

# Doxycycline prophylaxis for the prevention of bacterial sexually transmitted infections (STIs)

## 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

- Five studies from high-income settings have examined doxycycline as bacterial STI prophylaxis among men who have sex with men: two have been published in the peer-reviewed literature (1, 2), and three have been included in conference abstracts (3–5).
- While results from these five studies show that doxycycline appears to reduce the incidence of bacterial STIs (chlamydia, gonorrhea, syphilis), investigators (1–5) and the broader scientific community (6–9) have also voiced concerns regarding the potential for antimicrobial resistance.
- Three other trials examining the efficacy of doxycycline as STI prophylaxis are currently underway: two in Canada (10, 11), and one in Australia (12).
- There appears to be a general interest in using STI prophylaxis among men who have sex with men (13–16).
- Limited data from a few small studies indicate that about 2–10% of men who have sex with men are self-prescribing doxycycline for STI prophylaxis (17–20).

## Rapid Response: Evidence into Action

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## The Issue and Why it's Important

In Canada, bacterial STIs are a significant public health concern as incidence rates have risen markedly since 2010 (21). Between 2010 and 2019, the number of reported cases of chlamydia, syphilis, and gonorrhoea all increased, by 33.1%, 393.1%, and 181.7%, respectively (21). One study from 2022 that examined trends and differences in STIs globally found that between 2010 and 2019, North America had the greatest increase in age-standardized incidence rates for chlamydia and gonorrhoea (22).

The incidence of STIs are of particular concern for men who have sex with men, as men who have sex with men with a bacterial STI are at greater risk for acquiring HIV: the risk is two times greater for chlamydia, and as much as four times greater for syphilis and gonorrhoea (23). One systematic review found that men who have sex with men on HIV pre-exposure prophylaxis (PrEP) who engage in higher-risk sexual behaviours, such as condomless sex with casual partners, have a high incidence of various STIs (24). Another systematic review found that the global estimate of syphilis was disproportionately high among men who have sex with men (7.5%) compared to men in the general population (0.5%) (25).

The need for new and effective approaches to curb the increasing trend in STI incidence has been advocated for in the academic literature (26–30). One biomedical approach currently being investigated as a novel prevention strategy for bacterial STIs is the use of doxycycline prophylaxis (28, 31–34). Doxycycline is in a class of antibiotic medications called tetracyclines, and works by preventing the spread and growth of bacteria (35, 36). It can be administered orally, is inexpensive, is available worldwide, and is generally well-tolerated (33, 36). A 2005 systematic review found that the most common adverse events associated with doxycycline were gastrointestinal, but noted that the incidence of any adverse events was low (37). In Canada and the U.S., doxycycline is recommended as first-line treatment for chlamydia (38, 39), and in Canada, is listed as an alternative treatment for syphilis if an individual is allergic to penicillin (40).

A 2011 study by Wilson *et al.* used mathematical modelling to estimate the impact STI PrEP would have on syphilis among gay men in Australia (41). The model was calibrated to match the estimated infectious syphilis diagnoses among gay men in the state of Victoria (41). Authors found that STI PrEP could potentially have a substantial impact: 70% effectiveness among 50% of gay men would result in a 49% reduction in the total number of syphilis cases within 12 months; a 77% reduction would be expected within five years, and an 85% reduction after ten years (41). However, a second modelling study in Philadelphia suggested that doxycycline prophylaxis among sexual minority men would have only a modest impact on syphilis incidence when assuming an uptake scenario of 20% with an adherence level of 80% (42).

## References

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The overarching concern regarding use of doxycycline prophylaxis is that widespread use could contribute to increases in antimicrobial resistance (7, 8, 28, 43). Antimicrobial resistance occurs when bacteria are exposed to antibiotics, and over time, develop the ability to defeat the antibiotic effect; thus, the bacteria are not destroyed and continue to grow (44). A 2022 systematic review using data from small prospective studies found that oral tetracyclines taken for 2–18 weeks may increase antimicrobial resistance in normal human flora (45). Authors advise that more research regarding antimicrobial resistance needs be done before doxycycline prophylaxis is widely adopted as a prevention strategy against STIs (45).

This review primarily examines the current evidence of doxycycline prophylaxis for bacterial STIs. This is followed by a short discussion presenting data on the acceptability of STI prophylaxis as well as current use of STI prophylaxis among men who have sex with men.

## What We Found

### Studies demonstrating effectiveness of doxycycline prophylaxis

Recent reviews include studies that have examined the efficacy of using doxycycline pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP).

A 2022 scoping review by Tran *et al.* examined “non-conventional” interventions to prevent gonorrhea or syphilis among men who have sex with men (46). Authors focused on interventions “...that [did] not traditionally focus on increasing condom use and/or testing” (46). Authors identified two randomized controlled trials that demonstrated doxycycline may be an effective biomedical intervention to prevent gonorrhea and syphilis among men who have sex with men: Bolan *et al.* (2015) and Molina *et al.* (2018) (46).

