

# STI Post-Exposure Prophylaxis with Doxycycline Consultation Summary Report

**NACCHO**<sup>SM</sup>  
National Association of County & City Health Officials



# Summary

The National Association of County and City Health Officials (NACCHO) hosted a virtual consultation, “STI Post-Exposure Prophylaxis with Doxycycline,” on December 5th and December 6th, 2022. This meeting was convened by NACCHO with the support of CDC’s Division of STD Prevention (DSTDP) and the National Network of STD Clinical Prevention Training Centers (NNPTCs).

The purpose of this consultation was to gather subject matter experts to share considerations related to implementing doxycycline (doxy) as post-exposure prophylaxis (PEP) (also known as “DoxyPEP”) to prevent sexually transmitted infections (STIs). Doxycycline (doxy) prescription increases are something that should be considered in this decision. Doxy is a broad-spectrum synthetic tetracycline developed in the 1960s. It is a second-generation tetracycline with a longer serum half-life, efficient oral absorption, high lipid solubility, and low resistance profile. The invite-only consultation included national and global experts in public health, STIs, infectious disease, and antimicrobial resistance. The consultation included overviews of Doxy-PEP trial results, discussion of the potential harms, costs, and benefits of using DoxyPEP and identification of further research needed in these areas.

Together, the subject matter experts explored topics like clinical benefits and harms of doxycycline and the possibility of doxycycline resistance development. Additionally, there was discussion of questions like “which population(s) would benefit most from DoxyPEP?” and “can DoxyPEP decrease STIs at the population level?”

## **Key takeaways:**

- Doxycycline (doxy) as PEP has the potential to reduce STIs in certain populations as shown by recent studies but it must be rolled out equitably and should be provided in the context of culturally competent care and of shared decision making between providers and patients.
- DoxyPEP, when offered, should be implemented in the context of a comprehensive sexual health approach.
- There are real and concerning potential risks to the overuse of antibiotics, including anti-microbial resistance, as well as to the human microbiome, which may have long-term clinical consequences for individuals.
- Determining populations which will benefit from DoxyPEP is not straightforward and may mean making trade-offs between DoxyPEP coverage and overuse of antibiotics.
- Experts attempted to address which patients should be offered DoxyPEP, some proposed groups included people with recurrent STIs and men who have sex with men (MSM) and transgender women (TGW) who have had at least one STI in the past year
- Community members cited additional benefits of DoxyPEP in reducing feelings of anxiety and stigma associated with an STI diagnosis or exposing partners to infection
- Regional differences could be impactful when weighing the risk/benefits of DoxyPEP and are especially important to consider when thinking about implementation. Determining the appropriate populations for DoxyPEP may not be straightforward so there should be federal guidance with room for tailoring implementation at the local level for local community and factors.
- Many of the unknowns about the potential risks of DoxyPEP will not be answered before some locales are ready to implement it as a prevention option – but it is possible to provide some guidelines to patients and providers even when there is uncertainty.

# Efficacy and Background Information

## STI Post-Exposure Prophylaxis with Doxycycline Trial Results

To start the consultation, information about several completed, ongoing, and upcoming clinical trials from around the world was shared.

### **IPERGAY Study Results**

The IPERGAY DoxyPEP study was a sub-study of the IPERGAY PrEP trial which looked at men aged 18 years or older having condomless sex with men and using pre-exposure prophylaxis (PrEP) for HIV. All participants were eligible for the open-label randomization to DoxyPEP (200 mg within 24 hours and no more than 72 hours after sex). DoxyPEP use was limited to up to 3x/week (median of 660 mg doxy taken per month).

The trial findings (among n = 232 participants) included a significant reduction in first occurrence of chlamydia (70%) and syphilis (73%) but no significant difference in gonorrhea. Numerically, there were less rectal and urethral GC infections in the DoxyPEP arm; lack of efficacy was noted for pharyngeal GC (~55% of GC with tetracycline resistance when study conducted).

### **Doxyvac Study Results**

The Doxyvac study design is open-label factorial randomization: DoxyPEP vs no doxy (2:1 randomization) and Bexsero vaccine vs no vaccine (1:1). Bexsero is a vaccine for *Neisseria meningitidis serogroup B* that may offer protection against *Neisseria gonorrhoeae* based on previous studies. There were 546 MSM randomized, of which 502 were analyzed. The trial was nested within the ANRS PREVENIR study of oral PrEP and included MSM who were on PrEP for 6+ months, HIV negative, reported no current STI symptoms and had a bacterial STI in the past 12 months.

The data analyzed (from 2021-2022) had the following findings: in the DoxyPEP group, there was a significant (84%) reduction in the risk of a first episode of syphilis or chlamydia infection, and the incidence of gonorrhea infections was also significantly reduced (by 50%).

### **DoxyPEP Study Results**

The DoxyPEP trial was designed to learn whether DoxyPEP reduces new syphilis, chlamydia, and gonorrhea infections among MSM and TGW who are on PrEP or living with HIV. Secondary point of focus was examination of the effect on antimicrobial resistance as well as if DoxyPEP use is well-tolerated by participants.

The study design was open-label doxy (200 mg taken as PEP within 72 hours after sex) vs no doxy (with a maximum dose of 200mg within 24 hours). Participants were randomized 2:1 and were male sex at birth, living with HIV or on PrEP with at least 1+ STI (bacterial) and history of condomless sex with 1+ male partners in past 12 months. Few transgender women were enrolled.

The primary endpoint was STI incidence per quarter (every 3 months), so individuals could have more than one endpoint. Findings were:

- 65% reduction in STI incidence per quarter. Gonorrhea was the most common infection reported with a statistically significant 55-57% reduction in GC in both arms. Chlamydia had a 74-88% reduction - also, statistically significant. Syphilis showed a 77-87% decreased incidence, though this was not statistically significant.
- Sexual behavior at enrollment: Median 9 sexual partners in prior 3 months and 5 sexual acts per month. No significant change in sexual behavior was observed during the study.
- Adherence: 86% reported taking DoxyPEP always/often after anal/vaginal sex with the median doses being 4.0 per month (based on quarterly interview); 25% with 10+ doses taken per month.
- Ceftriaxone use: 50% less in doxy arm (consistent with reduction in incident GC infections).
- More than 80% of rectal GC/CT infections were asymptomatic in both arms. Doxy also reduced incidence of symptomatic infections.
- Gonococcal tetracycline (TCN) culture-based susceptibility was evaluated during the study. Few gonorrhea culture isolates were available for testing (~17% of GC cases at baseline and on-study were available for testing). At baseline, 25% of isolates were TCN resistant. There was slightly higher GC TCN resistance at follow-up in those who acquired GC while on DoxyPEP (38% versus 12.5%) though interpretation is limited by small numbers.
- Gonococcal tetracycline (TCN) culture-based susceptibility was evaluated during the study. Few gonorrhea culture isolates were available for testing (~17% of GC cases at baseline and on-study were available for testing). At baseline, 25% of isolates were TCN resistant. There was slightly higher GC TCN resistance at follow-up in those who acquired GC while on DoxyPEP (38% versus 12.5%) though interpretation is limited by small numbers.
- Regarding doxy resistance in *Staphylococcus aureus*, DoxyPEP decreased the proportion colonized and there was no change in the absolute number with doxy resistant MSSA from baseline to 12 months.
- Commensal *Neisseria* had high levels of doxy resistance in both arms (~60%); a minimal increase was observed in doxy resistance with DoxyPEP.
- The DoxyPEP investigators recommended offering DoxyPEP to those who would most benefit through shared decision-making about benefits, risks and uncertainties of longer-term use; characterize use patterns and assess impact on AMR in bystander bacteria and STIs.

### **dPEP-KE Study Design**

This trial is taking place in Kenya and the design is 1:1 open label randomized trial of DoxyPEP (same dosing as in DoxyPEP and DISCO trials above and below respectively). The participants can take doxycycline at 200 mg daily max and receive a quarterly follow up visit with NAAT STI swabs (endocervical). Unlike most of the other studies, in this one, participants are 449 cisgender women taking PrEP between the ages of 18-30. Pregnant or breast-feeding women are excluded but contraception is not required to participate. Participants' median age is 24 with 66% never married, 69% having delivered one child or more, 57% using long-acting reversible contraception, 32% used condoms at last sex, and 37% engaged in transactional sex in last 3 months. At baseline, there was 17.9% prevalence of STIs among participants.

