Guidelines for the use of doxycycline post-exposure prophylaxis for bacterial sexually transmitted infection prevention

Background

Incidence of sexually transmitted infections (STIs) caused by *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Treponema pallidum* continues to increase in the United States (US). Novel approaches are needed to address the STI epidemic, especially for populations disproportionately affected (1). Post-exposure prophylaxis (PEP) involves taking a medication to prevent an infection after a possible exposure and is a common strategy for prevention of HIV and other infections. PEP is a form of chemoprophylaxis and distinct from pre-exposure prophylaxis (PrEP) which involves taking a medication *before* exposure occurs. Doxycycline, a broad-spectrum tetracycline antimicrobial, is used as pre or post-exposure prophylaxis to prevent infections such as malaria and Lyme disease (2). Doxycycline is well absorbed and tolerated, with a half-life of approximately 12 hours (3). Adverse effects most associated with doxycycline include photosensitivity and gastrointestinal symptoms including esophageal erosion and ulceration (4). Most adverse effects resolve with discontinuation of the medication. Doxycycline is the recommended treatment regimen for chlamydia and an alternative treatment for syphilis in non-pregnant patients with severe penicillin allergy or when penicillin is not available (5).

In 2015, daily oral doxycycline hyclate 100mg daily was studied as STI PrEP among 30 men who have sex with men (MSM) with HIV (6). At 48 weeks, individuals who were assigned daily STI PrEP had a 73% reduction in bacterial STI incidence compared to individuals in the comparison arm due to decreases in chlamydia and syphilis, but not gonorrhea. The 2021 CDC STI Treatment Guidelines included a systematic review of the available literature on STI PrEP and PEP and concluded that further studies were necessary to determine whether STI chemoprophylaxis would be an effective strategy for bacterial STI prevention (5). Since the study in 2015 there have been no new studies of STI PrEP, but several on STI PEP. This document is intended to provide updated clinical guidelines for healthcare providers to inform the use of doxycycline PEP for preventing bacterial STI infections. Additional information about implementation and considerations for monitoring for antimicrobial resistance will be described in a separate document.

Methods

A systematic literature review was conducted to inform the question: Does doxycycline taken after vaginal, anal or oral sex decrease bacterial STIs (gonorrhea, chlamydia, and syphilis) compared to not taking doxycycline? We included studies published through June 2023 using MEDLINE/Pubmed and Embase. Studies that met inclusion criteria were given a summary strength of evidence rating using the same approach as the HHS Panel on Antiretroviral Guidelines for Adults and Adolescents (Table 1) (7). We used the GRADE's Evidence-to-Decision framework to weigh the benefits and harms, values, acceptability, equity and feasibility. Abstracts presented at major scientific meetings were also reviewed. Literature reviews were also conducted to address the question: Does long-term doxycycline use cause

substantial harms such as the development of antimicrobial resistant pathogens, and dermatologic, gastrointestinal, neuropsychiatric, and metabolic side effects, though evidence was not graded. Further details regarding search strategies can be found at https://www.cdc.gov/std/treatment/guidelines-for-doxycycline.htm. In addition to the literature reviews, the National Association of County and City Health Officials held a two-day consultation December 5 and 6, 2022 during which multiple experts, stakeholders and community members discussed doxycycline PEP, including benefits and potential harms of use. The meeting report (STI-Post-Exposure-Prophylaxis-with-Doxycycline-Report.pdf (naccho.org)) was reviewed by CDC staff and findings from the consultation were taken into account during the development of these recommendations.

For the peer review, CDC staff, federal and academic experts in infectious diseases, STI and HIV prevention, antimicrobial resistance and therapeutics reviewed draft recommendations. Reviewers disclosed any potential conflicts of interest and conflicts, if present, were resolved. The document will be posted for 30 days on the federal registry for public comment. Comments from peer reviewers and the public will be addressed and the document revised as appropriate. Evidence and feedback were reviewed by CDC staff and final recommendations will be developed.

