The BCCDC Position Statement on Doxycycline as Prophylaxis for Sexually Transmitted Infections

December 15, 2023

Position statement

Recent clinical trials show that doxycycline post-exposure prophylaxis (doxyPEP) is efficacious in preventing certain sexually transmitted infections (STI) in gay, bisexual and other men who have sex with men (gbMSM) and transgender women (TGW) with a recent history of bacterial STI (i.e. in the previous year). Further, in many jurisdictions including here in BC, doxycycline is now being provided to some patients for STI prevention. Although there is strong evidence to support the use of doxyPEP to prevent STIs in these populations, it remains unclear what potential impacts this intervention will have at a broader scale, particularly around issues of antimicrobial resistance and impacts on the microbiome.

DoxyPEP has the potential to benefit the health of gbMSM/TGW through STI prevention and improved sexual health and well-being. The use of doxyPEP for STI prevention should be a discussion between patient and provider, covering all of the benefits and potential unknowns, using shared decision-making, and consulting with STI experts as necessary. Despite the unanswered questions, doxyPEP should not be withheld from gbMSM/TGW if it is expected to provide a clear benefit. All efforts should be made to make access to doxyPEP as timely and as easy as possible. At this time, there is no data supporting use of doxycycline for STI prevention in non-gbMSM/TGW populations, and no data in non-adult populations. More specifically, there is data from one study in cisgender women demonstrating no doxyPEP benefit, likely owing to poor adherence.

DoxyPEP should be implemented as part of comprehensive sexual health services, including regular (q3 month) STI screening, and HIV pre-exposure prophylaxis (PrEP)/HIV treatment when relevant. When prescribed as doxyPEP, doxycycline should be used as two, 100mg tablets taken within 72 hours after condomless sex, and a supply of 100 mg tablets (with refills) can be provided to eligible patients.

The BCCDC STI Team has expertise in this area, and is available for consultation around the use of doxycycline for STI prevention via the RACE line or by calling 604-707-5610.

Background

There is a growing epidemic of sexually transmitted infections (STIs) in Canada, where increases of 33%, 182% and 393% have been seen in the bacterial STIs chlamydia, gonorrhea, and syphilis, respectively, over the last decade[1]. In British Columbia and other parts of Canada, gay, bisexual, and other men who have sex with men (gbMSM) – including those living with HIV – are disproportionately impacted by bacterial STIs[2,3]. Further, these record-high rates are occurring alongside alarming increases in STI-related complications (e.g. neurosyphilis)[4,5,6], and increasing antimicrobial resistance (AMR) – particularly in gonorrhea – makes the prospect of untreatable gonococcal infection a real possibility[7]. Overall, these dramatic increases in bacterial STIs, the potential development of serious complications including AMR, and a decreased reliance on condoms as a sole prevention strategy signals the need for novel STI prevention strategies and tools to mitigate STIs and their sequelae.

To address this public health threat, several research groups, including the DISCO study in Canada led by Drs. Troy Grennan, Mark Hull, Ann Burchell and Darrell Tan, have investigated the use of doxycycline for STI prevention in those at highest risk, including gbMSM and transgender women (TGW). Currently, doxycycline is a recommended treatment for both chlamydia and syphilis; it is a first-line treatment for chlamydia (100mg twice daily x 7 days) and an alternate treatment option for syphilis (100mg twice daily x 14 or 28 days, for early/late infection). Two different approaches have been used with doxycycline: doxycycline as pre-exposure prophylaxis (doxyPrEP) and doxycycline as post-exposure prophylaxis (doxyPEP), In doxyPrEP, doxycycline 100mg is taken daily whereas in doxyPEP, doxycycline 200mg is taken within 72 hours of a sexual exposure. Clinical precedent exists for this type of biomedical prevention. Most notably, HIV PrEP remains standard of care for those at risk for HIV acquisition. As well, examples of doxycycline-based biomedical prevention abound, including as prophylaxis against leptospirosis and malaria.

To our knowledge, aside from some local US-based public health programs (e.g., San Francisco and Seattle/King County)[8,9], no other organization provides specific recommendations for the use of doxycycline as STI prophylaxis, though the US Centers for Disease Control and Prevention (CDC) will shortly be publishing guidelines on doxyPEP[10]. These guidelines base their recommendations for doxyPEP on the published studies presented below. Specifically, doxyPEP is recommended following a sexual encounter for sexually active gbMSM and TGW with a history of a bacterial STI in the previous year. Various other jurisdictions have published statements on the topic, though none explicitly endorse or recommend doxycycline[11,12,13]. The purpose of this statement is to provide healthcare providers with a summary of the evidence on this novel STI prevention intervention to allow for better, evidence-based decision making around doxycycline for STI prevention.

