Sexually Transmitted Infections: What's New in 2021?

Connie Celum, MD, MPH
Professor of Global Health and Medicine
Director, International Clinical Research Center
Director, Center for AIDS Research
University of Washington
Seattle, Washington

Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Celum has served as a scientific advisor to Merck & Co., Inc. and Gilead Sciences, Inc. (Updated 10/26/21)

Slide 2

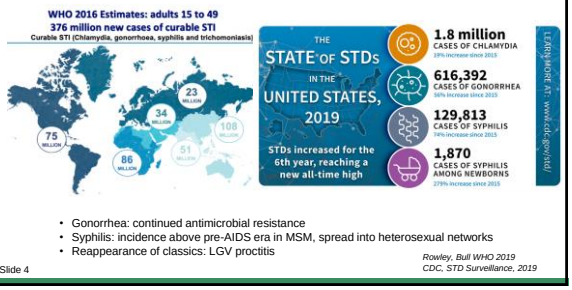
Learning Objectives

After attending this presentation, learners will be able to:

- Identify recent sexually transmitted infection (STI) trends
- Diagnose and treat syphilis, including complicated syphilis
- Screen for and treat extragenital gonorrhea and chlamydia
- Describe changes in the 2021 CDC STI Treatment Guidelines

Slide 3

Global impact of STIs



- Gonorrhea: continued antimicrobial resistance
- Syphilis: incidence above pre-AIDS era in MSM, spread into heterosexual networks
- Reappearance of classics: LGV proctitis

Rowley, Bull WHO 2019
CDC, STD Surveillance, 2019

Slide 4

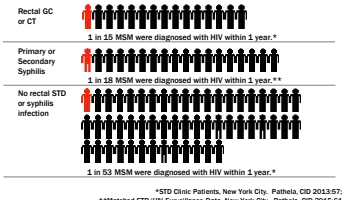
Why is this happening?

- Health disparities, stigma, social determinants of health
- Limited program capacity & access to prevention services
  - Aggravated by COVID
- Provider awareness
- High prevalence of asymptomatic infection
- Limited point of care diagnostics
- Antimicrobial resistance (GC, M Gen)
- Missed opportunities for vaccine preventable infections (HPV, HAV, HBV)
- Syndemics of substance use with HIV, HCV, STIs

Slide 5

Why should we care?

- STIs cause morbidity, especially syphilis
- STIs, including asymptomatic STIs, increase risk of HIV acquisition

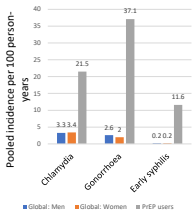


*STD Clinic Patients, New York City. Pathela, CID 2013:57;
**Matched STD/HIV Surveillance Data, New York City. Pathela, CID 2015:61

Slide 6

Rising STI rates:
A public health problem arising in part from public health successes

Pooled STI incidence in PrEP users



Ong, JAMA Network Open, 2019

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What can we do to impact the STI epidemic?

- Behavioral and biologic risk assessment
  - Gender-neutral 5Ps (**P**artners, **P**ractices, **P**rotection from STIs, **P**ast STI history, & **P**regnancy intention)
  - Harm reduction
- Pre-exposure vaccination (HPV, Hepatitis A, Hepatitis B)
- HIV PrEP & PEP, U=U
- Discuss STI prevention (male condoms, male circumcision), emergency contraception
- Align with *Recommendations for Providing Quality Sexually Transmitted D Clinical Services, 2020* (QCS)
- Retesting (chlamydia, gonorrhea, trichomonas) 3-month post therapy
- Partner Services - EPT permissive (MSM)- shared clinical decision making
- Be familiar with CDC STD Treatment Guidelines (www.cdc.gov/std/tg2021)

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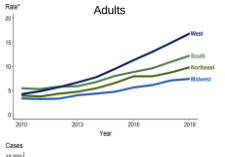
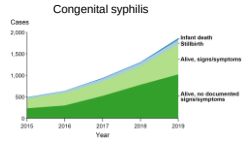
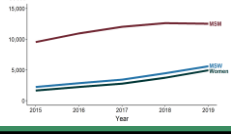
Syphilis is on the rise in adults… and neonates







