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REVIEW ARTICLE

Doxycycline prophylaxis for bacterial sexually transmitted infections: evaluating effectiveness, risks, and challenges

Profilaxia com doxiciclina para infeções sexualmente transmissíveis bacterianas: avaliando eficácia, riscos e desafios

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Abstract

The increase in sexually transmitted infections (STIs) in Europe and the USA, especially among men who have sex with men (MSM) and transgender women (TW), has raised concerns and prompted the exploration of doxycycline prophylaxis as a potential intervention. Doxycycline prophylaxis can be administered either as a daily 100 mg dose (DoxyPrEP) or a single 200 mg dose post-sexual activity (DoxyPEP). Recent clinical trials, primarily focusing on higher-risk groups, have shown reductions of approximately 70% in syphilis and chlamydia infections and conflicting results regarding gonorrhea infection (up to 50%). Despite these advancements, the effectiveness of doxycycline prophylaxis among women has not been established and this strategy raises concerns about community acceptability, adverse events, safety, antimicrobial resistance, microbiome disruption, and cost-effectiveness. Ongoing clinical trials and agent-based models aim to address these uncertainties to predict the impact on a population level and on specific groups. This review aims to assess the existing data of doxycycline STI prophylaxis, identify knowledge gaps, and synthesize existing literature and guidelines about the current recommendations.

Keywords: Doxycycline. Prophylaxis. Sexually transmitted infections.

Resumo

O aumento de infecções sexualmente transmissíveis (IST) na Europa e nos EUA, especialmente entre homens que fazem sexo com homens (HSH) e mulheres transexuais (TW), levantou preocupações e levou à exploração da profilaxia com doxiciclina como uma intervenção potencial. A profilaxia com doxiciclina pode ser administrada em dose diária de 100 mg (DoxyPrEP) ou em dose única de 200 mg pós-atividade sexual (DoxyPEP). Ensaios clínicos recentes, centrados principalmente em grupos de maior risco, mostraram reduções de aproximadamente 70% nas infecções por sífilis e clamídia e resultados conflituantes em relação à infecção por gonorreia (até 50%). Apesar destes avanços, a eficácia da profilaxia com doxiciclina entre as mulheres não foi demonstrada e esta estratégia levanta preocupações sobre a aceitabilidade da comunidade, eventos adversos, segurança, resistência antimicrobiana, perturbação do microbioma e relação custo-eficácia. Os ensaios clínicos em curso e os modelos baseados em agentes visam abordar estas incertezas para prever o impacto a nível populacional e em grupos específicos. Esta revisão tem como objetivo avaliar os dados existentes sobre a profilaxia de IST com doxiciclina, identificar lacunas de conhecimento e sintetizar a literatura e as diretrizes existentes sobre as recomendações atuais.

Palavras-chave: Doxiciclina. Profilaxia. ISTs.

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Introduction

In recent years, Europe has witnessed a concerning surge in sexually transmitted infections (STIs), reaching an alarming peak in 2019, with an increase by 9% for chlamydia, 55% for gonorrhea, and 25% for syphilis since 2015. While chlamydia remains prevalent among young women, cases have doubled among men who have sex with men (MSM). In this group, gonorrhea has been reported in 48% of the cases and syphilis in 68%, with a 44% increase of diagnoses among HIV-negative MSM individuals[1]. Moreover, a parallel pattern emerged in the USA in 2021 showing incidence increases of 4.1% in chlamydia, 4.8% in gonorrhea, and a 31.9% in syphilis[2]. The number of syphilis cases is concerning, since this infection can cause visual, auditory, or neurological complications in up to 8% of individuals[3]. Some of this increase is attributed to the reduction in condom use, as well as to the use of pre-exposure prophylaxis (PrEP) for human immunodeficiency virus (HIV) infection, but is not fully explained by only these factors, raising the need to find targeted interventions to address this public health issue[4].

Prophylactic use of doxycycline is a strategy being studied to reduce the number of bacterial STIs. Doxycycline is a second-generation tetracycline with a bacteriostatic action on the ribosomal protein synthesis unit. It has a half-life of 20 h which allows a once or twice daily dosing, and presents a good safety and tolerability profile[5]. It is used for prophylaxis of other infections such as malaria[6], leptospirosis[7], or Lyme disease[8] and also used on long-term treatments for dermatological conditions such as acne[9] or rosacea[10]. In addition, it is considered the first-line treatment for chlamydia[11] and an alternative treatment for syphilis[12]. A single dose of 200 mg of doxycycline has been shown to achieve concentrations in colon and rectal tissues above the minimum inhibitory concentration (MIC) for chlamydia within 4-6 h post-dose, suggesting it may be an adequate option for prophylaxis of STIs in MSM both in the context of doxycyline pre-exposure prophylaxis (DoxyPrEP) or as doxycycline post-exposure prophylaxis (DoxyPEP)[5].

