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Doxycycline Post-Exposure Prophylaxis to Prevent Bacterial Sexually Transmitted Infections

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Lead authors	Daniela E. DiMarco, MD, MPH; Marguerite A. Urban, MD
Writing group	Rona M. Vail, MD, AAHIVS; Sanjiv S. Shah, MD, MPH, AAHIVM, AAHIVS; Steven M. Fine, MD, PhD; Asa E. Radix, MD, MPH, PhD, FACP, AAHIVS; Jessica Rodrigues, MPH, MS; Brianna L. Norton, DO, MPH; Charles J. Gonzalez, MD; Christopher J. Hoffmann, MD, MPH, MSc, FACP
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Committee: Medical Care Criteria Committee
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Contents

Purpose of This Guideline

This guideline on the use of doxycycline post-exposure prophylaxis (doxy-PEP) for prevention of bacterial sexually transmitted infections (STIs), including syphilis, chlamydia, and gonorrhea, was developed by the New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program to support clinicians caring for adults and adolescents with and without HIV who are at risk of acquiring STIs. The goals of this guideline are to:

- Summarize the available evidence regarding the use of doxy-PEP for preventing syphilis, chlamydia, and gonorrhea infections
- Provide evidence-based clinical recommendations for the use of doxy-PEP
- Present practical considerations for prescribing doxy-PEP

The literature on this topic is evolving rapidly, with several clinical trials ongoing. To prepare this guideline, the authors conducted a review of the published literature through MEDLINE, conference presentations, and existing published guidance within the United States and internationally.

Biomedical Prevention of STIs

☑ RECOMMENDATIONS

Biomedical Prevention of STIs

- Clinicians should offer doxy-PEP to cisgender men and transgender women who engage in condomless sex with partner(s) assigned male sex at birth and who:
  - Have had a bacterial STI diagnosed within the past year (A1), or
  - Have no or unknown history of STIs and ongoing risk of STI exposure (A2)
- Clinicians should engage in shared decision-making with cisgender men who are at ongoing risk of STI exposure and engage in condomless sex with multiple partners assigned female sex at birth, offering doxy-PEP on a case-by-case basis. (B3)
- When prescribing doxy-PEP, clinicians should use the dosing regimen of oral doxycycline 200 mg taken ideally within 24 hours (up to 72 hours) after condomless sex (A1) and counsel patients (A*) on the key points for patient education outlined in Table 1: Considerations for Doxy-PEP Implementation.
- For individuals taking doxy-PEP, clinicians should screen for HIV, chlamydia, gonorrhea, and syphilis at least every 3 months. (A1)
- Clinicians should offer HIV PrEP to individuals who do not have HIV and are initiating or using doxy-PEP. (A*)
- Clinicians should offer HIV treatment to individuals with HIV who are not on antiretroviral therapy and are initiating or using doxy-PEP. (A1)

Abbreviations: doxy-PEP, doxycycline post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

The United States, including New York State, continues to see high rates of reportable STIs, specifically syphilis, chlamydia, and gonorrhea [CDC(b) 2024], despite decades of public health efforts and prevention strategies aimed at curbing the STI epidemic. Some populations, including men who have sex with men (MSM), young people, and some racial and ethnic minority groups, are disproportionately affected by STIs [CDC(b) 2024]. Centers for Disease Control and Prevention (CDC) STI surveillance data from 2022 note that reportable STIs continue to disproportionately affect people who identify as Black/African American and American Indian/Alaska Native [CDC(b) 2024], making clear that established STI prevention strategies are insufficient.

Biomedical methods for HIV prevention with HIV PrEP and PEP have been very effective. Researchers identified doxycycline as a candidate for biomedical prevention of STIs. In 2011, Wilson and colleagues used mathematical modeling based on sexual behavior factors to predict doxy-PEP efficacy among MSM in Australia. Assuming 50% uptake and 70% efficacy, the model predicted a 50% reduction in syphilis cases after 1 year and an 85% reduction after 10 years [Wilson, et al. 2011]. Doxycycline is an antibiotic in the tetracycline class and is approved by the U.S. Food and Drug Administration for the management of many different types of infections [Lexicomp 2023; FDA 2016]. Doxycycline is available in 2 different formulations: hyclate, which is more water soluble, and monohydrate, which is less water soluble so may have fewer gastrointestinal adverse effects. Common uses include treatment of chlamydia, syphilis, respiratory infections, and skin and soft tissue infections. Doxycycline has also been used as both a PrEP and PEP agent for certain bacterial and parasitic infections, including Lyme disease, leptospirosis, and malaria [Grant, et al. 2020].