The two aforementioned randomized controlled trials were also included in a 2020 review by Grant *et al.*, which examined the current state of research on doxycycline prophylaxis by meeting with international academic and government experts and conducting a literature review (32). In addition to the randomized controlled trials by Bolan *et al.* (2015) and Molina *et al.* (2018), Grant *et al.* (2020) included six other studies: one is the modelling study previously discussed by Wilson *et al.* (2011) (41), and the remaining five are based on real-world data (32):

- The Dual Daily HIV and Syphilis PrEP (DuDHS) trial in Canada (4);
- The Daily Doxycycline in HIV+ for Syphilis PrEP (DaDHS) trial in Canada (11);

6. Cohen J. Antibiotic after sex could help curb infections. *Science*. 2022;377(6605):459.
7. Venkatesan P. Doxycycline PEP for prevention of STIs. *The Lancet Infectious Diseases*. 2022;22(11):1545.
8. Lewis D. Use of antibiotics to avoid sexual diseases raises concerns. *Nature*. 2022;612:20–1.
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10. CIHR Canadian Trials Network. CTN 329: Doxycycline Intervention for bacterial STI Chemoprophylaxis (DISCO). 2022. Available from: <https://www.hivnet.ubc.ca/study/ctn-329-doxycycline-intervention-for-bacterial-sti-chemoprophylaxis-disco/> Accessed January 11, 2023.
11. CIHR Canadian Trials Network. CTN 313: The DaDHS Trial. Not dated. Available from: <https://www.hivnet.ubc.ca/study/ctn-313-the-dadhs-trial/> Accessed February 21, 2023.

- The Syphilaxis Study in Australia (12);
- The DoxyPEP trial in the U.S. (3);
- The ARNS Previnir PrEP study in France (5).

We identified one other study that is currently underway in Canada: the Doxycycline Intervention for bacterial STI Chemoprophylaxis (DISCO) (10, 47).

Thus, we have identified eight studies in total that examine the efficacy of doxycycline. These studies use real-world data, and results have either been published in a peer-reviewed journal (1, 2), presented as a conference abstract (3–5) or are currently underway (10–12). All eight of these studies are discussed in detail below.

#### Bolan et al. (2015)

When it was published in 2015, the Bolan et al. study was described as a novel approach to STI prevention that reflected “creative thinking” (48). Based in Los Angeles, Bolan et al. (2015) enrolled 30 men who have sex with men living with HIV who had contracted syphilis at least twice since having been diagnosed with HIV (2). Participants were randomized into one of two groups: 100 mg of doxycycline prophylaxis taken once daily for 36 weeks, or an incentive-based contingency management arm where participants would be financially compensated for remaining STI-free (2). Participants were told that condoms should be consistently used, as the investigators did not know if doxycycline would prevent syphilis (2).

At baseline and at 12-, 24-, and 36-week intervals, all participants were clinically evaluated for gonorrhea, chlamydia, and syphilis, and completed a behavioural risk questionnaire to assess number of partners, condom use, and drug use (2). For participants in the doxycycline arm, adherence was also measured at 12-, 24-, and 36-week intervals, defined as a blood concentration of at least 1000 ng/mL (2). While authors state that “...there is no established doxycycline concentration level known to prevent syphilis” (2), they do cite a 2009 study which found that the steady-state concentration of doxycycline was 1000–4000 ng/mL based on a daily dose of 100 mg (2, 49). Drug levels were not measured for participants in the contingency management arm due to cost constraints; authors considered this a limitation, as doxycycline is a commonly-prescribed antibiotic for a variety of other conditions, and suggest that individuals in the non-drug arm may have been prescribed doxycycline for other indications (2).

After 36 weeks, doxycycline prescriptions and financial incentives concluded, though participants were followed to 48 weeks to determine if there were any subclinical cases of syphilis that had not been prevented by doxycycline (2). At 48-weeks follow-up,

- Center Watch: The Trusted Source for Clinical Trials Information. Impact of the daily doxycycline pre-exposure prophylaxis (PrEP) on the incidence of syphilis, gonorrhoea, and chlamydia (Syphilaxis). 2022. Available from: <https://www.centerwatch.com/clinical-trials/listings/237904/impact-of-the-daily-doxycycline-pre-exposure-prophylaxis-prep-on-the-incidence-of-syphilis-gonorrhoea-and-chlamydia/> Accessed February 23, 2023.
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- 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.
- 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.

participants in the doxycycline arm were significantly less likely to test positive for gonorrhoea, chlamydia, or syphilis when compared to individuals in the contingency management arm (2). Additionally, authors found no significant differences in self-reported risk behaviours between the two groups (2). In terms of adverse events, one participant in the doxycycline arm reported gastroesophageal reflux (2). Authors concluded that further study with a much larger sample size was necessary to determine if their findings were reproducible (2).

### Molina et al. (2018)

The Conference on Retroviruses and Opportunistic Infections (CROI) 2017 featured an abstract (50) and presentation (51) from a prospective randomized open-label study that had noteworthy results: on-demand PEP with doxycycline reduced the incidence of syphilis and chlamydia among high-risk men who have sex with men (50, 51). While these findings were considered to be a highlight of the conference (52), they prompted some public health authorities—namely Public Health England (now the UK Health Security Agency [UKHSA]) and the British Association for Sexual Health & HIV (BASHH)—to a issue position statement that did not support the use of doxycycline PEP for STIs (53). Of note, as of May 2022, the UKHSA and BASHH published an updated position statement, stating that it “...remains the case that doxycycline taken as PEP or pre-exposure prophylaxis (PrEP) for STIs is not endorsed by BASHH or UKHSA” (43). A briefing published by HIV Prevention England in November of 2022 continues to support this position, noting that “there are currently no clinical guidelines for using antibiotics in this way” and that it is not recommended yet “mainly due to major concerns about the development of antimicrobial resistance” (54).

