



Memorandum

To: Oregon healthcare providers

From: Tim W Menza, MD, PhD

Date: July 17, 2023

Subject: Doxycycline post-exposure prophylaxis for the prevention sexually transmitted infections

Dear Colleague,

This letter discusses new recommendations regarding the use of doxycycline post-exposure prophylaxis (doxyPEP) for the prevention of bacterial sexually transmitted infections (STI). Three studies over the past several years show that taking 200 mg of doxycycline within 72 hours **after** condomless sex significantly reduces the acquisition of gonorrhea, chlamydia, and syphilis among [cisgender men](#) and transgender women ([Molina et al, 2018](#); [Leutkemeyer et al, 2023](#); [Molina et al, 2023](#); Table).

In the most recent U.S.-based trial, the [DOXYPEP study](#) conducted in Seattle and San Francisco, participants randomized to doxyPEP were 65% less likely to acquire a bacterial STI compared to those who were not randomized to doxyPEP. **The number of people needed to treat with doxyPEP to prevent one STI in a three-month period was five.** Doxycycline was acceptable to participants, safe and well-tolerated, and did not lead to any serious drug-related adverse events.

Given the consistent efficacy of doxyPEP across trials, doxyPEP may play an important role in STI prevention, an urgent public health priority in Oregon and nationally. At the same time, the long-term individual- and population-level effects of doxyPEP on antimicrobial resistance and on the microbiome are largely unknown.

As awareness about doxyPEP builds and healthcare providers and patients alike are interested in doxyPEP as an STI prevention tool, the Oregon Health Authority STD Program wants to provide clinicians with information and recommendations they can use to make informed decisions about prescribing doxyPEP.

Recommendations

- 1. Inform cisgender men, transgender women, and nonbinary people assigned male at birth who have sex with people with a penis and have had one or more bacterial STIs in the prior year about doxyPEP.** Discuss the effects of doxyPEP on the acquisition of bacterial STI and the potential benefits and risks of doxyPEP. Then, **prescribe doxyPEP using shared clinical decision-making with patients.** Consider prioritizing patients who:
 - a. Have had syphilis in the prior year, and/or
 - b. Have had two or more bacterial STIs in the prior year, and/or
 - c. Have been a contact to a sexual partner with early syphilis in the prior year

Counsel patients that doxyPEP may be particularly useful when they have sex outside of their usual sexual networks while traveling or attending events, when having sex with new or anonymous partners, participating in sex parties, engaging in group sex, going to bathhouses or sex clubs, and/or trading sex.

- 2. Currently, there is insufficient evidence to recommend doxyPEP to people who primarily have receptive vaginal/front hole sex.** In a [recent randomized trial](#) among Kenyan cisgender women, doxyPEP did not reduce the acquisition of gonorrhea and chlamydia (Table) despite [pharmacologic data](#) indicating that doxycycline levels in vaginal fluids should provide protection from bacterial STI. Due to low incidence, syphilis was not assessed as an outcome in this trial and the effect of doxyPEP on syphilis among people who have receptive vaginal/front hole sex in higher incidence settings, like Oregon, is unknown.
- 3. Cisgender women, transgender men, and nonbinary people assigned female at birth who primarily have oral and/or anal sex with people with a penis were not included in studies of doxyPEP.** Participants in the DOXYPEP study reported condomless anal or oral sex to be eligible for study participation. **DoxyPEP may be effective for all people who have oral and anal sex with people with a penis regardless of gender identity and sex assigned at birth** and providers should use shared clinical decision-making to help a patient decide if doxyPEP is right for them.
- 4. DoxyPEP should be part of comprehensive sexual healthcare** including HIV pre- and post-exposure prophylaxis (PrEP and PEP), condoms, routine HIV/STI testing, HIV treatment for people living with HIV, expedited partner therapy for chlamydia and gonorrhea, overdose prevention and harm reduction services for people who use drugs, and vaccinations against HPV, hepatitis A and B, meningitis, and mpox.

