McMaster University | HEALTH FORUM

Living Evidence Synthesis

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

19 December 2023

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Appendix 1: Detailed search strategy

Databases searched:

- PubMed: https://pubmed.ncbi.nlm.nih.gov/
- Embase: https://www.embase.com
- EBM Reviews via OVID: https://www.wolterskluwer.com/en/solutions/ovid/evidencebased-medicine-reviews-ebmr-904 (EBM Reviews - ACP Journal Club <1991 to August 2023>, Cochrane Central Register of Controlled Trials <August 2023>, Cochrane Database of Systematic Reviews <2005 to September 6, 2023>, Cochrane Clinical Answers <August 2023>, Cochrane Methodology Register <3rd Quarter 2012>, Health Technology Assessment <4th Quarter 2016>, NHS Economic Evaluation Database <1st Quarter 2016>)
- MedRxiv: https://www.medrxiv.org/
- Clinical trials registry: https://clinicaltrials.gov/

Search limits: none

Database retrieval: Effectiveness

Databases	10/09/2023
PubMed	73
Embase	79
MedRxiv	17
EBM Reviews via OVID	30
Clinical trials	17
TOTAL	**216**

Database retrieval: Acceptability

Databases	15/09/2023
PubMed	85
Embase	17
MedRxiv	164
EBM Reviews via OVID	29
Clinical trials	17
TOTAL	**295**

PubMed search:

#1	"doxycycline"[MeSH Terms] OR "doxycycline"[Title/Abstract] OR "Adoxa"[Title/Abstract] OR "Doryx"[Title/Abstract] OR "Doxy"[Title/Abstract] OR "Monodox"[Title/Abstract] OR "Oracea"[Title/Abstract] OR "Periostat"[Title/Abstract] OR "Vibramycin"[Title/Abstract] OR "Vibra-Tabs"[Title/Abstract] OR "VibraTabs"[Title/Abstract]	**20,382**
#2	"Post-Exposure Prophylaxis"[MeSH Terms] OR "Post-Exposure Prophylaxis"[Title/Abstract] OR "DoxyPEP"[Title/Abstract] OR "Doxy-PEP"[Title/Abstract] OR "preexposure prophylaxis"[Title/Abstract] OR "pre-exposure prophylaxis"[Title/Abstract] OR "PrEP"[Title/Abstract]	**13,286**
#3	**#1 AND #2**	**73**

Embase search:

#1	'doxycycline'/exp OR 'doxycycline' OR 'adoxa'/exp OR 'adoxa' 'doryx'/exp OR 'doryx' OR 'doxy'/exp OR 'doxy' OR 'monodox'/exp OR 'monodox' OR 'oracea'/exp OR 'oracea' OR 'periostat'/exp OR 'periostat' OR 'vibramycin'/exp OR 'vibramycin'	**71,320**
#2	'post exposure prophylaxis'/exp OR 'post-exposure prophylaxis' OR 'postexposure prophylaxis'/exp OR 'postexposure prophylaxis' OR 'preexposure prophylaxis'/exp OR 'preexposure prophylaxis' OR 'pre-exposure prophylaxis'/exp OR 'pre-exposure prophylaxis' OR 'doxypep' OR 'doxy-pep' OR 'doxyprep' OR 'doxy-prep'	**17,333**
#3	**#1 AND #2 AND** AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)	**79**

EBM via OVID search:

#1	doxycycline.sh. or doxycycline.hw. or doxycycline.ab. or Adoxa.ab. or Doryx.ab. or Doxy.ab. or Monodox.ab. or Oracea.ab. or Periostat.ab. or Vibramycin.ab.	**2268**
#2	Post-Exposure Prophylaxis.sh. or Post-Exposure Prophylaxis.hw. or Post-Exposure Prophylaxis.ab. or Postexposure Prophylaxis.ab. or pre-exposure prophylaxis.ab. or preexposure prophylaxis.ab. or DoxyPEP.ab. or Doxy-PEP.ab. or DoxyPrEP.ab. or Doxy-PrEP.ab.	**1234**
#3	**#1 AND #2** 0- EBM Reviews - ACP Journal Club <1991 to August 2023> 29- EBM Reviews - Cochrane Central Register of Controlled Trials <August 2023> 0- EBM Reviews - Cochrane Database of Systematic Reviews <2005 to September 6, 2023> 0- EBM Reviews - Cochrane Clinical Answers <August 2023> 0- EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012> 0- EBM Reviews - NHS Economic Evaluation Database <1st Quarter 2016>	**30**

MedRxiv search:

	(“doxycycline” AND “Post-Exposure Prophylaxis”) OR (“doxycycline AND “pre-exposure prophylaxis”) OR (“Doxy-PEP”) OR (“doxycycline” AND “PrEP”)	**17**
	Total	**17**

EEUU Clinical Trials search:

	(“doxycycline” AND (“Post-Exposure Prophylaxis”) (“doxycycline AND “pre-exposure prophylaxis”)	**9** **8**
	Total	**17**

Appendix 2: Summary of studies reporting on the effectiveness of doxycycline prophylaxis

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias

Bercot 2019 (1)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Mycoplasma genitalium
	• Location of STI
	  ○ Pharyngeal
	  ○ Anal
	  ○ Genital
	• Outcome
	  ○ Effectiveness
		Open-label randomized study)(this is a sub-study of Molina 2018) (3)
		
		Analysis: Intention-to-treat Chi-square or Fisher's exact tests, as appropriate
		
		Time of recruitment: July 2015 to June 2016
		
		Country: France
			MSM taking PrEP against HIV
			Randomized 1:1
			
			Sample: 210 adults
			Doxy PEP n=107
			No-PEP n=103
			
			Follow-up: six months
			
			Intervention: 200 mg of doxycycline within 24 hours after each sexual intercourse (with a limit of 600 mg/week)
			
			Comparison: No prophylaxis
				In total, 1,102 samples from 210 participants (378 urine samples, 353 anal swabs and 371 throat swabs) were screened for MG.
				• In total, 32 participants were found to have MG infections (22 at baseline and 19 at the six-month visit).
				• 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 PEP was used: 9.9% overall, 10.2% with PEP, 9.6% without.
				• The overall rate of MG resistance (prevalent and incident cases) to AZM and FQs 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.
				• Only 11 participants acquired a new MG infection during this six-month period: seven participants in the PEP arm and four in the non-PEP arm. These infections were detected in urine (n=5) and anal (n=6) or throat (n=1, also positive for an anal sample) samples.
					Overall judgement Some concerns

Luetkemeyer 2023 (2)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Chlamydia trachomatis
	  ○ Neisseria gonorrhoeae
	  ○ Treponema pallidum
	• Location of STI
	  ○ Pharyngeal
	  ○ Anal
	  ○ Genital
	• Outcome
	  ○ Effectiveness
	  ○ Safety
	  ○ Tetracycline resistance
	  ○ Adherence
	  ○ Acceptability
		Open-label randomized study
		
		Analysis: Modified intention-to-treat Modified Poisson model fitted according to generalized-estimating equation methods to account for repeated observations within individual participants
		
		Time of recruitment: 19 August 2020 to 13 May 2022
		
		Country: U.S. (San Francisco and Seattle)
			MSM and TGW taking PrEP against HIV who had had gonorrhoea, chlamydia or syphilis in the past year
			Randomized 2:1
			