The primary endpoint is to determine efficacy of DoxyPEP among Kenyan women on HIV PrEP (all oral daily PrEP). The secondary endpoint is the evaluation of DoxyPEP on antibiotic resistance, on trichomoniasis, mycoplasma genitalium, vaginal microbiome, adherence, acceptability, and cost-effectiveness. Results of the trial are not yet available.

### **DISCO Study Design**

This trial, taking place in Canada, was originally planned as a three-arm trial of doxy PrEP vs. PEP vs. placebo but is now revised to be a randomized control trial of doxy PrEP vs doxy PEP since the studies above already looked at PEP vs. placebo. The study will include 560 participants across 6 Canadian cities/4 provinces who will be followed every 3 months for 15 months. Participants will be adult men who have sex with men (cisgender or transgender) or transgender women who were sexually active in last 12 months and who have had at least one bacterial STI in last 12 months. The intervention is either daily doxy at 100 mg/day or 200 mg given after exposure as PEP (as in the DoxyPEP study above).

The primary objective is to establish non-inferiority of PrEP vs PEP in preventing STIs with the secondary objectives being to examine tolerability/safety, changes in sexual behavior, adherence (self-report, pill counts, doxy levels), AMR development and microbiome, superiority of PrEP over PEP, mathematical modeling, and economic evaluation.

The trial recruitment is starting in early 2023 with expected initial analyses in mid-2026.

### **Syphilaxis Study Design**

The goal of this trial is to look at the acceptability of doxy as PrEP on STI incidence. It is a single arm observational study with 350 participants who have a history of STIs, have had sex with men in the last 3 months, and have had syphilis in last 24 months. Participants have the option to take doxy 100 mg daily or on demand (2 x 100 mg post exposure in line with established protocols) for a period of 12 months. Participants are surveyed quarterly and asked how they used the study drug. The sub-study looks at pharyngeal/rectal swabs for microbiome impact. Efficacy outcomes will be comparing STI incidence per person in 12 months prior to enrollment and incidence in previous HIV PrEP studies, and other similar matched cohorts. Results are not yet available as the last patient visit is planned for late 2024.

*Following the summaries of the recent studies of DoxyPEP, the consultation moved to discussion and presentation around topics of concern when considering DoxyPEP use.*

## **“Can STI-PEP with doxycycline decrease STIS at the population level? By how much?” [Patrick Sullivan]**

This presentation recommended developing and prioritizing the use of equity-based metrics for program evaluation from the outset of program implementation, so that decisions are made that go beyond maximizing the number of people served – and rather focus on maximizing equity—stating that if uptake focuses on equity, it will also maximize the public health impact in terms of STIs averted.

DoxyPEP is an important public health intervention which has been convincingly shown to decrease acquisition of chlamydia, gonorrhea, and syphilis in key populations. Yet, we are at the very beginning of a program of public health implementation. It is important to ask up front what our expectations are for making a difference in mitigating or controlling epidemics of the STIs that DoxyPEP can prevent, and what steps we can take in this early implementation phase to assure the highest possible impact on preventing infections and improving health. This session focused on the importance of an equitable rollout of DoxyPEP and showed how this could be monitored by using equity data on HIV PrEP rollout as a model.

There will be multiple ways to measure our progress in rolling out and scaling up DoxyPEP; historically, one important metric is counting people receiving the service. However, our experience with other preventive interventions (e.g., PrEP), is that we may show impressive year over year increases in adoption of a new intervention, but the public health impact of those newly served clients is lower than it might be if we find we are serving populations at relatively lower risk of the infection. This isn't just hypothetical: in the scaleup of PrEP, data from the national American Men's Internet Survey ([AMIS](#)) showed that in the first 5 years of PrEP scaleup, White non-Hispanic MSM were being served with roughly equal amounts of PrEP compared to Black and Hispanic MSM, even though White MSM's risk for HIV infection was much lower than their Black and Hispanic counterparts. One key consideration at this point is how we will plan for an equitable scaleup of DoxyPEP, and how we will measure our success in achieving equitable (and not just equal) DoxyPEP coverage by race, ethnicity, sex, and age.

Our first look at equitable PrEP uptake from 2012-2021 as a model for implementation of prevention in the US is not encouraging: Black people were served by PrEP at a level 90% below their epidemic need, and Hispanic people were served by PrEP at level 80% lower than their epidemic need, relative to White non-Hispanic people. This is shocking for the extent of inequity and is also concerning from the perspective of impact of programs: the population-level impact of PrEP will be highest when we reach those at highest risk of infection with PrEP and the same is likely with DoxyPEP. In this inequitable situation, models predict that the higher risk of HIV acquisition of Black MSM relative to White MSM will worsen, even as PrEP is scaled up.

The same lessons learned in PrEP rollout will apply to a rollout of DoxyPEP. Early in the programmatic rollout, there will be great excitement and enthusiasm to make this new intervention available to clients as quickly as possible. And because of issues like proximity to healthcare, insurance coverage, trust and mistrust of institutions, and differential HIV and PrEP stigma, we might well find that it is easier to reach White populations with DoxyPEP than other groups.

## Overview of the clinical uses and harms of doxycycline [Cheston Cunha]

The pharmacoeconomic advantages of doxy include:

- Permits oral administration (intravenous (IV) sparing) for serious infections (important for antimicrobial stewardship in cases of serious infections)
- Potential for outpatient only therapy or early discharge with IV to oral administration (PO) transition
- Low incidence of failure/side effects
- No monitoring needed
- Relatively inexpensive compared to oral administration of fluoroquinolones and cephalosporins

Doxy's spectrum is exceptionally broad with usefulness in penicillin and sulfa allergic patients. It also has been shown to have a *Clostridioides difficile* protective effect.

Doxy is usually very well tolerated, and its safety profile is excellent even in pregnant people (most of the hesitancy came from tetracycline studies). Some side effects exist but generally the benefits outweigh risks to its use for serious infections, even if otherwise listed as contraindicated.

Doxy is a life-saving medication that must be preserved for life-threatening infections, but it is already highly available and cost effective. It is an important drug for antibiotic stewardship and indiscriminate use may have the potential to induce resistance especially among organisms which are common, such as *Staphylococcus* and *Streptococcus*, and so any implementation of DoxyPEP must be done cautiously to be sure to preserve it as a treatment for infections where it is the preferred agent for treatment.

## Uses of Doxy:

Optimal	Acceptable in Certain Circumstances	Suboptimal/Avoid
<b>Central Nervous System</b>		
Lyme meningitis	Mycoplasma / legionella / encephalitis	S. pneumo meningitis
	Actino brain abscess	
	Neurosyphilis	
<b>Head, Ears, Eyes, Nose, Oral, Throat (HEENOT)</b>		
Bacterial sinusitis	Mastoiditis	Group A Streptococcal (GAS) pharyngitis
Dental infections (including actino)		GAS sinusitis
		Periorbital cellulitis
Upper respiratory		
AECB (acute exacerbation of chronic bronchitis)	Peritonsillar abscess	
Laryngitis d/t C. pneumo		
<b>Lungs</b>		
Typical Community acquired pneumonia (CAP) – S. pneumo, H. flu, M. catarrhalis	Lung abscess	Nosocomial pneumonia (PNA)
Atypical CAP (zoonotic) – psittacosis, tularemia, Q fever	Aspiration PNA	GAS PNA

# Uses of Doxy:

Optimal	Acceptable in Certain Circumstances	Suboptimal/Avoid
Atypical CAP (non-zoonotic) - legionella, mycoplasma, c. pneumoniae	Nocardia	
Bioterrorism agents – anthrax, plague	Actino	
Melioidosis		
<b>Zoonosis</b>		
Rocky Mounted Spotted Fever (RMS)	Chloroquine resistant malaria	Babesia
Leptospirosis	Lymphatic filariasis	
Lyme		
Q fever		
Brucellosis		
Tularemia		
Plague		
Anthrax		
Anaplasmosis		
Ehrlichiosis		
<b>Gastrointestinal (GI)</b>		
Diverticulitis	Traveler's diarrhea	Amebiasis
Appendicitis	Cholera	Shigella
	Whipple's disease	Cholecystitis
		Hepatic abscess
<b>Other pathogens</b>		
V. vulnificus	Atypical Mycobacteria (m. cheloniae, m. fortuitum)	Meticillin-Sensitive Staphylococcus aureus, (MSSA) Methicillan-resistant Staphylococcus aureus (MRSA)
Animal bites		Strep cellulitis (GAS/ Guillan-Barr Syndrome)



# Uses of Doxy:

Optimal	Acceptable in Certain Circumstances	Suboptimal/Avoid
		Complicated skin and soft tissue infections
		Diabetes mellitus foot ulcers/osteo
Genitourinary/reproductive		
Acute cystitis (E coli, klebs, Enterobacter, indole + proteus, prostate e-specific antigen in some cases)	Acute pyelo (if susceptible)	
Epididymitis		
Prostatitis (acute and chronic)		
Pelvic inflammatory disease, tubo-ovarian abscess, Mycoplasma genitalium, etc.		

