

Updated Guidance, January 2025

Doxycycline Post-Exposure Prophylaxis (Doxy PEP) to Prevent Bacterial Sexually Transmitted Infections (STIs)

Background

Doxycycline postexposure prophylaxis (doxy PEP) is a biomedical strategy with proven efficacy (Table 1) in preventing bacterial sexually transmitted infections (STIs) including syphilis, chlamydia and, to a lesser extent, gonorrhea among cisgender gay, bisexual and other men who have sex with men (MSM) and transgender women (TW).^{1,2} Public Health – Seattle & King County (PHSKC) issued guidelines for the use of doxy PEP in June of 2023.³ Since that time, the US Centers for Disease Control and Prevention (CDC) released doxy PEP guidelines,⁴ new studies and meta-analyses on doxy PEP have been published and presented, and doxy PEP use has grown substantially in King County and elsewhere in the US. These new guidelines update prior guidance to reflect new data and local experience.

Randomized trials conducted over the last decade found that doxy PEP was well tolerated and efficacious in preventing syphilis, chlamydia, and gonorrhea among cisgender MSM and transgender women.^{1,2} In the US DoxyPEP trial, the average participant took approximately 43 extra days of antibiotics over the course of a year to prevent 1.4 STI. The number needed to treat with doxy PEP was 5 to prevent one STI per 3 months.⁵ Fifty percent of prevented STIs were gonorrhea, 43% were chlamydia, and 7% were syphilis; 70% of prevented STIs were asymptomatic. Of note, doxy PEP was particularly effective in preventing syphilis – incidence decreased by 77% (range: 71-87%) across published trials;² participants taking doxy PEP had 8.6-11.6 fewer episodes of syphilis per 100 person-years of follow up than participants in the control groups.

Analyses from San Francisco, CA, where doxy PEP was implemented in late 2022, confirmed that doxy PEP decreased the risk of syphilis and chlamydia – but not gonorrhea – among persons taking it and found that the population-level incidence of syphilis and chlamydia among MSM and TW declined by 50% concurrent with the widespread roll-out of doxy PEP.⁶ Similarly, King County has seen a population-level decline in early syphilis among MSM of approximately 46% since doxy PEP guidance was released in Seattle.⁷ Other early adopter jurisdictions have also described similar trends in effectiveness for STI reduction after doxy PEP implementation.⁸⁻¹⁰ In over 2,250 adults on HIV PrEP in the Kaiser Permanente Northern California system, doxy PEP use reduced the quarterly incidence of chlamydia by 79% and syphilis by 80% in the year after initiation compared to the 24 months before initiation.¹⁰ In a cross-sectional analysis of participants visiting the PHSKC Sexual Health Clinic (SHC) from 2023-2024, doxy PEP use was associated with a 44% reduction in chlamydia and 46% reduction in syphilis positivity compared to persons not using doxy PEP.¹¹ The failure of doxy PEP to significantly reduce the incidence of gonorrhea in each of these studies – an observation that differs from the DoxyPEP and DOXYVAC trials – likely reflects a trend toward increasing tetracycline resistance in *Neisseria gonorrhoeae* in some jurisdictions. As of the second quarter of 2024, 65% of isolates from MSM in King County had high-level tetracycline resistance (*Olusegun Soge, personal communication, Nov 2024*). The initial trend toward increasing tetracycline resistance in *N. gonorrhoeae* antedates the roll out of doxy PEP and may reflect increased use of doxycycline for non-gonococcal urethritis (NGU), chlamydia and syphilis.

Since PHSKC issued its original guidelines, a CDC literature review and meta-analysis evaluating studies of daily doxycycline use ranging between 8 weeks to >3 years concluded that gastrointestinal and dermatologic side effects are relatively common in persons taking doxycycline, but that serious side-effects are uncommon and patients rarely discontinue doxycycline due to side-effects.¹² Analyses of rectal swabs from the US DoxyPEP trial also found that short-term use of doxy PEP (i.e., 6 months) does not seem to change the diversity of the gut bacterial microbiome.¹³ However, surveillance data from the PHSKC SHC suggest that doxy PEP use is associated with a decrease in *Staphylococcus aureus* colonization but an increase in colonization with doxycycline-resistant, methicillin-sensitive *S. aureus* (MSSA).¹⁴ Preliminary analyses also suggest that doxy PEP users are more frequently colonized with group A streptococcus than non-users. The clinical significance, if any, of these findings is unknown.