To reduce the incidence of bacterial STIs, more recent clinical trials have explored the use of doxycycline as a daily 100 mg dose (DoxyPrEP)[13] or a single 200 mg dose after condomless sex (DoxyPEP). These trials, predominantly among MSM and transgender women (TW), reported reductions of around 70% in syphilis and chlamydia infections, with varying effects on gonorrhea, ranging from approximately 50% reduction to no significant impact in some studies[14,15]. However, data regarding efficacy among women and other demographic groups have not shown benefit and remains limited[16].

There are concerns regarding STI chemoprophylaxis with doxycycline, namely, the potential development of antimicrobial resistance, adverse events, microbiome disruption and acceptance among patient and medical community. Furthermore, data on a population-level are still only obtainable from modeling studies that use multiple factors to make estimates that may differ from reality. Key questions remain about the target population, optimal dosage and formulation, efficacy across different groups, and a risk-benefit analysis[17]. Several studies and guidelines are in development, with a concerted effort to introduce this strategy to reduce the incidence of STIs, and the Centers for Disease Control and Prevention (CDC) solicited public input in October 2023 for the recently developed guidelines on doxycycline prophylaxis for bacterial STIs[18].

This review article aims to assess the knowledge on doxycycline STI prophylaxis, identify knowledge gaps, the existing literature, and current recommendations.

Published data on efficacy

Prophylactic use of doxycycline for STIs has shown efficacy in four open-label trials, specifically among MSM and TW (Table 1). This effectiveness extends to individuals with or without HIV infection, engaging in condomless sex, and having had a history of at least one STI in the past year.

Studies using a single 200 mg dose of doxycycline within 24-72 h after condomless sex have shown a reduction in chlamydia and syphilis infections by approximately 50-70% and the potential to reduce gonorrhea infections by around 40-50% in certain settings[13-15]. The pilot study conducted by Bolan et al. in 2015 showed a significant success in reducing bacterial STIs among MSM living with HIV and with a history of syphilis recurrence. Participants were divided into two groups: one receiving a daily 100 mg dose of doxycycline, while the other engaged in contingency management, with monetary incentives for STI-free behavior. Despite the small sample (n = 30), the DoxyPrEP group exhibited an impressive 73% reduction in bacterial STIs over the 48-week follow-up period[13].

Following this study, trials involving MSM and TW were conducted to evaluate the effectiveness of 200 mg doxycycline (DoxyPEP) as a post-exposure treatment to reduce bacterial STIs. These trials

Table 1. Clinical trials on doxycycline prophylaxis for bacterial STIs

Study	Design	Participants	Interventions	Primary endpoint	Follow-up
Bolan et al.[13] (2015)	Open-label RCT	30 HIV+ MSM who had syphilis ≥ 2 times since HIV diagnosis	Daily 100 mg doxycycline (n = 15) vs. contingency management (n = 15)	Contraction of syphilis, gonorrhea or chlamydia	48 weeks
ANRS IPERGAY[14] (2018)	Open-label RCT	232 MSM or TW on HIV PrEP and condomless sex with men	200 mg doxycycline once within 72 h after condomless sex (n = 116) vs. no doxycycline prophylaxis (n = 116)	Occurrence of a first STI during 10-month follow-up	Median time 8.7 months
DUHDS trial[20] (2021)	Open-label RCT	52 MSM on HIV PrEP with prior diagnosis of syphilis	Immediate (n = 26) vs. deferred (n = 26) daily doxycycline 100 mg	STI diagnosis	48 weeks
DoxyPEP[15] (2023)	Open-label RCT	501 MSM or TW on HIV PrEP or HIV+ who had bacterial STI last year	200 mg doxycycline once within 72 h after condomless sex (n = 339) vs. standard care (n = 162)	Incidence of STIs per follow-up quarter	Median time 270 days
DOXYVAC[21] (2023)	Open-label RCT	502 MSM on HIV PrEP who had bacterial STI last year	200 mg doxycycline once within 72 h after condomless sex (n = 332) vs. no doxycycline prophylaxis (n = 170) and 4CMenB vaccine vs. no vaccine (1:1)	Incidence of first episode of a STI	Median time 9 months
dPEP-KE[16] (2023)	Open-label RCT	449 women on HIV PrEP	200 mg doxycycline once within 72 h after condomless sex (n = 224) vs. standard care (n = 225)	Incidence of chlamydia, syphilis or gonorrhea	12 months

