

Systematic Review

Effectiveness, adherence, adverse events and antimicrobial resistance associated with doxycycline prophylaxis of bacterial sexually transmitted infections

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Table of Contents

Introduction.....	6
Methods.....	7
Study design.....	7
Search strategy.....	7
Eligibility and outcomes.....	7
Effectiveness and adherence.....	7
Adverse events and antimicrobial resistance.....	8
General criteria.....	8
Study selection.....	8
Data extraction.....	9
Data synthesis.....	9
Risk of bias assessment.....	9
Results.....	10
Study selection and included studies.....	10
Effectiveness outcomes.....	11
Characteristics of included studies.....	11
Summary effectiveness findings.....	11
Risk of bias for effectiveness.....	12
Adherence outcomes.....	12
Characteristics of included studies.....	12
Summary of adherence findings.....	13
Risk of bias for adherence.....	14
Adverse event outcomes.....	14
Characteristics of included studies.....	14
Summary of adverse events findings.....	15
Risk of bias for adverse events.....	16
Antimicrobial resistance outcomes.....	17
Characteristics of included studies.....	17
Summary of antimicrobial resistance findings.....	17
Risk of bias for antimicrobial resistance.....	19
Discussion.....	20
Summary of main findings.....	20
Effectiveness.....	20
Syphilis and chlamydia among MSM and transgender women.....	20
Gonorrhoea among MSM and transgender women.....	21

Cisgender women	21
Other pathogens	21
Adherence.....	21
Clinical adverse events (safety and tolerability outcomes)	22
Gut microbiome composition and diversity (biological outcomes).....	22
Antimicrobial resistance	23
STI pathogens and commensal organisms.....	23
Gut resistome.....	23
Gaps in evidence and research priorities	23
Conclusion.....	24
<i>Tables.....</i>	<i>25</i>
<i>Appendix 1. Search syntax</i>	<i>47</i>
<i>Appendix 2. Inclusion criteria</i>	<i>48</i>
<i>Appendix 3. Risk of bias assessment</i>	<i>50</i>

List of Tables

Table 1. Effectiveness of doxycycline prophylaxis for prevention of bacterial STIs	25
Table 2. Adherence to doxycycline prophylaxis for prevention of bacterial STIs	30
Table 3. Qualitative findings related to adherence to doxycycline prophylaxis for prevention of bacterial STIs ...	33
Table 4. Clinical adverse events associated with doxycycline prophylaxis and long-term doxycycline use	35
Table 5. Microbiome outcomes related to doxycycline prophylaxis and long-term doxycycline use	39
Table 6. Antimicrobial resistance associated with doxycycline prophylaxis and long-term doxycycline use	40

Introduction

Bacterial sexually transmitted infections (STIs) continue to increase in many high-income settings, with gay and bisexual men and other men who have sex with men (GBM) and transgender people experiencing a disproportionate burden of infection. Rising incidence of syphilis, chlamydia and gonorrhoea has been reported across Australasia, North America and Europe over the past decade, despite widespread access to testing and treatment services. In Australia, notifications of bacterial STIs have increased substantially over the past decade, with syphilis notifications increasing by 111% and gonorrhoea by 139% between 2015 and 2024.¹ Untreated syphilis can result in severe neurological, cardiovascular and ocular complications, while chlamydia and gonorrhoea may lead to urethritis and other reproductive tract sequelae. These trends underscore the limitations of existing prevention approaches and the need for additional, effective biomedical strategies for STI prevention in populations at highest risk.

Current public health responses to bacterial STIs in GBM have largely relied on frequent screening of asymptomatic individuals followed by prompt treatment. Although this test-and-treat paradigm is central to STI control, incidence has continued to rise, and evidence that intensified screening alone leads to sustained population-level reductions in STI prevalence remains limited.² In the absence of vaccines for most bacterial STIs, interest has therefore grown in chemoprophylactic approaches that could complement existing prevention strategies.

Doxycycline post-exposure prophylaxis (doxyPEP), involving a single 200 mg dose of doxycycline taken within 72 hours of condomless sexual exposure, represents the first major biomedical innovation for bacterial STI prevention in several decades. Randomised controlled trials conducted among cisgender GBM and transgender women have demonstrated substantial reductions in incident syphilis and chlamydia associated with doxyPEP use, with more variable and generally lower effectiveness observed for gonorrhoea.^{3,4} These findings have been supported by observational studies in real-world clinical settings, which have reported marked declines in syphilis and chlamydia diagnoses among individuals prescribed doxyPEP, alongside more modest or inconsistent effects on gonorrhoea.⁵ Daily doxycycline pre-exposure prophylaxis (doxyPrEP), involving continuous doxycycline at a dose of 100 mg taken prior to sexual exposure, has also been investigated,⁶ although evidence is currently more limited and derived primarily from small pilot trials and observational studies.

In parallel with emerging evidence of efficacy, the rapid uptake of doxyPEP has prompted important questions regarding adherence, tolerability, unintended adverse outcomes, and the potential for selection of antimicrobial resistance (AMR) in both STI pathogens and commensal organisms. Concerns have been raised about doxycycline resistance in *Neisseria gonorrhoeae*, resistance and microbiome impacts in non-target bacteria, and the long-term population-level implications of widespread prophylactic antibiotic use. These considerations are reflected in clinical guidelines in several countries, which generally recommend doxyPEP for individuals at highest risk of recurrent STIs while acknowledging uncertainty regarding longer-term safety and antimicrobial resistance, and emphasising its use within comprehensive sexual health care frameworks that include regular STI screening, HIV prevention, vaccination, and antimicrobial stewardship.

In the context of rapidly emerging evidence and ongoing concerns regarding safety and antimicrobial resistance, this systematic review was undertaken as part of a national guideline development process

to synthesis evidence on the effectiveness, adherence, adverse outcome and antimicrobial resistance associated with doxycycline pre- and post-exposure prophylaxis for bacterial STI prevention. The findings are intended to directly inform Australian clinical prescribing guidelines for doxyPEP.

Methods

Study design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aimed to synthesise evidence on the effectiveness, adherence, adverse events, and antimicrobial resistance (AMR) associated with doxycycline prophylaxis (including doxycycline post-exposure prophylaxis [doxyPEP] and pre-exposure prophylaxis [doxyPrEP]) for the prevention of bacterial sexually transmitted infections (STIs).

Search strategy

A comprehensive literature search was performed on 10 January 2026 using two electronic databases: PubMed and Embase (via Ovid). The search strategy combined controlled vocabulary terms (e.g. MeSH terms) and free-text keywords related to doxycycline, STI prophylaxis, bacterial STIs, and relevant outcomes.

Three separate searches were conducted: (1) effectiveness and adherence outcomes; (2) adverse events; and (3) antimicrobial resistance. For the adverse events and AMR searches, terms were expanded to include studies of long-term doxycycline use across all indications, rather than STI prophylaxis alone. Long-term doxycycline use was defined as use for 8 weeks or more. Search strategies were adapted for each database to account for differences in indexing and syntax. Full search strategies are provided in Appendix 1.

We did not conduct separate searches of conference proceedings or conference-specific databases, and conference abstracts were not included.

Eligibility and outcomes

Effectiveness and adherence

For effectiveness and adherence outcomes, studies were eligible if they evaluated doxycycline used as pre-exposure or post-exposure prophylaxis for prevention of bacterial STIs. Eligible study designs included randomised controlled trials, observational cohort studies, case-control studies, implementation studies, and ecological studies.

Effectiveness outcomes included STI incidence or acquisition, including syphilis, chlamydia, gonorrhoea, and *Mycoplasma genitalium*. Studies comparing doxyPEP/doxyPrEP users with non-users, pre/post analyses among doxyPEP/doxyPrEP users, and population-level trend analyses following doxyPEP implementation were all eligible.

Adherence outcomes included objective measures, such as doxycycline concentrations in plasma where available, as well as self-reported measures of doxyPEP adherence. These included the proportion of sexual exposures covered by doxyPEP and the proportion of instances in which doxyPEP was taken at the recommended dose and/or within the recommended time window following sexual exposure. We did not include measures of overall frequency of use that were not directly linked to sexual exposure (e.g., prevalence of recent doxyPEP use, absolute number of doses taken, pill counts, or dose availability between visits).

Adverse events and antimicrobial resistance

Given the extensive existing literature on the safety of doxycycline, we limited our assessment of adverse events and safety outcomes to studies published from January 2023 onwards. This approach was taken to build on a comprehensive prior systematic review and meta-analysis that evaluated adverse events associated with longer-term doxycycline use (defined as ≥ 8 weeks) in studies published between August 2003 and January 2023.⁷ That review included 67 studies across a range of clinical indications and concluded that longer-term doxycycline use was generally well tolerated, with predominantly mild to moderate gastrointestinal and dermatological adverse events and infrequent discontinuation due to toxicity. By restricting our review of adverse events to more recent studies, we aimed to avoid duplication of evidence while capturing new safety data relevant to contemporary doxycycline use for bacterial STI prevention, including post-exposure prophylaxis regimens and populations not well represented in earlier studies.

For both adverse events and AMR outcomes, studies were eligible if they evaluated doxycycline for STI prophylaxis or long-term doxycycline use, defined as use for more than eight weeks, for other indications. Outcomes included reported adverse events or safety outcomes, and evidence of antimicrobial resistance in STI pathogens and commensal organisms, or changes in the gut microbiome associated with doxycycline use.

Eligible study designs included randomised controlled trials, non-randomised trials, observational cohort studies, case-control studies, implementation studies, and ecological studies. Studies reporting AMR outcomes must have needed to include a comparator (no doxycycline exposure, less than 8 weeks exposure, or intermittent exposure).

General criteria

Studies conducted in any geographic setting and among any adult population were eligible. Non-original research articles, including editorials, commentaries, and narrative reviews, were excluded; however, reference lists of relevant reviews were screened to identify additional eligible studies.

Study selection

All records identified through the database searches were imported into Covidence and duplicates were removed. Titles and abstracts were screened independently by two reviewers (MT and BR). Full-text articles were retrieved for all potentially eligible studies and assessed independently against inclusion criteria. Discrepancies were resolved through discussion until consensus was reached. Regardless of the outcome for which a study was initially identified, all full-text articles were assessed

for relevance to all four outcome domains and included accordingly if eligibility criteria were satisfied.

Data extraction

Data were extracted using a standardised extraction form. Extracted variables included study characteristics (author, year, country, design), participant characteristics, doxycycline regimen and implementation details, outcome measures, main findings related to effectiveness, adherence, adverse events, and AMR. Disagreements were resolved by consensus.

Data synthesis

Given anticipated heterogeneity across study designs, populations, and outcome measures, results were synthesised narratively. Where feasible, quantitative summaries were presented. Effect estimates were reported as presented in the original studies.

Risk of bias assessment

Risk of bias was assessed separately for each outcome domain and according to study design. Randomised controlled trials were assessed using the Cochrane Risk of Bias 2 tool (RoB 2), while non-randomised studies were assessed using the ROBINS-I tool. Interrupted time-series and ecological analyses were assessed using criteria adapted from Cochrane Effective Practice and Organisation of Care (EPOC) guidance. Qualitative studies were assessed using the CASP qualitative checklist. Given the diversity of study designs and outcomes, risk of bias was summarised narratively by outcome domain rather than using a single aggregated score.

Results

Study selection and included studies

The search for studies evaluating effectiveness and adherence outcomes identified 246 unique records after removal of duplicates. Following title and abstract screening, 47 articles were retrieved for full-text review. Of these, 18 studies and 17 studies met the inclusion criteria for effectiveness and adherence outcomes, respectively, and were included in the final synthesis. The searches for adverse events and antimicrobial resistance identified 240 and 892 records, respectively, after removal of duplicates. Following screening and full-text review, 14 studies were included for adverse events outcomes and 13 for antimicrobial resistance (Figure 1).

Across the four outcome domains (effectiveness, adherence, adverse events, and antimicrobial resistance), a total of 42 unique studies were included in the review. Five studies contributed data across all four outcomes, providing integrated evidence on clinical impact, real-world use, safety, and resistance patterns. A further four studies reported on three outcome domains, most commonly effectiveness, adherence, and adverse events, while two studies contributed to two domains. The remaining 29 studies addressed a single outcome only, with effectiveness (n=7), adherence (n=7), adverse events (n=8), and AMR (n=7) reported in separate studies.

Although 40 unique studies were included across the four outcome domains, a substantial proportion of the evidence arose from a number of primary trials or cohorts, including the ANRS IPERGAY Study,⁸ the US DoxyPEP Study³ and its open-label extension⁹, the DOXYVAC Study,⁴ and the dPEP Kenya Study,¹⁰ the DuDHS Study.¹¹ These cohorts generated multiple linked publications spanning outcome domains. The remaining studies comprised clinical and observational cohorts, population-level ecological analyses, cross-sectional surveys, qualitative studies, and long-term doxycycline safety investigations.

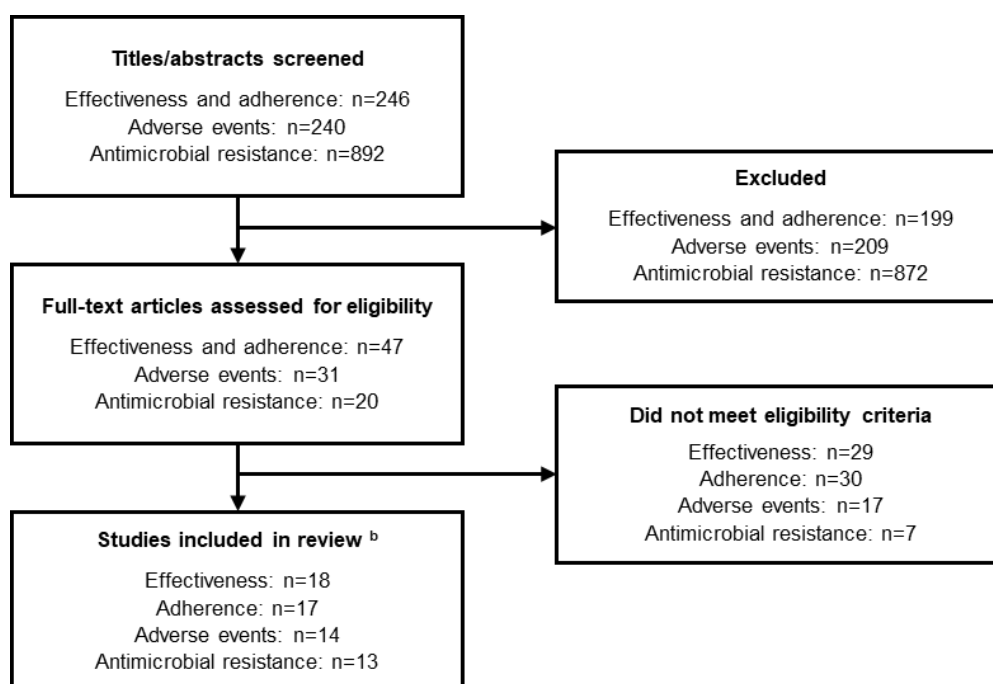


Figure 1. PRISMA flow diagram of study selection.

Effectiveness outcomes

Characteristics of included studies

A total of 18 studies reported effectiveness outcomes examining changes in STI incidence associated with doxyPEP or doxyPrEP use, spanning both interventional and observational designs (Table 1). Overall, effectiveness data were derived from 16 distinct cohorts. Two publications reported different outcomes from the IPERGAY Study (Molina et al., 2018; Bercot et al., 2021), and two publications reported sequential findings from the US DoxyPEP RCT, including preliminary results (Luetkemeyer et al., 2023) and final results with open-label extension data (Luetkemeyer et al., 2025).

