# Doxycycline prophylaxis for the prevention of bacterial sexually transmitted infections (STIs): doxyPrEP and doxyPEP

## Question

What is the evidence to support the use of doxycycline for prevention of bacterial STIs (pre- and post-exposure prophylaxis)?

## Key Take-Home Messages

- Rates of syphilis, chlamydia, and gonorrhea are increasing in Canada (1) and in the U.S. (2).
- Six randomized controlled trials examine doxycycline pre-exposure prophylaxis (doxyPrEP) (3, 4) and doxycycline post-exposure prophylaxis (doxyPEP) (5–8) to prevent bacterial STIs (syphilis, chlamydia, and gonorrhea). This is supplemented by four studies presenting real-life doxyPEP data from healthcare settings in San Francisco (9-12), after it became the first jurisdiction to issue doxyPEP guidance in 2022 (9).
- The vast majority of doxyPrEP and doxyPEP studies focus on men who have sex with men.
- One meta-analysis estimated that among men who have sex with men and transgender women, doxycycline post-exposure prophylaxis can reduce the risk of bacterial STIs by 53% (13).
- Doxycycline post-exposure prophylaxis appears to be most effective against syphilis and chlamydia (13, 14).
- There is concern that widespread use of doxycycline could contribute to increased antimicrobial resistance (15–24).
- There is interest among men who have sex with men to use doxycycline prophylaxis to prevent STIs (25–28).

### Rapid Response: Evidence into Action

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**Suggested Citation**
Rapid Response Service. Doxycycline prophylaxis for the prevention of bacterial sexually transmitted infections (STIs): doxyPrEP and doxyPEP. Toronto, ON: The Ontario HIV Treatment Network; November 2024.

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## The Issue and Why it's Important

Sexually transmitted infections (STIs) are rising globally: more than one million new infections of syphilis (caused by bacteria *Treponema pallidum*), gonorrhea (bacteria *Neisseria gonorrhoeae*), chlamydia (bacteria *Chlamydia trachomatis*), and trichomoniasis (protozoan *Trichomonas vaginalis*) occur each day worldwide (29). In Canada (1) and the U.S. (2), rates of bacterial STIs are also increasing: between 2011 and 2019 in Canada, rates of chlamydia, gonorrhea, and syphilis increased by 26%, 171%, and 389%, respectively (1).

While these three bacterial STIs—syphilis, gonorrhea, and chlamydia—are curable (29), academic literature cites the need for new and effective interventions to curb the increasing trend in STI incidence (30–33). One novel biomedical approach that has demonstrated promising results in preventing bacterial STIs is the use of doxycycline prophylaxis (3–8, 34, 35).

This strategy is of particular importance for men who have sex with men, the population group most affected by HIV in Canada (36) and in the U.S. (37). Among men who have sex with men, having a bacterial STI increases the risk of contracting HIV: a meta-analysis from 2021 found that the risk of acquiring HIV among men who have sex with men is two times greater for individuals infected with chlamydia, and as much as four times greater for individuals infected with syphilis and gonorrhea (38). This is due to a variety of biological mechanisms where the presence of an STI can enhance susceptibility to HIV (38-40). Additionally, among individuals initiating HIV pre-exposure prophylaxis (PrEP), there is a high burden of STIs: in a meta-analysis of 16 studies, the pooled prevalence (i.e. combined prevalence based on data from multiple studies) of chlamydia, gonorrhea, and early syphilis was nearly 24% before starting HIV PrEP (41).

This review examines several topics around the use of doxycycline prophylaxis for bacterial STIs. This includes a brief overview of the antibiotic, evidence for its use as prophylaxis for bacterial STIs, antimicrobial resistance, acceptability and use, and current guidelines for practice across several high-income countries.

## What We Found

### What is doxycycline?

Doxycycline is an antibiotic from the tetracycline class that treats infections by preventing the spread and growth of bacteria (42). It is generally well-tolerated (42). In Canada, doxycycline or azithromycin is recommended as first-line treatment for chlamydia (43, 44) and as an alternative treatment for syphilis among individuals with penicillin allergies (45). For uncomplicated anogenital gonorrhea infection, ceftriaxone or cefixime plus doxycycline is recommended as an alternative treatment (44, 46). Of note, treating gonorrhea

## References


1. Public Health Agency of Canada. Chlamydia, gonorrhea and infectious syphilis in Canada: 2020 (infographic). 2023. Available from: https://www.canada.ca/en/public-health/services/publications/diseases-conditions/chlamydia-gonorrhea-infectious-syphilis-canada-2020-infographic.html Accessed October 16, 2024.

2. National Academies of Sciences, Engineering and Medicine. Sexually transmitted infections: Adopting a sexual health paradigm. 2021. Available from: https://doi.org/10.17226/25955 Accessed October 24, 2024.

3. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: A randomized, controlled pilot study. Sexually Transmitted Diseases. 2015;42(2):98–103.

4. Grennan T, Darrell THS, Mohammed S, Azmin R, Burchell AN, Burgener AD, et al. A pilot, randomized controlled trial of doxycycline pre-exposure prophylaxis versus placebo for prevention of bacterial sexually transmitted infections in men who have sex with men living with HIV. 2024. Available from: https://plus.iasociety.org/sites/default/files/2024-09/e-poster_1872.pdf Accessed October 10, 2024.

is challenging because the bacteria readily develops resistance to antibiotics (44), a topic that will be discussed later.

A systematic review on the safety of doxycycline was published in 2005 (47). Across 24 clinical trials conducted between 1966 to 2003, the incidence of adverse events was described as "very low" (47, 48). The majority of the trials were of short-term duration; only three reported usage at or past 20 days (47, 48). The most commonly reported side effect across all studies was gastrointestinal events (47, 48). In 2023, a systematic review and meta-analysis on the safety of long-term (i.e. >8 weeks) use of doxycycline as post-exposure prophylaxis for the management of bacterial STIs was published (48). Authors reported that use for longer than eight weeks was "generally safe", and may be associated with minor side effects including neurological (e.g. headaches and dizziness) and gastrointestinal (e.g. nausea and vomiting) (48). As doxycycline has been used for malaria prophylaxis and treatment of skin conditions such as acne, there are also some studies examining effects of its longer-term use (49, 50). One synthesis from 2020 included seven studies and found that there is insufficient or inadequate evidence to determine an association between use of doxycycline for malaria prophylaxis and latent or persistent adverse events (49). On the other hand, there is some concern for the development of antibiotic resistance with widespread utilization of doxycycline for acne treatment (50).

## Current evidence on doxycycline prophylaxis for bacterial STIs

Evidence has been accumulating on the efficacy of doxycycline as prophylaxis for bacterial STIs: as of November 2024, six randomized controlled trials (3–8) and four analyses of real-world data (9–12) have been published in the literature. The details of these ten studies can be found in Table 1. Of these ten primary studies:

- Two studies examine doxycycline as pre-exposure prophylaxis (doxyPrEP: 100mg of doxycycline once daily) (3, 4). This includes the results from the Daily Doxycycline in HIV-positive gay, bisexual, and other men who have sex with men for STI prevention (DaDHS) pilot study, conducted in Vancouver and Toronto (4). The findings of this pilot study show that doxycycline pre-exposure prophylaxis use among men who have sex with men living with HIV resulted in significant reductions in bacterial STIs (syphilis, chlamydia, gonorrhea) over one year compared to the placebo group (4).

- Four randomized controlled trials (5–8) and four real-world data analyses (9–12) examine doxycycline as post-exposure prophylaxis (doxyPEP: 200mg within 24–72 hours of sexual exposure). Of these, seven were conducted in high-income countries (U.S. and France) among men who have sex with men and transgender women (5, 7, 8); one study from


5. Molina JM, Bercot B, Assoumou L, Rubenstein E, Algarte-Genin M, Pialoux G, et al. Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): A multicentre, open-label, randomised trial with a 2 x 2 factorial design. The Lancet Infectious Diseases. 2024;23:23.

6. Stewart J, Oware K, Donnell D, Violette LR, Odoyo J, Soge OO, et al. Doxycycline prophylaxis to prevent sexually transmitted infections in women. New England Journal of Medicine. 2023;389(25):2331–40.

7. Luetkemeyer AF, Donnell D, Dombrowski JC, Cohen S, Grabow C, Brown CE, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. New England Journal of Medicine. 2023;388(14):1296–306.