In early June 2024, CDC released national doxy PEP guidelines.⁴ Those guidelines largely agree with PHSKC’s prior guidance, recommending that medical providers inform MSM about doxy PEP based on the highest grade (AI) level of evidence, and highlight the need to ensure equitable access to doxy PEP.

Table 1. Results of randomized clinical trials of doxycycline PEP

Study (Location)	N	STI rate*		Relative Risk Reduction	Absolute Risk Reduction	Syphilis Rate		Relative Risk Reduction	Absolute risk Reduction
		Doxy PEP	No Doxy PEP			Doxy PEP	No Doxy PEP		
IPERGAY (Paris, France)	232	37.7 per 100 person-years	69.7 per 100 person-years	47%	32 per 100 person years	3.7 per 100 person-years	12.9 per 100 person-years	73%	9.2 per 100 person-years
DoxyPEP (Seattle & San Francisco, US)	501	10.7% per quarter	31.9% per quarter	65%	140 per 100 person years*			80%	~8.6 per 100 person-years*
ANRS 1764 DOXYVAC (Paris, France)	502	8.8 per 100 person-years	53.2 per 100 person-years	83%	44.4 per 100 person years	2.9 per 100 person-years	14.5 per 100 person-years	79%	11.6 per 100 person-years
dPEP Kenya (Kisumu, Kenya)	449	50 infections in 12 months	59 infections in 12 months	NS	9 per year				

*Trials reported differing STI outcomes and time periods. ANRS IPERGAY = incidence of a first episode of gonorrhea, chlamydia, or syphilis per 100 person-years; DoxyPEP = gonorrhea, chlamydia, or syphilis per 3 months; ANRS DOXYVAC = cumulative incidence of chlamydia and/or syphilis per 100 person-years; dPEP Kenya = total number of gonorrhea or chlamydia infections

*DoxyPEP absolute risk reduction estimates are based on unpublished data.

Recommendations

- Medical providers should discuss and offer to prescribe doxy PEP to patients if they meet all of the following criteria:**
 - Cisgender men, transgender women, or nonbinary people assigned male sex at birth, AND
 - Have sex with partners with a penis, AND
 - Condomless sex with multiple partners OR have a history of bacterial STI in the prior year. Providers should prioritize persons diagnosed with more than one bacterial STI in the prior year and/or persons with a history of early syphilis.
- Even in the absence of a recent bacterial STI, **providers should consider offering patients doxy PEP on an episodic basis when patients anticipate periods of increased sexual activity** - for example, during travel, large social events, and group sex events. Counseling should emphasize that doxy PEP may be especially useful for sex outside of a patient’s usual sexual networks, sex with new or anonymous partners, when attending sex parties or engaged in sex in venues like bathhouses or sex clubs, or when trading sex.
- Medical providers should consider offering doxy PEP to cisgender women, transgender men and nonbinary people assigned female sex at birth (AFAB) who are at particularly high risk for syphilis** (e.g., persons with a history of syphilis who use substances, are unstably housed or living homeless, and/or who engage in survival or exchange sex). In the one randomized trial performed in cisgender women in Kenya, doxy PEP did not reduce the risk of chlamydia or gonorrhea (syphilis is rare in Kenya).¹⁵ However, some women experienced GI side effects in the setting of food insecurity and doxycycline levels in the hair of some study participants were low, both suggesting that low adherence to doxy PEP may, at least in part, explain the null findings.^{15,16} One multi-center case

series of early adopter sites estimated approximately 0.6% of people prescribed doxy PEP were AFAB.¹⁷ A small study involving 30 female sex workers in Tokyo, Japan, showed doxycycline pre-exposure prophylaxis (doxy PrEP) reduced the combined risk of gonorrhea, chlamydia, and syphilis by 67%.¹⁸ Further, clinical experience using doxycycline for treatment of other infections and data from a pharmacologic study indicate that doxycycline reaches levels in genital tissue sufficient to inhibit these pathogens.¹⁹ See [Counseling Guidance](#) below for information on doxy PEP use in pregnancy and lactation.

