

DoxyPEP for STIs: Data, Questions, Controversies

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Agenda


1. Clinical trial data
2. Other data and considerations
3. Discussion and debate



A case

A 32-year-old man with well-controlled HIV presents for a routine follow-up visit. He is sexually active with other men and rarely uses condoms. He is asymptomatic today and has a normal physical examination. He had pharyngeal gonorrhea 3 months ago, for which he received intramuscular ceftriaxone. Routine STI testing today is negative aside from a newly positive treponemal antibody, with an RPR of 1:16. He is treated with IM penicillin.

Would you *recommend* doxyPEP for STIs for him (i.e., 200 mg taken 24-72 hours after sex)?

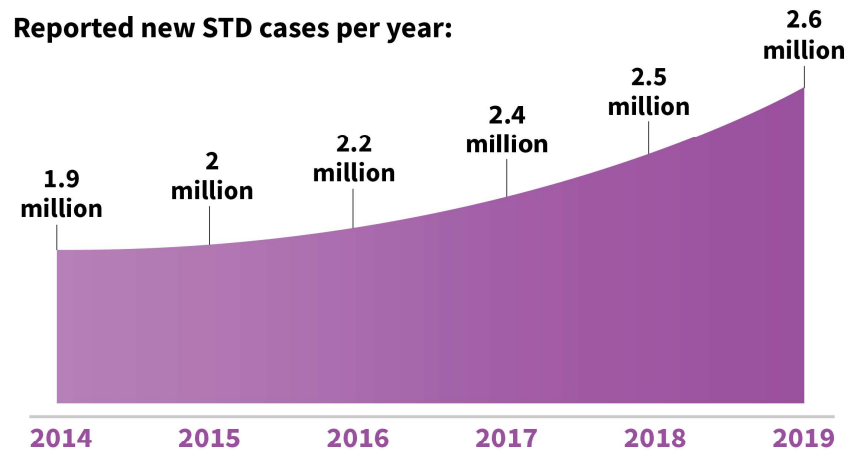
- A. Yes
 - B. No
 - C. I don't know.
- 

Why are we discussing doxyPEP now?

- Unchecked rise in reportable STIs
- Findings from a key trial showing benefit were presented this summer; additional data are expected at CROI.
- Patients are asking about doxyPEP (and some are noting doxyPEP use on their hookup app profiles).
- Some groups have already made recommendations for doxyPEP (e.g., San Francisco).
- CDC has published considerations for doxyPEP.

6th consecutive year of **RECORD-BREAKING** STD cases

Reported new STD cases per year:



For more information visit www.cdc.gov/nchhstp/newsroom



POPULATION HEALTH DIVISION
SAN FRANCISCO DEPARTMENT OF PUBLIC HEALTH



Recommendations

1. **Recommend doxy-PEP** to cis men and trans women who: 1) have had a bacterial STI in the past year and 2) report condomless anal or oral sexual contact with ≥ 1 cis male or trans female partner in the past year. These were the eligibility criteria used for the DoxyPEP study. Patients with a history of syphilis should be prioritized for doxy-PEP.
2. **Offer doxy-PEP using shared decision making** to cis men, trans men and trans women who report having multiple cis male or trans female sex partners in the prior year, even if they have not previously been diagnosed with an STI.

Clinical trial data

IPEGAY Study

Design: 1:1 randomized, open-label trial of doxycycline 200 mg within 24 hours after sex or no doxycycline, nested within a trial of on-demand PrEP

Population: MSM and transgender women in France who had condomless sex with at least 2 men in the past 6 months

Outcomes:

- **Primary:** Occurrence of a first STI (gonorrhoea, chlamydia, and syphilis)
- **Secondary:** Occurrence of all episodes of STI during the trial

