STIs in women

Who run the world? Girls, girls!!

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STD PTC at Johns Hopkins

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Sexually Transmitted Infections/Diseases

Bacterial

- *Neisseria gonorrhoeae (GC)*
- *Chlamydia trachomatis (CT)*
- *Treponema pallidum (Syphilis)*
- *Haemophilus ducreyi (Chancroid)*
- *Klebsiella granulomatosis*
- *Ureaplasma urealyticum*
- *Ureaplasma parvum*
- *Mycoplasma hominis*
- *Mycoplasma genitalium*
- *Gardnerella vaginalis* and other vaginal bacteria
- Group B *Streptoccus*
- *Mobiluncus ssp*
- *Helicobacter fennellia*
- *Shigella spp.*
- *Campylobacter spp.*

Viral

- *HIV (types 1 and 2)*
- *Herpes simplex virus (types 1 and 2)*
- *Human papillomavirus (HPV)*
- *Hepatitis B*
- *Molluscum contagiosum*
- *Cytomegalovirus*
- *Hepatitis C and D*
- *Epstein-Barr virus*
- *Human herpesvirus type 8 (Kaposi's sarcoma)*
- *Zika*
- *Ebola*
- *SARS-CoV-2*
- *Hepatitis A*

Protozoa, Ectoparasites, Fungi

- *Trichomonas vaginalis*
- *Phthirus pubis*
- *Candida albicans*
- *Sarcoptes scabiei*
- *Giardia lamblia*
- *Entamoeba histolytica*

RED = transmitted in adults predominantly by sexual intercourse
Green = sexual transmission described but not well defined
Purple = transmitted by fecal-oral exposure

This talk will focus on

Bacterial	Viral	Protozoa
Neisseria gonorrhea	Herpes simplex virus 1 & 2	*Trichomonas vaginalis*
Chlamydia trachomatis	Human papillomavirus	
Treponema pallidum		Other
Mycoplasma genitalium		Bacterial vaginosis

How to approach STIs

- By pathogen?
- By risk factor?
- By history?
- By exam?

How to approach STIs

- 21 year old woman attends her PCP with a complaint of vaginal discharge for 3 days
  - Itchy, thick ‘lumpy’ discharge
- 35 year old bisexual woman living with HIV attends the ED with rash, fever, enlarged LN
- 19 year old Transwoman attends STI clinic with 3 week history of left sided low abdominal pain and diarrhea

Common STIs

"Discharge"

Cervicitis/Urethritis
- Gonorrhea
- Chlamydia
- (*Mycoplasma genitalium*)

Vaginitis
- Trichomonas
- Bacterial vaginosis

Proctitis
- Gonorrhea, Chlamydia, LGV, HSV

Conjunctivitis
- Gonorrhea, Chlamydia

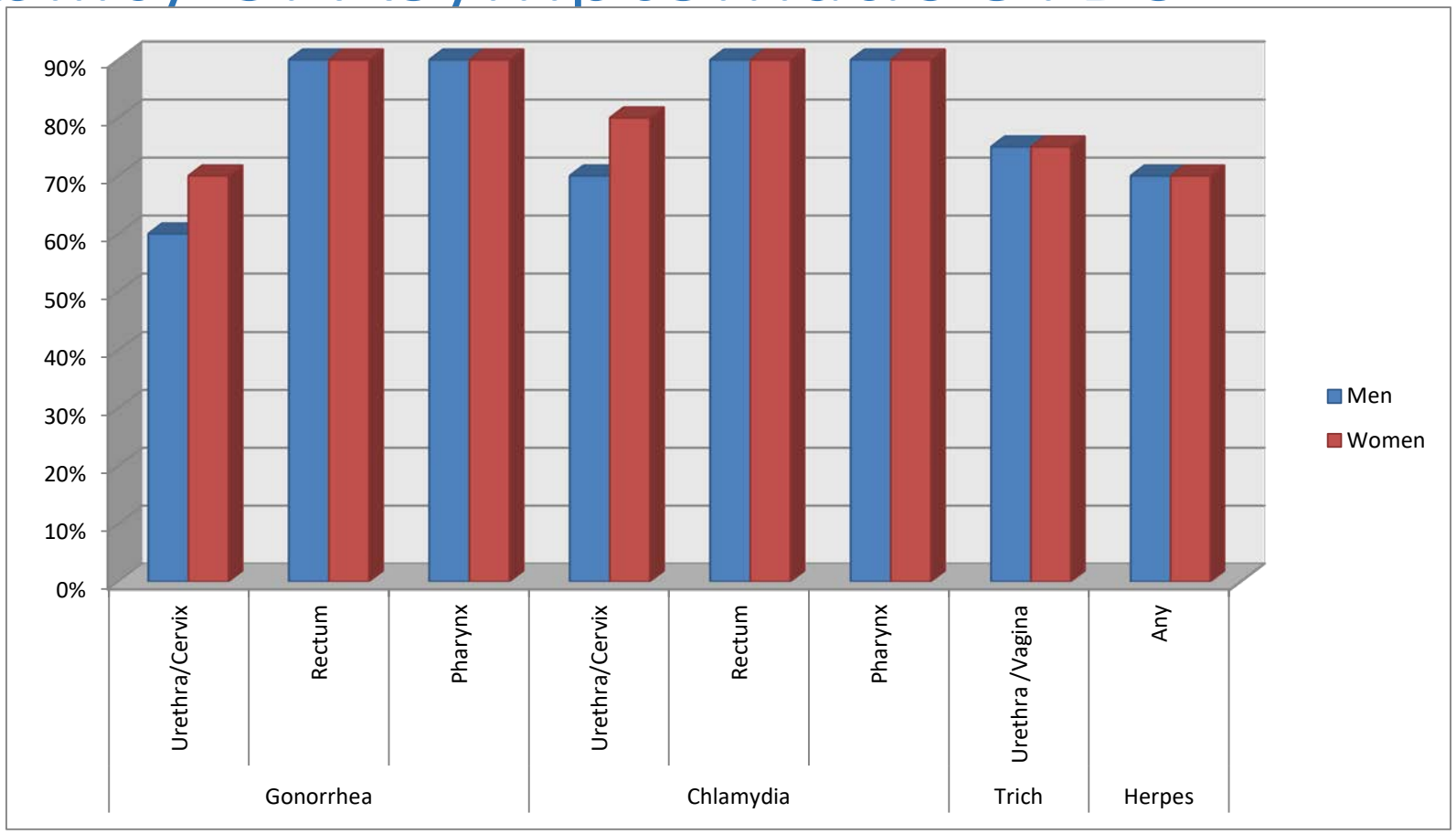
"Ulcers/Sores"

Painless – not always
- **Syphilis**
- LGV
- (Granuloma Inguinale)

Painful
- **Herpes**
- (Chanchroid)

Other STIs of concern: **HPV** (warts, cancer), **Hepatitis B**, **Hepatitis C** (HIV+ MSM)

Probability of Asymptomatic STDs



SCREENING is critical!

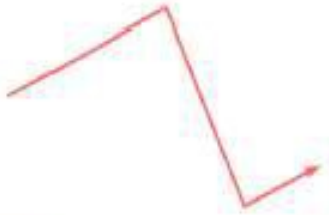
Preliminary 2021 STD Surveillance Data

2.5 million cases

Preliminary data show 2.5 million reported cases of chlamydia, gonorrhea, and syphilis in 2021.

STDs continued to increase during the second year of the COVID-19 pandemic, with no signs of slowing. This page presents preliminary STD surveillance data for chlamydia, gonorrhea, syphilis, and congenital syphilis. These data include cases reported to CDC through the National Notifiable Diseases Surveillance System (as of July 7, 2022), STD Surveillance Network (as of June 15, 2022), and Gonococcal Isolate Surveillance Project (as of June 23, 2022), and are considered preliminary as 2021 STD surveillance data will continue to be reported to CDC through the fall of 2022. Final 2021 data, including STD case counts and rates for states and territories, will be provided in the forthcoming 2021 STD Surveillance Report. Until then, the most current complete data for chlamydia, gonorrhea, and syphilis are available in *Sexually Transmitted Disease Surveillance, 2020*.

