Bacterial Sexually Transmitted Infections and Post-exposure Prophylaxis

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COIs

- No financial or personal COIs to disclose

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Learning Objectives

- Review the epidemiology and clinical presentations for bacterial STIs
- Review the data behind the recommendations for doxycycline post-exposure prophylaxis (doxyPEP)
- Discuss the indications for doxyPEP to prevent bacterial STIs
- Discuss the counseling required for doxyPEP

Definitions & Abbreviations

- STI: Sexually Transmitted Infections
  - Preferred over STD, since "disease" implies symptoms are present
- PLWH: People living with HIV
- PREP: Pre-exposure prophylaxis
  - Given a medication PRIOR to the exposure (intercourse) to prevent something
  - Intercourse does NOT mean only vaginal sex.
- PEP: Post-exposure Prophylaxis
  - Given medication AFTER intercourse has occurred

Definitions

- Transgender: someone who does not identify as the gender they were assigned at birth
- Cisgender: someone who identifies as the gender they were assigned at birth
- Nonbinary: someone who does not identify as male or female
- Gender diverse/fluid: someone who’s gender identity is not fixed as male or female
- MSM: Gay, bisexual or other men who have sex with men

Chlamydia

- *Chlamydia trachomatis*
- Gram negative bacteria
- Obligate intracellular organism
- Most common bacterial STI

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Chlamydia: Epidemiology

- Most commonly affects sexually active young women
- Ages 15-24; ≤ 19 years of age according to CDC surveillance
- Young men who have sex with women
- Chlamydia in a prepubertal child should warrant investigation for sexual abuse

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Chlamydia: Epidemiology

- Incubation period: ~1 week
- Transmission: Sexual contact with infected secretions, usually from an asymptomatic partner
- Can infect any mucosal site (vagina, urethra, rectum & oropharynx)
- Can persist for months to years
- Re-infection is very common

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Chlamydia: Clinical Presentation

- Asymptomatic: most common presentation; especially with re-infection
- GU tract: urethritis, cervicitis, endometritis, salpingitis, and pelvic inflammatory disease, with or without perihepatitis (Fitz-Hugh-Curtis syndrome)
- Proctocolitis: symptoms can mimic IBD

Chlamydia: Clinical Presentation

- Lymphogranuloma venereum (LCV): initial ulcerative lesion on the genitalia with painful suppurative inguinal or femoral lymphadenitis

- Reactive arthritis: uveitis, oligoarthritis and urethritis

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Chlamydia: Diagnosis

- Nuclear acid amplification testing (NAAT): OP, vagina or cervical swab, urine or rectal swab
  - Urine should be obtained without having the patient cleanse the area prior
  - Vaginal self swabs have equal sensitivity

- *Chlamydia* culture is available at reference labs
  - Required for cases of SA
  - Labor intensive

Chlamydia: Treatment

- Historically, this was treated with azithromycin, but was more recently changed to Doxycycline

- Uncomplicated: Doxycycline 100mg PO twice a day for 7 days
  - Pregnancy: Azithromycin 1 gram PO once

- LGV: Doxycycline for 21 days
- PID: Doxycycline in addition to Ceftriaxone + Metronidazole OR Cefotetan/Cefoxitin for 14 days

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Chlamydia: Follow up

- Treat partners
- Repeat testing within 3 months or at their annual physical
  - Pregnant people: Test of cure should be performed 4 weeks after treatment
- Screen for other STIs

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Gonorrhea

- *Neisseria gonorrheae*
- Gram-negative diplococci
- Abbreviated GC for gonococcal
- Transmission: Sexual contact with infected secretions

GC: Epidemiology

- 2nd most reported STI in the US
- ↑ infection rates among Black Americans and other ethnic/racial groups due to systemic racism, i.e., SES, barriers to education
- MSM have higher proportions of positive GC tests as well as other co-infections
- Incubation period: 2 – 7 days

Gonorrhea: Clinical Presentation

- Asymptomatic infections of the urogenital tract
  - Females: 80%
  - Males <10%

- Most pharyngeal & rectal infections are asymptomatic
  - Rectal co-infection can occur with 20-70% of urogenital infections in female patients

Gonorrhea: Localized Disease

- Conjunctivitis: inoculation into the eye with infected secretions

- Acute tonsillopharyngitis with cervical adenopathy

Gonorrhea: Disseminated Infection (DGI)

- 3% of untreated mucosal GC infection

- Petechial or pustular skin lesions
- Arthritis-Dermatitis syndrome: Asymmetric polyarthralgia, tenosynovitis or pyogenic oligoarthritis
  - Arthritis may also be reactive
  - Mnemonic is STD: Synovitis, Tenosynovitis & Dermatitis

Risk factors for Disseminated Infection (DGI)

