Efficacy of postexposure prophylaxis with doxycycline (Doxy-PEP) in reducing sexually transmitted infections

Sokoll, Paulo Roberto; Migliavaca, Celina Borges; Döring, Stephan; Traub, Uschi; Stark, Karlin; Sardeli, Amanda Veiga

DOI:
10.1136/sextrans-2024-056208

This article has been accepted for publication in SEXTRANS following peer review.
The definitive copyedited, typeset version is available online at
10.1136/sextrans-2024-056208

Efficacy of post-exposure prophylaxis with doxycycline (Doxy-PEP) in reducing sexually transmitted infections: A systematic review and meta-analysis

Paulo Roberto Sokoll[1§] (ORCID: 0000-0001-5812-7686)
Celina Borges Migliavaca[2] (ORCID: 0000-0003-1389-2311)
Stephan Döring[1]
Uschi Traub[1]
Karlin Stark[1] (ORCID: 0009-0008-5189-0820)
Amanda Veiga Sardeli[3] (ORCID: 0000-0003-0575-7996)

1 Ludwigsburg District Office, Health Department of Ludwigsburg, Germany
2 National Institute of Science and Technology for Health Technology Assessment (INCT/IATS), Clinical Research Center, Hospital de Clínicas de Porto Alegre (HCPA), Federal University of Rio Grande do Sul, Porto Alegre, Brazil
3 Institute of Inflammation and Ageing, University of Birmingham, United Kingdom

[§] Corresponding author: Paulo Roberto Sokoll
Health Department of Ludwigsburg
Hindenburgstraße 20/1
Ludwigsburg, 71683, Germany
paulo.sokoll88@outlook.de

Declarations

Competing interests: The authors declare no conflicts of interest.

Authors' contributions: PRS is the guarantor of this study and is responsible for the project ideation, study design, data extraction, data analysis, interpretation of results, and manuscript writing. CBM provided methodological guidance and conducted data extraction, data analysis, interpretation of results, and manuscript writing. SD, AVS, and UT acquired data, conducted research on the topic, and wrote the manuscript. KS wrote and corrected the manuscript.

Data availability statement: All data in the study are included in the article or uploaded as supplemental information.

Funding: None

Ethics Statement: Not applicable

Acknowledgments: We would like to thank Dr. Kevin S. Konecny for the grammatical review of this article.

Word count: Abstract: 274 / Main Text: 3075

ABSTRACT

Objectives: This systematic review aimed to identify the efficacy, adherence, safety, and impact on antimicrobial resistance of Doxy-PEP in different populations.

Methods: We searched MEDLINE (via PubMed), Embase, and Cochrane CENTRAL databases from inception to May 29, 2024. Two reviewers independently screened the studies and extracted data. We included randomized clinical trials that evaluated the efficacy of Doxy-PEP within 72 hours after condomless sex. A random-effects meta-analysis was conducted to compare the risk of bacterial sexually transmitted infections (STIs) between Doxy-PEP and no prophylaxis. The risk of bias was assessed with the RoB 2 tool and the certainty of evidence with GRADE. PROSPERO registration number: CRD42023454123.

Results: Four studies were included in the systematic review, totalling 1727 participants. Studies were conducted between 2015 and 2022. Most participants (73%) were men who have sex with men (MSM), and the median age of participants varied from 24 to 43 years. Doxy-PEP reduced the risk of having any bacterial STI in different populations by 46% (HR 0.54; 95% CI 0.39-0.75) certainty of evidence [CoE] moderate), the risk of chlamydia by 65% (RR 0.35; 95% CI 0.15-0.82; CoE low), and syphilis by 77% (RR 0.23; 95% CI 0.13-0.41; CoE high), without significant effect for risk of gonorrhea infection (RR 0.90; 95% CI 0.64-1.26; CoE very low). The self-reported adherence rate of Doxy-PEP was approximately 80% and one drug-related serious adverse event was reported.

Conclusion: Doxy-PEP reduced the incidence of chlamydia and syphilis infections. No significant reduction in gonorrhea infection was observed. This strategy seems promising for some high-risk groups; however, there is still a lack of information on the induction of bacterial resistance and long-term adverse events.

Keywords: Doxycycline, Post-exposure prophylaxis, Sexually Transmitted Infections, Syphilis, Gonorrhea, Chlamydia

WHAT IS ALREADY KNOWN ON THIS TOPIC

The incidence of bacterial sexually transmitted infections (STIs) such as chlamydia, gonorrhea, and syphilis remains alarming, especially in groups exposed to higher risk.
The prophylactic use of 200 mg of doxycycline within 72 hours after unprotected sex (Doxy-PEP) has emerged as a potential approach against these infections.

WHAT THIS STUDY ADDS

In our systematic review, we observed that Doxy-PEP reduced the risk of having any bacterial STI by 46% in different populations. In men who have sex with men (MSM) and transgender women alone, Doxy-PEP reduced this risk by 53%.
Doxy-PEP has shown efficacy in reducing chlamydia and syphilis but is not effective against gonorrhea.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

This systematic review presents pooled data that may help clinicians and patients make shared decisions about using Doxy-PEP.
Moreover, our review indicates that further research involving Doxy-PEP is needed, especially to assess the issue of long-term adverse events and the development of bacterial resistance.