			Sample: 501 adults
			Doxy PEP n=339
			No-PEP n=162
			
			Follow-up: median time 270 days
			
			Intervention: 200 mg of doxycycline within 72 hours after condomless sex
				• In the HIV PrEP cohort:
				  ○ Doxy group: an STI was diagnosed in 61 of 570 quarterly visits (10.7%)
				  ○ standard care group: an STI was diagnosed in 82 of 257 quarterly visits (31.9%)
				  ○ absolute difference of −21.2 percentage points and a relative risk of 0.34 (95% confidence interval [CI], 0.24 to 0.46; P<0.001).
				• In the people living with HIV cohort:
				  ○ Doxy group: an STI was diagnosed in 36 of 305 quarterly visits (11.8%)
				  ○ standard care group: an STI was diagnosed in 39 of 128 quarterly visits (30.5%)
				  ○ absolute difference of −18.7 percentage points and a relative risk of 0.38 (95% CI, 0.24 to 0.60; P<0.001).
				• The incidences of the three evaluated STIs were lower with doxycycline than with standard care; in the PrEP cohort, relative risks were:
				  ○ 0.45 (95% CI, 0.32 to 0.65) for gonorrhea
					Overall judgement Low risk

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
			Comparison: Standard care without doxycycline	○ 0.12 (95% CI, 0.05 to 0.25) for chlamydia ○ 0.13 (95% CI, 0.03 to 0.59) for syphilis. • The incidences of the three evaluated STIs in the People living with HIV cohort, the relative risks were: ○ 0.43 (95% CI, 0.26 to 0.71) for gonorrhea ○ 0.26 (95% CI, 0.12 to 0.57) for chlamydia ○ 0.23 (95% CI, 0.04 to 1.29) for syphilis. • Five grade 3 adverse events and no serious adverse events were attributed to doxycycline. • Of the participants with gonorrhea culture available, tetracycline-resistant gonorrhea occurred in five of 13 in the doxycycline groups and two of 16 in the standard-care groups. • At baseline, tetracycline resistance was observed in four of 15 *N. gonorrhea* isolates (27%); after enrolment, it was observed in five of 13 isolates (38%) in the doxycycline groups and two of 16 (12%) in the standard-care groups. • At baseline, *S. aureus* was isolated from the oronasopharynx in 45% of the participants, and 12% had doxycycline-resistant *S. aureus*. At month 12, S. aureus was isolated in 28% in the doxycycline groups and 47% in the standard-care groups (P=0.03), with doxycycline-resistant isolates in 16% and 8%, respectively (overall percentage with resistance, 5% in the doxycycline groups and 4% in the standard-care groups).	
Molina 2018 (3)	• Type of doxy prophylaxis ○ PEP • STI studied ○ Chlamydia trachomatis ○ Neisseria gonorrhoeae ○ Treponema pallidum • Location of STI ○ Pharyngeal ○ Anal ○ Genital • Outcome ○ Effectiveness ○ Safety ○ Tetracycline resistance ○ Adherence	Open-label randomized study Analysis: Intention-to-treat Kaplan-Meier method and compared with the log-rank test, hazard ratios (HRs) were estimated by use of Cox proportional hazards models Time of recruitment: 20 July 2015 to 21 January 2016 Country: France	MSM taking PrEP against HIV Randomized 1:1 Sample: 232 adults Doxy PEP n=116 No-PEP n=116 Follow-up: Median time 8.7 months (IQR 7.8–9.7) Intervention: 200 mg of doxycycline within 24 hours after sex Comparison: No prophylaxis	• Participants in the PEP group used a median of 680 mg doxycycline per month (IQR 280–1450). • 73 participants presented with a new STI during follow-up, 28 in the PEP group (nine-month probability 22%, 95% CI 15–32) and 45 in the no-PEP group (42%, 33–53; log-rank test p=0.007). • The occurrence of a first STI in participants taking PEP was lower than in those not taking PEP (hazard ratio [HR] 0.53; 95% CI 0.33–0.85; p=0.008). • The incidence of a first STI (chlamydia, gonorrhoea, or syphilis) during follow-up was 37.7 per 100 person-years in the PEP group and 69.7 per 100 person-years in the no-PEP group. • Similar results were observed for the occurrence of a first episode of chlamydia (HR 0.30; 95% CI 0.13–0.70; p=0.006) and of syphilis (0.27; 0.07–0.98; p=0.047); for a first episode of gonorrhoea the results did not differ significantly (HR 0.83; 0.47–1.47; p=0.52).	Overall judgement Low risk

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
				• The incidence of all STIs during follow-up was 45.9 per 100 person-years in the PEP group (38 participants) and 79.6 per 100 person-years in the no-PEP group (64 participants [HR 0. 57, 95% CI 0.13–0.62; p=0.014]). • No HIV seroconversion was observed, and 72 (71%) of all 102 STIs were asymptomatic. • Rates of serious adverse events were similar in the two study groups. • Gastrointestinal adverse events were reported in 62 (53%) participants in the PEP group and 47 (41%) in the no-PEP group (p=0.05). • 47 participants presented with a new episode of gonorrhea during follow-up, 22 in the PEP group (nine-month probability 16%, 95% CI 10–24) and 25 in the no PEP group (23%, 16–32; figure 2B). The occurrence of a first episode of gonorrhea did not differ significantly between the PEP and no-PEP group (HR 0.83, 95% CI 0.47–1.47; p=0.52). • 28 participants presented with a new episode of chlamydia during follow-up, seven in the PEP group (nine-month probability 6%, 95% CI 3–14) and 21 in the no-PEP group (19%, 13–28). The occurrence of a first episode of chlamydia in participants taking PEP was lower than in those not taking PEP (HR 0.30, 95% CI 0.13–0.70; p=0.006). • 13 participants presented with a new episode of syphilis during follow-up, three in the PEP group (9-month probability 3%, 95% CI 1–7) and 10 in the no-PEP group (11%, 6–19; figure 2D). The occurrence of a first episode of syphilis in participants taking PEP was lower than in those not taking PEP (HR 0.27, 95% CI 0.07–0.98; p=0.047).	
Bolan 2015 (4)	• Type of doxy prophylaxis o PrEP • STI studied o Chlamydia trachomatis o Neisseria gonorrhoeae o Treponema pallidum • Location of STI o Pharyngeal o Anal	Randomized controlled pilot Analysis: Intention-to-treat Generalized linear mixed models logistic random intercept Time of recruitment: 6 September 2011 to 30 January 2012	MSM or TGW who had syphilis twice or more since their HIV diagnosis Randomized 1:1 Sample: 25 adults Doxy PEP n=13 No-PEP n=12 Follow-up: 48 weeks	• Doxycycline arm subjects were significantly less likely to test positive for any selected bacterial STD during 48 weeks of follow-up (OR: 0.27; CI: 0.09-0.83) compared to CM arm subjects (p=0.02). • There were no significant self-reported risk behaviour differences between the doxycycline and CM arms at follow-up. • There were no significant differences between arms in only syphilis incidence or only NG/CT incidence at either the 36-week visits (the end of the on-drug phase	Overall judgement High risk

