

## Guidelines, June 2023

# Doxycycline Post-Exposure Prophylaxis (Doxy-PEP) to Prevent Bacterial STIs in Men who Have Sex with Men (MSM) and Transgender Persons who Have Sex with Men

### Background

Several studies over the last decade have demonstrated that doxycycline post-exposure prophylaxis (doxy-PEP) is efficacious in preventing syphilis, chlamydia, and gonorrhea among cisgender MSM and transgender women<sup>1</sup>. Two large studies in the past year demonstrated that doxycycline decreased STIs among study participants with a history of bacterial STI (Table 1) and was well tolerated with minimal side effects. The studies were conducted with populations at high risk for STIs. At the same time, there are many unknown, and perhaps unknowable, potential individual and population-level effects of using doxy-PEP. Many MSM and transgender people are interested in taking doxy-PEP and may ask medical providers about the intervention. Public Health – Seattle & King County wants to ensure that medical providers and patients who may be interested in doxy-PEP know about the intervention, that information related to doxy-PEP is accurate, and that access to doxy-PEP and information about it is equitable. These guidelines are designed to help medical providers and patients make informed decisions about doxy-PEP.

Table 1. Results of randomized clinical trials of doxycycline PEP

Study	Number of participants	STI rate*		Relative Risk Reduction	Absolute Risk Reduction
		Doxy PEP	No Doxy PEP		
DoxyPEP	501	10.7% per quarter	31.9% per quarter	65%	140 per 100 person years <sup>+</sup>
DoxyVac	502	26.1 per 100 person-years	76.7 per 100 person-years	66%	51 per 100 person years
IPERGAY	232	37.7 per 100 person-years	69.7 per 100 person-years	47%	32 per 100 person years

\*Trials reported differing STI outcomes and time periods. Doxy PEP = gonorrhea, chlamydia or syphilis per 3 months; DoxyVAC and IPERGAY = gonorrhea, chlamydia or syphilis per 100 person years.

<sup>+</sup>DoxyPEP absolute risk reduction estimated based on unpublished data.

<sup>1</sup> A single small study demonstrated the daily doxycycline pre-exposure prophylaxis was efficacious, but PrEP involves more use of antibiotics than PEP and data on PrEP are limited. As a result, these interim guidelines focus on doxy-PEP.

References: Molina JM et al, Lancet 2018; Luetkemeyer AF et al, NEJM 2023; Molina JM et al, CROI 2023; Stewart J et al, CROI 2023

## Recommendations

- 1) Medical providers should **inform** cis-gender MSM and transgender women who have sex with men with a history of bacterial STI in the prior year about doxy-PEP, its efficacy, the potential benefits and risks of the intervention, and the alternative options available to prevent, diagnose, and treat STIs.
- 2) The decision to prescribe doxy-PEP should result from a **shared decision-making** process between the medical provider and the patient. Providers should give particular consideration to prescribing doxy-PEP to patients with a history of syphilis or a history of multiple STIs in the prior year. Providers may consider prescribing doxy-PEP on an episodic basis when patients anticipate periods when their risk of STI may be higher (e.g., group sex events).
- 3) Doxy-PEP is not recommended for cisgender women. A recent study found no effect of doxy-PEP in cisgender women in Kenya in preventing STIs.
- 4) The potential benefits and risks for transgender men (and other gender diverse patients assigned female sex at birth) who have anal sex with men are unknown. This population was not included in prior studies.
- 5) Counseling related to doxy-PEP should include the following elements:
  1. Evidence for the benefits of doxy-PEP.
  2. The known side effects and potential toxicities of doxycycline.
  3. The potential but unknown risks of doxy-PEP related to the microbiome and antibiotic resistance.
  4. How doxy-PEP should be taken and the need for ongoing monitoring.
  5. Alternatives to doxy-PEP.
- 6) 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, HIV/STI testing and treatment, and vaccines.