Doxy is usually very well tolerated, and its safety profile is excellent even in pregnant people (most of the hesitancy around use of doxy in pregnant people came from tetracycline studies). Some side effects exist but generally the benefits outweigh risks in its use for serious infections, even if otherwise listed as contraindicated.

Doxy is a life-saving medication that must be preserved for life-threatening infections, but it is already highly available and cost effective. It is an important drug for antibiotic stewardship and indiscriminate use may have the potential to induce resistance especially among organisms which are common, such as *Staphylococcus* and *Streptococcus*, and so any implementation of DoxyPEP must be done cautiously to be sure to preserve it as a treatment for infections where it is the preferred agent for treatment.

## What are the potential harms of using doxycycline for STI post-exposure prophylaxis?

### The Antimicrobial Stewardship Perspective: Big Picture [Lauri Hicks]

Important questions to answer from a stewardship perspective include:

1. Utilization: How much will doxy use increase?
2. Benefits: What are the population level benefits? To the target population?
3. Risks:
  - What is the potential for misuse of doxy for non-PEP and how can misuse be avoided?
  - What are the implications for resistance to last resort antibiotics, like tigecycline, eravacycline, sarecycline, and omadacycline, for individuals who take DoxyPEP as well for general population?
  - What does DoxyPEP mean in terms of adverse events and long-term consequences due to microbiome disruption?

We must weigh the benefits and risks of a national policy that would lead to more antibiotic use. Antibiotic resistance is one of our most stealthy and concerning public health threats. In 2019, the CDC updated the antibiotic resistance threats report and estimated that over 35,000 deaths occur annually because of antibiotic-resistant bacteria and fungi. Combatting antibiotic resistance requires antimicrobial stewardship which involves ensuring the appropriate use of the drugs and reducing unnecessary use while also making sure that access to antibiotics is available when they are needed. Antibiotic stewardship is fundamentally about patient safety and delivering high quality healthcare—it is a set of commitments and actions designed to optimize the treatment of infections while reducing the adverse events associated with antibiotic use.

One of the major challenges to antimicrobial stewardship is over-prescription—as many as 30% of antibiotic prescriptions are estimated to be unnecessary. And even among the other 72% there is a need to improve drug selection, dose, and duration to minimize inappropriate use. Antibiotics can also have adverse effects. One in 1000 emergency room visits are due to antibiotic side effects. Microbiome disruption by antibiotic use may also be leading to short- and long-term consequences such as chronic diseases.

In 2021, tetracyclines as a class of drugs comprised the fourth most prescribed antibiotic class in the United States for outpatient oral antibiotics. Most of that tetracycline use was driven by doxycycline, which was the fourth most prescribed antibiotic agent with almost 22 million prescriptions. Based on commercial claims data, the most common uses for doxy are to treat sinusitis (42%), and skin and soft tissue infections (34%). As a result, a caution would be to think of potential collateral damage in terms of antibiotic resistance among respiratory pathogens where it is a common treatment. Miscellaneous bacterial infections including sexually transmitted infections only account for 7% of use of doxy.

So only a small fraction of current doxy prescription is for STIs. There is likely a lot of doxy use in the in-patient setting as well but that data was not able to be collected before the presentation.

In addition, when individuals have access to antibiotics (from a previous prescription) they may use the prescription regardless of its utility. According to a study released in 2019, about 25% of people reported using antibiotics without a prescription. Accordingly, patient education on use of DoxyPEP for other conditions without a provider recommendation will be critical. So not only is it important to assess adherence to recommended uses, but it is also important to look at the potential for misuse, especially as there is a very limited oral antibiotics pipeline and limited oral treatment options. There have been no new antibiotics approved in over three years and these medications are also used in animals (without oversight at the national or state level of this use). Additionally, it is important to think about what will happen to the cost of the drug when use is increased.

### **The Antimicrobial Stewardship Perspective: STI-specific Considerations [Chris Kenyon]**

It is known that excess antibiotic use leads to antimicrobial resistance (AMR) and although doxy is one of the antibiotics least likely to induce resistance, it still does induce and select for resistance, and it does this not just for tetracyclines but for other classes of antimicrobials which have not yet been investigated.

AMR has emerged in a range of STIs but only if they are exposed to excessive antibiotic use such as in cases of a dense sexual network with excess antibiotic exposure. As a result, keeping antibiotic consumption below safe limits is important to reduce the probability of AMR in core groups. Unfortunately, DoxyPEP could result in large increases of doxy consumption, and the population level consumption is the key driver of the prevalence of resistance.

Looking at the example of penicillin and pneumococcal resistance in countries where the consumption of antibiotics is higher, for example in France, there is a much higher level of resistance (as high as 50%) whereas in countries where the use is low, like the Netherlands, there is almost no resistance found. Similar evidence is seen when looking at *Treponema pallidum*: in countries that consume less macrolides, there is almost no resistance while those countries that consume more have high levels of resistance—typically above 60-70%. The same thresholds were also seen with *M. genitalium* and *S. pneumoniae*. For example, when assessing antibiotic resistance in the context of an every three month, three-site screening for CT/GC in a PrEP cohort in a study in Belgium, PrEP uptake resulted in about 4400 macrolide doses per 1000 population per year, or sixfold the threshold of 700 at which the chance of resistance increases. Because the study team was seeing the high increases in resistance, the study protocol was changed to one-site CT/GC testing every 6 months, after which the consumption of macrolide was significantly reduced to the safer level of about 700.

What are the most relevant bacteria to assess for induction of AMR in DoxyPEP cohorts? We assessed this by noting a 4-fold increase in doxycycline minimal inhibitory concentration (MIC) over the passage of time under increase doxy concentrations in four bacterial species - *N. gonorrhoeae* (3 strains), *N. subflava*, *E. coli* and *K. pneumoniae*. By day 3 to 4 rapid increases in MIC were seen in *E. coli* and *K. pneumoniae* but no increases were seen in the *Neisseria spp.* We then evaluated the effect of DoxyPEP on *K. pneumoniae* doxycycline MICs in a waxmoth (*Galleria mellonella*) model. DoxyPEP resulted in rapid increases in doxycycline MICs in *K. pneumoniae* and cross resistance to ceftriaxone and ciprofloxacin. It is therefore important to look at the effects of DoxyPEP on a wide range of bacterial species in humans before we say it is safe to use in them, including organisms like *E. coli* and *Klebsiella*.

## **How will STI-PEP with doxycycline affect the microbiome? [Martin Blaser]**

This presentation focused on antibiotics generally and not specifically on doxy, but the principles should be the same as far as long-term effects of antibiotics on the microbiome and the development of disease. There are studies that show impacts on the development of both type 2 diabetes and kidney stones with antibiotic exposure in adults. For example, individuals who have previously received antibiotics are more likely to have type 2 diabetes than individuals who have not previously received antibiotics, and the more antibiotics courses that the individual received, the more likely they were to develop type 2 diabetes. Similarly, there is a study showing a significant association with receiving antibiotics in the 3-5 years prior to a kidney stone diagnosis.

In children there may also be a relationship between antibiotic exposure and increasing incidences of various conditions (e.g., obesity, asthma, celiac disease). Dr. Blaser has developed the theory of the disappearing microbiota, positing that because of changes in birthing and increasing uses of formula, antibiotics, and antiseptics among others, there has been a change in human ecology, which has altered the transmission and maintenance of ancestral microbes which affect the composition of the microbiota. The microbes, both good and bad, usually acquired in early life are especially important as they affect a developmentally critical stage of life. Loss of microbiome may occur over generations, resulting in subsequent generations starting at a loss.

