


SYSTEMATIC REVIEW

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Efficacy of Doxycycline Prophylaxis for Prevention of Bacterial Sexually Transmitted Infections Among People with or Without HIV: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Introduction: Bacterial sexually transmitted infections (STIs) remain a significant burden among populations at high risk, including people living with HIV (PLWH) and HIV-negative individuals receiving HIV pre-exposure prophylaxis (PrEP). This study evaluated the efficacy and safety of doxycycline pre- and post-exposure prophylaxis for preventing bacterial STIs among people with or without HIV. **Methods:** This systematic review followed PRISMA 2020 guidelines and was prospectively registered in PROSPERO (CRD420251171815). We conducted comprehensive searches in PubMed, Embase, and Cochrane CENTRAL through October 2025. We included randomized controlled trials evaluating doxycycline prophylaxis versus standard care. Meta-analysis was performed using random-effects models in RevMan 5.4. **Results:** Seven randomized controlled trials (2,091 participants) were included. Doxycycline prophylaxis significantly reduced bacterial STI incidence by 57% (pooled RR 0.43, 95% CI 0.35–0.53; $p < 0.00001$; $I^2 = 42\%$). In the subgroup analysis of HIV-positive participants, doxycycline achieved a 62% reduction (RR 0.38; 95% CI 0.28–0.52). Pathogen-specific analysis showed a 72% reduction for chlamydia (RR 0.28), a 72% reduction for syphilis (RR 0.28), and a 44% reduction for gonorrhea (RR 0.56). Safety outcomes were summarized descriptively, with gastrointestinal symptoms most frequently reported; no pooled adverse-event or discontinuation estimate was calculated. The number needed to treat calculated from pooled event counts was approximately 4. **Conclusion:** Doxycycline prophylaxis reduced bacterial STI incidence in high-risk populations with and without HIV. These findings support considering doxycycline prophylaxis as a prevention strategy, while emphasizing limitations in regimen-specific evidence and the need for ongoing safety and antimicrobial-resistance monitoring.

Keywords: Doxycycline, HIV, meta-analysis, post-exposure prophylaxis, pre-exposure prophylaxis, sexually transmitted infections.

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INTRODUCTION

Bacterial sexually transmitted infections (STIs) remain a persistent global public health concern, with particularly disproportionate impacts among people living with HIV (PLWH).[1] Despite significant advances in HIV treatment, bacterial STI rates continue to rise globally, creating complex syndemic interactions that undermine HIV prevention efforts.[1] Untreated bacterial STIs can increase HIV viral shedding and transmission risk, while recurrent episodes are common among PLWH, suggesting traditional approaches may be insufficient.[2]

Current prevention strategies primarily rely on behavioral interventions, barrier methods, and intensified screening with prompt treatment.[3] However, real-world effectiveness has proven to be limited, as evidenced by persistently high STI incidence rates.[4] This limitation has prompted increased interest in biomedical prevention strategies that could complement existing approaches.[5]

Doxycycline, a broad-spectrum tetracycline antibiotic with activity against *Chlamydia trachomatis*, *Treponema pallidum*, and many strains of *Neisseria gonorrhoeae*, has emerged as a promising candidate for STI chemoprophylaxis.[6] Two primary dosing approaches have been investigated: post-exposure prophylaxis (doxy-PEP), taken within 24–72 hours after condomless sexual exposure, and pre-exposure prophylaxis (doxy-PrEP), taken daily.[7]

Recent years have witnessed completion of several large-scale randomized controlled trials evaluating doxycycline prophylaxis across diverse populations and geographic settings.[8] However, findings have varied across populations, HIV status, and dosing strategies. A comprehensive synthesis across people with and without HIV is therefore needed to inform clinical guidelines and public health policy. This systematic review aims to synthesize randomized controlled trial

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data on doxycycline prophylaxis for bacterial STI prevention and to examine efficacy by HIV status when sufficient data are available.