Seven controlled interventional studies were identified, including one small pilot RCT of daily doxyPrEP, four large randomised trials of doxyPEP compared with no doxycycline control, and one randomised comparison of immediate versus delayed doxyPrEP initiation. One early clinic cohort report (Scott et al 2025) was excluded as updated analyses from the same population were subsequently published with longer follow-up and more comprehensive outcome assessment (Spinelli et al 2025).

Effectiveness studies were conducted across diverse populations, predominantly among MSM and transgender women, most of whom were using HIV PrEP or living with HIV (n=17 studies), with one study conducted among cisgender women using HIV PrEP in Kenya (Stewart et al 2023) and one small cohort study among cisgender female sex workers in Japan (Abe et al 2025).

Nine studies were retrospective or prospective observational analyses conducted in routine clinical care settings, incorporating pre-post comparisons, cohort comparisons with non-users, and controlled interrupted time-series designs. Three ecological studies were also included, comprising two jurisdiction-level time-series analyses assessing population-level STI trends following the introduction of doxyPEP guidance in San Francisco, and one clinic-level pre-post implementation study.

Overall, 12 studies evaluated doxyPEP, three focused on doxyPrEP, and two examined outcomes following dissemination or implementation of doxyPEP clinical guidance. Studies were conducted predominantly in the United States (n=12), with data also from France (n=2), Kenya (n=1), Canada (n=1), Japan (n=1), and Spain (n=1).

Summary effectiveness findings

DoxyPEP

Across randomised trials and real-world observational studies, doxyPEP was consistently associated with substantial reductions in incident syphilis and chlamydia (Table 1). In large RCTs among MSM and transgender women, quarterly STI positivity was reduced by approximately 60-80% overall, with particularly marked reductions in syphilis and chlamydia with relative risk reductions typically ranging from approximately 70-90% for syphilis and 60-85% for chlamydia. In the DOXYVAC trial, incidence of first syphilis or chlamydia was reduced from 53.2 to 8.8 per 100 person-years (adjusted hazard ratio 0.17). Observational cohorts reported similar findings, with within-person analyses showing 60-80% reductions in chlamydia and syphilis and controlled interrupted time-series analyses demonstrating sustained declines of approximately 50% or more at the population level. Effect sizes were large and broadly consistent across study designs, with relative risk reductions typically ranging from approximately 70-90% for syphilis and 60-85% for chlamydia. These effects were consistent across

study designs and were sustained in longer-term follow-up and open-label extension phases, even in the context of increasing sexual risk behaviours.

In contrast, effectiveness against gonorrhoea was more variable. Several randomised and observational studies demonstrated modest but statistically significant reductions, typically in the range of approximately 30-55%, while many studies reported no significant protective effect, and some ecological analyses suggested attenuated or absent impact over time. Where reductions were observed, effects were consistently smaller in magnitude than for chlamydia and syphilis and in some settings were limited to specific anatomical sites. Reduced effectiveness coincided with high baseline prevalence of tetracycline resistance in *Neisseria gonorrhoeae* isolates.

Evidence among cisgender women was limited and less conclusive. The dPEP Kenya RCT (Stewart et al 2023) did not demonstrate a significant reduction in bacterial STI incidence, likely influenced by low objective adherence (see Table 2), and no reduction in gonorrhoea incidence was observed.

Evidence for effectiveness against *Mycoplasma genitalium* was limited to a single IPERGAY substudy (Bercot et al 2021), which found no meaningful change in prevalence associated with doxyPEP use over six months of follow-up.

DoxyPrEP

Evidence for doxyPrEP was more limited and derived primarily from a small trial and observational study. A small pilot RCT of daily doxycycline among MSM living with HIV suggested reductions in overall bacterial STI incidence, although individual STI-specific estimates were non-significant (Bolan et al 2015). In a small observational study among cisgender female sex workers in Japan, daily doxyPrEP was associated with reductions in chlamydia and syphilis incidence, with no significant effect observed for gonorrhoea (Abe et al 2025). Overall, while findings suggest potential effectiveness, the evidence base for doxyPrEP remains limited in size, duration, and generalisability.

Risk of bias for effectiveness

Overall risk of bias for effectiveness outcomes was low to moderate. Evidence from randomised trials was robust, while observational and ecological studies were more susceptible to confounding, selection bias, and secular trends, although findings were consistent across designs (see Tables S1 and S2).

Adherence outcomes

Characteristics of included studies

A total of 17 studies reported adherence outcomes related to doxycycline prophylaxis for prevention of bacterial STIs, including seven randomized controlled trials (RCTs) or trial extensions, three single-arm observational or intervention studies, four cross-sectional surveys assessing real-world adherence behaviours (Table 2), and three qualitative studies exploring perceived facilitators and barriers to adherence (Table 3). Populations included MSM and transgender women in the United States, France,

Canada, Belgium, and the Netherlands; cisgender women using HIV PrEP in Kenya; cisgender female sex workers in Japan; and PrEP users in routine clinical care in Spain and Italy.

Studies measured adherence to doxyPEP (typically 200 mg within ≤ 72 hours after sex) or daily doxycycline as doxyPrEP (100 mg once daily), with follow-up durations ranging from six to twelve months in interventional studies. Adherence was assessed using diverse measures including self-reported timing within the post-exposure window, dosing consistency and missed doses, proportion of sex acts covered, plasma doxycycline concentrations, hair-based detection, structured adherence questionnaires, and qualitative interviews.

Summary of adherence findings

DoxyPEP

Across RCTs conducted primarily among MSM and transgender women in high-income settings, adherence to doxyPEP was consistently high (Table 2). In the US DoxyPEP trial, most participants reported consistent dosing within 72 hours after sex and rarely missing indicated doses, with condomless sex act coverage exceeding 80% during the randomized phase and remaining high during the open-label extension. Dosing frequency remained stable at approximately five doses per month. Similarly, in the DOXYVAC trial, median use was six doses per month, more than 70% of participants reported using doxyPEP at their most recent sexual encounter, and median time to dosing was 15 hours post-sex, indicating generally early post-exposure administration. In IPERGAY, participants reported frequent episodic use with the majority of doses taken within 24 hours, and plasma detection supported regular post-exposure exposure patterns.

In contrast, the dPEP Kenya RCT among cisgender women showed a pronounced discrepancy between self-report and biologic adherence; despite near-universal reporting of timely post-exposure dosing, doxycycline was detected in less than one-third of hair samples, indicating low biologic exposure and likely explaining the lack of observed effectiveness in that trial.

Outside trial settings, adherence patterns were more variable. In a PrEP cohort in Spain (Palacios et al 2025), nearly all doxyPEP users reported dosing within the recommended window, whereas in a PrEP cohort in Italy (Rossotti et al 2025) only around half adhered to the recommended 200 mg within 72-hour regimen, with common deviations including reduced dosing, pre-exposure use, and non-standard schedules. A survey from the Netherlands (Teker et al 2025) demonstrated incomplete coverage of sexual exposures, particularly for oral and vaginal sex compared with anal sex, while a US online survey (Traeger et al 2024) similarly showed variability in dosing timing, exposure coverage, and correct dose use.

DoxyPrEP

Daily doxyPrEP trials also demonstrated relatively high adherence. Objective serum doxycycline levels in the Bolan et al pilot RCT were consistent with adherent daily exposure in most visits, while in the Canadian DuDHS trial (Grennan et al 2025), self-reported adherence was high but objective plasma levels suggested modest over-reporting, particularly in the delayed-start group. Daily doxyPrEP among female sex workers in Japan (Abe et al 2025) was associated with high self-reported adherence.

Qualitative adherence outcomes

Qualitative studies provided important contextual insight into adherence behaviours (Table 3). Among MSM and transgender women in the US DoxyPEP trial (Fredericksen et al 2024), participants generally described doxyPEP as easy to integrate into existing medication routines, with the flexible 24-72 hour dosing window facilitating consistent use. High personal organisation and pill-carrying strategies further supported adherence, while confusion about dosing indications, particularly regarding oral sex, represented a challenge. In contrast, cisgender women in Kenya (Kwach et al 2025) described substantial structural and social barriers including gastrointestinal side effects, stigma and privacy concerns, routine disruptions, and negative partner reactions, alongside facilitators such as strong belief in doxyPEP effectiveness, discreet pill carriers, social support, and routine integration. A separate US qualitative study among MSM (Eshan et al 2024) highlighted simplicity and single-dose convenience as key motivators for adherence, while uncertainty about correct dosing and timing represented perceived risks of misuse.

Risk of bias for adherence

Risk of bias for adherence outcomes was moderate overall. Trial-based estimates were strengthened by objective measures in some studies, but reliance on self-reported adherence and variability in real-world settings introduced potential measurement and selection bias (see Tables S1, S2 and S4).

Adverse event outcomes

Characteristics of included studies

Seventeen studies reported clinical adverse events outcomes, including ten studies evaluating doxyPEP or doxyPrEP directly for STI prevention and seven studies assessing longer-term doxycycline use (>8 weeks) for other clinical indications (Table 4). Study designs included large multicentre randomised controlled trials (RCTs), open-label extensions, pilot RCTs, platform and phase 2 trials, prospective and retrospective cohorts, and comparative controlled studies.

Among doxyPEP/doxyPrEP studies, populations included MSM, transgender women, cisgender women using HIV PrEP, female sex workers, and real-world PrEP cohorts across the United States, France, Kenya, Canada, Spain, Japan, and China. Follow-up ranged from 8 weeks to 12 months in prophylaxis trials, with open-label extension data available up to 12 months in the US DoxyPEP study.

Longer-term doxycycline exposure studies included adults treated for acne, rosacea, hidradenitis suppurativa, advanced NSCLC (as dermatologic prophylaxis), Parkinson's disease, and mixed clinical indications. Doses ranged from 40 mg to 200 mg daily, with treatment durations from 8 weeks to 12 months. All non-STI studies evaluating prolonged doxycycline use involved continuous daily dosing rather than intermittent or episodic regimens. These studies provided additional safety data relevant to repeated or sustained doxycycline exposure.

Across studies, reported outcomes included treatment-emergent adverse events (TEAEs), laboratory abnormalities, serious adverse events (SAEs), discontinuations due to adverse events, and tolerability patterns.

Four studies reported changes in the gut microbiome, including assessments of microbial diversity, taxonomic composition, and antimicrobial resistance gene (ARG) abundance using metagenomic and 16S sequencing approaches (Table 5).

Summary of adverse events findings

Clinical adverse events

Across doxyPEP and doxyPrEP trials, adverse events were predominantly mild to moderate and largely gastrointestinal in nature. The most commonly reported events were nausea, abdominal pain, diarrhoea, dyspepsia, reflux, and headache (Table 4).

In the US DoxyPEP RCT (N=501), no serious adverse events were attributed to doxycycline. One grade 2 laboratory abnormality (transaminitis) and five grade 3 events (three diarrhoea; two headache/migraine) were considered possibly or probably related. Approximately 2% discontinued due to unacceptable adverse events or preference. In the 12-month open-label extension, no additional serious adverse events were attributed to doxycycline; 12 participants permanently discontinued (six due to adverse events; six due to preference), and no discontinuations occurred during the OLE phase.

In the IPERGAY study (n=232), serious and grade 3-4 adverse events did not differ between arms. Gastrointestinal adverse events were more frequent in the doxyPEP group (25% vs 14%; p=0.03), and 7% discontinued due to drug-related adverse effects. In the larger DOXYVAC trial (N=1,101), drug-related adverse events occurred in 7% of participants receiving doxyPEP, most commonly nausea/vomiting (3%), abdominal pain (2%), and diarrhoea (1%). One drug-related serious adverse event (fixed drug eruption) was reported, and 2% discontinued due to gastrointestinal events.

In the Kenya dPEP trial (N=449), no serious adverse events were attributed to doxycycline. Nausea occurred more frequently in the doxyPEP arm than standard care (7.2% vs 4.6% of visits) but was generally mild. In the Canadian doxyPrEP pilot (N=52), no serious adverse events were attributed to doxycycline; adverse events were mainly gastrointestinal, with two participants reporting moderate/severe nausea.

Real-world cohorts were broadly consistent with trial findings. In a multicentre retrospective cohort (N=671), skin reactions occurred in 1.3% (predominantly fixed drug eruptions), all resolving after discontinuation (Chen et al 2025). In a PrEP cohort in Spain (Palacios et al 2025; n=197 doxyPEP initiators), no serious adverse events were reported; 4.5% discontinued, primarily due to mild gastrointestinal effects. Among cisgender female sex workers in Japan (Abe et al 2025; N=40), nausea/vomiting was reported by 21%, with one discontinuation and no serious adverse events. No changes in bacterial vaginosis or vulvovaginal candidiasis prevalence were observed in that cohort.

Studies which included long-term (>8 weeks) doxycycline exposure for non-STI prevention-related indications demonstrated a similar safety profile. Gastrointestinal adverse events were common but rarely severe. In a study from Saudi Arabia (Eljaaly et al 2023; N=189; median 44 days exposure), 6.3% experienced gastrointestinal adverse events, including esophagitis in 1.6%, and 2.6% discontinued. Gastrointestinal events were significantly more common in participants aged ≥50 years (8/50 vs

4/139; $p=0.003$) and occurred exclusively in those receiving 200 mg/day (12/93 vs 0/96; $p<0.001$), indicating dose and age effects.

In a study on acne treatment with 100 mg daily doxycycline (Atefi et al 2025; $N=80$), dyspepsia occurred in 22.5%, diarrhoea in 10%, and headache in 5%; probiotic co-administration reduced dyspepsia to 7.5%. In a rosacea trial (Bhatia et al 2025; $N=230$), TEAEs occurred in 22-33% of doxycycline recipients, with discontinuation rates of 0 to 1.7% and no serious adverse events attributed to doxycycline. In another rosacea cohort (Wu et al 2025; $n=38$), 39.5% experienced TEAEs, most commonly gastrointestinal discomfort (23.7%), with one discontinuation and no serious adverse events.

Across all included studies, serious adverse events attributable to doxycycline were rare. When present, they were isolated (e.g., one fixed drug eruption in DOXYVAC) and did not signal systemic or life-threatening toxicity. Discontinuation due to adverse events in large doxyPEP trials was generally low (approximately 2-7%), with higher rates primarily observed in small chronic dermatologic cohorts using higher daily doses (200 mg/day).

Gut microbiome diversity/composition

Gut microbiome composition and diversity remained largely stable in studies evaluating doxycycline prophylaxis over follow-up periods of up to 12 months (Table 5). In the US DoxyPEP microbiome substudy (Langlier et al 2024), no meaningful changes were observed in alpha diversity, beta diversity, taxonomic composition, or total bacterial mass over six months of follow-up.

Similarly, longitudinal 16S-based analyses in the DuDHS doxyPrEP study (Knodel et al 2025) demonstrated minimal compositional disruption, with no significant changes in genus-level alpha or beta diversity. A small decrease in phylum-level alpha diversity was observed in the immediate exposure arm, but no consistent or clinically meaningful shifts in overall microbial community structure were detected.

Overall, available evidence suggests that doxycycline prophylaxis is not associated with substantial changes in gut microbiome diversity or composition over 6 to 12 months of follow-up.

Risk of bias for adverse events

Risk of bias for clinical adverse event outcomes was low to moderate. Randomised trials provided the most reliable safety data, while observational studies were more prone to under-reporting and incomplete ascertainment of adverse events (see Table S1 and S2).

