Invited Review

Doxycycline Postexposure Prophylaxis for Prevention of Sexually Transmitted Infections

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Abstract: *Doxycycline postexposure prophylaxis (doxy-PEP) is a novel strategy now demonstrated in several clinical trials to dramatically reduce incidence rates of gonorrhea, chlamydia, and syphilis in some key populations at high risk of sexually transmitted infections. Even so, much remains unknown about the long-term consequences of doxy-PEP, and several concerns, including the potential for the development of antibiotic resistance and disturbances to the microbiome, balance the benefits. This review highlights the history of antibiotic prophylaxis for sexually transmitted infections, and the rationale, current evidence, and future directions for doxy-PEP.*

Keywords: STI, prevention, antibiotic, resistance, prophylaxis, doxy-PEP, sexual health, sexually transmitted infection, doxycycline

Introduction

More than 370 million curable bacterial sexually transmitted infections (STIs) were diagnosed globally in 2020, with increasing rates in many countries.[1,2] The Centers for Disease Control and Prevention (CDC) reported nearly 2 million cases of gonorrhea, chlamydia, and primary and secondary syphilis in 2021 in the US.[3] The health burden associated with bacterial STIs can be substantial, including reduced fertility in women, adverse perinatal outcomes, and increased risk of HIV acquisition. Complications of syphilis, particularly neurologic, otic, and ocular, may lead to irreversible organ damage and decreased quality of life. Even more concerning, the US and other countries have seen dramatic increases in the past several years in rates of syphilis in pregnancy and in rates of congenital syphilis, which are associated with the risk of stillbirth and severe neonatal morbidity, including congenital disabilities and developmental delays. Syphilis in pregnancy and congenital syphilis are preventable with timely diagnosis and treatment.

Men who have sex with men (MSM) and transgender women (TGW)—particularly those from minoritized racial or ethnic groups—experience the highest burden of STI diagnoses in the US, and syphilis cases are increasing among heterosexual cisgender women and men.[3] Campaigns to test, treat, and raise awareness of STIs have been a pillar of the public health response, but it remains unclear if these campaigns have substantially altered the trajectory of STI incidence over the past decade. The CDC and the US Department of Health and Human Services have collaborated to develop a multiyear federal plan for STI control that urgently calls for accelerated progress in STI research and innovation by 2025.[4]

Doxy-PEP is an evidence-based prevention intervention that involves a person at risk of bacterial STI (ie, gonorrhea, chlamydia, or syphilis) taking a single dose of doxycycline 200 mg after condomless sex to proactively prevent infection

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prevent infection. Doxy-PEP is an innovative intervention with high efficacy among MSM and TGW who have a history of STI in the past year, and implementation work is ongoing to learn how to deliver doxy-PEP as part of a comprehensive package of options for STI prevention. In this review, we discuss the history of prophylaxis for STIs, rationale, current evidence, known and unknown benefits and risks, and future directions for doxy-PEP.

History of Prophylaxis for STIs

Antimicrobial prophylaxis against bacterial STIs predates the advent of modern antibiotics, including doxycycline. During and shortly after World War I, military troops in Paris who visited local sex workers were mandated to attend treatment stations where attendants instilled silver proteinate suspensions into the urethra and bathed the genitals in a mercury chloride solution. The intervention was reported to be highly effective in those for whom treatment was verified, with an estimated 2571 cases of gonorrhea, chancroid, and syphilis prevented.[5] In the 1940s, soldiers receiving sulfathiazole as periexposure prophylaxis saw significant reductions in the incidence of gonorrhea and chancroid,[6] and penicillin proved effective for the prevention of gonorrhea.[7] By the next decade, penicillin prophylaxis was widely used in all US ship fleets stationed in the Pacific.[8] In the 1970s, minocycline—a longer-acting, second-generation tetracycline—provided partial prophylactic protection against gonorrhea for crew on US naval ships in the western Pacific.[9] However, there was concern at the time that the use of minocycline prophylaxis selected for resistant gonococci, which would substantially limit its broader effectiveness for STI control. Indeed, *Neisseria gonorrhoeae* developed resistance over time to several common oral antibiotics,[10] which in turn diminished enthusiasm for the prospect of antimicrobial prophylaxis for bacterial STIs.