4. Counseling related to doxy PEP should include the following elements:
 - a) Evidence on the benefits of doxy PEP
 - b) The known side effects and potential toxicities of doxycycline
 - c) The known and potential but unknown risks of doxy PEP use on the microbiome and antimicrobial resistance
 - d) How doxy PEP should be taken and expectations for ongoing monitoring
 - e) Alternatives to doxy PEP
5. Doxy PEP should be provided as part of comprehensive sexual health services and patients should be supported to make decisions about the full spectrum of prevention options available to them, including HIV PrEP, HIV treatment for people living with HIV, condoms, safer sex counseling, HIV/STI testing and treatment, pregnancy intention or planning, and vaccines against HPV, hepatitis A and B, mpox and meningitis (if applicable).
6. Medical providers should use drugs other than doxycycline to treat skin and soft tissue infections and community-acquired pneumonia in patients taking doxy PEP. Patients should be encouraged to inform all medical providers that they are using doxy PEP as this could inform empiric antibiotic choice for other conditions.

Risks and benefits for clinical providers to consider when prescribing doxy PEP and discussing doxy PEP with patients

Benefits of doxy PEP

- **STI prevention and promotion of sexual wellness:** Doxy PEP is highly effective in preventing chlamydia and syphilis in US MSM and TW with a substantial risk of STI.⁴ While clinical trials also show a benefit for gonorrhea, doxy PEP appears to be ineffective in areas in which tetracycline-resistant *Neisseria gonorrhoeae* is common, such as King County, WA.^{20,21}
 - In a randomized trial that enrolled MSM and TW living with HIV or taking HIV PrEP in Seattle and San Francisco, doxy PEP decreased the composite risk of STI by 65%, decreasing the risk of gonorrhea, chlamydia, and syphilis. Over 70% of the decrease in STI associated with doxy PEP reflected decreases in asymptomatic infections.⁵ Approximately 50% of averted STIs were gonorrhea, 43% chlamydia, and 7% syphilis.
 - The effectiveness of doxy PEP in preventing syphilis and chlamydia is further supported by another randomized trial²² as well as effectiveness studies undertaken in San Francisco, Seattle, New York and through Kaiser Permanente.^{6,8-11}
 - Doxy PEP is highly effective in preventing syphilis, the most serious and morbid bacterial STI.
 - Participants in the randomized trials and a subsequent analysis of data from the Sexual Health Clinic in Seattle found that doxy PEP users take a median of approximately 4 doses of doxy PEP per month.^{1,11} Accounting for the antibiotic courses averted by taking doxy PEP, the average study participant took approximately 43 extra days of antibiotics to avert 1.4 STI per year. If doxy PEP proves to be much less effective for gonorrhea prevention, as recent data suggest, the reduction in overall STI is likely to be approximately half that observed in the trial.
 - Many people taking doxy PEP report a decrease in anxiety and stigma associated with STI.²³
 - For some patients, using doxy PEP can be empowering, facilitate sex positivity, and allow people to take charge of their own sexual health.²³

- **Population-level benefits of doxy PEP:** Doxy PEP seems to decrease STI incidence at the population level.
 - After release of local doxy PEP guidelines, analyses of surveillance data in San Francisco from 2022-2023 showed a 50% reduction in population-level incidence of chlamydia and syphilis in MSM compared to cisgender women.⁶
 - Early syphilis cases among MSM have also decreased in King County by approximately 46% since 2023.⁷
 - While the magnitude of any broader population-level benefit of doxy PEP in the United States remains unknown, it will likely reflect the extent to which doxy PEP is offered to and used by people most at risk for STIs.