Chlamydia Cases



2017	2021
1,708,569	1,628,397

Gonorrhea Cases

2017	2021
555,608	696,764

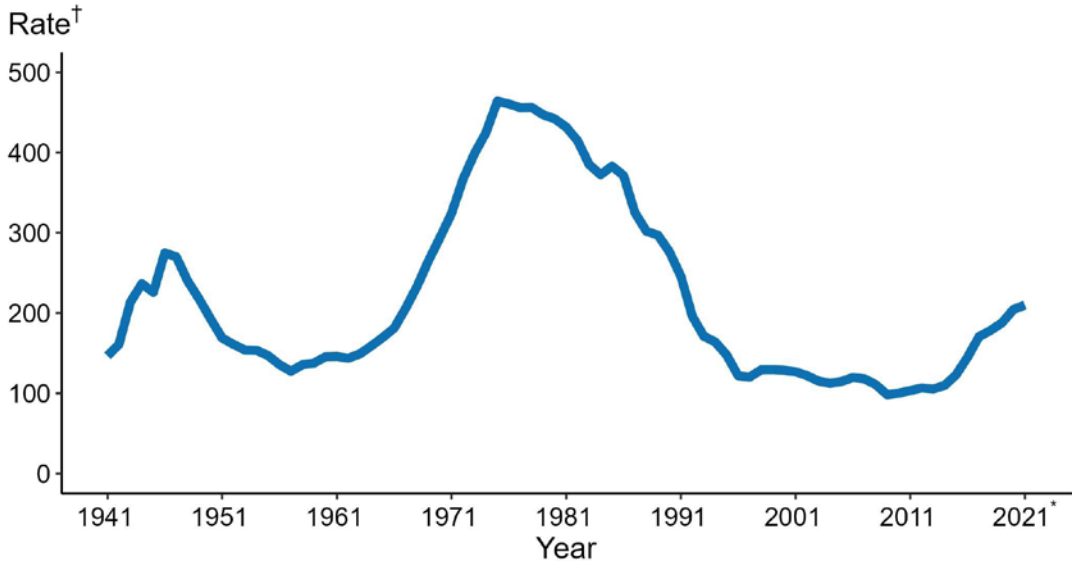
Syphilis Cases

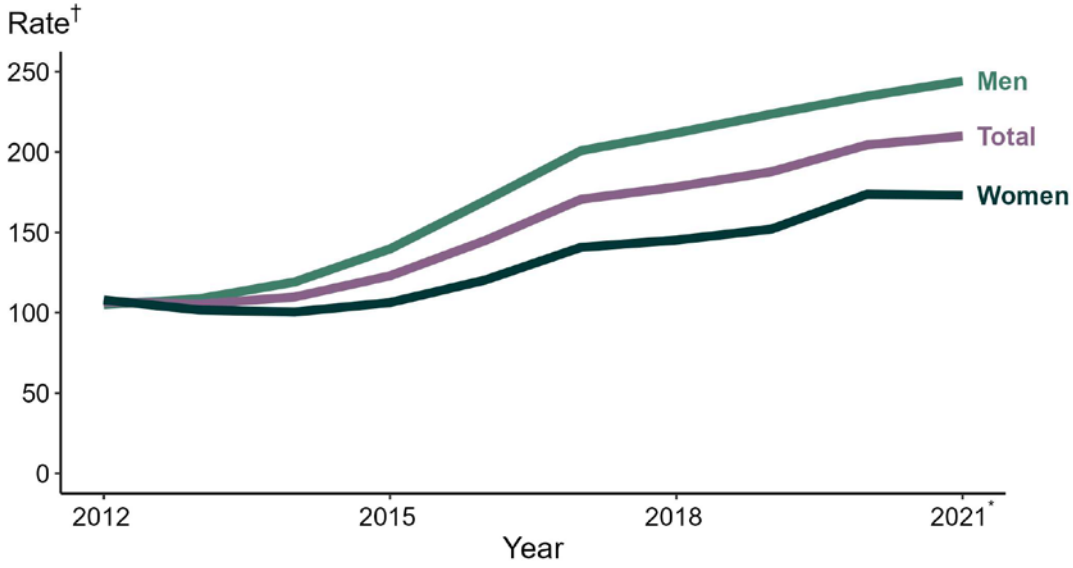
2017	2021
101,590	171,074

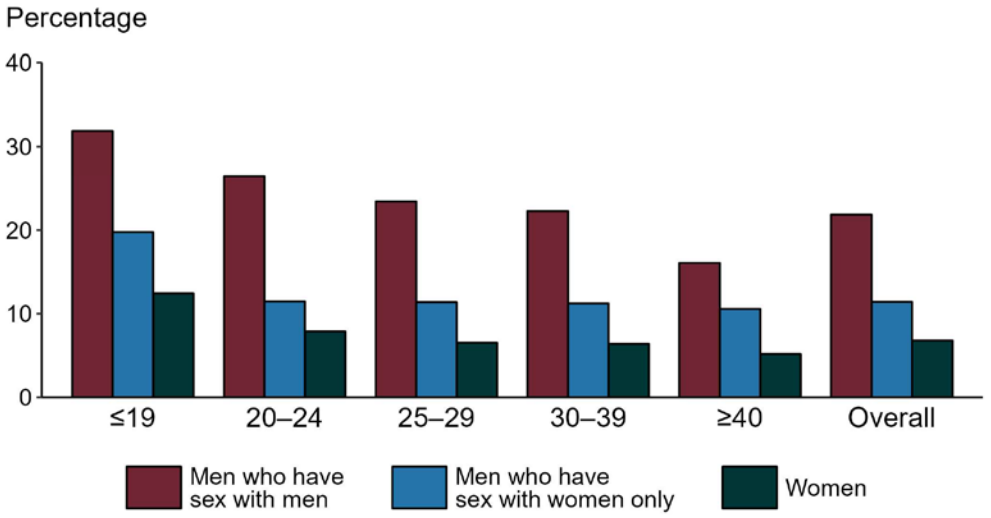
Congenital Syphilis Cases

2017	2021
941	2,677

Gonorrhea Epidemiology







- Over the last 10 years, the gonorrhea rate among men increased 132.6% (from 105.0 to 244.2 per 100,000) and the rate among women increased 60.4% (from 107.9 to 173.1 per 100,000).
- Estimated rates among MSM are 42 times that among men who have sex with women
- The rate among Blacks was 7.7 times the rate among Whites

CDC Sexually Transmitted Surveillance 2021

Therapy for Urogenital and Rectal NG Infections in the US 2021

Regimen for uncomplicated gonococcal infections of the cervix, urethra, or rectum:

Ceftriaxone 500 mg IM as a single dose for persons weighing <150 kg (300 lb).

- For persons weighing ≥150 kg (300 lb), 1 g of IM ceftriaxone should be administered.
- If chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally twice daily for 7 days. During pregnancy, azithromycin 1 g as a single dose is recommended to treat chlamydia.

Alternative regimens for uncomplicated gonococcal infections of the cervix, urethra, or rectum if ceftriaxone is not available:

Gentamicin 240 mg IM as a single dose plus azithromycin 2 g orally as a single dose OR

Cefixime 800 mg orally as a single dose. If treating with cefixime, and chlamydial infection has not been excluded, providers should treat for chlamydia with doxycycline 100 mg orally twice daily for 7 days. During pregnancy, azithromycin 1 g as a single dose is recommended to treat chlamydia.

St Cyr *MMWR* 2020

Why did the CDC change the dual treatment regimen recommendation and why did they increase the dose of ceftriaxone?

ANTIBIOTIC RESISTANCE THREATS IN THE UNITED STATES

2019

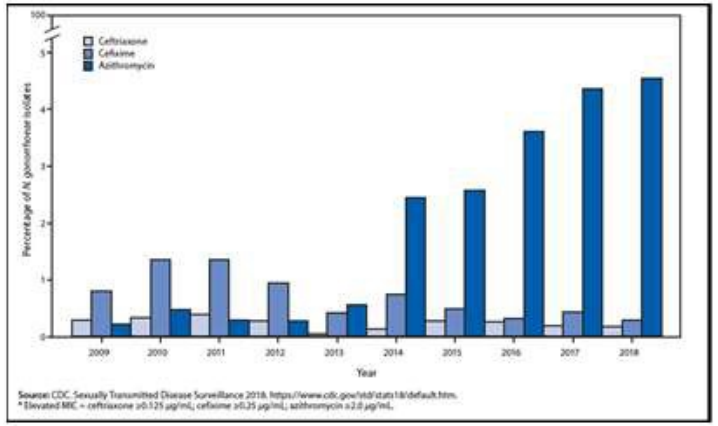
Urgent Threats

- Carbapenem-resistant *Acinetobacter*
- *Candida auris (C. auris)*
- *Clostridioides difficile (C. difficile)*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae (N. gonorrhoeae)*

Commit to Antibiotic Stewardship

Implement practice-level stewardship activities, including documenting antibiotic use data, examining use practices, and serving as an educational resource for clients. Engage veterinary diagnostic labs to provide antibiograms to help determine which antibiotics will effectively treat infections. Become familiar with and use the American Veterinary Medical Association established antibiotic use principles to build an antibiotic stewardship plan for your practice settings.

For the sake of **antimicrobial stewardship**



Because of **increasing macrolide resistance**

Antimicrobial Agents and Chemotherapy®

PHARMACOLOGY

Pharmacokinetic Data Are Predictive of *In Vivo* Efficacy for Cefixime and Ceftriaxone against Susceptible and Resistant *Neisseria gonorrhoeae* Strains in the Gonorrhea Mouse Model

Kristie L. Connolly,[a] Ann E. Eakin,[b] Carolina Gomez,[a] Blaire L. Osborn,[b] Magnus Unemo,[c] Ann E. Jerse[a]

To **optimize ceftriaxone dosing**: In a murine model, the lowest ceftriaxone dose that was 100% effective at eradicating the susceptible organism 48 hours after treatment was 5 mg/kg body weight. Translating into human doses, a 500-mg dose corresponds to 5 mg/kg body weight, whereas 250 mg only corresponds to 3 mg/kg body weight for an average person

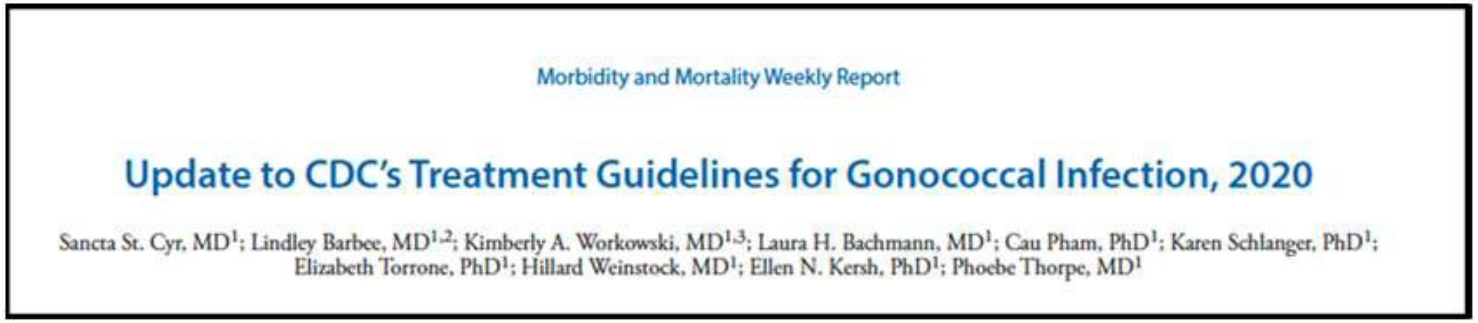
Therapy for Pharyngeal NG 2020

Recommended regimen for uncomplicated gonococcal infections of the pharynx:

Ceftriaxone 500 mg IM as a single dose for persons weighing <150 kg (300 lb).