IPEGAY DoxyPEP baseline characteristics

	PEP* (n=116)	No PEP (n=116)
Age		
Median age (years)	38 (33–48)	39 (32–44)
18–24	0 (0%)	5 (4%)
25–29	12 (10%)	11 (10%)
30–39	47 (41%)	41 (35%)
40–49	31 (27%)	44 (38%)
>49	26 (22%)	15 (13%)
Ethnic origin		
White	110 (95%)	110 (95%)
Other	6 (5%)	6 (5%)
Employed		
Employed	102 (88%)	98 (84%)
Not in a relationship		
Not in a relationship	82 (71%)	81 (70%)
Post-secondary education		
Post-secondary education	109 (94%)	103 (89%)
Use of recreational drugs†		
Use of recreational drugs†	49 (42%)	49 (42%)
Site of enrolment		
Paris, France	64 (55%)	72 (62%)
Lyon, France	25 (22%)	21 (18%)
Nice, France	9 (8%)	13 (11%)
Tourcoing, France	6 (5%)	8 (7%)
Nantes, France	12 (10%)	2 (2%)
Sexual risk factors at screening		
Number of partners in past 2 months	10 (5–15)	10 (5–20)
Number of sexual intercourse acts in past 4 weeks	10 (5–15)	10 (4–20)
Number circumcised (%)	28 (24%)	21 (18%)
STIs diagnosed at screening ‡	22 (19%)	16 (14%)

DoxyPEP reduced chlamydia and syphilis occurrence.

Hazard ratios of first STI

Sexually transmitted infection	Hazard ratio (95% CI) among those taking doxyPEP
Cumulative STI	0.53 (0.33-0.85)
Gonorrhea	0.83 (0.47-1.47)
Chlamydia	0.30 (0.13-0.70)
Syphilis	0.27 (0.07-0.98)

At the time of the study, 56% of gonococcal isolates in France were resistant to tetracyclines (versus ~20% in the United States).

DoxyPEP safety, use, and adherence

- No difference in serious adverse events, or grade 3 or 4 adverse events
- Drug-related gastrointestinal adverse events more common with doxycycline (25% versus 14%, $p=0.03$)
- 7% of participants discontinued doxycycline.
- Median use: 6.8 pills (100 mg) per month

DoxyPEP Study

Design: 2:1 randomized, open-label trial of doxycycline 200 mg within 72 hours after sex or no doxycycline

Population: MSM and transgender women either with HIV or on PrEP in San Francisco and Seattle, ≥ 1 STI in the past year, condomless sex with ≥ 1 man in the past year

Outcomes:

- **Primary:** STI (gonorrhea, chlamydia, and syphilis) incidence, assessed quarterly and when symptomatic
- **Secondary:** Safety; resistance within bacterial STIs, *Staphylococcus aureus*, and commensal *Neisseria* species; impact on the gut microbiome

The DSMB stopped enrollment in 5/2022 because a scheduled interim analysis showed benefit both for people taking PrEP and those with HIV.

DoxyPEP baseline characteristics

As of May 13, 2022

	PrEP	Living with HIV	Total
Participants* (ITT population)	327	174	501
Age	36 (31 - 42)	43 (36 - 54)	38 (32 - 47)
Race			
White	210 (67%)	111 (66%)	321 (67%)
Black	14 (5%)	22 (13%)	36 (8%)
Asian/Pacific Islander	45 (14%)	8 (5%)	53 (11%)
Multiple races/other	44 (14%)	28 (17%)	72 (15%)
Ethnicity: Hispanic/Latino	96 (29%)	55 (32%)	151 (30%)
Gender identity			
Man	319 (98%)	163 (94%)	482 (96%)
Trans woman/gender diverse	8(2%)	11 (6%)	19 (4%)
Gender of sexual partners: Male only	281 (86%)	153 (88%)	434 (87%)
STI in past 12 months**			
Gonorrhea	233 (71%)	110 (63%)	343 (69%)
Chlamydia	207 (63%)	85 (49%)	292 (58%)
Syphilis†	48 (15%)	52 (30%)	100 (20%)
Sexual partners in past 3 months	9 (4 - 17)	8.5 (3 - 20)	9 (4 - 17)
Substance use in past 3 months	178 (55%)	115 (68%)	293 (59%)
Stimulants (methamphetamine, cocaine, crack)	73 (23%)	73 (43%)	146 (30%)
Ecstasy, GHB, ketamine	97 (30%)	60 (35%)	157 (32%)
Amyl Nitrates (poppers)	140 (43%)	84 (49%)	224 (45%)

Table from Luetkemeyer A, AIDS 2022

DoxyPEP reduced STI incidence per quarter.