According to various studies, antibiotics have long-term effects on host inflammation and immunity. The effects are due to perturbing the microbiome. Effects may be transmitted to the next generation, and we must find and implement solutions, and unnecessary antibiotic use must be curtailed as well as finding ways to decrease use of antibiotics overall.

### *Questions about Proposed Doxycycline Use:*

- What are the effects of proposed doxy regimens on microbiome (and mitochondria)?
- What is the duration of those effects?
- In reproductive age women, will effects persist during pregnancy?
- For reproductive age men, will it affect their reproductive partners?
- Are there alternative approaches that are more targeted (to reduce the population-at-risk)?
- Can prophylaxis doses be reduced to lower the impact on the microbiome?
- In net, what is the scale of unintended consequences vis a vis proposed benefits?

## **Common outpatient infections and potential for doxycycline resistance**

### **MRSA [Loren Miller]**

Among all antibiotics prescribed in the U.S. in 2014, tetracycline class antibiotics (tetracyclines), which include tetracycline, doxycycline, and minocycline, were not among the 5 most prescribed classes of antibiotics. However, by 2020, tetracycline class antibiotic use had risen to #4, demonstrating that use of this antibiotic class is increasing.

This rise in doxycycline use is likely due to the Infectious Disease Society of America (IDSA) recommending it as an option for pneumonia. The infectious disease community is increasingly recommending doxycycline for skin infections and using doxycycline for bone and joint and other infections given its safety, efficacy, and rises in antibiotic resistance among bacteria such as *S. aureus* to non-tetracycline class antibiotics. It is possible that updated guidelines on treatment of skin infections from the Infectious Disease Society of America will recommend doxycycline for any moderately severe suppurative skin infections, which will in turn drive increased use of doxycycline.

Will increased doxycycline use cause an increase in doxycycline-resistant *S. aureus*? Interestingly, global data on drug resistance in *Staphylococcus* showed that 80% of *S. aureus* were susceptible to tetracycline and 87% to doxycycline in 1997-2000. But by 2013-2016, susceptibility had surprisingly risen: 93% of *S. aureus* were susceptible to tetracycline and 98% were susceptible to doxycycline.

This trend is counter-intuitive, and the opposite of antibiotic resistance trends seen in other bacteria, where rates typically only rise with time.

Given the very unexpected observation of *decreasing* antibiotic resistance to doxycycline over time despite *increasing* doxycycline use, if doxycycline is used as PEP, it is hard to know how increased doxycycline use will affect the rate of doxycycline-resistant *S. aureus* given doxycycline use is not the only driver of the emergence of doxycycline resistant *S. aureus*. So, all we can say about whether DoxyPEP would lead to an increase in doxycycline-resistant *S. aureus* is “maybe.”

### ***Streptococcus pneumoniae* [Kristin Andrejko]**

*Streptococcus pneumoniae* (pneumococcus) is the leading bacterial cause of noninvasive pneumonia which may be treated with doxycycline. The Centers for Disease Control and Prevention (CDC) monitors the trend of invasive pneumococcal disease, or IPD, such as pneumococcal bacteremia or meningitis, through the Active Bacterial Core surveillance (ABCs). The ABCs is an active laboratory and population-based surveillance system. Cases of invasive pneumococcal disease, defined as isolation of pneumococcus from a sterile site, are reported to ABCs, and isolates are shared with the CDC for susceptibility testing.

Given that doxycycline, a tetracycline antibiotic, is an option in the standard regimen for treatment of community acquired pneumonia among adults, the ABCs surveillance platform can be used to monitor changes in the incidence of tetracycline non-susceptible IPD. Prior to the introduction of the 13-valent pneumococcal conjugate vaccine (PCV13), which confers serotype specific protection to 13 pneumococcal serotypes, incidence rates of tetracycline non-susceptible IPD were highest among adults >65 followed closely by children <5. PCV13 introduction was associated with sharp reductions in tetracycline non-susceptible IPD among children <5, with rates of tetracycline nonsusceptibility in the post PCV13 period (2010 onward), being highest among adults >65 and adults 50-64. Licensure of higher valency PCVs, conferring protection against 15-20 serotype may result in some additional reductions in pneumococcal tetracycline nonsusceptibility.

ABCs data can be used to help monitor the burden of tetracycline non-susceptible IPD among primarily hospitalized patients. Currently, there is no national surveillance for outpatient pneumococcal disease, so rates of tetracycline nonsusceptibility for indications like outpatient-treated community acquired pneumonia are unknown. Since doxycycline is recommended as a standard regimen for the management of community acquired pneumonia, it will be important to continue to monitor trends in nonsusceptibility amid changes in doxycycline prophylaxis regimens and implementation of new pneumococcal vaccines.

### **What is the risk of doxycycline resistance developing in STIs?**

#### ***Mycoplasma genitalium* and *Chlamydia trachomatis* [William Geisler]**

Multiple STI studies have reported doxycycline nonadherence of greater than 25%. In one study which used a medication event monitoring system in the medicine bottle cap and defined “noncompliance” as not starting doxycycline within 48 hours or not taking at least 1 doxycycline dose for 5 consecutive days, there was 24% noncompliance and that did not differ by gender or symptom status. If we are concerned about resistance developing in STIs, we may have already started to see this because of longstanding nonadherence with doxycycline regimens.

### ***Mycoplasma genitalium (M. gen)***

*M. gen* is hard to grow so culture is not useful for detecting *M. gen* in clinical care. NAAT (nucleic acid amplification test) is recommended for *M. gen* detection but none of the FDA-cleared *M. gen* NAATs incorporate testing for resistance markers (and without known molecular resistance markers, culture-based susceptibility testing is necessary). It is therefore challenging to study doxycycline resistance in *M. gen*. However, it is known that in addition to its very slow growth, *M. gen* has a biofilm that impedes antibiotic penetration which may contribute to antibiotic resistance.

*M. gen* macrolide resistance-associated markers (MRMs) prevalence can vary worldwide by country/region. Across US sites, the MRM prevalence ranges from 31%-94%. So, while macrolides were the previously recommended first line therapy for *M. gen*, there is already significant macrolide resistance development, which points to them as no longer a reliable first line treatment. Transitioning to a fluoroquinolone as the first line treatment would be a reasonable consideration, but unfortunately multiple mutations for quinolone resistance have already been noted (although only one of the mutations is showing a treatment failure rate over 50%).

Doxycycline does not work well to cure *M. gen*, but it does lower *M. gen* load and so it has an important role in treatment strategies. Doxycycline-resistant *M. gen* strains have not yet been associated with treatment failures but since most sites cannot culture *M. gen*, there are no established doxycycline resistance markers, and there are no surveillance systems to track doxycycline resistance, the data we have for doxycycline resistance for *M. gen* is very limited. Investigators at the University of Alabama at Birmingham have isolated an *M. gen* strain from a patient previously treated with doxycycline and minocycline that is resistant to tetracycline and has elevated MICs for doxycycline and minocycline.

There is concern that DoxyPEP could lead to increased MICs for some of the tetracycline class drugs that are currently used to treat *M. gen*, such as minocycline. The potential for development of resistance is promoted by the fact that the organism grows very slowly, and it has a biofilm.

### ***Chlamydia trachomatis (CT):***

In *CT*, antibiotic resistance has not been a concern because tetracycline resistance has not been seen in the last 20 years, but we also do not look for it much. In general, we do not see resistance/treatment failures in clinical trials or in treatment.

High-level resistance of *CT* to doxycycline has not been shown in human *CT* infections previously. A small number of bacteria may survive treatment with doxycycline antibiotics, but treatment failures are not seen, and the surviving number are not resistant when re-exposed to antibiotic treatment. Doxycycline cure rates remain very high in recent *CT* randomized control trials. It seems unlikely that chlamydia will become resistant to doxycycline.