Risk of bias in microbiome studies was moderate. Although methods were robust, small sample sizes, short follow-up, and selection of trial subpopulations limit generalisability (see Table S2).

Antimicrobial resistance outcomes

Characteristics of included studies

A total of 14 studies evaluated antimicrobial resistance (AMR) outcomes associated with doxycycline prophylaxis or long-term doxycycline exposure (Table 6). These comprised nine studies assessing resistance in STI pathogens and commensal bacteria within doxyPEP or doxyPrEP cohorts (including nested resistance analyses within randomized trials, open-label extensions, prospective surveillance cohorts, and cross-sectional resistance studies), and four trial-linked substudies examining changes in the gut antimicrobial resistome.

AMR-relevant analyses were embedded within large randomized controlled trials (RCTs) (e.g., US DoxyPEP, DOXYVAC, dPEP Kenya, DuDHS), open-label extensions, prospective real-world cohorts, and cross-sectional resistance surveillance studies. Trial-linked substudies assessed changes in the gut antimicrobial resistome using prospectively collected longitudinal samples and molecular approaches, including whole metagenomic sequencing, metatranscriptomic profiling, and change-point dose-response modelling.

Populations included MSM and transgender women in the United States, France, and Canada; cisgender women using HIV PrEP in Kenya; and PrEP users in routine clinical care in Spain and the United States.

AMR outcomes included phenotypic and molecular resistance in *Neisseria gonorrhoeae*, molecular markers of tetracycline resistance in *Chlamydia trachomatis*, molecular resistance markers in *Mycoplasma genitalium*, carriage and resistance in commensal organisms (e.g., *Staphylococcus aureus*, Group A Streptococcus), detection of methicillin-resistant *Staphylococcus aureus* (MRSA) and ESBL-producing *E. coli*, and metagenomic measures of antimicrobial resistance genes (ARGs) within the gut microbiome

Summary of antimicrobial resistance findings

STI pathogens

Findings for tetracycline resistance in *Neisseria gonorrhoeae* were heterogeneous and strongly influenced by baseline resistance prevalence within study settings (Table 4). In the US DoxyPEP RCT, tetracycline-resistant gonorrhoea was detected more frequently among doxyPEP users than standard-care participants during early follow-up (38% vs 12%), although culture numbers were limited. However, analyses incorporating randomized and open-label extension phases (Luetkemeyer et al 2025) showed similar overall proportions of tetracycline resistance during doxyPEP and standard-care exposure periods (27% vs 24%), with high-level resistance observed in approximately 10% of isolates during doxyPEP use.(ref)

In the DOXYVAC trial (Bercot et al 2025), all cultured *Neisseria gonorrhoeae* isolates were tetracycline resistant at baseline and follow-up, reflecting high background resistance. High-level tet(M)-mediated resistance was significantly more common in the doxyPEP arm than the no-PEP arm (36% vs 13%). In the Kenya dPEP trial, the tet(M) gene was detected in 100% of gonorrhoea samples at baseline and follow-up in both arms, precluding assessment of doxyPEP-associated change. A nested molecular

analysis similarly demonstrated extremely high fluoroquinolone resistance (91%) and frequent multiclass resistance (91%), with no differences between doxyPEP and standard-care groups.

Across trials and observational cohorts, no tetracycline resistance was detected in cultured *Chlamydia trachomatis* isolates, and no increase in ceftriaxone resistance or other first-line gonorrhoea therapies was observed. Real-world prospective surveillance data from Spain (Palacios et al 2025) likewise found no significant difference in tetracycline resistance among *N. gonorrhoeae* isolates between doxyPEP users and non-users (43% vs 46%), suggesting that doxyPEP did not measurably increase resistance above high background prevalence.

In the IPERGAY molecular substudy (Bercot et al 2021), *Mycoplasma genitalium* prevalence and macrolide/fluoroquinolone resistance patterns did not differ between doxyPEP and control arms. A mutation in the 16S rRNA region potentially associated with tetracycline resistance was observed in a minority (12.5%) of specimens, without clear differences across study arms.

Commensal and opportunistic bacteria

Several studies identified increases in doxycycline-resistant *Staphylococcus aureus* among doxycycline-exposed individuals. In the US DoxyPEP cohort (including open-label follow-up), doxyPEP use was associated with a significantly increased hazard of detecting doxycycline-resistant *S. aureus* (HR 3.89), although overall carriage prevalence remained modest (X%). In the Canadian DuDHS doxyPrEP trial, emergent doxycycline-resistant *S. aureus* colonization was observed in several participants, particularly in the immediate-exposure arm, with persistent carriage in some individuals.

Cross-sectional surveillance data from the US (Soge et al 2025) further demonstrated higher prevalence of tetracycline-resistant *S. aureus* and Group A *Streptococcus* among doxyPEP users compared with non-users, particularly among individuals using more than three doxyPEP doses per month, suggesting a dose-response relationship. No consistent increases in MRSA or ESBL-producing *E. coli* were observed across RCTs or observational cohorts.

Gut resistome (tetracycline resistance genes)

Trial-linked longitudinal metagenomic studies consistently demonstrated enrichment of tetracycline resistance genes (ARGs) within the gut resistome following doxycycline prophylaxis. In the US DoxyPEP microbiome substudy, six months of doxyPEP use was associated with significant increases in both the proportional abundance and transcriptional expression of tetracycline ARGs, without parallel increases in resistance genes from other antibiotic classes. Dose-dependent effects were observed in secondary analyses, with change-point modelling identifying a threshold of approximately 65 doxycycline doses over six months above which substantial ARG enrichment occurred.

Findings from daily doxyPrEP exposure were consistent, with modest increases in tetracycline resistance genes observed over 12 months in the DuDHS Study.

Overall, doxycycline prophylaxis was consistently associated with enrichment of tetracycline resistance genes in the gut resistome, with evidence of dose-dependent effects, while changes in resistance genes from other antibiotic classes were not observed.

Risk of bias for antimicrobial resistance

Risk of bias for antimicrobial resistance outcomes was moderate to high. Evidence was limited by small sample sizes, incomplete isolate sampling, and heterogeneity in laboratory methods, although consistent patterns were observed across studies (see Table S2 and S3).

Discussion

Summary of main findings

This systematic review, undertaken to inform national clinical guideline development, demonstrates that doxycycline prophylaxis is highly effective for prevention of syphilis and chlamydia among MSM and transgender women, with more modest and heterogeneous effects for gonorrhoea, and limited evidence for reduction in other STI pathogens (e.g., *Mycoplasma genitalium*).

Across randomised controlled trials and multiple real-world observational and ecological studies, effect estimates were large, consistent in direction, and reproducible across settings. In contrast, evidence among cisgender women remains limited, with one large randomised trial failing to demonstrate effectiveness in the context of low biologic adherence.

Collectively, the evidence base now includes multiple large RCTs, open-label extension data, implementation studies, and population-level interrupted time-series analyses, substantially strengthening the evidence base for several outcomes and populations in the last few years. However, important uncertainties remain, particularly regarding antimicrobial resistance, long-term ecological effects, optimal implementation strategies, and effectiveness outside MSM and transgender women populations.

Overall, the certainty of evidence is high for effectiveness in MSM and transgender women for syphilis and chlamydia, moderate for adherence and short-term safety, and lower for antimicrobial resistance and long-term ecological effects.

Effectiveness

Syphilis and chlamydia among MSM and transgender women

The effectiveness evidence for MSM and transgender women is strong and internally consistent. Large RCTs in the United States and France demonstrated approximately 70 to 90% relative reductions in syphilis and 60 to 80% reduction in chlamydia, with sustained benefits in open-label extension phase. These findings have been replicated in diverse real-world cohorts and are supported by findings from ecological time-series analyses demonstrating population-level declines following guideline implementation.

The magnitude and consistency of effect for syphilis and chlamydia in MSM and transgender women support a high level of certainty that doxyPEP confers substantial individual-level benefit in populations at elevated risk of recurrent STIs (a common eligibility criteria for included studies). The reproducibility of findings across study designs further strengthen confidence in the impact of doxyPEP. For example, two ecological analyses from San Francisco demonstrated reductions in chlamydia and syphilis among MSM and transgender women, with no corresponding decline among cisgender women, for whom doxyPEP is not recommended under current guidelines.

Certainty of evidence: high

The consistency of findings across multiple well-conducted RCTs, supported by concordant observational and ecological data, provides high confidence in a substantial protective effect for these outcomes in MSM and transgender women at elevated risk of recurrent STIs.

Gonorrhoea among MSM and transgender women

In contrast, effectiveness against gonorrhoea is less certain. Although several studies demonstrated modest reductions, effect sizes were smaller and less consistent, and some analyses showed attenuation over time. Reduced effectiveness aligns with high baseline tetracycline resistance in gonorrhoeae in many settings. These findings indicate that the effectiveness of doxycycline prophylaxis is greatest for syphilis and chlamydia, while effects on gonorrhoea are smaller and more variable, likely reflecting underlying resistance patterns and setting-specific factors.

Certainty of evidence: moderate

While evidence from RCTs supports a possible protective effect, inconsistency in magnitude and direction across studies, likely influenced by underlying tetracycline resistance in *Neisseria gonorrhoeae*, reduces confidence in the overall effect estimate.

Cisgender women

Evidence among cisgender women is still weak, and comparable effectiveness has not yet been established. The large dPEP Kenya RCT did not show significant reductions in bacterial STI incidence, although low objective adherence likely contributed. A small observational cohort of female sex worker suggested potential benefit with daily doxyPEP, and a weekly directly observed strategy showed promising but non-significant reductions. However, these data are limited in size, duration and generalisability.

Certainty of evidence: Low

Limited number of studies, concerns regarding adherence, and lack of consistent findings reduce confidence in effectiveness in this population.

Other pathogens

Evidence for effectiveness against other STI pathogens was limited. A single substudy did not demonstrate meaningful changes in *M. genitalium* prevalence following doxycycline prophylaxis.

Certainty of evidence: Low

Evidence is sparse and limited to a small number of studies with short follow-up.

Adherence

Across randomised trials in MSM and transgender women, adherence to doxyPEP was consistently high, with most participants dosing within the recommended post-exposure window and achieving substantial coverage of sexual exposures. Open-label extension data suggest sustained adherence over time, even in the context of increased sexual risk behaviours. However, cross-sectional surveys conducted outside trial settings identified some variability in how closely individuals followed the recommended dosing schedule, including non-standard dosing patterns, reduced doses, pre-exposure use, and uncertainty about correct timing.

Objective adherence data among cisgender women in Kenya revealed substantial discordance between self-report and biologic exposure, underscoring the influence of social, structural, and gendered barriers. Qualitative findings highlighted stigma, partner opposition, pill burden, and routine disruption as important determinants of use.

These findings indicate that effectiveness is closely linked to adherence and context. While adherence was high in trial settings, variability in real-world use suggests that deviations from recommended dosing may influence effectiveness. Barriers such as stigma, partner dynamics, and uncertainty about dosing were identified as important determinants of use.

Certainty of evidence: Moderate

Adherence is well characterised in trial settings, supported by objective measures in some studies. However, variability in real-world settings and limited data in key populations reduce overall certainty.

Clinical adverse events (safety and tolerability outcomes)

Contemporary evidence published since 2023 does not identify new or unexpected safety concerns associated with doxyPEP or doxyPrEP. Across large prophylaxis trials, serious adverse events attributable to doxycycline were rare, and discontinuation due to adverse events was uncommon (generally 2 to 7%). Gastrointestinal symptoms were the most frequently reported adverse events and were typically mild to moderate.

Longer-term daily doxycycline studies conducted for non-STI indications similarly demonstrate acceptable tolerability, with higher gastrointestinal adverse event rates at 200 mg daily and in older populations. Importantly, no signal of severe systemic harms emerged over follow-up periods of up to 12 months.

Certainty of evidence: High (short- to medium-term)

Consistent findings across multiple RCTs and observational studies support a high level of confidence in short- to medium-term safety. However, long-term safety beyond 12-24 months of intermittent post-exposure use remains less well characterised.

Gut microbiome composition and diversity (biological outcomes)

Studies evaluating gut microbiome outcomes using longitudinal sequencing approaches did not demonstrate meaningful disruption of microbial diversity or composition over follow-up periods of up to 12 months. Measures of alpha diversity, beta diversity, taxonomic composition, and overall community structure remained largely stable.

Certainty of evidence: Moderate

Findings are consistent across a small number of studies using robust methods, but limited sample sizes and duration of follow-up reduce certainty.

Antimicrobial resistance

STI pathogens and commensal organisms

Evidence regarding AMR in STI pathogens was more heterogeneous. High baseline tetracycline resistance in *Neisseria gonorrhoeae* was observed in many settings, with no clear evidence of increased resistance to first-line therapies. No tetracycline resistance was detected in *Chlamydia trachomatis*, and limited data suggest no consistent changes in *Mycoplasma genitalium* resistance patterns. Increased carriage of doxycycline-resistant *Staphylococcus aureus* was reported in some studies.

Certainty of evidence: Low (clinical AMR outcomes)

Evidence is limited, heterogeneous, and often indirect, with uncertainty regarding the clinical significance of observed resistance patterns.

Gut resistome

Longitudinal metagenomic studies consistently demonstrated enrichment of tetracycline resistance genes within the gut resistome following doxycycline prophylaxis, with evidence of dose-dependent effects. No consistent increases were observed in resistance genes from other antibiotic classes.

Certainty of evidence: Moderate

Consistent findings across multiple studies support increased tetracycline resistance gene abundance, although clinical implications remain uncertain.

Gaps in evidence and research priorities

Several evidence gaps related to doxyPEP implementation remain. These include:

- Understudied populations: Data are sparse for cisgender women, transgender men, non-binary individuals, and populations in low- and middle-income countries outside of trial setting.
- Long-term outcomes: Follow-up beyond 24 months is limited, particularly for resistome and monitoring for effects on commensal organisms.
- Standardised adherence metrics: There is no consistent operational definition of adequate or ideal adherence for doxyPEP as an episodic, exposure-linked intervention.
- Optimal stopping criteria: Evidence is lacking to inform when doxyPEP prescribing should be de-escalated if population-level STI rates decline.
- Comparative dosing strategies: Data are limited on daily versus event-drive versus structured regimens (for example, once-weekly dosing).

Future research should prioritise pragmatic trials in cisgender women (with embedded adherence support), long-term AMR surveillance linked to prescribing volume and use, and modelling studies to inform thresholds for initiation and discontinuation at individual and population levels.

Conclusion

The available evidence provides high certainty that doxycycline prophylaxis is effective for prevention of syphilis and chlamydia among MSM and transgender women at elevated risk of recurrent STIs. Certainty is lower for gonorrhoea and for populations outside MSM and transgender women. Short- to medium-term safety is well supported, and no substantial disruption of gut microbiome composition has been observed over follow-up periods of up to 12 months.

However, uncertainty remains regarding antimicrobial resistance and longer-term ecological effects. Enrichment of tetracycline resistance genes in the gut resistome is consistently observed, while the clinical significance of these changes and their impact on STI pathogens and broader antimicrobial resistance patterns remain unclear.