8. Molina JM, Charreau I, Chidiac C, Pialoux G, Cua E, Delaugerre C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: An open-label randomised substudy of the ANRS IPERGAY trial. The Lancet Infectious Diseases. 2018;18(3):308–17.

9. Liu A, Hao J, Pickering TA, Klausner JD. Trends in sexually transmitted infections associated with the doxycycline post-exposure prophylaxis guidelines in San Francisco. Sexually Transmitted Diseases. 2024;11:11.

Table 1. Studies examining effectiveness of doxycycline prophylaxis for the prevention of sexually transmitted infections (STIs)

| Study/trial name<br><br>Author, year | Jurisdiction | Study design | Population | Intervention<br>–<br>Control (if any) | Study endpoint<br>(if applicable) | Findings related to reduction of the risk of STI acquisition |
|---|---|---|---|---|---|---|
| **Doxycycline pre-exposure prophylaxis** | | | | | | |
| Doxycycline Prophylaxis to reduce incident syphilis among HIV-infected Men who have Sex with Men (DPMSM)<br><br>Bolan *et al.,* 2015 (3) | Los Angeles, U.S. | Randomized controlled trial (pilot) | HIV-positive men who have sex with men or transgender women who have sex with men, age ≥18 years, at least 2 treated episodes of syphilis since HIV diagnosis (n=30) | 100 mg of doxycycline taken once daily for 36 weeks (n=15)<br>–<br>Incentive-based contingency management (n=15) | At 36 weeks, doxycycline prescriptions and financial incentives concluded; participants followed to 48 weeks | • At 48-weeks follow-up, participants in the doxycycline arm were significantly less likely to test positive for gonorrhea, chlamydia, or syphilis when compared to individuals in the control (contingency management) group (OR: 0.27; 95% CI: 0.09–0.83; p=0.02) |
| Daily Doxycycline in HIV-positive GBM for STI prevention (DaDHS)<br><br>Grennan *et al.,* 2024 (4) | Vancouver and Toronto, Canada | Randomized controlled trial (pilot) | Men who have sex with men living with HIV (n=52) | 100 mg doxycycline hyclate taken once daily for 48 weeks (n=26)<br>–<br>Placebo (n=26) | 48 weeks of daily doxyPrEP or placebo, and followed quarterly with questionnaires (e.g. adherence, sexual history), pill counts, STI screens (syphilis serology; multi-site gonorrhea and chlamydia testing) and routine labs | • No between-arm differences in sexual behaviours, adverse events or tetracycline resistance to *S. aureus*<br><br>• Most adverse events (78.2%) were mild, and the proportion of adverse events related to study drug did not differ by arm<br><br>• DoxyPrEP led to significant reductions in bacterial STIs:<br>✓ 79% reduction in syphilis incidence (rate ratio 0.21 [95% CI 0.04–0.97])<br>✓ 92% reduction in chlamydia incidence (rate ratio 0.0.08 [95% CI 0.01–0.49])<br>✓ 68% reduction in gonorrhea incidence (rate ratio 0.32 [95% CI 0.12–0.86])<br>✓ 80% reduction in total STI incidence (rate ratio 0.20 [95% CI 0.08–0.51]) |
| **Doxycycline post-exposure prophylaxis** | | | | | | |
| Intervention Préventive de l'Exposition aux Risques avec et pour les Gays HIV-prevention study (IPERGAY)<br><br>Molina *et al.,* 2018 (8) | France | Randomized controlled trial | Men who have sex with men or transgender women who have sex with men, age ≥18 years, taking HIV PrEP, engaging in condomless anal intercourse with at least two different partners during past six months (n=232) | 200 mg doxycycline taken within 24 hours but no later than 72 hours after sex (n=116)<br>–<br>No doxycycline PEP (n=116) | First or new occurrence of a bacterial STI during the 10-month follow-up | • During follow-up, 73 participants presented with a new STI<br>✓ 28 in the doxycycline PEP group (9-month probability 22% [95% CI 15–32])<br>✓ 45 in the no-PEP group (9-month probability 42% [95% CI 33–53])<br><br>• HR 0.53 (95% CI 0.33–0.85; p=0.008)<br><br>• The occurrence of a first episode of chlamydia or syphilis was lower in participants taking doxycycline PEP<br>✓ Chlamydia: HR 0.30 (95% CI 0.13–0.70; p=0.006)<br>✓ Syphilis: HR 0.27 (95% CI 0.07–0.98; p=0.047)<br><br>• The occurrence of a first episode of gonorrhea did not differ significantly between doxycycline PEP and no PEP groups<br>✓ Gonorrhea: HR 0.83 (95% CI 0.47–1.47) |

**OR=odds ratio; CI=confidence interval; HR=hazard ratio; aHR=adjusted hazard ratio; IRR=incidence rate ratio**

Table 1. Studies examining effectiveness of doxycycline prophylaxis for the prevention of sexually transmitted infections (STIs) (continued)

| Study/trial name<br><br>Author, year | Jurisdiction | Study design | Population | Intervention<br>–<br>Control (if any) | Study endpoint<br>(if applicable) | Findings related to reduction of the risk of STI acquisition |
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| **Doxycycline post-exposure prophylaxis** | | | | | | |
| DoxyPEP<br><br>Luetkemeyer *et al.*, 2023 (7) | San Francisco and Seattle, U.S. | Randomized controlled trial | Men who have sex with men and transgender women, age ≥18 years, taking HIV PrEP (PrEP Cohort) or living with HIV (PLWH Cohort) who had a bacterial STI (syphilis, chlamydia, gonorrhea) in the past year (n=501) | 200 mg of doxycycline taken within 24 hours but no later than 72 hours after condomless sex (n=327)<br>• PrEP Cohort: n=220<br>• PLWH Cohort: n=107<br>–<br>No doxycycline PEP/standard of care (n=174)<br>• PrEP Cohort: n=119<br>• PLWH Cohort: n=55 | Incidence of at least one bacterial STI per follow-up quarter | • PrEP Cohort<br>✓ STI diagnosed in 61 of 570 quarterly visits (10.7%) in the doxycycline PEP group<br>✓ STI diagnosed in 82 of 257 quarterly visits (31.9%) in the no doxycycline PEP groups<br>✓ RR 0.34 (95% CI 0.24–0.46)<br><br>• PLWH Cohort<br>✓ STI diagnosed in 36 of 305 quarterly visits (11.8%) in the doxycycline group<br>✓ STI diagnosed in 39 of 128 quarterly visits (30.5%) in the no doxycycline PEP groups<br>✓ RR 0.38 (95% CI 0.24–0.60)<br><br>• The incidence of gonorrhea, syphilis, and chlamydia decreased by two-thirds among participants taking doxycycline PEP compared to no doxycycline PEP group |
| dPEP<br><br>Stewart *et al.*, 2023 (6) | Kenya | Randomized controlled trial | Cisgender women, aged 18–30 years, on HIV PrEP, not pregnant (n=449) | 200 mg of doxycycline taken within 72 hours after condomless sex (n=224)<br>–<br>No doxycycline PEP/standard of care (n=225) | Incidence of at least one bacterial STI (syphilis, chlamydia, or gonorrhea) per follow-up quarter | • The quarterly incidence of STIs was not significantly lower with doxycycline PEP than with standard care (RR 0.88%; 95% CI 0.60–1.29; p=0.51)<br><br>• Among those assigned to the doxycycline PEP group, adherence was low |
| DOXYVAC<br><br>Molina *et al.*, 2024 (5) | Paris, France | Randomized controlled trial | Men who have sex with men, age ≥18 years, taking HIV PrEP, who had a bacterial STI in the past year (n=545) | 200 mg of doxycycline taken within 24 hours but no later than 72 hours after condomless sex (n=362)<br>–<br>No doxycycline PEP (n=183) | First episode of chlamydia, syphilis, or gonorrhea after the enrollment visit at baseline | • Chlamydia<br>✓ Doxycycline PEP: 24 events in 362 participants<br>✓ No doxycycline PEP: 68 events in 183 participants<br>✓ aHR 0.14 (95% CI 0.09–0.23; p<0.0001)<br><br>• Syphilis<br>✓ Doxycycline PEP: 12 events in 362 participants<br>✓ No doxycycline PEP: 27 events in 183 participants<br>✓ aHR 0.21 (95% CI 0.11–0.41; p<0.0001)<br><br>• Gonorrhea<br>✓ Doxycycline PEP: 144 events in 362 participants<br>✓ No doxycycline PEP: 94 events in 183 participants<br>✓ aHR 0.67 (95% CI 0.52–0.87; p=0.0025) |