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
	○ Genital • Outcome ○ Effectiveness ○ Adherence	Country: U.S (Los Angeles)	Intervention: 100mg doxycycline hyclate, once daily for 36 weeks Comparison: Contingency management (CM) with incentive payments for remaining free STDs	for the doxycycline arm and incentive payments for the CM arm) or the 48-week follow-up analysis. • There was a significant difference between the doxycycline and CM arms on the incidence of any STD in the follow-up analysis that included week 48 (p=0.02; OR=0.27, 95% CI 0.09–0.83), though not in the analysis through Week 36, with subjects in the doxycycline arm less likely to test positive for NG, CT, or syphilis (6 visits with STDs out of 53 total visits) compared to the CM arm (15 visits with STDs out of 49 visits). • There were no differences between study arms in either the self-reported number of regular partners (p=0.14) or casual partners (p=0.29) at follow-up.	
Molina 2023 (5)	• Type of doxy prophylaxis ○ PEP • STI studied ○ Chlamydia trachomatis ○ Neisseria gonorrhoeae ○ Treponema pallidum ○ Mycoplasma genitalium • Location of STI ○ Not disaggregated • Outcome ○ Effectiveness	Open-label randomized study Analysis: Intention-to-treat Time of recruitment: 19 January 2021 to 19 September 2022 Country: France	MSM taking PrEP against HIV, with bacterial STI in prior 12 months Randomized 2:1 Sample: 502 adults Doxy PEP n=332 No-PEP n=170 Follow-up: median time nine months IQR (6 to 12) Intervention: 200mg doxycycline within 24–72 hours after sex Comparison: No-PEP	• 65% reduction in STIs incidence (CT and syphilis approx. 80%; GC approx. 55%). • Time to first CT or syphilis infection: 49 subjects infected, 36 in No-PEP arm (incidence (35.4/100 PY), 13 in Doxy PEP arm (incidence 5.6/100 PY) HR adjusted 0.16 (95% CI: 0.08–0.30, p ≤0.0001). • Time to first CT and syphilis infection: 21 in no PEP (incidence 19.3/100 PY) 5 in Doxy PEP (incidence 2.1) CT HR adjusted 0.11 (95% IC: 0.04–0.30, p ≤ 0.0001), • Syphilis cases were 18 in No-PEP (incidence 16.3), 8 in PEP (incidence 3.4) HR adjusted 0.21 (95% IC 0.09–0.47; p ≤ 0.0001). • Time to first GC and MG infection: GC 40 in no PEP (incidence 4.1), 44 in Doxy PEP (incidence 20.5) Adjusted HR 0.49 (95% CI 0.32–0.76, p=0.001); MG 31 in no PEP (incidence 29.4), 37 in PEP (incidence 16.8) HR adjusted 0.55 (95% CI 0.34–0.9, p=0.015).	Not assessed because the article has not been published yet
Grennan 2021 (6)	• Type of doxy prophylaxis ○ PrEP • STI studied ○ Chlamydia trachomatis ○ Neisseria gonorrhoeae ○ Treponema pallidum • Location of STI ○ Not disaggregated • Outcome ○ Effectiveness	Randomized controlled pilot Analysis: Intention-to-treat Time of recruitment: Unknown Country: Canada	HIV-negative MSM and transgender women with prior syphilis Randomized 1:1 Sample: 52 adults Doxy PEP n=26 No-PEP n=26 Follow-up: every three months for one year	• No participants on doxy developed syphilis or chlamydia. • Receipt of doxy associated with reduced likelihood of any STI (OR 0.18 95% CI: 0.05–0.68; p=0.011). • Chlamydia: 10 cases in the deferred group (81.83 per 100 PY) vs. none in the immediate group in first 24 weeks (p=0.001). Nil thereafter. • Syphilis: one case in the deferred group (8.16 per 100PY) vs. none in the immediate group in first 24 weeks (p=0.98). Nil thereafter. • Gonorrhoea: eight cases in the deferred group (57.14 per 100 PY) vs. four cases in the immediate group (31.37 per	Not assessed because the article has not been published yet

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
	○ Safety ○ Tetracycline resistance ○ Adherence		Intervention: Immediate doxycycline 100 mg daily x 48 weeks Comparison: Deferred doxycycline 100 mg daily starting at week 24	100PY) in first 24 weeks (p=0.505). One case in MM post-24 weeks. • Tetracycline resistance in *S. aureus* in 1/3 and 3/6 samples at week 24 and week 48, respectively, in the immediate arm; 1/2 in deferred arm at week 48.	
Stewart 2023 (7)	• Type of doxy prophylaxis ○ PEP • STI studied ○ Chlamydia trachomatis ○ Neisseria gonorrhoeae ○ Treponema pallidum • Location of STI ○ Not disaggregated • Outcome ○ Effectiveness ○ Safety ○ Tetracycline resistance	Open-label randomized study Analysis: Intention-to-treat Time of recruitment: 2020–2022 Country: Kenya	Non-pregnant cisgender women aged 18 to 30 who were taking HIV PrEP Randomized 1:1 Sample: 449 adults Doxy PEP n=224 No-PEP n=225 Follow-up: Quarterly follow-up Intervention: 200 mg doxycycline within 72 hours of sex Comparison: Standard care (quarterly STI testing and treatment after diagnosis)	• The women completed 97% of expected follow-up visits. Median age was 24 years (IQR 21–27), 36.7% reported transactional sex at enrolment, and baseline STI prevalence was 17.9% (14.1% *C. trachomatis*, 3.8% *N. gonorrhoeae*, 0.4% *T. pallidum*). • Incident STI events were detected at 109 follow-up visits (85 *C. trachomatis*, 31 *N. gonorrhoeae*, including 8 with both; 1 *T. pallidum*): 50 among those assigned to doxycycline PEP and 59 among those assigned STI screening and treatment alone (RR 0.88, 95% CI 0.60–1.29, p=0.51). • First sexually transmitted infection was 49/222 (standard care), and 46/220 (Doxy PEP) (HR 0.95 [95% CI, 0.64–1.42]). • Analysis with follow-up time censored once participants became pregnant (n=80), analysis of each STI separately, and subgroup analyses (including by age, contraceptive use, transactional sex, and STI detected at baseline) found similar results. • There were no serious adverse events likely related to the use of doxycycline. • No incident HIV infections were detected. • Weekly SMS surveys had an overall 81% response rate, and women assigned to PEP reported taking doxycycline PEP at least as many days they had sex in 78% of surveys. • Of 76 *C. trachomatis* samples tested (20 at baseline, 25 during follow-up in the doxycycline-PEP group, and 31 during follow-up in the standard-care group), none had tet(C) gene cassette detected. • In a randomly selected 10% sample of enrolment visits, the hair samples were tested, and in a randomly selected 22% sample of participants in the doxycycline-PEP group, the hair samples that had been collected at all the follow-up visits were tested; in the standard-care group, hair samples were tested in a randomly selected 5% sample of follow-up visits.	Not assessed because the article has not been published yet

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
				• According to hair-sample analysis, the use of doxycycline PEP among those assigned to receive it was low. • At 176 of 755 visits (23.3%), participants reported not taking doxycycline after the last sexual intercourse.	