Relative risk reductions (95% CI):

PrEP: 0.34 (0.24-0.46)

People with HIV: 0.38 (0.24-0.6)

Total: 0.35 (0.27-0.46)

All $p < 0.0001$

Number needed to treat ~ 5

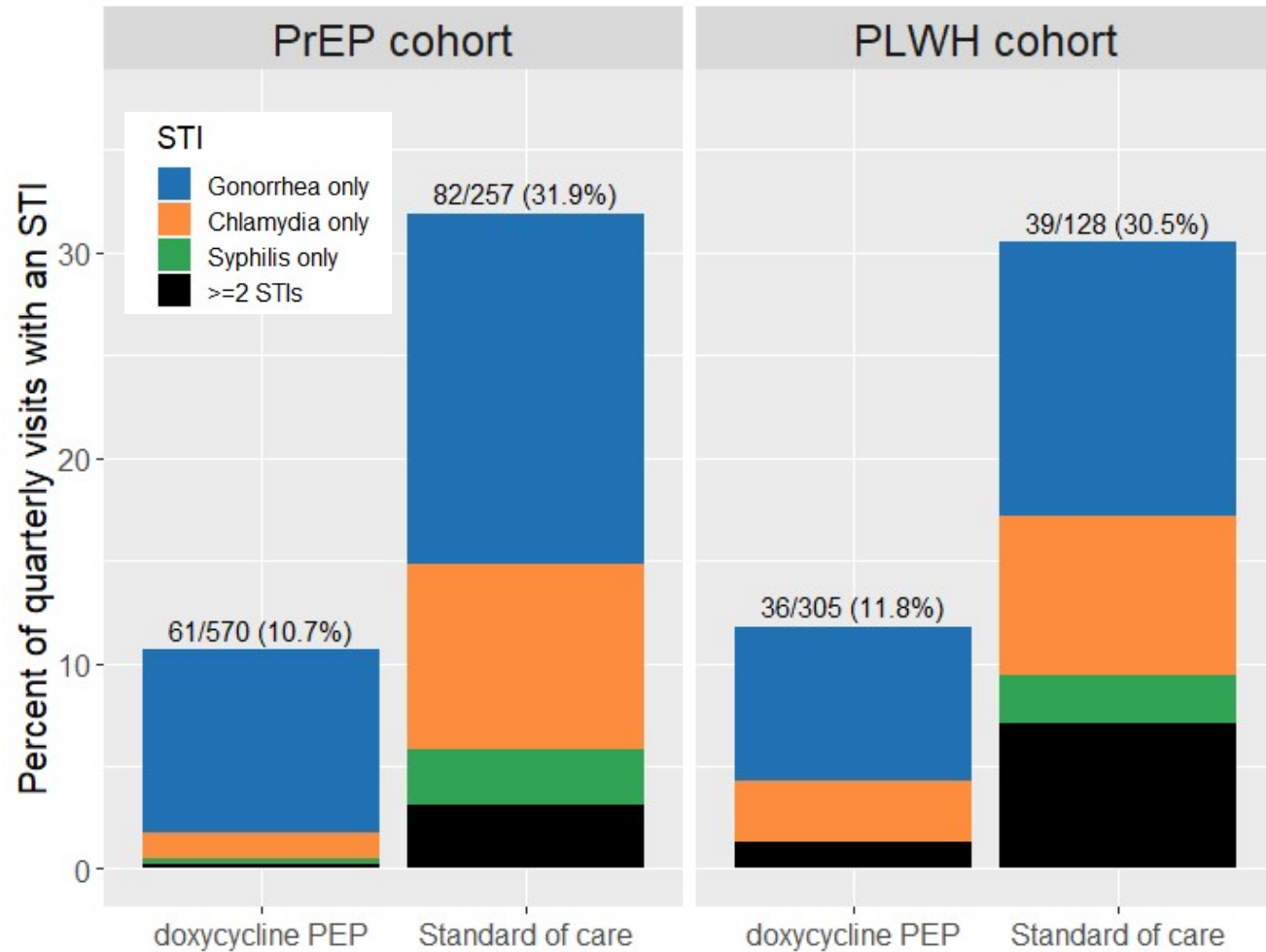


Figure from Luetkemeyer A, AIDS 2022

DoxyPEP also reduced gonorrhea incidence.