- For persons weighing ≥150 kg (300 lb), 1 g of IM ceftriaxone should be administered.
- If chlamydia coinfection is identified when pharyngeal gonorrhea testing is performed, providers should treat for chlamydia with doxycycline 100 mg orally twice a day for 7 days. During pregnancy, azithromycin 1 g as a single dose is recommended to treat chlamydia.
- No reliable alternative treatments are available for pharyngeal gonorrhea. For persons with a history of a beta-lactam allergy, a thorough assessment of the reaction is recommended.*
- For persons with an anaphylactic or other severe reaction (e.g., Stevens Johnson syndrome) to ceftriaxone, consult an infectious disease specialist for an alternative treatment recommendation.

St Cyr *MMWR* 2020



Morbidity and Mortality Weekly Report

Update to CDC's Treatment Guidelines for Gonococcal Infection, 2020

Sancta St. Cyr, MD[1]; Lindley Barbee, MD[1,2]; Kimberly A. Workowski, MD[1,3]; Laura H. Bachmann, MD[1]; Cau Pham, PhD[1]; Karen Schlanger, PhD[1]; Elizabeth Torrone, PhD[1]; Hillard Weinstock, MD[1]; Ellen N. Kersh, PhD[1]; Phoebe Thorpe, MD[1]

- For persons with pharyngeal gonorrhea, a **test-of-cure** is recommended, using culture or nucleic acid amplification tests 7–14 days after initial treatment, regardless of the treatment regimen
- **For EPT**: the partner may be treated with a single 800 mg oral dose of cefixime, provided that concurrent chlamydial infection in the patient has been excluded. Otherwise, the partner may be treated with a single oral 800 mg cefixime dose plus oral doxycycline 100 mg twice daily for 7 days
- Persons should be **retested 3 months after treatment** regardless of whether they believe their sex partners were treated.

St Cyr *MMWR* 2020

Why does the CDC only recommend ceftriaxone for pharyngeal NG infections and why recommend the test of cure for all pharyngeal infections?

Explaining the Poor Bacteriologic Eradication Rate of Single-Dose Ceftriaxone in Group A Streptococcal Tonsillopharyngitis: A Reverse Engineering Solution Using Pharmacodynamic Modeling

Jeffrey L. Blumer, PhD, MD*‡; Michael D. Reed, PharmD*‡; Edward L. Kaplan, MD§; and George L. Drusano, MD‖

- Ceftriaxone concentrations tend to be more variable in the pharynx
- Treatment of NG likely requires longer times above the strain's MIC
- Continued uncertainty regarding ceftriaxone PK/PD

ORIGINAL STUDY

A Phase 1 Pharmacokinetic and Safety Study of Extended-Duration, High-dose Cefixime for Cephalosporin-resistant *Neisseria gonorrhoeae* in the Pharynx

Lindley A. Barbee, MD, MPH,† Seema U. Nayak, MD,‡ Jeffrey L. Blumer, MD, MPH,§ Mary Ann O'Riordan,¶ Wesley Gray, MSc,§ Jonathan M. Zenilman, MD,‡ Matthew R. Golden, MD, MPH,*† and J. McLeod Griffiss, MD‖*

- Absence of cefixime in oropharyngeal fluid after the 400-, 800-, and 800-mg doses every 8 hours;
- While the 800-mg single dose regimen would effectively treat anogenital infections, only the 800 mg every 8 hours for 3 doses <u>may</u> cure pharyngeal infection if the MIC is 0.5 µg/mL or less

Clinical Infectious Diseases

MAJOR ARTICLE

Gentamicin Alone Is Inadequate to Eradicate *Neisseria Gonorrhoeae* From the Pharynx

Lindley A. Barbee,[1,2] Olusegun O. Soge,[3] Jennifer Morgan,[3] Angela LeClair,[3] Tamara Bass,[3] Brian J. Werth,[4] James P. Hughes,[5] and Matthew R. Golden[1,3,6]

Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: the G-TOG non-inferiority RCT

Jonathan DC Ross, Jan Harding, Lelia Duley, Alan A Montgomery, Trish Hepburn, Wei Tan, Clare Brittain, Garry Meakin, Kirsty Sprange, Sukhwinder Thandi, Louise Jackson, Tracy Roberts, Janet Wilson, John White, Claire Dewsnap, Michelle Cole and Tessa Lawrence on behalf of the G-TOG Collaborative Group

HEALTH TECHNOLOGY ASSESSMENT

- While effective for anogenital infections, gentamicin does <u>not</u> effectively eradicate pharyngeal NG infections

What’s to be done with the outpatient treatment of pelvic inflammatory disease (PID) without ceftriaxone?

PID

- 90% of cases of PID may be treated in the outpatient setting
- The only outpatient regimens recommended by the CDC are cephalosporin based
- Test all women for gonorrhea and chlamydia. The value of testing women with PID for *M. genitalium* is unknown
- The risk for PID associated with IUD use is primarily confined to the first 3 weeks after insertion. If an IUD user receives a diagnosis of PID, the IUD does not need to be removed
- **Using regimens with anaerobic activity should be considered**

All outpatient regimens to treat PID are cephalosporin-based

Recommended Intramuscular or Oral Regimens for Pelvic Inflammatory Disease

Ceftriaxone 500 mg IM in a single dose*

PLUS

Doxycycline 100 mg orally 2 times/day for 14 days

WITH

Metronidazole 500 mg orally 2 times/day for 14 days

OR

Cefoxitin 2 gm IM in a single dose and Probenecid 1 gm orally administered concurrently in a single dose

PLUS

Doxycycline 100 mg orally 2 times/day for 14 days

WITH

Metronidazole 500 mg orally 2 times/day for 14 days

OR

Other parenteral third-generation **cephalosporin** (e.g., ceftizoxime or cefotaxime)

PLUS

Doxycycline 100 mg orally 2 times/day for 14 days

WITH

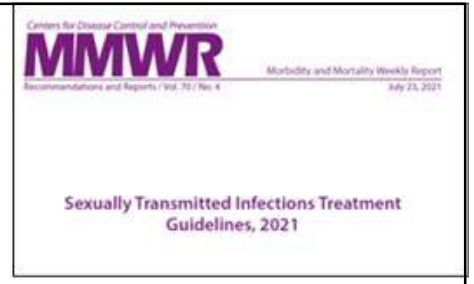
Metronidazole 500 mg orally 2 times/day for 14 days

*For persons weighing >150 kg (~300 lbs.) with documented gonococcal infection, 1 gm of ceftriaxone should be administered.

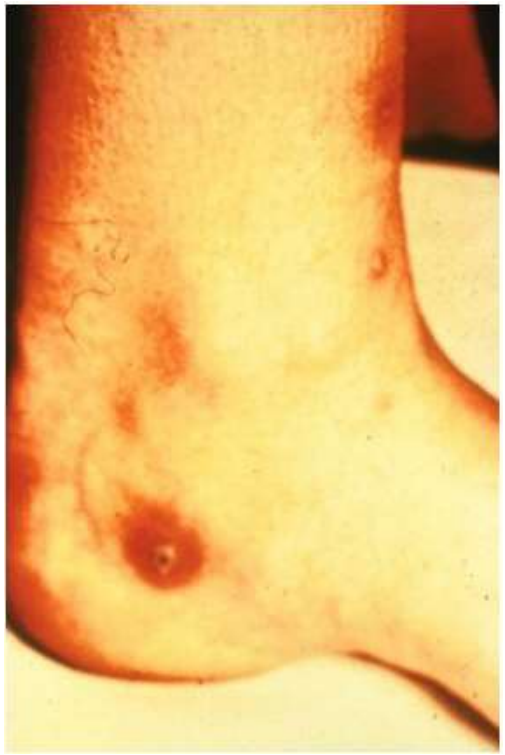
CDC 2021 STI Treatment Guidelines

Drug	Mechanism of Action	Status	Reference
Zoliflodacin (AZ D0914)	Topoisomerase inhibitor	Phase 2; limited activity at pharynx at lower doses	Taylor SN *NEJM* 2018
Gepotidacin (BTZ116576)	Topoisomerase inhibitor	Phase 2 complete ? Pharyngeal efficacy (1/2 cured)	Taylor SN *Clin Infect Dis* 2018
Solithromycin	Fluoroketolide; inhibits protein synthesis	Phase 2; 100% effective at all sites; Phase 3 study inferior-80% efficacy	Hook EW III *Clin Infect Dis* 2015 Chen MY *Lancet* 2019
Delafloxacin	Fluoroquinolone; activity against both DNA gyrase and topoisomerase IV	Phase III; not reliable-only 85.1% efficacy	Hook EW III *Sex Transm Dis* 2019
Aztreonam	Monobactam; cell wall inhibitor	Open label; only 33% efficacy at pharynx	Barbee LA *Antimicrob Agents Chemother* 2020

Disseminated gonococcal infection (DGI)



- DGI frequently results in petechial or pustular acral skin lesions (< 12 lesions and usually tender), tenosynovitis, and asymmetrical arthralgia, or (oligoarticular) septic arthritis
- The infection is occasionally complicated by perihepatitis and rarely by endocarditis or meningitis.
- Strains of *N. gonorrhoeae* that cause DGI may cause **minimal** genital inflammation
- Risk factor for DGI: terminal complement deficiency (acquired form often seen in SLE) and complement inhibitors (e.g. **Eculizumab**)
- Differential diagnosis: meningococcemia, RMSF, dengue, endocarditis, Reiter's
- **Test all mucosal surfaces using NAATs and culture (genital, rectal, pharyngeal). Culture is less sensitive but it allows for antimicrobial resistance testing**
- **Treatment: Start with IV ceftriaxone and once clinical status improves, de-escalate to oral regimen based on antimicrobial susceptibility testing. Short courses (i.e. <7 days) are adequate except for meningitis, endocarditis, and septic arthritis.**