Study	Findings	Limitations
Bolan[13] (2015)	At week 48, diagnosis of any studied bacterial STI had an OR = 0.27 (95% CI: 0.09-0.83; p = 0.02) for the doxycycline group.	Open-label study Short follow-up Small sample
ANRS IPERGAY[14] (2018)	DoxyPEP vs. no-DoxyPEP: Time to first STI had HR = 0.53 (95% CI: 0.33-0.85; p = 0.008); Time to first chlamydia episode had HR = 0.30 (95% CI: 0.13-0.70; p = 0.006); Time to first syphilis episode had HR = 0.27 (95% CI: 0.07-0.98; p = 0.047); No significant differences were observed for gonorrhea (HR = 0.83; 0.47-1.47; p = 0.52).	Open-label study Short follow-up
DUHDS TRIAL[20] (2021)	Immediate vs. deferred arm at 24 weeks: Chlamydia infection (rate 0 vs. 81.63/100 PY, p = 0.001); Syphilis infection (rate 0 vs. 8.16/100 PY, p = 0.98); Gonorrhea infection (rate 31.37 vs. 57.14/100 PY, p = 0.505); Only 1 gonorrhea infection after 24 weeks in each arm.	Open-label study Short follow-up Small sample
DOXYPEP[15] (2023)	In the HIV PrEP cohort, 10.7% Doxy-PEP vs. 31.9% no-DoxyPEP had a STI (RR = 0.34; 95% CI: 0.24-0.46; p < 0.001). In the HIV+ cohort, 11.8% Doxy-PEP vs. 30.5% no-DoxyPEP had a STI (RR = 0.38 95% CI: 0.24-0.60; p < 0.001).	Open-label study Short follow-up
DOXYVAC[21] (2023)	Lower incidence for all studied bacterial STIs on DoxyPEP group: Chlamydia (HR = 0.11; 95% CI: 0.04-0.30, p < 0.0001), incidence of 2.1/100 PY vs. 19.3/100 PY; Syphilis (HR = 0.21; 95% CI: 0.09-0.47, p < 0.001), incidence of 3.4/100 PY vs. 16.3/100 PY; Gonorrhea (HR = 0.49; 95% CI: 0.32-0.76, p = 0.001), incidence of 20.5/100 PY vs. 41.3/100 PY; *Mycoplasma genitalium* (HR = 0.55; 95% CI: 0.34-0.89, p = 0.015), incidence of 16.8/100 PY vs. 29.4/100 PY.	Open-label study Short follow-up
dPEP-KE[16] (2023)	DoxyPEP group vs. standard of care in STI incidence with no significant differences (RR = 0.88; 95% CI: 0.60-1.29; p = 0.51) with 25.1 vs. 29.0/100 PY. Chlamydia accounted for 78.0% of STIs; no difference between groups (RR = 0.73; 95% CI: 0.47-1.13).	Open-label study Short follow-up

CI: confidence interval; DoxyPEP: Doxycycline Post-exposure Prophylaxis; HIV: human immunodeficiency virus; HR: hazard ratio; MSM: men who have sex with men; OR: odds ratio; PrEP: pre-exposure prophylaxis; PY: person-year; RCT: randomized controlled trial; RR: relative risk; STI: sexually transmitted infection; TW: transgender women.

recruited participants with a history of STIs in the previous year, including individuals living with HIV or utilizing HIV PrEP. Notably, one study published in 2018 – the ANRS IPERGAY – enlisted 232 participants for an open-label randomized controlled trial to compare DoxyPEP to standard-care for bacterial STI treatment. The DoxyPEP group exhibited a 47% relative reduction in the incidence of new STIs. Furthermore, in the intention-to-treat analysis, there was a substantial 70% relative reduction in the risk of chlamydia infection and a 73% relative reduction in the risk of syphilis, with no notable differences observed for gonorrhea infection. In this study, the lack of effectiveness against this infection was linked to local resistance of *Neisseria gonorrhoeae* to tetracyclines[14]. Of note there is a substudy of this population where the authors confirmed that the prevalence of *Mycoplasma genitalium* infection remained stable at the 6-month follow-up, with no significant differences observed between the DoxyPEP arm and the no-DoxyPEP arm, indicating that prophylaxis also had no discernible impact on the incidence of this STI[19].

The DUHDS trial findings on MSM receiving daily 100 mg doxycycline were presented at the 2021 Conference on Retroviruses and Opportunistic Infections and recruited 52 participants who were randomly assigned to immediate or deferred doxycycline prophylaxis after 24 weeks. Doxycycline chemoprophylaxis on both groups reduced the probability of acquiring any STI with an odds ratio (OR) of 0.18 (95% confidence interval [CI]: 0.05-0.68) and also lowered the rate of chlamydia infection, but its impact on syphilis could not be determined, probably due to the limited sample size and short follow-up[20].