- Asymptomatic carriers
- Menstruating, pregnant or post-partum people
- MSM
- Complement deficiency (congenital or acquired)

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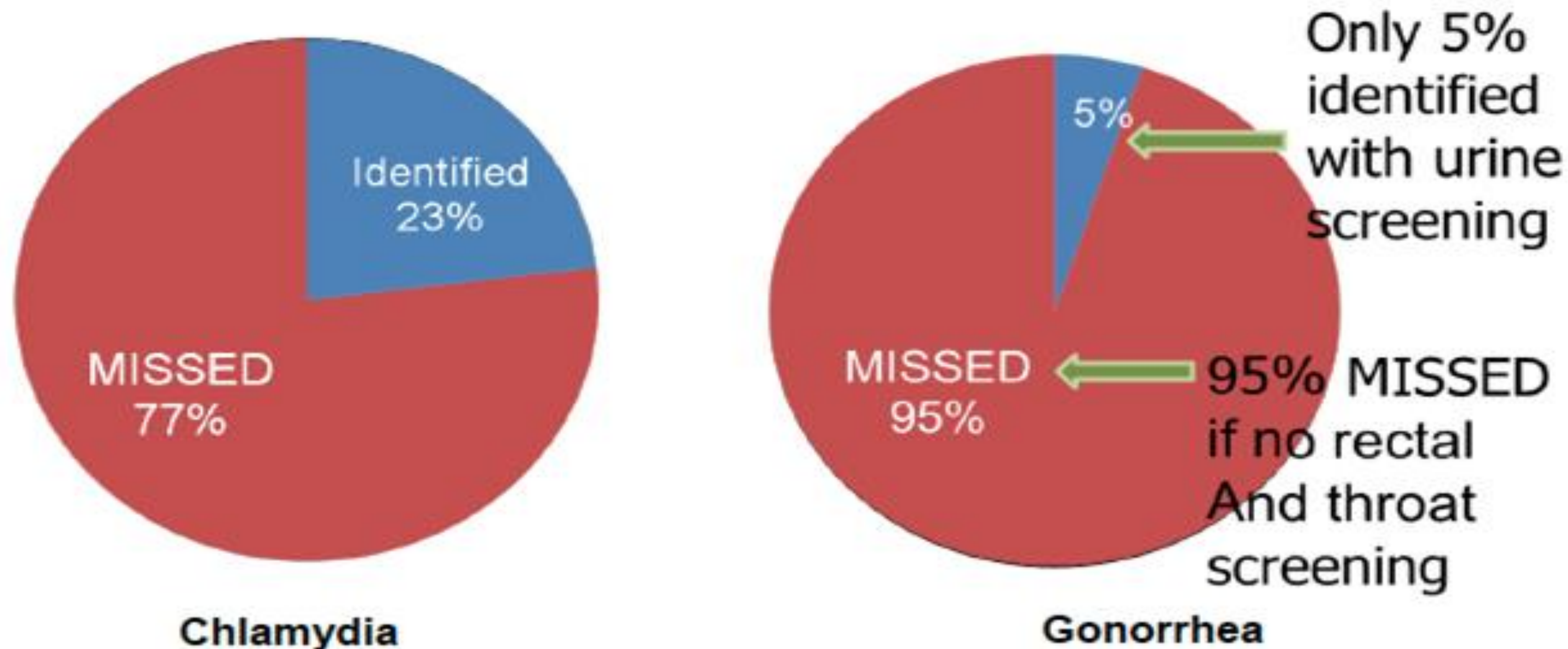
Gonorrhea: Diagnosis

- Nuclear acid amplification testing (NAAT): conjunctivae, OP, vagina or cervical swab, urine or rectal swab
  - Conjunctivae is not FDA-cleared but offered at some reference labs
  - Urine should be obtained without having the patient cleanse the area prior
  - Vaginal self swabs have equal sensitivity

- *N gonorrhoeae* grows on Martin–Lewis agar
  - Fastidious growth, especially from synovial fluid
  - Must be inoculated into culture quickly as it is very sensitive to temperature and/or humidity

Sexually transmitted infections can be missed if just screening urine



Marcus, et al. Sex Transm Dis. 2011; 38:922-4.

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Gonorrhea: Treatment

- Uncomplicated: Ceftriaxone 500mg IM

- DGI: 7 days
  - Ceftriaxone with stepdown to Cefixime is susceptible

Gonorrhea: Follow up

- Treat partners
- Repeat testing within 3 months
- Screen for other STIs

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Syphilis

- *Treponema pallidum*
- Gram-negative Spirochete
  - Lacks LPS
- Transmission: Sexual contact with infected secretions or exudate
- Incubation period varies depending on stage of illness

Syphilis: Epidemiology

- Gay & Bisexual men
- ↑ rates reported between 2016 – 2020 in both men & women
- Co-infection is not uncommon
- Presence of HIV infection is thought to alter the clinical expression of syphilis, response to therapy, and the results of serologic tests.