When used in nonpregnant adults, doxycycline is safe and well tolerated, has excellent oral bioavailability, is low cost, and is widely available. Adverse effects of doxycycline are generally mild, with gastrointestinal symptoms being the most common. Other adverse effects include photosensitivity and esophageal injury. Doxycycline is contraindicated in pregnancy because of potential adverse effects on the fetus [Lexicomp 2023]. Doxycycline is also used safely for prolonged periods for some conditions, including acne [Zaenglein, et al. 2016] and prosthetic joint infections [Osmon, et al. 2013]. A systematic review and meta-analysis evaluated the safety of long-term (8 weeks or more) doxycycline use for treatment or prevention of a variety of conditions, identifying 67 studies for analysis over a 20-year period ending in January 2023 [Chan, et al. 2023]. Nearly one-third of the studies reported mild to moderate adverse effects, most frequently gastrointestinal and dermatologic. Severe adverse effects were uncommon. These factors make doxycycline a promising prophylactic agent; however, the effects on antimicrobial resistance and the microbiome with widespread use are still under investigation.

Doxycycline as PEP

Available evidence on doxy-PEP to prevent bacterial STIs is limited but increasing. Current data are from randomized clinical trials, observational studies, modeling studies, and surveys on acceptability for use. Studies predominantly included cisgender men and transgender women who have sex with men, were receiving HIV PrEP or in care for HIV infection, were aged 35 years and older, and were White.

In 4 randomized clinical trials comparing doxy-PEP with standard of care (routine STI testing), participants received HIV PrEP or HIV care, and in 3 of the 4 trials participants had a history of ≥1 bacterial STI in the prior year. The study protocols used oral doxycycline 200 mg taken ideally within 24 hours or up to 72 hours of condomless sex to prevent bacterial STIs. All participants were tested for STIs every 3 months during the study period [Molina, et al. 2024; Luetkemeyer, et al. 2023; Stewart, et al. 2023; Molina, et al. 2018]. In the 3 trials conducted among cisgender men and transgender women who have sex with men, there were significant reductions in chlamydia and syphilis, but results were mixed regarding the efficacy of doxy-PEP in preventing gonococcal infections, likely at least in part because of geographic variability in prevalence of tetracycline resistance in gonococci [Molina, et al. 2024; Luetkemeyer, et al. 2023; Fairley and Chow 2018; Molina, et al. 2018; Siguier and Molina 2018]. In a study that included only cisgender women taking HIV PrEP, doxy-PEP was not effective at preventing bacterial STIs [Stewart, et al. 2023].

A modeling study analyzed data from an LGBTQ-focused health center in the United States to assess the effect of doxy-PEP use on STI incidence among more than 10,000 individuals assigned male sex at birth (including cisgender men, transgender women, and nonbinary individuals) who had male sex partners and STI testing (chlamydia, gonorrhea, or syphilis) on record [Traeger, et al. 2023]. STI incidence was 35.9 per 100 person-years. Modeling demonstrated that, rather than prescribing doxy-PEP based solely on HIV or PrEP engagement, prescribing based on STI history resulted in an efficient strategy that balanced uptake and preventive impact. An approach combining these factors, as was done in the clinical trials, was not modeled in this projection. Seven different strategies for prescribing doxy-PEP over 12 months were modeled [Traeger, et al. 2023]. Prescribing to all in the sample, an estimated 71% of gonorrhea, chlamydia, and syphilis cases could have been averted (number needed to treat [NNT] for 1 year to avert 1 STI diagnosis of 3.9). Prescribing to individuals with HIV (12%) or who were taking HIV PrEP (52%) could have averted 60% of STI diagnoses in this group (NNT of 2.9). Limiting prescribing to individuals with an STI diagnosis, the proportion using doxy-PEP was reduced to 38% and would have averted 39% of STI diagnoses (NNT of 2.4).

This committee's recommendations on provision of doxy-PEP are outlined above, and implementation considerations are discussed in the guideline section Practical Considerations for Doxy-PEP Implementation. The risk-benefit profile for doxy-PEP is expected to vary based on individual patient factors and community and sexual network STI prevalence. Factors associated with increased likelihood of STI exposure include having multiple sex partners, engaging in group sex, engaging in transactional sex, and combining sex and substance use [Workowski, et al. 2021]. An individualized assessment is an important aspect of shared decision-making between patient and clinician.

The A-level recommendations for doxy-PEP use among cisgender men and transgender women who have sex with men are based on the significant reductions in bacterial STIs reported in the 3 clinical trials [Molina, et al. 2024; Luetkemeyer, et al. 2023; Molina, et al. 2018], described in detail below, and post-implementation observational data [Sankaran, et al. 2024; Scott, et al. 2024]. Although the majority of STIs among these populations are asymptomatic and without complications, the significant decrease in STI occurrence provides potential benefits to individuals and the broader community and likely outweighs the potential harms of doxycycline use. Based on the lack of efficacy reported for doxy-PEP in cisgender women in Kenya [Stewart, et al. 2023] , there is insufficient evidence to recommend its use in individuals at risk of STIs through receptive vaginal sex. However, hair samples examining doxycycline levels point to possible adherence issues [Stewart, et al. 2023], and pharmacologic data from an unrelated study suggest adequate tissue and secretion levels for protection [Haaland, et al. 2023].

