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Living Evidence Synthesis

Effectiveness of doxycycline post-exposure and pre-exposure prophylaxis for the prevention of bacterial STI for populations disproportionately impacted by sexually transmitted infections

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Context

- The number of cases and the rates of reportable sexually transmitted infections (STIs) (gonorrhea, chlamydia and syphilis) in Canada have steadily increased over the last decade (based on the most recent data from 2021), with:
  - chlamydia case counts and rates increasing between 2012 and 2019, decreasing slightly between 2019-2021, but still with an overall high rate of infection of 273.2 cases per 100,000 population (1)
  - gonorrhea case counts and rates increasing by 124% between 2012-2021
  - syphilis case counts and rates rapidly increasing by 410% between 2012-2021.
- While high overall, these increases in cases and rates of STI also disproportionately affect some groups more than others, particularly gay, bisexual and other men who have sex with men (gbMSM); transgender women (TGW); cisgender women (CGW), particularly Indigenous cisgender women; sex workers; people living with HIV; and people taking HIV pre-exposure prophylaxis (PrEP).(2-20)
- This growing public health concern has focused attention on approaches to more effectively prevent STIs, particularly for the groups disproportionately affected by and/or at high risk for STI noted above.
- Evidence about the effectiveness of preventing HIV infections through HIV pre-exposure prophylaxis (PrEP) (21-23) pharmaceuticals has led to increasing interest in the potential of doxycycline PrEP (Doxy-PrEP) and post-exposure prophylaxis (Doxy-PEP) to prevent STIs.

Questions

Primary research question

1) What is the effectiveness of Doxy-PEP and Doxy-PrEP for the prevention of STI (*Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Treponema pallidum* [syphilis]) in people who are disproportionately affected by or deemed to be at high risk for STI as compared to no treatment, placebo, usual care or any other intervention?

Secondary research questions

1) What is the effectiveness of Doxy-PEP and Doxy-PrEP for specific populations that are known to be disproportionately affected by STI, including gay, bisexual, and other men who have sex with men (gbMSM), transgender women (TGW), cisgender women (CGW), cisgender Indigenous women, sex workers, people living with HIV, people taking HIV PrEP, and other people identified as being at high risk for STI (e.g., as determined through screening questions)?
2) What is the effectiveness of Doxy-PEP and Doxy-PrEP for preventing complications of bacterial STI, including pelvic inflammatory disease, congenital syphilis and hospitalization?
3) What acceptability and adherence considerations must be realized to implement Doxy-PEP and Doxy-PrEP for populations disproportionately affected by or deemed to be at high risk for STI?

High-level summary of key findings

Evidence identified

- We identified 494 articles and included 20 studies (with one study having two publications), of which:
  - nine studies addressed the primary question about effectiveness
  - 14 studies addressed the secondary question about acceptability and adherence
  - three Studies addressed both questions
  - eight were randomized studies
    - four randomized control trials (RCTs) assessing Doxy-PEP, three with finished data analysis
    - two RCTs assessing HIV PrEP and used as indirect evidence for outcomes of acceptability
    - two pilots, one assessing Doxy-PrEP (finished data analysis) and one assessing Doxy-PEP (unfinished data analysis)
  - eight were observational studies, cross-sectional (n=7), cohort (n=1)
  - three were modelling studies
  - one was a qualitative study
- The risk of bias:
  - in randomized studies was assessed as low (n=3), some concerns (n=3), high (n=1) and not assessed in the studies with unfinished data analysis (n=2)
  - in observational studies was assessed as moderate (n=3), serious (n=3) and critical (n=2)
  - in the qualitative study was low (8/10 items were assessed as high quality)
  - in modelling studies (n=3) was not performed
- We performed meta-analyses for all comparisons, by each condition, outcome, and subgroup of infections by anatomical location, and we retained a pooled analysis when the heterogeneity was lower than 40% (I^2 estimator).

Key findings in relation to effectiveness

- No studies with finished data analysis included transgender men.
- Overall, Doxy-PEP was effective in reducing the incidence of any bacterial STI among cisgender gbMSM and TGW taking HIV PrEP or living with HIV.
- One randomized study reported no effectiveness of Doxy-PEP in reducing the incidence of any bacterial STI among CGW in Kenya.
- Only one randomized controlled pilot study assessed the effectiveness of Doxy-PrEP among cisgender gbMSM or TGW living with HIV (n=25), and reported that participants taking Doxy-PrEP were significantly less likely to test positive for any selected bacterial STI during 48 weeks of follow-up compared to participants who were assigned to a contingency management intervention in which they received incentive payments for remaining free from STI.
- Among people taking HIV PrEP, two studies found Doxy-PEP to not be effective in preventing total gonorrhea infections, one reported an RR of 1.59 [95% CI 0.79, 3.20] and the other an RR of 0.71 [95% CI 0.47, 1.08], and one study found Doxy-PEP effective (RR 0.45 [95% CI 0.32,0.64]).
  - Disaggregated by anatomical location, pooled analysis of two studies found Doxy-PEP to be effective in reducing the incidence of urethral (RR 0.18 [95% CI 0.07, 0.45] I2 0%) and anal infections (RR 0.45 [95% CI 0.30, 0.68] I2 0%).
  - For pharyngeal gonorrhea, one study reported an RR of 0.50 [95% CI 0.32, 0.78], and the other study reported an RR of 1.25 [95% CI 0.61, 2.55].
  - One study mentioned that effectiveness against gonorrhea might depend on background tetracycline resistance in gonococci, which was roughly 30% in the U.S. and 60% in France at the time of the studies.
  - Tetracycline resistance in gonococci was reported in Canada at approximately 64.6% in 2021.
- Among people taking HIV PrEP, two studies found Doxy-PEP to be effective in preventing chlamydia at any anatomical location, one study reported an RR of 0.12 [95% CI 0.05, 0.25],(24) and the other reported an RR of 0.33 [95% CI 0.16, 0.71], while one study found Doxy-PEP not to be effective in preventing endocervical chlamydia infections (RR 0.73 [95% CI 0.47–1.13]).

  - Disaggregated by anatomical location, the pooled effect of two studies found Doxy-PEP effective in reducing the incidence of urethral chlamydia (RR 0.10 [95% CI 0.02, 0.43] I2 0%).
  - For pharyngeal chlamydia infection, two studies found Doxy-PEP not to be effective, one study reported an RR of 0.23 [95% CI 0.53, 1.23], and another study reported an RR of 2.0 [95% CI 0.18, 21.75].
  - For anal chlamydia infection, two studies found Doxy-PEP to be effective, one study reported an RR of 0.14 [95% CI 0.06, 0.32], and the other study reported an RR of 0.33 [95% CI 0.14, 0.81].(25)
  - One study in cisgender women in Kenya, found Doxy-PEP not to be effective in preventing endocervical infection RR 0.73 [95% CI 0.47–1.13].
- One study performed among cisgender gbMSM and TGW living with HIV found Doxy-PEP to be effective in reducing the incidence of chlamydia at any anatomical location (RR 0.27 [95% CI 0.13, 0.53]).
- Doxy-PEP was found to be effective in preventing syphilis in gbMSM and TGW taking HIV PrEP or living with HIV.
- Among three modelling studies, one found that prescribing Doxy-PEP to people using HIV PrEP would have averted 60% of STI diagnoses, and the other two studies found Doxy-PEP might be effective as a short-term solution for reducing the burden of gonorrhea infections, and that it might lead to modest declines in the cumulative incidence of syphilis.
- One RCT cisgender gbMSM and TGW (n=501) reported that the time to first STI was lower by 66% with Doxy-PEP for those taking HIV PrEP, and 52% lower for those living with HIV; another RCT in CGW (n=442) reported no difference in the time to first STI between those with Doxy-PEP and without it.
- We did not identify evidence addressing the effectiveness for preventing complications of bacterial STI (including but not limited to pelvic inflammatory disease (PID), congenital syphilis and hospitalization).

Key findings in relation to adverse effects

- Adverse events did not differ significantly between people receiving and not receiving Doxy-PEP.
- Serious adverse events were not associated with the use of Doxy-PEP.
- Use of Doxy-PEP may increase the likelihood of tetracycline-resistant Neisseria gonorrhoeae infections.
- One study assessed the incidence of *Mycoplasma genitalium* in people exposed and not exposed to Doxy-PEP and found no difference in the baseline and follow-up prevalence of this bacteria.

Key findings in relation to acceptability and adherence

- Most studies assessed acceptability hypothetically rather than based on experience, though for some Doxy-PEP and Doxy-PrEP studies, participants drew from experiences with HIV PrEP.
- When assessed as an overall indicator, acceptability was variable but relatively high overall; however, when assessed in terms of willingness or intention to use Doxy-PEP and Doxy-PrEP, currently available studies indicate a lower willingness, suggesting a potential disconnect between acceptability and actual motivation to use Doxy-PEP and Doxy-PrEP.
- Beyond overall acceptability, a subset of studies provided nuanced perspectives on aspects that affect acceptability views.
  - These included concerns about stigma and side effects (affective attitude), views about dosing schedules and frequency of follow-up clinic visits (burden), similarity to HIV PrEP (intervention coherence), affordability, sleep/diet disruption and risk of being denied sex (opportunity costs), and whether Doxy-PEP and Doxy-PrEP was effective (perceived effectiveness) were all reported as specific factors affecting acceptability.
- While adherence within trials and pilots were consistently strong, there is a need to understand and support adherence outside of trial settings.