METHODS

Protocol Registration and Search Strategy

This systematic review followed PRISMA 2020 guidelines and was prospectively registered in PROSPERO (CRD420251171815). We conducted comprehensive searches of PubMed/MEDLINE, Embase, and Cochrane CENTRAL databases through October 1, 2025. We searched clinical trial registries (ClinicalTrials.gov, WHO ICTRP) for ongoing studies. The search strategy combined four key concepts: (1) intervention terms (doxycycline, post-exposure prophylaxis, pre-exposure prophylaxis), (2) condition terms (sexually transmitted infections, chlamydia, gonorrhea, syphilis), (3) population terms (HIV, men who have sex with men, transgender women, cisgender women), and (4) study design terms (randomized controlled trial). We used both MeSH terms and text words. No language restrictions were applied.

Eligibility Criteria

- **Population:** Adults (≥ 18 years) at risk for bacterial STIs, including PLWH, HIV-negative individuals receiving HIV pre-exposure prophylaxis, men who have sex with men, transgender women, and cisgender women.
- **Intervention:** Doxycycline prophylaxis as post-exposure (typically 200 mg within 24–72 hours) or pre-exposure prophylaxis (typically 100 mg daily).
- **Comparator:** Standard care (no prophylaxis) or placebo.
- **Outcomes:** Primary outcome was incidence of any bacterial STI (laboratory-confirmed chlamydia, gonorrhea, syphilis). Secondary outcomes included pathogen-specific incidence, adverse events, adherence, antimicrobial resistance, and HIV-related outcomes.
- **Study design:** Randomized controlled trials including individual and cluster-randomized designs.

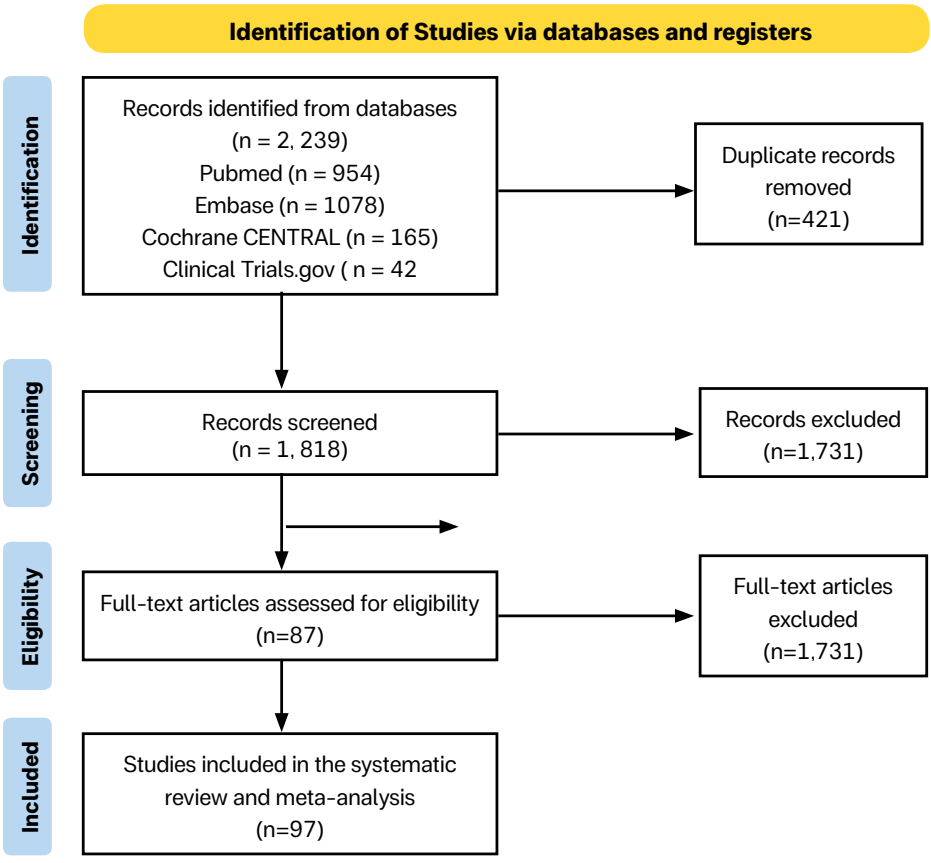

Figure 1. PRISMA flow diagram of the study-selection process.