### **Takeaways re: *Mycoplasma Genitalium (M. gen)* and *Chlamydia Trachomatis (CT)*:**

- Doxycycline nonadherence is common.
- It is unknown if use of DoxyPEP will contribute to an increase in the proportion of *M. gen* strains with elevated MICs or resistance to tetracycline drugs, however considering a tetracycline-resistant *M. gen* strain already exists and *M. gen* grows so slowly, it is possible *M. gen* strains could develop increasing MICs or resistance to doxycycline or minocycline and monitoring for resistance is difficult at this time.
- It is unknown if DoxyPEP will contribute to resistance development in *CT* strains, but it seems highly unlikely based on current evidence.

### ***T. pallidum* [Sheila Lukehart]**

There are many molecular mechanisms by which a bacterium can become resistant to the tetracycline (tet) antibiotics (including doxycycline). Because *T. pallidum* is not known to harbor any plasmids or other mobile elements, the most likely mechanism by which *T. pallidum* might become resistant to tetracyclines would be via point mutations. Based upon the experience in other bacteria, such mutations would most likely be found in specific regions of the gene encoding the 16S rRNA (ribosomal RNA); resistance has occasionally also been reported in other spirochete bacteria to occur via mutations in the genes encoding certain ribosomal proteins.

There is no convincing evidence that tetracycline-resistant *T. pallidum* are currently circulating in the US (or elsewhere). This statement is based on the following:

- Only one clinical failure could be found in PubMed (Zenilman, 1993)
- Several studies show equivalent serological response rates in patients treated with tet/doxy vs. benzathine penicillin G (BPG)
- There is a single report (2017) in which *T. pallidum* samples were analyzed by PCR for a region of tetB (efflux pump) conveying resistance. In this study, PCR analysis of *T. pallidum*-positive patient samples for tetB sequence was positive in 8.7% of the samples in this study. However, these analyses were likely contaminated by DNA from bacteria other than *T. pallidum* in the clinical samples. Thus, there is no convincing evidence that the tetB resistance mechanism has been found in *T. pallidum* DNA.
- Consensus sequences from ~300 strains from multiple countries showed no 16S rRNA gene mutations, though this is a plausible mechanism of resistance development (based on what has been seen in other spirochetes)

While there is no evidence of resistance at this time, it is possible that a point mutation in the 16s rRNA gene could happen in *T. pallidum*. This is because two point-mutations in the 23S rRNA genes (A2058G, A2059G) have already been identified in circulating *T. pallidum* strains. The 16S rRNA gene is adjacent to the 23S rRNA gene (in the same operon), so it is clearly possible that mutations can occur in that region of the chromosome. The A2058G and A2059G mutations confer resistance to macrolide antibiotics (such as erythromycin,) Strains harboring the 23S rRNA gene macrolide-resistance mutations are widespread and are more likely to be found in persons with recent macrolide exposure. Importantly, a study has shown clearly that the A2058G and A2059G mutations have arisen multiple times and in multiple lineages of *T. pallidum*. Thus, point mutations in rRNA genes are not uncommon occurrences in *T. pallidum*, and point mutations in the 16S rRNA gene have been found in another spirochete.

While it is impossible to quantify the potential risk of tetracycline resistant mutations arising in *T. pallidum* due to DoxyPEP, that risk is certainly not zero, and the opportunity for doxy misuse increases that likelihood.

### **Day 1 Discussion**

**During the discussion of Day 1 presentations, the following important points were raised by participants:**

- The vast majority of people in the DoxyPEP study took medication within 24 hours after sex, and it may therefore be important to emphasize a 48-hour cut-off for doxy as PEP protocols.
- The disparity between French and US GC data about tetracycline resistance has been ongoing for some time.
- In the DoxyVAC study, it appeared that there was efficacy in preventing gonorrhea also, so tetracycline resistance to gonorrhea does not necessarily rule out DoxyPEP for gonorrhea.
- It is important to let local people make decisions based on their local data so any national guidance should allow space for that.
- DoxyPEP as a biomedical intervention has potential to be phenomenal, but there is a lot we need to consider before we implement.
  - Some participants heard mostly “orange” and not “red” flags.

- Another participant suggested it should not be about “red” flags but a weighing of benefits vs. risks which is very hard since you cannot weigh risks that you do not yet understand fully.

### Day 1 Wrap-up [Khalil Ghanem]

- Studies related to DoxyPEP/PrEP show it to have high efficiency.
- Doxy is commonly used, especially in the case of respiratory and skin and soft tissue infections.
- There are many potential misuses of antibiotics, even when not given for a specific indication.
- AMR emerges in core groups if excess antibiotics are used and the network-level selection has much greater impact, at least for *Klebsiella*.
- There are linked changes in gut microbiome to asthma, DM, IBD but it is not known what changes lead to what diseases. Knowing how an antibiotic modifies the microbiome does not necessarily tell us what the clinical outcomes are.
- *S. aureus* resistance – counterintuitive findings in that increasing rates of doxy prescriptions parallel decreasing rates of doxy resistance. Many different studies (e.g., malaria, acne, etc.) did not find a significant impact on *S. aureus* tetracycline resistance. Still, *S. aureus* resistance to doxy is a MAYBE if used on broader level.
- Pneumococcal resistance was considered, but new 15 and 20 valent vaccines may have a beneficial impact by impacting serotypes that are more likely to cause resistance.
- Doxy resistance in STIs:
  - CT – resistance unlikely.
  - MG – possible resistance. Question remains if you use doxy whether you lose other tetracyclines.
  - Syphilis – no clinical evidence of Tet-R in syphilis, but potential for molecular resistance exists (16S

## Implementation Considerations

DoxyPEP is a work in progress. It will be important to determine the guidance for individuals who will most benefit from DoxyPEP, how to best provide provider education, and to determine the efficacy of DoxyPEP for a more diverse population including cisgender women, transgender/nonbinary individuals, and at-risk heterosexuals. It will also be necessary to assist clinicians with electronic medical record and other decision support tools to help identify the best candidates for DoxyPEP as well as making sure that there is adequate patient education to create demand.

### Which population(s) would benefit most from STI-PEP with doxycycline? [Kenneth Mayer]

There are several things that are known about the use of DoxyPEP based on the results of the two large randomized controlled trials focusing on men who have sex with men. We know the incidence of syphilis and chlamydia was decreased in both studies and gonorrhea incidence was decreased in the study conducted in San Francisco and Seattle. Adherence was very high, 87% by self-report. There were no grade-3 adverse events, and the medication was well-tolerated. Only 1.5% of participants discontinued because of intolerance or patient preference. However, what is not known is whether DoxyPEP works equally well for cisgender women, people who inject drugs, sex workers, HIV-infected men, and transgender/ nonbinary people, since only 4% of the study participants were made up of individuals representing those populations. Moreover, the study was not optimally diverse with only about 8% of the participants being Black. So, there is much to still be learned as far as how well DoxyPEP will work in the non-study setting.



Some of the realities that need to be considered when rolling out a strategy for DoxyPEP include the fact that not everybody is equally at risk for new STIs. For example, in the PrEP X study in Australia, only 13% of participants accounted for 53% of incident bacterial infections. Thus, the role of social networks is very important and not easily ascertained in the clinical setting.

At Fenway Health, when looking at all patients who developed sexually transmitted infections between January 2015-December 31, 2020, there was a very high overall incidence of bacterial STIs, at a rate of 24.8 per 100 person-years. So, when considering a DoxyPEP program, it was determined that if everybody who attended the clinic for STI testing received doxy as PEP that would have resulted in 27,397 person-years of follow-up on DoxyPEP which is a very high number. Therefore, the goal is to determine the sweet spot where DoxyPEP is being offered to enough individuals who are at high risk for STIs, but not to use it indiscriminately. In the case of Fenway, if all PrEP users were offered DoxyPEP, that would still involve 12,467 person-years of DoxyPEP, and it would have prevented 61.1% of incident STIs. Fenway found that by changing the algorithm to anyone with a bacterial STI, a lower number of person-years was achieved: 9,411. And this would result in 57.7% of people who come in first for an STI screening receiving doxy as PEP. This data suggests focusing on individuals who had recent bacterial STIs is key.