Congenital syphilis

- 1/3 of congenital syphilis due to delayed prenatal care
- 1/3 due to delayed treatment after syphilis diagnosis

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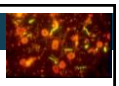
Syphilis



Clinical diagnosis

- Primary syphilis can be atypical (painful when anal, multiple lesions)
- Vigilance for subtle neurologic presentations (ocular, otic manifestations)

Serologic testing: traditional or reverse sequence algorithm use automated treponemal tests

Treponemal tests (i.e., EIA)
- Specific to *T Pallidum*
- Qualitative
- Reactivity persists over lifetime

If + reflex

Non-treponemal tests (i.e., RPR, VDRL)
- Non-specific to *T Pallidum*
- Quantitative
- Reactivity declines with time

- If treponemal tests for screening are +, reflex to quantitative RPR or VDRL for clinical management
- False-positive EIAs can occur, especially in low prevalence populations
  - EIA R, RPR NR, TP-PA NR→ false +
  - EIA R, RPR NR, TP-PA R→ current or past syphilis; if possible recent exposure, repeat RPR

Serologic response after treatment

- Four-fold decline 12 months after primary, secondary, early latent; & 24 months after LL or unknown duration (unless low pre-treatment titers <1:4)

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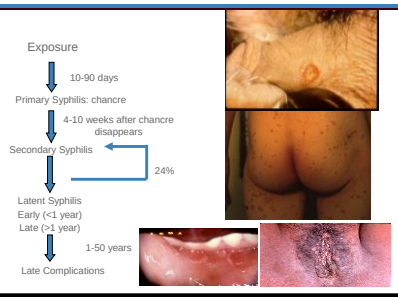
Natural history of syphilis



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Syphilis in pregnancy

- Serologic screening at 28 wks prepartum & delivery (based on community prevalence, maternal risk)
- Maternal risk factors expanded
  - Multiple partners, sex with drug use, transactional sex; late to prenatal care or no prenatal care; meth or heroin use; incarceration; unstable housing/homelessness
- Rescreen if risk of reinfection (ongoing risk or partner not treated)
- Treat with parenteral PCN G
- Reinfection or treatment failure – 4x increase in titer post-treatment > 2 weeks
- Repeat RPR 8 weeks after treatment
  - unless signs of primary or secondary syphilis

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Case 1

One of your HIV patients comes to clinic for routine HIV follow-up. He is doing well and has been virally suppressed for 5 years. He lives with his longtime partner, with whom he does not use condoms, but uses condoms for anal sex with others. 4 sex partners in the last 3 months. He's versatile. He denies any recent rash, urethral discharge or genital/anal or oral ulcer.

PMH: Two episodes of secondary syphilis - the last 24 months ago. RPR 1:128 at diagnosis ->1:64->1:16->1:8->1:8->1:4 3 months ago.

PE: Unremarkable

Lab: RPR 1:16

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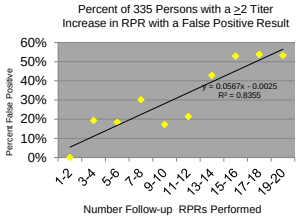
Increased Frequency of Syphilis Testing

- Among HIV- persons, 28% of 1° syphilis & 44% of 2° cases remain RPR+ at 36 months
- Among 335 persons with syphilis, the positive predictive value of a 2-titer RPR increases was 73%
- **Implication: 2-titer increases often need to be confirmed**



Source: Romanoski B. Ann Int Med 1991:114:1005. Avoundjian, T. PHSKC (unpublished)

Slide 15

Case 2

Pt is a 29 y.o. HIV+ man (CD4=219 VL=41K off ART) presents with loss of vision, which started about 3 months ago L>R. Progressive since then with floaters. Pt also c/o paresthesia of his feet and hands and sore joints. Reports having a rash on his torso about 8 months ago. 40lb weight loss, and bed bound for 8 weeks. Diarrhea. "Oh yeah, my husband has similar symptoms."