Full results from the Molina *et al.* (2018) trial were published in December 2017 in *The Lancet Infectious Diseases* (1). Molina *et al.* (2018) sought to determine if doxycycline PEP could reduce the incidence of bacterial STIs among men who have sex with men (1); this was a sub-study of the ARNS IPERGAY trial, which investigated the efficacy of on-demand PrEP for HIV prevention among men who have sex with men (55). Between July 2015 and January 2016, participants (n=232) from the ARNS IPERGAY trial in France were randomly assigned to take a single oral dose of 200 mg doxycycline PEP 24–72 hours after unprotected anal intercourse or oral sex (n=116), or no PEP (n=116) (1). Follow-up occurred every two months until June 2016; prior to each follow-up, all participants reported on sociodemographic characteristics, sexual behaviour, and recreational drug use via computer-assisted structured interview (1). For the doxycycline PEP group, follow-up appointments included dispensation of doxycycline, pill count to measure adherence, and adherence counselling (1). At baseline and at follow-up visits, all participants had a physical examination of the skin, throat, and anogenital area, and were tested for syphilis, chlamydia, and gonorrhoea (1).

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The study endpoint was the first or new occurrence of a bacterial STI during the ten-month follow-up (1). At baseline, the PEP and non-PEP groups both had a median of ten partners in the past two months, as well as a median of ten acts of sexual intercourse in the past four weeks (1). During follow-up, 73 participants presented with a new STI: 28 in the PEP group, and 45 in the no-PEP group (1). At nine months, the cumulative probability of a new STI in the PEP group was 22% (95% CI 15–32) compared to 42% (95% CI 33–53;  $p=0.007$ ) in the no-PEP group (1). The first presence of an STI in participants taking PEP was lower compared to those not taking PEP; investigators observed an overall 47% relative reduction in the incidence of acquiring a new bacterial STI among participants on doxycycline PEP (hazard ratio [HR] 0.53; 95% CI 0.33–0.85;  $p=0.008$ ) (1). Results were similar for the first occurrence of syphilis and chlamydia: participants taking PEP had a lower occurrence of a first episode compared to the no-PEP group (1). However, the occurrence of a first episode of gonorrhoea did not differ significantly between the PEP and no-PEP groups (1). Gastrointestinal adverse events were reported more commonly in the PEP group compared to the no-PEP group (1). Authors advised their results be interpreted with caution, suggesting that doxycycline PEP “...could be considered a short-term strategy included in a comprehensive prevention package for high-risk individuals with a high incidence of STIs, to be phased out once other preventive measures are in place” (1).

The authors also discuss the high prevalence of tetracycline resistance to strains of *Neisseria gonorrhoeae* in France (1, 56) and note that because of this, they expected the benefit of doxycycline PEP to vary between STIs (1). Furthermore, a commentary published in the same issue of *The Lancet* briefly outlines the benefits and drawbacks of the findings of the Molina *et al.* (2018) study, raising concerns related to the “inevitable increased resistance” to *Neisseria gonorrhoeae* if doxycycline use increases (57). However, the commentary does note that “selective introduction” of doxycycline PEP could reduce the reproductive rate for syphilis in men who have sex with men, which may cause syphilis rates in this population to decrease (57).

### The Dual Daily HIV and Syphilis PrEP (DuDHS) trial

At the 29th annual Canadian Conference on HIV/AIDS Research (CAHR) in 2020, an oral abstract detailed preliminary results of the DuDHS study, a randomized controlled trial which sought to assess the feasibility of combining PrEP for HIV and PrEP for syphilis among men who have sex with men (4, 58). Situated in Vancouver, participants who had a syphilis infection in the 36 months prior were recruited between May 2018 and June 2019 (58, 59). Most participants had a history of multiple STI diagnoses, and not having a main sex partner was common (59). Participants ( $n=52$ ) were randomized 1:1 to an immediate treatment arm ( $n=26$ ; daily emtricitabine/tenofovir + 100 mg doxycycline for weeks 1–48) or to a deferred treatment arm ( $n=26$ ; daily emtricitabine/tenofovir for

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weeks 1–24; daily emtricitabine/tenofovir + 100 mg doxycycline for weeks 25–48) (4, 58).

Analysis was conducted following the first 24 weeks of follow-up, when the deferred treatment arm had not yet received doxycycline (4, 58). During the first 24 weeks of follow-up, participants attended four visits and were assessed for adverse events, STIs, adherence (e.g. pill counts and doxycycline levels), antimicrobial resistance, substance use, depression, and sexual behaviours (4). Outcomes included incidence of recurrent syphilis infection, incidence of gonorrhoea or chlamydia infection, and the proportion of individuals reporting adverse events (4). During the first 24 weeks, there were four STIs in the immediate treatment arm equating to an incidence rate of 34.9 cases per 100 person-years (95% CI 13.1–93.0) and 17 STIs in the deferred treatment arm equating to an incidence rate of 159.7 cases per 100 person-years (95% CI 99.3–257.9) (4). There were no cases of syphilis or chlamydia in the immediate treatment arm; in the deferred treatment arm, there was one case of syphilis (8.7 per 100 person-years; 95% CI 1.2–62.0) and nine cases of chlamydia (78.7 per 100 person-years; 95% CI 40.9–151.2) (4). Individuals in both treatment arms contracted gonorrhoea; four in the immediate treatment arm (34.9 per 100 person-years; 95% CI 13.1–93.0) and seven in the deferred treatment arm (62.0 per 100 person-years; 95% CI 29.6–130.1) (4). As of February 2023, investigators are in the process of submitting the study for publication (60).

### The DoxyPEP trial

Investigations into the efficacy of doxycycline PrEP/PEP continue. At the 24th International AIDS Conference in 2022, findings from the DoxyPEP trial were shared (3, 61). DoxyPEP is a randomized, open-label trial among men who have sex with men and transgender women living in Seattle and San Francisco (61). Inclusion criteria included diagnosis with chlamydia, gonorrhoea, or syphilis at least once in the past year, and having condomless anal intercourse with at least one male partner in the past year (3). It is also worth highlighting that unlike the Molina *et al.* (2018) study, the DoxyPEP trial included a cohort of individuals on PrEP for HIV **and** a cohort of individuals living with HIV (61). Participants were randomized 2:1 to receive 200 mg doxycycline within 72 hours of condomless anal intercourse (n=374) or no doxycycline (n=180) (61). Individuals were followed for 12 months; testing for STIs occurred at baseline, once every three months, and when symptomatic (61). Adherence to doxycycline was self-reported (3). The primary endpoint for the study was an occurrence of one bacterial STI during a follow-up quarter (3).

