SYSTEMATIC REVIEW

REVISED Impact of daily, oral pre-exposure prophylaxis on the risk of bacterial sexually transmitted infections among cisgender women: a systematic review and narrative synthesis [version 2; peer review: 2 approved]

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Abstract

Background: There are concerns that the use of pre-exposure prophylaxis (PrEP) may result in an increased incidence of sexually transmitted infections (STIs). Evidence for this is mixed and has mostly been based on reviews focussed on gay and bisexual men and transgender women, while none have summarised evidence in cisgender women.

Methods: We conducted a systematic review to explore whether daily, oral PrEP use is associated with changes in bacterial STI occurrence (diagnoses or self-reported) and/or risk among HIV seronegative cisgender women (ciswomen). The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool.

Results: We included 11 full text articles in a narrative synthesis, with the studies published between 2012 and 2021. The studies were mostly based in Africa (n=7, 63.6%) and reported on 3168 ciswomen using PrEP aged 16–56 years. Studies had marked differences in variables, including measurements and definitions (e.g., STI type) and limited data available looking specifically at ciswomen, principally in studies with both male and female participants. The limited evidence suggests that PrEP use is not associated with increased STI rates in

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ciswomen generally; however, adolescent girls and young women in Sub Saharan Africa have a higher prevalence of bacterial STIs prior to PrEP initiation, compared to adult ciswomen and female sex workers.

Conclusions: We suggest future PrEP research make efforts to include ciswomen as study participants and report stratified results by gender identity to provide adequate data to inform guidelines for PrEP implementation.

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Keywords
pre-exposure prophylaxis, bacterial sexually transmitted infections, women's health, health risk behaviors, HIV prevention, systematic review

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REVISED **Amendments from Version 1**

The minor changes in this revised manuscript are as follows:

Introduction:

1. Clarifications were made in relation to describing a theoretical 'syndemic' relationship between STIs and HIV prevention and implications for any causal inferences, including a new reference added.

2. Rewording the term 'unprotected' sex to condomless sex.

3. Additional information on the underrepresentation of pregnant, breastfeeding and women of childbearing potential in PrEP trials, including a new reference.

4. In general, clarifications of this paper focussing on oral PrEP and no other modalities.

Methods:

5. Further detail on how to interpret GRADE assessments for quality, including an additional reference to the Cochrane Handbook.

Results:

6. Addition of citations for included studies in relation to study characteristics.

7. Table 1 - addition of outcome measurement tool used in included studies and interpretation of study quality symbols.

8. Table 2 – footnote added for how percentage change was calculated.

9. Further detail on how study outcome (sexual behaviour) was measured across studies.

10. Description of findings from GRADE assessment of included studies.

Discussion:

11. Additional information on different modalities of PrEP, including injectables and vaginal rings, and the limitation of our study being focussed on oral PrEP only, including reference to the new literature on vaginal rings.

12. Reflection on limitation of our review not searching specific trial registers for those registered in Africa.

Any further responses from the reviewers can be found at the end of the article

Introduction

The use of daily antiretroviral pre-exposure prophylaxis (PrEP) has demonstrated efficacy for the prevention of HIV transmission amongst men who have sex with men (MSM), transgender women and heterosexual couples[1–6]. PrEP can be administered as a daily, oral tablet or long-acting injection, with global estimates indicating that approximately 925,000 people were enrolled on PrEP in December 2020, with just under a quarter (22%) based in the United States.

A theoretical 'syndemic' relationship has been described between HIV prevention and other sexually transmitted infections (STIs), although the causal connection between the two remains unclear[7]. There is a perceived risk between PrEP uptake, increased condomless sex and an increased risk of STIs being reported[8–10]. Among PrEP users, there have been reports of actual or intended changes in risks after uptake, including increased condomless sex acts and multiple partners[11,12], and increased STI incidence[13]. For instance, a systematic review and meta-analysis of 17 studies[14] describe a 24% increased pooled risk of any STI diagnosis following PrEP use by HIV-negative MSM and transgender women [OR, 1.24; 95% CI 0.99, 1.54; p = 0.059]. Ong *et al.*[15] undertook a random effects meta-analysis of any bacterial STI and reported an overall pooled incidence of 72.2 per 100 person-years (95% CI 60.5, 86.2) following PrEP initiation.