Risks of doxy PEP, including possible but unknown risks

- **Side effects:** Doxycycline is generally well tolerated. Possible side effects include nausea, upset stomach, sun sensitivity, pill esophagitis, and risk for allergy (e.g., fixed drug eruptions). Gastrointestinal distress may be especially bothersome for some people who have receptive anal sex (bottom). Taking doxycycline with food may help alleviate gastrointestinal side effects.
- **Use during pregnancy and lactation**
 - Doxycycline is an FDA pregnancy category D medication, largely based on historical risk of cosmetic yellowing of teeth in the 2nd or 3rd trimesters or inhibition of bone growth due to tetracycline (an older generation drug of the same class that is much more calcium-avid in teeth and bones). No published human data exist to show these fetal toxicities occur with doxycycline *in utero*. In 2001, [FDA advised](#) that therapeutic doses of doxycycline are unlikely to pose a substantial teratogenic risk but recognize that data are insufficient to suggest there is no risk. Doxycycline is the first-line treatment in pregnancy for certain rickettsial infections that have a high risk of mortality. Though no supporting data exist at present, congenital syphilis is also a highly morbid, and potentially fatal, infection that could be averted with doxy PEP. Thus, the benefits of doxy PEP may outweigh the risks for some persons who could become pregnant or who currently are pregnant. The decision to use doxy PEP in these patients requires specific counseling on potential risks during pregnancy and should always result from shared decision-making with the patient.
 - Short-term doxycycline use in persons who are lactating is safe. The effects of prolonged infant exposure to doxycycline in milk are not known; infants who are exposed should be monitored for GI toxicity.
- **Antibiotic resistance:** Doxy PEP is likely to lead to increased antibiotic resistance to tetracyclines, both at the individual and the population level. Table 2 summarizes the likelihood that doxy PEP will induce changes in antibiotic resistance among selected bacteria and classes of bacteria that commonly result in illness.

Table 2. Likelihood of doxy PEP impacting resistance of various bacteria

Microorganisms	Estimated likelihood that doxy PEP will affect antimicrobial resistance for different bacteria
<i>Neisseria gonorrhoeae</i>	High likelihood doxy PEP increases resistance to doxycycline
<i>Staphylococcus aureus</i>	High likelihood doxy PEP increases resistance to doxycycline
Group A <i>Streptococcus</i>	Largely resistant in the absence of doxy PEP. Doxy PEP may lead to increased group A Strep colonization.
<i>Streptococcus pneumoniae</i>	Intermediate risk of increased resistance
<i>Mycoplasma genitalium</i>	Possible increased resistance
Gram negatives in intestinal flora	Possible increased resistance
<i>Chlamydia trachomatis</i>	Very low risk of increased resistance (no known resistance at present)
<i>Treponema pallidum</i>	Very low risk of increased resistance (no known resistance at present)

- **Microbiome changes:** Doxy PEP may result in changes in the microbiome (the microorganisms that live in and on a person’s body and that are important for general health). The DOXYVAC trial found no significant increase in

extended-spectrum beta-lactamase (ESBL) producing *E. coli* in doxy PEP users over time.²⁴ In the US DoxyPEP trial, genetic sequence analyses performed on rectal swabs from doxy PEP users found no difference in the overall diversity or total bacterial mass of the gut microbiome compared to non-doxy PEP users. The proportion of all antibiotic resistance genes detected in samples was higher for the tetracycline class in doxy PEP users but remained unchanged for other antibiotic classes.¹³ Surveillance data from the PHSKC SHC suggests that doxy PEP may lead to more frequent colonization with group A Strep.¹⁴ The clinical significance, if any, of these findings is not well understood. While some studies have associated changes in the microbiome with chronic illnesses, such as diabetes and inflammatory bowel disease, whether doxy PEP increases the risk of these conditions is unknown.