Tables

Table 1. Effectiveness of doxycycline prophylaxis for prevention of bacterial STIs

Study	Population and setting	Intervention	Design / comparison	Relevant findings
Randomised controlled trials				
Bolan et al (2015)⁶	MSM with HIV and ≥2 prior syphilis infections, Los Angeles, USA (n=30)	DoxyPrEP: 100 mg daily for 36 weeks	Open-label pilot RCT (1:1); comparator: contingency management; total follow-up 48 weeks (36 on drug + 12 post)	Any bacterial STI reduced over follow-up (syphilis/CT/NG): OR 0.27 (95% CI 0.09–0.83), p=0.02. Reductions for CT/NG combined (OR 0.42, 95% CI 0.09–1.89) and syphilis alone (OR 0.24, 95% CI 0.04–1.33) were not statistically significant, consistent with limited power. No differences in self-reported sexual risk behaviours between arms.
Molina et al (2018)⁸ <i>IPERGAY Study</i>	MSM on HIV PrEP, France (n=232)	DoxyPEP: 200 mg ≤72 h post-sex (preferably ≤24 h)	Open-label RCT (1:1); median follow-up 8.7 months	Reduced time to first syphilis and chlamydia in the doxyPEP arm, with no clear effect on gonorrhoea. Incidence per 100 PY (doxyPEP vs control) with HRs: Overall 37.7 vs 69.7 (HR 0.53, 95% CI 0.33–0.85); Syphilis 3.7 vs 12.9 (HR 0.27, 0.07–0.98); Chlamydia 8.7 vs 28.6 (HR 0.30, 0.13–0.70); Gonorrhoea 28.7 vs 34.5 (HR 0.83, 0.47–1.47).
Bercot et al (2021)¹² <i>IPERGAY Study</i>	MSM on HIV PrEP, France. Subset of IPERGAY participants tested for MG at baseline and 6 months (n=210)	DoxyPEP: 200 mg ≤72 h post-sex (preferably ≤24 h)	Open-label RCT (1:1); median follow-up 8.7 months	Baseline <i>Mycoplasma genitalium</i> prevalence was 10.5% and remained similar at 6 months (9.9% overall), with no meaningful difference between doxyPEP and no-PEP groups (10.2% vs 9.6%), indicating no observed reduction in MG prevalence associated with doxyPEP use.
Stewart et al (2023)¹⁰ <i>dPEP Kenya Study</i>	Cisgender women on PrEP, Kenya (n=449, n=224 to doxyPEP arm)	DoxyPEP: 200 mg ≤72 h post-sex (max 200 mg/day)	Open-label RCT (1:1); 12 months; primary endpoint any incident CT/NG/Tp	No significant reduction in any bacterial STI in the doxyPEP arm: Incidence 25.1 vs 29.0 per 100 PY (doxyPEP vs SOC); RR 0.88 (95% CI 0.60–1.29), p=0.51. Chlamydia RR 0.73 (0.47–1.13); Gonorrhoea RR 1.64 (0.78–3.47) Syphilis very rare (1 case overall), limiting inference.

				However, objective adherence was low in the trial; see Table 2.
Luetkemeyer et al (2023)³ <i>DoxyPEP Study</i>	MSM & transgender women with HIV or on PrEP, with a prior gonorrhoea, chlamydia or early syphilis diagnosis in the preceding year, USA (n=501; HIV PrEP cohort n=327, PWH cohort n=174)	DoxyPEP: 200 mg within ≤72 h (preferably ≤24 h) after condomless anal, vaginal or oral sex	Open-label RCT (2:1); median follow-up 8.9 months with quarterly follow-up visits	Significant reductions in quarterly STI positivity in the doxyPEP arms in both PrEP and HIV cohorts. PrEP cohort: Overall RR 0.34 (0.24–0.46); Syphilis RR 0.13 (0.03–0.59); Chlamydia RR 0.12 (0.05–0.25); Gonorrhoea RR 0.45 (0.32–0.65). PWH cohort: Overall RR 0.38 (0.24–0.60); Chlamydia RR 0.26 (0.12–0.57); Gonorrhoea RR 0.43 (0.26–0.71); Syphilis RR 0.23 (0.04–1.29) (directional reduction but not statistically significant).
Molina et al (2024)⁴ <i>DOXYVAC Study</i>	MSM on PrEP, France (n=1,101)	DoxyPEP: 200 mg ≤72 h post-sex (no more than three doses of 200mg per week); factorial with 4CMenB vaccine	Multicentre open-label 2×2 factorial RCT; 12 months	Primary endpoint (first chlamydia or syphilis) markedly reduced: 8.8 vs 53.2 per 100 PY (doxyPEP vs no PEP), aHR 0.17 (0.12–0.26), p<0.0001. Chlamydia aHR 0.14 (0.09–0.23); Syphilis aHR 0.21 (0.11–0.41); Gonorrhoea aHR 0.67 (0.52–0.87) (modest but significant reduction).
Luetkemeyer et al (2025)⁹ <i>DoxyPEP Study OLE</i>	MSM & transgender women with HIV or on PrEP, with a prior gonorrhoea, chlamydia or early syphilis diagnosis in the preceding year, USA (n=637; 411 initially randomised to doxyPEP)	DoxyPEP: 200 mg within ≤72 h (preferably ≤24 h) after condomless anal, vaginal or oral sex	Open-label RCT (2:1) followed by open-label extension where all participants offered doxyPEP	During the randomised phase, STIs occurred in 12.0% of quarters among doxyPEP users compared with 30.5% in standard care (RR 0.39, 95% CI 0.31–0.49; absolute reduction 19 percentage points), with reductions observed across syphilis, chlamydia, and gonorrhoea. During the open-label extension, low quarterly STI incidence was sustained among those continuing doxyPEP (13%) and declined to 17% among participants who initiated doxyPEP, despite increased sexual risk behaviours
Grennan et al (2025)¹¹ <i>DuDHS Study</i>	MSM & transgender women, Canada (n=52)	DoxyPrEP: 100 mg daily (with daily TDF/FTC for HIV PrEP)	Open-label RCT, immediate vs delayed start (1:1); delayed arm initiated at week 24	Strong effect on chlamydia: 0 cases immediate vs 10 deferred at 24 weeks (0 vs 78.4/100 PY, p=0.002). Syphilis was rare (0 vs 1).

				Gonorrhoea was lower in immediate arm but not statistically significant. Over 48 weeks, doxyPrEP associated with reduced any STI (aOR 0.36). No chlamydia or syphilis cases occurred after starting doxyPrEP.
Observational cohort studies				
Abe et al (2025)¹³	Cisgender female sex workers Tokyo, Japan (n=40).	DoxyPrEP: doxycycline 100 mg once daily	Retrospective observational EHR cohort with within-person pre/post doxyPrEP initiation comparison.	Overall STI incidence declined significantly following initiation of daily doxyPrEP, from 232.3 to 79.2 per 100 person-years (IRR 0.33, p=0.020). Syphilis incidence fell to zero, and chlamydia showed a marginally significant reduction (IRR 0.35, p=0.056), while no significant changes were observed for gonorrhoea or non-bacterial conditions (BV, VVC).
Traeger et al (2025)⁵	HIV PrEP users (mostly MSM), California USA (n=2,253)	DoxyPrEP dispensed via pharmacy (200 mg ≤72 h)	Retrospective EHR cohort; within-person pre/post + comparison vs non-recipients. Measured quarterly STI positivity.	After doxyPrEP initiation, large declines in chlamydia (RR 0.21) and syphilis (RR 0.20) quarterly positivity. Modest overall gonorrhoea decline (RR 0.88) driven by rectal (RR 0.81) and urethral (RR 0.56) reductions; no decline in pharyngeal gonorrhoea. No STI declines were observed among non-recipients over same period.
Lewis et al (2025)¹⁴	MSM at public STI/HIV PrEP clinic, Philadelphia USA (N=508; n=416 dispensed doxyPrEP)	DoxyPrEP (200 mg ≤72 h; dispensed 12 doses/3 months)	Observational cohort comparison + crossover pre/post among recipients	Cohort comparison (doxyPrEP vs PrEP-only): Any STI HR 0.61 (0.40–0.93); Chlamydia HR 0.40 (0.21–0.78); non-significant for gonorrhoea (HR 0.75) and syphilis (HR 0.51). Within-user pre/post: Any STI IRR 0.38 (0.29–0.50); Chlamydia IRR 0.28 (0.20–0.39); Gonorrhoea IRR 0.49 (0.37–0.65).

Osmundson et al (2025)¹⁵	LGBT health centre, Los Angeles USA (n=2,083)	DoxyPEP (200 mg ≤72 h)	Retrospective EHR pre/post (6 months before vs after initiation)	Substantial reductions following doxyPEP initiation: Syphilis RR 0.14 (0.07–0.25); Chlamydia RR 0.14 (0.07–0.25); Gonorrhoea RR 0.45 (0.38–0.55). Effects observed across anatomical sites. Breakthrough infections for syphilis/chlamydia occurred mainly among individuals with low doxyPEP use.
Spinelli et al (2025)¹⁶	PrEP cohort at a sexual health clinics, San Francisco USA (n=4,592; n=2,524 initiated doxyPEP)	DoxyPEP (200 mg ≤72 h)	Controlled ITS with contemporaneous non-user control; follow-up up to 96 weeks	Adjusted ITS showed sustained reductions in chlamydia and syphilis combined (AOR 0.17, 95% CI 0.12–0.25) and smaller reduction in gonorrhoea (AOR 0.56, 0.44–0.71). Gonorrhoea declined initially but increased later; chlamydia/syphilis reductions sustained through 96 weeks.
Huang et al (2025)¹⁷ <i>Doxy-care study</i>	MSM & transgender women, Northern Manhattan USA (early adopters n=100; matched comparator n=355)	DoxyPEP (200 mg ≤72 h)	Prospective cohort; within-person pre/post + propensity-matched comparison	Within-user comparison (pre/post): reduced any STI positivity IRR 0.56 (0.37–0.81); marked reductions in chlamydia overall IRR 0.24 (0.09–0.51) including rectal IRR 0.24 (0.08–0.55); no significant gonorrhoea reduction. Matched analysis: reduced chlamydia (aIRR 0.30) including rectal (aIRR 0.23), but not overall STI incidence or gonorrhoea.
Palacios et al (2025)¹⁸ <i>PRIDOX study</i>	PrEP cohort (MSM & transgender women), Málaga Spain (n=876 PrEP; n=197 initiated doxyPEP)	DoxyPEP: 200 mg ≤72 h (preferably ≤24hr)	Prospective pre/post; Cox models; mean post-doxyPEP follow-up 14 months	STI incidence declined for: Chlamydia, from 31.4 to 7.8/100py (HR 0.24, 0.13–0.42; p<0.0001); and syphilis 21.5 to 3.2/100py (HR 0.14, 0.05–0.31; p<0.0001). Gonorrhoea declined from 41.5 to 28.9/100py, but this was not statistically significant (HR 0.70; p=0.10 as reported).
Ecological / population-level studies				
Sankaran et al (2025)¹⁹	MSM & transgender women, San Francisco USA (jurisdiction-wide surveillance)	DoxyPEP guideline implementation (Oct 2022)	Population-level ITS of monthly STI diagnosis notified to health department (observed vs	By November 2023, cases among MSM/TGW were approximately 50% lower than projected for chlamydia (–49.6%) and early syphilis (–51.4%);

			projected based on no doxyPEP guidelines)	gonorrhoea increased relative to projections (+25.6%). No concurrent decline in chlamydia among cisgender women (not targeted), supporting a doxyPEP-associated pattern; ecological inference only.
Liu et al (2024)²⁰	San Francisco, USA citywide surveillance – STI diagnoses among men	DoxyPEP guideline implementation (Oct 2022)	Ecological ITS with COVID/Omicron breakpoint	The mean monthly number of STI cases declined following doxyPEP guidance for male rectal chlamydia, male rectal gonorrhoea, and adult male syphilis; there was a significant trend change for rectal chlamydia from increasing to decreasing.
Jarolimova et al (2025)²¹	Boston sexual health clinic, USA (n=670 initiated doxyPEP)	DoxyPEP rollout in routine clinic care	Clinic-level before-after doxyPEP implementation comparison with seasonal adjustment.	Positivity declined post-doxyPEP implementation: Chlamydia RR 0.45 (0.34–0.60); Syphilis RR 0.59 (0.37–0.96). Overall gonorrhoea remained unchanged (RR 0.88), though rectal gonorrhoea decreased (RR 0.59).

Table 2. Adherence to doxycycline prophylaxis for prevention of bacterial STIs

Study	Population and setting	Intervention	Adherence measure	Relevant findings
Randomised controlled trials				
Bolan et al (2015)⁶	MSM living with HIV with ≥2 prior syphilis infections in the preceding year, attending an HIV clinic in Los Angeles, USA (n=30).	DoxyPrEP: 100 mg doxycycline orally once daily for 36 weeks (with 12-week post-intervention follow-up).	Objective serum doxycycline concentrations at weeks 12, 24, and 36 (≥1000 ng/mL defined as adherent exposure)	Objective serum measurements indicated high adherence to daily doxyPrEP, with doxycycline concentrations ≥1000 ng/mL detected in 24 of 39 study visits across weeks 12, 24, and 36.
Molina et al (2018)⁸ <i>IPERGAY Study</i>	MSM using HIV PrEP, France (n=232)	DoxyPEP: 200 mg taken as soon as possible after sex (target ≤24 h; max 72 h)	Self-reported pill use (pills/month) + timing of dosing after sex	Median 6.8 pills/month (IQR 2.8–14.5); 83% of doses ≤24 h post-sex. Doxycycline detected in 30% of plasma samples and in 63% of doxyPEP users at least once, consistent with regular but episodic post-exposure dosing.
Luetkemeyer et al (2023)³ <i>DoxyPEP Study</i>	MSM and transgender women, with a prior gonorrhoea, chlamydia or early syphilis diagnosis in the preceding year, USA (n=501; HIV PrEP cohort n=327, PWH cohort n=174)	DoxyPEP: 200 mg within ≤72 h (preferably ≤24 h) after condomless anal, vaginal or oral sex	Quarterly computer-assisted self-report assessing timing within ≤72 h, consistency (“always/often”), missed doses when indicated, and doses per month.	Self-reported adherence was high, with 86% of participants reporting consistent doxyPEP use (always or often within 72 h after sex) and 71% reporting never missing indicated doses.
Luetkemeyer et al (2025)⁹ <i>DoxyPEP Study OLE</i>	MSM & transgender women with HIV or on PrEP, with a prior gonorrhoea, chlamydia or early syphilis infection in the preceding year, USA (n=637; 411 initially randomised to doxyPEP)	DoxyPEP: 200 mg within ≤72 h (preferably ≤24 h) after condomless anal, vaginal or oral sex	Quarterly computer-assisted self-report assessing timing within ≤72 h, consistency (“always/often”), missed doses when indicated, and doses per month.	82% of condomless sex acts were covered during the randomised phase (median 15 doses/quarter ≈5/month); 91% reported consistent dosing within 72 hours. In the OLE, coverage remained 77-81% with similar dosing frequency and 88-90% reporting consistent use, demonstrating sustained high adherence.
Molina et al (2024)⁸ <i>DOXYVAC Study</i>	MSM on HIV PrEP, France (n=1,101)	DoxyPEP: 200 mg within ≤72 h after condomless sex (preferably ≤24 h), (no more than three doses of 200mg per week)	Self-reported pills/month, self-reported use at most recent sex, and self-reported time-to-dose after sex	Median doxyPEP use was 6 pills (3 doses) per month (IQR 3-13). More than 70% of participants reported using doxyPEP at their most recent sexual encounter at each follow-up visit. Median time to dosing was 15 hours post-sex (IQR 5–30 hours), indicating high adherence to the recommended prophylactic window with typically early post-exposure dosing.