The findings from reviews are predominantly based on open-label clinical trials, limiting the application of results outside a controlled setting[16–18]. It is unclear what may be driving differences in risk seen among PrEP users however some theories have been postulated. Firstly, that participants of PrEP trials may be more likely to engage in 'risky' sexual practices and, subsequently, be generally more likely to acquire STIs[10,14,19]. For instance, an intended benefit of PrEP use is the freedom for people to have condomless sex, if they wish, without the risk of acquiring HIV[20]. Secondly, temporal changes suggest an increased trend in the risk of STIs amongst the general population; some argue that increased STI rates were observed before the introduction of PrEP[10]. Alternatively, some studies have reported no significant difference in either STI incidence nor risk[1–3,16,21–25]. Overall, the evidence for any causal relationship between PrEP use and increased risk remains inconclusive[10,15,26,27].

Reported changes in STI incidence following PrEP initiation could also be attributed to the sexual risk context. Factors such as partnership practices (e.g. multiple sexual partners), behaviours (e.g. condom use)[9], the socio-structural context (e.g. transactional, 'survival' sex or mobility) and gender identities or relationship dynamics[9,28–30] may, in turn, directly or indirectly influence the likelihood of an individual acquiring a bacterial STI. In addition, the socio-political context and nature of the healthcare system could influence the frequency of screening. Providers' perceptions of risk profiles of patients or educational initiatives could influence STI testing decisions, introducing a detection bias of predominantly asymptomatic STIs within a particular population[31]. Thus, the association between PrEP and risk is context-specific, whether by country, setting or study design[10]; population group[28–30]; or the availability of other prevention methods[16,17].

Systematic reviews and meta-analyses exploring the impact of PrEP on STI acquisition have primarily focussed on MSM and often subsume transgender women who have sex with men within analyses, report small sample sizes of ciswomen or group ciswomen with other 'non-MSM' populations[15,26,32]. This limits the generalisability and interpretation of findings due to differing psychosocial factors, including behavioural vulnerabilities[33]. The values, preferences and acceptability of PrEP among women have been previously explored, however few clinical trials have reported results specifically on ciswomen, despite accounting for almost half of new HIV infections in adults globally[19,34]. For instance, there is a well-established underrepresentation of pregnant, breastfeeding and women of childbearing potential in PrEP trials who are either explicitly

excluded in study protocols or unenrolled if a pregnancy occurs during the study, ultimately limiting the acquisition of safety data[35]. Ancillary studies of clinical trials with female participants have begun to explore the population sexual risk context and its influence on PrEP adherence[30,36–38]. One study[39] reports no evidence of any change in sexual behaviour among cisgender female participants of the Partners Demonstration Project, however this study does not report STI diagnoses.

We aim to synthesise evidence from the published literature on the association between oral pre-exposure prophylaxis and the risk of bacterial sexually transmitted infections among cisgender women (gender identity is aligned with sex assigned at birth), including the impact of PrEP on sexual behaviour.

Methods

The review is registered on PROSPERO (registration: CRD42019130438, 12 April 2019) and we use Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to report the findings[40,41]. A protocol was developed and followed but not published[41].

Eligibility criteria

We included open-label RCTs, demonstration and implementation projects and observational studies. We assessed each article according to our inclusion criteria as stated in our PICO statement[41].

Ciswomen were defined to be over the age of 15 to align with UNAIDS statistics. We excluded studies if they solely related to perceptions, acceptability or willingness to take PrEP, rather than actual PrEP use or if they exclusively measured HIV acquisition during PrEP use, rather than STI, as previously described[14]. To be eligible for inclusion, studies had to include at least three-months follow-up of STI diagnoses, which could be reported as a composite measure (i.e., including non-bacterial STIs).

We included publications that were full-text, peer-reviewed journal articles, conference abstracts or grey literature published in English, with no restrictions placed on publication date, status, and geographic location.