There are no published data evaluating doxy-PEP use among cisgender men with sex partners assigned female sex at birth. However, doxy-PEP use among cisgender men (with female sex partners) who have similar STI risk factors as the doxy-PEP study populations (i.e., history of STIs, multiple sex partners, high-prevalence populations) could also potentially provide individual and community benefits outweighing the risks of doxycycline use. The NNT and degree of potential protective effect with insertive vaginal sex are unknown. This strategy has the possibility of indirectly extending the potential benefits of doxy-PEP use to cisgender women (who have sex with men) and to neonates, who experience the majority of complications of bacterial STIs, through reduction of community rates and may be considered by clinicians on a case-by-case basis. Doxy-PEP has not been studied in adolescents younger than 18 years, and adherence and efficacy in this group are unknown.

Evidence from the IPERGAY trial: The first published evidence on doxy-PEP was derived from a substudy of the ANRS IPERGAY randomized trial of on-demand HIV PrEP among cisgender men and transgender women who have sex with men in France. The substudy demonstrated an approximately 70% reduction in incident chlamydia and syphilis infections but no significant reduction in gonorrhea infections in a population reporting sex practices placing them at high risk of STIs [Molina, et al. 2018]. In this open-label extension, more than 200 participants (cisgender men and transgender women who have sex with men) taking HIV PrEP were randomized to receive doxycycline hyclate 200 mg as a single dose within 24 to 72 hours after condomless sex or no doxy-PEP. Study participants were mostly White, aged 30 years and older, and reported having multiple sex partners (10 in 2 months) and engaging in condomless sex acts (10 in 4 weeks). Participants were instructed not to exceed 3 doses per week; the median number of doxy-PEP doses used per month was 3.4, which was fewer than the number of reported condomless sexual encounters. Of participants, 83% took doxy-PEP within 24 hours of sex. Gastrointestinal adverse effects were reported by more than half of the participants, resulting in 8 discontinuations. Doxy-PEP was associated with significant reductions in the incidence of first STI and, in individual analyses, of incident chlamydia and syphilis infections. For incident gonorrhea, however, there was no significant reduction in the doxy-PEP group, which was attributed to the high prevalence of tetracycline resistance among gonococcal isolates in France.

Evidence from the DoxyPEP trial: The open-label randomized DoxyPEP study analyzed data from 501 adult cisgender MSM (96%) and transgender women who have sex with men (4%) who were either taking HIV PrEP (n = 360) or had HIV (n = 194) and who had a bacterial STI and reported condomless sex with a male partner within the past year. Participants were randomized to receive either doxy-PEP as 200 mg of delayed-release doxycycline hyclate (ideally within 24 hours but no later than 72 hours after condomless sex) or standard of care [Luetkemeyer, et al. 2023]. STI testing was performed every 3 months over 1 year of follow-up. Participants had a high prevalence of baseline bacterial STIs and a median of 9 sex partners in the 3 months before enrollment, and 59% reported substance use. The median participant age was 38 years, and 67% were White, 7% were Black, 11% were Asian or Pacific Islander, 15% were multiracial or other, and 30% were Hispanic or Latino. The maximum dose of doxycycline was 200 mg within a 24-hour period, and the medication was dispensed at 3-month intervals. The initial doxycycline supply included enough tablets for daily use, and the amount dispensed each quarter was adjusted in follow-up based on frequency of sex and doses used.

The DoxyPEP study was stopped early after interim analysis noted a significant protective effect in the intervention arm, and participants in the standard-of-care group were offered doxy-PEP [Luetkemeyer, et al. 2023]. Modified intention-to-treat analysis included participants who completed a median of 9 months of follow-up. Gonorrhea was the most common STI diagnosed, and there were very few cases of early syphilis. Median doxy-PEP use was 4 doses per month, with 25% of participants reporting more than 10 doses per month. This study demonstrated a 52% quarterly reduction in any incident STI among participants with HIV (hazard ratio [HR], 0.48; 95% confidence interval [CI], 0.28-0.83), and a 66% reduction among those taking HIV PrEP (HR, 0.34; 95% CI, 0.23-0.51) [SFDPH 2024; Luetkemeyer, et al. 2023; Luetkemeyer, et al. 2022]. Among participants taking HIV PrEP, the relative risk (RR) of any incident STI was 0.34 (95% CI, 0.24-0.46; *P*<.001), and the NNT was 4.7, whereas among participants with HIV, the RR for any incident STI was 0.38 (95% CI, 0.24-0.60; *P*<.001), and the NNT was 5.3 [Luetkemeyer, et al. 2023].