Table 1. Studies examining effectiveness of doxycycline prophylaxis for the prevention of sexually transmitted infections (STIs) (continued)

| Study/trial name<br><br>Author, year | Jurisdiction | Study design | Population | Intervention<br>–<br>Control (if any) | Study endpoint<br>(if applicable) | Findings related to reduction of the risk of STI acquisition |
|---|---|---|---|---|---|---|
| **Doxycycline post-exposure prophylaxis** | | | | | | |
| Analysis of monthly STI surveillance reports of the San Francisco Department of Public Health<br><br>Liu *et al.*, 2024 (9) | San Francisco, U.S. | Interrupted time-series analysis | Cases of male rectal chlamydia, male rectal gonorrhea, and adult male syphilis | San Francisco Department of Public Health Guidance on doxyPEP issued in October 2022 | 30 months before and 12 months after guidance | • Change in average number of monthly cases before and after doxyPEP guidance:<br>✓ Chlamydia cases: 174 before to 135 after, with a mean difference of 39 fewer monthly cases (95% CI 11–67)<br>✓ Gonorrhea cases: 163 before to 133 after, with a mean difference of 29 fewer monthly cases (95% CI 8.5–50)<br>✓ Syphilis: 131 before to 95 after, with a mean difference of 36 fewer monthly cases (95% CI 25–48) |
| Association between doxyPEP program implementation and citywide STI incidence<br><br>Sankaran *et al.*, 2024 (11) | San Francisco, U.S. | Time-series analysis | Monthly reported cases of chlamydia, gonorrhea, and early syphilis | San Francisco Department of Public Health Guidance on doxyPEP issued in October 2022 | 4 months before and 13 months after guidance | • Among men who have sex with men and transgender women:<br>✓ Chlamydia cases decreased by 51% (95% CI 39%–60%) compared to expected counts in November 2023<br>✓ Syphilis cases decreased and 50% (95% CI 38%–59%) compared to expected counts in November 2023<br>✓ No significant change in gonorrhea cases (p=0.087)<br><br>• Among cis women, the number of monthly reported chlamydia cases in the post-guidance period increased significantly (2.43%/month, p<0.01) |
| DoxyPEP effectiveness in men who have sex with men and transgender women on HIV PrEP<br><br>Bacon *et al.*, 2024 (10) | San Francisco, U.S. | Pre-post analysis | Men who have sex with men and transgender women receiving HIV PrEP at an STI clinic in San Francisco (n=506) | 200 mg of doxycycline taken within 24 hours but no later than 72 hours after condomless sex (n=367)<br>–<br>No doxycycline PEP (n=139) | 12 months before and 12 months after offering doxyPEP | Change in STI positivity among doxyPEP users compared with non-users:<br><br>• Chlamydia<br>✓ Chlamydia positivity decreased 90% (RR 0.10, 95% CI 0.05–0.21) among doxyPEP users vs. 27% (RR 0.73, 95% CI 0.44–1.21) among non-users<br><br>• Syphilis<br>✓ Early syphilis positivity decreased by 56% (RR 0.44, 95% CI 0.21–0.92) among doxyPEP users vs. 32% (RR 0.68, 95% CI 0.20–2.30) among non-users<br>✓ The reduction among doxyPEP users was not significantly greater than among non-users<br>✓ The reduction among doxyPEP users was significantly greater than among non-users<br><br>• Gonorrhea<br>✓ Nonsignificant decreases in gonorrhea positivity in users and nonusers |

Table 1. Studies examining effectiveness of doxycycline prophylaxis for the prevention of sexually transmitted infections (STIs) (continued)

| Study/trial name<br><br>Author, year | Jurisdiction | Study design | Population | Intervention<br>–<br>Control (if any) | Study endpoint<br>(if applicable) | Findings related to reduction of the risk of STI acquisition |
|---|---|---|---|---|---|---|
| **Doxycycline post-exposure prophylaxis** | | | | | | |
| Doxycycline as bacterial STI post-exposure prophylaxis (DPEP)<br><br>Scott *et al.* 2024 (12) | San Francisco, U.S. | Pre-post and controlled interrupted time-series analysis | HIV PrEP users at a San Francisco sexual health clinic (n=3,081; 91% gay cis men) | 200 mg of doxycycline taken within 24 hours but no later than 72 hours after condomless sex for at least 30 days (n=1,209) | 6 months before clinic started offering doxyPEP and after clinic started offering doxyPEP | • In the pre- post-doxyPEP analysis:<br>✓ doxyPEP was associated with decreased STI incidence for any STI (IRR: 0.42, 95% CI: 0.24–0.74; p=0.003), chlamydia (IRR: 0.33, 95% CI: 0.23–0.46; p<0.001), and syphilis (IRR: 0.22, 95% CI: 0.07–0.54; p=0.001); but not gonorrhea (IRR: 0.89, 95% CI: 0.69–1.15; p=0.383)<br><br>• In the controlled interrupted time series analysis:<br>✓ doxyPEP was associated with a significant decline for any STI incidence (IRR: 0.67, 95% CI: 0.46–0.96; p=0.03). This decline was also significant for chlamydia (p=0.021) and gonorrhea (p=0.003), but not syphilis (p=0.360) |

Kenya investigated doxyPEP effectiveness among cisgender women (6).

Evidence from these primary studies has also been included in two meta-analyses:

- A 2024 meta-analysis (13) examined the four aforementioned randomized controlled trials on doxycycline post-exposure prophylaxis (5-8). The authors concluded that among men who have sex with men and transgender women, 200 mg of doxycycline taken within 72 hours after unprotected sex reduced the risk of having any bacterial STI by 53% (13). Specifically, in the subgroup of men who have sex with men and transgender women, the risk of chlamydia was reduced by 78% (RR 0.22; 95% CI 0.13–0.38), gonorrhea by 22% (RR 0.78; 95% CI 0.65–0.94) and syphilis by 77% (RR 0.23; 95% CI 0.13–0.41) (13). Authors were not able to identify a definitive association between the use of doxycycline and the development of antimicrobial resistance due to the limited number of cultured samples across studies (13). One drug-related serious adverse event was reported: an allergic skin reaction (a fixed drug eruption) in one participant from the DOXYVAC trial (one of the four doxyPEP trials mentioned above) (5, 13).

- Another meta-analysis from 2024 examined all six aforementioned primary studies (3–8) on doxycycline pre- and post-exposure prophylaxis (14). Across all six studies, authors observed a 56% decrease in the overall incidence of STIs (RR=0.44; 95% CI: 0.30–0.65) (14). The certainty of evidence for doxycycline post-exposure prophylaxis in reducing bacterial STIs specifically among men who have sex with men and among transgender women (n=3 studies) was graded as "high", meaning that authors were confident the true effect of the intervention was close to the estimate of the effect (14). Authors concluded that while doxycycline post-exposure prophylaxis significantly reduced the number of new infections of chlamydia and syphilis, its effectiveness against gonorrhea may be influenced by local antimicrobial resistance patterns (14). It should be noted that across these six included studies, two were conducted in France: IPERGAY (8) and DOXYVAC (5). The author of these French studies noted that there is already a high prevalence of tetracycline resistance among *Neisseria gonorrhoeae* strains in France (5, 8), a finding consistent with other literature (51, 52).

Other ongoing doxycycline prophylaxis studies include the Syphilaxis Study in Australia (53, 54), and the DISCO study in Canada (54, 55).

Some studies examined potential public health scenarios where doxycycline prophylaxis could have a positive impact. A mathematical modelling study suggested that doxycycline prophylaxis, alongside


10. Bacon O, Kohn RP, Glidden DV, Sankaran M, Levy M, Nguyen TQ, et al. Doxy-PEP effectiveness in men who have sex with men (MSM) and transgender Women (TGW) on HIV PrEP. Conference on Retrovirus and Opportunistic Infections 2024. Available from: https://www.croiconference.org/abstract/doxy-pep-effectiveness-in-men-who-have-sex-with-men-msm-and-transgender-women-tgw-on-hiv-prep/ Accessed November 5, 2023.