Primary Syphilis

- Incubation period: 3 weeks (10 – 90 days)
- 30% of cases

- Single painless papule → ulcer with reddened base & rolled edges
  - Oral & anogenital regions (penis, vulva, vagina, cervix, anus or rectum)
  - Inoculum of fewer spirochetes may just cause a painless papule
  - Heals within 3-6 weeks

- May also have painless inguinal lymphadenopathy for months

Secondary Syphilis

- Incubation period: 6 – 12 weeks
- 15% of cases
- Primary genital lesions still present
- Systemic disease
- Mucocutaneous lesions
  - Trunk → extremities including the palms & soles
  - Salmon-pink macules → copper-colored papules → follicular or pustular
  - May become hypo- or hyperpigmented & last for months

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Secondary Syphilis

- Painless inguinal lymphadenopathy: 80%

- Condylomata lata: raised, enlarged, broad flat papules
  - 10% of cases
  - Develop in warm, moist areas (vulva, anus, scrotum & axilla)
- White-to-grey patches on mucous membranes: 10%
- Patchy alopecia: < 10%

- CNS involvement is common though usually asymptomatic
  - Acute meningitis: 1-2%
- Resolves within 3-12 weeks without treatment

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Latent Syphilis

- Early latent: within 1st year after infection
  - Relapses of 2ndary syphilis occur among 25% of untreated patients

- Late latent > 1 year after infection
  - Asymptomatic
  - CSF abnormalities may be present and predict development of neurosyphilis

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3° Syphilis

- 30% of untreated cases
- Incubation period: 2-3 months (meningeal) to 20-40 years after 1° infection

- Neurosyphilis: meningeal, meningovascular, and parenchymatous syphilis (including general paresis and tabes dorsalis

- Cardiovascular syphilis: aortic aneurysms, aortic root dilation and CAD
  - 10-40 years after 1° infection

Syphilis: Diagnosis

- Serology
  - *T pallidum* particle agglutination test (TP-PA): Preferred diagnostic test
  - Fluorescent treponemal antibody absorption (FTA-ABS)
  - *T pallidum* enzyme immunoassay (TP-EIA):

- Rapid Plasma Reagin (RPR): Non-treponemal test
  - False positives due to infection (EBV, HIV, Hep B, etc...), SLE, IVDU and older age
  - False negatives: early 1° syphilis, latent stage of long duration & "prozone"

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Syphilis: Treatment

- Penicillin
- More recent studies suggest doxycycline may also be effective

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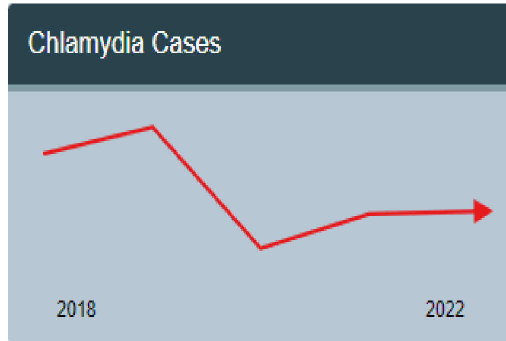
Syphilis: Follow up

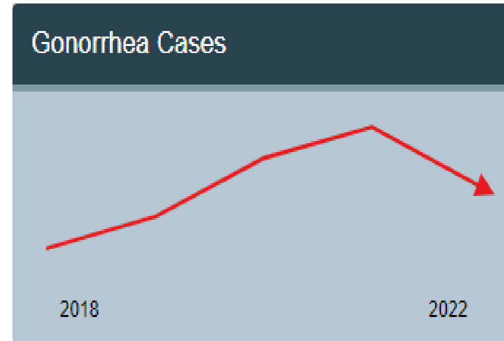
- Treat partners
- Repeat RPR at 6 & 12 months (1° & 2°)
- Some individuals may have low persistent RPR titers (serofast)