Dosing, Prescribing and Monitoring Guidance

- Patients should take 200 mg of doxycycline as soon as possible, ideally within 24 hours but no later than 72 hours, after condomless oral, anal, or vaginal sex.
- Doxycycline can be taken as often as every day, depending on frequency of sexual activity, but individuals should not take more than 200 mg within a 24-hour period. To reduce their total exposure to antibiotics, patients may instead choose to take doxy PEP every 48-72 hours if having sex frequently or use doxy PrEP (100 mg doxycycline daily). For persons taking HIV PrEP either daily or in an event-driven fashion (“2-1-1”), additional counseling may be useful to clarify differences in dosing schedules.
- Patients should take doxycycline with food or fluids and remain upright for at least 30 minutes after the dose. Taking doxycycline with food may increase tolerability.
- Medical providers should encourage patients who take doxy PEP frequently to use sunscreen or cover their skin with long sleeves or a hat to reduce risk for photosensitivity.
- Either doxycycline hyclate or doxycycline monohydrate immediate release 100 mg tabs (2 tabs taken simultaneously) are acceptable. Delayed release formulations could reduce GI side effects but are often more expensive and may not be covered by insurance.
- Patients should not take doxycycline concurrently with polyvalent cations such as iron and calcium carbonate and should take doxycycline at least 1 hour before or 2 hours after antacids, calcium or iron containing products.
- Check for drug interactions and use caution with medications including some anti-epileptic drugs, digoxin, rifampin, isotretinoin, and warfarin.
- For ICD-10 diagnosis code, use Z20.2 (Contact with and [suspected] exposure to infections with a predominantly sexual mode of transmission) or Z29.89 (Need for prophylaxis against sexually transmitted infection)
- There is no standard number of doxycycline pills and refills to prescribe. Based on the US trial data that most people used between 1-10 (median 4) doses of doxy PEP per month, some clinics are dispensing 30 tabs with 1 refill, or the equivalent of 30 total doxy PEP courses. Some people may require more or desire to have fewer pills. The decision on number of pills and refills to prescribe is left to the provider’s discretion and should be based on discussion with the patient regarding anticipated need, expectations for frequency of follow-up and requests for additional medication.
- No laboratory monitoring is needed for doxy PEP.
- Approximately 66% of MSM who are contacts to gonorrhea or chlamydia test negative for these STIs and thus receive unnecessary antibiotics for empiric treatment.²⁵ Medical providers should consider forgoing presumptive (empiric or “epi”) treatment of persons following an exposure to chlamydia or gonorrhea if the patient reports that they are willing to wait for test results, and particularly if the patient used doxy PEP appropriately. Instead, the patient can be offered testing at all anatomic sites of exposure and treatment based on results. This guidance does not apply only to patients on doxy PEP but may be particularly germane for such patients since doxy PEP provides substantial protection against chlamydial infection. Presumptive treatment for known syphilis exposures remains recommended due to long incubation periods for *T. pallidum* infection and relatively long window period between *T. pallidum* infection and detection of infection using serologic tests.

- Routine screening for bacterial STIs should occur every 3-6 months for persons on doxy PEP. HIV screening (for persons without HIV) should be performed at the time of doxy PEP initiation and at every visit thereafter, or following the intervals recommended in current [2021 CDC PrEP guidelines](#) if taking HIV PrEP.
- Treat all incident STIs according to current [2021 CDC STI Treatment Guidelines](#).

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Plain Language Summary of Key Information for Discussing Doxy PEP with Patients

Benefits of Doxy PEP

- Doxy PEP is highly effective in preventing chlamydia and syphilis in men who have sex with men (MSM) and transgender women (TW) with a substantial risk of STI
 - In a randomized trial that enrolled MSM and TW in Seattle and San Francisco, doxy PEP decreased the risk of STI by 65%. Doxy PEP is highly effective in preventing chlamydia and syphilis. Most gonorrhea among MSM in Seattle are now resistant to doxycycline and doxy PEP is likely to have little if any impact on gonorrhea risk.
 - Most prevented STIs did not cause symptoms.
 - The average study participant took approximately 43 days of extra antibiotics to prevent 1.4 STIs.
 - Many people taking doxy PEP report a decrease in anxiety and stigma associated with STI.
 - Using Doxy PEP can be empowering for some patients, allowing them to take charge of their own sexual health.
 - Two French studies also found that doxy PEP decreases the risk of STI, though doxy PEP did not decrease gonorrhea in one of those studies, likely because of the high prevalence of doxycycline-resistant gonorrhea in the population studied.
- Doxy PEP might decrease how many STIs there are in the population as a whole depending on how many and which people ultimately use it. National and local 2023-2024 data show a decrease in early syphilis among MSM for the first time in 10 years, which is likely a consequence of doxy PEP use.