In May 2022 at the scheduled interim study analysis, the Data Safety Monitoring Board advised that enrollment be halted due to evidence of significant effectiveness, and that all participants assigned to the standard of care arm be offered doxycycline PEP (3). Results presented at the aforementioned 2022 conference by

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principal investigator Dr. A. Luetkemeyer were based on individuals enrolled up to May 2022 who had at least one quarter of follow-up to contribute (3). This included 327 individuals on HIV PrEP and 174 individuals living with HIV, for a total of 501 participants (3). Baseline characteristics were similar in both groups; for example, the median number of sexual partners in the past three months was 9 in the HIV PrEP cohort and 8.5 in the living with HIV cohort (3).

In the **HIV PrEP cohort**, there was a 31.9% incidence of new STIs in the standard of care arm and a 10.7% incidence of new STIs in the doxycycline PEP arm; the risk of acquiring an STI was reduced by 66% among individuals taking doxycycline PEP (risk ratio [RR] 0.34; 95% CI 0.24–0.46;  $p < 0.0001$ ) (3). In the **cohort of individuals living with HIV**, there was a 30.5% incidence of new STIs in the standard of care arm and an 11.8% incidence of new STIs in the doxycycline PEP arm; the risk of acquiring an STI was reduced by 62% among individuals taking doxycycline PEP (RR 0.38; 95% CI 0.24–0.60;  $p < 0.0001$ ) (3). Thus, the relative risk reduction of acquiring a bacterial STI was similar in both cohorts of participants taking doxycycline PEP (i.e. 66% in the HIV PrEP cohort; 62% in the cohort of individuals living with HIV) (3). Overall, investigators observed that the risk of acquiring an STI was reduced by 65% among all participants taking doxycycline PEP per quarter (RR 0.35; 95% CI 0.27–0.46;  $p < 0.0001$ ) (3).

Gonorrhea was the most commonly diagnosed STI among participants, followed by chlamydia, then syphilis (3). Most STIs were asymptomatic, though it was noted that STIs were less symptomatic in the doxycycline PEP arm when compared to STIs in the standard of care arm (3). The relative risk reduction for each type of STI for participants on doxycycline PEP was similar in the HIV PrEP cohort and in the cohort of individuals living with HIV, as presented in Table 1 (3). There was a statistically significant reduction of each bacterial STI per quarter, with the exception of syphilis in the cohort of individuals living with HIV (3).

The substantial reduction in gonorrhea among individuals in the doxycycline PEP arm is a finding considerably different from what Molina *et al.* (2018) observed, which was that there was no change in the occurrence of a new episode of gonorrhea with doxycycline PEP (1, 3). Luetkemeyer *et al.* (2022) suggests that this may be due to the differences in population-level gonorrhea resistance (3): the prevalence of tetracycline resistance to gonorrhea is about 20% in the U.S. (3, 62–64), but in France, it is substantially higher (3, 56, 65): the proportion of gonorrhea isolates (i.e. collected samples from the population) resistant to tetracycline was 56% in 2014, and 64% in 2016 (65). At CROI 2023, additional data from the DoxyPEP study was presented by Luetkemeyer, who found no marked increase in doxycycline resistance against gonorrhea (66).

In the DoxyPEP trial, doxycycline was found to be safe and acceptable: there were no serious adverse events, and only a small proportion of

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**Table 1: Relative risk reduction of STI incidence in each cohort assigned to the doxycycline PEP arm (3)**

STI	Doxycycline PEP arm	
	HIV PrEP cohort	Cohort of individuals living with HIV
Gonorrhea	Relative risk reduction: 55% (RR 0.45*; CI 95% 0.32-0.65; p<0.0001)	Relative risk reduction: 57% (RR 0.43*; CI 95% 0.26-0.71; p=0.001)
Chlamydia	Relative risk reduction: 88% (RR 0.12*; CI 95% 0.05-0.25; p<0.0001)	Relative risk reduction: 74% (RR 0.26*; CI 95% 0.12-0.57; p=0.0007)
Syphilis	Relative risk reduction: 87% (RR 0.13*; CI 95% 0.03-0.59; p=0.0084)	Relative risk reduction: 77% (RR 0.23; CI 95% 0.04-1.29; p=0.095)

\* indicates statistical significance

participants (1.5%) discontinued doxycycline due to intolerance or preference (3). Additionally, 88% reported that doxycycline PEP was acceptable or very acceptable (3).

The U.S. Centers for Disease Control and Prevention (CDC) published an immediate response to the presentation of these data at the conference, noting that “[f]urther review of the data presented, and potentially additional analyses, will be needed to develop clinical guidance on the safe and effective use of this strategy for bacterial STI prevention among gay and bisexual men and transgender women” (67). However, in October of 2022, the San Francisco Department of Public Health in California recommended that doxycycline be used as post-exposure prophylaxis for cis-men and transgender women who: “1) have had a bacterial STI in the past year and 2) report condomless anal or oral sexual contact with ≥ 1 cis male or trans female partner in the past year” (68). Additionally, the recommendations suggest that patients with a history of syphilis infection be prioritized for doxycycline PEP (68). The San Francisco Department of Public Health was one of the first U.S. health departments to make a recommendation regarding doxycycline as PEP for high-risk individuals (8).