11. Sankaran M, Glidden DV, Kohn RP, Liebi C, Torres TS, Buchbinder SP, et al. Doxy-PEP associated with declines in chlamydia and syphilis in MSM and trans women in San Francisco. Conference on Retrovirus and Opportunistic Infections 2024. Available from: https://www.croiconference.org/abstract/doxy-pep-associated-with-declines-in-chlamydia-and-syphilis-in-msm-and-trans-women-in-san-francisco/ Accessed November 5, 2024.

12. Scott S, Roman J, Spinelli MA, Bena J, Torres TS, SP B. Doxycycline PEP: High uptake and significant decline in STIs after clinical implementation. Conference on Retrovirus and Opportunistic Infections 2024. Available from: https://www.croiconference.org/abstract/doxycycline-pep-high-uptake-and-significant-decline-in-stis-after-clinical-implementation/ Accessed November 5, 2024.

increased STI testing, may be an "effective complementary strategy" in British Columbia to minimize syphilis incidence among men who have sex with men living with HIV (56). Another study from Massachusetts examined electronic health records among men who have sex with men, transgender women, and nonbinary individuals assigned male sex at birth with two or more STIs (chlamydia, gonorrhea, syphilis) between 2015–2020 (57). The authors used this health data to evaluate the potential impact and efficiency of hypothetical doxycycline post-exposure prophylaxis prescribing strategies (57). Authors concluded that among 10,546 individuals, prescribing doxycycline post-exposure prophylaxis could have averted 71% of STI diagnoses; among individuals living with HIV and those on HIV PrEP, 60% of STI diagnoses could have been averted (57).

## Antimicrobial resistance

One concern repeatedly discussed in the literature is that widespread use of doxycycline as a prophylaxis could contribute to the increase of antimicrobial resistance (15–24, 35, 58). Antimicrobial resistance occurs when bacteria are exposed to antibiotics, and over time, develop the ability to withstand their effects (59). As a result, the antibiotics fail to kill the bacteria, allowing them to survive and continue growing (59). Overuse and misuse of antimicrobial agents contributes to rapid development of antimicrobial resistance (60). This makes infections harder to treat, increasing the risk of disease spread and leading to severe illness or death, even after routine medical procedures (e.g. surgery) (60). Antimicrobial resistance was identified as one of the top ten global public health threat by the World Health Organization in 2019 (60, 61).

Although antimicrobial resistance is not routinely studied in *Chlamydia trachomatis* or *Treponema pallidum* (19), there is no known resistance of these microorganisms to doxycycline (5, 62, 63). However, antimicrobial resistance to *Neisseria gonorrhoeae* is well-documented (64–66). As a result, treating gonorrhea is challenging (44); resistance to historically recommended first-line and/or second-line antimicrobials has already occurred (67). Indeed, antimicrobial resistance has seriously compromised the management and control of gonorrhea (64).

A report published by the Public Health Agency of Canada (PHAC) in 2024 states that *Neisseria gonorrhoeae* "…is considered a serious public health threat since it has been increasingly developing resistance to antimicrobial drugs recommended as treatment" (68), a notion supported by other Canadian research (69). In 2021, of the 3,439 *Neisseria gonorrhoeae* isolates that were received from laboratories across Canada and tested, 72.7% (n=2,501) were resistant to at least one antibiotic (70); this represents a nearly three-fold increase in resistant cultures from 2000 to 2021 (68). Additionally, data from the Enhanced Surveillance of Antimicrobial-Resistant Gonorrhea system (launched in 2013 by PHAC) shows that


13. Sokoll PR, Migliavaca CB, Doring S, Traub U, Stark K, Sardeli AV. Efficacy of postexposure prophylaxis with doxycycline (Doxy-PEP) in reducing sexually transmitted infections: A systematic review and meta-analysis. Sexually Transmitted Infections. 2024;03:03.

14. Szondy I, Meznerics FA, Lorincz K, Kemeny LV, Walter A, Mohammed AA, et al. Doxycycline prophylaxis for the prevention of sexually transmitted infections: A systematic review and meta-analysis of randomised controlled trials. International Journal of Infectious Diseases. 2024:107186.

15. Vanbaelen T, Manoharan-Basil SS, Kenyon C. 45 years of tetracycline post exposure prophylaxis for STIs and the risk of tetracycline resistance: A systematic review and meta-analysis. BMC Infectious Diseases. 2024;24(1):376.

16. Siguier M, Molina JM. Doxycycline prophylaxis for bacterial sexually transmitted infections: Promises and perils. ACS Infectious Diseases. 2018;4(5):660–3.

17. Whiley DM, Tickner JA, Kundu RL, Hogan TR, van Hal SJ, Lahra MM. Selection of *Neisseria gonorrhoeae* ceftriaxone resistance using doxycycline post-exposure prophylaxis. The Lancet Infectious Diseases. 2023;23(8):e268–e9.

in 2021, the burden of antimicrobial resistant gonorrhea was highest among men who have sex with men: 85.2% of cultures isolated from men who have sex with men were resistant to at least one tested antimicrobial (68). For heterosexual males, 73.5% of cultures were resistant, and for females, 66.7% of cultures were resistant (68). Increased tetracycline resistance in *Neisseria gonorrhoeae* isolates has also been observed in other high-income countries, most notably in isolates from men who have sex with men (71). Furthermore, regional differences to *Neisseria gonorrhoeae* resistance may vary: one study from the U.S. found that the lowest proportion of isolates with high-level resistance was from the East Coast and Southeastern U.S. (72).

Evidence regarding use of oral tetracyclines and antimicrobial resistance has been examined in systematic reviews (15, 73). A systematic review from 2022 found that oral tetracycline use for 2–18 weeks increased resistance in subgingival (i.e. under the gums), gastrointestinal, and upper respiratory tract flora (73). One 2024 systematic review found that post-exposure prophylaxis with tetracyclines (such as doxycycline and minocycline) was associated with selecting (i.e. creating an environment where only resistant bacteria would survive and grow) tetracycline resistance in *Neisseria gonorrhoeae* (15).

All six of the aforementioned randomized controlled trials presented in Table 1 discuss the impact of antimicrobial resistance to some extent (3–8). Other researchers have provided responses to these studies, published in the peer-reviewed literature (20, 21, 74, 75). Additionally, one publication suggests that the doxyPEP study (7) and the IPERGAY study (8) did not adequately assess the risk of promoting antimicrobial resistance, and asserts that no conclusion can be drawn on whether or not doxycycline post-exposure prophylaxis contributes to the spread of antimicrobial resistance (76).

Replying to results from the DOXYVAC trial (5), a correspondence in *The Lancet Infectious Diseases* re-evaluated the provided data on antimicrobial resistance and found a statistically significant increase in the proportion of participants with methicillin-resistant *Staphylococcus aureus* (MRSA) (74). The authors note that their re-evaluation of the DOXYVAC trial data is an "alternative" interpretation, suggesting that studies of post-exposure prophylaxis with doxycycline should consider population-level selection for antimicrobial resistance and this selection should be classified as hypothetical until it is confirmed or refuted by future studies (74).

Another correspondence suggested that estimating the number of doses of doxycycline administered for post-exposure prophylaxis could inform considerations for the risk of antimicrobial resistance (21). Using the enrollment criteria from the doxyPEP trial (7), it was estimated that 0.86 million Americans would be eligible for doxycycline post-exposure prophylaxis (21). If 75% of this group


18. Vanbaelen T, Manoharan-Basil SS, Kenyon C. Doxycycline postexposure prophylaxis could induce cross-resistance to other classes of antimicrobials in *Neisseria gonorrhoeae*: An in silico analysis. Sexually Transmitted Diseases. 2023;50(8):490–3.

19. Calcagno A, Tutone M, Del Re S, Delmonte S, Agosta D, Ghisetti V, et al. Doxycycline post-exposure prophylaxis and sexually transmitted infections in Italy, 2023. Clinical Infectious Diseases. 2024;24:24.

20. Kenyon C. The importance of not downplaying the risks that doxycycline postexpoure prophylaxis will select for antimicrobial resistance. Clinical Infectious Diseases. 2024;ciae139.

21. Roster KIO, Grad YH. Estimating changes in antibiotic consumption in the USA with the introduction of doxycycline post-exposure prophylaxis. The Lancet Microbe. 2024;5(1):e9.