Traeger 2023 (8)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Not disaggregated
	• Location of STI
	  ○ Not disaggregated
	• Outcome
	  ○ Efficacy
		Modelling
		
		Analysis: Counterfactual scenarios
		
		Country: U.S. (Boston)
			Gay and bisexual men (GBM), TGW and nonbinary people with ≥2 STI tests at an LGBTQ-focused health center
			
			10,546 health records
				• The study defined 10 hypothetical Doxy-PEP prescribing strategies based on PrEP use, HIV status, or STI history. The study estimated Doxy-PEP use and STI diagnoses averted in counterfactual scenarios in which people meeting prescribing criteria received Doxy-PEP, assuming STI rates during use would have been reduced by clinical trial efficacy.
				• The study evaluated three strategies in which Doxy-PEP would be prescribed indefinitely to the following groups defined by HIV status and use of PrEP: 1) all individuals (from their first STI test); 2) all people diagnosed with HIV (from date of HIV diagnosis or from cohort entry if the diagnosis was prior to 2015) and all PrEP users (from first PrEP prescription); and 3) all PrEP users only (from first PrEP prescription) estimates.
				• Among 10,546 individuals (94% GBM), rate of any STI was 35.9/100 person-years.
				  ○ Prescribing Doxy-PEP to all individuals would have averted 71% of STI diagnoses (number needed to treat for one year to avert one STI diagnosis [NNT]=3.9); prescribing to PrEP users/PWH (52%/12% of individuals) would have averted 60% of STI diagnoses (NNT=2.9).
				  ○ Prescribing Doxy-PEP for 12 months after STI diagnosis would have reduced the proportion using Doxy-PEP to 38% and averted 39% of STI diagnoses (NNT=2.4).
				  ○ Prescribing after concurrent or repeated STIs maximized efficiency (lowest NNTs) but prevented fewer STIs.
					Pending

Reichert 2023 (9)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Neisseria gonorrhoeae
	• Location of STI
	  ○ Not disaggregated
	• Outcome
	  ○ Efficacy
		Modelling
		
		Analysis: Deterministic compartmental model transforming the model into a susceptible-exposed-infectious-susceptible (SEIS) model
		
		Country: U.S.
			MSM
			
			Simulated cohort of 1,000,000
				• Using a deterministic compartmental model of gonorrhea transmission in an MSM population, the study introduced Doxy-PEP at various uptake levels (10–75%) and compared 20-year prevalence and resistance dynamics relative to those at baseline (i.e., no Doxy-PEP introduction, baseline tetracycline resistance levels in *N. gonorrhoeae* of 26.8%).
				• Uptake of Doxy-PEP resulted in initial drops in the prevalence and incidence of gonorrhoea infection, but
					Pending

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
				also accelerated the spread of doxycycline resistance, with increasing Doxy-PEP use driving steeper initial declines followed by faster spread of resistance. This resulted in the total loss of Doxy-PEP's clinical efficacy within one to two decades in almost all scenarios explored. The magnitude by which Doxy-PEP initially reduced the prevalence of infection was constrained by the extent of pre-existing doxycycline-resistant strains in the population. De novo emergence of doxycycline resistance did not influence these dynamics. Additionally, the implementation of Doxy-PEP had minimal impact on extending the clinically useful lifespan of ceftriaxone monotherapy. • Model findings suggest Doxy-PEP can be an effective but short-term solution for reducing the burden of gonorrhea infection, as its selection for doxycycline-resistant strains results in the loss of its prophylaxis benefit. Increasing levels of Doxy-PEP uptake and higher starting prevalence of doxycycline resistance resulted in a faster loss of its efficacy and had little change in extending the clinical lifespan of ceftriaxone for the treatment of *N. gonorrhea* infections.	

Tran 2022 (10)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Treponema pallidum
	• Location of STI
	  ○ NA
	• Outcome
	  ○ Efficacy
		Modelling
		
		Analysis: Simulated parameters
		
		Country: U.S. (Philadelphia)
			Sexual Minority Men (SMM)
			
			Simulated cohort of 10,320
				Parameter inputs were derived from the literature, and ABM outputs during the pre-intervention period were calibrated to local surveillance data. Intervention scenarios varied doxycycline uptake by 20, 40, 60, 80 and 100%, while assuming continued condom use and syphilis screening and treatment. Under each intervention scenario, the study incorporated treatment adherence at the following levels: 0, 20, 40, 60, 80 and 100%. The long-term population impact of prophylactic doxycycline was measured using the cumulative incidence over the 10-year period and the percentage of infections prevented attributable to doxycycline at year 10.
				• An uptake scenario of 20% with an adherence level of 80% would reduce the cumulative incidence of infections by 10% over the next decade, translating to 57 fewer cases per 1,000 SMM.
				• At year 10, under the same uptake and adherence level, 22% of infections would be prevented due to doxycycline PEP in the instances where condoms were not used or failed.
				• The model in this study indicated that implementation of doxycycline PEP would result in modest declines in the cumulative incidence of syphilis among SMM over a 10-
					Pending

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
				year period. Assuming an uptake scenario of 20% (a plausible level of uptake) and an adherence level of 80% (similar to prior clinical trials with 84% adherence), syphilis incidence decreased only by 10% over follow-up (57 fewer cases per 1,000 SMM). • At year 10, the study found evidence that under realistic level of uptake (20%) and adherence (80%) among SMM, doxycycline PEP would prevent roughly one-quarter of syphilis infection in the instances where condom use failed. • These data suggest that doxycycline PEP might be most beneficial as a targeted prevention strategy for syphilis infections that are often underdiagnosed such as oral secondary syphilis.	

Appendix 3: Summary of studies reporting on the acceptance and adherence of doxycycline prophylaxis

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias

Luetkemeyer 2023 (2)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Chlamydia trachomatis
	  ○ Neisseria gonorrhoeae
	  ○ Treponema pallidum
	• Location of STI
	  ○ Pharyngeal
	  ○ Anal
	  ○ Genital
	• Outcome
	  ○ Effectiveness
	  ○ Safety
	  ○ Tetracycline resistance
	  ○ Adherence
	  ○ Acceptability
		Open-label randomized study
		
		Analysis: Modified Intention-to-treat Modified Poisson model fitted according to generalized-estimating equation methods to account for repeated observations within individual participants
		
		Time of recruitment: 19 August 2020 to 13 May 2022
		
		Country: U.S. (San Francisco and Seattle)
			MSM and TGW taking PrEP against HIV who had had gonorrhoea, chlamydia or syphilis in the past year
			Randomized 2:1
			
			Sample: 501 adults
			Doxy PEP n=339
			No-PEP n=162
			
			Follow-up: median time 270 days
			
			Intervention: 200 mg of doxycycline within 72 hours after condomless sex
			
			Comparison: Standard care without doxycycline
				• Of participants assigned to the doxycycline groups, 2% discontinued because of unacceptable adverse events or patient preference.
				• The observed difference in annualized mean absolute weight change, adjusted for baseline weight, was not substantial: −0.78 kg (95% CI, −2.12 to 0.54) in the doxycycline groups and 0.20 kg (95% CI, −1.32 to 1.72) in the standard-care groups.
				• Among participants in the doxycycline groups, 89% reported that taking doxy-PEP was acceptable or very acceptable.
				• In the doxycycline groups, 86% of participants reported taking doxy-PEP consistently (always or often) within 72 hours after condomless anal or vaginal sex and 71% reported never missing doxycycline after condomless sex.
				• On the basis of quarterly computer-assisted questionnaires, the median number of doxycycline doses taken after condomless anal or vaginal sex per month was estimated to be 4.0 doses (interquartile range, 1.0 to 10.0).
					Overall judgement Low risk

Molina 2018 (3)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Chlamydia trachomatis
	  ○ Neisseria gonorrhoeae
	  ○ Treponema pallidum
	• Location of STI
	  ○ Pharyngeal
	  ○ Anal
	  ○ Genital
	• Outcome
	  ○ Effectiveness
	  ○ Safety
	  ○ Tetracycline resistance
	  ○ Adherence
		Open-label randomized study
		
		Analysis: Intention-to-treat Kaplan-Meier method and compared with the log-rank test, hazard ratios (HRs) were estimated by use of Cox proportional hazards models
		
		Time of recruitment: 20 July 2015 to 21 January 2016
		
		Country: France
			MSM taking PrEP against HIV
			Randomized 1:1
			
			Sample: 232 adults
			Doxy PEP n=116
			No-PEP n=116
			
			Follow-up: median time 8.7 months (IQR 7.8–9.7)
			