Known Side Effects of Doxycycline

- Doxycycline is generally well tolerated.
- Doxycycline can cause a rash when people go out into the sun.
- The drug can cause irritation of the esophagus – called pill esophagitis – leading to heartburn, trouble swallowing, or regurgitation of food back into your throat or mouth. Taking the medication with fluids and remaining upright for at least 30 minutes after the dose can reduce this risk.
- Some people taking doxycycline report stomach upset or loose stools/diarrhea while taking doxycycline. Taking this medicine with food can help prevent this.

Possible Side Effects

- **Antibiotic resistance:** Doxy PEP can lead to increased antibiotic resistance. When bacteria become resistant to an antibiotic, the antibiotic is no longer effective in treating infections caused by that bacteria. How much doxy PEP might affect antibiotic resistance is not known, but the risk will vary for different bacteria. Some bacteria that might be affected by doxy PEP include:
 - **Gonorrhea** - In many parts of the world, including King County, WA, gonorrhea is already frequently resistant to doxycycline. There is a relatively high risk that doxy PEP will lead to further increases in gonorrhea resistance. At current levels of resistance, doxy PEP probably has relatively little efficacy in preventing gonorrhea.
 - **Staphylococcus aureus** - *Staph aureus* is commonly found on the skin and can be transmitted through close contact. It can cause skin infections and, less frequently, serious infections such as endocarditis (a heart infection), bone or joint infections, and infections in other parts of the body. Antibiotic resistance in *Staph aureus* is an important problem, particularly when *Staph aureus* is resistant to drugs in the penicillin class (i.e., methicillin resistant *Staph aureus* [MRSA]). Doxycycline is sometimes used to treat *Staph aureus*, particularly MRSA, and if resistance increases, that drug will no longer be an option to treat Staph infections. Doxy PEP appears to increase the risk that a person carries doxycycline resistant

Staph aureus on their body. We don't know what impact, if any, doxy PEP has on how often people get *Staph aureus* infections or how often it might complicate the treatment of staph infections.

- **Streptococcus pneumoniae** - *S. pneumoniae* is the most common cause of pneumonia. Doxycycline is commonly used to treat pneumonia in patients who are not hospitalized. Doxy PEP could lead to more *S. pneumoniae* resistance, but we don't know how likely that is.
 - **Syphilis** - Doxycycline is sometimes used to treat syphilis. There are no known instances of doxycycline resistance in *T. pallidum* (the bacterium that causes syphilis) and the risk of resistance is thought to be very low.
 - **Chlamydia trachomatis** - Doxycycline is the most common treatment for chlamydia. There are no known instances of doxycycline resistance in *C. trachomatis* and the risk of resistance is thought to be very low.
 - **Group A Streptococcus** - Group A streptococcus causes skin infections and strep throat. Preliminary data suggest that doxy PEP increases how often people carry group A strep in their nose and throat. We do not know if this results in any increase in the risk of group A strep infections, like strep throat or skin infections.
- **Microbiome changes:** All of us carry millions of bacteria on our skin, in our mouths, in our intestines, and in other parts of our bodies. The bacteria and other microorganisms that people carry on and in their bodies is called the microbiome. A normal microbiome is required to keep us healthy. Doxy PEP might result in changes in the microbiome of people who take it. Some studies have associated changes in the microbiome with chronic illnesses, such as diabetes and inflammatory bowel disease (like ulcerative colitis), but we don't really know if frequent antibiotic use puts a person at long-term risk for these chronic diseases. The extent to which doxy PEP changes patients' microbiome and the clinical significance, if any, of these potential changes is unknown.
 - **Population-level effects:** Changes in antibiotic resistance and in people's microbiomes could have important population-level effects. Bacteria are often transmissible from person to person. As a result, the development of increased antibiotic resistance has implications beyond just the person taking a medication. The extent to which the use of doxy PEP will influence antibiotic resistance or people's microbiome at the population-level is unknown. If such changes occur at the population-level, they are likely to have the first and greatest impact on cisgender MSM and transgender women, the populations in which doxy PEP has been used most often.
 - **Alternatives to doxy PEP:** Doxy PEP is an effective intervention to prevent some STIs. Other options to minimize how much STIs affect you include being tested for STIs on a regular basis and being treated when you have one, using condoms consistently and correctly, and limiting your number of sex partners.