22. Kong FYS, Kenyon C, Unemo M. Important considerations regarding the widespread use of doxycycline chemoprophylaxis against sexually transmitted infections. Journal of Antimicrobial Chemotherapy. 2023;78(7):1561–8.

began to take doxycycline post-exposure prophylaxis, monthly antibiotic consumption would increase to 2.52 million doses; if the entire eligible population began to take doxycycline post-exposure prophylaxis, this number would increase to 3.36 million doses per month (21). Authors encouraged the monitoring of changes in antibiotic consumption to better understand the effects of doxycycline post-exposure prophylaxis (21). Of note, others have suggested the importance of assessing antimicrobial consumption in different doxycycline post-exposure prophylaxis strategies (77). However, a recent review notes that a significant reduction in STI prevalence—especially among individuals who are at a greater risk for repeat infections—may lead to a much larger reduction on overall antibiotic consumption (35).

*Clinical Infectious Diseases* also published a correspondence suggesting that doxycycline post-exposure prophylaxis interventions could create an environment where only bacteria resistant to antimicrobial drugs would survive and grow, a process known as "selecting" for antimicrobial resistance (20). The response contends that a review article by Hazra *et al.* on doxycycline post-exposure prophylaxis (54) "downplay" two types of evidence: first, that doxycycline post-exposure prophylaxis selects for tetracycline resistance in *Neisseria gonorrhoeae* and second (20), that doxycycline post-exposure prophylaxis may lead to resistance in other classes of antimicrobials across broader bacterial species (20, 78).

Hazra *et al.* respond to this, summarizing the current state of affairs:

"*There is a need and demand for novel, effective STI prevention interventions. Uptake of doxy-PEP* [doxycycline post-exposure prophylaxis], *both with and without public health guidance, is occurring in real time. The threat of gonococcal* AMR [antimicrobial resistance] *cannot be understated. Both statements can be true and exist simultaneously.*" (33)

The impact of doxycycline prophylaxis on antimicrobial resistance continues to be explored, with studies examining how this intervention may impact antimicrobial resistance genes present in the gut microbiome (79), mathematical models evaluating the effect of the uptake of doxycycline post-exposure prophylaxis on gonorrhea prevalence and resistance (80), genetic linkages between resistance to tetracycline and other antimicrobials (81), and if resistance to doxycycline could be induced in *Treponema pallidum* (syphilis) in a laboratory setting (82).


23. Celum C, Cohen SE, Dombrowski JC, Cannon C, Luetkemeyer A. STD 50-year anniversary issue reflections on navigating the winding road from efficacy to implementation for HIV preexposure (PrEP) and doxycycline PEP (Doxy-PEP). Sexually Transmitted Diseases. 2024;51(9):597–8.

24. Mardh O, Plachouras D. Using doxycycline for prophylaxis of bacterial sexually transmitted infections: Considerations for the European Union and European Economic Area. Euro Surveillance: European Communicable Disease Bulletin. 2023;28(46):11.

25. Fusca L, Hull M, Ross P, Grennan T, Burchell AN, Bayoumi AM, et al. High Interest in syphilis pre-exposure and post-exposure prophylaxis among gay, bisexual and other men who have sex with men in Vancouver and Toronto. Sexually Transmitted Diseases. 2020;47(4):224–31.

26. Spinelli MA, Scott HM, Vittinghoff E, Liu AY, Coleman K, Buchbinder SP. High interest in doxycycline for sexually transmitted infection postexposure prophylaxis in a multicity survey of men who have sex with men using a social networking application. Sexually Transmitted Diseases. 2019;46(4):e32–e4.

27. Park JJ, Stafylis C, Pearce DD, Taylor J, Little SJ, Kojima N, et al. Interest, concerns, and attitudes among men who have sex with men and health care providers toward prophylactic use of doxycycline against chlamydia trachomatis infections and syphilis. Sexually Transmitted Diseases. 2021;48(9):615–9.

## Acceptability of doxycycline prophylaxis

Interest in doxycycline STI prophylaxis has been demonstrated in multiple studies published in the academic literature:

- One study among men who have sex with men recruited from sexually transmitted infection clinics in Vancouver and Toronto (n=424) found that 60.1% were willing to use doxycycline post-exposure prophylaxis to prevent future syphilis infections (25);
- A study among U.S. men who have sex with men using a gay social-networking app (n=1,301) found that 84% were interested in doxycycline post-exposure prophylaxis (26);
- An online cross-sectional survey in Southern California among men who have sex with men (n=212) found that 67.5% would take doxycycline pre-exposure/post-exposure prophylaxis to prevent chlamydia and syphilis infections if offered by their provider (27);
- A cross-sectional survey among individuals receiving HIV treatment or HIV PrEP at a Nebraska clinic (n=166; 83.1% male, 13.9% female, 1.2% transgender women, 1.8% non-binary) found that while most participants were unaware of doxycycline post-exposure prophylaxis (75.3%; n=125), about half (44.6%; n=74) said they would be "extremely likely" to take doxycycline prophylaxis if it were offered to them (83);
- Participants enrolled in the intervention arm of the doxyPEP study (n=44; 98% men who have sex with men and 2% transgender women) found it to be acceptable, easy to adhere to, and benefitting their quality of life and mental health (84);
- A qualitative study among men who have sex with men (n=24) in the U.S. found that participants were generally interested in doxycycline post-exposure prophylaxis; however, concerns about antibiotic resistance, side-effects, medication interactions, and stigma were raised (28);
- Another qualitative study among men who have sex with men at high risk of acquiring a bacterial STI (n=13) from Sydney, Australia, found that participants perceived several benefits to doxycycline pre-exposure prophylaxis which included reduced incidence of STIs and "peace of mind" (i.e. knowledge that a risk mitigation strategy was in place) (85).


28. Ehsan R, D'Angelo AB, Westmoreland DA, Grov C. Perceptions about doxycycline post-exposure prophylaxis (Doxy-PEP) as an STI-prevention strategy among gay and bisexual men (GBM) in the United States: Results from a qualitative study. Preventive Medicine. 2024;183:107977.
29. World Health Organization. Implementing the global health sector strategies on HIV, viral hepatitis and sexually transmitted infections, 2022-2030: Report on progress and gaps 2024. 2024. Available from: https://www.who.int/ publications/i/ item/9789240094925 Accessed October 16, 2024.
30. Chow EP, Grulich AE, Fairley CK. Epidemiology and prevention of sexually transmitted infections in men who have sex with men at risk of HIV. The Lancet HIV. 2019;6(6):e396–e405.
31. Cannon CA, McLaughlin SE, Ramchandani MS. On the horizon: Novel approaches to sexually transmitted infection prevention. Medical Clinics of North America. 2024;108(2):403–18.
32. Celum C, Luetkemeyer AF. Doxycycline for sexually transmitted infection prevention: Evolving evidence and implementation perspectives. Sexually Transmitted Diseases. 2021;48(9):620–1.

## Use of doxycycline prophylaxis and practice guidelines

An earlier Rapid Response (published in March 2023) on doxycycline prophylaxis for the prevention of bacterial STIs (86) identified four studies where men who have sex with men in high-income settings had self-prescribed doxycycline (87–90). Evidence continues to emerge that doxycycline is being used as prophylaxis among men who have sex with men in many jurisdictions, including the U.S. (91, 92), Germany (93, 94), Belgium (95), Italy (96), and Spain (97).

Though uptake of doxycycline to prevent STIs is apparent, guidelines for approved use vary across jurisdictions. Currently, Health Canada has not authorized doxycycline prophylaxis for preventative use of STIs (98). However, some Ontario healthcare providers, such as the Village Pharmacy in Toronto, are prescribing doxycycline post-exposure prophylaxis for STI prevention (i.e. "off-label" use) (99). Also, the British Columbia Centre for Excellence in HIV/AIDS (BC-CfE) provides doxycycline post-exposure prophylaxis for prevention of bacterial STIs (100) to eligible participants in BC-CfE's HIV PrEP Program and the HIV Treatment Program (101).