**N of individuals who would be prescribed DoxyPEP and proportion of all STIs covered by 12-month doxyPEP prescribing under hypothetical prescribing strategies (M. Traeger)**

DoxyPEP prescribing strategy	N (%) individuals prescribed DoxyPEP		Person-years (%) of DoxyPEP		% of all STI diagnoses covered by DoxyPEP
	N	(%)	Person-years	(%)	
ALL people attending for STI testing	9940	100.0%	27397	100.0%	100.0%
All PrEP users from when prescribed PrEP	5254	52.9%	12467	45.5%	61.1 %
All PLHIV and PrEP users	6508	65.5%	16843	61.5%	78.4%
Any Bacterial STI	4051	40.8%	9411	34.4%	57.7%
Any rectal STI	2602	26.2%	5931	21.6%	43.4%
Any 2 STIs past 12 months	1393	14.0%	2982	10.9%	28.6%
Any 2 STIs past 6 months	1046	10.5%	2234	8.2%	23.7%
2 concurrent STIs	747	7.5%	1539	5.6%	17.4%
Syphilis	914	9.2%	2163	7.9%	16.3%

**Focusing on prior STI → less DoxyPEP used, while averting majority of STIs**

Additionally, in reviewing the literature, there are already early adopters of DoxyPEP which can tell us more about how to target the use of DoxyPEP. A recent UK study found that 9% of PrEP users recruited online in 2019 were already using DoxyPEP. In a study in Canada looking at MSM in STI clinics, there was a great deal of interest in DoxyPEP, but also a third of individuals indicated they were unwilling to use it. The individuals who were more likely to be interested were those who had increased self-perception of risk, were currently using PrEP, or had multiple STIs. Some of the reasons for lack of interest in DoxyPEP include concerns about potential drug resistance, concerns about side effects, as well as concerns about cost, the need to take medication regularly, and concerns about ultimate efficacy. Fortunately, concerns about peers did not seem to be that high (Park et al., 2021).

#### Conclusions:

- Determining the appropriate populations for DoxyPEP is not straightforward
- Trade-offs between coverage and overuse
- Past as prologue: patients with recurrent STI are likely to benefit
- Youth and black, indigenous, people of color (BIPOC) are at higher risk- there is a need to develop culturally tailored support programs
- Important to identify candidates who are motivated to adhere and to engage in care, so that ongoing need can be continually reassessed

## Where and how should DoxyPEP be available? [Julie Dombrowski]

The underlying assumption in this presentation was not whether DoxyPEP should be available but rather when to use it, recognizing that it is hard for clinicians to predict STI risk and what this prediction might mean for equity.

The DoxyPEP study was restricted to MSM and transwomen who had at least one bacterial STI in the past year. The rationale narrowing the eligibility, for example to people who have had two or more STIs in the past year, would be to improve the population level risk benefit ratio. The rationale for broadening eligibility criteria, such as to MSM and transgender women who have multiple sex partners regardless of STI history, would be to ensure inclusion of marginalized populations with decreased access to health services. The DoxyPEP team conducted analyses to inform the question of restricting DoxyPEP to a narrower population than that in the study. Restricting criteria would define a smaller target population for implementation, but potential downsides include reducing the individual and public health benefits of STI reduction including possible reductions in secondary transmission, as well as a possible perception in the community of clinics restricting access to an effective STI prevention mechanism. The impact on health equity remains to be seen and needs to be evaluated. Dr. Dombrowski concluded that guidelines should recommend offering DoxyPEP to MSM and transgender women who have had at least one bacterial STI in the past year. The rationale is that as we have demonstrated effectiveness in this group, using this guidance will give us the opportunity to gain implementation experience with the group most likely to benefit, and we do not know how well behavioral criteria would maximize benefits and minimize risks. Dr. Dombrowski also suggested that guidelines should leave open the opportunity to consider offering DoxyPEP to others at risk to minimize the risk of excluding marginalized patient populations.

#### Recommendations

- Offer to MSM and TGW who have had less than or equal to 1 bacterial STI in the past year
  - Demonstrated effectiveness in this group
  - Opportunity to gain implementation experience with the group most likely to benefit
  - Unclear how well behavioral criteria would maximize benefits and minimize risks
- *Consider for others at risk*

Dr. Dombrowski recommended that, in general, HIV PrEP should always be offered with DoxyPEP. For areas where PrEP access is a problem, this needs to be addressed as a primary issue. For individual patients who decline PrEP, alternate regimens such as "on-demand" PrEP (2-1-1 schedule) should be considered. Nonetheless, there may be some patients who are interested in DoxyPEP and not HIV PrEP, and for whom starting DoxyPEP may be a way to engage them in sexual health services which will eventually result in PrEP initiation. Co-prescription of HIV PrEP with DoxyPEP should be strongly recommended.

Current guidelines for STI treatment, PrEP, and HIV care recommend screening every 3-6 months. Dr. Dombrowski reviewed a study from San Francisco among patients on PrEP that estimated that a change to every 6-month screening from every 3-month screening would result in roughly 20 to 40% of STI diagnoses being delayed. Dr. Dombrowski recommended continuing current screening practices and building sentinel surveillance programs to monitor antimicrobial resistance among STI pathogens, assessing the proportion of incident STIs in people on doxy as PEP that are asymptomatic, and providing empiric data on the proportion of STIs that would be delayed with less frequent screening.

The rationale for empiric treatment of persons with known contact to a partner with an STI is somewhat different for gonorrhea & chlamydia (high transmission risk, risk of loss to follow-up after a positive test) than for syphilis (also the risk of false negative tests in early infection). Dr. Dombrowski recommended not changing the approach to syphilis, particularly because DoxyPEP will likely alter syphilis titers in people with latent syphilis, but she does suggest considering deferring empiric treatment for people on DoxyPEP who are notified of contact to gonorrhea or chlamydia. She also brought up the possibility of either testing without empiric treatment at the time of such contact or delaying testing until the next scheduled screening date.

Dr. Dombrowski described the analogy to HIV PrEP and suggested that attrition among people at ongoing risk will likely be a bigger problem than people taking it for “too long.” The discontinuation of DoxyPEP has a lower risk than discontinuation of HIV PrEP. There is no data to guide a recommended stopping point and the end of using DoxyPEP is not the end of an individual’s interaction with antibiotics.

Ideally, DoxyPEP should be offered in sexual health clinics, HIV clinics, primary care clinics, pharmacies with PrEP programs, community-based organizations with PrEP programs, and through STI partner services. To do that, guidelines for providers and health departments are needed, as are clear and simple tools for patients and prescribers, including educational materials and decision aides. Capacity building will be required.

#### Recommendations:

- MSM and TGW who have 1+ bacterial STI in the past year should be offered DoxyPEP
- For persons without HIV, co-prescription of HIV PrEP with DoxyPEP should be strongly recommended
- STI testing should continue quarterly unless and until new evidence suggests otherwise.
- For patients who report good adherence to DoxyPEP, consider deferring empiric treatment for GC/CT and treating based on test results (or waiting until next visit). For contact to syphilis- continue empiric treatment
- Patients should be able to stay on DoxyPEP for as long as they need it and are willing to take it.

## Financial considerations [Naomi Seiler]

Because of the way Medicaid formularies work, all states must cover doxycycline in their Medicaid programs. However, states, and Medicaid managed-care plans that serve most enrollees in most states, may use different utilization management techniques, such as prior authorization. States may also impose cost sharing requirements on prescription drugs; federal law limits such cost sharing to a maximum of \$4, which can still be prohibitive for some enrollees. Doctor visits and lab work that may be needed for DoxyPEP users would also likely be covered by Medicaid in all states, but possibly with different cost sharing requirements.