Relative risk reduction (95% CI) of STI incidence per quarter

Sexually transmitted infection	PrEP cohort	People with HIV cohort
Gonorrhea	0.45 (0.32-0.65)	0.43 (0.26-0.71)
Chlamydia	0.12 (0.05-0.25)	0.26 (0.12-0.57)
Syphilis	0.13 (0.03-0.59)	0.23 (0.04-1.29)

DoxyPEP reduced ceftriaxone use by ~50%.

DoxyPEP safety, use, and adherence

- No grade 3 adverse events, grade 2 or higher lab abnormalities, or serious adverse events
- 88% of participants said doxyPEP was acceptable or very acceptable.
- 1.5% of participants discontinued doxycycline.
- Participants took doxyPEP for 87% of sexual encounters, by self report.
- Median use: 4 doses per month, based on CASI

Antimicrobial resistance and microbiome effects

Resistance data are available for ~30% of gonococcal endpoints.

Impacts on *Staphylococcus aureus*, commensal *Neisseria* species, and the gut microbiome are not yet publicly available.

Tetracycline susceptibility for cultured isolates of *N. gonorrhoeae*

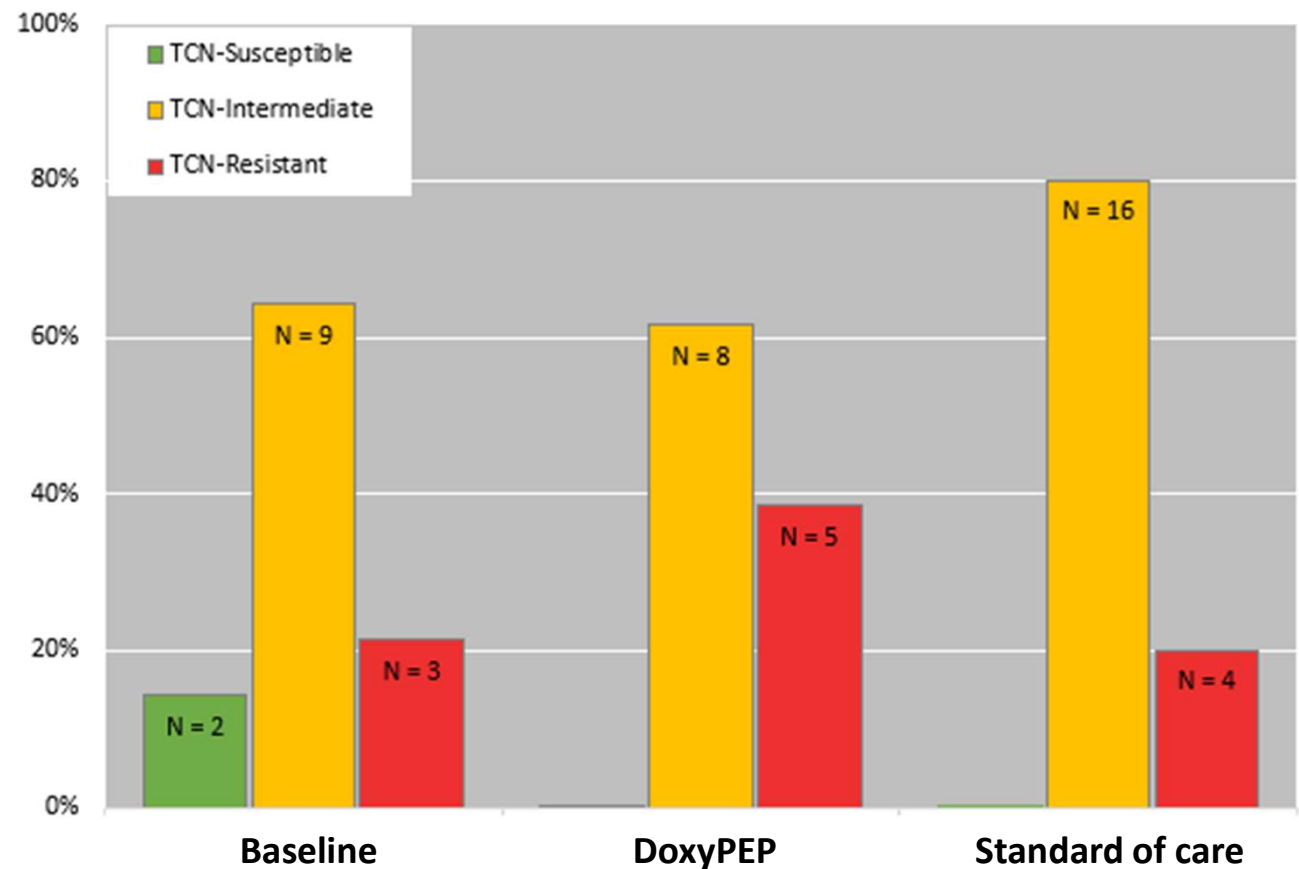


Figure from Luetkemeyer A, AIDS 2022

Other clinical trials

- **ANRS Prevenir Study:** 2:1 randomized, open label study of doxyPEP versus no PEP combined with a 1:1 randomized study of meningococcal type B vaccination among MSM
- **dPEP Study:** 1:1 randomized, open label study of doxyPEP (200 mg 24-72 hours after sex) among young Kenyan women taking PrEP
- **Syphilaxis Study:** Non-randomized single arm trial with before-after comparison of doxycycline 100 mg daily among MSM and transgender people
- **DISCO Study:** 1:1:1 randomized, open label study of doxycycline 100 mg daily, doxycycline 200 mg within 72 hours of condomless sex, and standard of care among MSM

Other data and considerations