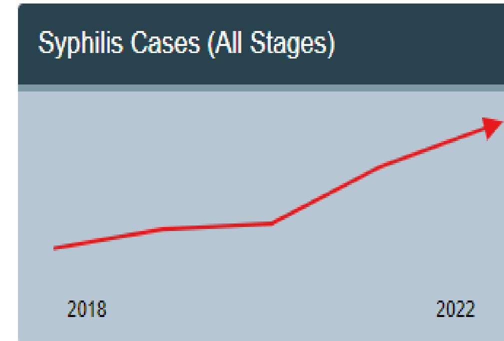
STI Prevalence

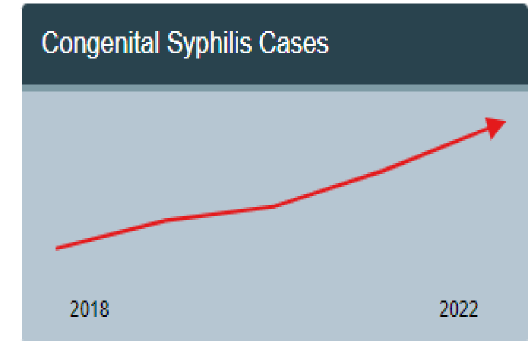
- Anyone who has sex can get an STI, though some groups are more affected
  - Ages 15-24
  - Pregnant people
  - MSM
  - Racial & ethnic minority groups

CDC's 2022 STI Surveillance Report: Incident Cases of Syphilis is on the Rise









Disease	Cases					Percent Change	
	2018	2019	2020	2021	2022	5 Year	1 Year
Chlamydia	1,758,668	1,808,703	1,579,885	1,644,416	1,649,716	-6.2	0.3
Gonorrhea	583,405	616,392	677,769	710,151	648,056	11.1	-8.7
Syphilis (All Stages)	113,739	127,943	131,797	173,858	203,500	78.9	17.0
Congenital Syphilis	1,325	1,882	2,162	2,875	3,755	183.4	30.6
Total Reported STIs	**2,457,137**	**2,554,920**	**2,391,613**	**2,531,300**	**2,505,027**	**1.9**	**-1.0**

CDC. Sexually Transmitted Infections Surveillance 2022. Accessed Feb 2024

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Sexually Transmitted Infections & PrEP

- Reports of increased sexually transmitted infection among PrEP users

- PrEP users' perception of decreased risk of HIV acquisition may lead them to engage in overall riskier sexual practices and increase their chances of acquiring sexually transmitted infections (STIs). (Blumenthal, et al. 2014)

- PrEP should therefore be used in combination with other education and other prevention measures against STIs. (Barreiro 2018)

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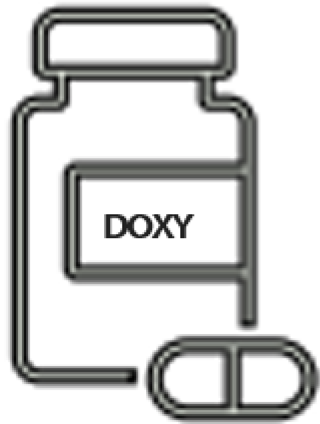
Doxycycline as post-exposure prophylaxis for sexually transmitted infections in MSM and transgender women



DoxyPEP Interim Guidance

Take two 100mg **doxycycline (total of 200mg)** within 24 hours, but no later than 72 hours after condomless sex (oral, anal, vaginal).

For MSM or transgender women with at least 1 bacterial STI in the past 12 months.

Maximum 200mg doxycycline every 24 hours.

Highleyman L. AIDSMap. Oct 11, 2023

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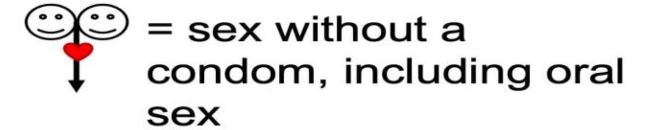
DoxyPEP

Doxy PEP – How to Take

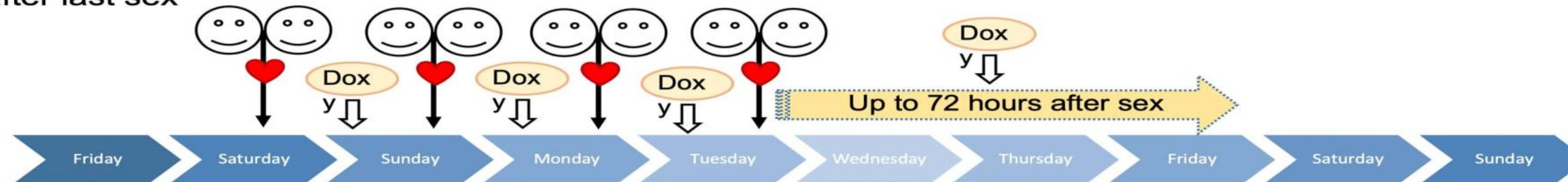
Two 100 mg pills of doxycycline ideally <u>within 24 hours</u> but no later than 72 hours after condomless oral, anal or vaginal sex



Example: Sex on Sat; take dose of doxy by Tues

Example: Sex on Thursday; take dose of doxy by Sunday

Example 2: Daily (or more) sex Sat-Tues; take daily dose of doxy and last dose within 24 hours *but not later than 72 hours* after last sex