Background

The number of cases and the rates of reportable sexually transmitted infections (STIs) (gonorrhea, chlamydia and syphilis) in Canada have steadily increased over the last decade (based on the most recent data from 2021). Specifically:

- chlamydia case counts and rates increasing between 2012 and 2019, decreasing slightly between 2019-2021, but still with an overall high rate of infection of 273.2 cases per 100,000 population
- gonorrhea case counts and rates increasing by 124% between 2012-2021
- syphilis case counts and rates rapidly increasing by 410% between 2012-2021.(1)

While high overall, these increases in cases and rates of STI also disproportionately affect some groups more than others, including:

- adolescents and young adults, particularly cisgender women (CGW)
- gay, bisexual and other men who have sex with men (gbMSM)
- transgender and gender diverse individuals
- some First Nations, Inuit and Métis communities
- African, Caribbean and Black communities and other racialized communities
- people living with HIV
- people on HIV PrEP
- sex workers
- people who use drugs
- people who have experienced incarceration.(2-20)

This growing public health concern has focused attention on approaches to more effectively prevent STIs, particularly for the groups

Box 1: Approach and supporting materials

We retrieved candidate studies by searching: 1) PubMed, 2) Embase, 3) EBM Reviews via OVID, 4) pre-print servers (MedRxiv); and 5) ClinicalTrials.gov. We also included studies identified by subject-matter experts who reviewed the protocols and final report. Searches were conducted for studies reported in English, French, Spanish, Portuguese, Arabic and Chinese conducted with humans and published since database inception until 15 September 2023. Our detailed search strategy is included in **Appendix 1**.

For efficacy/effectiveness outcomes, any experimental design such as interventional trials or observational designs including cohort, case-control, before-after studies, interrupted time-series and case series were considered for inclusion. For adherence and acceptability outcomes, we considered any study design, with particular emphasis on behavioural science and implementation research. For all outcomes, evidence syntheses were tracked, and any relevant primary studies from them were pulled out for our analysis. A full list of included studies is provided in **Appendices 2 and 3**. Studies excluded at the last stages of reviewing are provided in **Appendix 4**.

Population of interest: Those disproportionately affected by STI including gay, bisexual and other men who have sex with men (gbMSM), transgender women (TGW), cisgender women (CGW), Indigenous women, sex workers, people living with HIV, people identified as being at high risk for STI (e.g., as determined through screening questions) and people taking HIV PrEP.

Intervention and control/comparator: The interventions were: 1) Doxy-PrEP (Doxycycline 100 mg orally daily), and 2) Doxy-PEP (Doxycycline 200 mg orally within 24 hours to 72 hours of condomless sex). Interventions were compared with no prophylaxis, placebo, standard care or any other intervention.

Primary outcomes: 1) Incidence of gonorrhea infections and chlamydia infections (including LGV) (disaggregated for pharyngeal, anal and genital locations), and syphilis infections; 2) time to first bacterial STI; 3) incidence of complications from bacterial STI, including but not limited to pelvic inflammatory disease (PID), congenital syphilis and hospitalization; and 4) incidence of adverse effects and serious adverse effects from the medications.

Secondary outcomes: 1) Adherence to Doxy-PEP and Doxy-PrEP (frequency of use and timing of use); 2) acceptability of Doxy-PEP and Doxy-PrEP; 3) change in sexual activity (number of partners, condom use); and 4) baseline and follow-up attitudes toward STI screening and treatment.

Data extraction: Data extraction was conducted by one team member.

Critical appraisal: The risk of bias (ROB) of individual studies was assessed using validated ROB tools. For randomized controlled trials, we used ROB-2, and for observational studies, we used ROBINS-I. Judgements for the domains within these tools were decided by one reviewer and details are provided in **Appendices 5 and 6**.

We also organized the findings using the GRADE evidence to decision framework for public health decisions. A full GRADE analysis is provided in **Table 3**.

Summaries: We summarized the evidence by presenting narrative evidence profiles across studies by outcome measure. When appropriate, statistical pooling of results was performed using random effects methods. The presence of heterogeneity was measured with the I^2 estimator. When heterogeneity was higher than 40%, we suppressed the meta-analysis and reported the findings only narratively.

The next update to this document is to be determined.

disproportionately affected by and/or at high risk for STI noted above. With this attention, evidence about the effectiveness of preventing HIV infections through HIV pre-exposure prophylaxis (PrEP) pharmaceuticals (21-23) has led to increasing interest in the potential of doxycycline PrEP (Doxy-PrEP) and post-exposure prophylaxis (Doxy-PEP) to prevent STIs.(26)

However, while there is potential for Doxy-PEP and Doxy-PrEP for STI prevention, there is uncertainty about its effectiveness for populations, types of STI and infection location, as well as the influence of antimicrobial resistance (AMR) patterns.(27) As a result, it is unsurprising that there are conflicting recommendations for the use of Doxy-PrEP and Doxy-PEP, with:

- some key agencies not endorsing its use, including the United Kingdom (U.K.) Health Security Agency and the British Association for Sexual Health and HIV (28) and the International Antiviral Society – USA Panel (29)
- a number of agencies recommending Doxy-PEP prescribing for specific STIs (principally syphilis) and populations at highest risk of STIs (principally gbMSM), including the United States (U.S.) Centers for Disease Control,(30) the British Columbia Centre for Disease Control,(31) the San Francisco Department of Public Health,(32) Public Health Seattle and King County,(33) New York State Department of Health AIDS Institute (34) and the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM).(35)

To inform ongoing efforts to update and refine recommendations for the use of Doxy-PrEP and Doxy-PEP, there is a need for a high-quality and routinely updated synthesis of the best-available evidence about their effectiveness for prevention STIs at a population level for those who are disproportionately affected by or deemed to be at high risk for STIs.

Our primary research question was:

1) What is the effectiveness of Doxy-PEP and Doxy-PrEP for the prevention of STI (*Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Treponema pallidum* [syphilis]) in people who are disproportionately affected by or deemed to be at high risk for STI as compared to no treatment, placebo, usual care or any other intervention?

Our secondary research questions were:

1) What is the effectiveness of Doxy-PEP and Doxy-PrEP for specific populations that are known to be disproportionately affected by STI, including gay, bisexual, and other men who have sex with men (gbMSM), transgender women (TGW), cisgender women (CGW), cisgender Indigenous women, sex workers, people living with HIV, people taking HIV PrEP, and other people identified as being at high risk for STI (e.g., as determined through screening questions)?
2) What is the effectiveness of Doxy-PEP and Doxy-PrEP for preventing complications of bacterial STI, including pelvic inflammatory disease, congenital syphilis and hospitalization?
3) What acceptability and adherence considerations must be realized to implement Doxy-PEP and Doxy-PrEP for populations disproportionately affected by or deemed to be at high risk for STI?

What we found

We identified 494 articles, and after removing 77 duplicates, we screened 417 titles and abstracts (see Figure 1 for details). We reviewed 37 full-text articles and included 21 articles representing 20 single studies (one study has two publications), of which:

- Nine studies (10 articles) address the research questions about effectiveness
  - four randomized clinical trials, with finished (n=3)(24; 25; 36) and unfinished data analysis (n=1) (37)
  - two randomized controlled pilot studies, with finished (n=1) (38) and unfinished data analysis (n=1) (39)
  - three modelling studies (40-42)

- Three of the studies (four articles) described above also address adverse effects and serious adverse effects from the medications (24; 25; 36; 43)
- 14 studies address the research question about acceptability and adherence
  - 10 reported on acceptability and have finished data analysis, which included cross-sectional studies (n=7),(44-50) one survey within an RCT,(24) one qualitative study,(51) and one pilot study (52)
  - seven reported on adherence and have finished data analysis, which included randomized clinical trials (n=3),(24; 25; 36) randomized controlled pilot studies (n=2),(38; 53) cross-sectional studies (n=2),(45) and a cohort study (54)
  - two reported on acceptability and adherence: one randomized clinical trial (24) and one cross-sectional study (45)

Two studies are still pending assessment, because one is in a foreign language and we have not been able to conduct an in-depth assessment and the second is from a journal supplement that we have not been able to identify.(55; 56)

Among the studies with finalized data analysis, six were randomized clinical trials, of which four studies (five articles) focused on doxycycline prophylaxis (24; 25; 36; 38; 43) and two focused on HIV prophylaxis.(52; 53) The HIV PrEP studies were used for indirect evidence about the acceptability of Doxy-PEP and Doxy-PrEP. The risk of bias in the randomized studies was low in three,(24; 25; 52) some concerns in three,(36; 43; 53) and high in one.(38)

The other 12 studies with finished data analysis included cohort studies (n=1),(54) cross-sectional studies (n=7),(44-50) modelling studies (n=3),(40-42) and qualitative research (n=1).(51) The risk of bias in the observational studies was moderate in three,(46; 49; 54) serious in three (44; 45; 47) and critical in two.(48; 50) The overall appraisal of the qualitative study allowed the inclusion in this synthesis (see Appendix 7 for details of the quality appraisal). A quality appraisal of the modelling studies has not been conducted given the lack of an accepted tool for this purpose.