38. Government of Canada. Chlamydia and LGV 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/chlamydia-lgv/treatment-follow-up.html> Accessed March 2, 2023.
39. Centers for Disease Control and Prevention. Summary of CDC STI treatment guidelines, 2021. 2021. Available from: <https://www.cdc.gov/std/treatment-guidelines/wall-chart.pdf> Accessed March 2, 2023.
40. Government of Canada. Syphilis 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/syphilis/treatment-follow-up.html> Accessed March 2, 2023.
41. Wilson DP, Prestage GP, Gray RT, Hoare A, McCann P, Down I, et al. Chemoprophylaxis is likely to be acceptable and could mitigate syphilis epidemics among populations of gay men. *Sexually Transmitted Diseases*. 2011;573-9.
42. Tran NK, Goldstein ND, Welles SL. Countering the rise of syphilis: A role for doxycycline post-exposure prophylaxis? *International Journal of STD & AIDS*. 2022;33(1):18-30.

Additionally, in the months following the conference, academic journals such as *The Lancet*, *Science*, and *Nature* featured articles highlighting the promising nature of these results, but also noting concerns surrounding antibiotic resistance (6–8).

[ARNS 174 DOXYVAC trial \(cited as ARNS Prevenir PrEP study in Grant et al. \[2020\]\)](#)

Taking place in February 2023, CROI included findings from another study conducted by Molina *et al.* (2018) regarding the use of doxycycline as PEP (69).

In the ARNS 174 DOXYVAC trial, investigators randomly assigned 546 HIV-negative men who have sex with men on HIV PrEP to one of four groups (5):

- 200 mg doxycycline PEP (n=332)
- No doxycycline PEP (n=170)
- Two shots of the meningococcal B vaccine (n=257)
- No shots of the meningococcal B vaccine (n=245)

Participant characteristics across all treatment groups were balanced (5). The final analysis included 502 participants, with a median follow-up time of nine months (5).

Participants taking 200 mg of doxycycline PEP had 13 new episodes of chlamydia or syphilis compared to 49 new episodes in the no doxycycline PEP arm, equating to an incidence rate of 5.6 vs 35.4 per 100 person-years (0.16;  $p < 0.0001$ ), respectively (5). For gonorrhea, incidences rates were 41.3 per 100 person-years (0.49;  $p = 0.001$ ) in the no doxycycline PEP arm, compared to an incidence rate of 20.5 per 100 person-years in the 200 mg doxycycline PEP arm (5). Thus, taking 200 mg of doxycycline PEP substantially reduced the incidence of chlamydia and syphilis, and had an impact on the incidence of gonorrhea (5).

Additionally, it is worth noting that two doses of the meningococcal B vaccine reduced the incidence of a new episode of gonorrhea by nearly 50% (5).

An interim position statement on doxycycline PEP was released by the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) in March 2023 (9). ASHM noted the promising nature of the results from both the Doxy-PEP and DOXYVAC studies, but highlighted “significant unknowns” regarding unintended consequences, such as disruption to an individual’s microbiome and the potential for community-level antimicrobial resistance (9). ASHM intends to explore the potential issues associated to doxycycline prophylaxis (9). Specifically, ASHM has stated that in 2023, they

43. 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.
44. Centers for Disease Control and Prevention. About antimicrobial resistance. 2022. Available from: <https://www.cdc.gov/drugresistance/about.html> Accessed March 3, 2022.
45. 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. *Journal of Antimicrobial Chemotherapy*. 2022;4(1):dlac009.
46. Tran J, Fairley CK, Bowesman H, Aung ET, Ong JJ, Chow EPF. Non-conventional interventions to prevent gonorrhea or syphilis among men who have sex with men: A scoping review. *Frontiers in Medicine*. 2022;9:952476.
47. Mohammed S, Hull M, Burchell AN, Edward J, Singer J, Wong J, et al. Doxycycline as an intervention for bacterial Sexually transmitted infection ChemOprophylaxis (DISCO) study: Design of a national, multicentre randomized-controlled trial. 2022. Available from: <https://www.cahr-acrv.ca/wp-content/uploads/2022/06/CAHR-2022-Abstract-Book.pdf> Accessed January 11, 2023.

will “...convene a forum of community representatives, clinicians, and experts in infectious diseases, public health, epidemiology, and antimicrobial resistance, to thoroughly review relevant data, exchange expertise, and aim to develop clear guidance for the community and clinicians on the utility and potential risks of Doxy-PEP, and to identify relevant research priorities” (9).

### The Daily Doxycycline in HIV+ for Syphilis PrEP (DaDHS) trial

The purpose of the DaDHS trial is to examine doxycycline PrEP among men who have sex with men living with HIV who have a history of syphilis infection (32). In this double-blind randomized controlled trial, participants were recruited from clinical sites in Toronto and Vancouver (11), and randomized 1:1 to receive either 100 mg daily doxycycline or placebo (32). Currently, this study has 34 participants at the Vancouver site, and 18 at the Toronto site; according to the Vancouver study coordinator, this study is about one year away from completion (70).

### The Syphilaxis Study

The Syphilaxis Study, currently underway in Australia, is examining the efficacy of doxycycline PrEP in reducing the incidence of chlamydia, gonorrhoea, and syphilis among men who have sex with men (12). In this single arm, non-randomized trial, before-and-after comparisons will be made with unenrolled men who have sex with men with matching risk profiles (32). Participants are eligible for the study if they are living with HIV or are on HIV PrEP, and have been diagnosed with syphilis in the past 12 months, or any STI in the last 12 months and syphilis in the last 24 months (32). The study endpoints are a diagnosis of chlamydia, gonorrhoea, or syphilis; additionally, authors will conduct a microbiome sub-study on antimicrobial resistance among 100 participants (32). As of April 2022, the study was recruiting participants and had an estimated end date of December 2024 (12).