			Intervention: 200 mg of doxycycline within 24 hours after sex
			
			Comparison: No prophylaxis
				• Sexual practices remained similar between study groups during the study period.
				• No significant differences were observed between groups in the number of sexual intercourse acts in the 4 weeks before scheduled visits (p=1.00), the numbers of sexual partners within the past 2 months (p=0.57), the proportion of condomless receptive anal intercourse acts (p=0.26), and the proportion of condomless anal sex acts at the last sexual intercourse (p=0.23).
				• However, a slight but significant decrease in condom use was reported during the study period in the no-PEP group, with 80% of participants reporting condomless anal sex during their last intercourse at baseline and 90% at the month 8 visit (p for trend=0.01).
					Overall judgement Low risk

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias

Bolan 2015 (4)	• Type of doxy prophylaxis
	  ○ PrEP
	• STI studied
	  ○ Chlamydia trachomatis
	  ○ Neisseria gonorrhoeae
	  ○ Treponema pallidum
	• Location of STI
	  ○ Pharyngeal
	  ○ Anal
	  ○ Genital
	• Outcome
	  ○ Effectiveness
	  ○ Adherence
		Randomized controlled pilot
		
		Analysis: Intention-to-treat Generalized linear mixed models logistic random intercept
		
		Time of recruitment: 6 September 2011 to 30 January 2012
		
		Country: U.S (Los Angeles)
			MSM or transgender women who had syphilis twice or more since their HIV diagnosis Randomized 1:1
			
			Sample: 25 adults
			Doxy PEP n=13
			No-PEP n=12
			
			Follow-up: 48 weeks
			
			Intervention: 100 mg doxycycline hyclate, once daily for 36 weeks
			
			Comparison: Contingency management (CM) with incentive payments for remaining free STDs
				• There were no differences between study arms in either the self-reported number of regular partners (p=0.14) or casual partners (p=0.29) at follow-up.
				• There were also no differences between study arms in self-reported condom use for regular partners (p=0.55), condom use for casual partners (p=0.30), meth use (p=0.78), sex without a condom in the past three months (p=0.10), sex with an anonymous partner (p=0.45) in the past three months or having a main/primary partner (p=0.14).
				• Adherence to doxycycline was defined as a blood concentration of at least 1,000 ng/mL at a given visit.
				• Most subjects in the doxycycline arm were adherent to the medication at weeks 12, 24 and 36, with doxycycline serum levels exceeding 1,000 ng/mL in 24 out of 39 visits.
					Overall judgement High risk

Park 2021 (11)	• Type of doxy prophylaxis
	  ○ PrEP
	  ○ PEP
	• STI studied
	  ○ Not disaggregated
	• Location of STI
	  ○ Not disaggregated
	• Outcome
	  ○ Acceptability
		Cross-sectional Online survey
		
		Country: U.S. (Southern California)
			212 MSM and 76 healthcare providers with prescribing authority in Southern California	• 67.5% of 212 community members participants indicated they would take doxycycline PrEP/PEP if offered by their provider.
				• Higher acceptability was significantly associated with several characteristics, including recent history of bacterial sexually transmitted infection diagnosis and current use of HIV PrEP.
				• For healthcare providers, 89.5% of 76 enrolled participants expressed willingness to prescribe doxycycline PrEP/PEP to their patients if recommended by the Centers for Disease Control and Prevention, but only 43.4% were willing if not.
				• Both community members and healthcare providers demonstrated high levels of concern toward possible drug resistance.
				• Community members reported the highest level of concern for "possible drug resistance" (Likert average=3.54) and "possible side effects" (Likert average=3.08). Concerns associated with "judgment from peers" were lowest (Likert average=1.50). Similarly, 80.3% of healthcare providers claimed they were concerned about drug resistance regarding prophylactic use of antibiotics.
					Overall judgement Serious risk

Horn 2020 (12)	• Type of doxy prophylaxis ○ PrEP	Qualitative study Country: Australia (Sidney)	13 high-risk GBM	• STI-PrEP was regularly conceptualized by participants through comparisons with HIV PrEP. Participants' experiences with or knowledge of HIV PrEP frequently	Not assessed

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias

	• STI studied
	  ○ Not disaggregated
	• Location of STI
	  ○ Not disaggregated
	• Outcome
	  ○ Acceptability
				emerged when discussing STI-PrEP. HIV PrEP was often central to participants' understanding of the perceived risks and benefits of STI-PrEP, preferred dosing strategies and effectiveness.
				• STI-PrEP was viewed with cautious optimism among participants, who often stated that they would be interested in taking a regular antibiotic to prevent bacterial STIs occasionally under the condition that more information was available.
				• A reduction in the incidence of STIs was identified as a potential benefit of STI-PrEP by almost all participants through either a community-level reduction or a personal reduction in STIs.
				• A consistently identified benefit of STI-PrEP was the 'peace of mind' in sexual settings that it may offer those who take it. Knowledge that a risk mitigation strategy was in place was theorized by participants to relieve concerns of contracting STIs allowing them to enjoy sexual encounters more freely.
				• Antibiotic resistance, although sometimes poorly understood, was raised as a potential risk by some participants.
				• Daily dosing of STI-PrEP was preferred almost unanimously compared with event-driven or episodic strategies. Most participants were engaging in condomless anal intercourse multiple times per week and felt that a daily dosing strategy would offer greater security.
				• Some participants described the dissipation of side effects from their HIVPrEP medication and suggested that if side effects from STI-PrEP did occur but subsided over time they would be more likely to consider taking the medication long-term.
				• Concerns regarding the risk of stigmatization of STI-PrEP users were common and were often compared with similar stigmatization experienced by HIV PrEP users.	

Spinelli 2019 (13)	• Type of doxy prophylaxis
	  ○ PEP
	• STI studied
	  ○ Not disaggregated
	• Location of STI
	  ○ NA
	• Outcome
	  ○ Acceptability
		Cross-sectional Anonymous online survey of users of a gay social-networking app over two 24-hour periods in April 2018
		
		Country: U.S. (Atlanta, Birmingham, Chicago,
			5,827 users of a gay social-networking app (96% were cisgender men, 1% TGW, 1% transgender men and 2% gender queer or nonbinary)	• Overall, 84% of participants expressed interest in trying doxycycline-PEP for prevention of STIs.	Overall judgement Critical risk

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
		New York, San Francisco, and Seattle)			

Master 2023 (14)	• Type of doxy prophylaxis
	  ○ PrEP
	  ○ PEP
	• STI studied
	  ○ Not disaggregated
	• Location of STI
	  ○ NA
	• Outcome
	  ○ Acceptability
		Cohort study (October 2021–October 2022)
		Logistic regression analysis
		
		Country: The Netherlands
			593 MSM	• 102 MSM (17.2%) were aware of STI-PrEP/PEP and 15 (2.5%) had ever used it.
				• STI-PrEP/PEP awareness was associated with living with HIV, HIV PrEP use in the preceding six months and sexualized drug use with casual partner(s).
				• Higher intention to use STI-PrEP/PEP was associated with HIV PrEP use, sexual contact with casual partners, being worried about getting an STI, self-protection as reason to use it, the intention to reduce STI testing and sexual experimenting.
				• Stigmatizing beliefs regarding STI-PrEP/PEP users were associated with lower use intentions.
					Overall judgement Moderate risk

Haines 2022 (15)	• Type of doxy prophylaxis
	  ○ Indirect from HIV
	• STI studied
	  ○ NA
	• Location of STI
	  ○ NA
	• Outcome
	  ○ Acceptability
		Implementation research (Prospective intervention)
		