PE: Cachexic man
Visual exam: Sees shapes and light only. Cannot count fingers.
Unable to stand due to weakness.
Ophtho exam – bilateral anterior uveitis –retinal detachments bilaterally
CSF:WBC 318 (38% PMN, 58% L, 12% M) VDRL 1:4 FTA- reactive

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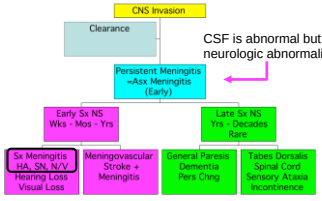
Natural history of CNS syphilis



Screen, rapidly evaluate & treat complicated syphilis

- **Complicated Syphilis:** 3.5% of all syphilis
  - Neurosyphilis (asymptomatic or symptomatic)
  - Otosyphilis (may have normal MRI and LP)
  - Ocular Syphilis (abnormal eye exam, may have normal LP)
- **Key Questions to ask**
  - Change in vision, floaters, flashing lights or photophobia?
  - Change in hearing?
  - New or changed tinnitus?
  - Difficulty walking?
- **Evaluation**
  - If vision symptoms: urgent ophthalmologic eval, including slit lamp
  - If hearing symptoms: urgent audiologic eval
  - LP if clinical signs of neurosyphilis (cranial nerve dysfunction, meningitis, stroke, AMS, decreased vibratory sense)
- **Treatment**
  - Do not delay treatment for evaluation
  - Give Bicillin long-acting if plan is uncertain at end of visit

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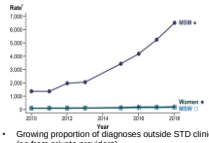
What is old with a new twist: Gonorrhea

- **Antibiotic resistance**
  - Increasing azithro resistance
  - Need higher doses of cephalosporins for pharyngeal infection
- **Diagnostic testing**
  - Urine-based NAAT work well, but don't identify antibiotic resistance
- **Annual screening of sites exposed** (urethra, pharynx, rectum)
  - Extragenital infections are common in MSM and majority are asymptomatic
  - More frequent (3-6 month) screening based on risk

Gonorrhea Cases by MSM, MSW, and Women, STD Surveillance Network, 2010–2018



- Growing proportion of diagnoses outside STD clinics (eg from private providers)

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Gonorrhea – Mono treatment is here in 2021

- **500 mg Ceftriazone recommended for uncomplicated GC (1 gm if >150 kg)**
  - Doxy 100 mg bid if CT not excluded
  - No longer recommend co-treatment; resistance to azithro is increasing
- Alternatives
  - Gentamycin 240 mg IM + azithro 2 gm, *or*
  - Cefixime 800 mg PO
- Test of cure for pharyngeal GC recommended
- EPT: cefixime 800 mg (& doxy 100 mg bid if CT not excluded)
- GC drug pipeline: Solithromycin, zolifodacin

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Case 3

An asymptomatic HIV+ patient you see in clinic tests positive for rectal chlamydial infection.

His pharyngeal and urine GC/CT tests are negative. He is RPR negative.

How do you treat him?

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Chlamydia

Clinical manifestations
- Majority are asymptomatic
- Causes urethritis, cervicitis- usually not purulent
- Reiter's syndrome

Diagnosis
- NAAT for rectal, pharyngeal sites FDA cleared (CT,GC)
- Rectal testing for MSM
  - MSM
  - Consider in women, shared clinical decision-making

Treatment
- Doxycycline efficacious for urogenital, rectal, and oropharyngeal infection
- Concern about azithromycin effectiveness (rectal)
- Nonadherence concerns (rectal)- azithromycin 1 g once (testing after treatment)

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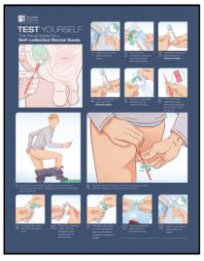
Multisite Screening in MSM and TGW