Efficacy of doxycycline as PEP for reducing bacterial STIs

We found four studies on the efficacy of doxycycline PEP for reducing bacterial STIs that are summarized below. In the open-label extension phase of the French IPERGAY Study, doxycycline was evaluated as PEP among a cohort of 232 HIV-negative MSM and transgender women (TGW) taking tenofovir disoproxil fumarate and emtricitabine (TDF/FTC) as PrEP for

HIV prevention. Participants were randomized to either take a single oral dose of 200mg doxycycline, ideally within 24 hours and no later than 72 hours after having condomless anal or oral sex up to three times per week versus no medication prophylaxis (8). The primary endpoint was occurrence of a first bacterial STI infection (gonorrhea, chlamydia, or syphilis) during a 10-month follow-up period. Individuals who took doxycycline PEP were found to have a reduced risk of acquiring chlamydia and syphilis by 70% (HR 0.30 (95% CI 0.13-0.70)) and 73% (HR 0.27 (95% CI 0.07-0.98)), respectively. There was no significant difference in gonorrhea infections between the two groups (HR 0.83 (0.47-1.47)).

In 2022, a randomized open-label clinical trial (DoxyPEP) in San Francisco and Seattle evaluating 501 MSM and TGW with HIV (N=174) or on HIV PrEP (N=327) with a history of condomless sex with ≥ 1 male partner and ≥ 1 STI in the past 12 months found that oral doxycycline hyclate 200mg self-administered ideally within 24 hours but no later than 72 hours after condomless sex significantly reduced the incidence of chlamydia, gonorrhea, and syphilis (9). Among persons taking HIV PrEP and persons with HIV, reductions were noted in relative rates of gonorrhea (RR 0.45; 95% CI 0.34-0.65 and RR 0.43; 95% CI 0.26-0.71), chlamydia (RR 0.12; 95% CI 0.05-0.25 and 0.26, 95% CI 0.12-0.57) and early syphilis (RR 0.13; 95% CI 0.03-0.59 and 0.23; 95% CI 0.04-1.29). The number needed to treat (NNT) to prevent a quarterly visit with an incident STI was 4.7 in the PrEP cohort and 5.3 in persons living with HIV. Participants were advised to take no more than 200mg of doxycycline every 24 hours. In the intervention arm, 86% reported taking doxycycline always/often and 71% reported never missing doxycycline within 72 hours of condomless sex.

Also in 2022, the French ANRS DOXYVAC study, which enrolled MSM on HIV PrEP for at least six months and who had at least one STI in the 12 months prior to enrollment, was stopped

early due to intervention efficacy. This trial randomly assigned MSM to 1) PEP with doxycycline monohydrate within 24-72 hours of sex (N=332) or 2) no doxycycline PEP (N=170); and then to 3) vaccination with 4CMenB (Bexsero®), a vaccine that is FDA-approved for use in individuals aged 10 through 25 to prevent invasive disease caused by *Neisseria meningitidis* serogroup B infection, but which some sources suggest has potential efficacy against gonorrhea (N=257); or 4) no vaccine (N=245). Participants were followed up to 96 weeks with the primary efficacy endpoint of impact of doxycycline PEP on time to first episode of syphilis or chlamydia. Initial results demonstrated that doxycycline PEP was associated with significant reductions in gonorrhea (aHR of 0.49 (95% CI 0.32-0.76), chlamydia 0.11 (95% CI 0.04-0.30) and syphilis, 0.21 (95% CI 0.09-0.47) (10).

An open-label 1:1 randomized trial of doxycycline 200mg within 72 hours of sex versus standard of care conducted during 2020 to 2022 in 449 cisgender Kenyan women found no reduction in all bacterial STIs (RR 0.88; 95% CI 0.60-1.29), *C. trachomatis* (RR 0.73; 95% CI 0.47-1.13), or *N. gonorrhoeae* (RR 1.64 (95% CI 0.78-3.47) (11). There were only two syphilis infections during the study. While women assigned to doxycycline PEP reported event-driven dosing coverage in 78% of weekly surveys, hair studies found that doxycycline was detected in only 44% of participants in the doxycycline arm, suggesting that non-adherence may have been the reason for lack of efficacy. (12).