Stewart et al (2023)¹⁰ <i>dPEP Kenya Study</i>	Cisgender women (18–30y) on HIV PrEP, Kisumu, Kenya (n=449, n=224 to doxyPEP arm)	DoxyPEP: 200 mg within ≤72 h after sex (max 200 mg/day)	(i) Self-reported pill use and timing after sex; plus (ii) objective adherence via doxycycline detection in hair samples (subset n=50)	Median doxyPEP use was 4 doses per month (IQR 0-8). Nearly all reported doses were taken ≤24 h after sex. However, objective adherence was low: doxycycline detected in 29% of hair samples, aligning with low biologic exposure despite favourable self-report.
Grennan et al (2025)¹¹ <i>DuDHS Study</i>	MSM & transgender women without HIV, with a prior syphilis infections in the preceding 36 months, Canada (n=52; immediate n=26, deferred n=26)	DoxyPrEP: 100 mg daily (immediate vs delayed start at week 24) alongside daily TDF/FTC HIV PrEP	(i) ACTG adherence questionnaire (% reporting ≥95% adherence) and (ii) plasma doxycycline levels (≥1000 ng/mL as proxy for recent/steady-state use)	At week 48, self-reported doxycycline adherence (≥95% of doses take) was 70.8% (immediate) vs 61.9% (deferred). However objective adherence (≥1000 ng/mL) at week 48 was lower, at 66.7% immediate vs 28.6% deferred (p=0.011).
Single-arm observational / intervention studies				
Abe et al (2025)¹³	Cisgender female sex workers Tokyo, Japan (n=40).	DoxyPrEP: doxycycline 100 mg taken once daily	Self-reported daily use during routine follow-up visits	High daily adherence, with 73% reporting no missed doses and 27% missing only 1-2 doses per month; no frequent non-adherence observed.
Palacios et al (2025)¹⁸ <i>PRIDOX study</i>	MSM & transgender women on PrEP, Málaga Spain (n=876 on PrEP; n=197 initiated doxyPEP)	DoxyPEP: 200 mg ≤72 h (preferably ≤24 h)	Self-reported dosing timing at quarterly visits.	93% reported always or almost always dosing within 72 h after sex.
Cross-sectional studies				
Rossotti et al (2025)²²	PrEP users attending a sexual health service in Milan, Italy (n=703; 97% men; n=62 reported doxyPEP use; 100% men)	Survey on doxyPEP use	Self-reported adherence to recommended doxyPEP regimen, including timing of dosing after sex and dose taken	Only 52% of participants reported using doxyPEP according to the recommended regimen (200 mg within 72 hours after sex). Among those not adhering, common deviations included taking a reduced 100 mg dose (21%), initiating dosing before sex as PrEP (5%), or using highly variable non-standard regimens (23%).
Teker et al (2025)²³	MSM, transgender and gender-diverse individuals in the Netherlands (n=1,633; n=246 reported doxyPEP/doxyPrEP use in the past 6 months)	Survey on doxyPEP/doxyPrEP use	Self-reported coverage of sexual exposures with doxycycline by anatomical site over the prior 6 months	In the past 6 months, the proportion of participants reporting always or mostly using doxyPEP after oral sex was 28.9%, after vaginal sex was 26.8% and after anal sex was 57.3%.

Van Baelen et al (2025)²⁴	MSM and trans and gender diverse people in Belgium (N=875, 98% men; n=81 had ever used doxyPEP)	Survey on doxyPEP/doxyPrEP use	Self-reported adherence to doxyPEP regimen, including timing after sex and dosing strategy (post-exposure vs daily use)	Among individuals who had ever used doxyPEP, the majority (86.4%) used the recommended regimen of 200 mg after sex, while small proportions reported daily dosing (100 mg daily: 4.9%; 200 mg daily: 6.2%) or other non-standard regimens (4.9%).
Traeger et al (2024)²⁵	US adults recruited via dating apps (n=903; 96.2% MSM; n=189 reported STI prophylaxis use)	Survey of real-world antibiotic prophylaxis use (predominantly doxycycline)	Self-reported adherence including: (i) proportion of sex acts covered (some/most/all), (ii) timing of dosing after sex, and (iii) dose taken	Among participants using antibiotic prophylaxis after sex (78% had used doxycycline), 49% reported dosing within 24 hours and 41% within 24–72 hours, with 9% dosing beyond the recommended window. Coverage of sexual exposures varied, with 47% using prophylaxis for some sex acts, 29% for most, and 24% for all encounters with casual partners. Correct 200 mg dosing was reported by 65%, while 21% used lower doses and 22% were unsure of dose

Table 3. Qualitative findings related to adherence to doxycycline prophylaxis for prevention of bacterial STIs

Qualitative studies		
Study	Population, setting and study design	Main findings related to adherence, including barriers and facilitators
Fredericksen et al (2024)²⁶ <i>DoxyPEP Study</i>	In-depth interviews with MSM and transgender women in the intervention arm of DoxyPEP Study (n=44)	<p>A key theme that emerged was “Easy to use/adhere to prescribed regimen”.</p> <ul style="list-style-type: none"> Participants generally found doxycycline post-exposure prophylaxis (doxyPEP) easy to use and integrate into existing medication routines, particularly those already accustomed to daily antiretroviral therapy or HIV PrEP. Although the large pill size was commonly disliked and described as cumbersome or difficult to swallow, most participants reported becoming accustomed to it over time and did not perceive it as a barrier to adherence. The 24-72 hour post-exposure dosing window was viewed as a key facilitator, allowing flexibility to remember doses and align doxyPEP with other daily medications. High levels of personal organisation, including carrying pills during daily activities and planning ahead around sexual encounters, further supported consistent use. Some participants experienced confusion regarding dosing indications, particularly around whether doxyPEP was needed following oral sex, reflecting gaps in understanding of risk and provider communication. Overall, adherence was strongly supported by routine-based medication habits and dosing flexibility, while challenges related primarily to regimen clarity rather than pill burden or acceptability.
Kwach et al (2025)²⁷ <i>dPEP Kenya Study</i>	In-depth interviews (3 time points during dPEP study, months 1, 6 and 12) with cisgender women on HIV PrEP in the intervention arm of dPEP Kenya Study (n=44) and 4 focus groups (following dPEP study completion) (n=29)	<p>Four main themes emerged for both barriers and facilitators to doxyPEP adherence.</p> <p>Barriers to doxyPEP adherence:</p> <ol style="list-style-type: none"> Side effects and pill burden: Gastrointestinal side effects, including nausea, vomiting, fatigue, and gastric irritation, were the most frequently cited barrier and often led to missed doses or doubts about continuing doxyPEP, particularly when tablets were taken on an empty stomach. Managing doxyPEP alongside daily HIV PrEP and other medications further compounded pill burden and reduced adherence for some participants. Stigma and privacy concerns: Fears of being judged, labelled as promiscuous, or assumed to have an STI discouraged open use of doxyPEP and led many participants to hide their medication from partners, family members, or others in their households. Concerns about confidentiality and social perception directly interfered with consistent dosing. Forgetfulness and disruptions to routine: Missed doses commonly occurred during periods of travel, work commitments, or changes in daily schedules, when established medication routines were interrupted. Forgetfulness increased over time and was frequently linked to lack of structured habits around pill-taking.

		<p>4. Partner influence and negative reactions: Scepticism, opposition, and misconceptions from partners, such as fears about infertility, concerns about infidelity, or questioning the need for doxyPEP, undermined adherence. Partner disapproval often created pressure to skip doses or discontinue use altogether.</p> <p>Facilitators of doxyPEP adherence:</p> <ol style="list-style-type: none"> 1. Perceived effectiveness in preventing STIs: Strong belief in doxyPEP's ability to protect against sexually transmitted infections was a central motivator for consistent use. Participants who felt confident in its preventive benefits were more likely to persist with the regimen despite side effects or logistical challenges. 2. Use of discreet pill carriers: Disguised pill containers, such as lipstick-style holders, enabled participants to carry doxyPEP privately and avoid unwanted attention or stigma. These tools were widely valued for supporting confidentiality and making adherence easier in daily life. 3. Social support and encouragement: Encouragement from friends, family members, and partners fostered confidence and sustained motivation to remain adherent. Open discussions about doxyPEP and reassurance from trusted individuals helped normalize use and reduced concerns about stigma. 4. Integration into daily routines: Linking doxyPEP use with existing habit, such as mealtimes or daily PrEP dosing, helped participants remember doses consistently. Those with structured routines reported fewer missed doses and greater ease maintaining adherence over time.
<p>Ehsan et al (2024)²⁸ <i>Together 5000 study (T5K)</i></p>	<p>In-depth interviews with MSM in the US recruited from a national internet-based cohort (n=24, of which n=1 had used doxyPEP)</p>	<p>This study explored participants' familiarity with doxyPEP, interest in its use, perceived benefits, and concerns. Only a minority of participants had prior awareness of doxyPEP (7 of 24), and just one participant had previously been prescribed it.</p> <p>Across four emergent themes ('Knowledge of DoxyPEP', 'Motivating Factors', 'Major Concerns', and 'Information Needs and Sources'), two subthemes were relevant to perceived barriers and facilitators to adherence:</p> <p>Motivating factors – Benefits of Doxy-PEP at the personal and community level Participants highlighted the ease of use of doxyPEP as a key motivator for potential use and adherence. The single-dose, post-exposure regimen and the flexible timeframe for administration were viewed as substantially more manageable than daily pill-taking or more complex HIV PrEP dosing strategies (such as 2-1-1).</p> <p>Major concerns – Adherence to Doxy-PEP regimen Some participants also shared concerns about the possibility of misusing Doxy-PEP via improper adherence. These concerns were raised as questions they desired answers for regarding Doxy-PEP's recommended regimen and dosing schedule; though these concerns were not always viewed as barriers to taking up Doxy-PEP. Participants were concerned about taking the wrong dosage, and not taking Doxy-PEP within the recommended timeframe. Participants who were familiar with Doxy-PEP expressed concern that there were variations in how and when individuals were taking Doxy-PEP.</p>

Table 4. Clinical adverse events associated with doxycycline prophylaxis and long-term doxycycline use

Study	Population and setting	Intervention	Design	Relevant findings
DoxyPEP / doxyPrEP studies (directly relevant to STI prophylaxis)				
Luetkemeyer et al (2023)³ <i>DoxyPEP Study</i>	MSM & transgender women, USA (N=501; HIV PrEP n=327, PLWH n=174)	DoxyPEP: 200 mg doxycycline ≤72 h after sex	Open-label RCT; median follow-up ~9 months	No serious AEs attributed to doxycycline. One grade 2 lab abnormality (transaminitis) and five grade 3 events possibly/probably related (3 diarrhoea; 2 headache/migraine). 2% discontinued due to unacceptable AEs or preference.
Luetkemeyer et al (2025)⁹ <i>DoxyPEP Study OLE</i>	MSM & transgender women, USA (N=592 in RCT, doxy-PEP group n=411, plus N=282 in OLE, doxy-PEP group n=207)	DoxyPEP: 200 mg ≤72 h after sex	RCT + open-label extension; quarterly follow-up up to 12 months	Across doxyPEP quarters: one grade 2 lab abnormality and five grade 3 AEs possibly/probably related; no serious AEs attributed. 12 permanently discontinued doxyPEP (6 due to AEs; 6 preference). No discontinuations occurred during the OLE period.
Molina et al (2018)⁸ <i>IPERGAY Study</i>	MSM using HIV PrEP, France (n=232)	DoxyPEP: 200 mg taken as soon as possible after sex (target ≤24 h; max 72 h)	Open-label RCT (1:1); median follow-up 8.7 months	Serious and grade 3-4 adverse events did not differ between groups, and no deaths occurred. Gastrointestinal adverse events were more frequent among doxyPEP users (25% vs 14%; p=0.03). Eight participants (7%) discontinued doxyPEP due to drug-related side effects, most commonly abdominal pain, nausea, diarrhoea, bloating, gastric reflux, fatigue, and dizziness.
Molina et al (2024)⁴ <i>DOXYVAC Study</i>	MSM on HIV PrEP, France (N=1,101)	DoxyPEP: 200 mg ≤72 h (preferably ≤24 h) after condomless sex, no more than three doses of 200mg per week	Multicentre open-label 2×2 factorial RCT; up to 12 months	One drug-related serious AE (fixed drug eruption). Drug-related AEs: 7% in doxyPEP group; most common nausea/vomiting (3%), abdominal pain (2%), diarrhoea (1%). Discontinuation due to AEs was 2% (GI).
Stewart et al (2023)¹⁰ <i>dPEP Kenya Study</i>	Cisgender women on HIV PrEP, Kenya (N=449, n=224 to doxyPEP arm)	DoxyPEP: 200 mg ≤72 h after sex	Open-label RCT; 12 months	No serious AEs related to doxycycline (per investigators). Nausea was most frequent doxy-related AE (7.2% of visits in doxyPEP vs 4.6% standard care), generally mild.
Grennan et al (2025)¹¹ <i>DuDHS Study</i>	MSM & transgender women, Canada (N=52)	DoxyPrEP: 100 mg daily	Pilot RCT (immediate vs delayed start); 48 weeks	No doxyPrEP-related serious AEs. AEs generally mild and GI-predominant; two participants had nausea graded moderate/severe.

Chen et al (2025)²⁹	MSM using doxyPEP, multicentre real-world cohort (N=671)	DoxyPEP (routine care)	Multicentre retrospective cohort	Skin reactions in 1.3% (mostly fixed drug eruption, plus one photosensitivity). Reactions typically within 24 h of exposure; all affected individuals discontinued doxyPEP; symptoms resolved within 1-3 weeks.
Palacios et al (2025)¹⁸ <i>PRIDOX study</i>	MSM & transgender women on PrEP, Málaga Spain (n=876 on PrEP; n=197 initiated doxyPEP)	DoxyPEP (200 mg ≤72 h, preferably ≤24 h)	Prospective pre/post; Cox models; mean post-doxyPEP follow-up 14 months	No serious adverse events were reported. DoxyPEP discontinuation occurred in 4.5% of participants (9/197), primarily due to mild gastrointestinal side effects; additional discontinuations were related to reduced STI risk behaviours, patient preference, medical indication, and loss to follow-up.
Bolan et al (2015)⁶	MSM with HIV and ≥2 prior syphilis infections, Los Angeles, USA (n=30)	DoxyPrEP: 100 mg daily for 36 weeks	Open-label pilot RCT (1:1); comparator: contingency management; total follow-up 48 weeks (36 on drug + 12 post)	One participant discontinued doxyPrEP due to a drug-related adverse event (gastroesophageal reflux), which resolved following cessation of doxycycline.
Abe et al (2025)¹³	Cisgender female sex workers, Tokyo, Japan (N=40, follow-up clinical evaluations n=22)	DoxyPrEP: 100 mg daily	Retrospective cohort	Nausea/vomiting reported by ~21%; nearly all continued with post-prandial dosing; one discontinuation due to nausea. No serious AEs or allergic reactions reported. There was no change in the prevalence of bacterial vaginosis or vulvovaginal candidiasis, potentially suggesting little impact of doxyPEP on vaginal flora.
Long-term doxycycline exposure studies (included to inform adverse outcomes in >8 week use, post-January 2023)				
Atefi et al (2025)³⁰	Adults with moderate acne, Iran (N=80)	100 mg daily doxycycline for 3 months for acne treatment	Randomised controlled trial; 100 mg daily doxycycline (control) vs 100 mg daily doxycycline plus one probiotic capsule daily (intervention)	At 3 months, in doxycycline-only group, adverse events included dyspepsia (22.5%), diarrhoea (10%), headache (5%). Co-administration of probiotics was associated with lower dyspepsia (7.5%) and similar rates of headache (7.5%), suggesting reduced gastrointestinal intolerance with probiotic supplementation.
Bhatia et al (2025)³¹	Adults with papulopustular rosacea, US and Germany (N=230 across trials)	Doxycycline 40 mg daily for 16 weeks for treatment of papulopustular rosacea	Two phase 3 double-blind RCTs (3:2:2): 40 mg daily minocycline; 40 mg daily doxycycline; and daily placebo	Treatment-emergent adverse events (TEAEs) were common but occurred less frequently in the doxycycline group (22% and 33% across phases) compared to the placebo group (36% and 37%) with no clinically meaningful safety differences. Most common AEs in the doxycycline arm were nasopharyngitis (1.7% and 8.3% across phases) and headache (1.7% and 5.0%).