***No more than* 200 mg every 24 hours**

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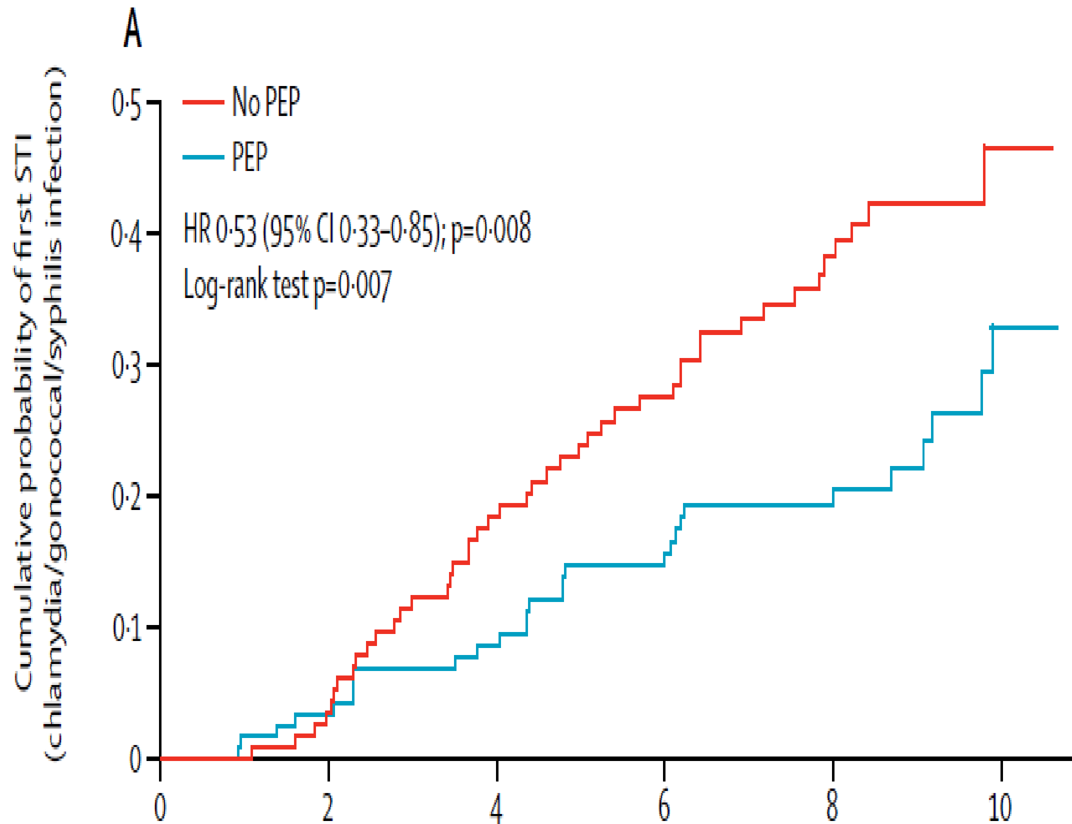
IPERGAY study 2018



- France
- N = 232
- Population: MSM who are on HIV PREP

- 47% reduction in bacterial STIs
  - Chlamydia 70% reduction
  - Syphilis 73% reduction
  - ↓ GC not statistically significant
  - Trend down towards reduction of GC detection in anogenital sites

Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. Lancet Infect Dis. 2018 Mar;18(3):308-317.

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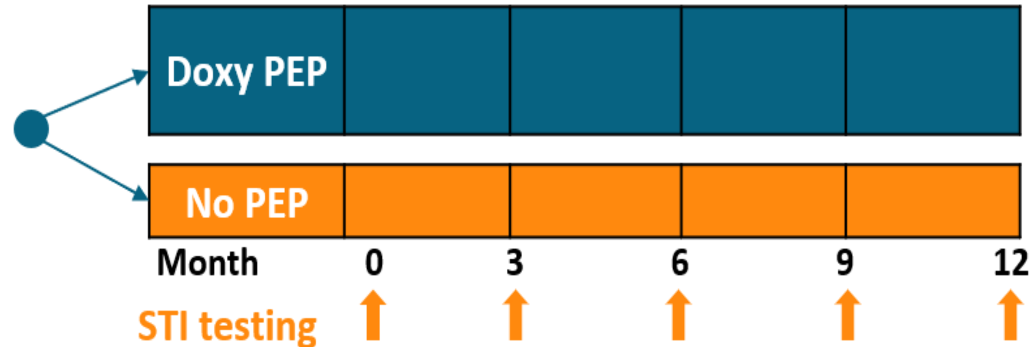
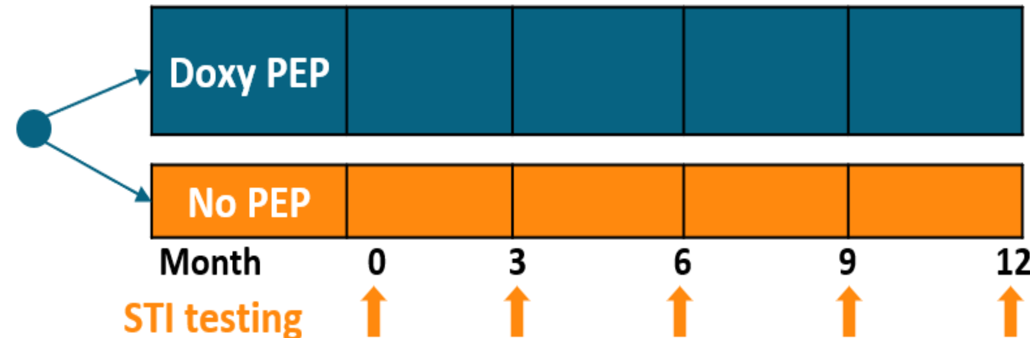
DoxyPEP Study Design