Study Selection and Data Extraction

Two reviewers independently screened titles, abstracts, and full texts using Covidence software. Data extraction was performed independently using standardized forms. Disagreements were resolved through discussion.

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Risk of Bias 2.0 tool.[9] This tool evaluates five domains: randomization process, deviations from interventions, missing data, outcome measurement, and selective reporting.

Statistical Analysis

Meta-analysis was performed using Review Manager (RevMan) 5.4.[10] Pooled risk ratios with 95% confidence intervals were calculated using Mantel-Haenszel random-effects models. Statistical heterogeneity was assessed using the I^2 statistic. Subgroup analyses were planned for HIV status, dosing strategy, and geographic region when at least two sufficiently comparable studies were available within each subgroup. Evidence certainty was evaluated using the GRADE approach.

RESULTS

Study Selection and Characteristics

The systematic search identified 2,239 records. After removing 421 duplicates, 1,818 records were screened, and 87 full-text articles were assessed for eligibility. The final analysis included seven randomized controlled trials involving 2,091 participants **(Figure 1** and **Table 1)**.

The studies were conducted between 2015 and 2025 across the USA (n = 3), France (n = 2), Canada (n = 1), and Kenya (n = 1). The cumulative sample size across the seven trials was 2,091, with individual study sizes ranging from 30 to 502 participants. The follow-up duration ranged from 9 to 48 months (median 12 months).[11–17]

The study population was predominantly male (85.7%) with a median age of 33 years. Men who have sex with men (MSM) comprised the majority (95.8%), while transgender women accounted for 4.2%. Regarding HIV status, 347 participants (16.6%) were people living with HIV (PLWH), while the remaining 1,744

Table 1. Study characteristics.

Study ID	Year	Trial Registration	Study Design	Setting	Study Period	Sample Size (Total)	HIV+ (n)	HIV+ (%)	HIV- on PrEP (n)	Median Age (years)	Male (%)	Transgender Women (%)	MSM (%)	Baseline STI Prevalence (%)	Follow-up Duration (months)	Lost to Follow-up (%)
Luetkemeyer (DoxyPEP)[11]	2023	NCT03980223	Open-label RCT	USA (San Francisco, Seattle)	2020–2022	501	174	34.7	327	33	100	7.2	92.8	23.8	12	4.2
Molina (IPERGAY)[12]	2018	NCT01473472	2 × 2 factorial RCT substudy	France (Paris)	2012–2014	232	30	12.9	202	35	100	0.0	100.0	31.5	9	8.6
Molina (DOXYVAC)[13]	2024	NCT04050371	Open-label RCT	France (multiple sites)	2021–2023	502	0	0.0	502	34	100	5.8	94.2	28.4	12	6.4
Stewart (dPEP Kenya)[14]	2023	NCT04050800	Open-label RCT	Kenya (Kisumu)	2020–2022	449	0	0.0	449	24	0	0.0	0.0	15.2	12	23.2
Grennan (DuDHS)[15]	2025	NCT03798381	Open-label RCT	Canada (Toronto, Vancouver)	2019–2023	82	52	63.4	30	32	100	0.0	100.0	41.5	12	12.2
Bolan (Pilot)[16]	2015	NCT01903161	Open-label pilot RCT	USA (San Francisco)	2012–2014	30	30	100.0	0	37	100	0.0	100.0	46.7	48	6.7
DoxyPEP Open-Label Extension[17]	2024	NCT03980223	Open-label RCT	USA (San Francisco)	2022–2023	295	61	20.7	234	33	100	6.4	93.6	25.3	12	3.1

participants (83.4%) were HIV-negative individuals receiving HIV pre-exposure prophylaxis (PrEP). Baseline bacterial STI prevalence was high across studies, ranging from 15.2% to 46.7% (median 28.9%).[11–17]

Intervention Characteristics

Four studies (57%) evaluated post-exposure prophylaxis using 200 mg doxycycline within 24–72 hours after sex. Three studies (43%) evaluated pre-exposure prophylaxis using 100 mg doxycycline daily. All studies provided comprehensive co-interventions including quarterly STI screening, HIV testing, risk reduction counseling, and condom provision. Self-reported adherence ranged from 29.2% to 88.1% (median 74.3%) **(Table 2).**

Risk of Bias Assessment

Overall risk of bias was "some concerns" for all studies, primarily due to open-label design. All studies showed low risk of bias for randomization processes, outcome measurement, and selective reporting.