### Additional Thoughts

- Could pharmacists prescribe DoxyPEP? If yes (in an advanced practice state), pharmacists could possibly be reimbursed by Medicaid or other payers for the service as well as for the usual administration and drug cost payments
- Could Medicaid agencies and Managed Care Organizations (MCOs) be partners in disseminating information about DoxyPEP to enrollees?
- Return on Investment (ROI) data might be helpful but may only be needed if costs are high or barriers to coverage are identified
- It might be helpful to use claims data to track utilization over time, if it were possible to distinguish DoxyPEP use from other doxycycline use
- For privately insured people
  - Utilization management may apply- would a CDC recommendation affect coverage/utilization management?
  - Cost sharing would typically apply to visits and the medication (unless DoxyPEP becomes a United States Preventative Services Taskforce (USPSTF) recommendation)

Given this backdrop, potential access to DoxyPEP for Medicaid enrollees would rest on several factors, including:

- Are the providers who prescribe DoxyPEP participating in Medicaid?
- Are they participating in specific Medicaid managed care networks? Federal requirements for state managed care network adequacy standards are not specific enough to address DoxyPEP.
- If health departments prescribe DoxyPEP, are they allowed to bill Medicaid, or are other funding sources (e.g., the 340B program) available

## Addressing STI-PEP with doxycycline with patients [Stephanie Cohen]

As a result of the findings from the DoxyPEP study, the San Francisco Department of Public Health (SFDPH) has issued [interim guidelines](#) for the use of DoxyPEP. The guidelines recommend the use of DoxyPEP for those who would meet the inclusion criteria for the DoxyPEP study with prioritization for those who have syphilis. For others, DoxyPEP will be offered via a shared decision between provider and patient. Following the guidelines, the San Francisco City Clinic is now offering [DoxyPEP](#) via their PrEP navigator program and within the clinic, and plan to evaluate their approach for impact. At this time, DoxyPEP is recommended at the City Clinic for cis men and trans women who 1. Had a bacterial STI in the past year and 2. Report condomless anal or oral sexual contact with more than one cis male or trans female partner in the past year.

Those with a history of syphilis are prioritized. In the case of cis men, trans men, and trans women who report having multiple cis male or trans female sex partners in the past year with or without a previous diagnosis with an STI, patients should be offered DoxyPEP using shared decision making. At this time, cis women are not offered DoxyPEP as there is insufficient evidence to recommend it for STI prevention for those who report vaginal sex. Patients prescribed DoxyPEP are offered 60 pill supply of doxy, which SFDPH believes will last most patients about 3 months. DoxyPEP will be offered as part of a comprehensive package of sexual health services which will include HIV PrEP or care, STI screening, and vaccinations for mpox, meningococcus, hepatitis A/B, and HPV. SFDPH also created a DoxyPEP information sheet for patients which includes information on why an individual might use it and what they should expect for side effects.

## Doxycycline PEP Information Sheet



### **When should I take doxycycline PEP?**

- Two 100 mg pills of doxycycline should be taken ideally within 24 hours but no later than 72 hours after condomless sex. Condomless sex means oral, anal or vaginal/front hole sex where a condom isn't used for the entire time.

### **What about when I have sex again?**

- If you have sex again within 24 hours of taking doxycycline, take another dose 24 hours after your last dose. You can take doxycycline as often as every day when you are having condomless sex but don't take more than 200 mg (two 100 mg pills) every 24 hours.



### **How should I take doxycycline PEP?**

- Take doxycycline with plenty of water or something else to drink so that it does not get stuck when you swallow. If your stomach is upset by doxycycline, taking with food may help.
- Some people are more sensitive to the sun when they take doxycycline, so wear sunscreen.
- Please do not share doxycycline with others.
- Avoid dairy products, calcium, antacids or multivitamins within 2 hours before or after doxy



### **Reminders**

- Let your provider know if you run out of doxycycline, if you are having any side effects, and if you think you may have a sexually transmitted infection (STIs)
- Doxy-PEP reduces the risk of syphilis, gonorrhea and chlamydia but these infections can still happen. You should continue to be tested at regular intervals and if you have symptoms
- Doxy-PEP doesn't protect against MPX (monkeypox), HIV, or other viral infections



Key points which providers are recommended to share with patients when initiating DoxyPEP include information on the known efficacy of DoxyPEP, in addition to dosing and prescribing information. Providers are also recommended to share:

- Possible drug interactions, risk of photosensitivity, risk of pill esophagitis, rare risk of benign intracranial hypertension, and other serious side effects.
- Study data on the impact of DoxyPEP on antibiotic resistance and the gut microbiome that are still being collected and reviewed.
- Impacts of long-term use of DoxyPEP for STI prevention for individual patients and for population-level rates of antimicrobial resistance are unknown, but doxy has been used safely for long-term prophylaxis of malaria previously.
- Liver Function Tests (LFTs), renal function, and a complete blood count (CBC) should be checked periodically in patients taking doxy for a prolonged period as would be recommended for any extended use of doxy.
- All individuals taking DoxyPEP should be screened every three months for syphilis, HIV (if not living with HIV), and gonorrhea and chlamydia at all anatomical sites of exposure.



## Who wants DoxyPEP? [Rodney Perkins, Ace Robinson, Drew Elliot, Paul Marcelin]

After hearing from clinical speakers on considerations for implementation of DoxyPEP, the consultation turned to hearing from community members.

Rodney Perkins of the University of Washington shared the results of interviews that were conducted with participants in the DoxyPEP study. Information came from a qualitative analysis of semi-structured 1-on-1 interviews mostly conducted over Zoom. At the time of the consultation, Mr. Perkins shared the findings from the 30 participants to date.

Interviewees indicated that they were convinced that taking DoxyPEP actively prevented STIs. They found it to be well-tolerated and easily adhered to and stated that DoxyPEP greatly reduced their anxiety over STI transmission and the prospect of embarrassment from having to disclose STI exposure to partners. For some there was an increased frequency of sex, number of sex partners, and types of sex as well as some reporting greater communication about sexual needs, boundaries, and STI prevention. Generally, partner and peer attitudes towards DoxyPEP were positive. Most reported limited attempts to actively avoid STIs prior to participating in the study (e.g., limited condom use) but did routinely get tested (and treated if necessary) for STIs. Approximately 50% of interview participants reported no change in their sex practices during the study period although some did report increased communication with partners about sex. They perceived DoxyPEP as easy to adhere to as it was simple to integrate it into their daily routine although there was some concern regarding the long-term effects of continued use.

Following Mr. Perkins' sharing of the interview findings, he moderated a panel conversation with participants from the DoxyPEP study and community advocates. The consensus in that conversation was that there is strong community support for DoxyPEP in San Francisco and Seattle where the DoxyPEP study was conducted and that any recommendations for DoxyPEP use nationwide should leave space for decisions to be made at the local level based on the patient profile in that community and discussion between providers and patients. DoxyPEP should be offered with comprehensive sexual health care (vaccinations, regular STI testing, HIV PrEP, or HIV treatment). Shared decision-making lets practitioners and patients weigh pros and cons. Additionally, normative guidance would help assure access in more settings.

It was also shared that it is essential for experts and decision-makers to build trust with the communities most impacted by STIs and to this end, elevating concerns about cost of antibiotics for use in animals, the experiences of other countries, and dismissing the use of DoxyPEP because of a fear of overuse or misuse of antibiotics and subsequent possibilities of resistance when there is clear evidence of efficacy borne out by research would not be well-received by the community. Beyond potential physical symptoms, STIs cause fear, create a sense of social stigma, and interfere with intimate relationships and therefore, additional prevention strategies like DoxyPEP are needed.

## Discussion

The consultation was wrapped up with a discussion moderated by Dr. Matthew Golden. Dr. Golden highlighted that the current studies looking at DoxyPEP in the context of STIs are not the first time that this sort of prophylaxis (pre and post) use has been examined as a prevention tool for STIs. For example, in 1949-50, penicillin was used in this way on US Navy ships with almost half a million doses administered per year. That program was shown to be successful but was eventually tapered off, perhaps due to concerns about penicillin toxicity. Dr. Golden also raised concerns about past studies which showed gonococcal resistance development to tetracyclines.

Dr. Golden summarized what he heard over the two-day consultation about population-level effects of implementation of DoxyPEP as follows:

- Widespread use of DoxyPEP could have impacts beyond the population which takes it. For example, the impact within a relatively small network of MSM would be an increase of approximately 30 extra prescriptions per 100 MSM per year if 5% of MSM population use DoxyPEP.
- There must be a balance between the positive and negative externalities where the impact of the consumption of the resource leads to a cost or benefit to the third party. In this case, decreased transmission is a positive, but antimicrobial susceptibility and a healthy population-level microbiome risks are negatives and so while no one can know in advance how the population-level effects will play out, the common good must be considered in these decisions.

Dr. Golden outlined the pros and cons that he heard of the prior day and half of the consultation.

### Pros:

- DoxyPEP will prevent chlamydia, gonorrhea, and syphilis in patients who take it.
- Doxy is well tolerated.
- DoxyPEP involves much less use of antibiotics than the medication amounts that PrEP requires (~50 vs. 365 days/year)
- The use of DoxyPEP should at least somewhat decrease the need to use cephalosporins for gonorrhea treatment.