In addition, we did not perform a quality assessment of the two studies with unfinished data analysis (see Tables 1 and 2 for details of the studies included).(37; 39)

We performed meta-analyses for all comparisons, by each condition, outcome, and subgroup of infections by anatomical location, and we retained the pooled analysis when the heterogeneity was lower than 40% (I2 estimator).

Key findings in relation to effectiveness

We found nine studies (10 articles) addressing the primary research question about the effectiveness of Doxy-PEP and Doxy-PrEP for the prevention of STI (*Chlamydia trachomatis*, *Neisseria gonorrhoeae* and *Treponema pallidum*).(24; 25; 36-43) Two articles were analyses of the same sub-study of the ANRS IPERGAY trial.(25; 43) Six studies (seven articles) were randomized studies,(24; 25; 36-39; 43) of which four (five articles) have completed statistical analysis and were included in the meta-analyses presented below.(24; 25; 36; 38; 43) The other two RCTs have finalized recruitment and have preliminary findings presented at an international conference but have not completed the statistical analyses and we therefore only include them in a narrative analysis of key findings below and not in the meta-analysis.(37; 39; 57) Note that one of these studies is undergoing independent audit and re-analysis of results for the vaccine arm of the trial, but this does not affect the doxycycline effectiveness results.(37; 58) The other three were modelling studies, which we include in the narrative analysis below.(40-42)

Among the four randomized studies with finished statistical analyses, three studies (with four articles) were open-label (24; 25; 36; 43) and one was a pilot.(38) One study (with two articles) was performed in France,(25; 43) two in the U.S. (24; 38) and one in Kenya.(36) Three studies (four articles) assessed the effectiveness of Doxy-PEP (200 mg within 24-72 hours after sex),(24; 25; 36; 43) and one assessed Doxy-PrEP (100 mg once daily for 36 weeks).(38) Four studies covered the three STI,(24; 25; 36; 38) one study also covered *Mycoplasma genitalium* (not encompassed in the primary research question but included given the increase in the number of cases and its importance for tetracycline resistance).(43) In one study (two articles), the populations were gbMSM and TGW who have sex with

men taking HIV PrEP (n=232, and a subset of n=210).(25; 43) One study included two cohorts of gbMSM and TGW who have sex with men, who were either living with HIV (n=194) or were taking HIV PrEP (n=360).(24) One study included gbMSM or TGW who have sex with men who had syphilis twice or more since their HIV diagnosis (n=25).(38) And the other study included non-pregnant cisgender women taking HIV PrEP.(36)

As presented below in detail, we identified evidence for answering the primary outcomes 1 (incidence of gonorrhea infections, chlamydia infections and syphilis infections), 2 (time to first bacterial STI) and 4 (incidence of adverse effects) listed in Box 1, but not for primary outcome 3 (incidence of complications from bacterial STI).

Primary outcome 1: Incidence of gonorrhea infections and chlamydia infections (including LGV) (disaggregated for pharyngeal, anal and urethral locations), and syphilis infections.

Prevention of any STI

Overall, two studies found Doxy-PEP to be effective for reducing the incidence of any STI,(24; 25) and one study found it to be ineffective (see Figure 2).(36) Among people taking HIV PrEP, one study in cisgender gbMSM and TGW who have sex with men reported a risk ratio (RR) of 0.34 [95% CI 0.24,0.46],(24) one study reported a hazard ration (HR) of 0.53 [95% CI 0.33, 0.85],(25) and another study in cisgender women reported an RR of 0.88 [95% CI 0.60,1.29].(36) Among people living with HIV, one study in gbMSM and TGW who have sex with men reported an RR of 0.38 [95% CI 0.24, 0.60].(24)

Only one pilot study assessed the effectiveness of Doxy-PrEP in gbMSM and TGW who have sex with men. It found that participants (n=25) taking Doxy-PrEP were significantly less likely to test positive for any selected bacterial STI during 48 weeks of follow-up (OR: 0.27 [95% CI: 0.09–0.83]) compared to participants who were assigned to a contingency management intervention in which they received incentive payments for remaining STI-free.(38)

The randomized studies that have unfinished statistical analyses were conducted in Canada (39) and France.(37) The study conducted in Canada (n=52) assessed the effectiveness of Doxy-PrEP, and the study conducted in France (n=502) assessed the effectiveness of Doxy-PEP; both studies were focused on HIV-negative gbMSM and TGW who have sex with men taking HIV PrEP.(37; 39) Preliminary analyses of the studies conducted in Canada (cities of Vancouver and Toronto) and France found Doxy-PEP to be effective, with one reporting a reduction in the likelihood of any STI (OR 0.18 [95% CI: 0.05–0.68]; p=0.011),(39) while the other reported a 65% reduction in all STI incidence (CT and syphilis approximately 80%; GC approximately 55%).(37)

Three modelling studies assessed potential effects of Doxy-PEP in preventing STI at a population level and without individual-level data, with one reporting on prevention of any STI and the others reporting on prevention of gonorrhea and syphilis (findings from these are reported in the relevant sub-sections below). The study focused on any STI used counterfactual scenarios using 10,546 health records of gbMSM, TGW and nonbinary people assigned male at birth with ≥2 STI tests at an LGBTQ-focused health centre in Boston.(41) The study modelled three strategies in which Doxy-PEP would be prescribed indefinitely to the following groups defined by HIV status and use of HIV PrEP: a) all individuals (from their first STI test); b) all people diagnosed with HIV (from date of HIV diagnosis or from cohort entry if the diagnosis was prior to 2015) and all HIV PrEP users (from first PrEP prescription); and c) all PrEP users only (from first HIV PrEP prescription) (see details in Appendix 2).(41) The study found that prescribing Doxy-PEP indefinitely to all individuals would have averted 71% of STI diagnoses and prescribing to all people living with HIV, and HIV PrEP users would have averted 60% of STI diagnoses (with number needed to treat for one year to avert one STI diagnosis [NNT] of 3.9 and 2.9, respectively). Prescribing Doxy-PEP for 12 months after any STI diagnosis would have reduced the proportion using Doxy-PEP to 38% and averted 39% of STI diagnoses (with a NNT of 2.4). The study concluded that prescribing Doxy-PEP for 12 months after concurrent or repeated STI maximized efficiency but prevented fewer STI.(41)

Effectiveness of Doxy-PEP for preventing Neisseria gonorrhoeae

Among people taking HIV PrEP, two studies found Doxy-PEP to not be effective in preventing total gonorrhea infections, one reported an RR of 1.59 [95% CI 0.79, 3.20] (36) and the other an RR of 0.71 [95% CI 0.47, 1.08].(25) One study found Doxy-PEP effective (RR 0.45 [95% CI 0.32,0.64]).(24) Disaggregated by anatomical location, pooled analysis of two studies (24; 25) found Doxy-PEP to be effective in reducing the incidence of urethral (RR 0.18 [95% CI 0.07, 0.45], and rectal infections (RR 0.45 [95% CI 0.30, 0.68]) (see Figure 3). For pharyngeal gonorrhea, one study reported an RR of 0.50 [95% CI 0.32, 0.78],(24) and the other study reported an RR of 1.25 [95% CI 0.61, 2.55].(25) For the endocervical location, one study reported an RR of 1.64 [95% CI 0.78, 3.47).(36)

Among cisgender gbMSM and TGW living with HIV, one study found Doxy-PEP effective in reducing the incidence of gonorrhea at any anatomical location (RR 0.43 [95% CI 0.26, 0.71]).(24) One study in France (with an unfinished statistical analysis) reported Doxy-PEP to be effective (RR 0.56 [95% CI 0.38, 0.83]).(37) One article mentioned that effectiveness at preventing gonorrhea might depend on background tetracycline resistance in gonococci.(6; 26) It is suggested that the lack of effectiveness for preventing gonorrhea in the French study may have been due to high background rates of tetracycline resistance,(26) which was reported around 60% in France, similar to the Canadian rate (64.6%) in 2021.(6)

In addition, one of the modelling studies used a deterministic compartmental model of gonorrhea transmission in a gbMSM population. The study introduced Doxy-PEP at various uptake levels (10, 25, 50 and 75%) and compared 20-year prevalence, antibiotic use and antibiotic resistance dynamics relative to those at baseline (i.e., no Doxy-PEP introduction).(40) Using a tetracycline resistance rate of gonorrhea among men who have sex with men (MSM) of 26.8%, the model suggested that Doxy-PEP could be an effective short-term solution for reducing the burden of gonorrhea infection, as its selection for doxycycline-resistant strains results in the loss of its benefit. The model also showed that Doxy-PEP had little impact on the clinical lifespan of ceftriaxone for the treatment of gonorrhea infections. Increasing levels of Doxy-PEP uptake and higher starting prevalence of doxycycline resistance resulted in a faster loss of its efficacy.(40)