Table 2. Intervention protocols.

Study	Year	Intervention Type	Dose	Frequency	Maximum Frequency	Formulation	STI Screening Frequency	HIV Testing Frequency (HIV-)	Condom Provision	Counseling Provided	Adherence Support	Self-Reported Adherence (%)
Luetkemeyer[11]	2023	Doxy-PEP	200 mg	Within 24–72h post-sex	Once per 24h	Doxycycline hyclate	Quarterly	Quarterly	Yes	Risk reduction	SMS reminders, app	86.3
Molina[12]	2018	Doxy-PrEP	100 mg	Daily	Once daily	Doxycycline monohydrate	Quarterly	Quarterly	Yes	Risk reduction	Pill diary	72.1
Molina[13]	2024	Doxy-PEP	200 mg	Within 24–72h post-sex	Once per 24h	Doxycycline hyclate	Quarterly	Quarterly	Yes	Risk reduction + vaccination	SMS reminders	83.7
Stewart[14]	2023	Doxy-PEP	200 mg	Within 24–72h post-sex	Once per 24h	Doxycycline hyclate	Quarterly	Quarterly	Yes	Risk reduction	SMS reminders	29.2
Grennan[15]	2025	Doxy-PrEP	100 mg	Daily	Once daily	Doxycycline monohydrate	Quarterly	Quarterly	Yes	Risk reduction	Pill diary	68.5
Bolan[16]	2015	Doxy-PrEP	100 mg	Daily	Once daily	Doxycycline hyclate	Monthly	N/A	Yes	Risk reduction	Pill counts	74.3
DoxyPEP OLE[17]	2024	Doxy-PEP	200 mg	Within 24–72h post-sex	Once per 24h	Doxycycline hyclate	Quarterly	Quarterly	Yes	Risk reduction	SMS reminders, app	88.1

Primary Outcome: Overall STI Efficacy

Seven RCTs contributed data for bacterial STI incidence. Meta-analysis demonstrated that doxycycline prophylaxis significantly reduced overall bacterial STI incidence by 57% compared with standard care (pooled RR 0.43, 95% CI 0.35–0.53; $p < 0.00001$; $I^2 = 42\%$; **Figure 2**). Statistical heterogeneity was moderate ($Chi^2 = 10.31$, $p = 0.11$), suggesting reasonable consistency across studies.

In the subgroup analysis of HIV-positive participants (n = 347), doxycycline achieved a 62% reduction in STI incidence (RR 0.38; 95% CI 0.28–0.52; $p < 0.001$; $I^2 = 24\%$). This effect size was comparable to that observed in HIV-negative individuals on PrEP, with no statistically significant difference between the two subgroups ($p = 0.32$). Planned subgroup analyses by dosing strategy and geographic region were not performed because the number of studies within each stratum was small and the study populations, regimens, and settings were insufficiently comparable for reliable pooled estimates.

Pathogen-Specific Efficacy

- **Chlamydia:** Five studies (1,916 participants) showed a 72% reduction (RR 0.28; 95% CI 0.18–0.44; $p < 0.00001$; $I^2 = 37\%$; **Figure 3**).
- **Gonorrhea:** Five studies (1,916 participants) showed a 44% reduction (RR 0.56; 95% CI 0.45–0.69; $p < 0.00001$; $I^2 = 0\%$; **Figure 5**).
- **Syphilis:** Four studies (1,834 participants) showed a 72% reduction (RR 0.28; 95% CI 0.19–0.43; $p < 0.00001$; $I^2 = 0\%$; **Figure 4**).