CDC 2021 STI Treatment Guidelines

Gonorrhea: Take-Home Points

- The treatment of uncomplicated gonorrhea is now >=**500 mg of intramuscular ceftriaxone**; if chlamydia is present or is not ruled out, add one week of 100 mg of oral doxycycline taken twice daily
  - Alternate regimens for **urogenital or rectal infections** include oral cefixime 800 mg; intramuscular gentamicin 5mg/kg plus 2 g oral azithromycin
- Patients with pharyngeal gonorrhea should be treated with ceftriaxone- **no alternate regimens are recommended**; a test-of-cure should be performed one to two weeks later
- A reported history of penicillin allergy should prompt clinicians to obtain more information about the nature of that allergy; a majority of these patients may be safely treated with ceftriaxone
- Re-screen all persons diagnosed with gonorrhea in 3 months
- Treat all sex partners in the preceding 60 days of index patients diagnosed with gonorrhea

Chlamydia Treatment Update

- Doxycycline 100mg orally twice daily will be the **preferred option** to treat *Chlamydia trachomatis* infections
  - Azithromycin 1g orally is a second-line regimen
- Azithromycin was 3% less effective when treating urogenital infections compared with doxycycline NEJM 2015; 373;26:2513-2521
- **Two recent RCTs demonstrated that azithromycin was 20% less effective when treating rectal chlamydia infections compared with doxycycline**


Clinical Infectious Diseases

Doxycycline Versus Azithromycin for the Treatment of Rectal Chlamydia in Men Who Have Sex With Men: A Randomized Controlled Trial

- Microbiologic cure was higher with doxycycline than azithromycin (91% [80 of 88] vs 71% [63 of 89]; absolute difference, 20%; 95% CI, 9–31%; P < .001)
- The mechanism of azithromycin treatment failure in rectal CT is not known but is **not** likely due to antibiotic resistance, inadequate tissue penetration of the drug, or the prevalence of LGV biovars.


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Azithromycin or Doxycycline for Asymptomatic Rectal *Chlamydia trachomatis*

Andrew Lau, M.S., Fabian Y.S. Kong, Ph.D., Christopher K. Fairley, Ph.D.,

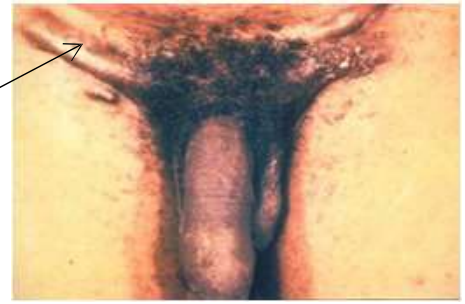
- Microbiologic cure occurred in 281 of 290 men (96.9%; 95% CI: 94.9 to 98.9) in the doxycycline group and in 227 of 297 (76.4%; 95% CI, 73.8 to 79.1) in the azithromycin group, for an adjusted risk difference of 19.9 percentage points (95%CI, 14.6 to 25.3; P<0.001)

Chlamydia trachomatis L1-L3: LGV

- Classical manifestation is a short-lived **painless** genital ulcer accompanied by **painful** inguinal lymphadenopathy
- Outbreaks in US and Western Europe associated with **proctitis** particularly **among MSM**********
  - **Rectal pain, tenesmus, rectal bleeding/discharge**
  - **May be mistaken for Crohn's disease on biopsy**

Genital elephantiasis (chronic)

"Groove sign"



Chlamydia Proctitis Take-Home Points

- There are currently no commercial tests that distinguish between LGV and non-LGV strains of *Chlamydia trachomatis*
- **The treatment duration for chlamydia proctitis depends on symptoms:**
  - **Asymptomatic and mildly symptomatic** persons should be treated with **one week** of doxycycline
  - **Moderately to severely symptomatic persons** should be treated with **3 weeks** of doxycycline

Proctitis/ Proctocolitis

COMMON

- Neisseria gonorrhoeae
- Chlamydia trachomatis D-K
- Chlamydia trachomatis L1-L3 (LGV)
- T. pallidum
- HSV (severe especially among HIV+)
- Monkeypox

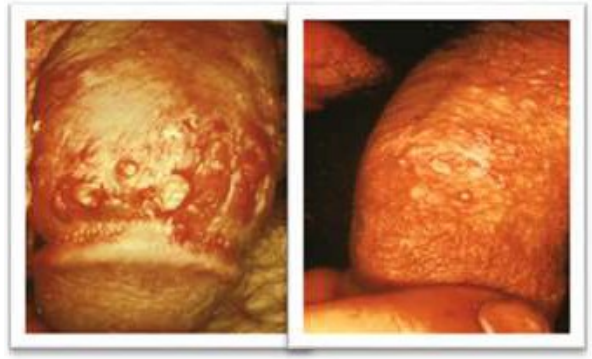
- OTHER CAUSES
- Campylobacter
- Shigella
- Entamoeba
- CMV
- Giardia lamblia* (mainly enteritis; especially among MSM)

Empiric Treatment of Symptomatic Proctitis: Ceftriaxone 500mg IM X1 PLUS Doxycycline 100mg PO BID for 3 weeks (will cover GC, CT, LGV, and early syphilis)

Mycoplasma genitalium

- Causes ~20% of cases of urethritis and ~35% of cases of **persistent** urethritis
  - Also associated with cervicitis and proctitis; weaker association with PID and infertility
- Many cases are asymptomatic
  - Currently there are **no recommendations to screen asymptomatic persons**
- Nucleic acid amplification tests (NAATs) are the gold standard diagnostics
  - In Europe/Australia, NAATs also provide information about macrolide resistance
- Partners: If you can test partners, treat those who are positive; if you cannot, consider treating the partner with the same regimen used to treat the patient

HSV 1 and 2



- Both HSV-1 (particularly among young women and MSM) and 2 cause genital infections
- HSV-2 twice as prevalent in women vs. men
- ~70% of people are unaware that they are infected
- Up to 25% of persons who present with a first clinical episode of genital herpes may have longstanding infection (**BE CAREFUL**)
- Asymptomatic shedding is the most common reason for transmission
  - Shedding is highest during the first few years after infection
- Condoms and antiviral suppressive therapy decrease risk of male to female transmission by 30% and 55% over time, respectively (condoms less effective from female to male)
- Currently, no formal screening recommendations; only testing
- C-section ONLY in patients **who have active lesions or prodromal symptoms at the time of delivery**

JAMA. 2022;327(2):161-172.

How do we diagnose HSV?

- **Symptomatic Patients**
  - Tzanck smear (only 40% sensitive)
  - Culture (sensitivity 30-70%)
    - Main use is to test for antiviral susceptibility
  - Antigen detection (~70% sensitive)
  - **PCR (FDA cleared, >90% sensitive)**
    - **The best diagnostic test when lesions are present**

- **Asymptomatic Patients**
  - 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
  - **NEVER order or try to interpret IgM serologies**

REMEMBER:
- Antibodies may be negative in early primary infection
- The **specificity** of HSV-2 serological tests is not perfect
- The **sensitivity** of HSV-1 serological tests is not perfect

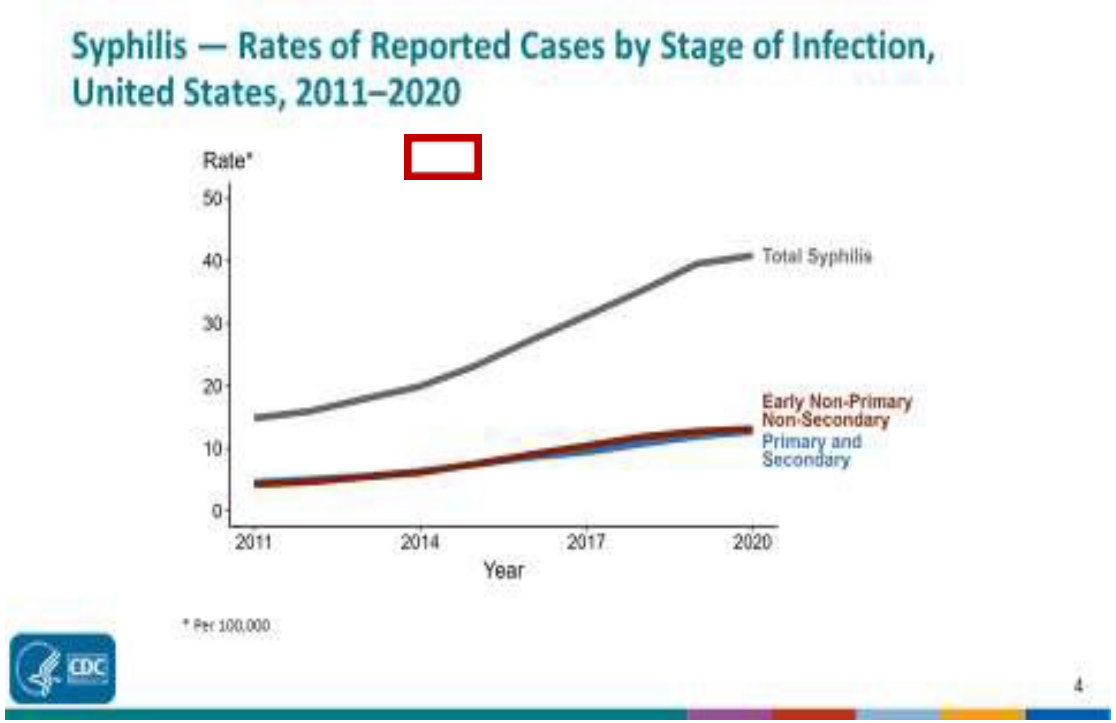
JAMA. 2022;327(2):161-172.

