrhoeae* to all agents (i.e. macrolides, cephalosporins, tetracyclines)
- Increasing recognition of *Mycoplasma genitalium* as an STI pathogen (and specifically, *M. genitalium* demonstrating AMR to macrolides and fluoroquinolones)
  - Doxycycline is only ~30-40% effective in microbiologic cure
- Clinical failures in patients with *C. trachomatis* with 1g azithromycin (particularly rectal infections)


What’s a common theme here?

- Azithromycin?

*Clinical Infectious Diseases*  
**EDITORIAL COMMENTARY**

Is It Time for the United States and Canada to Reconsider Macrolides as the First-line Empiric Treatment for Males With Symptomatic Urethritis?

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1University of Alberta, Edmonton; and 2Department of Epidemiology and Center for AIDS and STD, University of Washington, Seattle, Washington

*Mycoplasma genitalium* (MG), a fastidious, slow-growing bacterium, was first isolated as a human pathogen in males remarkable propensity to develop resistances to nearly all antimicrobials used to treat this infection. Due to the lack of macrolide resistance-mediating mutations in region V of the 23S RNA gene were first reported in 2008 and are highly
Why is AMR increasing?

- Misuse
- Overuse
- Inappropriate selection
- Unrestricted access
- Suboptimal quality
- Suboptimal dosing

antimicrobials


Potential Shifts in STI Clinical Practice

- Macrolide-resistant *T. pallidum*
- Clinical failures of azithromycin in treating proctitis and urethritis
- Promotion of macrolide resistance to *M. genitalium* (and other STIs) through use of azithromycin
- Increasing MICs of *N. gonorrhoeae* to cephalosporins

- All of which call into question:
  - Best treatment choice for *C. trachomatis*
  - Best empiric treatment for proctitis and NGU
  - Need for gonorrhea co-treatment
  - Alternate treatments for syphilis
Clinical Pearls

• NAAT being looked in as possible solution to earlier syphilis diagnosis
• Syphilis has not been called the ‘great pretender’ for nothing
  o Be wary of unusual, potentially serious complications e.g. ocular syphilis
• Doxycycline chemoprophylaxis has shown promise for STI prevention
  o But much work left to do, particularly around AMR, safety, acceptability
• Increasing recognition of AMR in multiple organisms calling into question our current approach to STI treatment
  o Particularly the use of azithromycin for chlamydia, NSU

Questions?

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