Are there other things like doxyPEP?

- Antimicrobial prophylaxis for STIs in the U.S. navy
- Doxycycline PEP for Lyme disease after tick bites
- Post-coital UTI prophylaxis for women

Long courses of doxycycline are prescribed for acne/rosacea, malaria prophylaxis, and antibiotic suppression.



Older Studies of STI PrEP & PEP

- 1949-50 – PCN PEP rolled out in various ships – 21-74% reduction in gonorrhea
- In 1951, PCN PEP was rolled out to all ships in the Pacific fleet

TABLE 5. Penicillin prophylaxis studies, total areas of use

Area	Liberties		Cases per 1,000 liberties				Ratio	
	Thousands	Percent requesting penicillin	Gonorrhea		Syphilis	Chancroid	Gonorrhea to syphilis	Gonorrhea to chancroid
			Total cases	Cases in men who took penicillin*				
Mediterranean	757	39	1.32	0.42	0.26		5.2:1	
Japan-Philippines China	476**	31**	2.34	0.86	0.0316	1.52	74:1	1.5:1
West Indies Caribbean	103	18	1.7	0.1162	0.0968	0.1646	17.5:1	10.3:1
European	17	21	1.8	0.66	0	0	0	0
Total	1,353	34	1.7	0.54	0.1594	0.58	10.7:1	21:1

*Cases occurring in men *all or part* of whose liberties were protected by penicillin.

**These figures represent only those ships which used tablets and submitted reports, and for these it does not cover the entire year. No data are available from ships which did not participate in phase C studies in this area.

- 460,000 doses of PCN administered in <1 year
- Authors report ~50% reduction in gonorrhea with parallel declines in syphilis and chancroid


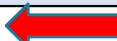
“When the men became aware of the program it was soon impossible to withhold treatment on control ships because many believed that they were being denied the use of a very effective drug.”