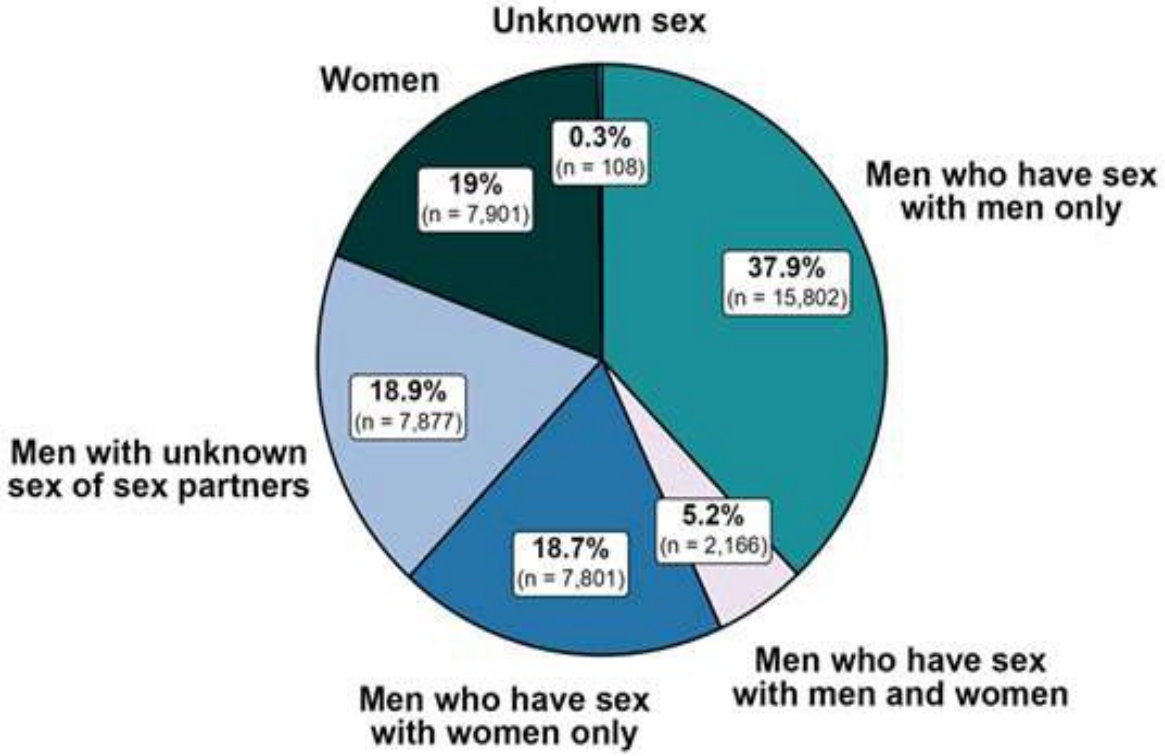
HSV-2 Serological Diagnosis: 2-Step Testing

- If lesions are presents, PCR is the best diagnostic test
- If lesions are absent, the recommended serological tests for HSV-1 and HSV-2 are the Glycoprotein-G-based IgG EIAs [e.g., HerpeSelect HSV EIA]
  - There are issues with the SPECIFICITY of the IgG-2 EIAs with EIA index values <3.0 [in one study, the specificity was 38%]
  - Laboratories should provide index values for all HSV-2 IgG EIA results
  - If the index value <3.0, a second more specific test should be performed to confirm the original EIA result. There are two options for the second test:
    - HSV-2 Western Blot- only performed at the University of Washington
      - https://depts.washington.edu/uwviro/
    - HSV-2 Biokit Rapid Test (Biokit USA, Lexington MA)
- NEVER IgM serologies- they are neither sensitive nor specific to diagnose a recent infection

Agyemang *STD* 2017 CDC 2021 STI Treatment Guidelines

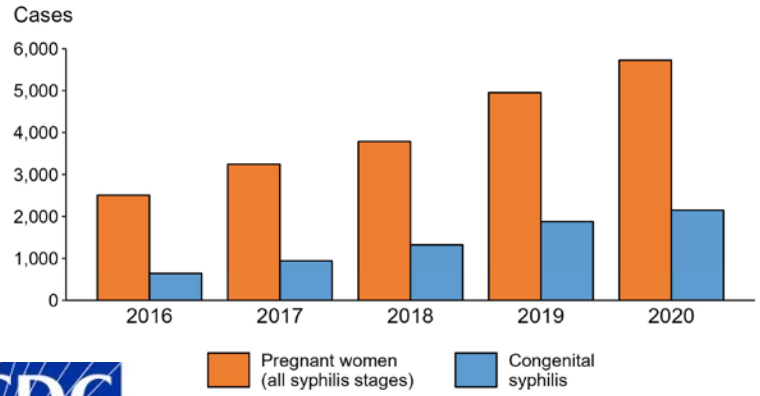
Syphilis in the 2020s -United States



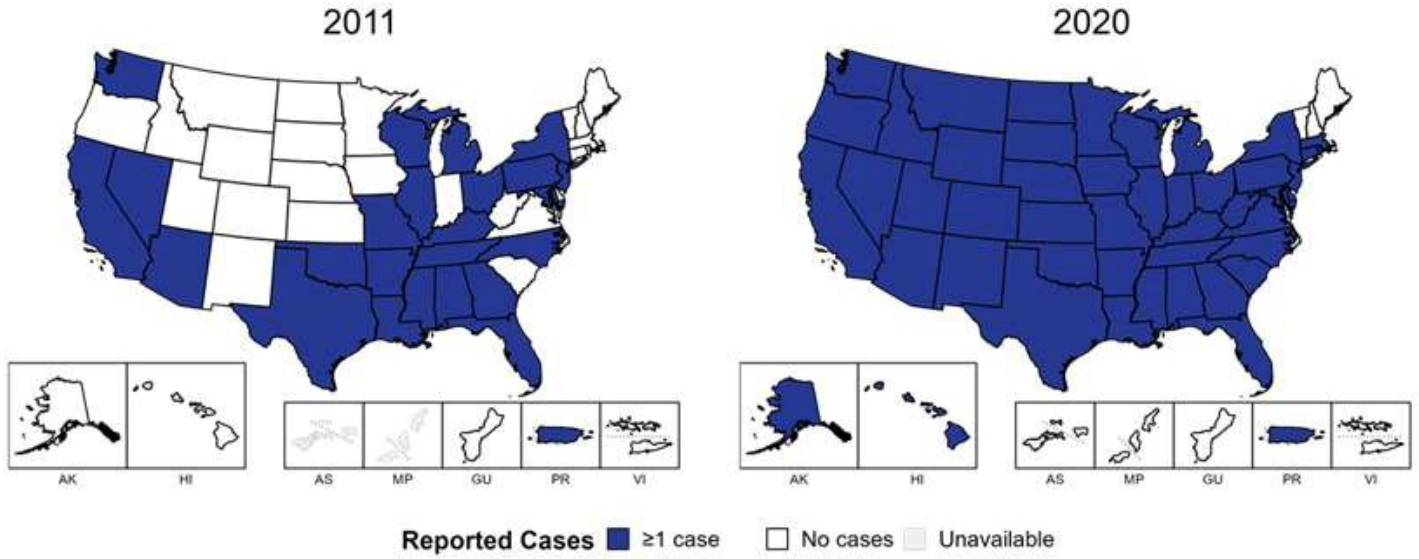


CDC
Centers for Disease Control and Prevention

Syphilis in the 2020s: Congenital Syphilis



Congenital Syphilis



Syphilis Serologies

- Nontreponemal (lipoidal) tests: RPR and VDRL
  - Nonreactive in 30% of persons with primary syphilis
  - False positives occur (older age; autoimmune diseases; HIV & other infections)
  - May become nonreactive over time with or without treatment
- Treponemal tests: (EIA, CIA, FTA-ABS, TPPA, etc.)
  - Nonreactive in 30% of persons with primary syphilis
  - False positives occur (non-syphilitic treponematoses; severe gingivitis)
  - Once reactive always reactive-independent of treatment history

Table 1. Traditional and Reverse-Sequence Algorithms for Serologic Testing.*

Algorithm	NTT	TT	Confirmatory TT†	Interpretation‡
Traditional	Nonreactive			No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Treated or long-standing untreated syphilis
Traditional	Reactive	Nonreactive		Biologic false positive NTT§
Traditional and reverse-sequence	Reactive	Reactive		Untreated syphilis (likely) Treated syphilis (likely) Endemic treponematoses
Reverse-sequence	Nonreactive	Reactive	Nonreactive	Biologic false positive TT¶
Reverse-sequence	Nonreactive	Reactive	Reactive	Treated syphilis (most likely) Long-standing untreated syphilis Early primary syphilis (before NTT has turned positive) Prozone reaction (more common with VDRL test than with RPR test)
Reverse-sequence		Nonreactive		No serologic evidence of syphilis (most likely) Early primary syphilis (extremely recent infection cannot be ruled out) Long-standing treated syphilis if TT shows seroreversion

* The traditional algorithm starts with a nontreponemal test (NTT) followed, if reactive, by a confirmatory treponemal test (TT). The reverse-sequence algorithm starts with a TT (e.g., fluorescent treponemal-antibody absorption test, *Treponema pallidum* particle agglutination test, or automated enzyme or chemiluminescence immunoassay), followed, if reactive, by an NTT. RPR denotes rapid plasma reagin, and VDRL Venereal Disease Reference Laboratory.
† The confirmatory TT should be different from the TT performed initially.
‡ The likely or most likely interpretation of test results is noted for each algorithm.
§ Causes of a biologic false positive NTT include older age, autoimmune diseases, infections (e.g., human immunodeficiency virus infection), and drug use; pregnancy as a cause is controversial.
¶ Causes of a biologic false positive TT include infections (e.g., Lyme disease), autoimmune diseases, and older age.