		Country: Canada
			42 individuals within the safer opioid supply program	• Almost half of the group that accepted HIV PrEP (n=23) were able to successfully stay on HIV PrEP and maintained good medication adherence.	Not assessed

Merrill 2023 (16)	• Type of doxy prophylaxis
	  ○ Indirect from HIV
	• STI studied
	  ○ NA
	• Location of STI
	  ○ NA
	• Outcome
	  ○ Acceptability
		Randomized controlled pilot
		
		Country: South Africa
			59 adolescent girls and young women and their female caregivers	• The study assessed a family-based intervention (IMARA-SA) aimed to reduce the risk of HIV and other STIs among adolescent girls and young women in South Africa.
				• One of the outcomes measured was the differences in HIV PrEP uptake among those receiving the IMARA-SA intervention and those who did not.
				• Regarding feasibility, intervention participation levels were high in the intervention group; 90% (n=26) completed the first intervention day and 76% (n=22) completed the full 10-hour intervention.
				• 89 evaluations of the program were analyzed, including 46 from Intervention Day 1 (85% of those who completed Day 1) and 43 from Intervention Day 2 (93% of those who completed Day 2).
				• Mean scores on the six Likert items ranged from 4.7 to 4.9 on a scale of 1 (not at all) to 5 (extremely).
				• At least 76% of adolescents and young women reported being “extremely” in agreement with the acceptability statements.
					Overall judgement Low risk

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
				• In open-ended responses, adolescents and young women described what they had learned. • Almost half of responses (49%) focused on learning about communication strategies with mothers and/or partners, 17% on risky sexual behavior and condom use, 13% on HIV PrEP, 11% on HIV/STI risk and 10% on other topics (e.g., self-worth, coping with stress).	
Argenyi 2022 (17)	• Type of doxy prophylaxis o Indirect from HIV • STI studied o NA • Location of STI o NA • Outcome o Acceptability	Retrospective analysis of 2017 to 2018 primary and secondary syphilis cases in a cohort of people taking PrEP against HIV Country: U.S. (Massachusetts)	662 people with primary and secondary syphilis living in Massachusetts	• Of 1,077 syphilis cases, partner services engaged 662 of 787 (84%) HIV-negative cases; 490 were HIV PrEP-naive, 266 received education, 166 were offered referral, 67 accepted referral, 30 attended an initial appointment and 22 were prescribed HIV PrEP. • Of 16 with pharmacy data, 14 obtained medication and eight persisted on HIV PrEP at two to three months. • Continuum progression was lowest from 1) HIV PrEP-naïve to receiving HIV PrEP education, 2) offered referral to referral acceptance and 3) referral acceptance to initial HIV PrEP appointment. • Men with male partners were more likely to receive HIV PrEP education or accept a referral. Higher social vulnerability was associated with increased HIV PrEP referral acceptance.	Overall judgement Moderate risk
Fusca 2020 (18)	• Type of doxy prophylaxis o PEP • STI studied o Treponema pallidum • Location of STI o NA • Outcome o Acceptability	Cross-sectional study Multivariable logistic regression Country: Canada (Vancouver and Toronto)	424 participants gbMSM from community-based sexual health clinics in Toronto (1 site) and Vancouver (2 sites) during routine visits for sexual health services Toronto n=242 (56.4%) Vancouver n=194 (43.6%)	• 60.1%/44.1%indicated willingness to use syphilis PEP/PrEP; 36.6% were unwilling to use either. • Among HIV-negative participants, 74.0% and 75.2% were willing to use HIV PrEP and PEP, respectively. • Most participants were familiar with antibiotic resistance (89.0%) and agreed that syphilis rates are rising in Canada (68.2%), but only 55.4% believed they were at risk for syphilis. • Odds of being willing to use syphilis PEP were higher in Toronto versus Vancouver (aOR, 2.0; 95% CI, 1.2–3.4) and increased with the number of different STIs previously diagnosed (aOR, 1.4; 95% CI, 1.2,1.7). • Although most participants (60.1%) indicated a willingness to use syphilis PEP in the future, only 44.1% of participants responded similarly for syphilis PrEP. • Moreover, 40.8% of participants were willing to use both syphilis prevention techniques, and 36.6% were unwilling to use either (kappa statistic=0.56). • Few participants had ever heard of antibiotic-based prophylaxis prior to completing the questionnaire (13.1%).	Overall judgement Serious risk

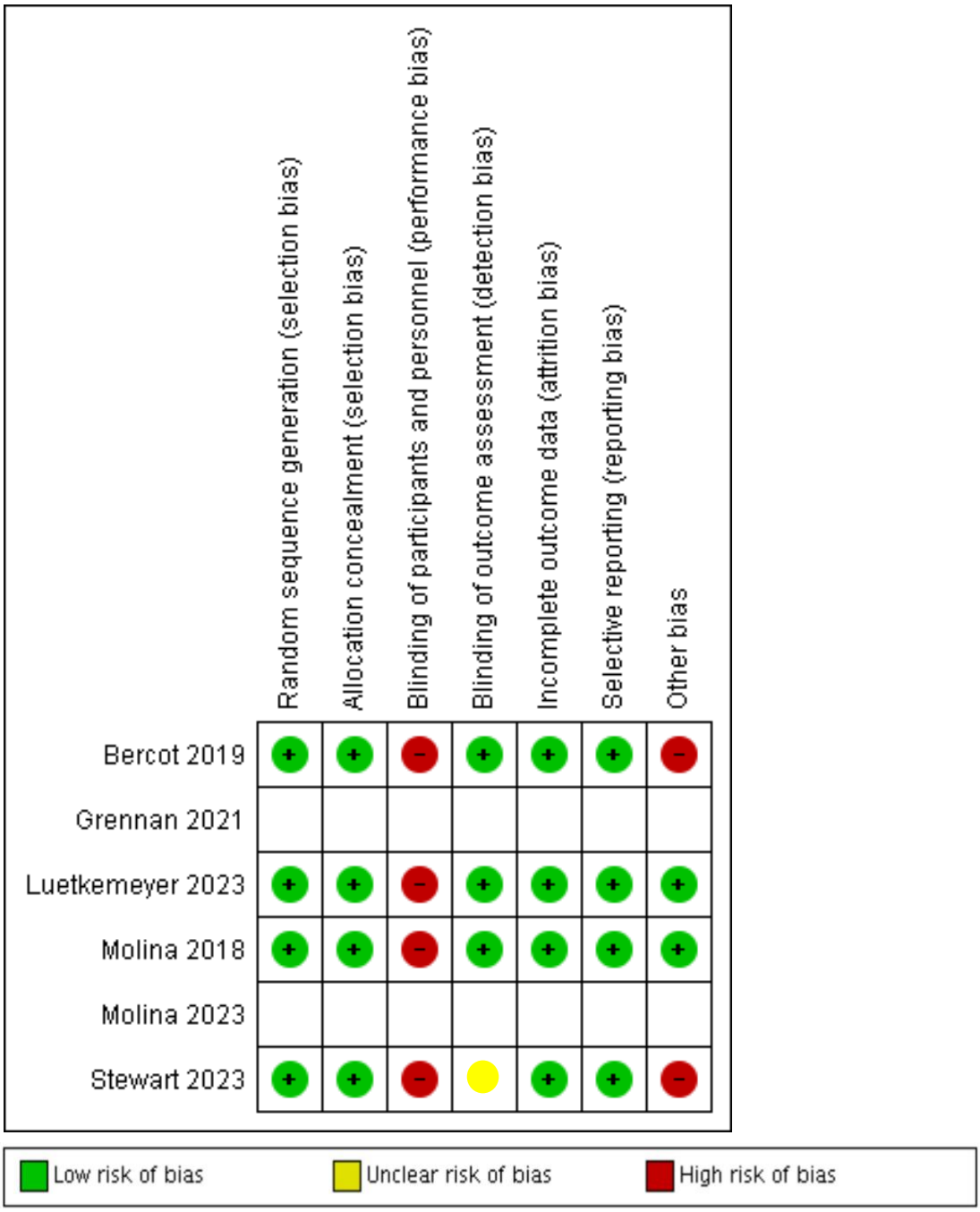
Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
				• Most participants were familiar with the concept of antimicrobial resistance, particularly that some bacteria are becoming harder to treat with antibiotics (89.0%) and can acquire resistance via antibiotic misuse (89.0%). • The belief that condom use is "the only truly effective means of STI prevention" was common (58.9%) but not unanimous. • In contrast, only 44.8% of participants had up-to-date knowledge about the "undetectable equals untransmittable" concept and agreed with the statement that "a person with an undetectable HIV viral load cannot pass on the virus through sex." • Most (68.2%) agreed that syphilis is on the rise in Canada and 55.4% of participants felt that they were at risk for syphilis. Although there were some differences in knowledge between Toronto and Vancouver, no clear pattern was discernible.	
Katz 2019 (19)	• Type of doxy prophylaxis o Indirect from HIV • STI studied o NA • Location of STI o NA • Outcome o Acceptability	Cross-sectional Country: U.S. (Seattle)	3,739 MSM at risk for HIV	• Of the 33 randomly sampled men who accepted a referral at the initial interview but did not initiate HIV PrEP, 27 remembered receiving a referral, of whom eight (30%) decided they were not interested in HIV PrEP, 15 (56%) were interested but did not contact a provider, two (7%) scheduled an appointment with a provider but did not attend, one (4%) reported having an upcoming appointment and one (4%) had an appointment but decided against initiating HIV PrEP. • Among the 33 referred, the most reported barriers to HIV PrEP were not thinking they were at risk (45%) and the frequency of provider visits for follow-up (42%). • Of the 88 men who reported not being on HIV PrEP at follow-up, 39 (44%) were interested in starting HIV PrEP, 30 (77%) of whom accepted a referral to a HIV PrEP provider or indicated they would seek HIV PrEP from their own medical provider. • Of men interested in starting HIV PrEP, 27 (69%) were identified as being at high risk based on their follow-up interview, including 13 of 24 who had been classified as intermediate risk at the initial interview.	Overall judgement Serious risk
Tan 2018 (20)	• Type of doxy prophylaxis o Indirect from HIV • STI studied o NA • Location of STI	Open label single-arm pilot study Country: Canada (Toronto)	52 adult gay and bisexual men at high risk of HIV infection	• HIV pre-exposure prophylaxis acceptability was high: all participants reported their experience as "good" or "very good." • The median adherence rate with daily HIV PrEP was high, at 100% (IQR 95%–100%) by self-report and 96.9% (IQR 93.4%– 98.4%) by pill count.	Overall judgement Some concerns