Study or Subgroup	Doxycycline Events	Doxycycline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Bolan[16]	3	15	9	15	3.0%	0.33 [0.11, 0.99]	2015
Molina[12]	12	116	38	116	8.5%	0.32 [0.17, 0.57]	2018
Stewart[14]	56	224	89	225	21.4%	0.63 [0.48, 0.83]	2023
Luetkemeyer[11]	58	327	127	324	22.0%	0.45 [0.35, 0.59]	2023
Molina[13]	45	251	112	251	20.1%	0.40 [0.30, 0.54]	2024
DoxyPEP OLE[17]	32	147	81	148	17.7%	0.40 [0.28, 0.56]	2024
Grennan[15]	8	41	28	41	7.3%	0.29 [0.15, 0.55]	2025
Total (95% CI)		**1121**		**1120**	**100.0%**	**0.43 [0.35, 0.53]**	
Total events	214		484				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 10.31$, df = 6 ($p = 0.11$); $I^2 = 42\%$
Test for overall effect: Z = 8.37 ($p < 0.00001$)

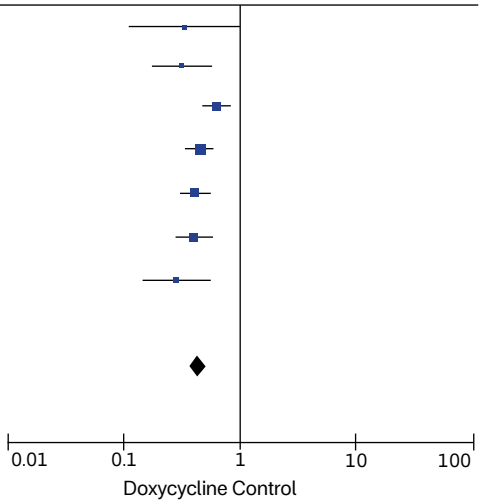

Figure 2. Forest plot of the primary outcome showing the pooled risk ratio for any bacterial STI (chlamydia, gonorrhea, or syphilis) comparing doxycycline prophylaxis with standard care. Seven RCTs, 2,091 participants. Random-effects model: RR 0.43 (95% CI 0.35–0.53), $p < 0.00001$, $I^2 = 42\%$.

Study or Subgroup	Doxycycline Events	Doxycycline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Molina[12]	3	116	15	116	11.4%	0.20 [0.06, 0.67]	2018
Luetkemeyer[11]	12	327	46	324	28.0%	0.26 [0.14, 0.48]	2023
Stewart[14]	15	224	28	225	28.8%	0.54 [0.30, 0.98]	2023
Molina[13]	8	251	42	251	23.1%	0.19 [0.09, 0.40]	2024
Grennan[15]	2	41	11	41	8.6%	0.18 [0.04, 0.77]	2025
Total (95% CI)		**959**		**957**	**100.0%**	**0.28 [0.18, 0.44]**	
Total events	40		142				

Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 6.31$, df = 4 ($p = 0.18$); $I^2 = 37\%$
Test for overall effect: Z = 5.43 ($p < 0.00001$)

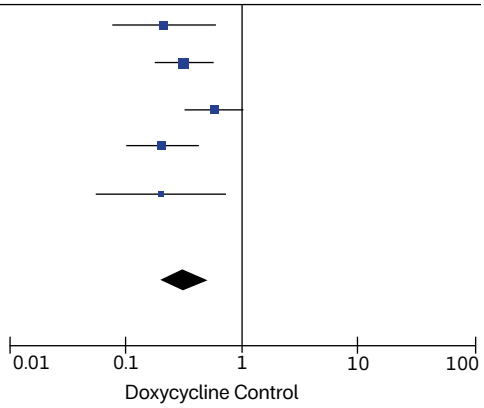

Figure 3. Forest plot of chlamydia-specific incidence. Five RCTs, 1,916 participants. Random-effects model: RR 0.28 (95% CI 0.18–0.44), $p < 0.00001$, $I^2 = 37\%$

Study or Subgroup	Doxycycline Events	Doxycycline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Molina[12]	2	116	8	116	7.2%	0.25 [0.05, 1.15]	2018
Luetkemeyer[11]	8	327	34	324	29.6%	0.23 [0.11, 0.50]	2023
Stewart[14]	9	224	21	225	29.3%	0.43 [0.20, 0.92]	2023
Molina[13]	9	251	38	251	33.9%	0.24 [0.12, 0.48]	2024
Total (95% CI)		**918**		**916**	**100.0%**	**0.28 [0.19, 0.43]**	
Total events	28		101				