MSM & TGW
living with HIV
(planned n = 390)



2:1 randomization

MSM & TGW
on HIV PrEP
(planned n = 390)



Inclusion criteria:

- Male sex at birth
- Living with HIV or on PrEP
- ≥ 1 STI in past 12 months
- Condomless sex with ≥ 1 male partner in past 12 months

STI Testing: Quarterly 3 site GC/CT testing + RPR, GC culture before treatment

Sites: San Francisco & Seattle HIV & STI clinics

Luetkemeyer AF, et al. N Engl J Med . 2023 Apr 6;388(14):1296-1306.
Image from the presentation by Luetkemeyer AF, et al. AIDS2022 (Montreal, Canada)

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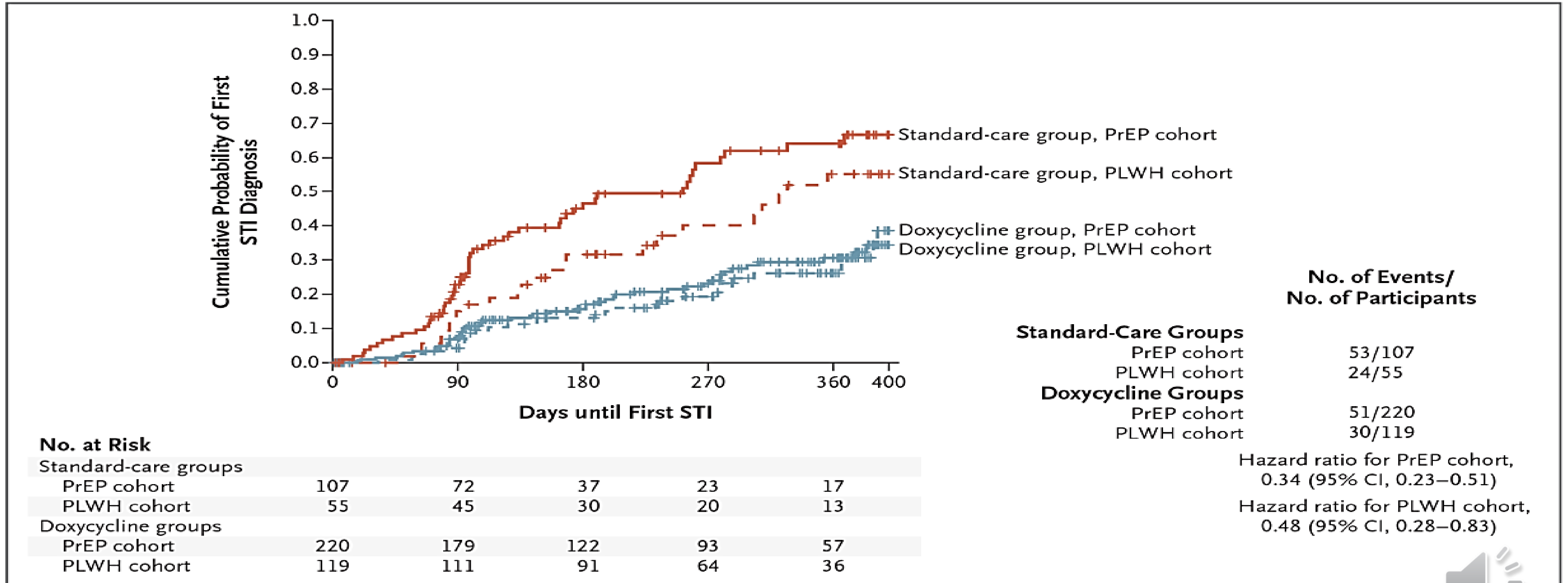
Combined incidence of gonorrhea, chlamydia, and syphilis was lower by 2/3 with DoxyPEP vs standard care



Luetkemeyer AF, et al. N Engl J Med . 2023 Apr 6;388(14):1296-1306.