				<p>Discontinuation due to TEAEs was low with doxycycline (1.7% in phase 1; 0% in phase 2) and similar to other arms. No serious adverse events were attributed to doxycycline.</p> <p>Laboratory parameters and vital signs did not differ between groups, indicating good overall tolerability over 16 weeks.</p>
Cho et al (2025)³²	Patients with EGFR-mutated advanced NSCLC receiving amivantamab-lazertinib in a global randomized clinical trial (N=199)	Tetracycline antibiotics (doxycycline or minocycline) 100 mg twice daily for 12 weeks as part of prophylactic dermatologic management	Phase 2 open-label multicentre randomized controlled trial comparing enhanced dermatologic management (including prophylactic tetracyclines during weeks 1-12) versus standard-of-care dermatologic management without routine antibiotic prophylaxis	<p>Treatment-emergent adverse events were common but similar across groups.</p> <p>Discontinuation due to tetracycline-related adverse events occurred in 1 participant. Dose reductions were required in 3 participants and temporary interruptions in 7 participants.</p> <p>Serious adverse events were rare and unrelated to tetracycline use.</p> <p>No differences in infection rates or liver toxicity were observed between intervention and standard care arms, indicating good short-term safety of prophylactic tetracycline exposure.</p>
Eljaaly et al (2023)³³	Adults receiving doxycycline for >1 month for varied clinical indications, Saudi Arabia (N=189)	Doxycycline 100–200 mg daily; median duration 44 days (IQR 30-60); 51% used 100 mg/day and 49% used 200 mg/day	Retrospective observational cohort with prolonged exposure (at least 25% ≥8 weeks)	<p>Gastrointestinal adverse events were reported in 12 patients (6.3%), including esophagitis in 3 patients (1.6%). Doxycycline discontinuation due to GI adverse effects occurred in 5 patients (2.6%).</p> <p>GI adverse events were significantly more common among participants aged ≥50 years compared with those <50 years (8/50 vs 4/139; p=0.003), and occurred exclusively in those receiving 200 mg/day versus 100 mg/day (12/93 vs 0/96; p<0.001).</p> <p>Esophagitis cases resolved following doxycycline cessation and supportive treatment.</p> <p>Overall, higher dose and older age were associated with increased risk of GI toxicity during prolonged doxycycline use.</p>
Ingram et al (2024)³⁴	People with hidradenitis suppurativa (chronic disease affecting flexures and other skin regions), UK (N=80; of which 23 received doxycycline)	Oral doxycycline 200 mg daily for up to 12 months	Nonrandomised 12-month prospective cohort study offering 5 interventions (based on participant preference and shared decision making): oral doxycycline 200 mg daily; oral clindamycin and rifampicin both 300 mg twice daily for 10 weeks, extended for longer in some cases; laser treatment targeting hair follicles; deroofing; and conventional surgery.	<p>No serious adverse events were reported. In the doxycycline arm, nine gastrointestinal adverse events and one episode of fever occurred over follow-up, and treatment discontinuation due to adverse effects occurred in eight participants (35%).</p> <p>Adherence declined substantially over time: among the 23 participants who initiated doxycycline, treatment receipt was 52% at 3 months (n=12), 57% at 6 months (n=13), 26% at 9 months (n=6), and 17% at 12 months (n=4).</p>

Santos-Lobato et al (2023) ³⁵	People with Parkinson's disease (study on dyskinesia) (N=8)	Doxycycline 200 mg daily for 12 weeks	Single-arm, open-label, phase 2 study	No serious AEs reported. Dyspepsia most common and mostly mild; no discontinuations attributed to dyspepsia. One participant had moderate abdominal pain persisting several months.
Wu et al (2025) ³⁶	Patients with moderate-to-severe rosacea, Shanghai, China (n=38 in doxycycline arm)	Doxycycline 100 mg daily for 8 weeks for rosacea treatment	Prospective, randomised, evaluator-blind controlled study comparing photodynamic therapy versus doxycycline; follow-up to 24 weeks	Treatment-emergent adverse events occurred in 39.5% of participants receiving doxycycline (15/38). The most common were gastrointestinal discomfort (23.7%; 9/38), infection (7.9%; 3/38), dizziness/headache (5.3%; 2/38), and menstrual delay (2.6%; 1/38). One participant discontinued due to severe abdominal pain, which resolved after stopping doxycycline. No serious adverse events were reported.

Footnotes:

^a Studies published prior to 2023 that were captured through the effectiveness and adherence search were also assessed and included for adverse event outcomes where eligible.

Table 5. Microbiome outcomes related to doxycycline prophylaxis and long-term doxycycline use

Study	Population and setting	Intervention/exposure	Design (AMR-relevant analysis)	Main findings
Langelier et al (2024) ³⁷ <i>DoxyPEP Study</i>	MSM and TGW participating in the DoxyPEP RCT; substudy of n=100 doxyPEP arm and N=50 SOC arm	DoxyPEP	Trial-linked microbiome substudy with longitudinal metagenomic sequencing and resistome profiling over 6 months	Overall microbial diversity and taxonomic composition remained stable over 6 months.
Manoharan-Basil et al (2026) ³⁸ <i>DoxyPEP Study</i>	MSM and TGW participating in the DoxyPEP RCT; N=150 selected based on sample availability for metagenomic analysis	DoxyPEP (dose-dependent exposure) categorized as 0 doses, > 0-20 doses, and > 20 doses per 6 months.	Trial-linked microbiome substudy with longitudinal change-point analysis of resistome and microbiome	Only limited, taxon-specific changes in microbiome composition detected.
Chu et al (2025) ³⁹ <i>DoxyPEP Study</i>	MSM and TGW participating in the DoxyPEP RCT; substudy of n=100 doxyPEP arm and N=50 SOC arm	DoxyPEP use (median number of doxyPEP doses taken since baseline)	Trial-linked microbiome substudy with longitudinal metagenomic analysis DNA-seq data were analysable from 127 samples derived from 89 participants, and RNA-seq data were analysable from 86 samples derived from 70 participants	No significant changes in alpha diversity, beta diversity, total bacterial mass, or taxonomic composition despite resistome enrichment.
Knodel et al (2025) ⁴⁰ <i>DuDHS Study</i>	MSM on HIV PrEP participating in the DuDHS doxyPrEP RCT (subset with longitudinal samples n=41)	DoxyPrEP: 100 mg daily for 12 months	Longitudinal 16S rRNA sequencing at baseline, week 24, week 48 with resistome assessment	Minimal changes in overall microbiome composition. No significant changes in taxa or genus-level alpha/beta diversity; small (<10%) decrease in phylum-level alpha diversity in immediate arm only.

Table 6. Antimicrobial resistance associated with doxycycline prophylaxis and long-term doxycycline use

Study	Population and setting	Intervention/exposure	Design (AMR-relevant analysis)	Pathogen	Main findings
Studies assessing AMR in STI pathogens and commensal bacteria among doxyPEP/PrEP cohorts					
Luetkemeyer et al (2023)³ <i>DoxyPEP Study</i>	MSM and transgender women, USA (N=501)	DoxyPEP: 200 mg ≤72 h after condomless sex	Nested culture-based resistance surveillance within randomized trial	<i>N. gonorrhoeae</i> <i>S. Aureus</i>	Tetracycline-resistant <i>N. gonorrhoeae</i> detected in 38% of post-enrolment isolates in doxyPEP vs 12% in standard care (limited cultures). Doxycycline-resistant <i>S. aureus</i> detected in 16% vs 8% respectively; overall prevalence low. No cephalosporin resistance observed.
Luetkemeyer et al (2025)⁹ <i>DoxyPEP Study OLE</i>	MSM & transgender women, USA (n=637; 411 initially randomised to doxyPEP)	DoxyPEP: 200 mg ≤72 h after condomless sex	Longitudinal resistance surveillance across randomized and open-label phases	<i>N. gonorrhoeae</i> <i>C. trachomatis</i> <i>S. Aureus</i> MSRA	Tetracycline resistance in <i>N. gonorrhoeae</i> in 27% of isolates during doxyPEP vs 24% during standard care; high-level resistance in 10% during doxyPEP. Doxycycline-resistant <i>S. aureus</i> increased significantly with doxyPEP use (HR 3.89). No increase in MRSA or cephalosporin resistance. All cultured <i>C. trachomatis</i> isolates remained tetracycline-susceptible.
Bercot et al (2021)¹² <i>IPERGAY Study</i>	MSM on HIV PrEP, France. Subset of IPERGAY participants tested for MG at baseline and 6 months (n=210)	DoxyPEP: 200 mg ≤72 h post-sex (preferably ≤24 h)	Nested molecular resistance analysis within randomized trial	<i>M. genitalium</i>	The all-site prevalence of MG at baseline was 10.5% (6.3% in urine samples, 4.3% in anal swabs, 0.5% in throat swabs) and remained unchanged at 6 months whether or not PEP was used: 9.9% overall, 10.2% with PEP, 9.6% without. The overall rate of MG resistance (prevalent and incident cases) to azithromycin and <i>fluoroquinolones</i> was 67.6% and 9.1%, respectively, with no difference between arms. An in vivo mutation of the MG 16S rRNA, which could be associated with tetracycline resistance, was observed in 12.5% of specimens tested.
Bercot et al (2025)⁴¹ <i>DOXYVAC Study</i>	MSM on PrEP, France (N=1,101)	DoxyPEP: 200 mg ≤72 h post-sex; factorial with 4CMenB vaccine	Multicentre culture-based resistance surveillance within RCT	<i>N. gonorrhoeae</i> <i>C. trachomatis</i> MSRA ESBL- <i>E. coli</i>	All <i>N. gonorrhoeae</i> isolates tetracycline-resistant; high-level resistance significantly higher in doxyPEP arm (36% vs 13%). No tetracycline resistance detected in <i>C. trachomatis</i> . No significant change in MRSA or ESBL-producing <i>E. coli</i> between arms.

Stewart et al (2023) ¹⁰ <i>dPEP Kenya Study</i>	Cisgender women on PrEP, Kenya (N=449, n=224 to doxyPEP arm)	DoxyPEP: 200 mg ≤72 h post-sex (max 200 mg/day)	Nested molecular resistance substudy within randomized trial	<i>N. gonorrhoeae</i> <i>C. trachomatis</i>	tet(M) gene conferring high-level tetracycline resistance in <i>N. gonorrhoeae</i> was present in 100% of samples at baseline and follow-up in both arms. No tetracycline resistance detected in <i>C. trachomatis</i> . Effectiveness limited by low adherence.
Grennan et al (2025) ¹¹ <i>DuDHS Study</i>	MSM & transgender women, Canada (N=52)	DoxyPrEP: 100 mg daily (with daily TDF/FTC for HIV PrEP)	Longitudinal colonization and resistance surveillance within doxyPrEP trial	<i>S. Aureus</i>	Emergent doxycycline-resistant <i>S. aureus</i> observed in several participants, particularly in immediate doxyPrEP arm. Persistent carriage noted in some individuals. STI pathogen resistance not the primary outcome.
Palacios et al (2025) ¹⁸ <i>PRIDOX study</i>	MSM & transgender women on PrEP, Málaga Spain (n=197 initiated doxyPEP)	DoxyPEP in routine care	Prospective culture-based resistance surveillance cohort	<i>N. gonorrhoeae</i> MSRA ESBL- <i>E. coli</i>	No significant difference in tetracycline resistance in <i>N. gonorrhoeae</i> between doxyPEP users and non-users (~43% vs 46%). MRSA and ESBL-producing <i>E. coli</i> prevalence remained low and unchanged.
Soge et al (2025) ⁴²	DoxyPEP users vs non-users, USA	DoxyPEP exposure	Cross-sectional colonization surveillance with resistance phenotyping	<i>S. Aureus</i> Group A <i>Streptococcus</i>	Higher prevalence of tetracycline-resistant <i>S. aureus</i> and GAS among doxyPEP users, particularly among those using >3 doses/month. Any doxyPEP use was not associated with resistance, suggesting dose effect.
Studies assessing changes in gut resistome					
Langelier et al (2024) ³⁷ <i>DoxyPEP Study</i>	MSM and TGW participating in the DoxyPEP RCT; substudy of n=100 doxyPEP arm and N=50 SOC arm	DoxyPEP	Trial-linked microbiome substudy with longitudinal metagenomic sequencing and resistome profiling over 6 months	Gut antimicrobial resistance genes (ARGs)	DoxyPEP use was associated with a significant increase in tetracycline resistance genes in the gut resistome over 6 months. No significant increases were observed in non-tetracycline ARG classes.
Manoharan-Basil et al (2026) ³⁸ <i>DoxyPEP Study</i>	MSM and TGW participating in the DoxyPEP RCT; N=150 selected based on sample availability for metagenomic analysis	DoxyPEP (dose-dependent exposure) categorized as 0 doses, > 0-20 doses, and > 20 doses per 6 months.	Trial-linked microbiome substudy with longitudinal change-point analysis of resistome and microbiome	Gut resistome enrichment	A clear dose-dependent increase in tetracycline resistance genes was observed, with a threshold at approximately 65 doxycycline doses over 6 months above which significant ARG enrichment occurred.
Chu et al (2025) ³⁹ <i>DoxyPEP Study</i>	MSM and TGW participating in the DoxyPEP RCT; substudy of n=100	DoxyPEP use (median number of doxyPEP doses taken since baseline)	Trial-linked microbiome substudy with longitudinal metagenomic analysis DNA-seq data were	Gut resistome (metagenomic + metatranscriptomic ARGs)	DoxyPEP use over 6 months was associated with a significant increase in the proportional abundance and expression of tetracycline resistance genes in the gut resistome (metagenome: 46% to 51%; metatranscriptome: 4% to 15%), with evidence of a dose-response relationship.

	doxyPEP arm and N=50 SOC arm		analysable from 127 samples derived from 89 participants, and RNA-seq data were analysable from 86 samples derived from 70 participants		No significant increases were observed in other resistance gene classes.
Knodel et al (2025) ⁴⁰ <i>DuDHS Study</i>	MSM on HIV PrEP participating in the DuDHS doxyPrEP RCT (subset with longitudinal samples n=41)	DoxyPrEP: 100 mg daily for 12 months	Longitudinal 16S rRNA sequencing at baseline, week 24, week 48 with resistome assessment	ARG abundance	Modest increases in tetracycline resistance genes were observed, but without major community-level disruption.