INTRODUCTION

The World Health Organization (WHO) estimates that globally, approximately one million sexually transmitted infections (STIs) are acquired daily, resulting in approximately 374 million new cases annually.[1] Bacterial STIs such as chlamydia, gonorrhea, and syphilis continue to pose a significant public health challenge, particularly among high-risk populations, such as men who have sex with men (MSM), transgender women, and sex workers.[1]

Although the cases of chlamydia and gonorrhea decreased worldwide between 1990 and 2019,[2] studies report that the incidence of syphilis has increased significantly, especially among MSM[2 3] and women of reproductive age.[4 5]

These trends underscore the need for comprehensive public health interventions, as highlighted by the WHO Global Health Sector Strategy on STIs, which aims to end the epidemics of these infections by 2030.[6]

To reduce the incidence of bacterial STIs, the prophylactic use of doxycycline has been investigated as a potential approach.[7 8] Data from a study published in 2015 involving HIV-positive MSM and transgender women observed that participants who took doxycycline prophylactically were significantly less likely to test positive for bacterial STIs.[8]

Doxycycline, a second-generation tetracycline introduced in 1967, inhibits bacterial protein synthesis and is effective against some STI-causing bacteria, such as *Chlamydia trachomatis* (CT) and *Treponema pallidum* (TP), in the absence of resistance mechanisms.[9] As a drug that is considered safe and well tolerated,[9 10] doxycycline is also well accepted, and there is great interest among some MSM in its use as a form of STI prophylaxis.[11]

Doxy-PEP involves taking a 200 mg dose of doxycycline within 72 hours of unprotected sex, and this regimen has been shown to be effective in reducing bacterial STIs in MSM.[12]

There is still disagreement among available guidelines as to what criteria are necessary for the use of Doxy-PEP. However, in general, Doxy-PEP may be considered for MSM or transgender women who have had at least one bacterial STI in the last 12 months and are engaged in condomless sex with more than one male partner.[13-17]

Although potentially effective, there are still issues of concern regarding Doxy-PEP, such as the possible induction of bacterial resistance and the high rates of tetracycline-resistant *Neisseria gonorrhoeae* (NG) that have already been reported in some settings.[18] For this reason, some guidelines and position statements indicate that Doxy-PEP should be prescribed cautiously, and clinicians should evaluate the potential risks and benefits of this prophylaxis on a case-by-case basis.[13 15-17 19]

These unresolved issues highlight the complexity of recommending Doxy-PEP, and a comprehensive synthesis of existing evidence could aid in formulating informed public health policies. Therefore, this systematic review and meta-analysis aimed to assess the efficacy, adherence, safety, and association with antimicrobial resistance of Doxy-PEP in different populations.

METHODS

Study design and protocol

We conducted a systematic review in accordance with the Cochrane Handbook for Systematic Reviews of Interventions[20] and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; supplementary material 1).[21] The protocol of this study was registered at the International Prospective Register of Systematic Reviews (PROSPERO), on August 27, 2023 (CRD42023454123).

Literature search

We searched MEDLINE (via PubMed), Embase, and Cochrane CENTRAL from inception to May 29, 2024. The complete search strategy is presented in supplementary material 2. The search terms used were doxycycline, post-exposure prophylaxis, and sexually transmitted infections, including controlled vocabularies (such as MeSH and Emtree) and synonyms. The searches did not include language or other restrictions such as type or date of publication. We used EndNote (V.20, Thomson Reuters) to deduplicate the retrieved records. We also screened the reference lists of the included studies for additional studies.

Study selection and eligibility criteria

Two reviewers (PRS and CBM) independently screened the titles and abstracts of all the retrieved references and read the full texts of the potentially eligible papers. Disagreements regarding study selection were resolved through consensus or by a third reviewer (AVS). Title and abstract screening were conducted using Rayyan, and full-text review with a MS Excel spreadsheet designed for the review.

We included randomized clinical trials evaluating the efficacy of Doxy-PEP (a single dose of 200 mg of doxycycline within 72 hours after condomless sex) in comparison with no doxycycline use. The primary outcomes of interest were the risk of having any STI, risk of chlamydia, risk of gonorrhea, and risk of syphilis infection. We also evaluated data referring to adherence, antimicrobial resistance, and drug-related adverse events. There were no restrictions related to the population of the studies, the duration of follow-up, or the study's language, date, country, or type (full text or conference abstract) of publication. We excluded secondary studies, such as reviews or guidelines, and studies assessing the efficacy of doxycycline prophylaxis for non-sexually transmitted bacterial infections.

Data extraction

Two independent reviewers (PRS and CBM) extracted the data using a MS Excel spreadsheet developed for this systematic review. Disagreements were resolved through consensus or by a third reviewer (AVS). The following data were extracted from each included study: study identification (authors, year of publication, full title, DOI), year and country of study conduction, details of the intervention, control, and population studied, time of follow-up, number of individuals included, characteristics of participants (age, gender, use of HIV PrEP), and outcomes of interest. In case of missing data from the included studies, we contacted the corresponding authors via e-mail to request the necessary information.