- Sexually active MSM and transgender or non-binary persons who have sex with men
- Rectal or pharyngeal exposure in past year
- Screen at least annually, or
- Screen Q3 months if any of the following:
  - Bacterial STD in the past year
  - Methamphetamine or popper use in past year
  - ≥10 sex partners (oral or anal) in the past year
  - Condomless anal intercourse with an HIV serodiscordant partner in the past year
  - Taking PrEP



Self-testing is acceptable & sensitive

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2021: Doxycycline is superior to azithro for chlamydia

- Retrospective studies suggested that doxy 100 mg bid is more effective than azithromycin 1 gm
  - Pooled efficacy: 99.6% for doxy vs 83% for azithro
- Randomized double-blind, placebo-controlled trial of azithro 1 gm vs doxycycline 100 mg bid x 7 days in 177 MSM with rectal chlamydia
  - 100% efficacy of doxy & 74% of azithromycin

Table 2. Microbiologic Cure at 4 Weeks, by Treatment Group, in Each Analysis Population

	Complete Case Population[a]		Intent-to-Treat Population[b]		Per Protocol Population[c]	
	Doxycycline (n = 70)	Azithromycin (n = 65)	Doxycycline (n = 88)	Azithromycin (n = 89)	Doxycycline (n = 46)	Azithromycin (n = 48)
Participants with microbiologic cure, n	70	48	80	63	46	37
Participants with microbiologic cure, % (95% CI)	100 (90–100)	74 (56–86)	91 (83–95)	71 (61–79)	100 (92–100)	77 (63–87)
Difference in proportion, %	26 (16–36)		20 (9–31)		23 (11–37)	
P value	<.001		<.001		<.001	

Khosinpour STD 2014
Kong JAC 2015
Dombrowski 2021

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Mycoplasma genitalium

- 15-25% of NGU & 40% of persistent urethritis
- Natural history not defined
- No role for population-based screening
- Test for persistent or recurrent urethritis
  - NAAT FDA cleared (urine, urethral, penile, endocervical, vaginal)
- Treatment based on availability of macrolide resistance testing

•*If not available*, doxy 100 mg bid x 7 days then moxifloxacin 400 mg x 7 days	•*If available*, doxy 100 mg bid x 7 days then azithro 500 mg x 3 days (macrolide sensitive) or moxifloxacin 400 mg x 7 days (macrolide resistant)

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HPV

- 2.6 fold increased risk of HIV among African women in VOICE trial
  - HPV vaccination may offer HIV prevention benefits
- HPV vaccine: catch up vaccination through age 27; shared decision-making for ages 27-45
- Cervical cancer screening guidance (USPTSTF, ACOG, ACS)
- HPV also accounts for oropharyngeal cancer, esp in men
- Anal cancer screening
  - 2021: ANCHOR study reported reduced progression to anal CA with removal of HSIL
  - Will inform anal cancer screening guidance & require training of providers in high-resolution anoscopy

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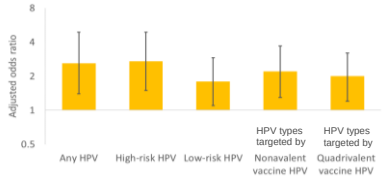
Association between HPV infection and HIV acquisition

- Case-control study of 138 women who seroconverted to HIV and 412 non-HIV seroconverters from VOICE, matched on age, site and visit
- Infection with vaccine–preventable HPV types increased HIV acquisition by 2x



*Adjusted for age, education, study product randomization, sexual behaviors, and other STIs

Liu G IAS 2021

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HSV

- Most common cause of GUD; increased proportion due to HSV-1
- HSV PCR preferred diagnostic test on GUD
- Type-specific serologic testing for persons with recurrent GUD
  - Be aware of lower specificity with low index values (<3)
  - Use second HSV type-specific EIA for confirmation
- No changes in treatment regimens with valacyclovir, acyclovir
  - Suppressive therapy if frequent recurrences or HIV+ with CD4<200
- No HSV preventive or therapeutic vaccine

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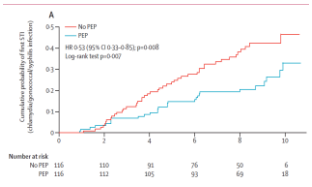
Beyond testing and treating: Doxy PEP as a future intervention???