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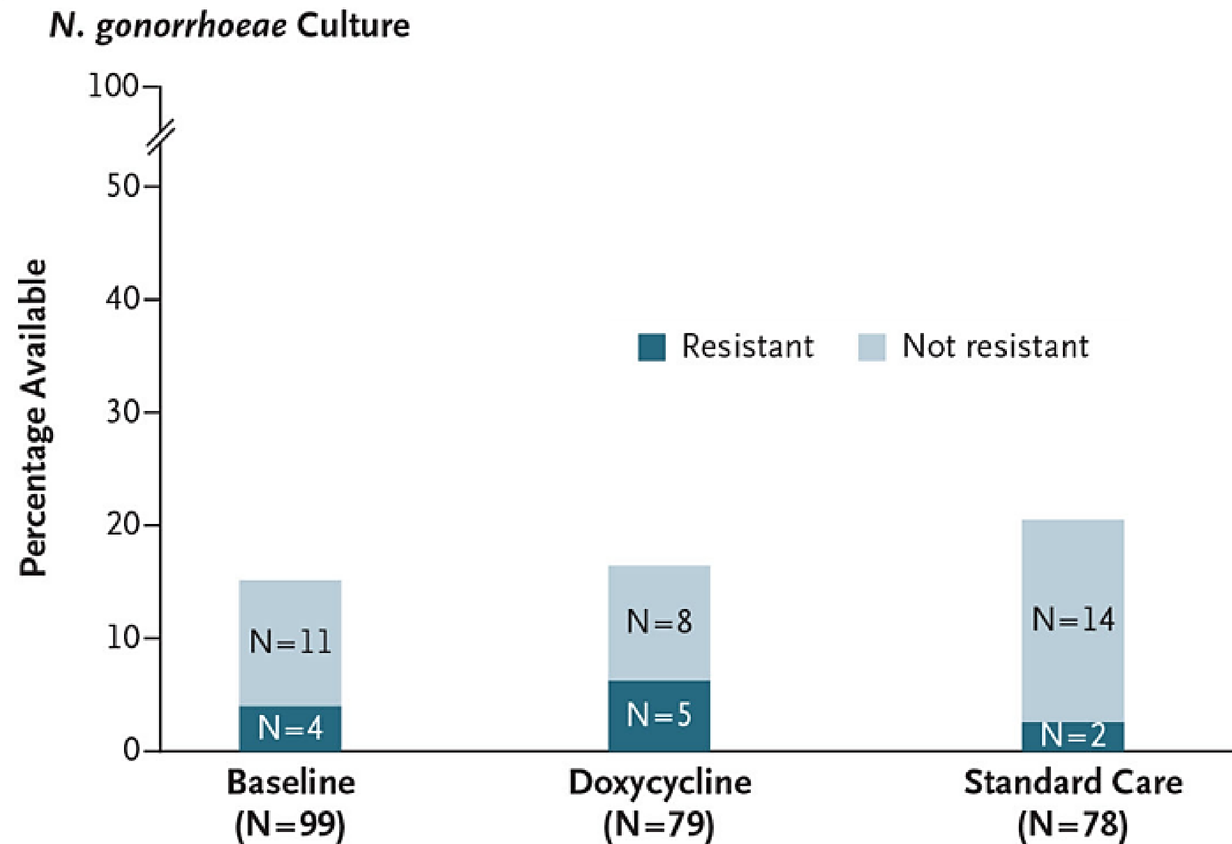
DoxyPEP: Adherence and Safety

- 86% of participants reported taking doxy-PEP consistently (always or often).
- The median number of doxycycline doses taken was estimated to be 4.0 doses (interquartile range, 1.0 to 10.0)
- Most AEs were mild/moderate
- No serious adverse events

Luetkemeyer AF, et al. N Engl J Med . 2023 Apr 6;388(14):1296-1306.

DoxyPEP: Risk of Antimicrobial Resistance



Of the participants with gonorrhea culture available, tetracycline-resistant gonorrhea occurred in 5 of 13 in the doxycycline groups and 2 of 16 in the standard-care groups.

Luetkemeyer AF, et al. N Engl J Med . 2023 Apr 6;388(14):1296-1306.