The British Association for Sexual Health and HIV (BASHH) & UK Health Security Agency (UKHSA) do not endorse doxycycline pre- or post-exposure prophylaxis for prevention of STIs (102). Similarly, the Belgian Research on AIDS and HIV Consortium (BREACH) does not recommend widespread use of doxycycline post-exposure prophylaxis as of November 2023 (103). The German STI Society (Deutsche STI-Gesellschaft, DSTIG) also does not recommend broad implementation of preventative doxycycline in sexually active individuals, but does approve use on a case-by-case basis according to outlined criteria (104). In June of 2024, the International Union Against Sexually Transmitted Infections (IUSTI) Europe Council acknowledged the benefit of doxycycline post-exposure prophylaxis in some settings and suggested that decisions to offer this intervention be taken in the context of local STI epidemiology and capacity of sexual health services, and not at the expense of already established STI and HIV controls such as access to testing, treatment, partner notification, and HIV PrEP (105).

The Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) released a consensus statement in April 2024 stating that there was broad consensus that doxycycline post-exposure prophylaxis should be considered primarily for the prevention of syphilis in gay, bisexual, and other men who have sex with men, with a secondary benefit of reductions in other bacterial STIs (106).

As of June 2024, the U.S. Centers for Disease Control and Prevention (CDC) recommends that men who have sex with men, as well as transgender women, who have had a bacterial STI (specifically syphilis, chlamydia, or gonorrhea) diagnosed in the past 12 months


33. Hazra A, Celum C, Luetkemeyer AF, Molina JM, Klausner JD. Reply to Kenyon: Risk of antimicrobial resistance with doxy-PEP is real, as is the need for its well-Informed implementation. Clinical Infectious Diseases. 2024;ciae152.

34. Mogaka FO, Stewart J, Omollo V, Bukusi E. Challenges and solutions to STI control in the era of HIV and STI prophylaxis. Current HIV/AIDS Reports. 2023;20(5):312–9.

35. Allan-Blitz L-T, Mayer KH. Doxycycline post-exposure prophylaxis for bacterial sexually transmitted infections: The current landscape and future directions. Current HIV/AIDS Reports. 2025;22(1):1–11.

36. Public Health Agency of Canada. Estimates of HIV incidence, prevalence and Canada's progress on meeting the 90-90-90 HIV targets, 2020. 2022. Available from: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/estimates-hiv-incidence-prevalence-canada-meeting-90-90-90-targets-2020/estimates-hiv-incidence-prevalence-canada-meeting-90-90-90-targets-2020.pdf Accessed October 23, 2024.

37. HIVinfo.NIH.gov. HIV and specific populations: HIV and gay and bisexual men. 2024. Available from: https://hivinfo.nih.gov/understanding-hiv/fact-sheets/hiv-and-gay-and-bisexual-men Accessed October 23, 2024.

should be offered a prescription for doxycycline post-exposure prophylaxis to be self-administered within 72 hours after having oral, vaginal, or anal sex (107). This follows guidelines from the San Francisco Department of Public Health, which began to recommend doxycycline post-exposure prophylaxis in October 2022 (9, 108). A recently published study examined if these adopted guidelines in San Francisco had a population-level impact on the number of bacterial STI cases within the city and county (9). Authors found an association between the newly implemented guidelines and decreases in the average number of monthly cases of male rectal chlamydia, male rectal gonorrhea, and adult male syphilis (9). Additionally, three conference abstracts from the 2024 Conference on Retroviruses and Opportunistic Infections cited reductions in bacterial STIs in real-life settings in San Francisco (10-12).

In the U.S., integration of doxycycline post-exposure prophylaxis for STI prevention is in its early stages; thus, there is limited evidence to guide healthcare providers on the operational details of this intervention (109). Furthermore, literature exploring issues related to equitable distribution of doxycycline prophylaxis for STIs is emerging. Some preliminary evidence in the U.S. found that having condomless anal intercourse and a recent STI diagnosis were associated with receiving a prescription for doxycycline post-exposure prophylaxis (110). Alternatively, another U.S. study found that socio-environmental factors, such as living in areas of lower sexual minority equality (e.g. the Southern U.S.), may limit the awareness and uptake of this approach to preventing STIs (111). Other research in the U.S. has found that providers who more frequently treat STIs are more likely to prescribe doxycycline as prophylaxis, believing that the benefits outweigh the risks for increased antimicrobial resistance (112).

Ethical issues regarding doxycycline prophylaxis—including uncertainty regarding long-term impacts due to a lack of follow-up data, antibiotic stewardship efforts, equitable availability to those disproportionately burdened by STIs, and meaningful stakeholder engagement to guide messaging and guideline development—should be identified and addressed as policies related to doxycycline post-exposure prophylaxis are being developed and implemented (113). Regarding equity of this intervention, one author states that "…equitable implementation of doxycycline postexposure prophylaxis will require evaluation of who is offered and initiates it, understanding patterns of use and longer term STI incidence and antimicrobial resistance, provider training, and tailored community education" (54).


38. Malekinejad M, Barker EK, Merai R, Lyles CM, Bernstein KT, Sipe TA, et al. Risk of HIV acquisition among men who have sex with men infected with bacterial sexually transmitted infections: A systematic review and meta-analysis. Sexually Transmitted Diseases. 2021;48(10):e138–e48.

39. Rebbapragada A, Kaul R. More than their sum in your parts: The mechanisms that underpin the mutually advantageous relationship between HIV and sexually transmitted infections. Drug Discovery Today: Disease Mechanisms. 2007;4(4):237–46.

40. Cohen MS, Council OD, Chen JS. Sexually transmitted infections and HIV in the era of antiretroviral treatment and prevention: The biologic basis for epidemiologic synergy. Journal of the International AIDS Society. 2019;22:e25355.

41. Ong JJ, Baggaley RC, Wi TE, Tucker JD, Fu H, Smith MK, et al. Global epidemiologic characteristics of sexually transmitted infections among individuals using preexposure prophylaxis for the prevention of HIV infection: A systematic review and meta-analysis. JAMA Network Open. 2019;2(12):e1917134-e.

42. National Institutes of Health: Medline Plus. Doxycycline. 2024. Available from: https://medlineplus.gov/druginfo/meds/a682063.html Accessed September 27, 2024.

## Factors That May Impact Local Applicability

The evidence presented in this review regarding doxycycline prophylaxis to prevent bacterial STIs is based on a limited number of published studies and real-world data, overwhelmingly focused on men who have sex with men. There is more published literature on doxycycline post-exposure prophylaxis compared to doxycycline pre-exposure prophylaxis. As discussed, there is a lack of long-term data on the outcomes of doxycycline prophylaxis paired with widespread concern regarding the potential for an increase in antimicrobial resistance. Furthermore, there is no global consensus regarding clinical practice guidelines on doxycycline prophylaxis of bacterial STIs.

## What We Did

We searched Medline (including Ovid MEDLINE and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations) using text terms (Doxycycline* and [prophyla* or prevention] and [STIs or STD* or sexually transmitted or chlamydia or gonorrhea or gonorrhoea or syphilis]) or (DoxyPEP* or DoxyPrEP*) or (Doxy-PEP* or Doxy-PrEP*) or ([post exposure prophylaxis adj3 doxycycline] or [postexposure prophylaxis adj3 doxycycline] or [preexposure prophylaxis adj doxycycline] or [preexposure prophylaxis adj 3 doxycycline]). Searches were conducted on September 3, 2024 and results limited to articles published in English. Reference lists of identified articles were also searched. Google (grey literature) searches using different combinations of these terms were also conducted. The searches yielded 364 references from which 113 were included.


43. Government of Canada. Chlamydia and LGV guide: Key information and resources. 2024. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/chlamydia-lgv.html#a1.4 Accessed October 1, 2024.

44. Van Ommen CE, Malleson S, Grennan T. A practical approach to the diagnosis and management of chlamydia and gonorrhea. Canadian Medical Association Journal. 2023;195(24):E844–E9.

45. Government of Canada. Syphilis guide: Treatment and follow-up. 2024. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/syphilis/treatment-follow-up.html#a2 Accessed October 1, 2024.

46. Government of Canada. Gonorrhea guide: Treatment and follow-up. 2022. Available from: https://www.canada.ca/en/public-health/services/infectious-diseases/sexual-health-sexually-transmitted-infections/canadian-guidelines/gonorrhea/treatment-follow-up.html#a1_23 Accessed October 1, 2024.

47. Smith K, Leyden JJ. Safety of doxycycline and minocycline: A systematic review. Clinical Therapeutics. 2005;27(9):1329–42.