Effectiveness of Doxy-PEP for preventing Chlamydia trachomatis

Among people taking HIV PrEP, two studies found Doxy-PEP to be effective in preventing chlamydia at any anatomical location, one study reported an RR of 0.12 [95% CI 0.05, 0.25],(24) and the other reported an RR of 0.33 [95% CI 0.16, 0.71].(25) One study found Doxy-PEP not to be effective in preventing endocervical chlamydia infections (RR 0.73 [95% CI 0.47–1.13]).(36) Disaggregated by anatomical location, the pooled effect of two studies (24; 25) found Doxy-PEP effective in reducing the incidence of urethral chlamydia (RR 0.10 [95% CI 0.02, 0.43], I^2 0%) (see Figure 4). For pharyngeal chlamydia infection, two studies found Doxy-PEP not to be effective, one study reported an RR of 0.23 [95% CI 0.53, 1.23],(24) and another study reported an RR of 2.0 [95% CI 0.18, 21.75].(25) For anal chlamydia infection, two studies found Doxy-PEP to be effective, one study reported an RR of 0.14 [95% CI 0.06, 0.32],(24) and the other study reported an RR of 0.33 [95% CI 0.14, 0.81].(25) Additionally, one study in cisgender women in Kenya, found Doxy-PEP not to be effective in preventing endocervical infection RR 0.73 [95% CI 0.47–1.13].(36) Among cisgender gbMSM and TGW living with HIV, one study found Doxy-PEP to be effective in reducing the incidence of chlamydia at any anatomical location (RR 0.27 [95% CI 0.13, 0.53]).(24) In addition, one study conducted in France (with an unfinished statistical analysis) reported Doxy-PEP as being effective in preventing a first episode of chlamydia among gbMSM and TGW.(37; 59)

Effectiveness of Doxy-PEP for preventing syphilis infections

We aggregated data from two studies.(24; 25) Overall, among people taking HIV PrEP, Doxy-PEP was found to be effective in preventing syphilis (RR 0.21 [95% CI 0.08, 0.57]) (see Figure 5). Among people living with HIV, one study found Doxy-PEP not effective for reducing the incidence of syphilis (RR 0.28 [95% CI 0.05, 1.65]).(24) A study of cisgender women in Kenya did not report subgroup analysis for syphilis given a small sample size.(36) In addition, one study in France (with an unfinished statistical analysis) reported Doxy-PEP as being effective for preventing syphilis (HR adjusted 0.21 [95% IC 0.09-0.47; $p \leq 0.0001$].(37; 59)

One modelling study assessed intervention scenarios that varied Doxy-PEP uptake by 20, 40, 60, 80 and 100% in a population of sexual minority men, while assuming continued condom use and syphilis screening and treatment.(42) Under each intervention scenario, the study incorporated treatment adherence at the following levels: 0, 20, 40, 60, 80 and 100%. The model in this study indicated that implementation of Doxy-PEP would result in modest declines in the cumulative incidence of syphilis among sexual minority men over a 10-year period.(42) Assuming an uptake scenario of 20% (a plausible level of uptake) and an adherence level of 80% (similar to prior clinical trials with 84% adherence), syphilis incidence decreased only by 10% over follow-up (57 fewer cases per 1,000 sexual minority men).(42)

Primary outcome 2: Time to first bacterial STI

One RCT conducted in the U.S. in cisgender gbMSM and TGW (n=501) reported that the time to first STI was lower by 66% with Doxy-PEP for those taking HIV PrEP, and 52% lower for those living with HIV.(24) Another RCT in cisgender women (n=442) reported no difference in the time to first STI between those with Doxy-PEP and without it (HR 0.95 [95% CI, 0.64–1.42]).(36)

Primary outcome 3: Incidence of complications from bacterial STI, including but not limited to pelvic inflammatory disease (PID), congenital syphilis and hospitalization

No evidence was identified for this outcome.

Primary outcome 4: Incidence of adverse effects and serious adverse effects from the medications

We aggregated data from two studies.(24; 25) Adverse events did not differ significantly between people receiving and not receiving Doxy-PEP (RR 0.74 [95% CI 0.30, 1.84]) (see Figure 6). Serious adverse events were not associated with the use of Doxy-PEP (RR 0.30 [95% CI 0.14, 0.67]) (see Figure 7).

One study reported more gastrointestinal adverse effects in the group taking Doxy-PEP than in those not (25% vs 14% respectively, p 0.03).(25) Another study reported nausea to be the most frequent doxycycline-related adverse effect among people taking Doxy-PEP in comparison to those not taking PEP (7.2% vs 4.6% respectively, p value not provided).(36) This former study also reported three cases of social harm among participants taking Doxy-PEP given the unintentional disclosure of this information.(36)

Use of Doxy-PEP might increase the likelihood of infection with tetracycline-resistant strains of *Neisseria gonorrhoeae*. Our aggregated data showed a non-statistically significant increase in tetracycline-resistant strains (RR 1.32 [95% CI 0.16, 11.26]) (see Figure 8). Doxycycline resistance has so far only been described for gonorrhea and it is unclear whether this tetracycline resistance represents selective infection or induction of resistance mutations.(26) However, the Australasian Society for HIV, Viral Hepatitis and Sexual Health Medicine (ASHM) highlighted the risk of inducing tetracycline resistance in *Chlamydia trachomatis* (for which it is the first line and most effective treatment) and *Treponema pallidum* (for which it is the treatment of choice in case of penicillin allergy).(35)

One study assessed the incidence of *Mycoplasma genitalium* in people exposed and not exposed to Doxy-PEP and found no difference in the baseline and follow-up prevalence of this bacteria (RR 1.07 [95% CI 0.45, 2.51]).(43) The number of cases of *Mycoplasma genitalium* is progressively increasing in the gbMSM population, and most strains are resistant to tetracyclines.(60)

The CDC has also compiled a list of adverse effects of long-term doxycycline use for different conditions.(61)

Key findings in relation to the secondary questions (acceptability and adherence)

We identified 10 studies reporting on findings related to acceptability (based on views and perceptions) (24; 44-51; 53): three studies on acceptance of HIV PrEP (based on agreeing to receive it) (45; 54; 62) and seven studies provide findings about adherence.(24; 25; 36; 38; 43; 45; 54)

Acceptability

We identified 10 studies (24; 44-51; 53) reporting on acceptability views, which included seven cross-sectional surveys,(44-50) one survey within an RCT,(24) one qualitative study (51) and one pilot study.(53) Studies reporting acceptability focused primarily on views from gbMSM, with one study also including views of TGW (48) and another focused on anyone using or trying to access HIV PrEP.(50) Seven studies focused on acceptability of Doxy-PEP and Doxy-PrEP (24; 44; 46-48; 50; 51) while the remaining three studies focused on HIV PrEP (used as indirect evidence).(45; 49; 53)

The risk of bias in the observational studies was moderate in two,(24; 46; 49; 54) serious in three (44; 45; 47; 50) and critical in two.(48; 50) The overall appraisal of the qualitative study allowed the inclusion in this synthesis (see Appendix 7 for details of the quality appraisal) (see Table 1 for details of studies included).

We sought to extract data from included studies that report on the acceptability of Doxy-PEP and Doxy-PrEP for bacterial STI (or of HIV PrEP as a proxy). Given that acceptability has been defined in many ways, we used the Theoretical Framework of Acceptability (TFA) (63) to characterize the core factors of acceptability reported in included studies. The TFA describes seven factors of acceptability: 1) *affective attitude* (how the recipient of an intervention feels about the intervention), 2) *burden* (how much effort is perceived to be needed to engage in the intervention), 3) *ethicality* (whether the intervention aligns with the recipients' value system), 4) *intervention coherence* (extent that recipients understand how the intervention works), 5) *opportunity costs* (how much and what needs to be given up to enable engaging with the intervention), 6) *perceived effectiveness* (whether the intervention is perceived to work or likely to work), and 7) *self-efficacy* (confidence that the recipient can engage in what is needed to take part in the intervention).(63) Where sufficient detail was provided, we coded acceptability perspectives into one or more TFA factors; where acceptability was assessed more generically, we coded at an overall acceptability level (consistent with acceptability measurement tools).(63) The TFA also distinguishes the timing at which acceptability can be assessed: prospectively (prior to receipt of the intervention), concurrently (during receipt of an intervention) or retrospectively (after receipt of the intervention). Where possible, we identified the timing of acceptability assessment in included studies reporting on acceptability.

<u>Overall acceptability</u>

Most (n=7) studies assessed acceptability prospectively (i.e. hypothetically),(44; 46-51) while two assessed it concurrently (24; 53) and one retrospectively.(45) Most (n=8) studies assessed acceptability as an overall indicator (mostly using a self-reported Likert scale), asking about acceptability directly, or indirectly via intention or willingness. These overall indicators suggest that acceptability substantially varies, but this may be a function of the prospective (hypothetical) nature of most acceptability assessments to date. In a study asking about willingness to take doxycycline as PrEP and/or PEP for syphilis, willingness was strongest for Doxy-PEP (60.1% reported being willing), and lower for Doxy-PrEP (44.1%) or both (40.8%).(44) In another study, only 11.8% indicated a high intention to use antibiotics to prevent STI (STI-PrEP or HIV PEP).(46) In studies that measured acceptability more directly (rather than in terms of willingness or intention), acceptability was reported to be higher, with one study reporting that 67.5% would take Doxy-PEP and Doxy-PrEP if offered for the prevention of syphilis and chlamydia (47) and another reporting 84% expressing an interest in trying Doxy-PEP.(48) This variability across studies is perhaps best summarized by the single qualitative study reporting on overall acceptability, which suggested that "[o]verall, participants were cautiously optimistic about the prospect of STI-PrEP."(51) Interestingly, the two studies with concurrent assessments of acceptability showed even higher levels of acceptability (e.g., 89% of participants in a

trial arm randomized to receive Doxy-PEP reported it to be acceptable or very acceptable).(24) More studies are needed to substantiate whether the experience of taking Doxy-PEP affects its acceptability relative to the hypothetical acceptability, how acceptability translates into willingness, intention and ultimately adherence, and how characterizing the intervention itself in terms of preventing different STI moderates acceptability.