In subgroup analyses, among participants taking HIV PrEP, the significant risk reduction was maintained for each STI individually, including infections at extragenital sites, except for pharyngeal chlamydia [Luetkemeyer, et al. 2023]. Among participants with HIV, doxy-PEP did not significantly reduce incident early syphilis or urethral or pharyngeal chlamydia or gonorrhea. Doxycycline was well tolerated, and self-reported adherence was high. Antimicrobial resistance was also evaluated in this study and is discussed below (see guideline section Antimicrobial Resistance, below).

Evidence from the DOXYVAC trial: In the phase III randomized 2×2 factorial designed DOXYVAC trial, the efficacy of both doxy-PEP for bacterial STI prophylaxis and meningococcal serotype B vaccination for preventing gonococcal infection was investigated among 446 cisgender men and transgender women who have sex with men taking HIV PrEP in France [Molina, et al. 2024]. Participants were predominantly White, had a median age of 40 years, were long-term HIV PrEP users, reported multiple sex partners, and had multiple prior STIs. Unblinded early interim analysis revealed significant reductions in any incident STI, and participants were all offered doxy-PEP. Doxy-PEP significantly reduced the incidence of the first episode of chlamydia (adjusted HR [aHR], 0.14; 95% CI, 0.09-0.23; *P*<.0001), syphilis (aHR, 0.21; 95% CI, 0.11-0.41; *P*<.0001), and gonorrhea (aHR, 0.67; 95% CI, 0.52-0.87; *P*=.0025) infections. Self-reported adherence was high in this study at more than 70% (detectable concentrations in plasma and urine were more than 60% in the doxy-PEP group at 6 months), with a median use of 3 doses per month and a median time to doxy-PEP intake after sex of 15 hours. Additionally, antimicrobial resistance was analyzed and is discussed below (see guideline section Antimicrobial Resistance, below).

Doxy-PEP and receptive vaginal sex: Data from a randomized trial in Kisumu, Kenya, that compared doxy-PEP with the standard of care among cisgender women aged 18 to 30 years taking HIV PrEP found that doxy-PEP was not effective for bacterial STI prevention in this population [Stewart, et al. 2023]. The study enrolled 449 participants from 2020 to 2022, with

very little loss to follow-up. At baseline, 18% of participants were diagnosed with an STI (14% with chlamydia, 4% with gonorrhea, and <1% with syphilis). Adherence by self-report demonstrated at least 80% of condomless sex encounters were covered, with almost all doses taken within 24 hours of condomless sex. Incident STIs were similar between groups (annual incidence of 27%), with no significant reduction in the doxy-PEP group. No incident HIV infections were reported. Fifty participants (22%) in the doxy-PEP group were randomly selected for hair sampling to assess doxycycline concentrations using an assay developed by study investigators; in this subgroup, doxycycline was detected in the hair of 56% of participants on at least 1 visit and in 32.6% on all visits for which hair specimens were collected (58/178 total visits) [Stewart, et al. 2023]. The investigators reported that a study to validate the assay with intermittent dosing of doxycycline is in development [Kojima and Klausner 2024].

The reason for the lack of demonstrable efficacy of doxy-PEP in this study is unclear. Possible factors influencing these results include the prevalence of high-level tetracycline resistance among gonococcal isolates in Kenya [Soge, et al. 2023], adherence being less than what was ascertained by self-report, and biologic or anatomic differences. An unrelated study in the United States evaluated drug concentrations with event-driven oral dosing and showed that 200 mg of doxycycline hyclate achieved concentrations above minimum inhibitory concentrations (MICs) for syphilis, chlamydia, and gonorrhea in rectal, vaginal, and cervical tissues as well as rectal and vaginal secretions; these concentrations were sustained at least 2 days after dosing, although the degree above MIC was much lower for *Neisseria gonorrhoeae* [Haaland, et al. 2023]. Higher doxycycline concentrations were sustained for a longer duration in rectal secretions than in vaginal secretions, although the levels remained above the MIC.

Additional studies on doxy-PEP to prevent STIs through receptive vaginal sex are in development.

Doxy-PEP post-implementation: In a large sexual health clinic setting in San Francisco, California, following the release of the DoxyPEP trial results, all individuals on HIV PrEP were offered doxy-PEP (approximately 3,000 patients). At 9-month follow-up there was approximately 39% uptake of doxy-PEP [Scott, et al. 2024]. Baseline incidence rates for any STI (gonorrhea, chlamydia, syphilis) were approximately 3 times higher in the doxy-PEP group than in the group not on doxy-PEP. By the last quarter of the study period, STI incidence rates in the doxy-PEP group were significantly reduced and comparable to those in the no-doxy-PEP group, although the reduction was not significant for the individual outcome of gonorrhea [Scott, et al. 2024]. These results demonstrate not only the effect of doxy-PEP on preventing STIs but also the STI risk stratification of individuals by self-selection of who accepted or declined doxy-PEP.