Ghanem NEJM 2020

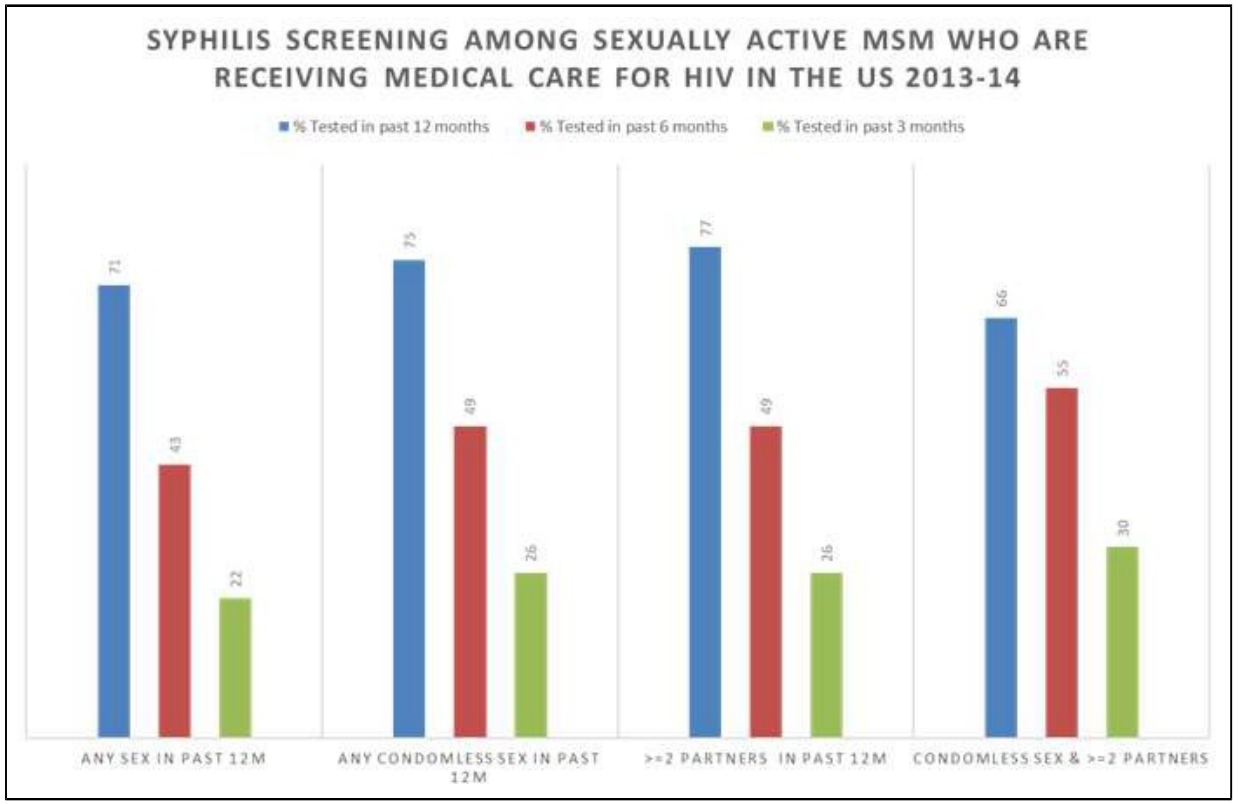
The Challenge of Screening

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA hivma

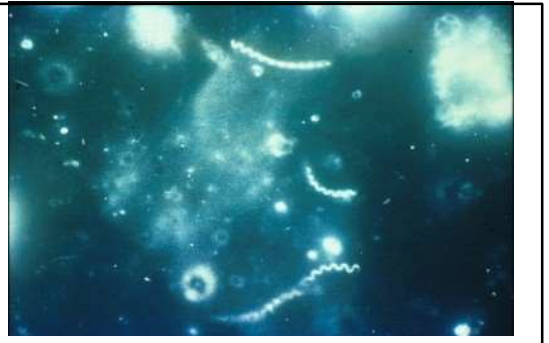
Syphilis Testing Among Sexually Active Men Who Have Sex With Men and Who Are Receiving Medical Care for Human Immunodeficiency Virus in the United States: Medical Monitoring Project, 2013–2014



"Nearly one-third of sexually active HIV-positive MSM were not tested annually, and many at increased risk were not tested at recommended frequencies. Efforts to improve compliance with screening guidelines for high-risk HIV-positive MSM are warranted"

CID 2019:68 (15 March)

Neurosyphilis: Diagnostics



- No single test can be used to diagnose neurosyphilis;
  - 50% of neurosyphilis cases may have negative CSF VDRL; it is highly specific, but **insensitive**
  - **CSF pleocytosis is the most sensitive test but it is not very specific**
  - Elevation of CSF protein is nonspecific; if it is the only CSF abnormality, be careful with its interpretation
  - CSF treponemal tests (e.g. CSF FTA-ABS) are very sensitive BUT they are NOT specific; in other words, a negative test helps to rule out neurosyphilis, but a reactive test does not rule it in
  - Remember that ~30% of persons with LATE neurosyphilis may have negative SERUM non-treponemal test

Otic and Ocular Syphilis Take-Home Points

Otosyphilis

- Clinical manifestations: cochleovestibular dysfunction and syphilis infection without an alternate diagnosis; ~50% bilateral
  - Symptoms: **Hearing loss, vertigo, and/or tinnitus** (ringing in the ears)
  - Diagnosis is presumptive; **CSF examination is normal in 90% of cases and is NOT recommended if patient only has otic signs and symptoms**
- Therapy: IV penicillin (+ corticosteroids)
- Prognosis: 23% experience improvement in hearing; up to 80% experience improvement in tinnitus and vertigo

Ocular Syphilis

- Clinical manifestations: any portion of the eye; any ocular manifestation; **immediate ophthalmological examination**
  - Symptoms: Redness, pain, floaters, flashing lights, visual acuity loss
  - Diagnosis is presumptive; **CSF examination is normal in 40% of cases and is NOT recommended if patient only has ocular signs and symptoms**
- **Therapy**: IV penicillin (+ corticosteroids)

JAMA. 2022;327(2):161-172.

Syphilis therapy

- Early stages (primary, secondary, early latent)
  - 2.4 MU of long-acting benzathine penicillin or doxycycline 100mg PO BID X 14 days
- Late latent/unknown duration
  - 2.4 MU of long acting benzathine penicillin G IM X3 (over 2 weeks) [7.2 MU total] or doxycycline 100mg po BID X 4 weeks
- Neurosyphilis
  - Aqueous penicillin 18 to 24 MU IV X 10-14 days
  - Procaine penicillin 2.4 MU IM + probenecid 500 mg po QID X 10-14 days
  - Ceftriaxone 1-2g IV/IM X 10-14 days
- Jarisch-Herxheimer: within 24 hours after therapy (most likely in early stages but rarely occurs in late stages); antipyretics only; may induce early labor

What to do with VDRL/RPR Titers that Don't Respond Appropriately

- **Lack of a fourfold decline in titers** after waiting a **full 12m** following therapy for early syphilis and a **full 24m** following therapy for late syphilis:
  - Any neurological signs/symptoms or are the titers >=1:64? **If yes, perform LP**
  - Could the patient have been reinfected? **If yes, treat**
  - If both above are negative, you can either follow the patient carefully or you can give additional antibiotics. Several observational studies suggest that there are **NO short/intermediate-term benefits to additional antibiotics**
- A **four-fold increase in titers** after appropriate therapy:
  - Any neurological signs/symptoms? **If yes, perform LP**
  - Could the patient have been reinfected? **If yes, treat**
  - If the patient denies the possibility of reinfection, and the titer continues to be elevated when repeated two weeks later, **consider performing a LP**

Syphilis: CSF Examination

- Perform a lumbar puncture (LP) in persons who:
  - **Have neurological signs and symptoms**
  - Are diagnosed with tertiary syphilis (cardiovascular, gummas)
  - Consider in those who are asymptomatic but whose serological titers increase four-fold after stage-appropriate therapy and in whom the likelihood of reinfection is low and in those whose titers fail to decline four-fold if the titers are >=1:64
- No data to support routine LP in asymptomatic PWH
- No need for follow-up LP 6 months after the diagnosis and treatment of neurosyphilis in HIV uninfected or PWH who are on ART if they improve clinically, and their serological titers are responding appropriately

Syphilis & Pregnancy

- Screen everyone at 1st prenatal visit
- Screen all high-risk patients and those living in high-prevalence areas twice in the 3rd trimester: at 28 weeks and again at the time of delivery
- Screen those who deliver a stillborn infant after 20 weeks' gestation
- Pregnant penicillin-allergic patients with syphilis need to be desensitized to penicillin and treated with a penicillin-based regimen. There are NO OTHER OPTIONS (not even ceftriaxone)

The State of Syphilis in the 2020s

- Increasing rates in both men and women
- Rising rates of congenital syphilis- each case representing a failure of an **overburdened** and **under-resourced** public health system
- Stark **inequities** reflecting multiple complex factors including poverty, stigma, mental health, substance use, and structural racism
- Challenges with traditional control measures particularly screening and partner notification

Trichomonas vaginalis

- Majority of infections asymptomatic in both men and women; causes vaginitis and NGU (especially among heterosexual men)
- Older women and MSW are at higher risk
- Diagnosis: culture and **PCR**; wet mount is not sensitive
- Vaginal pH usually >4.0
- Therapy: **Metronidazole 500mg PO BID X 7 days for all women** [never use topical gel formulations]; Metronidazole 2g PO X1 is ok for men; **Tinidazole 2g orally X1 ok for both men and women**
  - Recent study suggests that 1 week of metronidazole better than 2g in HIV-uninfected women (Kissinger P, et al. *Lancet Infectious Diseases* 2018)
- Resistance: ~5% of strains have low-level resistance to metronidazole; <1% have high level resistance
- Partners in the preceding 60 days must be treated
- **Screen women with HIV annually**

Bacterial Vaginosis

- Vaginal dysbiosis where anaerobes/facultatives become the dominant communities (as compared to lactobacilli)
  - We now understand that the causes are heterogeneous
  - We are beginning to understand that the approach to therapy will need to be personalized
- Rx: Metronidazole 500mg PO BID X 7days OR Clindamycin 300mg PO TID X 7 days OR topical metronidazole gel or clindamycin cream
  - 60% will relapse within the next 3-6 months
  - **A recent RCT of the probiotic Lactin-V used as a supplement to therapy decreased recurrences by 34% at 12 weeks and 27% at 24 weeks** Cohen C et al. N Engl J Med 2020:1906-1915
- **Do NOT use metronidazole 2g PO X1**
- **BV during pregnancy:** associated with preterm labor, premature rupture of membranes, post-partum endometritis
  - Treat all **symptomatic** cases of BV during pregnancy
  - **USPSTF: "The current evidence is insufficient to assess the balance of benefits and harms of screening for BV in pregnant persons at increased risk for preterm delivery"** JAMA. 2020;323(13):1286-1292