Heterogeneity: Tau² = 0.00; Chi² = 1.71, df = 3 (p = 0.64); I² = 0%
Test for overall effect: Z = 6.04 (p < 0.00001)

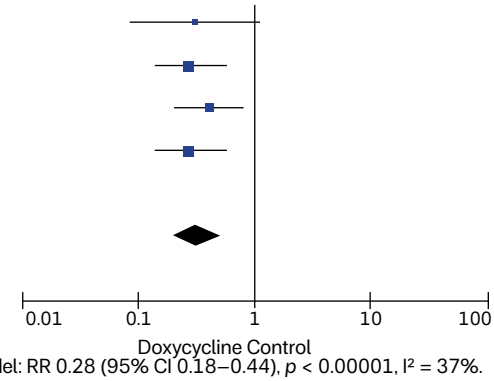

Figure 4. Forest plot of gonorrhea-specific incidence. Five RCTs, 1,916 partic ipants. Random-effects model: RR 0.28 (95% CI 0.18–0.44), p < 0.00001, I² = 37%.

Study or Subgroup	Doxycycline Events	Doxycycline Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI	Year
Molina[12]	7	116	18	116	6.6%	0.39 [0.17, 0.90]	2018
Stewart[14]	32	224	48	225	27.9%	0.67 [0.45, 1.01]	2023
Luetkemeyer[11]	38	327	67	324	34.3%	0.56 [0.39, 0.81]	2023
Molina[13]	28	251	53	251	25.8%	0.53 [0.35, 0.81]	2024
Grennan[15]	5	41	13	41	5.3%	0.38 [0.15, 0.98]	2025
Total (95% CI)		**959**		**957**	**100.0%**	**0.56 [0.45, 0.69]**	
Total events	110		199				

Heterogeneity: Tau² = 0.00; Chi² = 2.16, df = 4 (p = 0.7); I² = 0%
Test for overall effect: Z = 5.36 (p < 0.00001)

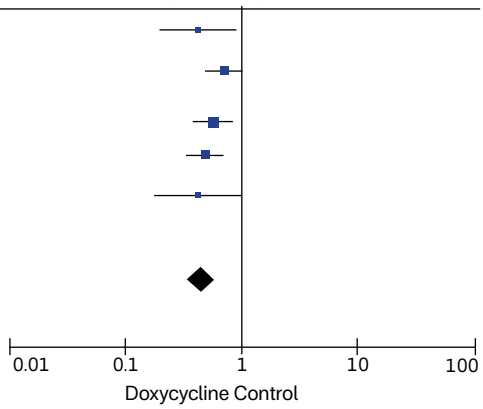

Figure 5. Forest plot of syphilis-specific incidence. Five RCTs, 1,916 participants. Random-effects model: RR 0.56 (95% CI 0.45–0.69), p < 0.00001, I² = 0%.

Number Needed to Treat

Using the pooled event counts shown in **Figure 2** (214/1,121 in the doxycycline groups and 484/1,120 in the control groups), the absolute risk reduction was 24.1%, corresponding to a NNT of 4.1 over the analyzed follow-up period. An HIV-specific NNT was not calculated because subgroup-specific absolute event counts were not reported.

Safety and Adverse Events

Safety outcomes were summarized descriptively because adverse-event definitions and reporting varied across trials. **Table 3** presents study-specific rates of selected adverse events, with gastrointestinal symptoms, particularly nausea and diarrhea, most frequently reported. The Grade 3+ event counts and discontinuation counts were not pooled and cannot be used to calculate a comparative discontinuation rate between study arms; therefore, no pooled discontinuation estimate is reported.[11–16]

Acceptability

Acceptability outcomes were not pooled because measurement instruments and denominators differed across trials. Study-specific findings are presented in **Table 4**. In Luetkemeyer, *et al*., 82% indicated willingness to continue and 91% rated the regimen as easy or very easy.[11] Molina, *et al*., reported that 68% experienced no or minimal impact on sexual spontaneity.[12] In the Kenyan trial, 38% indicated willingness to continue.[14] No direct comparison between event-driven and daily dosing was performed.