Assessment of risk of bias and certainty of evidence

Two reviewers (PRS and CBM) assessed the risk of bias for each individual outcome, for each study, using the RoB 2 tool,[22] attributing a judgment of low, some concerns, or high risk of bias for each domain. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework[23] by two reviewers (PRS and CBM). Disagreements were resolved by consensus or by a third reviewer (AVS). Publication bias was not evaluated considering the small number of included studies.

Data analysis

For efficacy results, we conducted a random effects meta-analysis using the inverse variance method and presented the results as hazard ratio (HR), preferably, or as relative risks (RR), depending on the data available, and 95% confidence intervals (95% CI). Statistical heterogeneity was assessed with the I^2. For all outcomes, we showed the results for the subgroups of MSM or transgender women and cisgender women, as well as the overall effect across these subgroups. All analyses were conducted using R (V.4.2.3) and the package meta (V.6.2-1). Adherence, safety, and antimicrobial resistance outcomes were described narratively, due to the varied presentation of these data in the included studies.

RESULTS

Study selection

The search identified a total of 1207 references, of which 141 were removed as duplicates. We screened 1066 titles and abstracts and read the full text of 28 of them. Of these, four studies met the inclusion criteria and were included. These four studies were reported in five publications.[12 24-27] The complete study selection process is depicted in Figure 1. The list of studies excluded after full-text review is available in supplementary material 3.

Figure 1. PRISMA Flowchart

Main characteristics of the included studies

Table 1 shows the main characteristics of the included studies. The studies were carried out between 2015 and 2022. Two of them (50%) were conducted in France (there was no overlap of participants between these two studies),[12 27] one in the United States of America (USA)[24] (25%), and one in Kenya[25 26] (25%). A total of 1727 individuals were included (1041 in the intervention groups and 686 in the control groups). Of these participants, 1259 (73%) were MSM, 19 (1%) were transgender women, and 449 (26%) were cisgender women. Across all studies, the median age of the included participants ranged from 24 to 43 years old. During the study period, 1553 (90%) participants were taking HIV PrEP. In three studies,[12 24 27] all participants reported having multiple sexual partners during study follow-up. Polymerase chain reaction (PCR) was used to detect CT and NG, while serological tests were used to detect TP.

Risk of bias and certainty of evidence

The complete risk of bias assessment for the four included studies is reported in supplementary material 4. The assessment of all outcomes for each study was consistent. Therefore, the assessment is reported by grouping all evaluated outcomes from each study. No study was classified as having a high risk of bias. The ANRS IPERGAY study[12] was classified as having a low risk of bias across all domains and overall. The other three studies[24-27] were judged to have some concerns regarding the risk of bias. In these studies, the concerns mainly arose from the fact that patients and those delivering the intervention were aware of the intervention to which participants had been assigned; it was unclear whether there were deviations from the intended intervention that might have arisen due to the trial context. In the DoxyPEP study,[24] there were additional concerns related to missing outcome data, since 21% of randomized participants were not included in their main analyses.

The certainty of evidence, assessed with GRADE, is presented along with the outcomes and is reported in detail in the supplementary material 5.

Study (NCT)	Country and years of study conduction	Follow-up (months; median (IQR))	Population	N (intervention/ control)	Age (years; median (IQR))	Gender identity (N)	Number of sexual partners in the past 3 months (median; (IQR))	Bacterial STI diagnostic at baseline (n; (%))[a]
ANRS IPERGAY[12] (NCT01473472)	France 2015 - 2016	8.7 (7.8 - 9.7)	HIV-negative MSM taking HIV PrEP, aged 18 years or older, and at high risk for HIV, with at least two different partners during the past 6 months.	116 / 116	Intervention: 38 (33 - 48) Control: 39 (32 - 44)	232 men (MSM)[b]	Intervention: 10 (5 - 15)[c] Control: 10 (5 - 15)[c]	Intervention: 22 (19%) Control: 16 (14%)
DoxyPEP[24] (NCT03980223)	USA 2020 - 2022	9 (3.5 - 12.4)	MSM and transgender women taking HIV PrEP or PLWH, aged 18 years or older, with a history of condomless anal or oral sex with men in the previous 12 months, and with a history of bacterial STI in the prior 12 months.	339 / 162	Intervention: - HIV PrEP: 36 (31 - 42) - PLWH: 43 (36 - 54) Control: - HIV PrEP: 36 (31 - 42) - PLWH: 42 (37 - 50)	Intervention: - HIV PrEP: 212 men (MSM), 8 transgender women - PLWH: 109 men (MSM), 10 transgender women Control: - HIV PrEP: 107 men (MSM) - PLWH: 54 men (MSM), 1 transgender woman	Intervention: - HIV PrEP: 8 (4 - 17) - PLWH: 7 (3 - 18.5) Control: - HIV PrEP: 10 (5 - 16.5) - PLWH: 10.5 (3 - 20)	Intervention: - HIV PrEP: 65/219 (30%) - PLWH: 34/114 (30%) Control: - HIV PrEP: 27/106 (25%) - PLWH: 20/55 (36%)
DoxyVAC[27] (NCT04597424)	France 2021 - 2022	14 (9 - 18)	MSM, aged 18 years or older, on HIV PrEP, with a history of bacterial STI in the prior 12 months and no STI symptoms.	362 / 183	Intervention: 40 (34 - 49) Control: 40 (34 - 48)	545 men (MSM)[b]	Intervention: 10 (5 - 20) Control: 10 (5 - 20)	Intervention: 82 (23%) Control: 37 (20%)
dPEP Kenya Stud[25 26] (NCT04050540)	Kenya 2020 - 2022	12 (NR)	Nonpregnant cisgender women, aged 18 to 30 years, receiving daily doses of HIV PrEP.	224 / 225	Intervention: 24 (22 - 27) Control: 24 (22 - 27)	449 cisgender women[b]	Intervention: 2 (1 - 5) Control: 2 (1 - 4)	Intervention: 40 (18%) Control: 40 (18%)