Clinical guidance on doxyPEP use

Based on the data from clinical trials (presented below), the following is a summary of information to guide clinicians on how to prescribe and manage doxyPEP.

1. **Intended population:** gbMSM and TGW with bacterial STI (i.e. chlamydia, gonorrhea, syphilis) in previous year.
2. Provide a prescription (with refills), with the instructions that 200mg of doxycycline (i.e. 2 x 100mg capsules) be taken within 72 hours of condomless sex. No more than one dose to be taken per day. Patients can be told the "3-2-1 rule": within 3 days of sex, 2 tablets, no more than 1 dose per day.
3. Doxycycline should be taken with a full cup of water, and patients should remain upright for at least 30 minutes following administration, to minimize gastrointestinal symptoms (e.g. reflux).
4. Clinical follow-up while on doxyPEP:
    a. Baseline and regular (e.g. quarterly) STI screening
    b. Management of STI contacts should generally be managed as per usual standard of care; if doxycycline is being used for treatment of chlamydia or syphilis contacts (which is provided at a dose/frequency of 100mg twice daily), doxyPEP is not necessary during the treatment period (7 or 14 days for chlamydia and syphilis, respectively).
    c. Assessment and mitigation of HIV risk if HIV-negative (i.e. provision of HIV PrEP)
    d. Counselling around potential side effects, dosing, and drug interactions
    e. Necessary monitoring during use (e.g. pregnancy, periodic routine bloodwork including complete blood count, renal and liver function tests).

Summary of studies: Efficacy

See **Table 1** for a summary of all completed studies on doxyPEP and doxyPrEP. Briefly, there are two studies on doxyPrEP and three studies on doxyPEP among gbMSM and TGW, all of which show a statistically significant reduction in all STIs. A fourth study on doxyPEP among cisgender women did not find a statistically significant difference in STI rates.

Trials on doxyPEP

The clinical trial data on doxyPEP use in gbMSM and TGW comes from three studies, with a total of 1279 participants (follow-up ranging from 9-12 months).

- The first published study on doxyPEP was a substudy of the IPERGAY HIV PrEP study, wherein 232 HIV-negative gbMSM on HIV PrEP in France were randomized 1:1 to doxyPEP (200mg of doxycycline within 72 hours of sex; maximum 600mg weekly), or no intervention[14]. The incidence of a first STI was halved in those randomized to receive doxycycline (hazard ratio [HR] 0.53; 95% CI 0.33 – 0.85), with key

reductions for syphilis (HR 0.27; 95% CI 0.07-0.98) and chlamydia (HR 0.30; 95% CI 0.13-0.70); there was no impact on gonorrhea.

- More recently, results from the US-based doxyPEP study were published[15]. This open-label trial randomized 501 gbMSM and TGW participants in Seattle and San Francisco in a 2:1 fashion to doxyPEP vs. no doxycycline (standard of care). The study population had a history of a bacterial STI (syphilis, chlamydia, or gonorrhea) in the last year, and was divided into two cohorts: those taking HIV PrEP, and persons living with HIV (PLWH). Though the doxyPEP dosing was the same as the above-cited French trial (i.e. 200mg within 72h of a sexual encounter), the maximum dose in this study was 200mg daily. In May 2022, an interim analysis of the enrolled participants resulted in early discontinuation of the study due to significant doxyPEP efficacy. The results demonstrated a significant reduction in all STIs for both the PrEP cohort (relative risk [RR] 0.34; 95%CI 0.24-0.46) and the PLWH cohort (RR 0.38; 95%CI, 0.24-0.60). Significant reductions in incidence were largely seen for all three evaluated STIs. In the PrEP cohort, the RR was 0.13 (95%CI, 0.03-0.59) for syphilis, 0.12 for chlamydia (95%CI, 0.05-0.25), and 0.45 (95%CI, 0.32-0.65) for gonorrhea. In the PLWH cohort, the RR was 0.23 (95%CI, 0.01-1.29) for syphilis, 0.26 for chlamydia (95%CI, 0.12-0.57), and 0.43 (95%CI, 0.26-0.71) for gonorrhea.

- Finally, the ANRS Doxyvac open-label trial in France randomized 546 gbMSM participants on HIV PrEP with STI in previous year in a 2 x 2 factorial, open-label RCT: participants were randomized 2:1 to doxyPEP and 1:1 to the multicomponent meningococcal vaccine (4CMenB; Bexsero®, included given some cross-protection against gonorrhea)[16]. This study was also prematurely discontinued for significant benefit in the doxyPEP arms, with an adjusted HR of 0.16 (95%CI, 0.08-0.30) for syphilis and chlamydia combined, and an adjusted HR of 0.49 (95%CI 0.32-0.76) in gonorrhea.