In the DoxyPEP trial (2023), 501 participants were randomly assigned in a 2:1 ratio to either take 200 mg of doxycycline within 72 h after condomless sex or to receive standard care without doxycycline. The included participants were MSM or TW on HIV pre-exposure prophylaxis (PrEP) or HIV positive (HIV+) individuals who had experienced a bacterial STI in the previous year. On those on HIV PrEP, the relative risks (RR) were 0.45 (95% CI, 0.32-0.65) for gonorrhea, 0.12 (95% CI, 0.05-0.25) for chlamydia, and 0.13 (95% CI, 0.03-0.59) for syphilis. In the HIV+ cohort, the relative risks were 0.43 (95% CI, 0.26-0.71), 0.26 (95% CI, 0.12-0.57), and 0.23 (95% CI, 0.04-1.29), respectively. Compared to the previous studies, prophylaxis demonstrated some efficacy against gonorrhea incidence (around 50%) with an overall reduction of approximately two-thirds in bacterial STI incidence[15].

In the DOXYVAC trial (2023), efficacy in reducing bacterial STIs among high-risk MSM on HIV PrEP was also evident. This study randomized participants into DoxyPEP or standard-care in a 2:1 ratio. On an unblinded early interim analysis a notable 65% reduction in STI incidence was observed and all participants were offered DoxyPEP, with the initial 9-month follow-up period showing significant reductions in chlamydia by 89%, syphilis by 79%, gonorrhea by 51%, and *M. genitalium* by 45%[21].

When considering other populations, only one trial has provided data, indicating a lack of efficacy in women. The dPEP-KE (2023) involved 449 women in Kenya who were on HIV PrEP, and randomly assigned them to receive a single 200 mg dose of doxycycline within 72 h after engaging in condomless sex or the standard care. After a year of follow-up, no significant differences were observed in STI incidence between the groups. While participant-reported adherence was moderately high, the results of doxycycline testing in hair indicated that 44% of those assigned to receive DoxyPEP may not have taken any doxycycline[16]. Doxycycline in vaginal secretions peaks around 8 h after a 200 mg dose and remains at inhibitory levels against syphilis and chlamydia for 3-4 days post-dosing, and around 2 days for gonorrhea[22]. This suggests that doxycycline should be effective also for women but adherence may have been a significant problem. In addition, this trial found that all *N. gonorrhea* isolates were resistant to tetracyclines, potentially contributing to the lack of efficacy of the intervention[16].

Ongoing clinical trials are actively trying to determine the concentration levels achieved in body fluids and compare different outcomes of interventions with DoxyPEP and DoxyPrEP, as summarized in table 2[23-28].

Several additional studies have been using mathematical models of transmission to assess potential efficacy[29-31]. One study used a model to assess the impact of syphilis within an MSM population using doxycycline 100 mg daily, assuming an use effectiveness of 70% on 50% of MSM. It projected a reduction on incidence of syphilis cases by 49% within a 12-month period and by 85% over a span of 10 years. In addition, it suggested that the greatest preventive impact would be by targeting subpopulations of men with higher sexual activity[29]. Another study using electronic health records of 10,546 MSM and TW with a history of ≥ 2 STI tests determined that if DoxyPEP were prescribed to all individuals, it would prevent 71% of STI diagnoses, with a number needed-to-treat (NNT) of 3.9 to avert one STI diagnosis/year. However, targeting specific subgroups,

Table 2. Ongoing clinical trials

Study ID	Design	Participants	Interventions	Primary endpoints	Estimated follow-up
DOXY-PK[23] NCT06007534 2023	Open-label	MSM on HIV PrEP taking doxycycline for STI prevention (n = 25)	Blood and urine samples, oropharyngeal swabs and hair samples before and after taking 200 mg of doxycycline	Concentration of doxycycline in collected samples	6 months
Project PEACH[24] NCT05072093 2021	Open-label	MSM followed at PRISM Health Research Clinic (n = 200)	DoxyPEP after condomless sex in a single 200 mg dose within 72 h	Change in STI diagnoses from baseline at 12 and 24 months	2 years
Combo-PEP[25] NCT04860505 2021	Open-label	HIV negative person reporting sex with another man in the last year (n = 20)	Doxycycline and bictegravir, emtricitabine and tenofovir alafenamide simultaneous intake 1 h before specimen collection	Plasma, rectal and vaginal doxycycline concentration	12 months
Syphilaxis[26] NCT03709459 2019	Observational	MSM who have had ≥ 2 screenings for syphilis, chlamydia and gonorrhea in the past 12 months, and at least one episode of syphilis in the past 2 years (n = 100)	Doxycycline 100 mg/day for 12 months duration	Incidence of STI per 100 PY. Patterns of use and adherence	12 months
DOXY-PEP (Atlanta)[27] NCT05853120 2023	Open-label RCT	Healthy male or female people (n = 40)	Doxycycline 100 mg or 200 mg taken on days 0, 3, 7 and 10	Doxycycline concentration in vaginal and rectal tissues	8 weeks
DISCO[28] NCT04762134 2023	Open-label RCT	MSM with > 1 male partner and previous diagnosis of STI in the past 12 months (n = 560)	Doxycycline 100 mg orally daily for 12 months vs. doxycycline 200 mg orally once within 72 h following condomless sex	Plasma doxycycline levels. Frequency of STIs over time	60 weeks