Doxy-PEP for STIs is a user-driven intervention that may be acceptable and prioritized for persons who cannot or choose not to use condoms

However, as rates of all bacterial STIs began to rise in the mid-2010s, interest in the use of prophylaxis resurged because of the increasing utilization and success of antiretroviral therapy (ART) and preexposure prophylaxis (PrEP) for HIV prevention. Reports of condomless sex have increased over time for gay, bisexual, and other MSM, likely reflecting a greater temporal trend that preceded and now has continued during HIV PrEP rollout.[11,12]

Modern Doxy-PEP Studies

Doxy-PEP for STIs is a user-driven intervention that may be acceptable and prioritized for persons who cannot or choose not to use condoms. Table 1 details key findings from several seminal trials that have evaluated or proven that doxy-PEP substantially reduces risk of bacterial STIs in MSM and TGW.

An early pilot trial randomly assigned 30 MSM and TGW with HIV and a history of more than 1 episode of syphilis since their HIV diagnosis to use daily doxycycline prophylaxis or receive incentive payments for testing negative for STI at follow-up visits. Although the intervention was effective at reducing incidence of all 3 bacterial STIs (odds ratio [OR], 0.27; 95% CI, 0.09-0.83), the authors recognized that daily use of an antibiotic was unlikely to be feasible or desirable on a large scale.[13] Notwithstanding, doxycycline remained a candidate drug of interest, as it is commonly used, safe, well tolerated, and highly effective against *Chlamydia trachomatis* and *Treponema pallidum* subsp. *pallidum*, the causative agent of syphilis. To date, there has never been a report of doxycycline resistance in either bacterium. In contrast, doxycycline currently has variable activity against gonorrhea; intermediate and high-level resistance is widespread in sub-Saharan Africa, ranges from 20% to 25% in the US, and is greater than 50% in parts of Europe.[14-17]

Based on data from a proof-of-concept pilot in MSM and TGW with HIV, France's National Agency for Research on AIDS and Viral Hepatitis (ARNS) launched the first major trial to evaluate doxy-PEP within the parent IPERGAY (Intervention Préventive de l'Exposition aux Risques avec et pour les Gays) study, which sought to examine the use of event-driven PrEP among MSM who were HIV negative in France.[18] A total of 232 participants were randomly assigned 1:1 to receive either open-label doxy-PEP taken once orally as 200 mg within 24 to 72 hours after condomless sex (with a maximum of 3 doses per week) or no doxy-PEP. The participants used a median of 680 mg of doxycycline per month. Among participants in the intervention arm, use of doxy-PEP was associated with a 47% relative risk

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Table 1. Evidence From Randomized Clinical Trials for Doxy-PEP, 2015 to 2023

Study (location, date)	Participating population		STI rate or outcome		Relative risk reduction (95% CI or *P*)	Absolute risk reduction	Comments
			Doxy-PEP	No doxy-PEP			
IPERGAY* (France, 2015-2016)	232 MSM on HIV PrEP		37.7 per 100 person-years	69.7 per 100 person-years	47%* (15-67)	32 per 100 person-years	Signal toward reduction of gonorrhea incidence at anogenital sites
DoxyPEP (US, 2020-2022)	501 MSM and TGW with bacterial STIs in prior 12 months	PWH (n = 174)	11.8% per quarter	30.5% per quarter	62% (40-76)	18.7% per quarter	Risk reduction seen for all 3 bacterial STIs
		PrEP users (n = 327)	10.7% per quarter	31.9% per quarter	66% (54-76)	21.2% per quarter	
DOXYVAC* (France, 2021-2022)	502 MSM on HIV PrEP with a bacterial STI in prior 12 months		5.6 per 100 person-years	35.4 per 100 person-years	84% (70-92)	30 per 100 person-years	Effect for gonorrhea found to be independent of 4CMenB vaccine
dPEP (Kenya, 2020-2022)	449 cisgender women on PrEP		50 total chlamydia/ gonorrhea infections	59 total chlamydia/ gonorrhea infections	12% (*P* = .51)	9 total infections at 12 months	Noneficacy likely due to suboptimal adherence