- RCT in open label extension of IPERGAY PrEP study
- Doxy 200mg x1 24-72 hours after sex
- Median 7 pills/month (IQR: 3-15)
- No risk compensation



- 70% reduction in CT & syphilis
- No reduction in GC
  -70% TCN resistance in GC in France

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Questions after doxyPEP results from IPERGAY

- **Will doxycycline PEP work …?**
  - In MSM & TGW living with HIV?
    - Potentially different adherence, efficacy and effect on antimicrobial resistance
  - In persons taking daily PrEP ?
    - Different dosing strategies with daily HIV PrEP and event-driven STI PEP?
  - Have partial efficacy against GC?
    - Lower TCN resistance than in Europe
- **Will doxycycline increase tetracycline resistance?**
  - STIs (GC, CT, syphilis)
  - Sources of transferable resistance (*Neisseria* spp.)
  - *S. aureus* (doxycycline is sometimes used for MRSA)
  - Impact on gut microbiome

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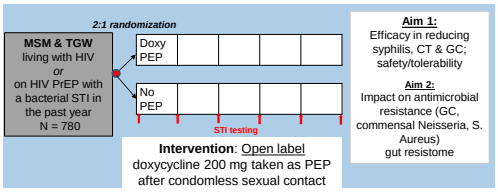
Ongoing doxy PEP Study in SF and Seattle



Intervention: Open label doxycycline 200 mg taken as PEP after condomless sexual contact

Aim 1:
Efficacy in reducing syphilis, CT & GC; safety/tolerability

Aim 2:
Impact on antimicrobial resistance (GC, commensal Neisseria, S. Aureus)
gut resistome

DOXYPEP

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Meningococcal vaccine and GC?

- Men-ACWY currently recommended in persons living with HIV & consideration for MSM without HIV
- 30% reduction of GC with New Zealand meningococcal B vaccine (retrospective analysis)
- Prospective trial with meningococcal Group B vaccine (rMenB+OMV NZ) which has additional outer membrane proteins with high homology with GC

Petousis-Harris, Lancet 2017

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A Phase II randomized, observer-blind, placebo-controlled study, to assess efficacy of meningococcal Group B vaccine rMenB+OMV NZ in preventing GC

- NIAID established collaboration with STI CTG, GSK, & Uniformed Services University of Health Sciences (USUHS)
  - Multicenter (U.S., Thailand) 2200 participants
- Primary Objective: To demonstrate efficacy of meningococcal B vaccine in prevention of urogenital and/or anorectal gonococcal infection
- Secondary Objectives:
  - Estimate efficacy of meninogococcal B vaccine in prevention of overall gonococcal infection and by anatomical site (urogenital, anorectal or pharyngeal)
  - Assess safety of meningococcal vaccine

Sexually Transmitted Infections (STI) Clinical Trials Group (CTG) DMID Protocol 19-0004: Vaccine Development
MAGI Study: started fall 2020

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Summary: STIs in 2021

- Be aware of local and national epidemiology
- Ask about behaviors and exposures, “5Ps”
- Test to identify asymptomatic infections, appropriately treat and prevent secondary transmission
- Screen for extragenital GC and CT in MSM
- Screen for complicated syphilis (photophobia, vision loss, hearing loss)
- Follow 2021 STI treatment guidelines
  - Ceftriaxone 500 mg IM; no cotreatment for CT if neg PCR
  - Doxycycline 100 mg bid first line treatment for CT
  - Test/treat for *M gen* if persistent urethritis
  - Give HPV, HAV and HBV vaccines

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RESOURCES

stdccn.org

www.std.uw.edu

- www.cdc.gov/std/tg2021

Download CDC STD treatment guidelines app

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Acknowledgments

Julie Dombrowski

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Gui Liu

Jeanne Marrazzo

Kim Workowski

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Question-and-Answer Session