HIV: human immunodeficiency virus; MSM: men who have sex with men; PrEP: pre-exposure prophylaxis; PY: person-year; RCT: randomized controlled trial; STI: sexually transmitted infection.

there would be a lower NNT for HIV PrEP users or HIV+ people (NNT = 2.9), averting 60% of STI diagnoses, and for individuals with a history of STI within the previous year (NNT = 2.4), averting 39% of STI diagnoses. DoxyPEP on those with repeated or recent STIs improved efficiency (lower NNTs) but prevented fewer STIs due to lower population coverage, concluding that strategies based on STI history rather than HIV status or PrEP use were more efficient. While promoting DoxyPEP to a wider population would prevent more STI diagnoses, limiting it to high-risk groups would minimize DoxyPEP usage while maximizing its benefit[30]. An additional study using an agent-based model on a population of 10,230 MSM determined that if a 20% uptake and 80% adherence level of DoxyPEP were achieved, a 10% reduction in syphilis infections would occur over a decade, amounting to 57 fewer cases/1000 individuals, and a 22% reduction of infections in situations where condoms were not used or had failed. This model suggests a moderate impact on syphilis incidence and considered DoxyPEP as a secondary prevention measure alongside condoms and improved syphilis screening[31].

In terms of the impact on antibiotic usage, a study projected an increase of approximately 2.52 million monthly doses, underscoring that while doxycycline prophylaxis may lead to a reduction in STIs, it is anticipated to elevate overall doxycycline consumption, despite the concurrent decrease in antibiotics used for treating these infections[32].

While doxycycline prophylaxis shows effectiveness in reducing bacterial STIs, especially in high-risk groups, there is a potential for it to contribute to a rise in overall antibiotic usage, and model-based studies are yet to definitively determine its impact on a population level.

Community acceptability

The effectiveness of public health strategies among MSM, such as bacterial STI prevention using doxycycline prophylaxis, depends on community and healthcare provider acceptance for success. Several studies, primarily based on surveys or interviews, indicate that the use of doxycycline for preventing bacterial STIs is generally accepted among MSM[33-36].

Before the awareness of recent trials regarding DoxyPEP efficacy, an online survey targeting MSM in Australia studied the potential acceptability of syphilis chemoprophylaxis. Among the 2095 participants surveyed, 52.7% (95% CI: 50.6-54.8%) expressed likelihood to use chemoprophylaxis to the lower their risk of acquiring syphilis. This percentage notably increased to 75.8% (95% CI: 74.0-77.6%) if chemoprophylaxis was shown to help reduce infections within this community[29]. Also in Australia, another online survey on 1347 MSM identified 54.3% willing to use DoxyPrep and linked willingness to participants with high number of sexual partners (> 10), recent methamphetamine use, being conscious about avoiding STIs, having a history of more STIs since starting HIV PrEP, and using condoms only on a partner's request[33]. In China, an online survey on 725 participants verified that willingness to use syphilis chemoprophylaxis was greater among those without a history of prior doxycycline use ($p = 0.009$). Among respondents, 67.8% preferred a post-exposure strategy, while 60.0% expressed concerns about potential side effects as their primary worry[34]. In Canada, 424 MSM completed a questionnaire during routine STI clinic visits and results showed that 60.1% and 44.1% were likely to use DoxyPEP or DoxyPrEP, respectively. The study identified several factors associated with this compliance. For DoxyPrEP, factors included a belief of being at risk for syphilis (OR = 1.6; 95% CI: 1.0-2.5), previous or current HIV PrEP use (OR = 2.2; 95% CI: 1.1-4.3), and a high level of concern about STI acquisition (OR = 1.9; 95% CI: 1.0-3.4). Regarding DoxyPEP, willingness was associated with a higher number of diagnosed STIs (OR = 1.4; 95% CI: 1.2-1.7). Participants' subjective assessments of STI risk had more impact on considering doxycycline prophylaxis rather than traditional epidemiological risk factors, such as the total number of sex partners or a prior history of syphilis. Notably, 89% of participants were aware of antimicrobial resistance, but this did not influence the acceptability of doxycycline prophylaxis[35]. In the US, a similar willingness trend was observed on 212 MSM that answered an online survey with 67.5% indicating they would consider taking doxycycline prophylaxis if recommended by their provider, especially those with recent diagnosis of bacterial STI (OR = 2.8, 95% CI: 1.22-6.45, $p = 0.02$) or using HIV PrEP (OR = 3.7, 95% CI: 1.64-8.24, $p \leq 0.01$)[36]. This survey also included health-care providers, with 89.5% expressing readiness to prescribe doxycycline PrEP/PEP if recommended by the CDC, but only 43.4% willing to do so without this guidance. Both community and healthcare participants exhibited concern regarding potential drug resistance[36].