Reference	Dimension of organizing framework	Study characteristics	Sample description and intervention	Summary of key findings in relation to the outcome	Risk of bias
	○ NA • Outcome ○ Acceptability				
Zhou 2012 (21)	• Type of doxy prophylaxis ○ Indirect from HIV • STI studied ○ NA • Location of STI ○ NA • Outcome ○ Acceptability	Cohort taken form a clinical trial Country: China (Beijing)	152 MSM	• Seventeen participants (11.2%) had ever heard of HIV PrEP before the study; 69.1% reported having ever heard that ARV drugs can help control AIDS development; and 32.9% reported having ever heard of side effects of ARV drugs. • With regard to the potential risks of HIV PrEP, 63.8% expressed being worried about not working due to the side effects from HIV PrEP; 44.1% expressed worry that HIV PrEP has no prevention efficacy; 44.7% expressed worry about diet and sleep being disrupted by HIV PrEP; 21.7% expressed worry about drug resistance from HIV PrEP; 20.1% expressed worry about being treated as an AIDS patient by people; 14.5% expressed worry about being refused sex by male partners after using ARV drugs; and 26.3% expressed worry about not being able to afford ARV drugs. • Univariate logistic regression found that having ever heard of HIV PrEP and the side effects of ARV drugs, and being worried about not being able to afford ARV drugs, were significantly associated with the willingness to use HIV PrEP.	Overall judgement Moderate risk

Appendix 4: Documents excluded at the final stage of reviewing

Hyperlinked title	Reason for exclusion
Post-exposure prophylaxis with doxycycline protects	No full-text available
Estimating the impact of doxycycline postexposure prophylaxis on the incidence of syphilis among gay, bisexual and other men who have sex with men in England – a modelling study	Protocol
Preventing syphilis and co. with doxycycline: Post-exposure prophylaxis is effective, but questionable with regard to resistance	No full-text available
Sexually transmitted infections prophylaxis, is this the answer?	Wrong study design
Evaluation of doxycycline post-exposure prophylaxis to reduce sexually transmitted infections in men who have sex with men and transgender women living with HIV or using HIV PrEP: The pre-COVID cohort	No full-text available
Initiation of doxycycline post-exposure prophylaxis in patients attending an HIV PrEP clinic-Philadelphia, 2019	No full-text available
Doxycycline prophylaxis use among cisgender men and transgender persons who have sex with men in Seattle	No full-text available
A review of current guidelines and research on the management of sexually transmitted infections in adolescents and young adults	Wrong study design
Antibiotic prophylaxis for STIs: Promises or perils	Wrong study design
A pay-it-forward intervention with adjunctive social network distribution to increase doxycycline postexposure prophylaxis uptake among MSM in China: a three-arm randomized controlled trial	No full-text available
Combination therapy between doxycycline, pentoxifylline, and nitazoxanide in sexually active men	Protocol
Doxycycline post-exposure prophylaxis for prevention of sexually transmitted infections among Kenyan women using HIV pre-exposure prophylaxis: study protocol for an open-label randomized trial	Protocol
Oral doxycycline for the prevention of syphilis in men who have sex with men	This is a clinical trial unfinished
Comparison of preventive treatments against bacterial STIs in PrEP users	No full-text available
Already current practice? A snapshot survey on doxycycline use for prevention of sexually transmitted infections in parts of the German MSM community.	Wrong study design
Selection of Neisseria gonorrhoeae ceftriaxone resistance using doxycycline post-exposure prophylaxis	Wrong study design
Important considerations regarding the widespread use of doxycycline chemoprophylaxis against sexually transmitted infections.	Wrong study design
Doxycycline prophylaxis for bacterial sexually transmitted infections	Wrong study design
The challenges of preexposure prophylaxis for bacterial sexually transmitted infections	Wrong study design
Preexposure prophylaxis to prevent bacterial sexually transmitted infections in men who have sex with men	Wrong study design
To pool or not to pool samples for sexually transmitted infections detection in men who have sex with men? An evaluation of a new pooling method using the GeneXpert instrument in West-Africa	Wrong intervention
Evaluation of doxycycline post-exposure prophylaxis to reduce sexually transmitted infections in PrEP users and HIV-infected men who have sex with men	Protocol
Integrating enhanced HIV Pre-exposure prophylaxis into a sexually transmitted infection clinic in Lilongwe: Protocol for a Prospective cohort study	Protocol

Appendix 5: Risk-of-bias assessments for randomized trials included in the synthesis