Source: Babione RW. Navy Experience with the Oral Use of Penicillin as Prophylaxis. US Armed Forces Medical Journal. 1952

Slide courtesy of Dr. Matthew Golden

Our world is
awash in
tetracyclines.

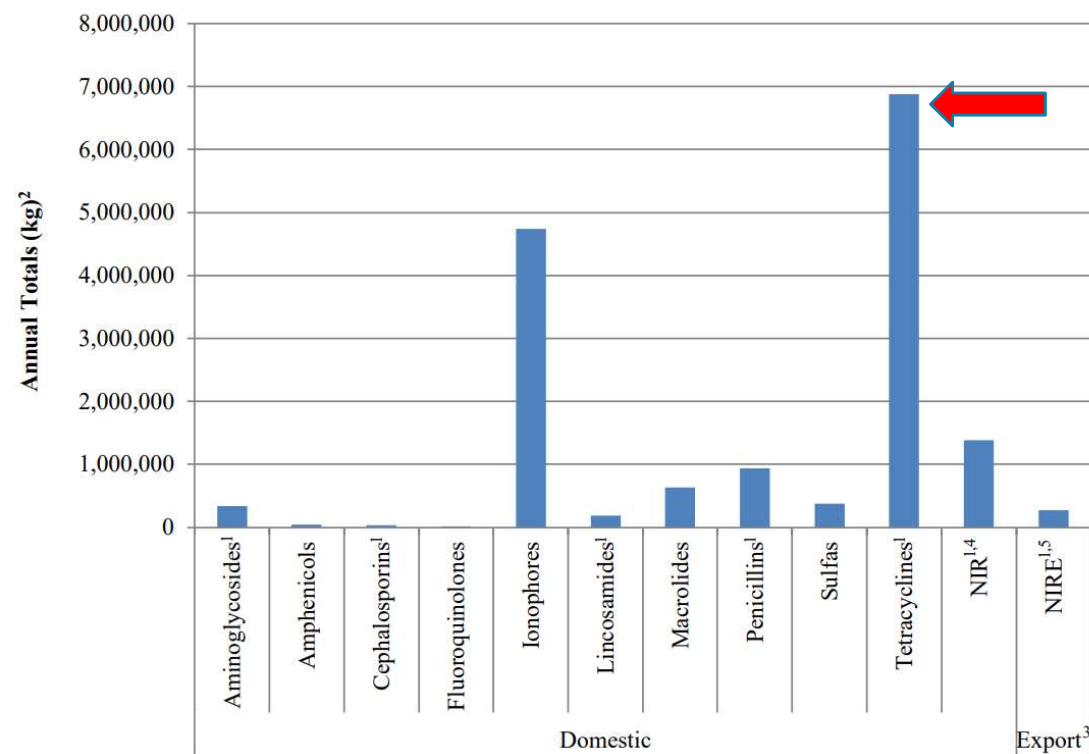
Table 2. Top oral antibiotic classes and agents—United States, 2020

Characteristics: Antibiotic class	Number of Antibiotic Prescriptions (Millions)	Antibiotic Prescriptions Per 1,000 Persons, Rate
Penicillins	43.2	131
Cephalosporins	30.2	92
Macrolides	29	88
Tetracycline	22.7 	69
B-lactams, increased activity	21	64
Characteristics: Antibiotic agent	Number of Antibiotic Prescriptions (Millions)	Antibiotic Prescriptions Per 1,000 Persons, Rate
Amoxicillin	39.3	119
Azithromycin	27.6	84
Amoxicillin\clavulanic acid	21	64
Cephalexin	19.6	60
Doxycycline	19.5 	59

<https://www.cdc.gov/antibiotic-use/pdfs/Annual-Report-2020-H.pdf>

Agricultural uses of tetracyclines dwarf human uses.