Table 1
Summary of genital tract infections and adverse outcomes

Infection (Organism)	Outcomes in Women	Pregnancy Outcomes	Fetal/Neonatal Outcomes
Chlamydia (*Chlamydia trachomatis*)	Cervicitis PID Ectopic pregnancy Tubal infertility	Ectopic pregnancy PROM Preterm delivery low birth weight	Fetal loss, preterm delivery, low birth weight Conjunctivitis, pneumonia
Gonorrhea (*Neisseria gonorrhoeae*)	Cervicitis PID Ectopic pregnancy Tubal infertility DGI	Ectopic pregnancy PROM Fetal growth restriction Low birth weight	Low birth weight, preterm delivery, ophthalmia neonatorum, DGI
Syphilis (*Treponema pallidum*)	Genital ulcer disease Uveitis Alopecia Meningovascular disease Cardiovascular disease (aortitis)	Fetal loss stillbirth Preterm delivery Low birth weight congenital syphilis	Fetal loss stillbirth Preterm delivery Low birth weight Congenital syphilis
Herpes Simplex (HSV Type 1 + 2)	Recurrent genital ulcer disease Viral hepatitis Keratitis Meningitis/ Encephalitis	Spontaneous abortion Preterm delivery Stillbirth	Preterm delivery, low birth weight, encephalitis, disseminated disease, skin, eye, and mouth disease

Abbreviations: DGI, disseminated gonococcal infection; PROM, premature rupture of membranes.

Table 2
Diagnostic options for genital tract infections in women and newborns in LMIC

	Gold Standard Testing (Often Unavailable in LMIC)	Testing in LMIC Settings	Rapid or Point of Care Test	Self-collection Option	Newborn Testing
Syphilis	Serologic screening with confirmatory test	Serologic screening with or without confirmation	Rapid treponemal test with 75–99% sensitivity. Dual syphilis/HIV available	Pilot studies in HIC	VDRL/RPR
HSV 1 + 2	HSV culture HSV PCR of active lesion	Serology	Available in HIC or research study	Pilot studies in HIC	Clinical; culture of lesions; PCR
CT/NG	CT/NG culture or RNA/DNA NAAT	CT serology	N/A	Option per WHO	CT/NG: Culture of conjunctival swab
TV	NAAT	Direct microscopy (wet mount)	Available in HIC or research only	Option per WHO	Not available
BV	Nugent Score on Gram stain vaginal fluid smear	Amsel score	Under investigation	Option per WHO	Not available
Candidiasis	culture	Microscopy	Available in HIC or research only	Option per WHO	Not available
Pelvic Inflammatory Disease	Laparoscopic examination, endometrial biopsy or pelvic imaging studies	None. Clinical diagnosis.	CT/NG/MG NAAT in HIC or research study	HIC only	Not applicable

Abbreviations: HIC, high-income countries; MG, *Mycoplasma genitalium*; NAAT, nucleic acid amplification test; RPR, rapid plasmin regain; VDRL, Venereal Disease Research Laboratory.

Table 3
Treatment of common genital tract infections in women, pregnancy, and neonates according to 2021 guidelines from the WHO and US CDC

	Women	Pregnancy	Neonates
Syphilis	Early: Benzathine penicillin G 2.4 MU intramuscularly in a single dose Late or latent[a]: Benzathine penicillin G 2.4 MU intramuscularly weekly x 3 doses (same for WHO and CDC)	Early: Benzathine penicillin G 2.4 MU intramuscularly in a single dose Late or latent WHO[a]: erythromycin 500 mg orally 4 times a day for 14 days Late or latent CDC[a]: Benzathine penicillin G 2.4 MU intramuscularly weekly x 3 doses	WHO: Aqueous benzyl penicillin 50 000 U/kg/12 hrs intravenously for 10–15 days OR Procaine penicillin 50 000 U/kg/day single dose intramuscularly for 10–15 days CDC: Aqueous crystalline penicillin G 50,000 U IV/kg/12 hrs × 7 days then every 8 hours × 3 days to complete 10 day regimen OR Procaine penicillin G 50,000 U IM/kg/day x 10 days
HSV (same for WHO and CDC)	Primary infection: Acyclovir 400 mg orally daily 3 times a day for 10 days. Recurrent infection: Acyclovir 400 mg orally daily 3 times a day for 5 days.	Primary infection: Acyclovir 400 mg orally daily 3 times a day for 10 days. Recurrent infection: Acyclovir 400 mg orally daily 3 times a day for 5 days.	Acyclovir 60 mg/kg/day in divided doses 8 hourly for 21 days if disseminated or CNS disease OR 14 days if not
CT/NG (uncomplicated) (CT treatment same for WHO and CDC)	CT: doxycycline 100 mg orally twice daily for 7 days NG WHO: ceftriaxone 250 mg IM, single dose + azithromycin 1 gram orally, single dose NG CDC: ceftriaxone 500 mg IM, single dose alone if CT has been ruled out)	CT: Azithromycin 1 gram orally, single dose OR Erythromycin 500 mg orally, 4 times a day for 7 days NG WHO: ceftriaxone 250 mg IM, single dose + azithromycin 1 gram orally, single dose NG CDC: ceftriaxone 500 mg IM, single dose alone if CT has been ruled out)	CT: Azithromycin 20 mg/Kg orally for 3 days OR Erythromycin 50 mg/Kg/per day in 4 divided doses for 14 days NG: ophthalmia Ceftriaxone 50 mg/Kg IM single dose DGI: Ceftriaxone 25–50 mg/Kg/day once IV/IM for 10–14 days (Cefotaxime 50 mg/Kg 12 hourly)
PID	PID WHO outpatient mgmt: ceftriaxone 250 mg IM, single dose + azithromycin 1gm PO, single dose + doxycycline 100 mg PO twice daily x 14 days + metronidazole 400 or 500 mg PO twice daily x 14 days PID CDC: Ceftriaxone 1g Q24 hrs + Doxycycline 100 mg PO/IV q 12 hrs + Metronidazole 500 mg PO/IV q12 hrs	PID CDC: Consult with ID Expert Consider Ceftriaxone 1g Q24 hrs + Azithromycin 500 mg PO/IV q 24 hrs + Metronidazole 500 mg PO/IV q12 hrs (no PID regimen in pregnancy specified by WHO)	N/A

		MG (same for WHO and CDC)	Azithromycin 500 mg orally D1, then 250 mg orally on D2-5.	Azithromycin 500 mg orally D1, then 250 mg orally on D2-5.	Guidance not established
		TV (same for WHO and CDC)	Metronidazole 2 grams orally in a single dose	Metronidazole 200 mg or 250 mg orally three times a day for 7 days	Guidance not established
			(avoid 1st trimester use, if possible)		
BV (same for WHO and CDC)	Metronidazole 400 mg or 500 mg orally twice daily for 7 days			Metronidazole 200 mg or 250 mg orally three times a day for 7 days (avoid 1st trimester use) Alternative: clindamycin 300 mg orally	Routine treatment not indicated for exposure
			twice daily for 7 days)		
Candidiasis (*C albicans*)	Miconazole vaginal suppository 200 mg at night for 3 nights	Miconazole vaginal suppository exposure		Routine treatment not indicated for (same for WHO and CDC)	200 mg at night for 3 nights

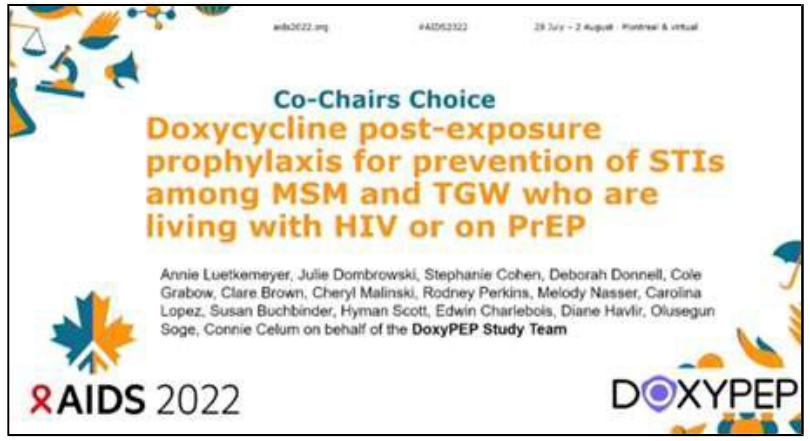
STI screening recommendations for women

Population	Routine Screening recommendations	Screening frequency	Additional recommendations
Age <25 years	Genital chlamydia*	Annually	Screen for syphilis, trichomoniasis, and HBV if at increased risk.[¶] Screen for HCV if age >18 years (in areas with HCV positivity >0.1%).
	Genital gonorrhea*	Annually	
	HIV	At least once	
Age ≥25 years	HIV	At least once	Screen for gonorrhea, chlamydia, syphilis, trichomoniasis, and HBV if at increased risk.[¶] Screen for HCV if age >18 years (in areas with HCV positivity >0.1%).
Pregnant	Genital chlamydia	First trimester (if <25 years or at increased risk[¶])	Repeat screening for these infections in third trimester if at increased risk. All pregnant women at risk for HCV infection should be screened at the first prenatal visit. Pregnant women with HIV are also screened for trichomoniasis at the first prenatal visit.
	Genital gonorrhea	First trimester (if <25 years or at increased risk[¶])	
	Syphilis	First trimester	
	HIV	First trimester	
	HBV	First trimester	
With HIV infection	Genital chlamydia	Annually	
	Genital gonorrhea	Annually	
	Genital trichomoniasis	Annually	
	Syphilis	Annually	
	HBV	First visit	
	HCV	First visit	
WSW and WSWM	WSW and WSWM should not be assumed to be at lower risk for STIs on the basis of their sexual orientation. Screening for cervical cancer and STIs should be conducted according to guidelines for women, based on an open discussion of sexual and behavioral risk factors.		