## Counseling Guidance

### *Benefits of doxy-PEP*

- **STI Prevention** - Doxy-PEP is highly effective in preventing chlamydia, gonorrhea, and syphilis in US populations with a substantial risk of STI
  - In a randomized trial that enrolled MSM and transgender women in Seattle and San Francisco, doxy-PEP decreased the 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. Approximately 50% of averted STIs were gonorrhea, 43% chlamydia, and 7% syphilis.
  - Participants took a median of approximately 4 doses of doxycycline per month. Accounting for the antibiotic courses averted by taking doxy-PEP, the average study participant took approximately 43 extra days of antibiotics per year to avert 1.4 STIs per year.
  - Many people taking doxy-PEP report a decrease in anxiety and stigma associated with STI.
  - For some patients, using doxy-PEP can be empowering, facilitate sex positivity, and allow people to take charge of their own sexual health.
- **Population-level benefits of doxy-PEP** - Doxy-PEP could decrease STI incidence at the population level.
  - While the magnitude of any population-level benefit of doxy-PEP is unknown, it is likely to 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 sun sensitivity, pill esophagitis, and gastrointestinal distress.
- **Antibiotic resistance** - Doxy-PEP could lead to increased antibiotic resistance, both at the individual and the population level. Table 2 summarizes the likelihood of changes in antibiotic resistance that doxy-PEP could induce.
- **Weight gain** – Some studies suggest that long-term use of doxycycline can result in abnormal weight gain, though this was not observed in the doxy-PEP trial.

- **Microbiome changes** - Doxy-PEP may result in changes in the microbiome (the microorganisms that live in and on a person’s body that are important for general health). Some studies have associated changes in the microbiome with chronic illnesses, such as diabetes and inflammatory bowel disease. The extent to which doxy-PEP changes patients’ microbiome and the clinical significance, if any, of these potential changes is unknown.

Table 2.

Microorganisms	Estimated likelihood that doxy-PEP will affect antimicrobial resistance for different microorganisms and classes of microorganisms
<i>Neisseria gonorrhoeae</i>	High risk of increased resistance
<i>Staphylococcus aureus</i>	Intermediate risk of increased resistance
<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>	Low risk of increased resistance (no known resistance at present)
<i>Treponema pallidum</i>	Low risk of increased resistance (no known resistance at present)

Dosing and Prescribing Guidance

- 200 mg of doxycycline should be taken 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.
- Take doxycycline with fluids and remain upright for 30 minutes after the dose. Taking doxycycline with food may increase tolerability.
- Either doxycycline hyclate OR doxycycline monohydrate immediate release 100 mg tabs (2 tabs taken simultaneously) are acceptable.
- Do not take concurrently with polyvalent cations such as iron and calcium carbonate. Take doxycycline at least 1 hour before or 2 hours after antacids, calcium or iron containing products.
- No laboratory monitoring is needed with doxy-PEP
- For ICD-10 diagnosis code, use Z20.2 (Contact with and [suspected] exposure to infections with a predominantly sexual mode of transmission).
- 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. 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 expectations for frequency of follow-up and requests for additional medication.

# Counseling Messages when Discussing Doxy-PEP with Patients

## Benefits of Doxy-PEP

- Doxy-PEP is highly effective in preventing chlamydia, gonorrhea, and syphilis in US populations with a substantial risk of STI
  - In a randomized trial that enrolled MSM and transgender women in Seattle and San Francisco, doxy-PEP decreased the risk of STI by 65%. Doxy-PEP decreased the risk of gonorrhea, chlamydia, and syphilis.
    - Most prevented STIs are asymptomatic.
    - The average study participant took approximately 43 extra days of antibiotics per year to avert 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 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 much STI there is in the population as a whole.
  - Whether this will happen or not is not known and will likely depend on how many people use doxy-PEP.

## 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 – 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 30 minutes after the dose can reduce this risk.
- Some people taking doxycycline report stomach upset while taking doxycycline. Taking this medicine with food can help prevent this.

## Possible Side Effects

- **Antibiotic resistance** - Doxy-PEP could 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, gonorrhea is already resistant to doxycycline. There is a relatively high risk that doxy-PEP will lead to increased gonorrhea resistance. If that happens, doxy-PEP will stop preventing gonorrhea and doxycycline will not be a useful treatment for gonorrhea. This may decrease the overall effectiveness of doxy-PEP. (Doxycycline is not commonly used to treat 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 penicillin-like drugs (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. While there is a significant risk that doxy-PEP will lead to increased doxycycline resistant *Staph aureus*, we don't know if that will occur or when it might occur.
  - **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* 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.
- **Microbiome changes** – All of us carry lots 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, 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.
  - **Weight gain** – Some studies suggest that long-term use of doxycycline can result in abnormal weight gain, though this was not observed in the doxy-PEP trial.
  - **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. Insofar as 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 will be used.
  - **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 more often, and limiting your number of sex partners.