Until recently, despite lacking formal guidelines, prophylaxis for bacterial STIs was already being employed as an off-label strategy in some instances. An online survey involving 96 MSM in Germany revealed that 23% reported prior use of doxycycline as DoxyPEP and 6% as DoxyPrEP, most individuals having obtained the pills from leftover supplies of previous doxycycline treatments[37]. In Melbourne, Australia, 9.9% of 1065 MSM participating in a survey also admitted using doxycycline prophylaxis within the previous month[38]. In London, UK, a similar tendency was observed in 8% of 106 participants from a survey conducted in a sexual health clinic, admitting using antibiotics as a preventive measure against STIs and 75% of those specifically utilizing doxycycline, with half of them using antibiotics on a daily basis[39].

These studies have indicated that the general public is inclined to view doxycycline prophylaxis as a safe and acceptable intervention. Following a trajectory similar to HIV PrEP, the utilization of antibiotics for preventing bacterial STIs may have a rise in adoption among MSM and other populations and already shows signs of off-label usage by some whether prescribed or not. If challenges such as antimicrobial resistance or other issues arise, reversing this trend could prove to be difficult. Given its confirmed efficacy, ensuring the supervised use of doxycycline may be preferable to guarantee optimal effectiveness and safety.

Adverse events and safety profile

Doxycycline is generally considered safe and well-tolerated, yet adverse effects have been identified in clinical trials using this drug. Commonly reported side effects include the gastrointestinal tract and skin. Caution is advised, particularly avoiding its use during pregnancy and breastfeeding due to teratogenic risks[5].

Regarding clinical trials using doxycycline prophylaxis for bacterial STIs, adverse events were mostly mild and discontinuation due to these was relatively

low. In the trial conducted by Bolan et al., only one patient needed to discontinue the 100 mg daily doxycycline treatment by week 29 due to gastroesophageal reflux, with no serious adverse events reported[13]. In the ANRS IPERGAY study, serious adverse events occurred at similar rates between the studied groups, with no reported deaths among participants. Those on DoxyPEP had a median doxycycline usage of 680 mg/month, displaying a favorable safety profile overall, but there was an elevated occurrence of gastrointestinal adverse events compared to the HIV PrEP-only group (25% vs. 14%; p = 0.03). In particular, eight individuals (7%) in the DoxyPEP group discontinued doxycycline due to drug-related adverse events[14]. During the relatively short observation period of the DoxyPEP trial, no significant changes in weight were observed under doxycycline intake when compared to the control group and no serious adverse events were reported. A mere 2% of participants opted to discontinue doxycycline due to its adverse effects[15]. In the dPEP-KE study, participants experienced no serious adverse events attributable to doxycycline use. The most prevalent adverse effect was nausea, reported in 7.2% of follow-up visits in the DoxyPEP group and 4.6% in the standard-care group, with only 2.7% of participants discontinued the study due to adverse effects associated with the drug[16].

Adverse events due to prolonged doxycycline use are frequently reported, but severe side effects leading to discontinuation are rare. Overall, long-term use is deemed safe[40]. The majority of studies are focused on daily doxycycline use, but most bacterial STI chemoprophylaxis research explores mainly the use of doxycycline in the form of DoxyPEP, representing intermittent rather than daily administration. One hypothesis that may underlie this approach is that intermittent doxycycline use might potentially result in fewer side effects and reduced risk of antimicrobial resistance when compared to DoxyPrEP[40].