Table 1. Main characteristics of the included studies and their participants

1 IQR = interquartile range; NR = not reported; PLWH = people living with HIV; USA = United States of America. [a] *Neisseria gonorrhoeae*, *Treponema pallidum*, or *Chlamydia trachomatis*
2 infection. [b] Considering both intervention and control groups. [c] In the past 2 months.

Efficacy of Doxy-PEP

Four studies[12 24-27] with 1727 participants were included in the primary meta-analysis (Figure 2). Considering both populations, Doxy-PEP reduced the risk of having any bacterial STI (CT, NG, or TP) by 46% (HR 0.54; 95% CI 0.39-0.75). In MSM or transgender women this effect was 7% greater (53% [HR 0.47; 95% CI 0.38-0.60]). However, no effect was observed for cisgender women (HR 0.95; 95% CI 0.64-1.42). The certainty of evidence for this outcome was classified as high for MSM or transgender women but moderate for cisgender women due to imprecision (supplementary material 5).

Figure 2. Hazard ratio of the incidence of first episode of STI between Doxy PEP and no Doxy PEP.

Figure 3 shows the meta-analyses of the effect of Doxy-PEP on CT, NG, and TP infection, for both MSM or transgender women and cisgender women.

In the subgroup of MSM or transgender women, Doxy-PEP reduced the risk of chlamydia by 78% (RR 0.22; 95% CI 0.13 - 0.38), gonorrhea by 22% (RR 0.78; 95% CI 0.65 - 0.94), and syphilis by 77% (RR 0.23; 95% CI 0.13 - 0.41). For the subgroup of cisgender women, there was no significant effect of Doxy-PEP on the risk of chlamydia (RR 0.73; 95% CI 0.47 - 1.13) or gonorrhea (RR 1.64; 95% CI 0.78 - 3.46).

Considering both populations, the average effect on risk reduction was 65% for chlamydia (RR 0.35; 95% CI 0.15 - 0.82) and 10% for gonorrhea (RR 0.90; 95% CI 0.64 - 1.26).

Figure 3. Risk ratio of the incidence of first episode of CT, NG or TP infection between Doxy PEP and no Doxy PEP.

A: *Chlamydia trachomatis* (CT); B: *Neisseria gonorrhoeae* (NG); C: *Treponema pallidum* (TP)

Safety of Doxy-PEP

Table 2 summarizes the results for the safety of Doxy-PEP, including the outcomes: drug-related adverse events (AEs), drug-related serious adverse events (SAEs), and discontinuation of doxycycline due to AEs or SAEs.

The proportion of individuals reporting AE associated with the use of doxycycline ranged from 2 to 25%.

In total, 60 drug-related AEs were reported. Most events were gastrointestinal (such as nausea, diarrhea, and abdominal pain). Isolated events such as skin rash, headache, migraine, and abnormal transaminase have also been reported. In the DoxyVAC study,[27] one individual experienced a drug-related SAE (fixed drug eruption).

The proportion of discontinuation due to drug-related varied from 0,9 to 7% between the studies.

Adherence to Doxy-PEP

Adherence to Doxy-PEP was self-reported by participants and assessed through various metrics in the included studies, including the percentage of eligible sexual encounters in which Doxy-PEP was used, the proportion of patients with consistent use (defined as always or often) and the use of Doxy-PEP after the last sexual encounter.

In addition, three studies[12 25-27] evaluated the concentration of doxycycline in biological samples collected from the participants. The authors of ANRS Ipergay[12] found that during the entire study period, only 30% (141 of 465) of the plasma samples collected from the intervention group had detectable doxycycline concentrations. However, the used assay could only detect concentrations within 48 hours of drug intake.

In the DoxyVAC study,[27] 62% (167 of 270) of the plasma samples and 69% (188 of 272) of the urine samples from participants enrolled to intervention group showed doxycycline concentrations above the author's limit of quantification.

In contrast, in the dPEP Kenya study,[25 26] 50 participants from the intervention group were randomly chosen to evaluate doxycycline concentrations in hair samples. Hair testing detected doxycycline in 58 of 200 hair samples (29%) and revealed that 44% of participants assigned to the intervention may not have taken any doxycycline dose, contradicting the participant's self-reported adherence.