Thus far, there has only been one study done examining doxyPEP in cisgender women. The dPEP Kenya study enrolled 449 nonpregnant cisgender women, aged 18-30, in Kisumu, Kenya[17]. All participants were receiving HIV PrEP, and were randomized 1:1 to either doxyPEP, or standard of care (no doxycycline). Overall, there was no significant prevention benefit for overall STI prevention (RR 0.88; 95%CI, 0.60-1.29), nor was there any benefit seen individually for chlamydia or gonorrhea. Syphilis was not assessed since it occurs in very low rates in the region. The authors subsequently presented follow-up results, indicating that based on drug level measurements from hair samples, 44% of participants assigned to doxyPEP had no detectable drug, suggesting adherence as a cause for a lack of efficacy.

Trials on doxyPrEP

Thus far, there is minimal data available on doxyPrEP, making it premature to formulate recommendations or policy for this intervention. The clinical trial data on doxyPrEP in gbMSM and TGW comes from two pilot studies, with a combined total of 82 participants; another study in Vancouver is near-

completion, with an additional 52 participants. Currently, only one study has been published on doxyPrEP; another is currently being submitted for publication. The published study was a pilot randomized controlled trial (RCT) of doxyPrEP for STI prevention[18]. This study randomized 30 HIV-positive gbMSM in Los Angeles to receive doxycycline daily or a monetary incentive to remain STI-free. After 48 weeks, those on doxyPrEP were less likely to be diagnosed with any bacterial STI (odds ratio [OR]: 0.27; 95% confidence interval [CI]: 0.09-0.83). This study was not powered to evaluate efficacy in individual STIs. A second study (manuscript in progress) completed was the DuDHS study in Vancouver. This was an open-label, pilot RCT in 52 gbMSM and TGW concurrently using HIV PrEP who were randomized to receive either immediate daily doxyPrEP (i.e. 100mg daily for the full 48 weeks of the study), or deferred doxyPrEP beginning 24 weeks later (i.e. for the last 24 weeks of the study). Receipt of doxyPrEP was associated with a reduced likelihood of any bacterial STI (OR 0.18, 95% CI 0.05 - 0.68) during the first 24 weeks, and chlamydia infection (n=10) occurred only in the deferred arm during this time (rate 0 vs. 81.63/100 person-years, p = 0.001)[19].

Antimicrobial resistance and the human microbiome

Arguably, the greatest risks from doxycycline for STI prevention are its unknown impact on antimicrobial resistance (AMR) in both STI and non-STI organisms, and on the human microbiome. Specifically, the major concerns are around AMR in syphilis and chlamydia, as doxycycline is a mainstay of therapy in both of these infections[20]. AMR to doxycycline has never been reported for syphilis or chlamydia, nor is it generally considered likely to occur, based on the known mechanisms of AMR development[21,22]. As there are high rates of AMR in gonorrhea to doxycycline[23], it is not considered a reliable treatment for this infection[24]. Also important is an examination of AMR in colonizing or commensal organisms like *Staphylococcus aureus* (so-called 'off-target', or non-STI organisms), given the associations between colonization and subsequent clinical infections like surgical site infections and bacteremia[25]. A recently published systematic review examined the effect of chronic tetracycline (like doxycycline) use on AMR[26]. Overall, there were limited data, with some evidence of an increased burden of tetracycline resistance in subgingival, gastrointestinal and upper respiratory tract flora; however, persistent resistance was not seen. Though these data suggest an increased burden of AMR, data quality was poor. This signals the need to more comprehensively study the longer-term impact of doxycycline use on AMR.

One of the challenges with AMR assessments in STI is that the most established method to evaluate this is via culture. In gonorrhea, for instance, culture plate-based AMR determination can be performed with relative ease. Both syphilis and chlamydia are very difficult to culture[27], and though work is ongoing for molecular AMR determination in syphilis, molecular techniques for AMR determination in chlamydia are unreliable [28]. In the US-based doxyPEP study, at baseline, 4 of 15 (27%) *N. gonorrhoeae* isolates demonstrated tetracycline resistance[15]. This increased to 38% (5 of 13) of isolates after enrolment in the doxyPEP group, and 2 of 16

isolates (12%) in the standard of care group. In the Doxyvac study, though only 65 gonorrhea samples were sent for culture (15% of the PCR-positive samples), all isolates demonstrated resistance to tetracyclines. As indicated previously, the clinical implications of gonorrhea resistance to tetracyclines is less of a concern, as it is not a reliable agent for this infection.