Search strategy

Two authors (VP, EC): (1) used the search strategy[41] to search MEDLINE and EMBASE *via* Ovid, Cochrane CENTRAL and Web of Science from creation to 08/04/19; (2) manually searched trial databases including the EU Clinical Trials Register; ClinicalTrials.gov; WHO International Clinical Trials Registry Platform (ICTRP); Australian New Zealand Clinical Trials Registry (ANZCTR); and the ISRCTN from creation to 17/04/19; (3) conducted a hand search of conference abstract databases of the Conference on Retroviruses and Opportunistic Infections (CROI); British HIV Association (BHIVA); AIDS Impact; IAS Conference on HIV Pathogenesis, Treatment and Prevention; and International AIDS Conference *via* Abstract Archive, from creation to 25/04/19. Two authors (VP, FC) updated the search on 30/10/20 and hand searches on 03/11/20.

Study selection

Two authors (VP/EC) independently used a screening tool for the first 30 articles to cross-check for consistency in the process and then independently screened titles and abstracts for eligibility. We imported all references into Covidence (RRID:SCR_016484) and conducted screening of titles, abstracts and full texts. Any reasons for excluding studies were noted and one author (VP) contacted study authors where full-text articles were unavailable. Duplicate records were also excluded during screening.

If both conference abstracts and journal articles were reported for the same study, the most recent publication was included. If the selected study was a clinical trial, the most recent publication of results linked to the register was screened. Any conflicts were discussed and resolved by consensus.

Data extraction

We used a data extraction template[41] in Microsoft Excel (Version 2112) (RRID:SCR_016137) and contacted study authors to provide a breakdown of data by gender, if the results were reported as a combined dataset (e.g., heterosexual couples). The following data were recorded: (1) study design and characteristics; (2) participant demographics and baseline characteristics; (3) key findings and outcome measures; (4) follow-up time; and (5) assessment of study quality.

Risk of bias

The quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) tool[41,42] taking into account study limitations (e.g., risk of bias), imprecision of the effect estimates, inconsistency of results (or heterogeneity), indirectness of evidence and risk of reporting (or publication) bias[43]. For observational studies (or non-randomised studies of interventions), grading is completed by rating upwards (starting from 'low quality') whereas randomised controlled trials have a 'high-certainty' rating to begin with[42]. Assessments range across four levels of quality: high, moderate, low and very low and indicate whether further research would "change our confidence in the estimate of effect" or an association of interest[42,43].

Synthesis of results

We planned to report STI incidence rates with 95% confidence interval for each study presented on a forest plot. However, due to methodological heterogeneity between the studies identified, findings are presented as a narrative synthesis.

Results

Following the removal of duplicates, we screened a total of 2625 studies. Of these, 122 full-text studies were assessed for eligibility and 11 studies were included in the review[44–54]. Detail of our search is outlined in Figure 1.

Study characteristics

The 11 included studies were published between 2012 and 2021 (Table 1). Six studies were observational in design[44–47,51,54], three were demonstration projects[48,49,53] and two were RCTs[50,52]. Sub-groups of the studies included adolescent girls and young