Overall, considering these different measurement methods, the self-reported adherence rate was approximately 80%. Additionally, the studies provided information on the median monthly dosage of doxycycline, which ranged from 400 mg to 700 mg. Detailed results are shown in table 2.

Antimicrobial resistance after use of Doxy-PEP

Based on the available evidence, a definitive association between the use of Doxy-PEP and the development of bacterial resistance could not be conclusively established, mainly due to the limited number of cultured samples across studies.

In the ANRS IPERGAY study,[12] only two participants in the Doxy-PEP group had a positive culture for NG, and none were tetracycline-resistant. In comparison, in the control group, there were six patients with positive cultures, of which four were resistant.

Two participants from each group had a positive culture of CT, and no resistance against tetracyclines was detected; all minimum inhibitory concentrations (MICs) fell within normal ranges.

In the DoxyPEP study,[24] at baseline, resistance was detected in 4 out of 15 (27%) NG isolates from patients enrolled in both groups. During follow-up, 5 out of 13 (38%) NG isolates from the Doxy-PEP group and 2 out of 16 (12%) from the control group were tetracycline-resistant. The authors also attempted to determine the association between Doxy-PEP and the increase in resistant *Staphylococcus aureus* strains in oronasopharyngeal samples. After 12 months of intervention, *Staphylococcus aureus* carriage was lower in the intervention group; however, a higher rate of resistance was found in this group.[24]

In the dPEP Kenya study,[25 26] tetracycline-resistance was assessed by the presence of the *tet*(M) gene for NG and the *tet*(C) gene for CT. The gene *tet*(M) was detected in all samples, at both baseline and during follow-up. No *tet*(C) gene was detected.

In the DoxyVAC study,[27] all NG isolates were tetracycline resistant at both baseline and follow-up. High-level resistance was more common in the Doxy-PEP group than in the control group. Resistance in CT isolates was not detected. The authors also observed no change in the rate of β-lactamase-producing *Eschrerichia coli* in rectal swabs, and the detection rate of methicillin-resistant *Staphylococcus aureus* increased slightly during follow-up; however, there was no statistically significant difference between the groups.

No study has reported the evaluation of resistance in TP samples. Detailed results are shown in table 2.

Table 2. Adherence, safety, and antimicrobial resistance associated with the use of Doxy-PEP.

Study (NCT)	Safety n / N (%)	Doxy-PEP adherence	Antimicrobial resistance
ANRS IPERGAY[12] (NCT01473472)	Any drug-related SAEs: NR Any drug-related AEs: 29/116 (25%) Discontinuation due to drug-related AEs: 8/116 (7%)	Median (IQR) intake per month: 6.8 (2.8-14.5) pills, equivalent to 680 (280-1450) mg Use of Doxy-PEP up to 24 hours after sexual intercourse in 232 (83%) out of 280 occurrences.	NG: During follow-up 9 cultures, from 8 patients (2 in the Doxy-PEP group and 6 in the control group), were available for tetracycline resistance testing. Intermediate resistance was detected in 3 isolates[b] and full resistance in 4 (all from the control group). *Tet*(M) was identified in 1 of the resistant isolates. All resistant isolates were positive for the Val57Met mutation in the *rpsJ* gene and for mutations associated with MtrCDE (antibiotic efflux pump). CT: During follow-up, 5 cultures from 4 participants (2 in each group) were available for tetracycline resistance testing; no resistance was identified.
DoxyPEP[24] (NCT03980223)	Any drug-related SAEs: 0/339 (0%) Any drug-related AEs: 6/339 (2%) Discontinuation due to drug-related AEs: 7/[33]9 (2%)[a]	Median (IQR) intake per month: 4.0 (1.0-10.0) pills, equivalent to 400 (100-1000) mg Consistent use (always or often) of Doxy-PEP up to 72 hours after condomless anal or vaginal sex was reported by 291 (86%) participants; 207 (71%) reported never missing Doxy-PEP.	NG: At baseline, 15 cultures (7 from the Doxy-PEP group and 8 from the control group) were available for tetracycline resistance testing; 2 (29%) in the Doxy-PEP group and 2 (25%) in the control group were resistant. During follow-up, 29 cultures (13 in the Doxy-PEP group and 16 in the control group) were available for tetracycline resistance testing; 5 (39%) in the Doxy-PEP group and 2 (13%) in the control group were resistant. MRSA: At baseline, isolates from 45% of the participants were collected (both groups) and 12% of these isolates had doxycycline-resistant strains. During follow-up (at month 12), *S. aureus* was isolated in 28% of the samples from the doxycycline groups and 47% in the standard-care groups with doxycycline-resistant isolates in 16% and 8%, respectively (overall percentage with resistance, 5% in the doxycycline groups and 4% in the standard-care groups).
DoxyVAC[27] (NCT04597424)	Any drug-related SAEs: 1/362 (0,3%) Any drug-related AEs: 25/362 (7%) Discontinuation due to drug-related AEs: 6/362 (2%)	Median (IQR) intake per month: 6.0 (3.0-13.0) pills, equivalent to 700 (400 - 1100) mg Median (IQR) time to Doxy-PEP intake: 15 (5-30) hours after sex Use of Doxy-PEP at last sexual intercourse was reported by 91 (79.8%) participants after 12 months of follow-up.	NG: At baseline, 7 cultures were available for tetracycline resistance testing; during follow-up, 71 cultures (31 in the Doxy-PEP group and 40 in the control group) were available for tetracycline resistance testing. At both baseline and during follow-up, all cultures were tetracycline-resistant. 11 (35.5%) in the Doxy-PEP group and 5 (12.5%) in the control group presented high-level resistance (p=0.047).