References

1. King J, Kwon J, Gray R, McManus H, McGregor S. HIV, viral hepatitis and sexually transmissible infections in Australia: Annual surveillance report 2025, The Kirby Institute, UNSW Sydney, Sydney, Australia.
2. Kenyon C, Herrmann B, Hughes G, de Vries HJC. Management of asymptomatic sexually transmitted infections in Europe: towards a differentiated, evidence-based approach. *Lancet Reg Health Eur*. Nov 2023;34:100743. doi:10.1016/j.lanepe.2023.100743
3. Luetkemeyer AF, Donnell D, Dombrowski JC, et al. Postexposure Doxycycline to Prevent Bacterial Sexually Transmitted Infections. *N Engl J Med*. Apr 6 2023;388(14):1296-1306. doi:10.1056/NEJMoa2211934
4. 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 x 2 factorial design. *Lancet Infect Dis*. Oct 2024;24(10):1093-1104. doi:10.1016/S1473-3099(24)00236-6
5. Traeger MW, Leyden WA, Volk JE, et al. Doxycycline Postexposure Prophylaxis and Bacterial Sexually Transmitted Infections Among Individuals Using HIV Preexposure Prophylaxis. *JAMA Intern Med*. Mar 1 2025;185(3):273-281. doi:10.1001/jamainternmed.2024.7186
6. Bolan RK, Beymer MR, Weiss RE, Flynn RP, Leibowitz AA, Klausner JD. 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. *Sexually transmitted diseases*. Feb 2015;42(2):98-103. doi:10.1097/OLQ.0000000000000216
7. Chan PA, Le Brazidec DL, Becasen JS, et al. Safety of Longer-Term Doxycycline Use: A Systematic Review and Meta-Analysis With Implications for Bacterial Sexually Transmitted Infection Chemoprophylaxis. *Sexually transmitted diseases*. Nov 1 2023;50(11):701-712. doi:10.1097/OLQ.0000000000001865
8. 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*. Mar 2018;18(3):308-317. doi:10.1016/S1473-3099(17)30725-9
9. Luetkemeyer AF, Donnell D, Cohen SE, et al. Doxycycline to prevent bacterial sexually transmitted infections in the USA: final results from the DoxyPEP multicentre, open-label, randomised controlled trial and open-label extension. *Lancet Infect Dis*. Aug 2025;25(8):873-883. doi:10.1016/S1473-3099(25)00085-4
10. Stewart J, Oware K, Donnell D, et al. Doxycycline Prophylaxis to Prevent Sexually Transmitted Infections in Women. *N Engl J Med*. Dec 21 2023;389(25):2331-2340. doi:10.1056/NEJMoa2304007
11. Grennan T, Mohammed S, Edward J, et al. A pilot, randomized controlled trial of Dual Daily HIV and sexually transmitted infection pre-exposure prophylaxis using tenofovir disoproxil fumarate/emtricitabine and doxycycline in gay, bisexual and other men who have sex with men and transgender women: The DuDHS Study. *Clin Infect Dis*. Jan 30 2025;doi:10.1093/cid/ciaf043

12. Bercot B, Charreau I, Rousseau C, et al. High Prevalence and High Rate of Antibiotic Resistance of *Mycoplasma genitalium* Infections in Men Who Have Sex With Men: A Substudy of the ANRS IPERGAY Pre-exposure Prophylaxis Trial. *Clin Infect Dis*. Oct 5 2021;73(7):e2127-e2133. doi:10.1093/cid/ciaa1832
13. Abe S, Mizushima D, Ando N, et al. Doxycycline pre-exposure prophylaxis prevents sexually transmitted infections without affecting vaginal bacterial flora in female sex workers. *JAC Antimicrob Resist*. Apr 2025;7(2):dlaf054. doi:10.1093/jacamr/dlaf054
14. Lewis FMT, Cope AB, Clark K, et al. Doxycycline Postexposure Prophylaxis Is Effective and Highly Acceptable in an Urban Public Sexually Transmitted Disease Clinic: Philadelphia, 2019–2023. *Sexually transmitted diseases*. Dec 1 2025;52(12):734–738. doi:10.1097/OLQ.0000000000002224
15. Osmundson J, Holloway IW, Macias Gil R, Jann JT, Hong C, Bolan RK. Doxycycline Postexposure Prophylaxis for Bacterial STIs: Prescribing Patterns, Use, Short-term Outcomes Among 2083 Patients in a Los Angeles Federally Qualified Health Care Program, and Implications for Widespread Use. *Open Forum Infect Dis*. Mar 2025;12(3):ofaf089. doi:10.1093/ofid/ofaf089
16. Spinelli MA, Heise MJ, Roman J, et al. Sustained Effectiveness of Doxycycline Post-Exposure-Prophylaxis in a Large Sexual Health Clinic over 96 Weeks: An Interrupted Time Series Analysis. *Clin Infect Dis*. May 6 2025;doi:10.1093/cid/ciaf234
17. Huang S, Carnevale C, Neu N, et al. Implementation of Doxy-PEP in a Diverse Sexual Health Program in Northern Manhattan: The Doxy-Care Study. *Am J Public Health*. Oct 2025;115(10):1584–1588. doi:10.2105/AJPH.2025.308209
18. Palacios R, Gomez-Ayerbe C, Martin-Cortes S, et al. Post-exposure prophylaxis with doxycycline (DoxyPEP) to prevent STIs in a real-world setting: the PRIDOX study. *J Antimicrob Chemother*. Dec 2 2025;80(12):3306–3310. doi:10.1093/jac/dkaf366
19. Sankaran M, Glidden DV, Kohn RP, et al. Doxycycline Postexposure Prophylaxis and Sexually Transmitted Infection Trends. *JAMA Intern Med*. Mar 1 2025;185(3):266–272. doi:10.1001/jamainternmed.2024.7178
20. Liu A, Hao J, Pickering TA, Klausner JD. Trends in Sexually Transmitted Infections Associated With the Doxycycline Postexposure Prophylaxis Guidelines in San Francisco. *Sexually transmitted diseases*. Nov 1 2024;51(11):e46–e48. doi:10.1097/OLQ.0000000000001996
21. Jarolimova J, Bassett IV, Platt L, Germain C, Parker RA, Ard KL. Changes in Clinic-Level STI Burden After Doxycycline Post-Exposure Prophylaxis Implementation in an Urban Sexual Health Clinic. *Sexually transmitted diseases*. Jan 1 2026;53(1):e5–e8. doi:10.1097/OLQ.0000000000002206
22. Rossotti R, Caruso E, Calzavara D, et al. Knowledge, Use, and Misuse of Self-Prescribed Doxycycline Postexposure Prophylaxis in a Community-Based Preexposure Prophylaxis Service. *Sexually transmitted diseases*. Jun 1 2025;52(6):e18–e22. doi:10.1097/OLQ.0000000000002115
23. Teker B, Hoornenborg E, Schim van der Loeff MF, et al. Emergent informal use of doxycycline post- and pre-exposure prophylaxis among men who have sex with men

- and transgender and gender diverse people, the Netherlands, 2024. *Euro Surveill.* Jul 2025;30(26):doi:10.2807/1560-7917.ES.2025.30.26.2400707
24. Vanbaelen T, Rotsaert A, De Baetselier I, et al. Doxycycline post-exposure prophylaxis among men who have sex with men and transgender women in Belgium: awareness, use and antimicrobial resistance concerns in a cross-sectional online survey. *Sex Transm Infect.* Jan 29 2025;101(1):34-40. doi:10.1136/sextrans-2024-056261
 25. Traeger MW, Krakower DS, Mayer KH, Jenness SM, Marcus JL. Use of Doxycycline and Other Antibiotics as Bacterial Sexually Transmitted Infection Prophylaxis in a US Sample of Primarily Gay and Bisexual Men. *Sexually transmitted diseases.* Dec 1 2024;51(12):763-771. doi:10.1097/OLQ.0000000000002061
 26. 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.* Apr 2024;38(4):155-167. doi:10.1089/apc.2023.0289
 27. Kwach B, Kwenza Z, Violette LR, et al. Understanding barriers and facilitators to doxycycline post-exposure prophylaxis adherence among young women in western kenya: a qualitative study. *BMC Infect Dis.* Jul 1 2025;25(1):855. doi:10.1186/s12879-025-11209-6
 28. Ehsan R, D'Angelo AB, Westmoreland DA, Grov C. Perceptions about doxycycline post-exposure prophylaxis (Doxy-PEP) as an STI-prevention strategy among gay and bisexual men (GBM) in the United States: Results from a qualitative study. *Preventive medicine.* Jun 2024;183(107977):107977. doi:10.1016/j.ypmed.2024.107977
 29. Chen LY, Lin WT, Chen YT, et al. Dermatological adverse effects of doxycycline as post-exposure prophylaxis for sexually transmitted infections among men who have sex with men: real-world findings from a multicentre study. *J Antimicrob Chemother.* Nov 4 2025;80(11):3118-3122. doi:10.1093/jac/dkaf351
 30. Atefi N, Mohammadi M, Bodaghabadi M, et al. Evaluating the Effectiveness of Probiotic Supplementation in Combination With Doxycycline for the Treatment of Moderate Acne: A Randomized Double-Blind Controlled Clinical Trial. *J Cosmet Dermatol.* Jan 2025;24(1):e16614. doi:10.1111/jocd.16614
 31. Bhatia N, Del Rosso J, Stein Gold L, et al. Efficacy, Safety, and Tolerability of Oral DFD-29, a Low-Dose Formulation of Minocycline, in Rosacea: Two Phase 3 Randomized Clinical Trials. *JAMA Dermatol.* May 1 2025;161(5):499-507. doi:10.1001/jamadermatol.2024.6542
 32. Cho BC, Li W, Spira AI, et al. Enhanced Versus Standard Dermatologic Management With Amivantamab-Lazertinib in EGFR-Mutated Advanced NSCLC: The COCOON Global Randomized Controlled Trial. *J Thorac Oncol.* Oct 2025;20(10):1517-1530. doi:10.1016/j.jtho.2025.07.117
 33. Eljaaly K, Alghamdi H, Almehmadi H, Aljawi F, Hassan A, Thabit AK. Long-term gastrointestinal adverse effects of doxycycline. *J Infect Dev Ctries.* Feb 28 2023;17(2):281-285. doi:10.3855/jidc.16677

34. Ingram JR, Bates J, Cannings-John R, et al. Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS): a prospective cohort study. *Br J Dermatol*. Feb 16 2024;190(3):382-391. doi:10.1093/bjd/ljad388
35. Santos-Lobato BL, Brito M, Pimentel AV, Cavalcanti RTO, Del-Bel E, Tumas V. Doxycycline to treat levodopa-induced dyskinesias in Parkinson's disease: a preliminary study. *Arq Neuropsiquiatr*. May 2023;81(5):460-468. Doxyciclina no tratamento das discinesias induzidas pela doença de Parkinson: um estudo preliminar. doi:10.1055/s-0043-1768668
36. Wu Y, Fan Q, Liu X, et al. A Chlorin e6 derivative-mediated photodynamic therapy versus doxycycline for moderate-to-severe rosacea: A prospective, randomized, controlled study. *Photodiagnosis Photodyn Ther*. Feb 2025;51(104474):104474. doi:10.1016/j.pdpdt.2025.104474
37. Langelier C, Chu V, Glascock A, et al. Doxycycline post-exposure prophylaxis for sexually transmitted infections impacts the gut antimicrobial resistome. *Res Sq*. Apr 17 2024;doi:10.21203/rs.3.rs-4243341/v1
38. Manoharan-Basil SS, Vanbaelen T, Kenyon C. Threshold effects of doxycycline postexposure prophylaxis (PEP) on the gut resistome and microbiome: Evidence from change-point analyses. *Int J Infect Dis*. Feb 2026;163(108322):108322. doi:10.1016/j.ijid.2025.108322
39. Chu VT, Glascock A, Donnell D, et al. Impact of doxycycline post-exposure prophylaxis for sexually transmitted infections on the gut microbiome and antimicrobial resistome. *Nat Med*. Jan 2025;31(1):207-217. doi:10.1038/s41591-024-03274-2
40. Knodel S, Main L, DeLeon M, et al. Impact of doxycycline pre-exposure prophylaxis (doxyPrEP) for sexually transmitted infections on the microbiome of men who have sex with men on HIV PrEP. *Nat Commun*. Jul 3 2025;16(1):6143. doi:10.1038/s41467-025-61426-5
41. Bercot B, Assoumou L, Camelena F, et al. Antimicrobial drug-resistant *Neisseria gonorrhoeae* (GC) infections in men using doxycycline postexposure prophylaxis. A substudy of the ANRS 174 DOXYVAC trial. *Clin Infect Dis*. Nov 10 2025;(ciaf591)doi:10.1093/cid/ciaf591
42. Soge OO, Thibault CS, Cannon CA, et al. Potential Impact of Doxycycline Post-Exposure Prophylaxis on Tetracycline Resistance in *Neisseria gonorrhoeae* and Colonization With Tetracycline-Resistant *Staphylococcus aureus* and Group A *Streptococcus*. *Clin Infect Dis*. Jul 18 2025;80(6):1188-1196. doi:10.1093/cid/ciaf089

Appendix 1. Search syntax

<p>Search 1: Effectiveness and adherence</p> <p>Doxycycline AND prophylaxis terms</p> <p>AND</p> <p>STI terms</p>	<p>((("doxycycline" OR "doxycyclin*") AND ("pre exposure prophylaxis" OR "post exposure prophylaxis" OR "pre exposure prophylaxis" OR "post exposure prophylaxis" OR "preexposure prophylaxis" OR "postexposure prophylaxis")) OR ("doxyPEP" OR "doxy pep" OR "doxyPrEP" OR "doxy prep" OR "doxy pep" OR "doxy prep"))</p> <p>AND</p> <p>("sexually transmitted diseases" OR "sexually transmitted disease*" OR "sexually transmitted infection*" OR "sti" OR "std" OR "syphilis" OR "syphilis" OR "chlamydia" OR "chlamydia" OR "gonorrhea" OR "gonorrh*ea" OR "treponema pallidum" OR "Neisseria gonorrhoeae" OR "Mycoplasma genitalium" OR "Mycoplasma genitalium")</p>
<p>Search 2: Adverse events</p> <p>Doxycycline terms</p> <p>AND</p> <p>Adverse reaction terms</p> <p>Limit 2023-2025</p>	<p>"doxycycline"</p> <p>AND</p> <p>("adverse reaction" OR "adverse event" OR "side effect")</p>
<p>Search 3: AMR</p> <p>Anti-microbial resistance</p> <p>AND</p> <p>Other terms</p> <p>AND</p> <p>Doxy</p> <p>AND</p> <p>Doxy Prophylaxis Terms</p> <p>Limit 2023-2025</p>	<p>("drug resistance, microbial"[MeSH Terms] OR "anti-microbial stewardship"[All Fields] OR "Antimicrobial resistance"[All Fields] OR "AMR"[All Fields]) OR ("staphylococcus aureus"[All Fields] OR "streptococcus pneumoniae"[All Fields] OR "enteric pathogens"[All Fields] OR "shigella"[All Fields] OR "salmonella"[All Fields] OR "Mycoplasma genitalium"[All Fields] OR "malaria prophylaxis"[All Fields] OR "gonorrhoeae"[All Fields] OR "chlamydia"[All Fields] OR "treponema pallidum"[All Fields] OR "syphilis"[All Fields])) AND ("doxycycline"[MeSH Terms] OR "doxycyclin*"[All Fields] OR ("Vibramycin"[All Fields] OR "Periostat"[All Fields]) OR (((("pre exposure prophylaxis"[MeSH Terms] OR "post exposure prophylaxis"[MeSH Terms] OR "pre exposure prophylaxis"[All Fields] OR "post exposure prophylaxis"[All Fields] OR "preexposure prophylaxis"[All Fields] OR "postexposure prophylaxis"[All Fields] OR ("doxyPEP"[All Fields] OR "doxy pep"[All Fields] OR "doxyPrEP"[All Fields] OR "doxy prep"[All Fields] OR "doxy pep"[All Fields] OR "doxy prep"[All Fields])) AND ("doxycycline"[MeSH Terms] OR "doxycyclin*"[All Fields])) OR ("doxyPEP"[All Fields] OR "doxy pep"[All Fields] OR "doxyPrEP"[All Fields] OR "doxy prep"[All Fields] OR "doxy pep"[All Fields] OR "doxy prep"[All Fields])) AND "long-term"[All Fields]</p>

Appendix 2. Inclusion criteria

Effectiveness

ASHM Proposed Question: Among adults (16 years and older) at risk of bacterial STIs, what is the effectiveness of **doxycycline PrEP or PEP** in preventing **laboratory-confirmed STIs**?