Counseling messages for doxyPEP

Benefits of doxyPEP

Individual-level benefits of doxyPEP

- In a randomized controlled trial conducted in Seattle and San Francisco, 200 mg of doxycycline taken 24-72 hours after condomless oral or anal sex reduced the risk of gonorrhea, chlamydia, and syphilis by 65%.
 - a. Participants in the trial took a median of 4 doses per month with an interquartile range of 1-10 doses per month indicating that 25% of participants took more than 10 doses per month.
 - b. 86% of participants reported taking doxyPEP always or often within 72 hours after condomless sex and 71% reported never missing a doxyPEP dose within 72 hours after condomless sex.

- By preventing bacterial STIs, doxyPEP may help people avoid needing ceftriaxone for gonorrhoea treatment, benzathine penicillin G for syphilis treatment, and courses of doxycycline for chlamydia treatment.
- People taking doxyPEP may feel less anxious and experience less stigma around STI leading to greater sexual satisfaction and a greater sense of empowerment in caring for their health and the health of their partners.

Population-level benefits of doxyPEP

- DoxyPEP may decrease the incidence of bacterial STI at the population level. The effectiveness of doxyPEP depends on whether doxycycline is offered to and used by people who could benefit from doxyPEP most.

Risks of doxyPEP

Side effects

- Doxycycline is generally well-tolerated.
- Doxycycline carries a risk of increased sun sensitivity, pill esophagitis, and the rare risk of benign intracranial hypertension.
- Routine sun precautions are important when taking doxycycline.
- Taking doxycycline with a large glass of water and remaining upright for 30 minutes after a dose can reduce the risk of pill esophagitis
- Some people experience GI upset when taking doxycycline. Taking doxycycline with food may reduce the risk of GI upset.

Drug interactions

- Doxycycline interacts with antacids, Pepto-Bismol, warfarin, some anti-epileptic medications, and supplements containing calcium, magnesium, zinc, and iron. Take doxycycline 1 hour before or 2 hours after antacids and other medications or supplements containing calcium, magnesium, zinc, and iron.

Pregnancy and lactation

- Doxycycline should not be used during pregnancy. If doxyPEP is prescribed to a patient who can become pregnant, test for pregnancy at doxyPEP initiation and assess the patient's pregnancy plans and discuss contraceptive options.
- [Short courses of doxycycline](#) are safe in breastfeeding/[chestfeeding](#). Discuss the risks and benefits of doxyPEP and the planned duration and frequency of doxyPEP use with chestfeeding patients to decide whether to continue doxyPEP.

Antimicrobial resistance

- The effects of doxyPEP on antimicrobial resistance in *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Treponema pallidum*, *Staphylococcus aureus*, commensal *Neisseria* species and the microbiome are under study.
- The risk of antimicrobial resistance related to the use of doxyPEP is greatest for *Neisseria gonorrhoeae*. DoxyPEP is not effective against incident tetracycline-resistant gonorrhoea. The development of

gonorrhea resistance will limit the overall effectiveness of doxyPEP. We don't know when we will begin to see an increase in tetracycline-resistant gonorrhea but several sites around the U.S., including Multnomah County, routinely track [gonorrhea resistance](#).

- In the DOXYPEP trial, [Staphylococcus aureus colonization](#) was reduced by 16% without a significant increase in doxycycline resistance in *Staphylococcus aureus* overall and in methicillin-resistant *Staphylococcus aureus* (MRSA) specifically over one year of follow-up. We don't yet know the longer-term effects of doxyPEP on *Staphylococcus aureus* resistance and how it will affect the use of doxycycline for MRSA infections.
- Doxycycline is the recommended treatment for chlamydia and an alternative treatment for syphilis. At this time, there is no evidence of circulating doxycycline-resistant chlamydia or syphilis and the risk of this resistance related to doxyPEP is likely to be low.