Potential harms from doxycycline

Clinical adverse events in doxycycline as STI PEP trials

Three clinical trials of doxycycline PEP were found that reported on adverse events. In the IPERGAY study, gastrointestinal side effects were more commonly reported in the PEP group

(53% versus 41%; p=0.05) (8). In the DoxyPEP study, one grade 2 laboratory abnormality and five grade 3 adverse events occurred that were possibly or probably related to doxycycline. No serious adverse events were attributed to doxycycline. The observed difference in mean absolute annualized weight change adjusted for baseline weight was not statistically significant between the two groups. Eighteen participants discontinued the study early; five in the doxycycline PEP arm discontinued the medication due to intolerance or patient preference and 13 in standard of care arm, including six who discontinued so that they could take doxycycline PEP outside of the study (9). In the DOXYVAC study, three individuals (0.9%) discontinued PEP due to gastrointestinal adverse events (N=2) or fear of adverse events (N=1) (10).

Clinical adverse events – systematic literature review

We further examined data on daily longer-term (8+ weeks) doxycycline use by conducting a systematic literature review (https://www.cdc.gov/std/treatment/guidelines-for-doxycycline.htm) and meta-analysis (13). A total of 67 articles published from 1987 to 2022 were included in the review on clinical adverse events; half of the studies included doxycycline use for acne treatment (N=13), malaria prophylaxis (N=11), and rosacea treatment (N=14). A meta-analysis conducted by CDC staff included the 18 studies that enrolled generally healthy individuals and which also had a placebo arm to evaluate any adverse events between participants in the doxycycline group versus the no doxycycline (placebo) group. The meta-analysis found an increased risk of individuals on daily doxycycline experiencing gastrointestinal or dermatological adverse events compared to placebo. No significant differences were observed for any, severe, or neurological adverse events. Participants were more likely to be unenrolled from clinical trials due to adverse events in the doxycycline group compared to the placebo group. Serious side effects were rare.

Potential resistance in commensals and co-occurring pathogens

Another potential concern about doxycycline PEP is facilitating antimicrobial resistance both in bacterial STIs, as well as other common bacterial pathogens such as *Staphylococcus aureus*. Data from the 12-month DoxyPEP follow-up period evaluating tetracycline resistance in *S. aureus* isolates found that at baseline, *S. aureus* was isolated from the anterior nares and oropharynx of 44% (187/428) of individuals in the doxycycline arm and 48% (96/202) in the standard of care (SOC) arm. At 12-month follow-up, 31% (69/222) of individuals in the doxycycline arm were colonized with *S. aureus*, representing a 14% absolute reduction, compared to no significant change in the standard of care SOC arm (43% (28/65)). Baseline tetracycline resistance was observed in 5% (20/428) of *S. aureus* isolates in the doxycycline arm and 10% (21/202) in the SOC arm and at 12-month follow-up, in 13% (28/222) of isolates in the doxycycline arm and 5% (3/65) of isolates in the SOC arm, representing an 8% absolute increase in doxycycline resistant *S. aureus* in the doxycycline arm. While limited by low number of *N. gonorrhoeae* isolates with MIC data available (56/320), 24% (4/17) of gonococcal isolates were tetracycline resistant at baseline compared to 11% (2/19) of incident gonococcal isolates in the SOC arm and 30% (6/20) in the doxycycline arm. (9,14). Data from the ANRS DOXYVAC study found 100% of gonococcal isolates tested at baseline (N=7) were tetracycline resistant (defined as MIC >0.5 mg/L or for high level resistance, MIC>8 mg/L by Etest) (15,16). Among the gonococcal isolates recovered during follow-up in the PEP arm, 67% (14/21) and 33% (7/21) demonstrated resistance and high-level resistance, respectively, versus 81% (30/37) and 19% (7/37) in the no PEP arm (10). Limited phenotypic and genotypic testing of *C. trachomatis* strains failed to reveal significant trends in the development of resistance. Trends in MRSA and

extended-spectrum beta-lactamase-producing *Escherichia coli* colonization rates did not differ between study arms.