Abbreviations: doxy-PEP, doxycycline postexposure prophylaxis; DoxyPEP, Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-infected Men Who Have Sex With Men; DOXYVAC, Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis; dPEP (Kenya), doxycycline postexposure prophylaxis trial (Kenya), IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; MSM, men who have sex with men; PrEP, preexposure prophylaxis; PWH, people with HIV; STI, sexually transmitted infection; TGW, transgender women.

*Risk reduction estimate is for chlamydia and syphilis only.

reduction in time to first incident STI (syphilis or chlamydia), and an estimated absolute risk reduction (ARR) of 0.3 STI episodes per person-year. Efficacy was similar for reductions in the occurrence of a first episode of chlamydia (hazard ratio [HR], 0.30; 95% CI, 0.13-0.70; *P* = .006) and of syphilis (HR, 0.27; 95% CI, 0.07-0.98; *P* = .047). There was no significant difference between groups in time to first episode of gonorrhea (HR, 0.83; 95% CI, 0.47-1.47; *P* = .52). Although doxy-PEP did not significantly reduce overall gonorrhea incidence, there was a trend toward efficacy for anogenital gonorrhea; among doxy-PEP users, fewer polymerase chain reaction (PCR) tests were positive for gonorrhea from urine and anal swabs than from pharyngeal swabs.

Based on the promising findings of this IPERGAY substudy, investigators in Seattle and San Francisco initiated a larger randomized clinical trial called DoxyPEP (Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-Infected Men Who Have Sex With Men) to understand if taking doxy-PEP would decrease bacterial STI incidence in US-based populations of persons without HIV who typically use daily PrEP and of persons with HIV (PWH), as a potential HIV status-neutral approach for STI prevention.[16] An important objective was to explore the impact of intermittent doxycycline use on antibiotic resistance in the bacteria that cause STIs and other infections. The DoxyPEP trial recruited persons assigned male sex at birth (MSM or TGW) with a history of a bacterial STI and condomless sex with a man in the past year. Investigators designed the study to have sufficient statistical power to assess efficacy separately in the 2 cohorts of PWH and those taking PrEP.

Participants were randomly assigned to receive open-label doxy-PEP (doxycycline 200 mg once by mouth within 24-72 hours after condomless sex, and up to a maximum of 1 dose per day) or standard of care (quarterly STI testing with treatment per existing clinical protocols).[16] Over the course of the study, STI incidence in the control group reached 30% per quarter, which was substantially higher than the anticipated 10%. There was a single efficacy review by the data and safety monitoring board after a median of 9 months of follow-up, and further enrollment into the standard-of-care arm was halted early for high efficacy based on exceeding the prespecified interim efficacy bounds. In primary analyses, the researchers found that doxy-PEP led to a significant 65% relative risk reduction for all 3 bacterial STIs at 12 months, including symptomatic and asymptomatic infections. The relative risk

reduction differed slightly between the cohorts on PrEP and PWH for gonorrhea (55% vs 57%, respectively), chlamydia (88% vs 74%, respectively), and syphilis (87% vs 77%, respectively). In contrast to the earlier French study, the DoxyPEP trial saw an absolute risk reduction in STI of approximately 20% per quarter.