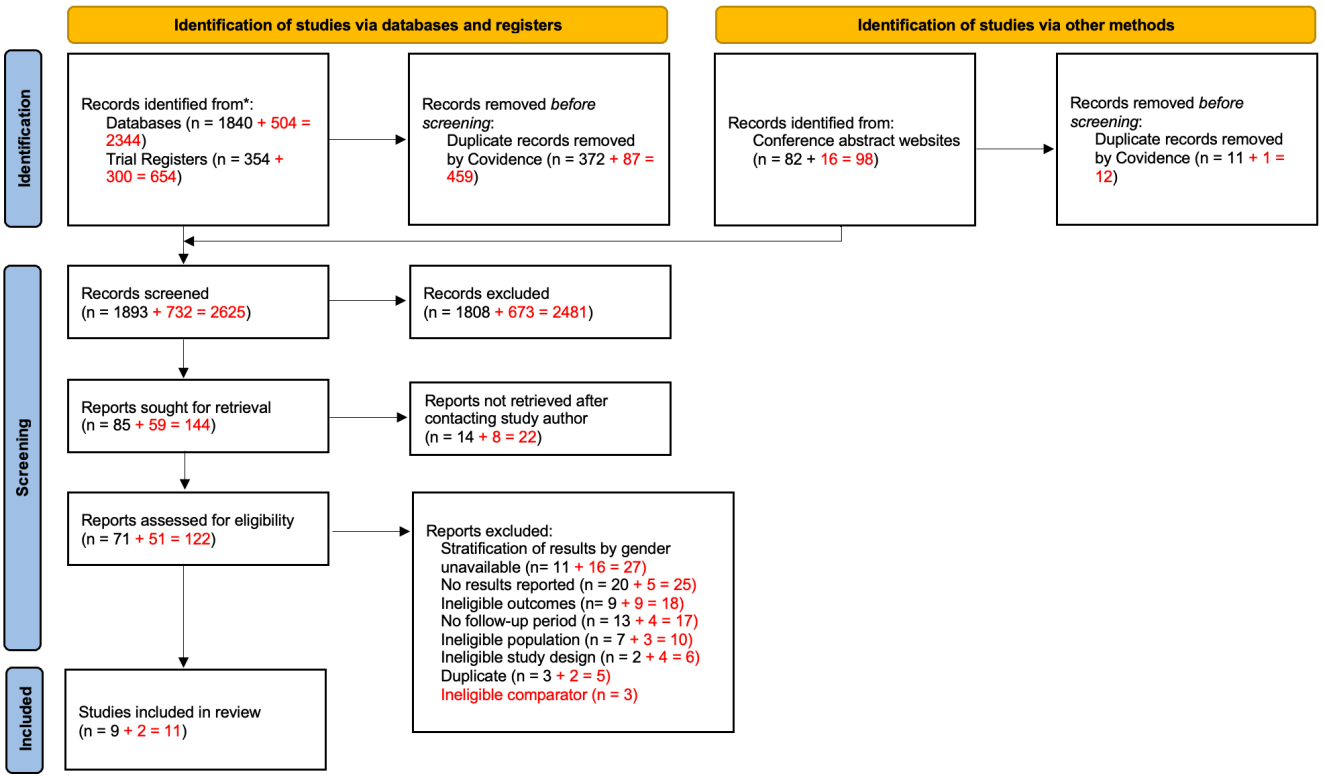

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 flow diagram. Adapted from Page *et al.*[40] We present both search methods together as we did not record these separately when conducting our review in 2019 as it was not a requirement of previous PRISMA guidelines. Text in red indicates updated search (November 2020).

women and female sex workers. Seven of the studies were conducted in Sub Saharan Africa[44,46,47,49–52], three in the United States[45,48,54], and one in Taiwan[53]. In total, the studies followed 3168 ciswomen (range 11–1062 participants) enrolled to or using PrEP and aged between 16 to 56 years old, with follow-up for an average of 1.5 years. Loss to follow-up ranged from 14% to 91%.

Synthesis of results: sexually transmitted infections

Table 2 provides a summary of baseline prevalence of STIs and reported risk after PrEP initiation. The definition of STIs across studies varied; some encompassed broader terminology of 'STI infections' and included viral types such as genital warts[44], while others used site-specific types such as genital gonorrhoea[45].

Baseline prevalence. The baseline prevalence of STI infections in five studies, using a broader definition, ranged between 6% to 47%[44,46–49]. Baseline prevalence of chlamydia was reported in six studies and ranged from 6% to 29%[45,46,49–52]. Two studies with a population of adolescent girls and young women reported a baseline prevalence of 25% and 29% respectively[49,50]. Gonorrhoea diagnoses at baseline were reported across six studies and ranged from 6% to 11%[45,46,49–52]. Syphilis diagnoses, reported in four studies, were low at baseline (prevalence ranging from 0% to 2%)[45,50,52,53].

Follow-up prevalence. Overall, the prevalence of diagnosed STIs reduced or remained stable during follow-up. However, there were no significant trends nor consistent methods for the measurement and reporting of STIs. Giguère *et al.*[46] found that STI prevalence (defined as trichomoniasis, chlamydia and gonorrhoea) declined from 15.7% (95% CI 11.8, 21.1) at baseline to 2.1% (95% CI 0.4, 10.2) at 24-months, but found no difference between baseline and 12 months, nor 12 to 24 months. Eakle *et al.*[44] reported bacterial STI diagnoses (including pelvic inflammatory disease, which can be used as an indicator of untreated gonorrhoea and chlamydia), at three-month intervals (up to 21 months) and also found no significant difference in diagnoses at baseline and follow-up.