Affective attitude

Three studies (45; 49; 51) provided acceptability-related data relevant to affective attitudes (i.e., how someone feels about the intervention). One study focused on Doxy-PrEP,(51) and two studies focused on HIV PrEP.(45; 49) Concerns about stigma were reported in a subset of participants across studies (45; 49; 51) as were concerns about side effects on the gut microbiome and on antibiotic resistance.(51) Mitigating these specific barriers to acceptability appears warranted. No studies focused on Doxy-PEP.

Burden

Three studies, two focused on Doxy-PrEP (47; 51) and one focused on HIV PrEP,(45) reported on the amount of effort required, (45; 47; 51) with two studies describing preferred dosing schedules among participants (e.g., daily dose to build into routines).(47; 51) Barrier-related burden factors raised in one study focused on HIV PrEP (45) included concern about the frequency of follow-up visits needed (42% of respondents expressed this concern) and 6% reported a daily pill being a burden. No studies focused on Doxy-PEP.

Intervention coherence

One qualitative study (51) spoke directly to intervention coherence, noting that participants tended to conceptualize STI-PrEP by comparing it to HIV PrEP.

Opportunity costs

Two studies (45; 49) identified potential opportunity costs affecting acceptability, with both focusing on HIV PrEP. Affordability featured in both, while concerns about sleep and diet disruption and concerns about being denied sex were also identified as opportunity costs. No studies focused on Doxy-PEP.

Perceived effectiveness

Three studies provided data on perceived effectiveness that informed acceptability views.(49-51) In a study of HIV PrEP, 44.1% of participants reported being concerned that it would not be effective, and in a study on STI-PrEP/PEP, 72% reported that their willingness was contingent on it being shown to be effective.

Gaps in evidence about acceptability

None of the identified studies provided acceptability-related data speaking to *ethicality* (i.e., alignment with values) or *self-efficacy*. Furthermore, none of the studies providing acceptability data speaking to *affective attitude*, *burden* or *opportunity costs* focused specifically on Doxy-PEP, which is the most likely form of doxycycline prophylaxis to be made available. Future studies seeking to assess acceptability of Doxy-PrEP and/or Doxy-PEP would benefit from drawing on frameworks such as the theoretical framework of acceptability and related measurement tools (63) to continue to develop a nuanced understanding of acceptability.

Acceptance

We distinguished data on acceptability of PEP and PrEP for sexually transmitted and blood-borne infections (which are based on views and perceptions) from data on acceptance of PEP and PrEP for sexually transmitted and blood-

borne infections (based on agreeing to receive it). We focused specifically on extracting data reporting on levels of acceptance of referrals for PEP and PrEP (directly for Doxy-PrEP/PEP if possible, and otherwise for HIV PrEP as a proxy).

Three studies reported on acceptance of a referral specifically with all three focused on HIV PrEP.(45; 54; 62) Study participants and designs ranged from a retrospective cohort study among people with a primary or secondary syphilis case,(54) a single arm pilot with people enrolled in a safer opioid supply program (62) and a mixed-methods study with gbMSM with syphilis, gonorrhea or chlamydia.(45) Referral acceptance ranged from 40–55%. There is a need to further quantify acceptance rates of referral for Doxy-PEP and Doxy-PrEP specifically.

Adherence

We extracted data on reported adherence to Doxy-PEP and Doxy-PrEP (as well as HIV PrEP) regimens, distinguishing the methods of adherence measurement (self-report, pill count, doses taken, chart reviews or blood tests) as well as adherence to referrals by extracting any objective or self-reported data on attendance to clinic appointments for providing Doxy-PEP and Doxy-PrEP. We further distinguished adherence data reported in the context of a trial from data reported in the context of a cohort or cross-sectional survey, given the added attention and focus of adherence data collection in the context of a trial.

Findings from randomized trials and pilots (n=5)

Four Doxy-PEP and Doxy-PrEP trials (in five articles) (24; 25; 36; 38; 43) assessed adherence to medication in different ways, and in some instances, in multiple ways within the same study. Self-reported adherence with Doxy-PEP was strong in trials with complete analyses, with one trial reporting that 86% of participants reported 'always' or 'often' taking Doxy-PEP within 72 hours of condomless sex, and 71% reporting not ever missing a dose after sex without a condom.(24). In another study, participants reported that they had been taking doxycycline within 24 hours in 83% of 280 occurrences of sexual intercourse, though there was variation within and between patients.(25) Another study, which assessed adherence using multiple indicators, showed that in the Doxy-PEP group completing weekly text message-based adherence reports, 55% of respondents (116 of 211 participants) indicated having taken doxycycline the same number of days (or more) as the number of days they had sex, and this reported adherence rate was observed in over 90% of weekly text-based surveys (response rate to weekly surveys was high at 78%). In the same study, participants who attended follow-up clinic visits reported not taking doxycycline after the last sexual intercourse in 176 of 755 visits (23.3%); this also aligns with reports from the same study using quarterly follow-back calendars that indicated at least 80% use of doxycycline after condomless sex in the last two weeks in the majority (91%) of reports.(36) The same study also reported that, during the trial, 44 of 224 women randomized to the Doxy-PEP group got pregnant, with only 10.1% holding on the Doxy-PEP during the follow-up.(36) In the single Doxy-PrEP pilot with adherence data, doxycycline serum levels at follow-up clinic visits exceeded the adherence threshold of 1,000 ng/mL in 24 of 39 clinic visits.(38) In the Doxy-PEP trials, number of doses taken ranged from a median of four per month (IQR 0–10) in two studies which used self-reporting (24; 36) to 6–8/month (IQR 3–15) in another, which used pill counting.(25) Median monthly dose levels were also relatively similar a across studies, ranging from 670 (IQR=270–1200) (24) to 680 IQR=280–1450).(25)

One HIV PrEP pilot trial (52) reported on attendance to appointments and found 100% attendance in both intervention and control groups.

Findings from cohort and survey studies (n=3)

For adherence to medication, two studies focused on self-reported initiation/use. While not a direct indicator of adherence, one study assessed self-reported initiation of HIV PrEP in a random sample of 132 gbMSM who were referred to an STI clinic for HIV,(45) and found that 33% of 132 respondents reported being on HIV PrEP at follow-up. In addition and also as indirect evidence of adherence, the second study reported only 9% of 1856

respondents to a survey of HIV PrEP users reported as using STI prophylaxis.(64) Two HIV PrEP studies assessed attendance to referral appointments for HIV PrEP,(45; 54) with self-reported attendance rates of 57% and objectively assessed attendance at 45%.

Table 1: Characteristics of all included studies

Study ID	Research question addressed	Geographical location	Design	Population	Analysis	Type of prophylaxis	Risk of Bias
Luetkemeyer 2023 (24) Status: published	- Incidence of bacterial STI - Time to first bacterial STI - Incidence of adverse events - Adherence - Acceptability	U.S. (San Francisco and Seattle)	Open-label randomized study	Cisgender gbMSM and TGW taking HIV PrEP or living with HIV who had had gonorrhea, chlamydia or syphilis in the past year (n=501) Randomized 2:1	Modified intention-to-treat Modified Poisson model fitted according to generalized estimating equation methods to account for repeated observations within individual participants	Doxy-PEP	RoB2: low risk
Molina 2018 (25) Status: published	- Incidence of bacterial STI - Incidence of adverse events - Adherence	France	Open-label randomized study	Cisgender gbMSM and TGW taking HIV PrEP (n=232) Randomized 1:1	Intention-to-treat Kaplan-Meier method and compared with the log-rank test, hazard ratios (HRs) were estimated by use of Cox proportional hazards models	Doxy-PEP	RoB2: low risk
Bolan 2015 (38) Status: published	- Incidence of bacterial STI - Incidence of adverse events - Adherence	U.S. (Los Angeles)	Randomized controlled pilot	Cisgender MSM or TGW living with HIV who had syphilis twice or more since their HIV diagnosis (n=25) Randomized 1:1	Intention-to-treat Generalized linear mixed models Logistic random intercept	Doxy-PrEP	RoB2: high risk
Bercot 2019 (43) Status: published	- Incidence of *Mycoplasma genitalium*	France	Open-label randomized study Note: this is a subset of participants in the study Molina 2018 (25)	Cisgender gbMSM and TGW taking HIV PrEP (n=210) Randomized 1:1	Intention-to-treat Chi-square or Fisher's exact tests, as appropriate	Doxy-PEP	RoB2: some concerns
Molina 2023 (37) Status: unpublished	- Incidence of bacterial STI - Incidence of adverse events	France	Open-label randomized study	Cisgender gbMSM taking PrEP against HIV, with bacterial STI in prior 12 months (n=502) Randomized 2:1	Intention-to-treat	Doxy-PEP	Not assessed because the full report is not ready
Stewart 2023 (36)	- Incidence of bacterial STI - Incidence of adverse events	Kenya	Open-label randomized study	Non-pregnant cisgender women aged 18 to 30 who were taking HIV PrEP (n=449) Randomized 1:1	Intention-to-treat	Doxy-PEP	RoB2: some concerns