### Doxycycline Intervention for bacterial STI Chemoprophylaxis (DISCO)

At CAHR 2022, an abstract detailed the design of a national, multicentre randomized controlled trial to assess the efficacy, safety, acceptability, and antimicrobial resistance of doxycycline in preventing bacterial STIs (47). The study is a prospective, open-label, three-arm randomized controlled trial that will enroll 447 sexually active men who have sex with men and transgender women who had an STI in the past year (47). Participants will be recruited from clinical sites across Canada: Vancouver, Calgary, Montreal, Toronto, Ottawa, and Hamilton (10, 47). Participants will be randomized to one of three study arms:

48. Golden MR, Handsfield HH. Preexposure prophylaxis to prevent bacterial sexually transmitted infections in men who have sex with men. *Sexually Transmitted Diseases*. 2015;42(2):104–6.
49. Binh VQ, Chinh NT, Thanh NX, Cuong BT, Quang NN, Dai B, et al. Sex affects the steady-state pharmacokinetics of primaquine but not doxycycline in healthy subjects. *The American Journal of Tropical Medicine and Hygiene*. 2009;81(5):747–53.
50. Molina J, Charreau I, Chidiac C, Pialoux G, Cua E, Delaugerre C, et al., editors. 91B On demand post exposure prophylaxis with doxycycline for MSM enrolled in a PrEP trial. [Abstract]. Conference on Retroviruses and Opportunistic Infections: Seattle, Washington; 2017. Available from: <https://user-degqumh.cld.bz/CROI-2017-Abstract-e-Book/38/> Accessed February 10, 2023.
51. Molina J. On demand post exposure prophylaxis with doxycycline for MSM enrolled in a PrEP trial. [Presentation]. Conference on Retroviruses and Opportunistic Infections: Seattle, Washington; 2017. Available from: <http://www.croiwebcasts.org/console/player/33431?mediaType=slideVideo&> Accessed February 10, 2023.
52. Crowell TA, Lyall H, Malatinkova E, Bhagani S, Hsu D, Colby DJ, et al. Highlights from the 24th Conference on Retroviruses and Opportunistic Infections. *Journal of Virus Eradication*. 2017;3(2):101–8.

- 100 mg daily doxycycline PrEP (10, 47);
- 200 mg doxycycline PEP 24–72 hours after an at-risk sexual encounter, up to a weekly maximum of 600 mg (10, 47);
- Standard-of-care (47), which includes routine STI screening and care (i.e. sexual health and STI education, condoms, risk reduction counselling, and comprehensive STI testing) (10).

The primary study outcome is incident STIs over the study period; secondary outcomes will include medication adherence, tetracycline resistance in gonorrhoea, antimicrobial resistance, adverse events, and changes in sexual risk behaviour (47). Participants will attend study visits at baseline and quarterly, up to week 60 (10, 47). Authors note that this will be the first study to do a “head-to-head” comparison of STI PrEP and PEP, and hypothesize that doxycycline as PrEP and PEP will be an acceptable, well-tolerated intervention with minimal impact on antimicrobial resistance (47).

## Attitudes and acceptability of doxycycline prophylaxis

In addition to developing a model that simulated the impact of chemoprophylaxis for syphilis among men who have sex with men, Wilson *et al.* (2011) also sought to determine if chemoprophylaxis for syphilis was acceptable among men who have sex with men in Australia (41). Use of doxycycline specifically was not mentioned in discussions with participants (41). Using an online survey, authors assessed the likelihood that participants would take pills everyday **to reduce their own chance of acquiring a syphilis infection** (41). Of the 2,095 participants, 52.7% responded that they would be likely to do so; 26.3% responded to this question with “very likely” (41). Participants were also asked if they would be willing to take pills everyday **to reduce infections in the gay community as a whole**; 75.8% said they would be likely to do so, including 48.6% who would be “very likely” to do so (41). Twenty-three individuals participated in focus group discussions; these men were generally enthusiastic about using a prophylactic to reduce syphilis infections, though long-term chemoprophylaxis was a less attractive option (41). Among the focus group participants living with HIV, some were enthused about taking an additional pill to avoid syphilis infection, as it was seen as an easy modification to their current regimen (41). Other participants living with HIV did not wish to add to their existing regimen due to concerns regarding drug interactions; others had a cautious attitude about taking a drug for a condition that had yet to affect them (41).

One study from Vancouver, conducted from 2016–2017, used in-depth interviews to explore syphilis-related knowledge and attitudes surrounding biomedical prevention strategies (71). Use of doxycycline specifically was not mentioned in discussions with

- Public Health England, British Association for Sexual Health and HIV. Position statement on doxycycline as post exposure prophylaxis for sexually transmitted infections. 2017. Available from: [https://www.bashhguidelines.org/media/1156/doxy\\_pep\\_statement\\_v5\\_phe\\_bashh.pdf](https://www.bashhguidelines.org/media/1156/doxy_pep_statement_v5_phe_bashh.pdf) Accessed January 11, 2023.
- HIV Prevention England. Using antibiotics to prevent STIs. 2022. Available from: [https://www.hivpreventionengland.org.uk/wp-content/uploads/2022/11/HPE-Using-antibiotics-to-prevent-STIs-v1\\_FINAL.pdf](https://www.hivpreventionengland.org.uk/wp-content/uploads/2022/11/HPE-Using-antibiotics-to-prevent-STIs-v1_FINAL.pdf) Accessed February 28, 2023.
- Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, Charreau I, *et al.* On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *New England Journal of Medicine*. 2015;373:2237–46.
- 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).
- Fairley CK, Chow EP. Doxycycline post-exposure prophylaxis: Let the debate begin. *The Lancet Infectious Diseases*. 2018;18(3):233–4.

participants (71). Twenty-five men who have sex with men living with HIV and/or with a history of syphilis were interviewed; while PrEP for syphilis was appealing, some individuals raised concerns about cost, side effects, and antibiotic resistance (71).