The ARNS followed the IPERGAY substudy with DOXYVAC (Combined Prevention of Sexually Transmitted Infections [STIs] in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine [TDF/FTC] for HIV Pre-Exposure Prophylaxis [PrEP]), a trial that used a factorial design to randomly assign MSM on PrEP for at least 6 months with a history of bacterial STI in the prior year to receive open-label doxy-PEP or no doxycycline in combination with the meningococcal type B (4CMenB) vaccine or no vaccine (as a preventive intervention for gonorrhea).[19] After results from the DoxyPEP trial were released, the data and safety monitoring board conducted an interim review of the results, and this trial was also halted early for efficacy. Despite baseline gonococcal resistance to tetracyclines being greater than 50% in France and the research team not expecting to find a significant effect on gonorrhea based on the IPERGAY substudy results, the DOXYVAC interim review found reductions in gonorrhea (51% risk reduction; 95% CI, 0.32-0.76; P = .001) and in chlamydia and syphilis (84% relative risk reduction; 95% CI, 0.08-0.30; P < .0001).[19] Similar to the initial substudy, use of doxy-PEP was associated with an approximate ARR of 0.3 bacterial STI episodes per person-year. The findings about borderline efficacy of the 4CMenB vaccine, which were presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in 2023, have been retracted and are being audited; the final results are pending.

The dPEP Kenya (doxy-PEP Kenya) study randomly assigned cisgender women taking PrEP to receive open-label doxycycline or standard of care (quarterly STI testing and treatment).[20] The primary study outcome was a reduction in chlamydia incidence given that nearly 100% of *Neisseria gonorrhoeae* isolates in Kenya harbor the tet(M) plasmid that confers high-level tetracycline resistance, and that syphilis is rare in Kenya, so achieving enough syphilis endpoints for analysis was not feasible. Despite an overall STI incidence of 27 per 100 person-years, the study found no statistical difference in chlamydia incidence between the 2 groups. Results did not change for STI incidence when analyzed among subgroups stratified by age, hormonal contraception use, transactional sex, and whether an STI was present at baseline. When preliminary results were presented at the 2023 CROI meeting, the study investigators noted that there were no new cases of HIV diagnosed in the trial, suggesting at least moderate adherence to PrEP and presumably also to doxy-PEP.[20] However, at the 2023 STI & HIV World Congress, investigators presented new information on the question of behavior versus biology as a primary contributor to the negative study results.[21] Among a random subset of 50 participants in the doxy-PEP arm, only 56% (28 of 50) had doxycycline levels detected in hair at least once, and only 29% (58 of 200) of all quarterly visits had detectable drug levels in hair.[21] This strongly suggests that low adherence to doxy-PEP was the most likely cause of the null effect seen for STI prevention in the dPEP Kenya trial.

Although yet unproven, it is plausible that the risk reduction from doxy-PEP also has the potential to decrease STI rates at the population level

Haaland et al show that doxycycline levels in vaginal secretions reach levels 5- to 20-times higher than the minimum inhibitory concentration (MIC) for *Treponema pallidum*, *Neisseria gonorrhoeae*, and *Chlamydia trachomatis* after a single oral dose, and that these levels persist above the MIC at which 90% of the isolates for the species were inhibited for 48 hours for *Neisseria gonorrhoeae*, for 72 hours for *Treponema pallidum*, and for 96 hours for *Chlamydia trachomatis*.[22] Thus, the pharmacokinetic-pharmacodynamic study establishes biologic plausibility, supporting that doxy-PEP may still be a useful intervention for cisgender women. Future studies will need to corroborate efficacy in this key population and may explore whether adherence could improve with different regimens, such as 2 fixed doses of doxycycline per week.