Study ID	Research question addressed	Geographical location	Design	Population	Analysis	Type of prophylaxis	Risk of Bias
Status: published	- Adherence						
Grennan 2021 (39) Status: unpublished	- Incidence of bacterial STI	Canada	Randomized controlled pilot	HIV-negative MSM and TGW with prior syphilis (n=52) Randomized 1:1	Intention-to-treat	Doxy-PrEP	Not assessed because the full report is not ready
Traeger 2023 (41) Status: published	- Incidence of bacterial STI	U.S. (Boston)	Modelling	Gay and bisexual men, TGW, and nonbinary people assigned male at birth with ≥2 STI tests at an LGBTQ-focused health centre 10,546 health records	Counterfactual scenarios	Doxy-PEP	No appropriate instrument to assess risk of bias
Reichert 2023 (40) Status: preprint	- Incidence of bacterial STI	U.S.	Modelling	MSM Simulated cohort of 1,000,000	Deterministic compartmental model transforming the model into a susceptible-exposed-infectious-susceptible (SEIS) model	Doxy-PEP	No appropriate instrument to assess risk of bias
Tran 2022 (42) Status: published	- Incidence of bacterial STI	U.S. (Philadelphia)	Modelling	Sexual Minority Men (SMM) Simulated cohort of 10,320	Simulated parameters	Doxy-PEP	No appropriate instrument to assess risk of bias
Fusca 2020 (44) Status: published	- Acceptability	Canada (Vancouver and Toronto)	Cross-sectional study	gbMSM from community-based sexual health clinics in Toronto (n=242) (1 site) and Vancouver (n=194) (2 sites) during routine visits for sexual health services	Multivariable logistic regression	Doxy-PEP	ROBBINS: serious risk
Horn 2020 (51) Status: published	- Acceptability	Australia (Sidney)	Qualitative	high-risk gay and bisexual men (n=13)	Qualitative analysis	Doxy-PrEP	Eight of 10 items in the tool were assessed as high quality
Katz 2019 (45) Status: published	- Adherence - Acceptability	U.S. (Seattle)	Cross-sectional	MSM at risk for HIV (n=3,739)	Descriptive analysis	HIV PrEP	ROBBINS: serious risk

Study ID	Research question addressed	Geographical location	Design	Population	Analysis	Type of prophylaxis	Risk of Bias
Matser 2023 (46) Status: preprint	- Acceptability	The Netherlands	Cross-sectional with in a cohort	MSM (n=593)	Logistic regression analysis	Doxy-PEP Doxy-PrEP	ROBBINS: moderate risk
Park 2021 (47) Status: published	- Acceptability	U.S. (Southern California)	Cross-sectional	MSM (n=212) and healthcare providers (n=76) with prescribing authority in Southern California	Descriptive analysis	Doxy-PEP Doxy-PrEP	ROBBINS: serious risk
Spinelli 2019 (48) Status: published	- Acceptability	U.S. (Atlanta, Birmingham, Chicago, New York, San Francisco and Seattle)	Cross-sectional	Users of a gay social-networking app (96% were cisgender men, 1% TGW, 1% transgender men, and 2% gender queer or nonbinary) (n=8,827)	Descriptive analysis	Doxy-PEP	ROBBINS: critical risk
Tan 2018 (53) Status: published	- Acceptability	Canada (Toronto)	Open label single-arm pilot study	Adult gay and bisexual men at high risk of HIV infection (n=52)	Descriptive analysis	HIV PrEP	RoB2: some concerns
Zhou 2012 (49) Status: published	- Acceptability	China (Beijing)	Cross-sectional from a clinical trial	MSM (n=152)	Descriptive analysis	HIV PrEP	ROBBINS: moderate risk
Newbigging-Lister 2021 (50) Status: only abstract	- Acceptability	U.K.	Cross-sectional	People who used or attempted to obtain HIV PrEP since January 2017 and were UK residents at the time (n=1,502)	Descriptive analysis	Doxy-PEP Doxy-PrEP	ROBBINS: critical risk
Merrill 2023 (52) Status: published	- Acceptability	South Africa	Randomized controlled pilot	Adolescent girls and young women (n=59)	Descriptive analysis	HIV PrEP	RoB2: low risk
Argenyi 2022 (54) Status: published	- Adherence	U.S. (Massachusetts)	Retrospec-tive cohort	People with primary and secondary syphilis living in Massachusetts (n=662)	Descriptive analysis	HIV PrEP	ROBBINS: moderate risk

Table 2: Details of randomized studies addressing the effectiveness of doxycycline prophylaxis

Study ID	Time of recruitment	Sample	Follow-up	Location of STI	STI	Intervention	Comparison	Outcomes
Luetkemeyer 2023 (24)	19 August 2020 to 13 May 2022	501 cisgender gbMSM and TGW who have sex with men on HIV PrEP or HIV+ Doxy-PEP (n=339) No-PEP (n=162)	Median time: 270 days	Pharyngeal, anal, urethral	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum*	200 mg of doxycycline within 72 hours after condomless sex	Standard care without doxycycline	• Incidence of at least one bacterial STI • Incidence of each individual STI • Time to first STI • Tetracycline resistance in *N. gonorrhoeae* and *S. aureus* • Safety • Adverse-event profile • Acceptability
Molina 2018 (25)	20 July 2015 to 21 January 2016	232 cisgender gbMSM and TGW who have sex with men on HIV PrEP Doxy-PEP (n=116) No-PEP (n=116)	Median time: 8.7 months (IQR 7.8–9.7)	Pharyngeal, anal, urethral	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum*	200 mg doxycycline within 24 hours after sex	No prophylaxis	• Occurrence of a first STI • Occurrence of each individual STI • Tetracycline resistance • Adherence • Adverse events
Bolan 2015 (38)	6 September 2011 to 30 January 2012	25 cisgender MSM or TGW living with HIV who had syphilis twice or more since their HIV diagnosis Doxy-PEP (n=13) No-PEP (n=12)	48 weeks	Pharyngeal, anal, urethral	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum*	100 mg doxycycline hyclate, once daily for 36 weeks	Contingency management (CM) with incentive payments for remaining free STDs	• Incidence of at least one bacterial STI • Incidence of each individual STI
Bercot 2019 (43)	July 2015 to June 2016	210 cisgender gbMSM and TGW taking HIV PrEP Doxy-PEP (n=107) No-PEP (n=103)	6 months	Pharyngeal, anal, urethral	*Mycoplasma genitalium*	200 mg of doxycycline within 24 hours after each sexual intercourse (with a limit of 600 mg/week)	No prophylaxis	• Baseline prevalence and incidence of *Mycoplasma genitalium*
Molina 2023 (37)	19 January 2021 to 19 September 2022 (stopped after interim analysis)	502 cisgender gbMSM taking HIV PrEP, with bacterial STI in prior 12 months Doxy-PEP (n=332)	Median time: 9 months IQR (6 to 12)	Not disaggregated	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum*	200 mg doxycycline within 24–72 hours after sex	No PEP	• Time to a first episode of an STI • Time to a first episode of each individual STI

Study ID	Time of recruitment	Sample	Follow-up	Location of STI	STI	Intervention	Comparison	Outcomes
		No-PEP (n=170)			*Mycoplasma genitalium*			
Grennan 2021 (39)	Unknown	52 HIV-negative MSM and TGW with prior syphilis Doxy-PEP (n=26) No-PEP (n=26)	Every 3 months for 1 year	Not disaggregated	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum*	Immediate doxycycline 100 mg daily x 48 weeks	Deferred doxycycline 100 mg daily starting at week 24	• Incidence of at least one bacterial STI • Tolerability acceptability • Tetracycline resistance • Adherence • Microbiome change
Stewart 2023 (36)	5 February 2020 to 30 October 2022	449 18-to-30-year-old cisgender women taking HIV PrEP Doxy-PEP (n=224) No-PEP (n=225)	Quarterly follow-up, weekly SMS surveys on frequency of sex and Doxy use	Vaginal	*Chlamydia trachomatis* *Neisseria gonorrhoeae* *Treponema pallidum* Only disaggregate Chlamydia	200 mg doxycycline within 72 hours of condomless sex	Standard care (quarterly STI testing and treatment after diagnosis)	• Incidence of at least one bacterial STI • Time to a first episode of an STI • Incidence of HIV • Tetracycline resistance • Adverse events