The same investigators tracked quarterly numbers of new patients starting doxy-PEP and examined the effect of doxy-PEP with early implementation on local STI epidemiology [Sankaran, et al. 2024]. It was concluded that early release of guidance and implementation for doxy-PEP at high-volume clinics was associated with substantial reductions in reported cases of chlamydia and early syphilis for just over 1 year among cisgender men and transgender women with sex partners assigned male sex at birth (an approximately 50% drop for each); notably, there was no community impact on gonococcal infections [Sankaran, et al. 2024]. The investigators noted that other factors, including changes in sex practices and activities in response to mpox, might have affected the results, although the results were sustained into 2023 [Sankaran, et al. 2024].

→ KEY POINTS

- Doxy-PEP is not 100% effective in preventing bacterial STIs.
- There is insufficient evidence to recommend doxy-PEP to protect against STI acquisition through receptive vaginal sex. If doxy-PEP is used in individuals who may become pregnant, pregnancy testing should be performed, as doxycycline use should generally be avoided during pregnancy.
- It is essential to provide counseling and education to patients on the limitations of doxy-PEP and to emphasize that ongoing condom use and engagement in sexual health services is necessary, including but not limited to routine STI screening, STI testing for symptomatic patients, and STI treatment or evaluation after an STI exposure.
- Evaluation by a clinician after a known or possible STI exposure is necessary to determine whether treatment is needed.
- For individuals using doxy-PEP who are diagnosed with gonorrhea, chlamydia, or syphilis, treat according to the recommendations in the CDC STI Treatment Guidelines.

Antimicrobial Resistance

Published research, previous guideline statements, and editorials have raised concerns about the impact of doxy-PEP on the emergence of antimicrobial resistance for bacterial STIs and other non-STI pathogens with widespread long-term use [Molina, et al. 2024; Cornelisse, et al. 2023; Luetkemeyer, et al. 2023; Kohli, et al. 2022; Lewis 2022; Luetkemeyer, et al. 2022; Grant,

et al. 2020; Molina, et al. 2018; Siguier and Molina 2018; Golden and Handsfield 2015]. Increasing antimicrobial resistance is a concern at both the individual and population levels [Cornelisse, et al. 2023]. It may take years to determine this effect, and additional research is needed [Siguier and Molina 2018]. To date, studies of doxy-PEP have not found detectable resistance in *Treponema pallidum* or *Chlamydia trachomatis* strains [Cornelisse, et al. 2023]. Doxycycline resistance is already a concern for other bacterial STIs, including *M. genitalium* and *N. gonorrhoeae*, and there are few alternative therapeutic options for *M. genitalium* [Workowski, et al. 2021]. Tetracycline (used as a surrogate for doxycycline) resistance in *N. gonorrhoeae* isolates varies geographically and is reported at 20.1% nationwide by the CDC Gonococcal Isolate Surveillance Project [CDC(b) 2024].

Doxycycline is an important antibiotic used to treat non-sexually transmitted infections when other oral treatment options are severely limited, including methicillin-resistant *Staphylococcus aureus* (MRSA). Doxycycline also remains an option for antimicrobial-resistant gonococcal infections if susceptibility is confirmed. The benefits of widespread use of doxycycline must be weighed against the known and potential risks of selecting for antimicrobial resistance and altering the various microbiomes (e.g., gastrointestinal, vaginal, skin). In an analysis of more than 2,000 gonococcal isolates in Europe, the presence of 2 common tetracycline-associated mutations was strongly associated with additional mutations conferring cross-resistance to other antibiotics, including beta-lactams, macrolides, and fluoroquinolones [Vanbaelen, et al. 2023]. This raises concern that selecting for gonorrhea tetracycline resistance may also impact the effectiveness of other antibiotic classes, including cephalosporins, which are the standard of care for gonorrhea treatment.

To assess the impact of doxy-PEP use on antimicrobial resistance, nares and oropharynx specimens were examined for *S. aureus* in the DoxyPEP study [Luetkemeyer, et al. 2023], and tetracycline resistance in extended-spectrum beta-lactamase (ESBL) *Escherichia coli* (as a marker of microbiome influence) and MRSA were assessed in the DOXYVAC study [Molina, et al. 2024]. In the DoxyPEP study, cultures were available for 17.2% of gonorrhea infections (n = 44) [Luetkemeyer, et al. 2023]. Of these, baseline tetracycline resistance (a surrogate for doxycycline resistance) was 27%. After enrollment, resistance was 38% in the doxycycline groups and 12% in the standard-of-care groups, and doxy-PEP appeared less protective for tetracycline-resistant gonorrhea, although the sample size was small [Luetkemeyer, et al. 2023; Luetkemeyer, et al. 2022]. *S. aureus* was cultured from the oronasopharynx in 45% of participants, and baseline doxycycline resistance was 12% [Luetkemeyer, et al. 2023]. At 1 year, *S. aureus* colonization identified by culture was significantly less in the doxy-PEP groups than the standard-of-care groups, and prevalence of doxycycline-resistant isolates was 16% in the doxycycline groups and 8% in the standard-of-care groups [Luetkemeyer, et al. 2023].