Antimicrobial Resistance

Four studies reported antimicrobial-resistance outcomes.[11,13–15] Because organisms, sampling methods, and resistance definitions differed, results were summarized descriptively rather than pooled. In Luetkemeyer, *et al*., among participants with evaluable gonococcal cultures, tetracycline resistance was 27% (8/29) in the doxy-PEP arm versus 24% (5/21) in the control arm (p = 0.95), and no ceftriaxone resistance was observed (0% in both arms).[11] The same study reported an 8-percentage-point increase in doxycycline-resistant *Staphylococcus aureus* in the doxy-PEP arm; this source-specific finding is presented in **Table 5**.[11]

DISCUSSION

This systematic review found that doxycycline prophylaxis reduced bacterial STI incidence in populations with and without HIV. The 57% overall reduction was clinically substantial, although the moderate heterogeneity (I^2 = 42%) indicates variability across populations and settings.[11,18]

Several key findings merit emphasis. First, the subgroup analysis suggested similar relative efficacy in HIV-positive participants and HIV-negative individuals receiving PrEP, with no statistically significant subgroup difference. Because only a minority of participants were HIV-positive and subgroup-specific absolute event data were unavailable, this finding should be interpreted cautiously.[11,15,18]

Second, pathogen-specific analyses showed larger reductions for chlamydia and syphilis (72% each) than for gonorrhea (44%). The more modest effect against gonorrhea reinforces the need to consider background tetracycline resistance; nevertheless, the pooled estimate remained statistically significant.[7,18]

Third, the review included both post-exposure prophylaxis (doxy-PEP) and pre-exposure prophylaxis (doxy-PrEP); however, it did not perform regimen-specific subgroup analyses. Consequently, the present meta-analysis cannot establish comparative efficacy or equivalence between post-exposure and pre-exposure dosing strategies.

Safety findings were summarized descriptively because reporting differed across trials. Gastrointestinal symptoms were most frequently reported, whereas Grade 3+ events and discontinuations were

Table 3. Study-specific adverse events; outcomes were summarized descriptively and were not pooled.

Study	Year	Adverse Event Type	Doxy Arm (%)	Control Arm (%)	Risk Difference (%)	*p*-value	Reported Grade 3+ Events (n)	Reported Discontinuations (n)
Luetkemeyer[11]	2023	Nausea	18.3	8.7	9.6	0.001	2	8
		Diarrhea	12.6	9.1	3.5	0.18	0	3
		Dyspepsia	9.4	5.2	4.2	0.04	0	1
		Photosensitivity	4.2	0.8	3.4	0.02	0	2
Molina[12]	2018	Nausea	15.7	7.2	8.5	0.01	1	3
		Diarrhea	10.3	8.1	2.2	0.32	0	1
Molina[13]	2024	Nausea	17.2	8.3	8.9	0.002	1	5
		Diarrhea	11.8	8.9	2.9	0.25	0	2
Stewart[14]	2023	Nausea	12.4	9.1	3.3	0.19	0	1
		Diarrhea	8.9	7.8	1.1	0.68	0	0
Grennan[15]	2025	Nausea	14.6	8.5	6.1	0.08	1	2
		Diarrhea	9.7	7.3	2.4	0.41	0	1
Bolan[16]	2015	Nausea	16.7	6.7	10.0	0.12	0	1
		Diarrhea	11.1	6.7	4.4	0.29	0	0

Table 4. Study-specific acceptability outcomes; measures were not pooled.

Study	Year	Would Recommend to Others (%)	Satisfaction			Would Continue if Available (%)	Ease of Use: Easy/ Very Easy (%)	Impact on Sexual Spontaneity: None/Minimal (%)	Concern About Resistance: Moderate/High (%)	Willingness to Pay Monthly (USD)
			Very Satisfied (%)	Somewhat Satisfied (%)	Dissatisfied (%)					
Luetkemeyer[11]	2023	87	68	24	8	82	91	73	42	25
Molina[12]	2018	82	61	28	11	76	85	68	38	20
Molina[13]	2024	86	67	25	8	81	89	71	45	22
Stewart[14]	2023	45	32	41	27	38	67	52	31	5
Grennan[15]	2025	79	58	31	11	73	83	66	41	18
Bolan[16]	2015	83	65	27	8	78	88	70	37	23
DoxyPEP OLE[17]	2024	89	71	22	7	85	93	76	39	28

Table 5. Study-specific antimicrobial-resistance outcomes; results were summarized descriptively and were not pooled.