48. Chan PA, Le Brazidec DL, Becasen JS, Martin H, Kapadia J, Reno H, et al. Safety of longer-term doxycycline use: A systematic review and meta-analysis with implications for bacterial sexually transmitted infection chemoprophylaxis. Sexually Transmitted Diseases. 2023;50(11):701–12.

49. National Academies of Sciences Engineering and Medicine. Assessment of long-term health effects of antimalarial drugs when used for prophylaxis. 2020. Available from: https://www.ncbi.nlm.nih.gov/books/NBK556591/pdf/Bookshelf_NBK556591.pdf Accessed October 1, 2024.

50. Swallow MA, Fan R, Cohen JM, Bunick CG. Antibiotic resistance risk with oral tetracycline treatment of acne vulgaris. Antibiotics. 2022;11(8):1032.

51. La Ruche G, Goubard A, Bercot B, Cambau E, Semaille C, Sednaoui P. Gonococcal infections and emergence of gonococcal decreased susceptibility to cephalosporins in France, 2001 to 2012. Eurosurveillance. 2014;19(34).

52. Unemo M, Cole MJ, Kodmon C, Day M, Jacobsson S. High tetracycline resistance percentages in *Neisseria gonorrhoeae* in Europe: Is doxycycline post-exposure prophylaxis unlikely to reduce the incident gonorrhoea cases? The Lancet Regional Health Europe. 2024;38:100871.

53. Kirby Institute. Impact of the daily doxycycline pre-exposure prophylaxis (PrEP) on the incidence of syphilis, gonorrhoea and chlamydia (Syphilaxis). 2023. Available from: https://clinicaltrials.gov/study/NCT03709459 Accessed October 15, 2024.

54. Hazra A, McNulty MC, Pyra M, Pagkas-Bather J, Gutierrez JI, Pickett J, et al. Filling in the gaps: Updates on doxycycline prophylaxis for bacterial sexually transmitted infections. Clinical Infectious Diseases. 2024;ciae062.

55. CIHR Pan-Canadian Network for HIV and STBBI Clinical Trials Research. CTN 329: Doxycycline intervention for bacterial STI ChemoprOphylaxis (DISCO). 2023. Available from: https://www.hivnet.ubc.ca/study/ctn-329-doxycycline-intervention-for-bacterial-sti-chemoprophylaxis-disco/ Accessed October 15, 2024.

56. Zhu J, Takeh BT, David J, Sang J, Moore DM, Hull M, et al. Impact of screening and doxycycline prevention on the syphilis epidemic among men who have sex with men in British Columbia: a mathematical modelling study. Lancet Regional Health Americas. 2024;33:100725.

57. Traeger MW, Mayer KH, Krakower DS, Gitin S, Jenness SM, Marcus JL. Potential impact of doxycycline post-exposure prophylaxis prescribing strategies on incidence of bacterial sexually transmitted infections. Clinical Infectious Diseases. 2023;18:18.

58. Phillips C, Vinuesa M, Fowler C, Soni S, Richardson D. Doxycycline postexposure prophylaxis (doxyPEP): Sexual health clinicians' knowledge and readiness. Sexually Transmitted Infections. 2024 Oct 29:sextrans-2024-056388.

59. Centers for Disease Control and Prevention. About antimicrobial resistance. 2024. Available from: https://www.cdc.gov/antimicrobial-resistance/about/index.html Accessed October 23, 2024.

60. EClinicalMedicine. Antimicrobial resistance: A top ten global public health threat. EClinicalMedicine. 2021;41(101221).

61. World Health Organization. Top ten threats to global health in 2019. 2019. Available from: https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019 Accessed October 24, 2024.

62. Sandoz KM, Rockey DD. Antibiotic resistance in Chlamydiae. Future Microbiology. 2010;5(9):1427–42.

63. Sanchez A, Mayslich C, Malet I, Grange PA, Janier M, Saule J, et al. Surveillance of antibiotic resistance genes in *Treponema pallidum* subspecies pallidum from patients with early syphilis in France. Acta Dermato-Venereologica. 2020;100(14).

64. Wi T, Lahra MM, Ndowa F, Bala M, Dillon J-AR, Ramon-Pardo P, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for international collaborative action. PLoS Medicine. 2017;14(7):e1002344.

65. Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: Past, evolution, and future. Clinical Microbiology Reviews. 2014;27(3):587–613.

66. Unemo M, Seifert HS, Hook III EW, Hawkes S, Ndowa F, Dillon J-AR. Gonorrhoea. Nature Reviews: Disease Primers. 2019;5(1).

67. Broom A, Peterie M, Ridge D, Lafferty L, Kenny K, Broom J, et al. Sex, drugs and superbugs: the rise of drug resistant STIs. SSM-Qualitative Research in Health. 2023;4:100310.

68. Public Health Agency of Canada. Report on the Enhanced Surveillance of Antimicrobial Resistant Gonorrhea (ESAG): Results from 2018 to 2021. 2024. Available from: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/enhanced-surveillance-antimicrobial-resistant-gonorrhea-esag-2018-2021/esag-report-results-from-2018-to-2021.pdf Accessed October 23, 2024.

69. Thorington R, Sawatzky P, Lefebvre B, Diggle M, Hoang L, Patel S, et al. Antimicrobial susceptibilities of *Neisseria gonorrhoeae* in Canada, 2020. Canada Communicable Disease Report. 2022;48(11/12):571–9.

70. Sawatzky P, Lefebvre B, Diggle M, Hoang L, Wong J, Patel S, et al. Antimicrobial susceptibilities of *Neisseria gonorrhoeae* in Canada, 2021. Canada Communicable Disease Report. 2023;49(9):388.

71. Pitt-Kendall R, Sun S, Hughes S, Merrick R, Donaldson H, Rayment M, et al. Investigating the cause of increased tetracycline-resistant *Neisseria gonorrhoeae* in England, 2016–20. Journal of Antimicrobial Chemotherapy. 2024;79(5):1060–8.

72. Mortimer TD, Grad YH. A genomic perspective on the near-term impact of doxycycline post-exposure prophylaxis on *Neisseria gonorrhoeae* antimicrobial resistance. Clinical Infectious Diseases. 2023;77(5):788–91.

73. Truong R, Tang V, Grennan T, Tan DHS. A systematic review of the impacts of oral tetracycline class antibiotics on antimicrobial resistance in normal human flora. JAC-Antimicrobial Resistance. 2022;4(1):dlac009.

74. Vanbaelen T, Manoharan-Basil SS, Kenyon C. Studies of post-exposure prophylaxis with doxycycline should consider population-level selection for antimicrobial resistance. The Lancet Infectious Diseases. 2024;21:21.

75. Chiu YJ, Tsai CY. Postexposure doxycycline for sexually transmitted infections: To the editor. New England Journal of Medicine. 2023;389(3):286.

76. Vanbaelen T, Manoharan-Basil SS, Kenyon C. Four recent insights suggest the need for more refined methods to assess the resistogenicity of doxycycline post exposure prophylaxis. Current Research in Microbial Sciences. 2024;6:100234.

77. Vanbaelen T, Tsoumanis A, Kenyon C. Total antimicrobial consumption in doxycycline postexposure prophyalxis cohorts and the intensity of screening for bacterially sexually transmitted infections. Clinical Infectious Diseases. 2024;78(3):803–5.

78. Gestels Z, Manoharan-Basil SS, Kenyon C. Doxycycline post exposure prophylaxis could select for cross-resistance to other antimicrobials in various pathogens: An in silico analysis. International Journal of STD & AIDS. 2023;34(13):962–8.

79. Chu VT, Glascock A, Donnell D, Grabow C, Brown CE, Ward R, et al. Impact of doxycycline post-exposure prophylaxis for sexually transmitted infections on the gut microbiome and antimicrobial resistome. Nature Medicine. 2024:1–11.

80. Reichert E, Grad YH. Effects of doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections on gonorrhoea prevalence and antimicrobial resistance among men who have sex with men in the USA: A modelling study. The Lancet Microbe. 2024.

81. Kenyon C. Doxycycline post-exposure prophylaxis could theoretically select for resistance to various antimicrobials in 19 pathobionts: An in silico analysis. International Journal of Infectious Diseases. 2024;142:106974.

82. Tantalo LC, Luetkemeyer A, Lieberman NAP, Nunley BE, Avendano C, Greninger AL, et al. In vitro exposure of *Treponema pallidum* to sub-bactericidal doxycycline did not induce resistance: Implications for doxy-PEP and syphilis. Journal of Infectious Diseases. 2024;jiae381.