Microbiome

- Doxycycline may alter the composition of the skin, oral, and gut microbiomes. We don't know the extent to which doxyPEP will change patients' microbiomes and the clinical significance of these changes.

Prescribing and follow-up while on doxyPEP

- Prescribe doxycycline 200 mg PO once 24-72 hours (ideally within 24 hours) **after** condomless oral or anal sex. There is no standard number of doxyPEP doses and refills to prescribe. Some clinics are prescribing 30-60 caps/tabs (15-30 doxyPEP doses) with 1-2 refills. The number of doses and refills to prescribe is up to the provider and should be based on a discussion about how much sex the patient anticipates having and the frequency of follow-up (ideally every three months).
- Either delayed release doxycycline hyclate (1 x 200 mg cap/tab per dose) or immediate release doxycycline hyclate or monohydrate (2 x 100 mg caps/tabs per dose) are acceptable and equally bioavailable. Delayed release formulations will be more expensive and may not be covered by insurance.
- Doxycycline can be taken daily depending on the frequency of sexual activity but should not be taken more than once per day (in contrast to routine doxycycline dosing which is 100 mg PO twice per day).
- Screen for gonorrhea and chlamydia at all anatomic sites of exposure (urogenital, pharyngeal, and rectal), as well as test for syphilis and HIV (if not known to be living with HIV) at initiation of doxyPEP and every three months thereafter.
- **Avoid presumptively treating for gonorrhea and chlamydia exposure if the exposure was covered by doxyPEP and the patient is asymptomatic. Instead, test all anatomic sites of exposure and provide treatment based on test results. Given the long incubation period of *T. pallidum* and window periods for serologic testing, we still recommend presumptive treatment for syphilis exposure regardless of doxyPEP use.**
- If diagnosed with an STI, treat according to current [CDC STI Treatment Guidelines](#).
- Laboratory monitoring is not needed while on doxyPEP in patients without known liver disease. Consider routine liver testing in those with or at risk for liver disease.
- Use ICD-10 code Z20.2 (contact with and [suspected] exposure to infections with a predominantly sexual mode of transmission) for billing.

Provide comprehensive preventative counseling and education to all sexually active individuals

- If HIV-negative and not already on [HIV pre-exposure prophylaxis \(PrEP\)](#), recommend that patients initiating doxyPEP also start HIV PrEP. Options for HIV PrEP include daily oral F/TDF (Truvada) and daily oral F/TAF (Descovy). On-demand oral F/TDF and injectable long-acting cabotegravir are options for those not interested in taking daily medications.
- Counsel patients about the availability of [HIV post-exposure prophylaxis \(PEP\)](#).
- Ensure that people living with HIV are in care and counsel patients that achieving and maintaining an undetectable viral load [eliminates the risk of sexual transmission](#).
- Screen patients for gonorrhea and chlamydia using urine, pharyngeal, and rectal nucleic acid amplification testing (NAAT) and serologic testing for HIV (if not known to be living with HIV) and syphilis and hepatitis B and C regardless of HIV status.
- Recommend [expedited partner therapy](#) for the partners of people diagnosed with gonorrhea or chlamydia.
- Connect people who use drugs to overdose prevention and [harm reduction services](#).
- Recommend vaccines against hepatitis A, hepatitis B, HPV, mpox, and meningitis.

Resources

DoxyPEP is an emerging, efficacious STI prevention modality. In the setting of uncertainties related to its use, shared clinical decision-making is a key component of its implementation.

The [California Department of Public Health](#), the [San Francisco Department of Public Health](#), and [Public Health – Seattle & King County](#) have also released recommendations for the use of doxyPEP.

The San Francisco City Clinic has published [patient-facing materials](#) that providers can use when talking to patients about doxyPEP. In addition, providers can consult the [National STD Clinical Consultation Network](#) or reach out to Dr. Tim W. Menza at timothy.w.menza@oha.oregon.gov with clinical questions and for guidance in prescribing doxyPEP.