Antimicrobial resistance and microbiome disruption

Due to the rapid development of resistances by *N. gonorrhoeae*, antimicrobial resistance is one of the main concerns regarding the use of doxycycline for prophylaxis of bacterial STIs[17], and several genes related to tetracycline resistance have already been identified, like the plasmid-encoded tetM gene and the mutations in chromosomal genes such as rpsJ, porB, and the mtr operon[41]. A study using whole genome sequencing data and MICs from a pool of 5644 *N. gonorrhoeae* isolates found that the selection for plasmid-encoded and chromosomally encoded tetracycline resistance was influenced by the antimicrobial resistance profiles. In isolates with plasmid-encoded resistance to tetracyclines, MICs to other antimicrobials were lower when compared to isolates with low-level tetracycline resistance. It was observed as well that isolates with tetracycline MICs ranging from 2 to 8 μg/ml also had higher MICs for ceftriaxone, azithromycin, and ciprofloxacin when comparing to non-tetracycline-resistant isolates ($p < 0.0001$). Co-resistance to tetracycline and azithromycin was associated with chromosomally encoded mutations and in 12.9% of plasmid-encoded tetM isolates there was a co-resistance of tetracycline and ciprofloxacin. Although tetracycline and ceftriaxone resistance is uncommon, it is most likely due to strains with chromosomally mediated tetracycline resistance, like those with the *penA* 60 allele. This data indicate that the population of *N. gonorrhoeae* exhibiting intermediate MICs could serve as a reservoir for rapid resistance evolution and DoxyPEP may select tetracycline-resistant lineages that also resist to other antimicrobials. However, if DoxyPEP primarily favors lineages with tetM-mediated resistance, it may decrease *N. gonorrhoeae* resistance to other antimicrobials because of the lower co-resistance in these lineages[41]. The prevalence of the tetM gene in certain populations is significant, as observed by a study involving 50 endocervical swab specimen's positive for *N. gonorrhoeae* from women in Kenya. In this study, the American-type plasmid-mediated tetM gene was identified in 96% of the samples, suggesting that DoxyPEP for STI prevention might have limited efficacy against gonorrhea in sub-Saharan Africa[42].

Tetracycline resistance on gonorrhea or *M. genitalium* has also been observed on efficacy clinical trials. In the ANRS IPERGAY trial, among positive gonorrhea isolates, 7 out of 9 exhibited resistance or intermediate resistance to tetracyclines with molecular testing identifying the tetM gene in one of the resistant isolates, as well as the Val57Met mutation in the rpsJ gene and mutations associated with the overexpression of the antibiotic efflux pump MtrCDE on all resistant isolates[14]. In a sub-study of this population, 210 participants underwent testing for *M. genitalium*, and their isolates were examined for antimicrobial resistance patterns. The infection's prevalence was found to be 10.5%, with isolates exhibiting resistance to azithromycin in 66.7%, fluoroquinolones in 9.1%, and tetracyclines in 12.5% (linked to an *in vivo* mutation of 16S rRNA). Importantly, no significant differences were observed between the

DoxyPEP and no-DoxyPEP arms[19]. In terms of tetracycline resistance among *N. gonorrhoeae* isolates from the DoxyPEP trial, participants baseline resistance stood at approximately 27% changing later to 38% in the doxycycline group and 12% in the standard-care group. This study, however, did not investigated whether resistant isolates became more prevalent due to doxycycline[15]. Finally, as expected for the sub-Saharan Africa, in the dPEP-KE study, the prevalence of the tetM gene in *N. gonorrhea* was 100% both at baseline and during follow-up visits in both the doxycycline-PEP group and the standard-care group. In this population, none of the 76 tested *C. trachomatis* samples exhibited the tet(C) gene cassette, also correlated to tetracycline resistance[16].

To explore the impact of DoxyPEP on gonorrhea transmission among MSM populations a study used a deterministic compartmental model with various uptake levels (10-75%) and a 20-year prevalence and resistance dynamics against a baseline scenario without DoxyPEP. Results indicated that DoxyPEP initially reduced gonorrhea prevalence and incidence, but accelerated the spread of doxycycline resistance, leading to the loss of clinical efficacy within 20 years. This initial reduction in infection prevalence was constrained by existing doxycycline-resistant strains in the population and doxycycline promoted the spread of resistant strains already present, rather than causing de novo resistance emergence. Moreover, while high DoxyPEP use (50-75%) initially reduced ceftriaxone treatments by over 50% in the first 5 years compared to the baseline, this reduction narrowed to 17.6% after 20 years. Increasing DoxyPEP uptake and higher initial doxycycline resistance prevalence accelerated the loss of efficacy and had minimal impact on extending the clinical lifespan of ceftriaxone for *N. gonorrhoeae* treatment. The model suggested that while DoxyPEP is effective in the short-term its reduction in cumulative infections was only around 13.5-14.6% at 20 years, and it hastens doxycycline resistance to 87% within 1.8-14.1 years, depending on uptake (10-75%)[43].