Various doxycycline studies have also examined AMR in off-target, non-STI organisms. The US doxyPEP study assessed for AMR in *Staphylococcus aureus* in the anterior nares and oropharynx, and non-gonococcal *Neisseria* species in the pharynx, at baseline, six months, and 12 months. Overall, at 12 months, the doxyPEP group had lower carriage of *S. aureus*, but marginally higher rates of AMR to tetracyclines (5% vs. 4%), though this latter result was not statistically significant. For non-gonococcal *Neisseria*, the doxyPEP group had similar rates of carriage, but higher rates of resistance to doxycycline (69.7% vs 44.6%, p = 0.017)[29]. The DuDHS study evaluated *S. aureus* in the anterior nares and oropharynx as well, with overall low carriage numbers seen: nine in the immediate arm, and 12 in the deferred arm. Resistance to doxycycline was noted in five isolates in the immediate arm, versus one isolate in the deferred arm (p = 0.077). Though many of the studies discussed above have examined AMR in both STI and non-STI organisms, much of this data is not yet available.

Aside from AMR, the other primary antibiotic-related concern with long-term doxycycline use is its impact on the microbiome. The human microbiome refers to the collection of microorganisms (i.e. bacteria, viruses, and fungi) performing essential functions for immune development, defense against pathogens, and nutrient metabolism[30]. The gut microbiome impacts (and is impacted by) various health conditions, including asthma, obesity, inflammatory bowel disease, and allergies[31,32]. The tetracyclines appear to be a more 'microbiome-friendly' antibiotic class, evidenced by a lower risk of *C. difficile* compared to other antimicrobials[33]. Still, like most other antibiotics, perturbations in the microbiome from tetracycline use do occur[34,35]. Though none of the microbiome-related data from the doxycycline studies have been published, the DuDHS study showed no significant changes in the rectal microbiome as a result of doxycycline use (*personal communication, Dr. Adam Burgener*).

Unanswered questions

Despite the strong efficacy data, there remain some unresolved issues around doxycycline use for STI prevention, discussed below:

- **Antimicrobial resistance (AMR).** As outlined above, there remains a paucity of evidence on AMR in both STI and non-STI organisms. More data are forthcoming from completed studies. Reassuringly, despite decades of tetracycline use, no AMR to either syphilis or chlamydia has been reported, nor do experts think it is likely to occur[21,22]. Though AMR occurs at high rates to gonorrhea, this is less of a concern as doxycycline is not a relied-upon treatment for this infection.

- **Efficacy of doxyPEP in other populations**. Thus far, doxyPEP has demonstrated efficacy in adult gbMSM and TGW, with one study showing no benefit in cisgender women. Further, studies have not yet looked at other populations (e.g. other transgender/gender-diverse individuals, youth). As presented in the dPEP Kenya study, doxyPEP did not demonstrate efficacy in a clinic-based cohort of cisgender women, likely owing to adherence. More research is required in these populations, potentially with enhanced adherence interventions, with consideration for the use of alternate methods of doxycycline delivery (e.g. doxyPrEP). Additionally, the studies on both doxyPEP and doxyPrEP have focused exclusively on adult populations, with no mention of youth or adolescents. In the case of doxycycline, this may be in part fueled by the common misconception that tetracyclines are contraindicated in youth. As these groups often experience disproportionately high rates of bacterial STIs, and have historically been excluded from research in important areas of prevention (including HIV PrEP), it is key that these populations be included in future studies.

- **Efficacy of doxyPEP in gonorrhea.** Thus far, efficacy results from doxyPEP in gonorrhea have been conflicting; there was an effect seen in the US doxyPEP study, though tempered when compared to the effect in syphilis and chlamydia. In the IPERGAY substudy in France, no statistically significant effect was seen in gonorrhea. This is potentially explained by differences in baseline rates of tetracycline resistance in gonorrhea between the US and France, with AMR rates of roughly 30% vs. 60%, respectively[15]. In the French Doxyvac study, there was a statistically significant effect seen for gonorrhea, though again a dampened effect compared to syphilis and chlamydia[16]. This suggests that even in the context of high baseline resistance, there is likely still a preventative role for doxycycline to play in gonorrhea.

- **The efficacy of doxyPrEP**. As outlined above, very little data exists for doxyPrEP. Two studies, with a total of 82 participants, have been completed, compared to the 1279 participants (excluding the dPEP Kenya study) where doxyPEP has been shown efficacious. Further research is needed and the currently-enrolling Canada-based DISCO Study will examine the efficacy of doxyPrEP vs. doxyPEP in gbMSM and TGW[36].