In the DOXYVAC study, baseline tetracycline resistance was found in all 78 specimens for which gonorrhea cultures were available, and the prevalence of high-level resistance was greater in the doxy-PEP group (36%) than in the standard-of-care group (13%); no *C. trachomatis* resistance was detected by culture or sequencing [Molina, et al. 2024]. As markers for assessing the impact of doxy-PEP on the microbiome, there was no significant difference between the groups in detection of ESBL *E. coli* from anal swabs or MRSA from the pharynx.

Based on these data, the efficacy of doxy-PEP for gonorrhea is expected to differ depending on the prevalence of tetracycline resistance in a given population or geographic region. For *S. aureus*, doxy-PEP is associated with increased resistance [Luetkemeyer, et al. 2023], which is an important consideration in the preservation of antimicrobial treatment options for MRSA infection.

Recommendations Outside of New York State

Several organizations have issued guidance regarding the use of doxy-PEP [Bachmann, et al. 2024; Cornelisse, et al. 2024; SFDPH 2024; Werner, et al. 2024; CDPH 2023; Gandhi, et al. 2023; NCSD 2023; PHSKC 2023; SCPHD 2023; Kohli, et al. 2022]. There is variability regarding implementation of this intervention, although dosing recommendations and the guidance to bundle doxy-PEP with comprehensive sexual health services have been uniformly consistent with studies to date.

The British Association for Sexual Health and HIV and the UK Health Security Agency do not endorse the use of doxycycline as prophylaxis, primarily because of concerns regarding antimicrobial resistance and limited long-term data [Kohli, et al. 2022]. The Australian Society for HIV, Viral Hepatitis, and Sexual Health Medicine recommends use of doxy-PEP primarily for the prevention of syphilis among gay, bisexual, and other men who have sex with men [Cornelisse, et al. 2024]. Disagreements noted are centered around the risks and benefits at the individual and population levels, including the potential for selection of antimicrobial resistance and impact on the microbiome [Cornelisse, et al. 2024; Kohli, et al. 2022]. The German STI Society released a position statement recommending against broad implementation of doxy-PEP (without further data regarding antimicrobial resistance), although they cited situations in which doxy-PEP use may be considered on a case-by-case basis [Werner, et al. 2024].

The San Francisco Department of Public Health (SFDPH) released the first set of guidelines on doxy-PEP use, recommending doxy-PEP for cisgender men and transgender women who meet 2 eligibility criteria outlined in the DoxyPEP study: 1) have a diagnosis of a bacterial STI within the last year, and 2) report condomless sex with at least 1 male partner in the past year [SFDPH 2024]. The SFDPH also recommends offering doxy-PEP via shared decision-making to cisgender men, transgender men, and transgender women who have had multiple sex partners assigned male sex at birth within the past year, even in the absence of a prior STI diagnosis. The SFDPH dosing and prescribing recommendations are the same as those used in the DoxyPEP study; however, the SFDPH notes that immediate- or extended-release doxycycline could be used, although the extended-release formulation may be more expensive. The California Department of Health (CDPH) sent out a Dear Colleague Letter on April 28, 2023, with recommendations on doxy-PEP [CDPH 2023]. The CDPH recommends doxy-PEP for cisgender men or transgender women with 1 or more bacterial STI in the past 12 months and suggests offering doxy-PEP via shared decision-making to all nonpregnant individuals at increased risk of STI acquisition, even if there is no history of an STI diagnosis. To date, there are 3 states in total with guidance on provision of doxy-PEP to any individual at risk for STIs: California [CDPH 2023], Minnesota [MDH 2024], and New Mexico [NMDPH 2023].

Public Health–Seattle and King County (PHSKC) recommends that clinicians engage in shared decision-making on doxy-PEP with cisgender men and transgender women with history of an STI in the past year and ongoing sex encounters with partners assigned male sex at birth [PHSKC 2023]. The PHSKC guidance also recommends stronger consideration for individuals in this population with a specific history of syphilis or multiple STIs in the prior year and that clinicians consider prescribing doxy-PEP episodically when patients anticipate their STI exposure risk to be elevated (e.g., group sex events).

In 2024, the CDC released formal guidelines on the use of doxy-PEP [Bachmann, et al. 2024]. For cisgender men and transgender women who have had a bacterial STI in the past year and have sex partners assigned male sex at birth, the CDC recommends providing counseling about doxy-PEP and offering this prevention strategy via shared-decision making. Comprehensive sexual health services, including STI prevention counseling, STI screening, immunizations, and linkage to HIV prevention and treatment, are also recommended.