Table. Summary of studies of doxycycline as post-exposure prophylaxis to prevent bacterial sexually transmitted infections.					
Study	Population	Randomized to doxycycline	Not randomized to doxycycline	Relative risk (95%CI)	Risk difference
IPERGAY Paris, France 2015-2016	MSM (n = 232)	Any STI 37.7/100 p-y ^a	Any STI 69.7/100 p-y	0.53 (0.33, 0.85)	-32/100 p-y
		Gonorrhea 28.7/100 p-y	Gonorrhea 34.5/100 p-y	0.83 (0.47, 1.47)	-5.8/100 p-y
		Chlamydia 8.7/100 p-y	Chlamydia 28.6/100 p-y	0.30 (0.13, 0.70)	-19.9/100 p-y
		Syphilis 3.7/100 p-y	Syphilis 12.9/100 p-y	0.27 (0.07, 0.98)	-9.2/100 p-y
DOXYPEP Seattle and San Francisco 2020-2022	MSM and transgender women on HIV PrEP or living with HIV (n = 501)	PrEP cohort^b		PrEP cohort	PrEP cohort
		Any STI 10.7%/qtr	Any STI 31.9%/qtr	0.33 (0.23, 0.47)	-21.2%/qtr
		Gonorrhea 9.1%/qtr	Gonorrhea 20.2%/qtr	0.45 (0.32, 0.65)	-11.1%/qtr
		Chlamydia 1.4%/qtr	Chlamydia 12.1%/qtr	0.12 (0.05, 0.25)	-10.7%/qtr
		Syphilis 0.4%/qtr	Syphilis 2.7%/qtr	0.13 (0.03, 0.59)	-2.3%/qtr
		PLWH cohort^b		PLWH cohort	PLWH cohort
		Any STI 11.8%/qtr	Any STI 30.5%/qtr	0.38 (0.24, 0.60)	-18.7%/qtr
		Gonorrhea 8.9%/qtr	Gonorrhea 20.3%/qtr	0.43 (0.26, 0.71)	-11.4%/qtr
Chlamydia 3.9%/qtr	Chlamydia 14.8%/qtr	0.26 (0.12, 0.57)	-10.9%/qtr		
		Syphilis 0.7%/qtr	Syphilis 2.3%/qtr	0.23 (0.04, 1.29)	-0.6%/qtr
DOXYVAC Paris, France 2021-2022	MSM (n = 502)	Gonorrhea 20.5/100 p-y ^a	Gonorrhea 41.3/100 p-y	0.49 (0.32, 0.76)	-20.8/100 p-y
		Chlamydia 2.1/100 p-y	Chlamydia 19.3/100 p-y	0.11 (0.04, 0.30)	-17.2/100 p-y
		Syphilis 3.4/100 p-y	Syphilis 16.3/100 p-y	0.21 (0.09, 0.47)	-12.9/100 p-y
		M gen 16.8/100 p-y	M gen 29.4/100 p-y	0.55 (0.34, 0.89)	-12.6/100 p-y
dPEP Kisumu, Kenya ^c 2020-2022	Cisgender women 18-30 years of age (n = 449)	Any STI 50 events	Any STI 59 events	0.88 (0.60, 1.29)	
		Gonorrhea 19 events	Gonorrhea 12 events	1.64 (0.78, 3.47)	
		Chlamydia 35 events	Chlamydia 50 events	0.73 (0.47, 1.13)	

^a Incidence of first STI; ^b incidence per or quarter; ^c there were only two syphilis diagnoses in the cohort at baseline; thus, syphilis was not assessed as an outcome. M gen, *Mycoplasma genitalium*; MSM, men who have sex with men; PLWH, people living with HIV; PrEP, pre-exposure prophylaxis; p-y, person-years; qtr, quarter.