Population	Adults 16 years or older
Intervention	Doxycycline-PrEP or Doxycycline-PEP for prevention of STIs
Comparator	“No treatment”, placebo, or standard of care without doxy-PrEP/PEP
Outcome	Incidence of bacterial sexually transmitted infections, namely: <ul style="list-style-type: none"> • Neisseria gonorrhoeae • Treponema pallidum • Chlamydia trachomatis infection • Mycoplasma genitalium.
Studies	Randomised controlled trials, non-randomised controlled including quasi-experimental, including observational analytical cohort, case-control, and cross-sectional studies
Excludes	Case reports, case series, conference abstracts, narrative, expert opinion, policy, reviews (systematic, scoping or literature)
Type of Review	Effectiveness (Primary question)

Adherence

ASHM proposed question: What is the reported adherence to doxycycline PrEP or PEP regimens for the prevention of STIs in adults, and what factors influence adherence?

Population	Adults 16 years or older
Intervention	Doxycycline-PrEP or Doxycycline-PEP for prevention of STIs
Comparator	
Outcome	Adherence rates (self-reported, doxy levels in plasma) Barriers and facilitators to adherence
Studies	Randomised controlled trials, non-randomised controlled including quasi-experimental, observational analytical cohort, case-control, and cross-sectional studies
Excludes	Case reports, case series, conference abstracts, narrative, expert opinion, policy, reviews (systematic, scoping or literature)
Approach:	Secondary question to question 1: From the studies identified what are the reported adherence rates and factors that influence adherence.

Adverse Events

ASHM Proposed question: What are the reported adverse events or harms associated with long-term doxycycline use for treatment or prevention?

Population	Adults 16+ years
Intervention	Long-term use of doxycycline for any medical indication including Doxy-PrEP AND Doxy-PEP Long term = 8 > weeks duration
Comparator	NA
Outcome	Adverse / events/harms Gut microbiome
Studies	Randomised controlled trials, non-randomised controlled including quasi-experimental, observational analytical cohort, case-control, and cross-sectional studies
Excludes	Case reports, case series, conference abstracts, narrative, expert opinion, policy, reviews (systematic, scoping or literature)

AMR

ASHM Proposed Question: Does long-term use of doxycycline impact antimicrobial resistance in STI (*Neisseria gonorrhoeae*, *Treponema pallidum*, *Chlamydia trachomatis* infection, *Mycoplasma genitalium*) or other bacteria?

Population	Adults 16+ years receiving long-term exposure to doxycycline for prevention (e.g. PrEP, PEP, malaria prophylaxis, acne, rosacea) or treatment (of any indication)
Intervention	Long-term (8 weeks or greater) doxycycline use
Comparator	No doxycycline exposure, less than 8 weeks doxycycline exposure, or intermittent exposure (less than 8 weeks) or alternative management
Outcome	Incidence of antimicrobial resistance e.g. i) STI pathogens (e.g. <i>Neisseria gonorrhoeae</i> , <i>Treponema pallidum</i> , <i>Chlamydia trachomatis</i> infection, <i>Mycoplasma genitalium</i>) ii) Opportunistic bacteria (e.g. <i>Staphylococcus aureus</i> ,
Studies	Experimental studies, quasi-experimental studies, observational analytical cohort, case-control, cross-sectional studies
Excludes	Case reports, case series, conference abstracts, narrative, expert opinion, policy, reviews (systematic, scoping or literature)

Appendix 3. Risk of bias assessment

Table S1. RoB 2 summary for randomised studies and trial-linked substudies

Study	Outcome domain(s)	Design	Tool	Overall judgement	Brief rationale
Bolan et al. 2015	Effectiveness; adherence; adverse events	Open-label pilot RCT	RoB 2	Some concerns	Open-label design and very small sample; objective adherence measure reduces outcome-measurement bias; randomisation likely adequate but limited reporting and imprecision.
Molina et al. 2018 (IPERGAY)	Effectiveness; adherence; adverse events	Open-label RCT	RoB 2	Low	Large randomised trial with objective STI outcomes and robust follow-up; open-label nature introduces limited concern for behavioural change, but overall bias likely low.
Bercot et al. 2021 (IPERGAY substudy)	Effectiveness (M. genitalium); AMR	Nested substudy within open-label RCT	RoB 2	Some concerns	Randomised parent trial strengthens internal validity, but small substudy sample selection and limited outcome events create some concern.
Stewart et al. 2023 (dPEP Kenya)	Effectiveness; adherence; adverse events; AMR	Open-label RCT	RoB 2	Some concerns	Objective outcomes and comparator arm are strengths; open-label design and substantial non-adherence raise concern for deviations from intended intervention and missing biologic adherence data in subsets.
Luetkemeyer et al. 2023 (DoxyPEP Study)	Effectiveness; adherence; adverse events; AMR	Open-label multicentre RCT	RoB 2	Low	Large randomised trial with objective STI outcomes and robust follow-up; open-label nature introduces limited concern for behavioural change, but overall bias likely low.
Molina et al. 2024 (DOXYVAC)	Effectiveness; adherence; adverse events	Open-label factorial RCT	RoB 2	Low	Large randomised trial with objective STI outcomes and robust follow-up; open-label nature introduces limited concern for behavioural change, but overall bias likely low.
Luetkemeyer et al. 2025 (DoxyPEP OLE/final RCT report)	Effectiveness; adherence; adverse events; AMR	RCT plus open-label extension	RoB 2	Some concerns	Randomised phase remains robust, but pooled analyses including open-label extension introduce potential post-randomisation behavioural change and selection bias.
Grennan et al. 2025 (DuDHS)	Effectiveness; adherence; adverse events; AMR	Open-label immediate-versus-delayed randomised trial	RoB 2	Some concerns	Randomised comparison and objective measures are strengths; however small sample and limited event counts reduce certainty.
Langelier et al. 2024	Microbiome	Nested microbiome substudy within RCT	RoB 2	Some concerns	Linked to a randomised trial with objective laboratory outcomes; however, inclusion was restricted to a subset of participants with available samples, introducing potential selection bias.
Chu et al. 2025	Gut resistome	Nested metagenomic/metatranscriptomic substudy within RCT	RoB 2	Some concerns	Linked to a randomised trial with objective molecular outcomes and longitudinal sampling; however, analyses were restricted to a subset of participants with available samples, introducing potential selection bias.
Manoharan-Basil et al. 2026	Gut resistome	Nested dose-response substudy within RCT	RoB 2	Some concerns	Linked to a randomised trial with objective sequencing outcomes; however, exposure was defined post-randomisation based on cumulative dose, introducing potential bias due to deviations from intended intervention and selection into dose categories.
Knodel et al. 2025	Microbiome / ARGs	Nested substudy within randomised doxyPrEP trial	RoB 2	Some concerns	Linked to a randomised trial with objective laboratory outcomes; however, analyses were restricted to a subset of participants with available samples and small sample sizes, introducing potential selection bias and imprecision.
Atefi et al. 2025	Adverse events (indirect safety evidence)	Double-blind RCT	RoB 2	Low	Randomised, double-blind trial with systematic adverse event ascertainment and appropriate comparative design; no major sources of internal bias identified. Indirectness to the doxyPEP population is considered a certainty issue rather than a risk of bias concern.
Bhatia et al. 2025	Adverse events (indirect safety evidence)	Phase 3 double-blind RCTs	RoB 2	Low	Randomised, double-blind trial with systematic adverse event ascertainment and appropriate comparative design; no major sources of internal bias identified. Indirectness to the doxyPEP population is considered a certainty issue rather than a risk of bias concern.
Cho et al. 2025	Adverse events (indirect safety evidence)	Open-label randomised trial	RoB 2	Some concerns	Randomised trial with systematic adverse event ascertainment and appropriate comparative design; however, the open-label design introduces potential bias in co-intervention delivery and adverse event attribution due to lack of blinding.

Table S2. ROBINS-I summary for non-randomised comparative studies

Study	Outcome domain(s)	Design	Tool	Overall judgement	Brief rationale
Traeger et al. 2025	Effectiveness	Retrospective EHR cohort with within-person pre/post and non-user comparison	ROBINS-I	Moderate	Observational cohort with within-person and comparator analyses; however, residual confounding by indication (history of STIs) and time-varying confounding remain possible, although the analytic design partially mitigates bias.
Lewis et al. 2025	Effectiveness	Observational cohort comparison plus within-user pre/post	ROBINS-I	Moderate	Observational cohort with within-person and comparator analyses; however, selection into doxyPEP and differential testing behaviour introduce potential bias, and confounding is only partially addressed.
Osmundson et al. 2025	Effectiveness	Retrospective EHR pre/post study	ROBINS-I	Moderate	Observational pre-post study without a strong concurrent control; susceptible to secular trends, changes in testing behaviour.
Spinelli et al. 2025	Effectiveness	Controlled interrupted time-series with contemporaneous non-user control	ROBINS-I	Moderate	Controlled interrupted time-series with a contemporaneous comparator; however, residual time-varying confounding and co-interventions during implementation remain possible.
Huang et al. 2025	Effectiveness	Prospective cohort with within-person pre/post and matched comparison	ROBINS-I	Moderate	Observational cohort with within-person and matched comparator analyses; propensity matching improves comparability, but early-adopter selection and residual confounding likely remain.
Palacios et al. 2025	Effectiveness; adherence; adverse events; AMR	Prospective pre/post cohort	ROBINS-I	Moderate	Prospective follow-up is a strength, but no true non-doxypEP comparator for main analyses and potential selection/testing differences remain.
Abe et al. 2025	Effectiveness; adherence; adverse events	Retrospective within-person cohort	ROBINS-I	Serious	Very small uncontrolled pre/post cohort with potential confounding, selection bias, and unstable effect estimates.
Rossotti et al. 2025	Adherence	Cross-sectional survey	ROBINS-I	Serious	Cross-sectional survey with self-selected participants and self-reported adherence measures; highly susceptible to selection bias and measurement bias.
Teker et al. 2025	Adherence	Cross-sectional survey	ROBINS-I	Serious	Cross-sectional survey with volunteer sampling and self-reported adherence measures; highly susceptible to selection bias and exposure misclassification.
Van Baelen et al. 2025	Adherence	Cross-sectional survey	ROBINS-I	Serious	Cross-sectional survey with self-selected participants and self-reported regimen classification; highly susceptible to selection bias and measurement bias.
Traeger et al. 2024	Adherence	Cross-sectional survey	ROBINS-I	Serious	Cross-sectional survey with convenience sampling and self-reported adherence measures; highly susceptible to selection bias and recall bias.
Chen et al. 2025	Adverse events	Multicentre retrospective cohort	ROBINS-I	Moderate	Retrospective ascertainment may miss milder events, but outcome definition was clinically clear and temporally linked to exposure.
Eljaaly et al. 2023	Adverse events (indirect safety evidence)	Retrospective observational cohort	ROBINS-I	Moderate	Dose and age comparisons are informative, but retrospective design and incomplete confounder control remain limitations.
Ingram et al. 2024	Adverse events (indirect safety evidence)	Non-randomised prospective preference-based cohort	ROBINS-I	Serious	Treatment selection by preference/shared decision-making introduces serious confounding and differential discontinuation risk.
Wu et al. 2025	Adverse events (indirect safety evidence)	Prospective evaluator-blind controlled study	ROBINS-I	Moderate	Non-randomised comparative allocation leaves moderate confounding risk despite prospective follow-up.
Luetkemeyer et al. 2025 (AMR OLE analyses)	AMR	Longitudinal resistance surveillance across randomised and open-label phases	ROBINS-I	Moderate	AMR analyses during open-label periods are susceptible to post-randomisation selection and differential exposure accumulation.
Bercot et al. 2025	AMR	Culture-based surveillance nested in RCT	ROBINS-I	Moderate	Comparative sampling is useful, but cultured-isolate availability is selective and outcome numbers are limited.
Soge et al. 2025	AMR	Cross-sectional colonisation surveillance	ROBINS-I	Serious	Cross-sectional exposure classification and selection of sampled individuals limit causal interpretation; dose-response signal is hypothesis-generating.

Table S3. EPOC summary for interrupted time-series and ecological studies

Study	Outcome domain(s)	Design	Tool	Overall judgement	Brief rationale
Spinelli et al. 2025	Effectiveness	Controlled interrupted time-series with contemporaneous non-user comparator	EPOC	Moderate	Controlled interrupted time-series with a contemporaneous comparator and extended follow-up; however, findings remain susceptible to co-interventions, changes in testing practices, and residual differences between users and non-users.
Sankaran et al. 2025	Effectiveness	Jurisdiction-level ecological interrupted time-series	EPOC	High	Ecological interrupted time-series supporting a temporal association; however, the ecological design, concurrent policy and behavioural changes, and absence of individual-level exposure data limit causal attribution.
Liu et al. 2024	Effectiveness	Citywide ecological interrupted time-series	EPOC	High	Ecological interrupted time-series providing an early signal of post-guideline change; however, short follow-up and reliance on ecological outcome data increase susceptibility to secular trends and concurrent changes.
Jarolimova et al. 2025	Effectiveness	Clinic-level before-after ecological implementation analysis with seasonal adjustment	EPOC	High	Before-after ecological implementation analysis with seasonal adjustment; however, the absence of a concurrent control series and potential changes in clinic population, testing intensity, and prescribing limit causal inference.

Table S4. CASP summary for qualitative studies

Study	Outcome domain(s)	Design	Tool	Overall judgement	Brief rationale
Fredericksen et al. 2024	Adherence	In-depth qualitative interviews nested within DoxyPEP trial	CASP	Good quality	Clear qualitative aims, appropriate interview design, and coherent analytical approach; findings are well-supported by the data. Limitations relate to transferability beyond trial participants and limited reporting of researcher reflexivity.
Kwach et al. 2025	Adherence	Longitudinal in-depth interviews plus focus groups within dPEP Kenya Study	CASP	Good quality	Clear qualitative aims, appropriate longitudinal interview and focus group design, and coherent analytical approach; findings are well-supported by rich contextual data. Limitations relate to potential social desirability bias and limited reporting of researcher reflexivity.
Ehsan et al. 2024	Adherence	In-depth qualitative interviews from a national internet-recruited cohort	CASP	Moderate quality	Appropriate exploratory design and useful insights into perceived adherence challenges, but only one participant had prior doxyPEP use, so findings are more informative about anticipated rather than experienced adherence.

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