			CT: During follow-up, 4 cultures in the control group were available for tetracycline resistance testing; none were tetracycline-resistant. 68 PCR swabs (8 in the Doxy-PEP group and 60 in the control group) were sequenced; no tetracycline-resistance-associated mutation was found. MRSA: At baseline, MRSA was detected in 1.9% of participants in the Doxy-PEP group and in 1.1% in the control group. During follow-up (at month 18), MRSA was detected in 12.1% of the participants in the Doxy-PEP group and in 10.3% in the control group. ESBL *E.coli*: At baseline, ESBL *E.coli* was detected in 31.9% of participants in the Doxy-PEP group and in 32.6% in the control group. During follow-up (at month 18), ESBL *E.coli* was detected in 36.4% of the participants in the Doxy-PEP group and in 38.7% in the control group.
dPEP Kenya Study[25 26] (NCT04050540)	Any drug-related SAE: 0/224 (0%) Any drug-related AE: NR Discontinuation due to drug-related AEs: 6/224 (3%)	Median (IQR) intake per month: 4.0 (0-8.0) pills, equivalent to 400 (0 - 800) mg Nearly all of the last doxycycline doses that were reported to have been taken were within 24 hours after sexual intercourse (reported at 575 of 579 visits).	NG: At baseline and during follow-up, *tet(M)* prevalence was 100% in both groups. CT: At baseline and during follow-up, *tet(C)* prevalence was 0% (20 samples at baseline and 56 during follow-up [25 in the Doxy-PEP group and 31 in the control group]).

[a] Also include cases of doxycycline discontinuation due to patient preference. [b] Authors do not report which samples belong to which group (intervention or control), AEs: Drug-related adverse events related to Doxy-PEP, SAEs: Drug-related serious adverse events related to Doxy-PEP, NR: Not reported, PCR: Polymerase chain reaction, MRSA: Methicillin-resistant *Staphylococcus aureus*, *S.aureus: Staphylococcus aureus,* ESBL: *Extended-spectrum beta-lactamase, E.coli: Escherichia coli*

DISCUSSION

In this systematic review, we observed that Doxy-PEP reduced the risk of having any bacterial STI (TP, CT, or NG) in different populations by 46%. Specifically, Doxy-PEP significantly reduced the risk of TP infection by 77% and CT infection by 65%, while it did not reach significance in reducing the risk of NG infection (10%).

Among MSM and transgender women, Doxy-PEP reduced the risk of any bacterial STI by 53%. On the other hand, among cisgender women, this reduction was only 5%, which may be related to non-adherence to Doxy-PEP, as evidenced by the low levels of the doxycycline detected in participants' hair samples.

Regarding safety, doxycycline has been shown in different studies to be a safe drug,[6 7 26] and the most common adverse events are gastrointestinal symptoms such as diarrhea, nausea, vomiting, as well as skin disorders.[7] These same symptoms were experienced by approximately 6% (61 of 1041) of the participants in the intervention groups.

The self-reported adherence rate to Doxy-PEP remained around 80%, and many participants described the drug as well tolerated, which aligns with the findings of other studies that reported good tolerability.[6 7] In addition, studies show that there is a high interest among MSM in using Doxy-PEP,[11 28 29] and there is also evidence that doxycycline is already being used prophylactically against STIs in some non-trial settings.[13 30]

The development of bacterial resistance mechanisms as a result of the frequent use of Doxy-PEP remains to be clarified. Although the authors of the included studies attempted to address this issue, the limited number of samples that yielded a positive culture prevented a definitive conclusion. Nevertheless, in the DoxyVAC study,[27] there was a significant increase in high-level resistant NG samples in the intervention group. Also, a high rate of resistant NG strains was identified at the baseline of some included studies.[25-27] These findings reinforce that doxycycline should not be recommended as the first choice for treating NG.[10]

Another important fact to emphasize is that bacterial resistance among MSM is becoming increasingly common[18 31 32] and the frequent use of antibiotics may further contribute to the increase in these cases.[33] This information should be considered and well discussed between clinicians and patients before initiating Doxy-PEP.

Our review has some limitations, such as the small number of studies included and the short duration of follow-up. Furthermore, except for the dPEP Kenya study,[25 26] the characteristics of the participants were very similar: MSM, living in high-income countries, and most of them HIV PrEP users. Although these limitations prevent the extrapolation of our findings to a broader population level, these groups have an elevated risk of STIs; thus, it makes sense that the current studies are directing their effort to them.

Despite these limitations, our study used a robust methodology to synthetize the available evidence, providing important information that can support evidence-based decisions regarding new public health policies.