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Doxy-PEP Studies: Summary

Table 1. Evidence From Randomized Clinical Trials for Doxy-PEP, 2015 to 2023

Study (location, date)	Participating population		STI rate or outcome: Doxy-PEP	STI rate or outcome: No doxy-PEP	Relative risk reduction (95% CI or P)	Absolute risk reduction	Comments
IPERGAY* (France, 2015-2016)	232 MSM on HIV PrEP		37.7 per 100 person-years	69.7 per 100 person-years	47%* (15-67)	32 per 100 person-years	Signal toward reduction of gonorrhea incidence at anogenital sites
DoxyPEP (US, 2020-2022)	501 MSM and TGW with bacterial STIs in prior 12 months	PWH (n = 174)	11.8% per quarter	30.5% per quarter	62% (40-76)	18.7% per quarter	Risk reduction seen for all 3 bacterial STIs
		PrEP users (n = 327)	10.7% per quarter	31.9% per quarter	66% (54-76)	21.2% per quarter	
DOXYVAC* (France, 2021-2022)	502 MSM on HIV PrEP with a bacterial STI in prior 12 months		5.6 per 100 person-years	35.4 per 100 person-years	84% (70-92)	30 per 100 person-years	Effect for gonorrhea found to be independent of 4CMenB vaccine
dPEP (Kenya, 2020-2022)	449 cisgender women on PrEP		50 total chlamydia/ gonorrhea infections	59 total chlamydia/ gonorrhea infections	12% (P = .51)	9 total infections at 12 months	Nonefficacy likely due to suboptimal adherence

Abbreviations: doxy-PEP, doxycycline postexposure prophylaxis; DoxyPEP, Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-infected Men Who Have Sex With Men; DOXYVAC, Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis; dPEP (Kenya), doxycycline postexposure prophylaxis trial (Kenya), IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PWH, people with HIV; STI, sexually transmitted infection; TGW, transgender women.

*Risk reduction estimate is for chlamydia and syphilis only.

Cannon CA, Celum CL. Doxycycline postexposure prophylaxis for prevention of sexually transmitted infections. Top Antivir Med. 2023 Dec 5;31(5):566-575. PMID: 38198668; PMCID: PMC10776032.

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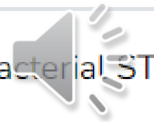
CDC DoxyPEP Recommendations

BOX 1. CDC recommendations for use of doxycycline as postexposure prophylaxis for bacterial sexually transmitted infections prevention

Recommendation*	Strength of recommendation and quality of evidence†
• Providers should counsel all gay, bisexual, and other men who have sex with men (MSM) and transgender women (TGW) with a history of at least one bacterial sexually transmitted infection (STI) (specifically, syphilis, chlamydia or gonorrhea) during the past 12 months about the benefits and harms of using doxycycline (any formulation) 200 mg once within 72 hours (not to exceed 200 mg per 24 hours) of oral, vaginal, or anal sex and should offer doxycycline postexposure prophylaxis (doxy PEP) through shared decision-making. Ongoing need for doxy PEP should be assessed every 3–6 months.	AI High-quality evidence supports this strong recommendation to counsel MSM and TGW and offer doxy PEP.
• No recommendation can be given at this time on the use of doxy PEP for cisgender women, cisgender heterosexual men, transgender men, and other queer and nonbinary persons.	Evidence is insufficient to assess the balance of benefits and harms of the use of doxy PEP

*Although not directly assessed in the trials included in these guidelines, doxy PEP could be discussed with MSM and TGW who have not had a bacterial STI diagnosed during the previous year but will be participating in sexual activities that are known to increase likelihood of exposure to STIs.



† See Table.

DoxyPEP: Initial Visit

- Screen for STIs at the appropriate anatomical sites

- Provide enough medication to last until their next follow up

- Counsel on use of prevention strategies including condom use, consideration of reducing the number of partners, and accessing HIV PEP, PrEP or HIV treatment as indicated.

- Assess Hepatitis B immunity status
- Consider screening for Hepatitis C

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DoxyPEP: Initial Visit

- Side effects: esophagitis, GI upset, photosensitivity and potential for antimicrobial resistance
- Take with food and with a full glass of liquid
- Sit upright for 1 hour afterwards to prevent esophagitis
- Take as prescribed and no more than 200mg within 24 hours

- Drug-interactions with other medications including supplements and OTC medications
- No interactions with gender-affirming care medications have been documented (estradiol, spironolactone, testosterone, etc…)

DoxyPEP: Follow up Visits

- Follow up visits every 3 – 6 months
- Screen for STIs at the appropriate anatomical sites
- Screen for HIV every 3 – 6 months if HIV negative
- Re-iterate need for additional risk reduction (condoms, reducing # of partners, etc…)

DoxyPEP: Follow up Visits

- Provide enough medication to last until their next follow up
- Refer to HIV care center if indicated
- Refer or counsel for mental health or substance use disorders if indicated
- Screen for Hepatitis C, especially among people who inject IV drugs (PWID)

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