Antimicrobial sale and distribution data for food-producing animals, by drug class



Domestic/Export³ and Drug Class

Antimicrobial resistance considerations

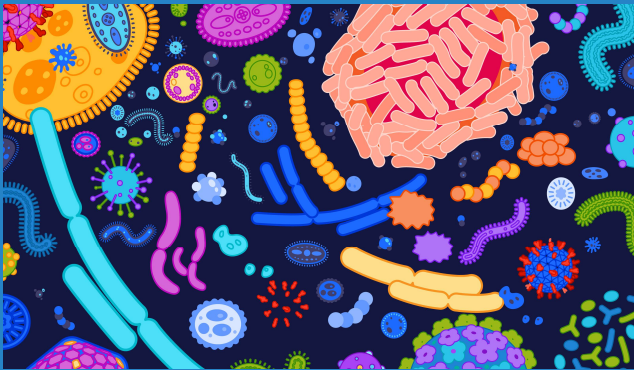
Sexually transmitted pathogens

- *Chlamydia trachomatis* and *Treponema pallidum* = Low likelihood of doxycycline resistance
- *Neisseria gonorrhoeae* = Higher likelihood of doxycycline resistance
 - DoxyPEP impact on gonorrhea may not be durable
 - Might doxycycline select for organisms with other antimicrobial resistance?
 - Does this matter?
- *Mycoplasma genitalium*
 - Efficacy of doxycycline alone against *M. genitalium* is low
 - Doxycycline is a component of the sequential treatment strategies recommended in the U.S.

Other pathogens

- *Staphylococcus aureus*

Microbiome considerations



- Microbiome perturbations associated with obesity and other chronic diseases
- Microbiome data from doxyPEP studies may not be useful in the short term:
 - We don't know how to counsel patients about specific microbiome changes.
 - Comparing microbiomes of people who received doxyPEP versus intermittent doxycycline, ceftriaxone, penicillin, etc.
- Doxycycline is one of the least *C. difficile*-promoting antibacterials (OR 0.91 in a meta-analysis).

<https://atlasbiomed.com/blog/7-crazy-facts-about-the-microbiome-and-gut-bacteria/>; Cox LM, Nat Rev Endocrinol, 2015; Desphande A, J Antimicrob Chemother, 2013

Is doxyPEP at odds with larger trends in medicine and public health?

- An era of antimicrobial stewardship
- What is the utility of detecting and treating (or preventing) asymptomatic STIs (especially chlamydia), particularly among MSM?
 - Low rates of morbidity
 - Limited impact on HIV transmission in the PrEP/U=U era
 - Harms of diagnosis/treatment: Antibiotic exposure, stigma, “arrested immunity”
 - This approach is not new: The U.S. does not broadly recommend chlamydia and gonorrhea screening in men, unlike in young women.

Review



OPEN ACCESS

Where to go to in chlamydia control? From infection control towards infectious disease control

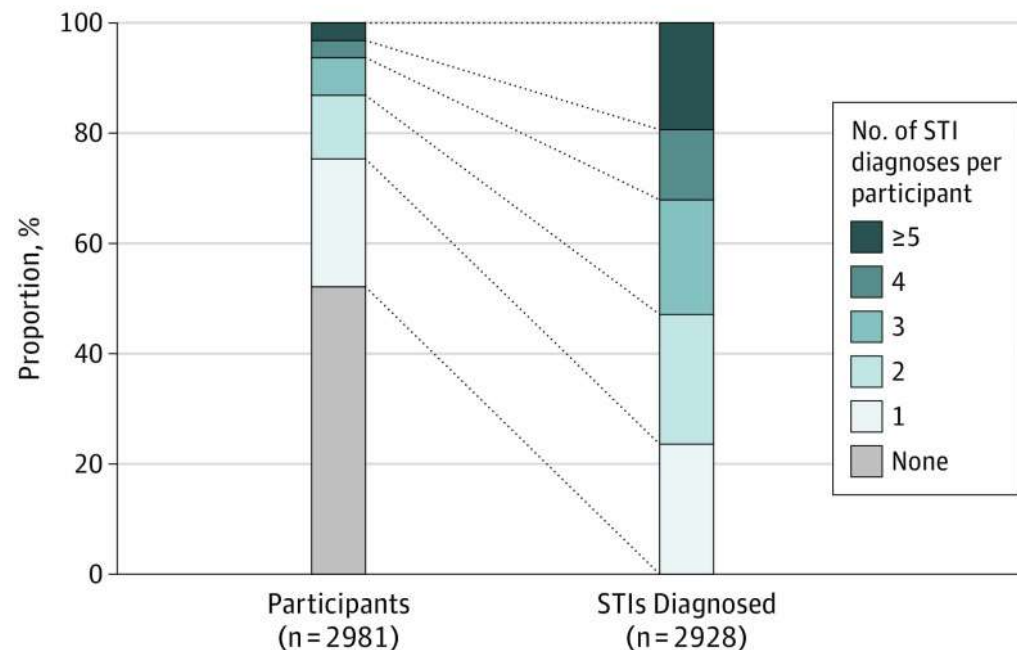
Jan E A M van Bergen ^{1,2,3} Bernice Maria Hoenderboom ³ Silke David ³ Febe Deug ² Janneke C M Heijne ³ Fleur van Aar ³ Christian J P A Hoebe ^{4,5} Hanna Bos ² Nicole H T M Dukers-Muijers ^{6,7} Hannelore M Götz ^{3,8} Nicola Low ⁹ Servaas Antonie Morré ^{10,11} Björn Herrmann ¹² Marianne A B van der Sande ^{13,14} Henry J C de Vries ^{15,16} Helen Ward ¹⁷ Birgit H B van Benthem ³