Figure 1. Prisma Chart

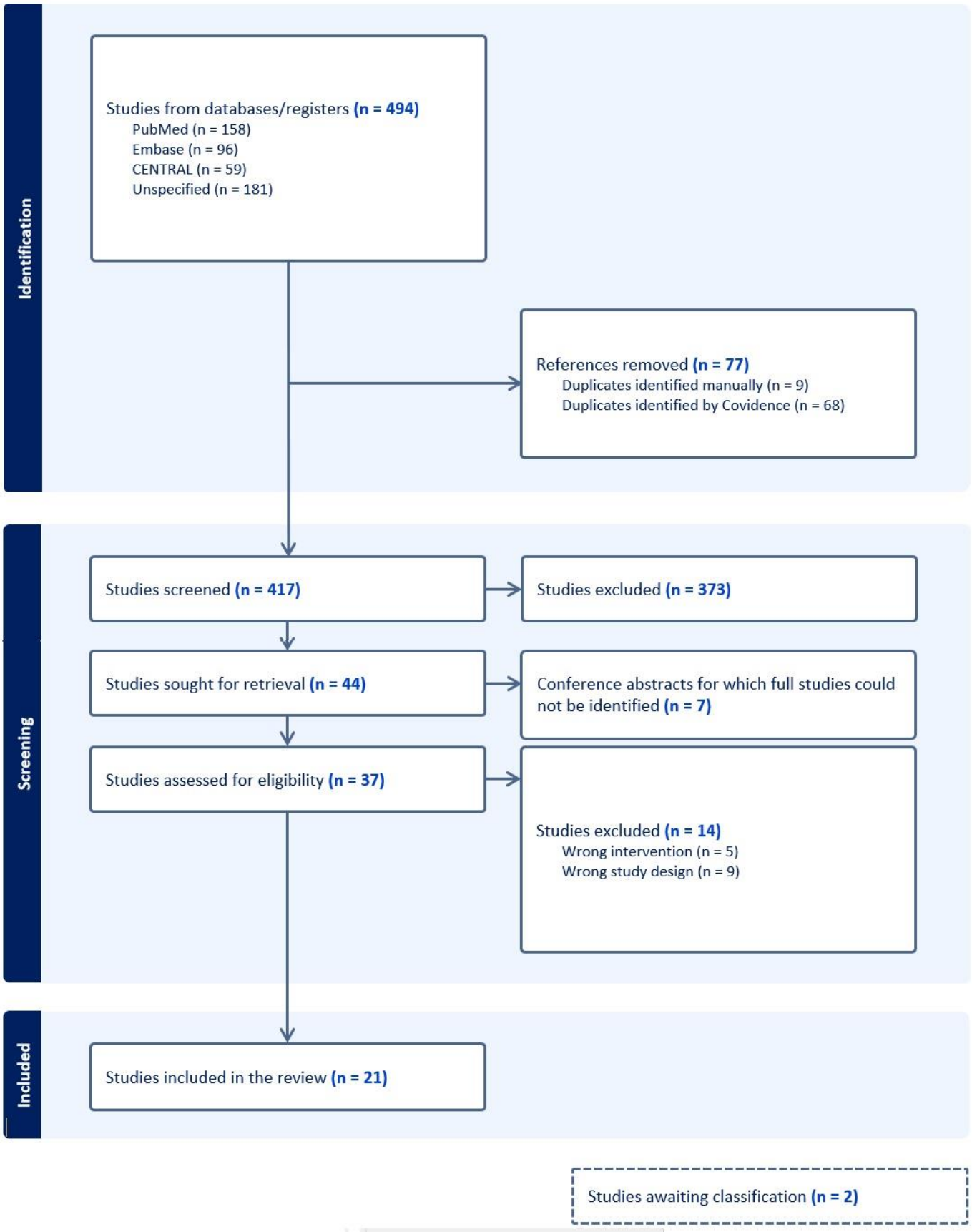
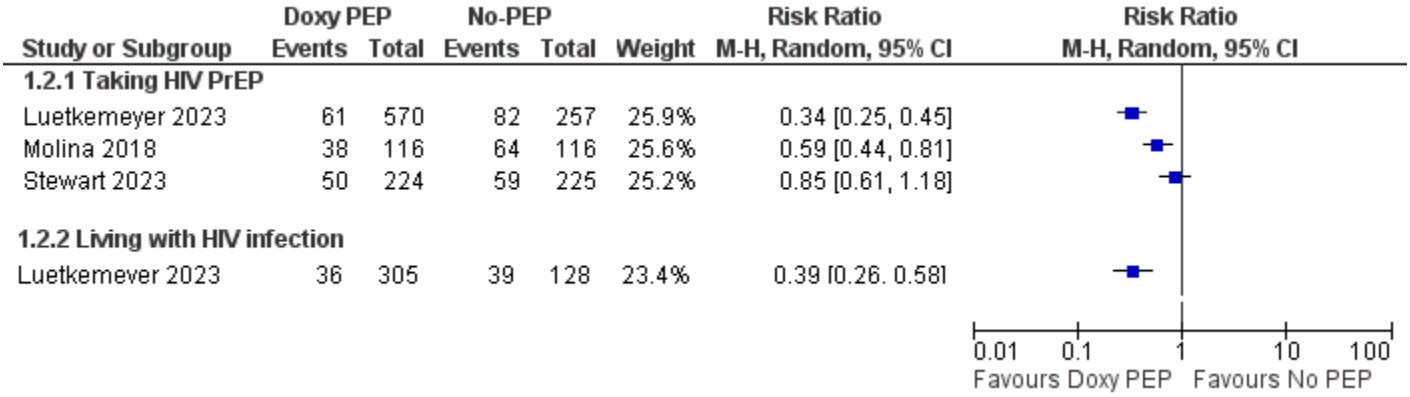
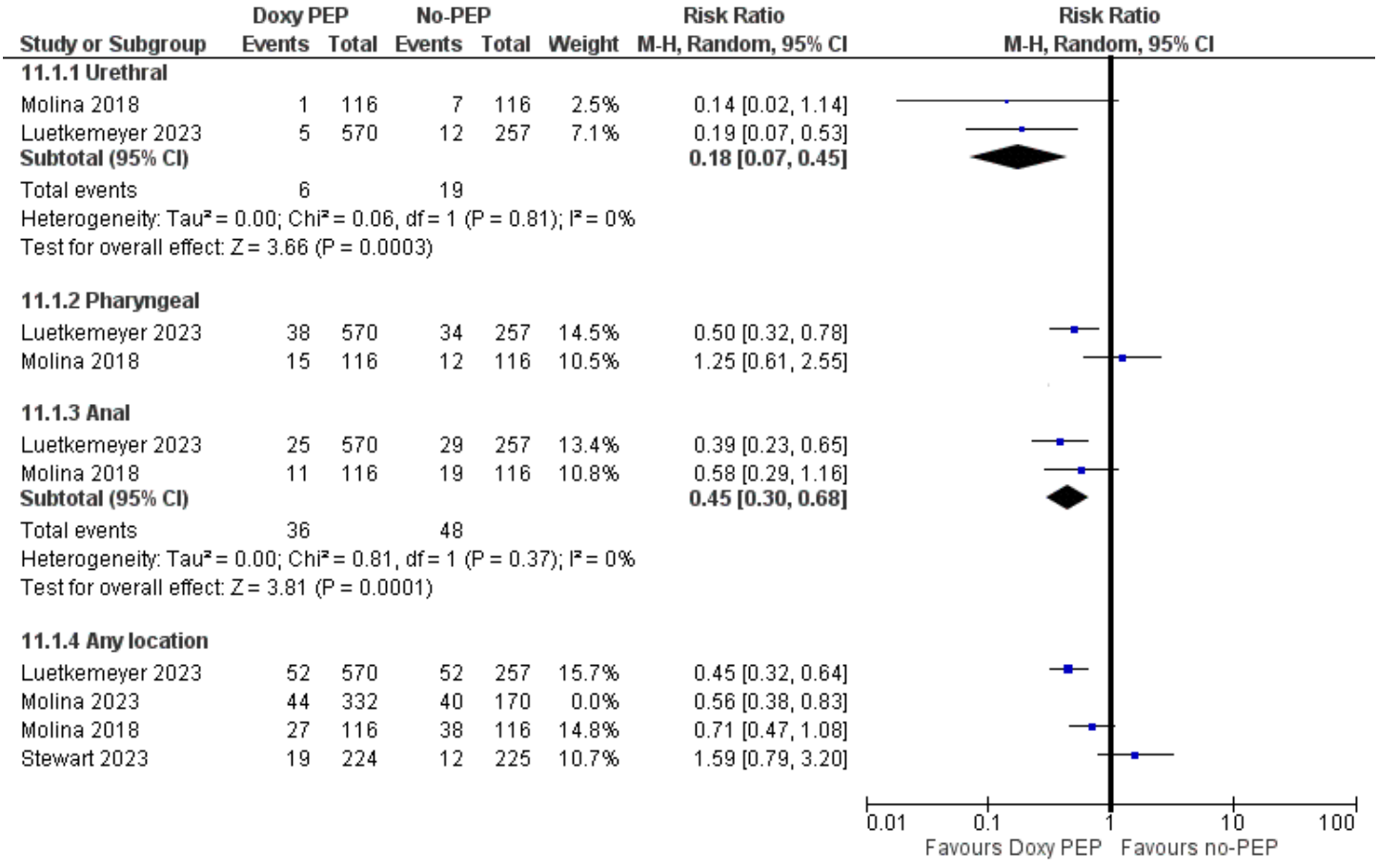


Figure 2. Effectiveness of Doxy-PEP in reducing the incidence of any STI according to reports of the studies*