Other studies evaluating impact of doxycycline on antimicrobial resistance are limited but data have been reported for acne treatment and malaria prophylaxis. Studies have largely found no relationship between daily doxycycline and doxycycline resistance in *Cutibacterium acnes*, *Staphylococcus epidermis*, or gastrointestinal pathogens causing diarrhea though it is important to note that lower doses of doxycycline were used in these studies (17,18). Few studies have examined the characteristics of *S. aureus* in those taking daily doxycycline, but one study found that Panton-Valentine leukocidin (PVL)-positive methicillin-sensitive *S. aureus* (MSSA) was more common in those on daily doxycycline than people taking other malarial prophylaxis, and all PVL-positive doxycycline-resistant MSSA isolates were found in people taking doxycycline (19). The ability to draw conclusions from these studies is limited by the heterogeneity of studies, and dosage and treatment duration compared with STI PEP, and consideration should be given to monitoring other pathogens such as those that cause community-acquired pneumonia, for example. There are no studies to date on long-term, intermittent use of doxycycline and the microbiome. Current data suggest overall benefit of the use of doxycycline PEP, but potential risks related to the development of resistance and impacts on the microbiome will need to be closely monitored after implementation of these guidelines.

Who would benefit the most from doxycycline PEP?

The goal of doxycycline PEP is to ensure that individuals who would benefit the most have access to the intervention, while minimizing antimicrobial use. For instance, among MSM taking HIV PrEP, a subset of individuals account for the majority of bacterial STIs. In one study

of 2,981 MSM, 25% of individuals accounted for 76% of bacterial STIs (20). While models indicate that a substantial number of MSM would need to use STI PEP/PrEP for population-level effectiveness, this effect would be most pronounced if focused on subpopulations with higher likelihood of STIs (21) compared to the broader MSM/TGW population (22,23). In a cohort of MSM/TGW and non-binary people assigned male sex at birth, prescribing doxycycline PEP for 12 months after an STI diagnosis was the most efficient strategy, averting 42% of STIs with the NNT for 1 year to avert any STI of 2.2 (24).

Considerations

Based on the clinical trials, systematic reviews, and studies of populations who would likely benefit most from an intervention to reduce bacterial STIs, the following considerations are recommended: doxycycline 200mg taken once orally within 72 hours of oral, vaginal or anal sex should be considered for gay, bisexual, and other MSM, and for TGW, with a history of at least one bacterial STI (i.e., gonorrhea, chlamydia or syphilis) in the last 12 months and who are at ongoing risk for acquisition of bacterial STIs. Although not directly assessed in the trials included in these guidelines, doxycycline PEP could be considered for MSM and TGW who have not been diagnosed with an STI in the prior year but will be participating in sexual activities that are known to increase likelihood of exposure to STIs, e.g., during weekend events, cruises, and festivals. Although the pharmacokinetics of doxycycline and experience in treating bacterial STIs suggest that STI PEP with doxycycline should be effective in other populations, data to support doxycycline as PEP in other populations (i.e., cisgender women, cisgender heterosexual men, transgender men, other queer and nonbinary individuals) are limited.

If STI PEP with doxycycline is prescribed, the recommended dose is 200mg once as soon as possible within 72 hours after having oral, vaginal or anal sex with a maximum dose of 200mg every 24 hours. MSM/TGW who are prescribed doxycycline PEP should undergo bacterial STI testing at anatomic sites of exposure at baseline and every 3-6 months thereafter. HIV screening should be performed for HIV-negative MSM/TGW according to current recommendations (5).

Conclusion

Doxycycline PEP has demonstrated benefit in reducing incident chlamydia, gonorrhea, and syphilis and represents a new approach to addressing STI prevention in populations at increased risk for these infections. Doxycycline PEP, when offered, should be implemented in the context of a comprehensive sexual health approach including risk reduction counseling, STI screening and treatment, recommended vaccination, and linkage to HIV PrEP, HIV care or other services, as appropriate(5).