The National Coalition of STD Directors released a doxy-PEP implementation toolkit with basic guidance on community engagement, workflow, education, program evaluation, and prescribing logistics [NCSD 2023]. Highlights from the toolkit emphasize ensuring equitable criteria for offering doxy-PEP and reducing unnecessary access restrictions.

Practical Considerations for Doxy-PEP Implementation

As with any drug therapy, a review of the patient's health history, current medications, and allergies to ensure there are no health concerns, drug-drug interactions, or medication allergies that would preclude use is indicated before initiating doxycycline post-exposure prophylaxis (doxy-PEP). Concurrent use of doxy-PEP with daily doxycycline or tetracycline for other conditions is contraindicated. Medications other than doxycycline have not been studied for bacterial sexually transmitted infection (STI) PEP. When doxycycline is not tolerated or contraindications to its use exist, doxy-PEP is not recommended. Practical considerations for prescribing and monitoring doxy-PEP are outlined in Table 1, below.

Table 1: Considerations for Doxy-PEP Implementation

Consideration(s)	Comments
Available formulations	• Doxycycline hyclate delayed-release 200 mg oral tablet • Doxycycline hyclate or monohydrate immediate-release 100 mg oral capsule or tablet (2 capsules or tablets taken together for a total of 200 mg) • The immediate-release formulations are more widely available and usually cost less than the delayed-release formulation.
Administration	• As doxy-PEP, 200 mg of doxycycline should ideally be taken within 24 hours after condomless sex, up to 72 hours maximum. • No more than 200 mg of doxycycline should be taken in a 24-hour period. • Milk and vitamins containing positive cations (e.g., calcium, zinc, magnesium) should be avoided within 2 hours of taking doxycycline, because these interfere with doxycycline absorption and may lower doxycycline levels, potentially reducing efficacy.

Table 1: Considerations for Doxy-PEP Implementation	
Consideration(s)	**Comments**
Contraindications, drug-drug interactions, and dose adjustments	• Doxy-PEP should not be used concurrently with other doxycycline therapy (or any other tetracycline-class antibiotic) for treatment or prevention of a health condition (e.g., acne, rosacea, malaria prophylaxis). • No significant drug-drug interactions exist between doxycycline and ARVs used for HIV treatment or PrEP. • No known drug reactions exist between doxycycline and gender-affirming hormone therapies. • No doxycycline dose adjustments are indicated for patients with renal dysfunction. • Doxycycline is generally contraindicated during pregnancy because of potential adverse effects on the fetus [FDA 2016].
Adverse effects	• GI adverse effects are common; taking doxycycline with food may help alleviate nausea or GI upset. Symptoms including nausea, vomiting, and reflux can be severe enough to require cessation of doxycycline. • Esophageal injury and irritation can occur. Doxycycline should be taken with an 8-oz glass of water and the individual should remain upright for 30 minutes to 1 hour after dosing. • Skin photosensitivity and phototoxicity can occur; wearing sunscreen, limiting sun exposure, and avoiding tanning beds can help prevent sunburn and other skin injury. • Intracranial hypertension is a rare but serious adverse effect. Refractory headaches or vision changes should be evaluated promptly by a clinician. • Doxycycline use may select for antibiotic-resistant organisms, which can cause infections in some circumstances and can disrupt the microbiome.
Supply of doxy-PEP medications	• A 30- to 90-day supply is recommended, with actual number of pills to be determined by anticipated or actual dosing frequency during that time (see dose quantity below). • Dose quantity: – For delayed-release doxycycline 200 mg tablets, the quantity dispensed should not exceed 90 doses per 3 months. – For immediate-release 100 mg capsules or tablets, the quantity dispensed should not exceed 180 doses per 3 months. – The quantities above are the maximum number to be dispensed; many patients will not need such a large quantity. Shared decision-making can determine the lowest quantity needed based on the frequency of condomless sexual encounters during the prescribing interval.
Follow-up and laboratory monitoring	• Engage patients taking doxy-PEP in ongoing comprehensive sexual health services that include STI screening, HIV PrEP, immunizations, and other health promotion strategies as indicated [a]. • At least every 3 months: – Screen for syphilis, HIV if not previously diagnosed, gonorrhea, and chlamydia (including extragenital testing when indicated), ensuring that tests have been obtained before providing a doxy-PEP prescription refill. – Screen for hepatitis B virus at initiation, and screen for hepatitis C virus at least annually [CDC(a) 2024]. – Offer HIV PrEP or HIV treatment as needed. – Assess for ongoing doxy-PEP needs and continue in shared decision-making as new evidence becomes available. • The doxycycline package insert advises periodic monitoring of hepatic function, renal function (specifically BUN), and CBC with prolonged therapy. Such monitoring may not be necessary with intermittent dosing.