Appendix 6: Risk-of-bias assessments for observational studies included in the synthesis

Study ID	Confounding or co-intervention	Selection	Misclassification	Deviation	Missing data	Outcome measurement	Outcome reporting	Overall judgment
Park 2021 (11)	S	S	M	M	M	M	M	S
Spinelli 2019 (13)	S	S	M	M	M	S	M	C
Matser 2023 (14)	M	L	M	L	M	M	L	M
Argenyi 2022 (17)	M	L	M	L	L	L	L	M
Fusca 2020 (18)	M	S	S	M	M	M	L	S
Zhou 2012 (21)	M	L	L	L	L	M	L	M

Appendix 7: Critical appraisal for qualitative research

Item	Judgement
1. Is there congruity between the stated philosophical perspective and the research methodology?	Yes
2. Is there congruity between the research methodology and the research question or objectives?	Yes
3. Is there congruity between the research methodology and the methods used to collect data?	Yes
4. Is there congruity between the research methodology and the representation and analysis of data?	Yes
5. Is there congruity between the research methodology and the interpretation of results?	Yes
6. Is there a statement locating the researcher culturally or theoretically?	No
7. Is the influence of the researcher on the research, and vice versa, addressed?	No
8. Are participants, and their voices, adequately represented?	Yes
9. Is the research ethical according to current criteria or, for recent studies, and is there evidence of ethical approval by an appropriate body?	Yes
10. Do the conclusions drawn in the research report flow from the analysis, or interpretation, of the data?	Yes

Vélez CM, Wilson MG, Woodward K, Presseau J, Lavis JN. Living evidence synthesis 23.1: Effectiveness of doxycycline pre-exposure and post-exposure prophylaxis for the prevention of bacterial STI for populations disproportionately impacted by sexually transmitted infections. Hamilton: McMaster Health Forum, 19 December 2024.

This living evidence synthesis was commissioned and funded by the Office of the Chief Science Officer, Public Health Agency of Canada. The opinions, results and conclusions are those of the team that prepared the evidence synthesis, and independent of the Government of Canada and the Public Health Agency of Canada. No endorsement by the Government of Canada or the Public Health Agency of Canada is intended or should be inferred.

References

1. Bercot B, Charreau I, Rousseau C, Delaugerre C, Chidiac C, Pialoux G, 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. *Clinical Infectious Diseases* 2021; 73(7): e2127-33.
2. Luetkemeyer AF, Donnell D, Dombrowski JC, Cohen S, Grabow C, Brown CE, et al. Postexposure doxycycline to prevent bacterial sexually transmitted infections. *New England Journal* 2023; 388(14): 1296.
3. Molina JM, Charreau I, Chidiac C, Pialoux G, Cua E, Delaugerre 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 Infectious Diseases* 2018; 18(3): 308.
4. 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. *Sexual Transmited Diseases* 2015; 42(2): 98-103.
5. Molina JM, Bercot B, Assoumou L, Michele AG, Rubenstein E, Pialoux G, et al. ANRS 174 DOXYVAC: An Open-label randomized trial to prevent STIs in MSM on PrEP. *Topics in Antiviral Medicine* 2023; 31(2): 49.
6. Grennan T, Hull M, Mohammed S, Tattersall T, Edward J, Gupta A, et al. Daily doxycycline in MSM on prep for prevention of sexually transmitted infections. *Topics in Antiviral Medicine* 2021; 29(1): 276.
7. Stewart J, Oware K, Donnell D, Violette LR, Odoyo J, Scoville CW, et al. Doxycycline prophylaxis to prevent sexually transmitted infections in women. *New England Journal of Medicine* 2023; 389(25): 2331-40.
8. Traeger MW, Mayer KH, Krakower DS, Gitin S, Jenness SM, Marcus JL. Potential impact of doxycycline post-exposure prophylaxis prescribing strategies on incidence of bacterial sexually transmitted infections. *Clinical Infectious Diseases* 2023: ciad488.
9. Reichert E, Grad YH. Resistance and prevalence implications of doxycycline post-exposure prophylaxis for gonorrhea prevention in men who have sex with men: a modeling study. *MedRxiv* 2023: 2023.04.24.23289033.
10. Tran NK, Goldstein ND, Welles SL. Countering the rise of syphilis: A role for doxycycline post-exposure prophylaxis? *International Journal STD AIDS* 2022; 33(1)18-30.
11. Park JJ, Stafylis C, Pearce DD, Taylor J, Little SJ, Kojima N, et al. Interest, concerns, and attitudes among men who have sex with men and health care providers toward prophylactic use of doxycycline against chlamydia trachomatis infections and syphilis. *Sexual Transmited Diseases* 2021; 48(9): 615-69.
12. Horn R, Callander D, Haire B. Perceptions of sexually transmissible infection pre-exposure prophylaxis: A qualitative study of high-risk gay and bisexual men in Sydney, New South Wales. *Sex Healt*h 2020; 17(2): 129-34.
13. Spinelli MA, Scott HM, Vittinghoff E, Liu AY, Coleman K, Buchbinder SP. High Interest in doxycycline for sexually transmitted infection postexposure prophylaxis in a multicity survey of men who have sex with men using a social networking application. *Sexual Transmited Diseases* 2019; 46(4)e32-e4.
14. Matser A, Hulstein B, Vries HJCd, Hoornenborg E, Prins M, Davidovich U, et al. What do men who have sex with men think of the use of antibiotics as pre- and post-exposure prophylaxis to prevent sexually transmitted infections? *med*R*xiv* 2023: 2023.09.06.23295017.
15. Haines M, O'Byrne P. Nurse-led safer opioid supply and HIV pre-exposure prophylaxis a novel pilot project. *Therapeutic Advances in Infectious Disease* 2022; 9: 20499361221091418.
16. Merrill KG, Atujuna M, Emerson E, Blachman-Demner D, Bray BC, Bekker L-G, et al. Preliminary effectiveness and implementation outcomes of the IMARA-South Africa sexual health intervention on adolescent girls and young women: A pilot randomized trial. *PLOS Global Public Health* 2023; 3(2): e0001092.
17. Argenyi MS, Molotnikov LE, Leach DH, Roosevelt KA, Klevens RM, Hsu KK. Gaps in HIV preexposure prophylaxis continuum of care following state partner services for Massachusetts primary and secondary syphilis cases, 2017 to 2018. *Sexual Transmited Diseases* 2022; 49(9): 657-61.

18. Fusca L, Hull M, Ross P, Grennan T, Burchell AN, Bayoumi AM, et al. High interest in syphilis pre-exposure and post-exposure prophylaxis among gay, bisexual and other men who have sex with men in Vancouver and Toronto. *Sexual Transmitted Diseases* 2020; 47(4): 224-31.

19. Katz DA, Dombrowski JC, Barry M, Spellman D, Bell TR, Golden MR. STD partner services to monitor and promote HIV pre-exposure prophylaxis use among men who have sex with men. *Journal of Acquired Immune Deficiencies Syndromes* 2019; 80(5): 533-41.

20. Tan DHS, Schnubb A, Lawless J, Szadkowski L, Grennan T, Wilton J, et al. Acceptability and tolerability of and adherence to HIV preexposure prophylaxis among Toronto gay and bisexual men: a pilot study. *Canadian Medical Association Journal Open* 2018; 6(4): E611-E7.

21. Zhou F, Gao L, Li S, Li D, Zhang L, Fan W, et al. Willingness to accept HIV pre-exposure prophylaxis among Chinese men who have sex with men. *PLoS One* 2012; 7(3): e32329.