83. Havens JP, Singh N, Lyden E, Bares SH. Doxycycline as post-exposure prophylaxis: Awareness, beliefs, and interest among patients with and at risk for HIV. AIDS and Behavior. 2024:1–10.

84. Fredericksen RJ, Perkins R, Brown CE, Cannon C, Lopez C, Cohee A, et al. Doxycycline as postsexual exposure prophylaxis: Use, acceptability, and associated sexual health behaviors among a multi-site sample of clinical trial participants. AIDS Patient Care & STDs. 2024;38(4):155–67.

85. Horn R, Callander D, Haire B. Perceptions of sexually transmissible infection pre-exposure prophylaxis: A qualitative study of high-risk gay and bisexual men in Sydney, New South Wales. Sexual Health. 2020;17(2):129–34.

86. Rapid Response Service. Doxycycline prophylaxis for the prevention of bacterial sexually transmitted infections (STIs). Toronto, ON: The Ontario HIV Treatment Network; March 2023. Available from: https://www.ohtn.on.ca/wp-content/uploads/2023/03/RR175-Doxycycline-prophylaxis-for-bacterial-STIs.pdf Accessed November 4, 2024.

87. Evers YJ, van Liere G, Dukers-Muijrers N, Hoebe C. Use of doxycycline and other antibiotics to prevent STIs among men who have sex with men visiting sexual health clinics in the Netherlands. Sexually Transmitted Infections. 2020;96(7):550–1.

88. Carveth-Johnson T, Stingone C, Nwokolo N, Whitlock G. Doxycycline use in MSM taking PrEP. The Lancet HIV. 2018;5(9):e482.

89. O'Halloran C, Croxford S, Mohammed H, Gill ON, Hughes G, Fifer H, et al. Factors associated with reporting antibiotic use as STI prophylaxis among HIV PrEP users: Findings from a cross-sectional online community survey, May–July 2019, UK. Sexually Transmitted Infections. 2021;97(6):429–33.

90. Kohli M, Reid D, Pulford CV, Howarth A, Brown J, Mohammed H, et al. Choice of antibiotics for prophylaxis of bacterial STIs among individuals currently self-sourcing. Sexually Transmitted Infections. 2022;98(2):158.

91. Chan PA, Malyuta Y, Parent H, Tao J, Erbe M, Salhaney P, et al. Early adopters of doxycycline as post-exposure prophylaxis to prevent bacterial sexually transmitted infections in a real-world clinical setting. Sexually Transmitted Infections. 2024;100(6):339–42.

92. Traeger MW, Krakower DS, Mayer KH, Jenness SM, Marcus JL. Use of doxycycline and other antibiotics as bacterial sexually transmitted infection prophylaxis in a U.S. sample of primarily gay and bisexual men. Sexually Transmitted Diseases. 2024;08:08.

93. Wagner L, Boesecke C, Baumgarten A, Scholten S, Schellberg S, Hoffmann C, et al. Is doxycycline post-exposure prophylaxis being utilised in Germany? Insights from an online survey among German men who have sex with men. Infection. 2024;23:23.

94. Hornuss D, Mathe P, Usadel S, Zimmermann S, Muller M, Rieg S. Already current practice? A snapshot survey on doxycycline use for prevention of sexually transmitted infections in parts of the German MSM community. Infection. 2023;51(6):1831-4.

95. Vanbaelen T, Rotsaert A, De Baetselier I, Platteau T, Hensen B, Reyniers T, et al. Doxycycline post-exposure prophylaxis among men who have sex with men and transgender women in Belgium: Awareness, use and antimicrobial resistance concerns in a cross-sectional online survey. Sexually Transmitted Infections. 2024 Aug 29:sextrans-2024-056261.

96. Raccagni AR, Bruzzesi E, Castagna A, Nozza S. Doxycycline postexposure prophylaxis may delay seroconversion in incident syphilis. Sexually Transmitted Infections. 2024;100(6):397.

97. Sergio VB, Ruben M, Luis V. A practice already in use: A snapshot survey on the use of doxycycline as a preventive strategy (Doxy-PEP and Doxy-PrEP) in the GBMSM population in Spain. Infection. 2024;25:25.

98. AIDS Committee of Toronto. Doxy-PEP (and Doxy-PrEP). 2024. Available from: https://www.actoronto.org/health-information/doxy-pep-and-doxy-prep/ Accessed October 29, 2024.

99. The Village Pharmacy. DoxyPEP to prevent STIs. 2024. Available from: https://www.thevillagepharmacy.ca/news/doxypep Accessed October 29, 2024.

100. British Columbia Centre for Excellence. Doxycycline for bacterial sexually transmitted infection prevention. 2023. Available from: https://bccfe.ca/wp-content/uploads/2023/12/doxycycline_pt_info_bsti-p_2023-11-30-v2_final.pdf Accessed November 21, 2024.

101. British Columbia Centre for Excellence. Doxycycline for bacterial sexually transmitted infection (B-STI) prevention. 2024. Available from: https://bccfe.ca/doxycycline-for-bacterial-sexually-transmitted-infection-b-sti-prevention/ Accessed October 29, 2024.

102. Kohli M, Medland N, Fifer H, Saunders J. BASHH updated position statement on doxycycline as prophylaxis for sexually transmitted infections. Sexually Transmitted Infections. 2022;98(3):235–6.

103. De Scheerder MA, Libois A, van Praet J, C K. Doxy post-exposure prophylaxis for STI not endorsed by BREACH. 2023. Available from: https://breach-hiv.be/wp-content/uploads/2024/03/DoxyPEP-Breach-statement-AL.pdf Accessed September 19, 2024.

104. Werner RN, Schmidt AJ, Potthoff A, Spornraft-Ragaller P, Brockmeyer NH. Position statement of the German STI Society on the prophylactic use of doxycycline to prevent STIs (Doxy-PEP, Doxy-PrEP). Journal der Deutschen Dermatologischen Gesellschaft. 2024;22(3):466-78.

105. Sherrard J, Gokengin D, Winter A, Marks M, Unemo M, Jensen JS, et al. IUSTI Europe position statement on use of DoxyPEP: June 2024. International Journal of STD & AIDS. 2024:9564624241273801.

106. Cornelisse VJ, Riley B, Medland NA. Australian consensus statement on doxycycline post-exposure prophylaxis (doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual and other men who have sex with men. Medical Journal of Australia. 2024;220(7):381–6.

107. Bachmann LH, Barbee LA, Chan P, Reno H, Workowski KA, Hoover K, et al. CDC clinical guidelines on the use of doxycycline postexposure prophylaxis for bacterial sexually transmitted infection prevention, United States, 2024. Morbidity & Mortality Weekly Report Recommendations & Reports. 2024;73(2):1–8.

108. Doxy-PEP prescribing guide for San Francisco providers. Updated September 2024. Available from: https://www.sfcityclinic.org/sites/default/files/2024-09/Doxy-PEP_Provider_rev9.10.24.pdf Accessed November 5, 2024.

109. Dombrowski JC, Donnell D, Grabow C, Cohen SE, Cannon CA, Brown CE, et al. Evidence-informed provision of doxycycline post-exposure prophylaxis for prevention of bacterial sexually transmitted infections. Clinical Infectious Diseases. 2024:ciae527.

110. Ogunbajo A, Henry C, Barney A, Anderson T, Brown J, Hickson D. Predictors of receiving a doxycycline postexposure prophylaxis (Doxy-PEP) prescription for the prevention of bacterial sexually transmitted infections (STIs) in a community-based clinic: A case-control study. Sexually Transmitted Infections. 2024.

111. Samuel KD, Ellis MS, Buttram ME. The impact of socio-environmental factors on doxycycline post-exposure prophylaxis awareness in the US: A cross-sectional study. Sexual Health. 2024;21.

112. Pearson WS, Emerson B, Hogben M, Barbee L. Use of doxycycline to prevent sexually transmitted infections according to provider characteristics. Emerging Infectious Diseases. 2024;30(1):197-9.

113. Sugarman J, Taylor HA, Bachmann LH, Barbee LA, Cahill S, Celum C, et al. Ethical considerations in implementing doxycycline postexposure prophylaxis for the prevention of bacterial sexually transmitted infections. Sexually Transmitted Diseases. 2024;51(3):135–8.