Several other ongoing studies are evaluating doxycycline as STI PEP and PrEP. The available evidence in the context of increased national incidence of gonorrhea, chlamydia and syphilis, support consideration of this approach in MSM/TGW at substantial likelihood for acquiring bacterial STIs. These guidelines will be updated as additional data become available.

TABLES

Table 1. Rating Scheme for Recommendations

Strength of Recommendations	Quality of Evidence Supporting a Recommendation
A. Strong recommendation for the statement	I. One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B. Moderate recommendation for the statement	II. One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C. Weak recommendation for the statement	III. Expert opinion

Box. Population recommended for consideration for use of doxycycline as PEP for bacterial STI prevention

Recommendation	**Strength of recommendation and quality of evidence**
• Doxycycline 200mg taken once orally within 72 hours of oral, vaginal or anal sex should be considered for gay, bisexual, and other men who have sex with men, and for transgender women, with a history of at least one bacterial STI (i.e. gonorrhea, chlamydia or syphilis) in the last 12 months.	**AI**
• No recommendation can be given at this time on the use of doxycycline PEP for cisgender women, cisgender heterosexual men, transgender men, other queer and nonbinary individuals. If this intervention is offered, it should be implemented with considerations for ancillary services detailed below.	**There is insufficient evidence to assess the balance of benefits and harms of the use of doxycycline PEP**

Box. Considerations for ancillary services to provide to individuals receiving doxycycline PEP for the prevention of bacterial STIs.

At initial PEP visit

- Screen and treat as indicated for STIs (obtain nucleic acid amplification test for gonorrhea and chlamydia at anatomic sites of exposure, and serologic testing for syphilis). For individuals without HIV receiving HIV PrEP, screen per CDC HIV PrEP guidelines (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf). For individuals without HIV not receiving HIV PrEP, consider screening for HIV every 3-6 months (5).

- Counsel on risk reduction strategies including condom use, consideration of reducing the number of partners, and accessing HIV PEP, PrEP or HIV treatment as indicated.

- Counseling should include:
    - A discussion of the benefits as well as known and unknown harms of doxycycline PEP including potential side effects such as photosensitivity, esophagitis and esophageal discomfort, gastrointestinal intolerance (nausea, vomiting, diarrhea) and the potential for the development of antimicrobial resistance in other pathogens and commensal organisms.
    - The need to take doxycycline exactly as prescribed and only for its intended purpose.
    - Counsel on potential drug interactions including the importance of separating the doxycycline dose by at least 2 hours from antacids and supplements that contain calcium, iron, magnesium or sodium bicarbonate. No clinically relevant interactions between doxycycline and gender-affirming hormonal therapy is likely, however, other forms of birth control should be used by people of reproductive potential who are on hormonal contraceptives.

- Provide enough doses of doxycycline to last until the next follow-up visit, based on individual assessment through shared decision making.

At follow-up visits

- Screen for gonorrhea and chlamydia at anatomic sites of exposure and syphilis every 3-6 months.
- For individuals without HIV receiving HIV PrEP, screen per CDC HIV PrEP guidelines (https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2021.pdf). For individuals without HIV not receiving HIV PrEP, consider screening for STIs and HIV every 3-6 months. Assess for the need for HIV PEP and encourage the use of HIV PrEP.
- Confirm or encourage linkage to HIV care for individuals living with HIV.
- Assess for side effects from doxycycline.
- Provide risk reduction counseling and condoms.
- Re-assess need for doxycycline PEP.
- Provide enough doses of doxycycline until next follow-up visit, based on individual assessment through shared decision making.

Additional services to consider

- Screen for hepatitis B and C infection; vaccinate against hepatitis B if susceptible. Administer other vaccines as indicated (MPOX, hepatitis A, human papillomavirus).
- Refer for comprehensive primary care, mental health services, substance use treatment and other services, as appropriate.

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