Taken together, the 3 trials (IPERGAY, DoxyPEP, and DOXYVAC) have provided consistent and robust evidence of the efficacy of doxy-PEP. Its primary benefit is a substantial reduction in risk of bacterial STIs in certain MSM and TGW, regardless of HIV status, who are at high risk of repeat infection based on their history of a recent STI. The number needed to treat to prevent 1 STI from the US DoxyPEP trial was approximately 5. Although yet unproven, it is plausible that the risk reduction

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from doxy-PEP also has the potential to decrease STI rates at the population level. Although doxy-PEP was not found to be efficacious in cisgender women in the dPEP Kenya study, efficacy seems to be tied to adherence, which was also the case with other prevention interventions like PrEP. If we can better understand how to support adherence, doxy-PEP may be useful for cisgender women in the future.

Beyond the established benefit of STI risk reduction, qualitative data from the DoxyPEP trial suggest that doxy-PEP is associated with increased sexual pleasure and peace of mind, decreased stigma about receiving and disclosing STI diagnoses, and the facilitation of positive discussions about sexual health with partners.[23] Doxycycline is an inexpensive, safe, and well-tolerated medication, and acceptability and adherence were high in clinical trials.[16,18-20] Ceftriaxone use was reduced by 50%,[16] and doxy-PEP as a strategy is associated with much lower use of antibiotics than daily oral tenofovir-based PrEP for HIV prevention (~50 days vs 365 days, respectively). Based on data from the trials, the average doxy-PEP user might take an approximate 43 extra days of antibiotics over 12 months to avert 1.4 STI episodes per year; of these averted infections, 50% are expected to be gonorrhea, 43% chlamydia, and 7% syphilis.[24] For these and other reasons, interest and demand for doxy-PEP in real-world settings are high.[25-27]

Evaluating Doxy-PEP Efficacy

The benefits of doxy-PEP must be balanced with several potential risks and unknowns. First, most STIs prevented in the clinical trials were asymptomatic. It is still uncertain whether doxy-PEP as an intervention will prevent morbidity from STIs. Of the 3 bacterial STIs that were reduced by doxy-PEP, syphilis has the highest risk of complications in MSM and TGW. The efficacy of doxy-PEP was very high against syphilis, as evidenced by the fact that very few incident diagnoses were observed in the doxy-PEP arms; it is anticipated that doxy-PEP would reduce syphilis morbidity, but the trials were stopped after a median of 9 months, limiting the opportunity to explore this further. It remains unknown if doxy-PEP will reduce the incidence of infectious or complicated syphilis, gonorrhea, or chlamydia at a population level. A recent analysis of doxy-PEP implementation scenarios at the Fenway Clinic in Boston, Massachusetts, demonstrated the efficiencies and trade-offs of different eligibility criteria, estimating that 39% of bacterial STIs could be averted if MSM and TGW with a history of recent STI were offered doxy-PEP.[28] If supplied with local and regional STI incidence data from sites implementing doxy-PEP, mathematical models could estimate its broader impact and inform how use in populations could maximize efficiencies while minimizing unnecessary antibiotic exposure. Implementation studies are being planned to examine the real-world uptake of doxy-PEP and will be crucial in helping define its impact on STI incidence within geographic areas and key populations.

One potential tradeoff of doxy-PEP use is the emergence of resistance in STI pathogens. *Neisseria gonorrhoeae* develops resistance to tetracyclines through numerous mechanisms, including efflux pumps and ribosomal subunit binding. If doxy-PEP uptake increases such that use becomes widespread, its effectiveness for gonorrhea prevention could diminish quickly as tetracycline-resistant strains predominate within the population. Mathematical modeling suggests this could occur within 10 years depending on the level of doxy-PEP uptake and coverage, and tetracycline resistance in *Neisseria gonorrhoeae* within the populations that use it.[29] Although tetracycline resistance (and by extension resistance to doxycycline) in *Chlamydia trachomatis* and *Treponema pallidum* subsp *pallidum* has never been reported and is thought to be highly unlikely to occur, it is theoretically possible. A single point mutation produced widespread macrolide resistance in *Treponema pallidum* subsp *pallidum*,[30] and some *Chlamydia suis* strains in animals are resistant to tetracycline, raising concern for possible horizontal transfer into species that affect humans.[31] It remains to be seen how or if intermittent doxycycline use will impact our ability to diagnose *Treponema pallidum* subsp *pallidum* using current serologic tests, as doxy-PEP could be considered subtherapeutic treatment for both infections.