- **The impact of doxycycline prophylaxis on the diagnostic testing of syphilis**. It is not yet known whether regular doxycycline use will impact the performance of syphilis serology in diagnosing new syphilis infections (e.g. could the presence of doxycycline – especially when taken intermittently – lead to delayed seroconversion or a dampened serologic response?). More longitudinal data is required

from studies to ascertain this issue, particularly as it relates to the potential impact this could have on serious outcomes (e.g. the development of neurosyphilis or late complications).

Table 1: Summary of studies on doxycycline prophylaxis

Author (Year)	Population	Study Design & Intervention[a]	Effect[b]	Safety & Tolerability
DoxyPrEP (100mg of doxycycline daily)				
Bolan (2015)	HIV+ gbMSM with prior syphilis (USA); n = 30	1:1 randomization to (1) doxyPrEP vs. (2) financial incentive; 48 weeks of follow-up	**OR 0.27** (95% CI, 00-9-0.83) for any STI	One participant stopped doxycycline due to GERD.
Grennan (2021); DuDHS Study	HIV- gbMSM/TGW with prior syphilis (Canada); n = 52	1:1 randomization to (1) HIV PrEP and doxyPrEP x 48 weeks vs. (2) HIV PrEP x 48 weeks and doxyPrEP x 24 weeks (deferred by 24 weeks).	**OR 0.26** (95% CI 0.08-0.85) for any STI	No doxycycline-related SAE or drug discontinuations.
DoxyPEP (200mg of doxycycline within 72 hours of sexual activity)				
Molina (2018); IPERGAY substudy	gbMSM on HIV PrEP (France); n = 232	1:1 randomization to (1) doxyPEP vs. (2) standard of care (no doxycycline); 10 months of follow-up (*maximum 600mg of doxycycline/wk*)	**HR 0.57** (95%CI 0.13-0.62) for all STI; **HR 0.53** (95%CI 0.33-0.85) for a first STI	No difference in SAE frequency between arms; eight participants stopped doxycycline due to AE.
Luetkemeyer (2023); DoxyPEP study	MSM and TGW on HIV PrEP or PLWH with STI in last year (USA); n = 501	2:1 randomization to (1) doxyPEP vs. (2) standard of care (no doxycycline) in two separate groups (on HIV PrEP, and PLWH); 12 months of follow-up (*maximum 200mg of doxycycline/day*)	**RR 0.34** (95%CI 0.24-0.46) and **RR 0.38** (95%CI 0.24-0.60) in the PrEP and PLWH groups, respectively.	No drug-related SAEs reported; 2% of participants on doxycycline discontinued due to AE or patient preference.

Author (Year)	Population	Study Design & Intervention[a]	Effect[b]	Safety & Tolerability
DoxyPrEP (100mg of doxycycline daily)				
Molina (2023); DoxyVAC Study	gbMSM with at least one STI in last year (France); n = 546	Factorial design; 2:1 randomization to (1) doxyPEP vs. (2) no doxycycline; and 1:1 randomization to either two does of menB vaccine (Bexsero) or no vaccine; 9 months of follow-up (*maximum 600mg of doxycycline/wk*)	**HR 0.16** (95%CI 0.08-0.30) for all STI	No drug-related SAEs reported; three participants discontinued study due to doxycycline-related AEs.
Stewart (2023); dPEP Kenya	HIV- cisgender women taking HIV PrEP (Kenya); n = 449	1:1 randomization to (1) doxyPEP vs. (2) no doxycycline; 48 weeks of follow-up (*maximum 200mg of doxycycline/day*)	**No difference** in STI rates between arms; RR 0.88 (95%CI 0.60-1.29) for all STI	No drug-related SAEs reported; fewer than 5% drug-related discontinuations

Abbreviations: AE, adverse event; CI, confidence interval; GERD, gastroesophageal reflux disease; HR, hazard ratio; menB, meningococcal B; gbMSM, gay, bisexual and other men who have sex with men; HIV, human immunodeficiency virus; OR, odds ratio; PEP, post-exposure prophylaxis; PLWH, person living with HIV; PrEP, pre-exposure prophylaxis; RR, relative risk; SAE, serious adverse event; STI, sexually transmitted infection; TGW, transgender women.

[a] doxyPEP is administered as doxycycline 200mg PO within 72 hours post-sexual encounter; doxyPrEP is administered as doxycycline 100mg PO daily

[b] Effect (i.e. OR, HR, RR) listed is that of the doxycycline arm vs. comparator arm; value below 1 indicates decreased odds/rate for doxycycline vs comparator.

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