Study	Year	Organism	Antibiotic	Baseline Resistance		End-of-Study Resistance		Absolute Change		*p*-value for Difference
				Doxy Arm (%)	Control Arm (%)	Doxy Arm (%)	Control Arm (%)	Doxy Arm (%)	Control Arm (%)	
Luetkemeyer[11]	2023	*N. gonorrhoeae*	Tetracycline	24	24	27	24	3	0	0.95
		N. gonorrhoeae	Ceftriaxone	0	0	0	0	0	0	1.0
		S. aureus	Doxycycline	5	5	13	5	8	0	0.01
		S. aureus	Methicillin	2	2	3	2	1	0	0.32
Molina[13]	2024	*N. gonorrhoeae*	Tetracycline	53	51	56	52	3	1	0.87
		S. aureus	Doxycycline	4	4	11	5	7	1	0.02
Stewart[14]	2023	*N. gonorrhoeae*	Tetracycline	18	19	21	20	3	1	0.71
		S. aureus	Doxycycline	3	3	8	4	5	1	0.09
Grennan[15]	2025	*N. gonorrhoeae*	Tetracycline	27	25	29	26	2	1	0.84
		S. aureus	Doxycycline	6	5	14	6	8	1	0.03

not pooled. The available data therefore support continued safety monitoring rather than a precise comparative estimate of discontinuations.[11–16,19]

From a public health perspective, doxycycline prophylaxis represents a promising addition to the STI prevention toolkit. Acceptability appeared favorable in several studies, but measures were not pooled and willingness to continue varied across populations. Appropriate patient selection remains crucial, with the intervention most suitable for individuals at high ongoing STI risk who can adhere to dosing requirements.[7,11,12,14,20]

Antimicrobial stewardship considerations are paramount. Four studies reported resistance outcomes, which were not pooled. The source-specific findings – no observed ceftriaxone resistance and an increase in doxycycline-resistant *S. aureus* in the DoxyPEP study – support robust resistance monitoring rather than broad conclusions across all trials.[11,13–15,20]

Several limitations warrant acknowledgment. Follow-up duration was relatively short (9–12 months), limiting conclusions about long-term efficacy and resistance development. Study populations were predominantly MSM from high-income countries, with limited representation of other populations. Adherence measurement relied primarily on self-report, which may overestimate true adherence. Planned subgroup analyses by dosing strategy and geographic region were not performed because too few sufficiently comparable studies were available, and safety, acceptability, and antimicrobial-resistance outcomes were too heterogeneous for pooling.[11,18]

Future research priorities include longer-term studies (≥ 2–3 years) to evaluate sustained efficacy and resistance patterns, implementation research to understand real-world effectiveness, and additional research in underrepresented populations, including cisgender women and low- and middle-income countries.

CONCLUSION

Doxycycline prophylaxis reduced bacterial STI incidence by more than 50% among high-risk populations with and without HIV, with larger relative reductions for chlamydia and syphilis than for gonorrhea. The findings support consideration of doxycycline prophylaxis as a biomedical prevention option for selected individuals at high ongoing STI risk. Comparative efficacy between doxy-PEP and doxy-PrEP remains uncertain, and continued monitoring of adverse events, adherence, and antimicrobial resistance is warranted.

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Conflict of Interest

The authors declare no competing interests.

Declaration on the Use of Artificial Intelligence (AI)

A generative artificial intelligence tool (ChatGPT, OpenAI) was used during revision solely to assist with language editing, consistency checking, and organization of responses to editorial comments. All AI-assisted changes were critically reviewed and verified by the authors, who retain full responsibility for the accuracy and integrity of the manuscript. The tool was not used to conduct the original study selection, data extraction, risk-of-bias assessment, or statistical analysis. The final manuscript was reviewed and approved by all authors, who take full responsibility for its content.

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