Among PrEP users, a small proportion of people acquire a majority of STIs.

Among a cohort of 2,981 MSM taking PrEP in Australia, 25% of participants accounted for 76% of all STIs.

STIs associated with:

- More anal sex partners
- Group sex



Clinicians and patients may prioritize different benefits of doxyPEP.


Clinicians and public health workers: STI control, morbidity reduction

Patients: Reduced stigma, decreased anxiety around sex, avoidance of relationship impacts and the inconvenience of obtaining treatment

Interest in doxyPEP is high among MSM: 84% were interested in an online survey, with higher interest among Black and Latinx MSM

Community member: “This feels like the beginning of PrEP and U=U all over again. The community is ready, but doctors are reluctant.”

Many implementation questions

- For which patients should doxyPEP be recommended?
 - What are key components of shared decision-making for doxyPEP?
 - How should STI exposures be handled among people taking doxyPEP?
 - What is the optimal frequency of STI testing among people taking doxyPEP?
 - What, if any, other laboratory monitoring should people on doxyPEP have?
 - How many pills should be prescribed at one time?
 - How can access and uptake be as equitable as possible?
- 

My perspective



- Offer doxyPEP to MSM and transgender women with an STI or multiple condomless sex partners in the past year (include cisgender women depending on the results of the dPEP study).
- Use a shared decision-making approach, potentially with tools developed for this purpose.
- Continue every-three-month STI screening for now. Other laboratory studies are not routinely necessary for people taking ≤ 4 doses per month.
- For patients taking doxyPEP, do not treat empirically for asymptomatic exposure to gonorrhea or chlamydia.
- Prescribe 30 pills at a time.


Image from <https://www.poison.org/articles/what-is-doxycycline>

Discussion and debate

A case

A 32-year-old man with well-controlled HIV presents for a routine follow-up visit. He is sexually active with other men and rarely uses condoms. He is asymptomatic today and has a normal physical examination. He had pharyngeal gonorrhea 3 months ago, for which he received intramuscular ceftriaxone. Routine STI testing today is negative aside from a newly positive treponemal antibody, with an RPR of 1:16. He is treated with IM penicillin.

Would you *recommend* doxyPEP for STIs for him (i.e., 200 mg taken 24-72 hours after sex)?

- A. Yes
 - B. No
 - C. I don't know.
- 

Summary

- 200 mg of doxycycline given 24-72 hours (doxyPEP) after sex reduces incidence of chlamydia, syphilis, and possibly gonorrhea among MSM and transgender women who have sex with men.
 - This strategy is generally well-tolerated.
 - Impacts on antimicrobial resistance and the microbiome are poorly understood.
 - DoxyPEP is of increasing interest to many people at risk for STIs.
- 