More recently published studies have also examined attitudes and acceptability of doxycycline PrEP/PEP specifically.

Spinelli *et al.* (2018) conducted an anonymous online survey of individuals using a gay social networking app in six U.S. cities to measure reported interest in doxycycline PEP (13). Of the individuals who completed the survey (n=1,301), 84% (n=1,093) were interested in trying doxycycline for prevention of STIs (13). In the second round of the survey, completed by 480 participants, 86% (n=413) were willing to participate in a doxycycline PEP study where there was a 50% chance of receiving a placebo (13).

Fusca *et al.* (2020) assessed whether or not doxycycline PrEP and PEP for syphilis was acceptable among a sample of men who have sex with men visiting STI clinics in Vancouver and Toronto (14). Of the 424 participants, 44.1% (n=187) were willing to use syphilis PrEP and 60.1% (n=255) were willing to use syphilis PEP; however, 36.6% (n=155) were unwilling to use either (14).

Horn *et al.* (2020) conducted in-depth semi-structured interviews with 13 gay and bisexual men in Sydney, Australia to investigate perceived risks, benefits, and preferred dosing strategies of doxycycline PrEP (16). Investigators found that PrEP for STIs was largely conceptualized by pre-existing knowledge of HIV PrEP (16). Perceived benefits—which included a reduced incidence of STIs and “peace of mind”—were seen to outweigh potential risks, which included side effects, antibiotic resistance, and stigmatization of consumers (16). Participants preferred a daily dosing regimen compared to using an on-demand strategy (16).

Park *et al.* (2021) examined acceptability of doxycycline PrEP/PEP among men who have sex with men and healthcare providers in Southern California via an online survey (15). Among the men who have sex with men, 67.5% (n=143/212) indicated that they would take doxycycline PrEP/PEP if offered by their provider; additionally, authors found that higher acceptability was associated with recent diagnosis of an STI and current use of HIV PrEP (15). Among healthcare providers, 89.5% (n=68/76) were willing to prescribe doxycycline PrEP/PEP if it was recommended by the CDC (15). Furthermore, both groups expressed “high levels of concern” regarding possible drug resistance (15).

58. Tattersall TL, Mohammed S, Edward J, Ablona A, Hull M, Grennan T. Preliminary results of the Dual Daily HIV and Syphilis Pre-exposure Prophylaxis (DuDHS) trial. 2022. Available from: <https://www.cahr-acrv.ca/wp-content/uploads/2020/04/CAHR-2020-Abstract-book.pdf> Accessed January 11, 2023.
59. Tattersall TL, Edward J, Mohammed M, Gupta A, Ablona A, Hull M, et al. The Dual Daily HIV and Syphilis Pre-Exposure Prophylaxis (DuDHS) Trial: Characteristics of Men who have sex with men interested in combined HIV and syphilis PrEP. 2020. Available from: <https://www.cahr-acrv.ca/wp-content/uploads/2020/04/CAHR-2020-Abstract-book.pdf> Accessed January 11, 2023.
60. Grennan, T. Inquiry re: DuDHS. Personal communication. [Email]. February 21, 2023.
61. Luetkemeyer A, Dombrowski J, Cohen S, Donnell D, Grabow C, Brown C, et al. Doxycycline post-exposure prophylaxis for STI prevention among MSM and transgender women on HIV PrEP or living with HIV: High efficacy to reduce incident STIs in a randomized trial. 2022. Available from: <https://programme.aids2022.org/Abstract/Abstract/?abstractid=13231> Accessed January 11, 2023.

## Self-prescribing

As previously discussed, doxycycline PrEP/PEP has been endorsed by some public health agencies, such as the San Francisco

Department of Health (68), but not by others, such as the CDC (67) and BASHH and the UKHSA (43). It does not appear that the Public Health Agency of Canada has issued a statement regarding doxycycline for STI PrEP/PEP.

Regardless of the position statements that have been issued, there is some evidence that individuals are already using doxycycline as PrEP (17–20).

In July 2018, 56 Dean Street, a sexual health clinic in London, UK, surveyed men who have sex with men attending the clinic for HIV PrEP monitoring (20). A paper questionnaire asked individuals if, since taking PrEP, they had taken antibiotics to prevent an STI (20). If the answer was affirmative, further questions were asked: which antibiotics they were taking, how frequently they were taking them, and where they sourced them from (20). Of the 592 men attending the clinic for follow-up, 107 were offered the questionnaire; eight individuals (8%) had taken antibiotics to prevent STIs (20). Five reported using doxycycline, one doxycycline and amoxicillin, and two did not state which antibiotic they used (20). Antibiotics were obtained from sexual health clinics, general practitioners, and from the internet (20).

The online PrEP User Survey in the UK (May–July 2019) targeted men who have sex with men who either reported HIV PrEP use, or tried to obtain HIV PrEP, since January 2017 (18). Only users of HIV PrEP were asked if they had used STI prophylaxis (defined as buying antibiotics), obtained privately or through the internet (18). Of the 1,856 HIV PrEP users, 9% (n=167) reported use of STI prophylaxis; this was significantly associated with  $\geq 5$  condomless sex partners in the past six months, chemsex drug use, and an STI diagnosis in the past 12 months (18).