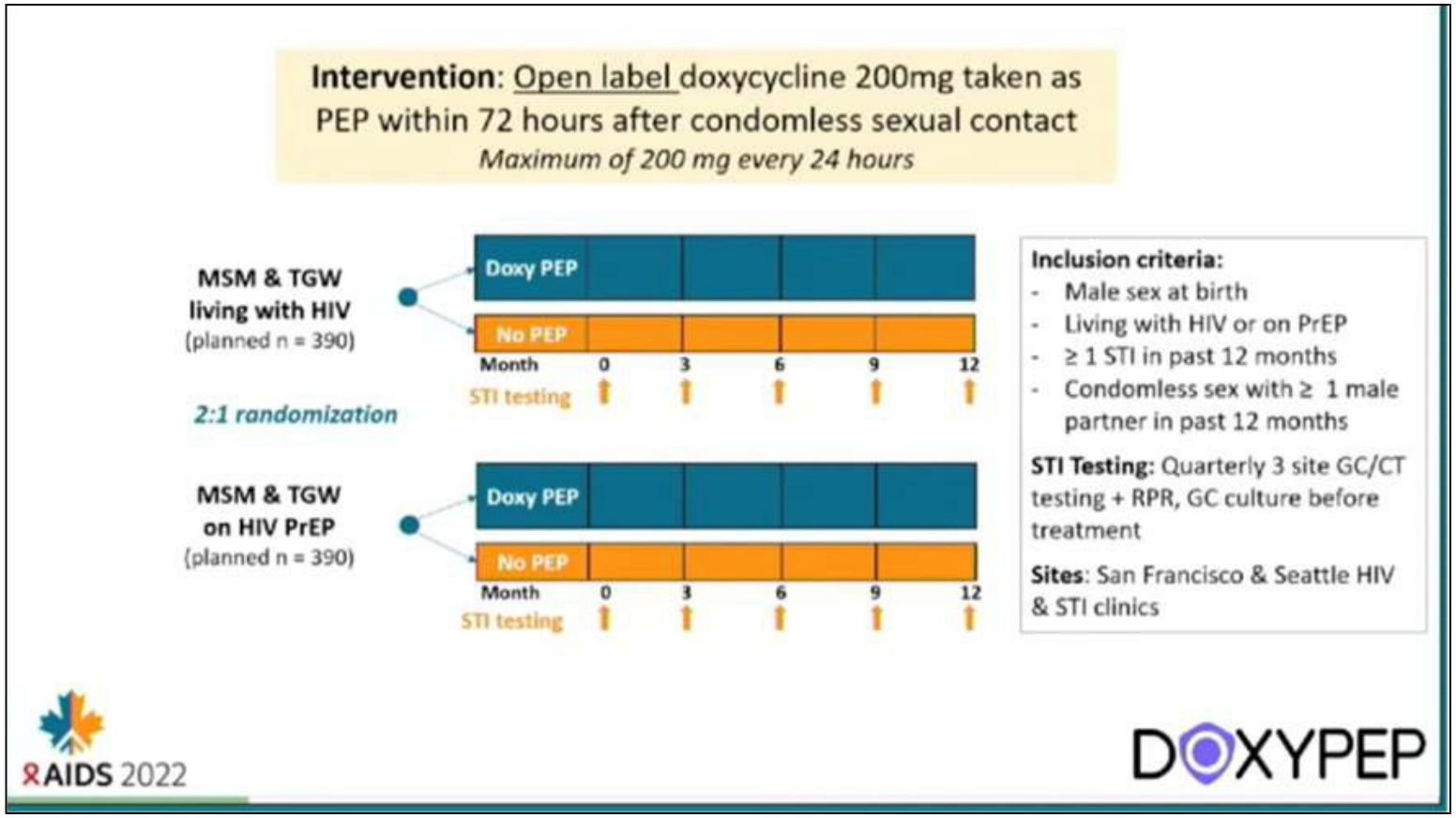
Are there potential near-term solutions to increasing rates of STIs?

STI

PEP



- 324 PrEP and 174 PLW
- Median age: 38
- **Median # of sex partners in prior three months: 9**
- 59% substance use
- >90% male with remainder TGW or gender diverse

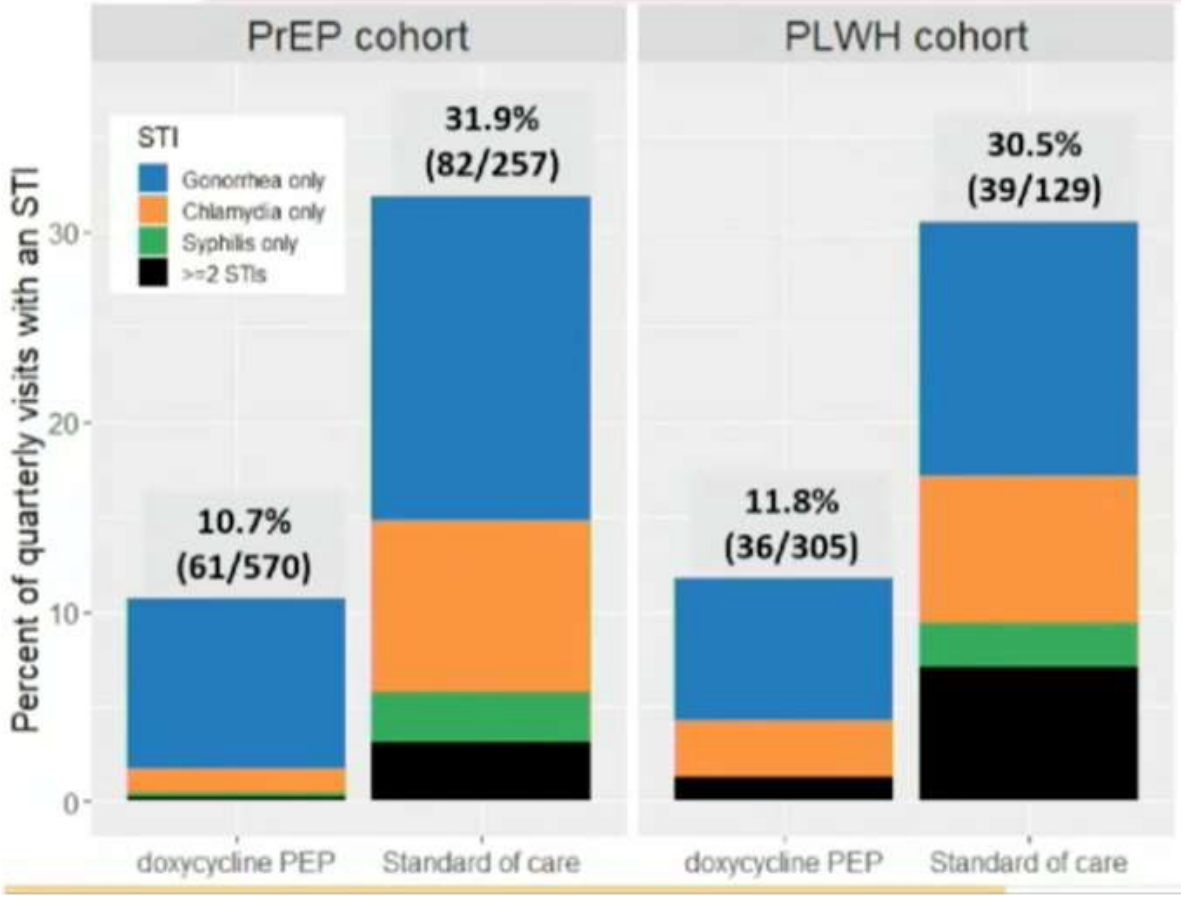


DSMB recommended halting study early

Luetkemeyer et al., Abstract 13231, AIDS 2022

Doxy-PEP results

Primary Endpoint: STI incidence per quarter



Reduction in STI incidence/quarter	
	risk reduction (95% CI)
PrEP	**0.34 (0.24 - 0.46)**
Living with HIV	**0.38 (0.24 - 0.60)**
Total	**0.35 (0.27 - 0.46)**

all p< 0.0001

Reduction in each STI per quarter		
	risk reduction (95% CI)	
	PrEP	**PLWH**
GC	0.45 (0.32 - 0.65) *p<0.0001*	0.43 (0.26 - 0.71) *p=0.001*
CT	0.12 (0.05 - 0.25) *p<0.0001*	0.26 (0.12 - 0.57) *p=0.0007*
Syphilis	0.13 (0.03 - 0.59) *p=0.0084*	0.23 (0.04 - 1.29) *p=0.095*

Luetkemeyer et al., Abstract 13231, AIDS 2022

Doxy-PEP results

- 88% acceptability, 1.5% discontinuation (intolerance/preference)
- Median of 7.3 sex acts, 87% covered by Doxy
- Doses per month
  - <10 doses per month 54%
  - 10-20 doses per month 30%
  - >=20 doses per month 16%
- 30% of gonorrhea endpoints had culture data for resistance testing
  - ~20% tetracycline resistance in baseline cultures
  - In IPERGAY ~56% resistance to tetracycline
  - Trend towards increase in tetracycline resistance in breakthrough infections

Luetkemeyer et al., Abstract 13231, AIDS 2022

The Main Challenge with DOXY PEP

- Uncertainty about long-term sequelae
  - Dysbiosis (but what does that mean clinically)
  - Resistome
    - STI pathogens
    - Other pathogens (S aureus)
  - Metabolic (weight gain)
  - Immunologic
  - Diagnosis and serological management of syphilis

Upcoming studies:

- dPEP/ Kenya: Doxy PEP in women taking HIV PrEP
- DoxyVacc/ France: MSM PEP
- DISCO/ Canada: Doxy PEP vs. PrEP
- Syphilaxis/ Australia: Observational study of Doxy PrEP

The NNPTC provides:

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