Based on in vitro experiments and observational data, many experts have raised concerns that doxy-PEP could also increase the risk of resistance in bystander bacteria like *Staphylococcus aureus*, *Streptococcus pneumoniae*, and gram-negative bacteria in the gut. This could result in the development of tetracycline-resistant bacterial strains that cause severe infections with fewer ambulatory treatment options. Investigators attempted to monitor for antimicrobial resistance (AMR) in 2 of the doxy-PEP trials. Among DOXYVAC participants, there was a slight absolute increase in methicillin-resistant *Staphylococcus aureus* (MRSA) isolated from pharyngeal swabs at month 12 compared with baseline in the doxy-PEP and the control arms (8.1% and 3.9%, respectively).[19] The DoxyPEP trial found a 14% absolute

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decrease ($P < .01$) in *Staphylococcus aureus* colonization in the doxy-PEP arm;[32] among those colonized with *Staphylococcus aureus* in the doxy-PEP arm, there was an 8% absolute increase in doxycycline resistance compared with baseline.[16]

To examine potential effects on the gut microbiome, the DOXYVAC trial collected serial anal swabs to test for extended-spectrum beta-lactamase *Escherichia coli* and found that rates for the doxy-PEP and control arms increased from 31.4% to 40% and from 32.1% to 35.6%, respectively, at month 12.[19] Characterizing and quantifying the breadth and extent of potential changes in the microbiome among doxy-PEP users and in the general population will be complex and challenging; however, this will be a crucial area of interest for future implementation studies.

Epidemiologic (epi) treatment or preemptive treatment of persons exposed to bacterial STIs is common practice in the US, and the CDC estimates that epi treatment could represent nearly 5% of all doses of overused antibiotics nationwide.[33] One study that sought to quantify the proportion of MSM who are overtreated after contact with gonorrhea or chlamydia found that 65% of contacts ultimately test negative after an exposure and thus receive empiric antibiotics unnecessarily.[34] Thus, if we take the fact that only one-third of MSM who are exposed to gonorrhea or chlamydia will test positive and combine this with the relative risk reduction for gonorrhea (56%) and chlamydia (81%) from the US Doxy-PEP trial, it can be estimated that for persons taking doxy-PEP as directed, the likelihood of testing positive is approximately 15% after an exposure to gonorrhea (ie, 0.33 x 0.44) and 6.5% after an exposure to chlamydia (ie, 0.33 x 0.12). These estimates would suggest that, for asymptomatic persons who are adherent to highly effective doxy-PEP and who have known gonorrhea or chlamydia exposures, the most prudent approach from an antimicrobial stewardship perspective may be to test only and to defer empiric treatment. Current standards of care are unlikely to change for the management of contacts to syphilis, who should continue to be tested and to be empirically treated due to risk of forward transmission and the potential lag in diagnosis associated with current serologic tests.

Implementation of Doxy-PEP

Implementation of doxy-PEP in communities began shortly after initial results from the DoxyPEP study were reported at the 2022 International AIDS Conference, followed by the DOXYVAC study at CROI 2023. The San Francisco Department of Public Health was the first to release recommendations in October 2022, and since then, more than 2500 early adopters have been initiated on doxy-PEP (H. Scott, MD, MPH, email, August 8, 2023). A retrospective analysis of 828 patients initiated on doxy-PEP at the San Francisco City Clinic between November 2022 and June 2023 found that uptake among MSM and TGW was 74% for those with 1 or more STI and 1 or more partner in the past year, and 60% for those with 2 or more partners but no STIs in the past year.[35] The main predictor of doxy-PEP uptake was having a higher number of sex partners, suggesting the intervention can successfully be targeted to those who might most benefit from it.