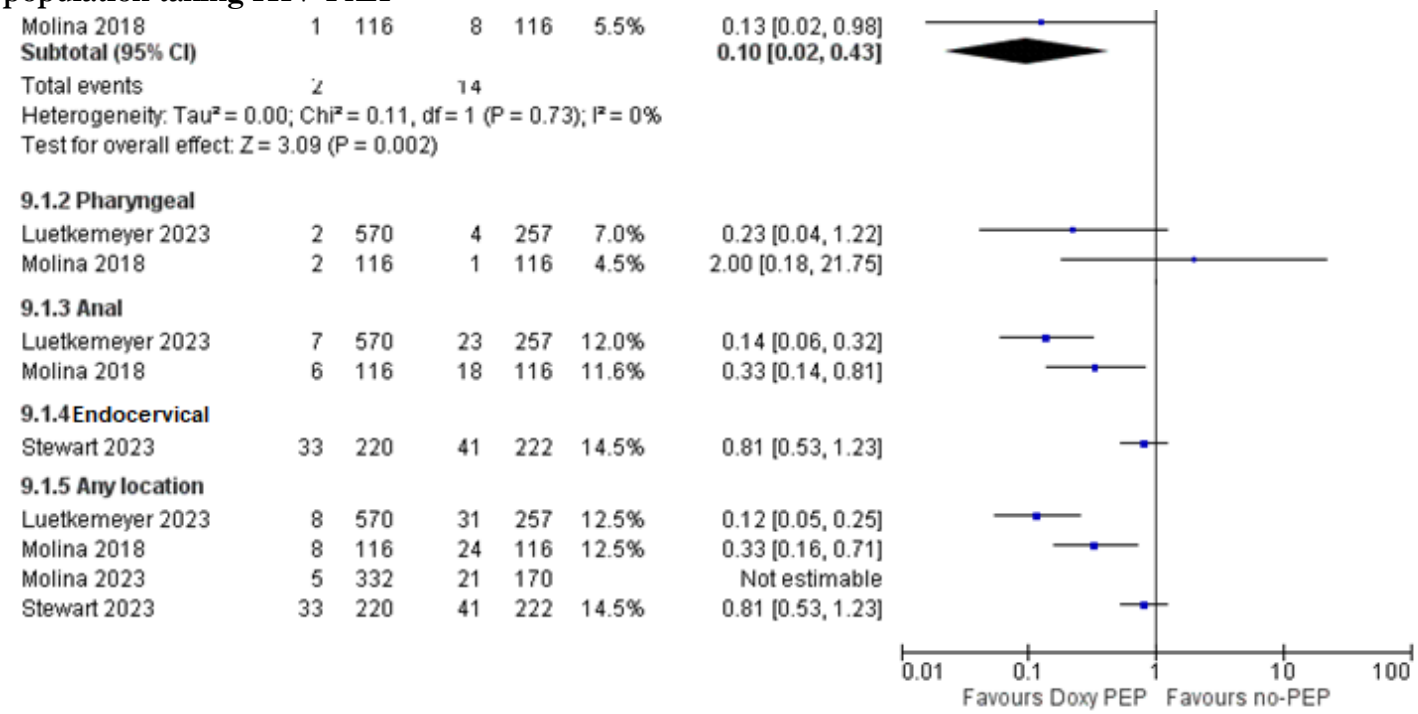
*Notes: Pooled analysis was not provided for this outcome given a heterogeneity higher than 40%. The outcome in Luetkemeyer 2023 was the incidence of any infection per visit, for Molina 2018 the outcome was total infections per person, and for Stewart 2023 the outcome was any infection per person.

Figure 3. Forest plot for the effectiveness of Doxy-PEP in reducing the incidence of gonorrhoea in the population taking HIV-PrEP*



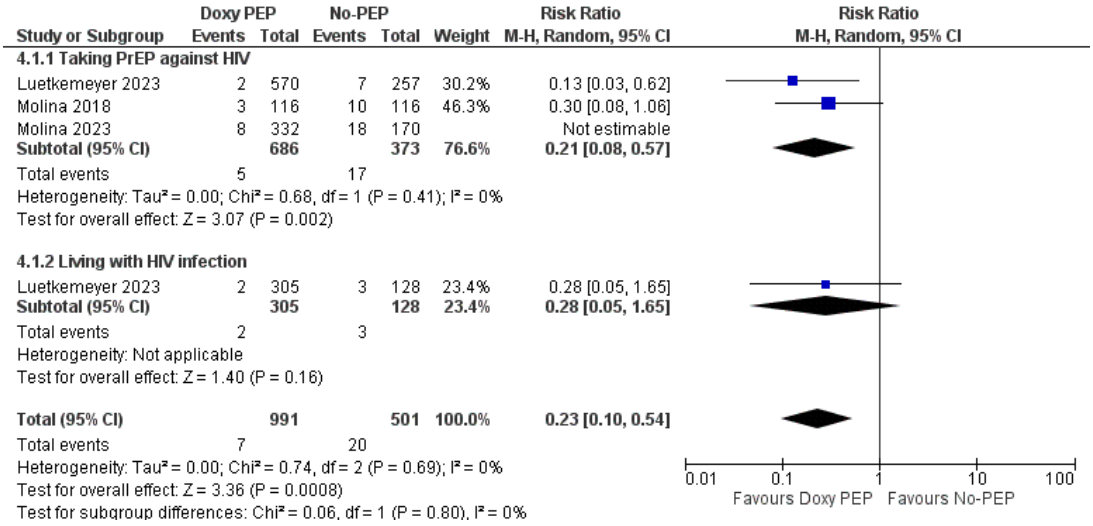
*Notes: Pooled analysis was not provided for pharyngeal and any location for this outcome given a heterogeneity higher than 40%. The outcome in Luetkemeyer 2023 was the incidence of any infection per visit, for Molina 2018 the outcome was total infections per person, and for Stewart 2023 the outcome was any infection per person and only for endocervical location.

Figure 4. Forest plot for the effectiveness of Doxy-PEP in reducing the incidence of chlamydia in the population taking HIV-PrEP*



*Notes: Pooled analysis was not provided for the pharyngeal, anal and any location infection for this outcome given a heterogeneity higher than 40%. The outcome in Luetkemeyer 2023 was the incidence of any infection per visit, for Molina 2018 the outcome was total infections per person, and for Stewart 2023 the outcome was any infection per person and only for endocervical location.

Figure 5. Forest plot for the effectiveness of Doxy-PEP in reducing the incidence of syphilis in the population taking HIV-PrEP and living with HIV infection*



*Notes: The outcome in Luetkemeyer 2023 was the incidence of any infection per visit, and for Molina 2018 the outcome was total infections per person.

Table 3. GRADE tables

Question: Doxy-PEP compared to no PEP for prophylaxis of any bacterial STI (gonorrhea, chlamydia and syphilis)
Setting: People taking HIV PrEP
Bibliography: Luetkemeyer 2023, Molina 2018, Stewart 2023

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxy-PEP	no PEP	Relative (95% CI)	Absolute (95% CI)		
Incidence (follow-up: median 250 days)												
3	randomized trials	not serious	very serious[a]	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect	149/910 (16.4%)	205/598 (34.3%)	**RR 0.45** (0.25 to 0.78)	**189 fewer per 1,000** (from 257 fewer to 75 fewer)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. High heterogeneity among studies (I2=86%)
b. High heterogeneity among studies (I2=89%)

Question: Doxy-PEP compared to no PEP for prophylaxis of *Neisseria gonorrhoeae*
Setting: People taking PrEP for HIV
Bibliography: Luetkemeyer 2023, Molina 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxy-PEP	no PEP	Relative (95% CI)	Absolute (95% CI)		
Incidence (follow-up: median 250 days)												
2	randomized trials	not serious	serious[a]	not serious	serious[b]	all plausible residual confounding would reduce the demonstrated effect	44/686 (6.4%)	40/373 (10.7%)	**RR 0.61** (0.32 to 1.18)	**42 fewer per 1,000** (from 73 fewer to 19 more)	⨁⨁⨁◯ Moderate	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. Heterogeneity for incidence of gonorrhea at any anatomical location was high (I2=77%)
b. Small population size

Question: Doxy-PEP compared to no PEP for prophylaxis of *Chlamydia trachomatis*
Setting: People taking PrEP for HIV
Bibliography: Luetkemeyer 2023, Molina 2018, Stewart 2023

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxy-PEP	no PEP	Relative (95% CI)	Absolute (95% CI)		
Incidence (follow-up: median 260 days)												
3	randomized trials	not serious[a]	serious[a]	not serious	serious[b]	none	49/906 (5.4%)	96/595 (16.1%)	**RR 0.20** (0.07 to 0.55)	**129 fewer per 1,000** (from 150 fewer to 73 fewer)	⨁⨁◯◯ Low	IMPORTANT

CI: confidence interval; **RR:** risk ratio

Explanations
a. Heterogeneity of the pooled incidence for all infection location (genital, oral, and anal) was important (I2 73%)
b. Heterogeneity of the pooled incidence for Chlamydia infection at any anatomical location was important (I2 90%)

Question: Doxy-PEP compared to no PEP for prophylaxis of *Treponema pallidum* (syphilis)

Setting: People taking PrEP for HIV
Bibliography: Luetkemeyer 2023, Molina 2018

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxy-PEP	no PEP	Relative (95% CI)	Absolute (95% CI)		
Incidence (follow-up: median 250 days)												
2	randomized trials	not serious	not serious	not serious	not serious	none	5/686 (0.7%)	17/373 (4.6%)	**RR 0.21** (0.08 to 0.57)	**36 fewer per 1,000** (from 42 fewer to 20 fewer)	⨁⨁⨁⨁ High	IMPORTANT

CI: confidence interval; **RR:** risk ratio

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