In summary, Doxy-PEP has shown significant potential in reducing CT and TP incidence, particularly in MSM; however, this approach is not significantly effective in reducing NG.

There is a lack of clinical trials testing the efficacy of this strategy in other populations, such as heterosexual cisgender men and women with increased risk of STIs exposure and sex workers, for example.

Future studies need to explore the long-term adverse events, the impact of Doxy-PEP on antimicrobial resistance rates through a significant number of samples, and changes in the participants' microbiome. This information is crucial to understand the risks and benefits of Doxy-PEP and to recommend it in different settings.

SUPPLEMENTARY MATERIALS

Supplementary material 1: PRISMA Statement

Supplementary material 2: Complete search strategies

Supplementary material 3: List of excluded after reading full-text

Supplementary material 4: Critical appraisal of included studies with RoB 2

Supplementary material 5: Certainty of evidence assessment with GRADE

REFERENCES

1. World Health Organisation (WHO). Sexually transmitted infections (STIs): WHO; 2019 [Available from: https://www.who.int/news-room/fact-sheets/detail/sexually-transmitted-infections (stis)#:~:text=STIs%20have%20a%20profound%20impact,and%20trichomoniasis%20(156%20million) accessed 11 March 2024.

2. Fu L, Sun Y, Han M, et al. Incidence Trends of Five Common Sexually Transmitted Infections Excluding HIV From 1990 to 2019 at the Global, Regional, and National Levels: Results From the Global Burden of Disease Study 2019. *Front Med (Lausanne)* 2022;9:851635. doi: 10.3389/fmed.2022.851635 [published Online First: 20220302]

3. Tsuboi M, Evans J, Davies EP, et al. Prevalence of syphilis among men who have sex with men: a global systematic review and meta-analysis from 2000-20. *Lancet Glob Health* 2021;9(8):e1110-e18. doi: 10.1016/s2214-109x(21)00221-7 [published Online First: 20210708]

4. Geremew H, Geremew D. Sero-prevalence of syphilis and associated factors among pregnant women in Ethiopia: a systematic review and meta-analysis. *Syst Rev* 2021;10(1):223. doi: 10.1186/s13643-021-01786-3 [published Online First: 20210812]

5. García-Cisneros S, Herrera-Ortiz A, Olamendi-Portugal M, et al. Re-emergence of syphilis in women of reproductive age and its association with the increase in congenital syphilis in Mexico during 2010-2019: an ecological study. *BMC Infect Dis* 2021;21(1):992. doi: 10.1186/s12879-021-06680-w [published Online First: 20210923]

6. World Health Organization (WHO). Global health sector strategies on, respectively, HIV, viral hepatitis and sexually transmitted infections for the period 2022-2030: WHO; 2022 [Available from: https://iris.who.int/bitstream/handle/10665/360348/9789240053779-eng.pdf?sequence=1 accessed 11 March 2024

7. Joseph S. Initiation of doxycycline pre-exposure prophylaxis in patients attending an HIV PrEP clinic—Philadelphia, 2019. STD Prevention Conference. Virtual. Available at: https://s6.goeshow.com/ncsd/prevention/2020/week_2_schedule.cfm?session_key=A70A6700-A0F0-B8AC-8A0D-58558450E557&session_date=Monday,%20Sep%2021,%202020. accessed 11 September 2024

8. Bolan RK, Beymer MR, Weiss RE, et al. Doxycycline prophylaxis to reduce incident syphilis among HIV-infected men who have sex with men who continue to engage in high-risk sex: a randomized, controlled pilot study. *Sex Transm Dis* 2015;42(2):98-103. doi: 10.1097/OLQ.0000000000000216

9. Holmes NE, Charles PGP. Safety and Efficacy Review of Doxycycline. *Clinical Medicine Therapeutics* 2009;1:CMT.S2035. doi: 10.4137/cmt.S2035

10. Peyriere H, Makinson A, Marchandin H, et al. Doxycycline in the management of sexually transmitted infections. *J Antimicrob Chemother* 2018;73(3):553-63. doi: 10.1093/jac/dkx420

11. Park JJ, Stafylis C, Pearce DD, 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. *Sex Transm Dis* 2021;48(9):615-19. doi: 10.1097/OLQ.0000000000001395

12. Molina JM, Charreau I, Chidiac C, et al. Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial. *Lancet Infect Dis* 2018;18(3):308-17. doi: 10.1016/S1473-3099(17)30725-9 [published Online First: 20171208]

13. New York City Department of Health and Mental Hygiene. Doxycycline Post-Exposure Prophylaxis (Doxy-PEP) to Prevent Bacterial Sexually Transmitted Infections 2023 [Available from: https://www.nyc.gov/assets/doh/downloads/pdf/std/dear-colleague-doxy-PEP-to-prevent-bacterial-STI-11092023.pdf accessed 26 May 2024

14. DiMarco DE, Urban MA, Fine SM, et al. Doxycycline Post-Exposure Prophylaxis to Prevent Bacterial Sexually Transmitted Infections: Baltimore (MD): Johns Hopkins University; 2023 [Available from: https://www.ncbi.nlm.nih.gov/books/NBK597440/ accessed 29 Mai 2024