The choice to prescribe doxy-PEP should result from a shared decision-making process between the health care practitioner and the patient

Other public health jurisdictions in the US have now released guidelines, including several counties in California, the California Department of Public Health, and Public Health Seattle & King County in Washington.[24,36] Most jurisdictions have focused their guidance on the populations studied in the clinical trials, and others have elected to expand their recommendations more broadly. Outside of these local provisional recommendations, official guidelines from national health organizations remain limited. The CDC recently released a set of guidelines that underwent a 45-day period of public review (ending November 16, 2023)[37,38] and the Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine have acknowledged doxy-PEP,[39] and their guidelines based on expert consensus and review of current evidence are forthcoming. The International Antiviral Society–USA recommends considering doxy-PEP on a case-by-case basis.[40] Public Health England and the British Association for Sexual Health and HIV currently do not endorse doxy-PEP due to concerns about AMR,[41] but there may be an updated statement to come. The Australian Sexual Health Medicine Association recently published a consensus statement about the evidence for and implementation of doxy-PEP for MSM with an emphasis on offering it to MSM with recent syphilis or

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Table 2. Number and Frequency of Reported Laboratory Abnormalities, Adverse Events, and Other Outcomes From Clinical Doxy-PEP Trials

Randomized clinical trial	Laboratory abnormalities	Adverse events	Discontinuations	Other outcomes
IPERGAY	Grade 4 transaminitis due to acute hepatitis C infection (n = 3)	Drug-related gastrointestinal adverse events (n = 29); more common in PEP group (*P* = .03)	29 (26%) for all reasons; 8 (7%) due to drug-related adverse events	No difference between groups in serious adverse events
DoxyPEP	Grade 2 transaminitis (n = 1)	Grade 3 diarrhea or headache (n = 5)	2%	No weight gain compared to standard of care
DOXYVAC	None as of July 2023	Gastrointestinal adverse events (n = 2)	3 (0.9%) due to gastrointestinal adverse events or fear of adverse events	Further data pending final review
dPEP (Kenya)	Not collected	7% (gastrointestinal side effects)	5%	Social harms related to PEP use among 3 participants

Abbreviations: DoxyPEP, Evaluation of Doxycycline Post-Exposure Prophylaxis to Reduce Sexually Transmitted Infections in PrEP Users and HIV-Infected Men Who Have Sex With Men; DOXYVAC, Combined Prevention of Sexually Transmitted Infections in Men Who Have Sex With Men and Using Oral Tenofovir Disoproxil Fumarate/Emtricitabine for HIV Pre-Exposure Prophylaxis; dPEP (Kenya), doxycycline postexposure prophylaxis trial (Kenya); IPERGAY, Intervention Préventive de l'Exposition aux Risques avec et pour les Gays; PEP, postexposure prophylaxis.

Note: Data obtained and compiled from Molina,[18] Luetkemeyer et al,[16] Molina,[19] and Stewart[20] (Jean-Michel Molina, MD, PhD, email, August 26, 2023; Jenell Stewart, DO, MPH, email, August 8, 2023).

numerous STIs.[42] Clinicians interested in offering doxy-PEP to their patients may consider adapting existing guidelines from US public health departments to their local context or choose to await official guidelines from the CDC or the World Health Organization, which are in developmental phases.

The choice to prescribe doxy-PEP should result from a shared decision-making process between the health care practitioner and the patient. Known benefits and risks should be reviewed at each discussion about initiation, as should the potential unknowns, including the possibility of emerging resistance in STI pathogens, bystander bacteria, and changes to the individual and population-level microbiome that could have future adverse health effects. The specific number of pills and refills to prescribe depends on the user's number of reported and anticipated sexual exposures. Based on the US DoxyPEP trial data, King County's guidelines recommend that for most persons 30 pills with 1 refill may be a reasonable quantity for an initial prescription.[24] Laboratory monitoring during doxy-PEP is likely not necessary given that adverse events and discontinuations were uncommon in all 3 trials (Table 2).