Regarding the impact on microbiome disruption, one systematic review studied the impact of oral tetracycline-class antibiotics on normal bacterial flora. The analysis included seven randomized controlled trials among adults, comparing daily oral tetracycline-class antibiotics versus non-tetracycline treatments. Most studies used doxycycline at 100-200 mg/day over 2-18 weeks, as well as other antibiotics of the same class. The outcomes revealed that oral tetracycline usage generally increased tetracycline-resistant strains in the body's normal flora. Subgingival flora exhibited a slight rise in tetracycline resistance during short-term therapy (2 weeks).

Gastrointestinal studies on stool cultures initially showed increased resistance in commensal *Escherichia coli*, but resistance levels returned to baseline 2 weeks after a 3-week course of 100 mg/day of doxycycline. Extended doxycycline use for 13 weeks heightened resistance in the upper respiratory flora, increasing the MIC by 3.74, and individuals were also 5.77 times more likely to harbor doxycycline-resistant isolates (95% CI: 1.40-23.74, p = 0.02). Conversely, the included studies showed skin flora did not display changes in *Cutibacterium acnes* tetracycline resistance after 18 weeks of oxytetracycline/minocycline treatment. While these antibiotics slightly increased resistance in specific floras, they had minimal impact on resistance to non-tetracycline antibiotics.

Overall, although these effects were modest and short-lived, limited data from small-scale studies suggest that oral tetracyclines used for 2-18 weeks may elevate resistance in some specific floras but do not seem to have significant impact on resistance to other non-tetracycline class antibiotics in commensal bacteria[44].

The DoxyPEP trial also investigated microbiome impact by studying *Staphylococcus aureus* carriage in participants. An initial positivity of 45%, with 12% of strains resistant to doxycycline was compared after 12 months of follow-up. Carriage of *S. aureus* was prevalent on 28% of the doxycycline user group, in comparison to 47% of the control group (p = 0.03), including 16% vs. 8% isolates resistant to doxycycline. However, the proportion of participants positive for carriage of doxycycline-resistant *S. aureus* remained similar between groups (5% in the DoxyPEP group vs. 4% in the control group)[15].

Collectively, studies suggest that antimicrobial resistance poses a substantial challenge for *N. gonorrhoeae*, raising concerns about a potential failure of DoxyPEP in addressing this infection and an increased risk of antimicrobial resistances development. Studies also highlight alterations in the microbiome's antimicrobial resistance patterns due to prophylactic use of doxycycline. However, the actual impact on health outcomes at a population level remains unclear.

Conclusion

DoxyPEP is acknowledged by current guidelines as a strategy for reducing the burden of bacterial STIs among at-risk populations. The European AIDS Clinical

Society, in its 2023 guidelines update, has introduced new recommendations indicating that the consideration of DoxyPEP can be proposed to individuals with recurrent STIs who are living with HIV or are on HIV PrEP on a case-by-case basis[45]. On 2023, the Australasian Society for HIV, Viral Hepatitis, and Sexual Health Medicine (ASHM) released a consensus statement regarding the use of DoxyPEP in Australia. Within the Australian context, it highlighted that among bacterial STIs, syphilis stands as the primary cause of morbidity among MSM, while chlamydia and gonorrhea seldom lead to complications in this population, recommending DoxyPEP primarily for preventing syphilis in at-risk MSM. The ASHM also acknowledges a potential indirect benefit for the broader community, particularly for women who also engage in sexual activities with MSM, as this demographic faces a higher risk of complications. However, there is no evidence supporting this conclusion[46]. Recently, the CDC published guidelines regarding the use of doxycycline prophylaxis for bacterial STIs and requested a public input to address any concerns related to these. The draft version recommends the use of DoxyPEP as a single 200 mg oral dose of doxycycline within 72 h of oral, vaginal, or anal sex for MSM or TW with a history of at least one bacterial STI in the past 12 months and who continue to be at risk for bacterial STI acquisition or for those engaging in sexual activities known to increase the likelihood of STI exposure. The guidelines emphasized a maximum daily dose of 200 mg, and screening for bacterial STIs and HIV to be conducted every 3-6 months following the initial use of DoxyPEP[47].

DoxyPEP presents a targeted and tailored approach to preventing bacterial STIs, focusing on individuals at high risk, such as MSM living with HIV, those on HIV PrEP, or those with multiple risk factors. The potential expansion of its role to include women demands careful study to address concerns of equity, especially given the significant impact of these diseases on women's reproductive health. While DoxyPEP likely reduces the incidence of syphilis and chlamydia, implementing it requires an investigation of the potential adverse effects, alterations to the microbiome, and antimicrobial resistances. As the global incidence of bacterial STIs continues to rise, the introduction of doxycycline prophylaxis may have a role on reverting this trend.

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Conflicts of interest

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Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article. Furthermore, they have acknowledged and followed the recommendations as per the SAGER guidelines depending on the type and nature of the study.

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