15. Cornelisse VJ, Riley B, Medland NA. Australian consensus statement on doxycycline post-exposure prophylaxis (doxy-PEP) for the prevention of syphilis, chlamydia and gonorrhoea among gay, bisexual and other men who have sex with men. *Medical Journal of Australia* 2024;220(7):381-86. doi: https://doi.org/10.5694/mja2.52258

16. Werner RN, Schmidt AJ, Potthoff A, et al. Position statement of the German STI Society on the prophylactic use of doxycycline to prevent STIs (Doxy-PEP, Doxy-PrEP). *J Dtsch Dermatol Ges* 2024;22(3):466-78. doi: 10.1111/ddg.15282 [published Online First: 20231220]

17. Bachmann LH, Barbee LA, Chan P, et al. CDC Clinical Guidelines on the Use of Doxycycline Postexposure Prophylaxis for Bacterial Sexually Transmitted Infection Prevention, United States, 2024. MMWR Recomm Rep 2024;73(No. RR-2):1–8. DOI: http://dx.doi.org/10.15585/mmwr.rr7302a1 accessed 17.06.2024 2024.

18. Unemo M, Cole MJ, Kodmon C, et al. High tetracycline resistance percentages in Neisseria gonorrhoeae in Europe: is doxycycline post-exposure prophylaxis unlikely to reduce the incident gonorrhoea cases? *Lancet Reg Health Eur* 2024;38:100871. doi: 10.1016/j.lanepe.2024.100871 [published Online First: 20240213]

19. Kohli M, Medland N, Fifer H, et al. BASHH updated position statement on doxycycline as prophylaxis for sexually transmitted infections. *Sexually Transmitted Infections* 2022;98(3):235-36. doi: 10.1136/sextrans-2022-055425

20. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.3 (updated February 2022). Cochrane, 2022. 2022

21. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Systematic Reviews* 2021;10(1):89. doi: 10.1186/s13643-021-01626-4

22. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898. doi: 10.1136/bmj.l4898 [published Online First: 20190828]

23. Iorio A, Spencer FA, Falavigna M, et al. Use of GRADE for assessment of evidence about prognosis: rating confidence in estimates of event rates in broad categories of patients. *Bmj* 2015;350:h870. doi: 10.1136/bmj.h870 [published Online First: 20150316]

24. Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. *N Engl J Med* 2023;388(14):1296-306. doi: 10.1056/NEJMoa2211934

25. Stewart J, Oware K, Donnell D, et al. Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women. *N Engl J Med* 2023;389(25):2331-40. doi: 10.1056/NEJMoa2304007

26. Oware K, Adiema L, Rono B, et al. Characteristics of Kenyan women using HIV PrEP enrolled in a randomized trial on doxycycline postexposure prophylaxis for sexually transmitted infection prevention. *BMC Womens Health* 2023;23(1):296. doi: 10.1186/s12905-023-02413-0 [published Online First: 20230603]

27. Molina JM, Bercot B, Assoumou L, et al. Doxycycline prophylaxis and meningococcal group B vaccine to prevent bacterial sexually transmitted infections in France (ANRS 174 DOXYVAC): a multicentre, open-label, randomised trial with a 2 × 2 factorial design. *Lancet Infect Dis* 2024 doi: 10.1016/s1473-3099(24)00236-6 [published Online First: 20240523]

28. Spinelli MA, Scott HM, Vittinghoff E, et al. High Interest in Doxycycline for Sexually Transmitted Infection Postexposure Prophylaxis in a Multicity Survey of Men Who Have Sex With Men Using a Social Networking Application. *Sex Transm Dis* 2019;46(4):e32-e34. doi: 10.1097/OLQ.0000000000000942

29. Fredericksen RJ, Perkins R, Brown CE, et al. Doxycycline as Postsexual Exposure Prophylaxis: Use, Acceptability, and Associated Sexual Health Behaviors Among a Multi-Site Sample of Clinical Trial Participants. *AIDS Patient Care STDS* 2024;38(4):155-67. doi: 10.1089/apc.2023.0289

30. Chow EPF, Fairley CK. Use of doxycycline prophylaxis among gay and bisexual men in Melbourne. *The Lancet HIV* 2019;6(9):e568-e69. doi: 10.1016/S2352-3018(19)30186-9

31. Sokoll PR, Migliavaca CB, Siebert U, et al. Prevalence of Mycoplasma genitalium infection among HIV PrEP users: a systematic review and meta-analysis. *Sex Transm Infect* 2023;99(5):351-59. doi: 10.1136/sextrans-2022-055687 [published Online First: 20230209]

32. Nacht C, Agingu W, Otieno F, et al. Antimicrobial resistance patterns in Neisseria gonorrhoeae among male clients of a sexually transmitted infections clinic in Kisumu, Kenya. *Int J STD AIDS* 2020;31(1):46-52. doi: 10.1177/0956462419881087

33. Prestinaci F, Pezzotti P, Pantosti A. Antimicrobial resistance: a global multifaceted phenomenon. *Pathog Glob Health* 2015;109(7):309-18. doi: 10.1179/2047773215y.0000000030 [published Online First: 20150907]