As doxy-PEP implementation begins to roll out in the US and other countries, clear guidance and data are needed to inform several remaining areas of clinical uncertainty. These areas include how to counsel and manage the use of doxy-PEP in populations that were not yet studied in clinical trials (eg, cisgender men who have sex with women), what the optimal intervals are for STI screening, whether a maximum number of uses of doxy-PEP per week or month should be recommended, and how to manage contacts of individuals with STIs who are taking doxy-PEP. Other key areas to explore are whether existing surveillance systems can be leveraged to monitor for the possibility of emergent resistance in *Chlamydia trachomatis* and *Treponema pallidum*, and the role of molecular resistance testing for incident STIs.

It is now time to proactively design and monitor doxy-PEP implementation using an equity lens. Previous studies have shown that the majority of STI burden falls on a small proportion of MSM.[43,44] It will be imperative to identify which key populations might benefit most from doxy-PEP while balancing the risk of excess antibiotic exposure. We must strive to avoid perpetuating the sort of disparities for doxy-PEP access and uptake that persist for HIV PrEP. Future implementation and demonstration projects may be useful in providing data on uptake and real-world use, STI incidence estimates for mathematical modeling, early signals of adverse impacts, and progress on equitable use in communities at risk. Additionally, for some persons who have very frequent sex and who would use doxy-PEP nearly daily, lower-dose doxy-PrEP may be a more appropriate option. Doxy-PrEP, in which doxycycline is taken daily rather than specifically after condomless sex, is currently being studied in clinical trials in Australia

and Canada,[45-47] and the same implementation and AMR concerns will need to be thoroughly evaluated for this strategy.

Conclusion

Doxy-PEP is an exciting new intervention that may become an important component in our arsenal of STI prevention tools. Evidence from 3 randomized trials has shown that use of doxy-PEP within 24 to 72 hours after condomless sex dramatically reduces the risk of gonorrhea, chlamydia, and syphilis in MSM and TGW with a history of an STI in the prior year. Having access to doxy-PEP may increase sexual pleasure and decrease stigma associated with STI. For persons who cannot or choose not to use condoms, doxy-PEP may be a preferred STI prevention option. The choice to prescribe or use doxy-PEP should result from a shared decision-making process during which the benefits of doxy-PEP are considered along with its numerous potential risks and concerns. These include eventual loss of efficacy against *Neisseria gonorrhoeae* if tetracycline-resistant strains predominate within affected communities, the potential for the emergence of resistance in STI pathogens and in important bystander bacteria such as *Staphylococcus aureus*, and possible alterations in the gut microbiome that may have adverse health impacts in the months and years after intermittent doxycycline exposure. Clinical trial data will eventually provide information about the relative efficacy and AMR associated with doxy-PrEP compared with doxy-PEP, and the aforementioned considerations will remain germane for both strategies. Much needs to be learned about the long-term effects of biomedical STI prophylaxis on individual and population levels, and real-world implementation data with monitoring of uptake, impact on AMR, and population-level STI rates may provide answers to these important questions in the future.

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Financial relationships with ineligible companies within the past 24 months: Dr Cannon reported consulting for Roche Diagnostics. (Updated November 22, 2023) Dr Celum reported serving as a scientific advisor to Merck, Gilead Sciences, and GSK/ViiV; grant support from Mayne Pharmaceuticals. (Updated November 27, 2023)

Reviewer 1 reported consulting or advisor fees from Antiva, Assembly Biosciences, Generate Biomedicines, and IGM Biosciences, and fees for participation in review activities, such as data monitoring boards, statistical analysis, or endpoint adjudication committees with Gilead Sciences, Inc. (Updated November 30, 2023) Reviewers 2 and 3 reported no relevant financial relationships with ineligible companies. (Updated November 30, 2023)

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