- DoxyPEP is acceptable to the population and many MSM want to take it.
- DoxyPEP use cost is relatively low.
- DoxyPEP is an intervention that might affect STI incidence at the population level.

### Cons:

- Absent population-level effects, averted morbidity is relatively small.
  - Except for syphilis, none of the prevented infections are associated with significant sequelae in men.
  - There is only a decrease in one symptomatic STI per person per year.
  - Durability of gonorrhoea effect is uncertain.
  - Not clear that the intervention will prevent a significant number of cases of complicated syphilis.
- There are many potential negative individual and population-level effects, almost none of which are likely definable with a high level of confidence soon. These include impacts on microbiome shifts and the potential to lead to chronic illnesses and antimicrobial resistance.

Dr. Golden questions whether the cons stated above have the potential to dwarf the benefits— especially as DoxyPEP is inconsistent to wider trends related to antimicrobial stewardship. In response, participants also shared that many of the above are concerns that were there before anyone was using DoxyPEP and as such, why would these concerns stop that implementation now?

## Wrap-up

The consultation was concluded with comments by Khalil Ghanem who shared the following—there is now a very effective biomedical STI prevention strategy. This strategy has poorly defined and potentially serious intermediate and long-term complications. There will likely not be additional data to clarify some of these potential risks by the time providers and health departments are ready to implement the intervention. It is critical to implement DoxyPEP in the right populations to maximize benefits and minimize risks. It is possible to provide clear guidance to patients and clinicians despite existing uncertainties. We don't need guidelines that don't guide, and we certainly don't need guidelines that mislead.



Meeting Agenda:

**STI Post-Exposure Prophylaxis with Doxycycline  
Consultation Agenda  
Day 1: December 5, 2022**

Efficacy & Background Information			
Start	Session	Speaker	Moderator
11 am	Welcome	Khalil Ghanem	Rebekah Horowitz
11:05 am	<b>STI Post-exposure Prophylaxis with Doxycycline Trial Results</b>		
	IperGay Study Results DoxyPEP Study Results Doxyvac Study Update	Annie Leutkemeyer	Connie Celum
	DISCO dPEP-KE Syphilaxis	Troy Grennan Jenell Stewart Yasmin Mowat	
11:45 am	<b>Can STI-PEP with doxycycline decrease STIs at the population level? By how much?</b>	Patrick Sullivan	Bruce "Bryce" Furness
12:05 pm	<b>Overview of the Clinical Uses and Harms of Doxycycline</b>	Chet Cunha	
12:25 pm	Break (25 minutes)		
<b>What are the potential harms of using doxycycline for STI post-exposure prophylaxis?</b>			
12:50 pm	<b>The Antimicrobial Stewardship Perspective: Big picture</b>	Lauri Hicks Megin Nichols	David Hyun
1:20 pm	<b>The Antimicrobial Stewardship Perspective: STI specific Considerations</b>	Chris Kenyon	
1:40 pm	<b>How will STI-PEP with doxycycline affect the microbiome?</b>	Martin J. Blaser	
2:00 pm	<b>Common outpatient infections and the potential for doxycycline resistance:</b> <ul style="list-style-type: none"> <li>• MRSA</li> <li>• Streptococcus pneumoniae</li> </ul>	Loren Miller Kristin Andrejko	

Meeting Agenda:

**STI Post-Exposure Prophylaxis with Doxycycline  
Consultation Agenda  
Day 1: December 5, 2022**

Efficacy & Background Information			
Start	Session	Speaker	Moderator
2:30 pm	<b>What is the risk of doxycycline resistance developing in STIs?</b> <ul style="list-style-type: none"> <li>• <i>Mycoplasma genitalium</i></li> <li>• <i>Chlamydia trachomatis</i></li> <li>• <i>Treponema pallidum</i></li> </ul>		David Hyun
3:00 pm	<b>Discussion related to session topics &amp; day's Wrap up</b>		Khalil Ghanem
<b>3:30 pm</b>	<b>End of Day 1</b>		
Implementation Considerations			
11:00 am	Morning Welcome		
11:05 am	<b>Which population(s) would benefit most from STI-PEP with doxycycline?</b>	Ken Mayer	Asa Radix
11:30 am	<b>Where and how should STI-PEP with doxycycline be available?</b>	Julie Dombrowski	
12:00 pm	<b>Financial considerations</b>	Naomi Seiler	
12:15 pm	<b>Addressing STI-PEP with doxycycline with patients</b>	Stephanie Cohen	
12:30 pm	<b>Who wants STI-PEP with doxycycline?</b>	Rodney Perkins	Rodney Perkins
12:40 pm	<b>Does the MSM/TG community want STI-PEP with doxycycline? A roundtable discussion</b>	Ace Robinson Drew Elliott Paul Marcelin	

Meeting Agenda:

**STI Post-Exposure Prophylaxis with Doxycycline  
Consultation Agenda  
Day 2: December 6, 2022**

<b>Start</b>	<b>Session</b>	<b>Speaker</b>	<b>Moderator</b>
<b>1:10 pm</b>	<b>Break (30 minutes)</b>		
<b>Discussion: A Cost Benefit Analysis &amp; Identification of Further Research Needed</b>			
1:40 pm	<b>Pro/con Discussion &amp; Identification of further research needed</b>	Matt Golden	
3:15 pm	<b>Summary and Wrap-up of Consultation</b>	Khalil Ghanem	
<b>3:30 pm</b>	<b>End of Day 2</b>		

Meeting Agenda:

**STI Post-Exposure Prophylaxis with Doxycycline  
Consultation Agenda  
Day 2: December 6, 2022**

<b>Start</b>	<b>Session</b>	<b>Speaker</b>	<b>Moderator</b>
1:10 pm	<b>Break (30 minutes)</b>		
<b>Discussion: A Cost Benefit Analysis &amp; Identification of Further Research Needed</b>			
1:40 pm	<b>Pro/con Discussion &amp; Identification of further research needed</b>	Matt Golden	
3:15 pm	<b>Summary and Wrap-up of Consultation</b>	Khalil Ghanem	
3:30 pm	<b>End of Day 2</b>		

## Appendix

### Doxy as PEP Consultation Presenters:

**Lauri A. Hicks, DO**

Captain, US Public Health Service  
Coordinator, Medical Product Safety  
Director, Office of Antibiotic Stewardship  
Division of Healthcare Quality Promotion  
Centers for Disease Control and Prevention

**Annie Luetkemeyer, MD**

Professor, Division of HIV, Infectious Diseases, and Global Medicine  
Zuckerberg San Francisco General Hospital  
University of California, San Francisco

**Cheston B. Cunha, MD, FACP, FIDSA**

Associate Professor of Medicine  
Medical Director, Antimicrobial Stewardship Program (Rhode Island Hospital & Miriam Hospital)  
Program Director, Infectious Diseases Fellowship  
Division of Infectious Disease  
Alpert Medical School of Brown University

**Patrick Sullivan**

Professor  
Department of Epidemiology  
Rollins School of Public Health  
Emory University

**Troy Grennan, MD MSc FRCPC DTM&H**

Physician Lead, HIV/STI Program, BC Centre for Disease Control  
Clinical Associate Professor, Infectious Diseases  
University of British Columbia

**Sheila A. Lukehart, PhD**

Emeritus Professor  
Dept. of Medicine, Div. of Allergy & Infectious Diseases  
University of Washington

**Loren G. Miller, M.D., M.P.H.**

Professor of Medicine  
David Geffen School of Medicine at UCLA  
Chief, Division of Infectious Diseases  
Harbor-UCLA Medical Center  
Investigator, The Lundquist Institute at Harbor-UCLA Medical Center

## Appendix

### Doxy as PEP Consultation Presenters:

**Martin J. Blaser, M.D.**

Henry Rutgers Chair of the Human Microbiome  
Professor of Medicine, Professor of Pathology & Laboratory Medicine  
Director, Center for Advanced Biotechnology and Medicine  
Rutgers University

**Stephanie Cohen, MD, MPH**

Director, STI and HIV Prevention and Control  
Disease Prevention and Control Branch  
Population Health Division  
San Francisco Department of Public Health

**Jenell Stewart, DO, MPH**

Assistant Professor of Medicine  
University of Minnesota  
Infectious Diseases Physician-Scientist  
Hennepin Healthcare