Table 1: Considerations for Doxy-PEP Implementation	
Consideration(s)	**Comments**
Key points for patient education	• **Medication administration instructions and contraindications:** See above. • **Protective effect:** Doxy-PEP is not 100% effective and is not effective against all STIs. For cisgender men and transgender women at risk of STIs who were engaged in routine sexual healthcare, doxy-PEP reduced the likelihood of an STI diagnosis by >50% [Luetkemeyer, et al. 2023]. Evaluation by a clinician after a possible STI exposure is necessary to determine whether treatment is needed. • **Adverse effects:** Doxycycline can cause GI adverse effects, photosensitivity, and esophageal irritation, which can be mitigated using strategies noted above. Long-term doxycycline use may increase the risk of developing an antibiotic-resistant infection. The potential long-term effects of doxy-PEP use are not known at this time. • **Ongoing screening:** Screening for STIs every 3 months is necessary while taking doxy-PEP. Routine HIV testing should continue in individuals at risk of HIV.
Abbreviations: ARV, antiretroviral medication; BUN, blood urea nitrogen; CBC, complete blood count; doxy-PEP, doxycycline post-exposure prophylaxis; GI, gastrointestinal; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection. **Note:** a. See the Centers for Disease Control and Prevention STI Treatment Guidelines and the NYSDOH AI guidelines PrEP to Prevent HIV and Promote Sexual Health and Immunizations for Adults With HIV.	

Managing STI Exposures in Patients Taking Doxy-PEP

Because doxy-PEP is not 100% effective at preventing STIs, it is important for patients using doxy-PEP who have sex partners diagnosed with bacterial STIs to undergo STI testing. Syphilis exposures are considered separately from chlamydia and gonorrhea exposures.

Patients taking doxy-PEP who are exposed to early syphilis within the prior 90 days can be treated presumptively per the Centers for Disease Control and Prevention (CDC) STI Treatment Guidelines [Workowski, et al. 2021] regardless of test results. If treatment is declined, repeat syphilis testing at 3 months is recommended because of the potential for an extended period of syphilis incubation. If the syphilis exposure was more than 90 days prior, management is based on test results.

Patients taking doxy-PEP who are exposed to chlamydia or gonorrhea can be treated based on test results. Alternatively, these individuals can be treated empirically per the CDC STI Treatment Guidelines as if they were not using doxy-PEP.

Managing Diagnosed STIs in Patients Taking Doxy-PEP

Treat incident STIs according to the Centers for Disease Control and Prevention (CDC) STI Treatment Guidelines [Workowski, et al. 2021].

All Recommendations

☑ ALL RECOMMENDATIONS: DOXYCYCLINE PEP TO PREVENT BACTERIAL STIs

Biomedical Prevention of STIs

- Clinicians should offer doxy-PEP to cisgender men and transgender women who engage in condomless sex with partner(s) assigned male sex at birth and who:
  - Have had a bacterial STI diagnosed within the past year (A1), or
  - Have no or unknown history of STIs and ongoing risk of STI exposure (A2)
- Clinicians should engage in shared decision-making with cisgender men who are at ongoing risk of STI exposure and engage in condomless sex with multiple partners assigned female sex at birth, offering doxy-PEP on a case-by-case basis. (B3)
- When prescribing doxy-PEP, clinicians should use the dosing regimen of oral doxycycline 200 mg taken ideally within 24 hours (up to 72 hours) after condomless sex (A1) and counsel patients (A*) on the key points for patient education outlined in Table 1: Considerations for Doxy-PEP Implementation.
- For individuals taking doxy-PEP, clinicians should screen for HIV, chlamydia, gonorrhea, and syphilis at least every 3 months. (A1)
- Clinicians should offer HIV PrEP to individuals who do not have HIV and are initiating or using doxy-PEP. (A*)
- Clinicians should offer HIV treatment to individuals with HIV who are not on antiretroviral therapy and are initiating or using doxy-PEP. (A1)

Abbreviations: doxy-PEP, doxycycline post-exposure prophylaxis; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

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Supplement: Guideline Development and Recommendation Ratings

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.

Table S2: Recommendation Ratings and Definitions		
Strength	**Quality of Evidence**	
A: Strong B: Moderate C: Optional	1	Based on published results of at least 1 randomized clinical trial with clinical outcomes or validated laboratory endpoints.
	*	Based on either a self-evident conclusion; conclusive, published, in vitro data; or well-established practice that cannot be tested because ethics would preclude a clinical trial.
	2	Based on published results of at least 1 well-designed, nonrandomized clinical trial or observational cohort study with long-term clinical outcomes.
	2†	Extrapolated from published results of well-designed studies (including nonrandomized clinical trials) conducted in populations other than those specifically addressed by a recommendation. The source(s) of the extrapolated evidence and the rationale for the extrapolation are provided in the guideline text. One example would be results of studies conducted predominantly in a subpopulation (e.g., one gender) that the committee determines to be generalizable to the population under consideration in the guideline.
	3	Based on committee expert opinion, with rationale provided in the guideline text.