Another online survey in the UK (November–December 2020) among men who have sex with men, carried out within the Reducing Inequalities and Improving Sexual Health (RiiSH-COVID) study, included questions on STI prophylaxis (19). Of the respondents who completed the questions on STI prophylaxis (n=1,520), 20% (n=308) had heard of STI prophylaxis, 3.6% (n=55) had ever used STI prophylaxis, and 1.8% (n=28) had used STI prophylaxis in the past 12 months (19). Of those who reported use (n=55), 56% (n=31) reported using doxycycline, 18% (n=10) azithromycin, 20% (n=11) amoxicillin, 4% (n=2) metronidazole, and 16% (n=9) were unsure (19).

A research letter submitted to Sexually Transmitted Infections estimated use of STI prophylaxis among men who have sex with men in the Netherlands, where doxycycline is not currently prescribed

62. Kirkcaldy RD, Harvey A, Papp JR, Del Rio C, Soge OO, Holmes KK, et al. *Neisseria gonorrhoeae* antimicrobial susceptibility surveillance—The gonococcal isolate surveillance project, 27 sites, United States, 2014. *Morbidity and Mortality Weekly Report: Surveillance Summaries*. 2016;65(7):1–19.
63. Centers for Disease Control and Prevention. *Gonococcal Isolate Surveillance Project (GISP)*. 2022. *Neisseria gonorrhoeae: Prevalence of tetracycline, penicillin, or ciprofloxacin resistance or elevated cefixime, ceftriaxone, or azithromycin minimum inhibitory concentrations (MICS), by year, 2000–2020*. 2022. Available from: <https://www.cdc.gov/std/gisp/> Accessed February 16, 2023.
64. Centers for Disease Control and Prevention. *Drug resistant neisseria gonorrhoeae*. 2019. Available from: <https://www.cdc.gov/drugresistance/pdf/threats-report/gonorrhea-508.pdf> Accessed February 16, 2023.
65. Ngangro NN, Viriot D, Fournet N, Pioche C, De Barbeyrac B, Goubard A, et al. Bacterial sexually transmitted infections in France: Recent trends and patients' characteristics in 2016. *Eurosurveillance*. 2019;24(5):1800038.
66. HIV.gov. *Doxy-PEP for STIs and more: Dr. Dieffenbach's highlights from day 1 of CROI 2023*. 2023. Available from: <https://www.hiv.gov/blog/doxy-peg-for-stis-and-more-dr-dieffenbachs-highlights-from-day-1-of-croi-2023> Accessed February 23, 2023.

for STI prophylaxis use (17). Recruited from STI clinics by staff during regular consultations, individuals were invited to participate in an online survey about behaviours such as chemsex, HIV PrEP use, and use of antibiotics for STI prophylaxis (17). Of the 785 individuals who were recruited, 321 completed the questionnaire (17). The median number of sex partners was six, 43.3% (n=139) reported chemsex, and 2.2% (n=7) reported antibiotic STI prophylaxis use (17). Of the men who reported antibiotic STI prophylaxis use, three men used azithromycin, two used doxycycline, one used ciprofloxacin, and one did not report specifically on what antibiotic was used (17).

## Factors That May Impact Local Applicability

The evidence presented in this review is based on a limited number of published studies investigating a biomedical intervention to prevent STI acquisition; while preliminary results are promising, there are concerns regarding antimicrobial resistance. Furthermore, there appear to be regional differences regarding population-level resistance to gonorrhoea that have resulted in different outcomes across studies (e.g. the DoxyPEP in the U.S. and the ARNS IPERGAY sub-study in France). Finally, no nationally governing health body currently endorses the use of antibiotics for STI prophylaxis.

## What We Did

We searched Medline (including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE®) using terms Doxycycline AND (prophylaxis or prevention) AND (STIs or STD\* or sexually transmitted or chlamydia or gonorrhoea or gonorrhoea or syphilis). Searches were conducted on January 6, 2023 and results limited to English articles published from 2015 to present. Reference lists of identified articles were also searched. Google (grey literature) searches using different combinations of these terms were also conducted. The searches yielded 235 references from which 71 were included.

67. Centers for Disease Control and Prevention. CDC response to Doxy-PEP data presented at 2022 International AIDS Conference. 2022. Available from: <https://www.cdc.gov/nchhstp/newsroom/2022/Doxy-PEP-clinical-data-presented-at-2022-AIDS-Conference.html> Accessed January 11, 2023.
68. San Francisco Department of Public Health. Health update: Doxycycline post-exposure prophylaxis reduces incidence of sexually transmitted infections. 2022. Available from: <https://www.sfdcp.org/wp-content/uploads/2022/10/Health-Update-Doxycycline-Post-Exposure-Prophylaxis-Reduces-Incidence-of-Sexually-Transmitted-Infections-SFDPH-FINAL-10.20.2022.pdf> Accessed January 11, 2023.
69. Molina JM, Bercot B, Assoumou L, Michele AG, Rubenstein E, Pialoux G, et al. ANRS 174 DOXYVAC: An open-label randomized trial to prevent STIs in MSM on PrEP. [Abstract]. Conference on Retroviruses and Opportunistic Infections: Seattle, Washington; 2023. Available from: <https://www.croiconference.org/abstract/anrs-174-doxyvac-an-open-label-randomized-trial-to-prevent-stis-in-msm-on-prep/> Accessed March 13, 2023.
70. Azmin, R. Inquiry re: DaDHS. Personal communication. [Email]. February 24, 2023.
71. Nath R, Grennan T, Parry R, Baharuddin F, Connell JP, Wong J, et al. Knowledge and attitudes of syphilis and syphilis pre-exposure prophylaxis (PrEP) among men who have sex with men in Vancouver, Canada: A qualitative study. *BMJ Open*. 2019;9(11):e031239.