Gonorrhoea diagnoses decreased during follow-up in most studies; for instance, Maljaars *et al.*[47] reported a 24.5% reduction in STI infections (including gonorrhoea) 12-weeks following PrEP initiation. Van Damme *et al.*[52] found gonorrhoea infections declined from 6.0% at baseline to 4.9% at follow-up among PrEP users (5.5% to 3.2% in placebo arm, P=0.25) and chlamydial infections from 15.1% to 13.3% (12.9% to 12.0% in placebo arm, P=0.65). However, 148 women (13.9%) were lost to follow-up[52]. One study[45] reported a small increase of genital gonorrhoea at one-year (0% to 3.3%) but this was based on a small sample (n=44), i.e., only 1.5% of the whole study were ciswomen).

Table 1. Characteristics of included studies in the review.

Study	Project/ Clinic	Design	Location	Participants* (PrEP users/ population screened, %)	Participant age in years [median (IQR)]	Reported outcomes (measurement tool)	Follow-up period	Lost to follow-up	Publication type	Study quality§§§
Blumenthal *et al.*, 2020[48]	PrEP Adherence Enhancement Guided by Individualized Texting and Drug Levels for Women (AEGiS)	Demonstration project	Los Angeles and San Diego (USA)	136/167 cisgender women, 81.4%	Mean 40 (SD=11)	STI infections; (lab testing); number of sexual partners (self-report)	4, 12, 24, 36 and 48 weeks	37/136†, 27.2%	Conference abstract/ poster	⊕ Very low
Clement *et al.*, 2021[54‡]	Two PrEP clinics (within academic hospital and a community health centre)	Observational (retrospective cohort)	Durham County, North Carolina (USA)	23/271 adults, 8.5%	Mean 33.2§	STI infection (chart review - clinical/lab testing)	51 months	18/23, 78.3%	Journal article	⊕ Very low
Delany-Moretlwe *et al.*, 2019[50]	Evaluation of Daily Oral PrEP as a Primary Prevention Strategy for Young African Women: A Vanguard Study (HPTN 082)	RCT	Cape Town, Johannesburg (South Africa) and Harare (Zimbabwe)	412 AGYW	21	Chlamydia, gonorrhoea, and syphilis diagnoses (vaginal swabs/urine sample); primary sexual partner (self-report); consistent condom use (self-report)	6 and 12 months	Not reported	Conference abstract/oral presentation	⊕ Very low
Eakle *et al.*, 2017[44]	Embedded within Sex Worker Programme (SWP)	Observational (prospective demonstration project)	Johannesburg and Pretoria (South Africa)	219/692 FSWs, 31.6%	28.9 (18.0 to 55.54)	STI infections (screening); number of sexual partners (self-report); consistent condom use (self-report)	1, 3, 6, 9 and 12 months	156/219**, 71.2%	Journal article	⊕ Very low
Giguère *et al.*, 2019[46]	Prospective early ART (E-ART) and PrEP demonstration project	Observational (prospective demonstration project)	Cotonou (Benin)	255/256 FSWs, 99.6%††	Mean 32.5 (SD=9.2)	STI infections (vaginal swabs); consistent condom use (self-report and vaginal swabs)	6, 12, 18, and 24 months	135/255‡‡, 52.9%	Journal article	⊕⊕ Low
Gill *et al.*, 2019[49]	3Ps for Prevention Study (Perception, Partners, Pills) (3P)	Demonstration project	Cape Town (South Africa)	200 AGYW	19 (17 to 21)	Chlamydia and gonorrhoea diagnoses (screening)	6 months	Not reported	Conference abstract	⊕ Very low
Maljaars *et al.*, 2017[47]	PlusPills	Observational (cohort)	Cape Town and Soweto (South Africa)	98/148 adolescents, 66.2%	18.0 (16.0 to 19.0)	STI infections (screening); consistent condom use (self-report)	4, 8 and 12 weeks	40/98, 40.8%§§	Journal article	⊕ Very low
Stewart *et al.*, 2019[51]	Prevention Options for Women Evaluation Research (POWER) Study	Observational (prospective cohort)	Kisumu (Kenya)	708 AGYW	Not reported	Chlamydia and gonorrhoea diagnoses (urine sample)	Up to 36 months (quarterly)	643/708, 90.8%	Conference abstract	⊕ Very low
Tabidze *et al.*, 2018[45]	Howard Brown Health Centre	Observational (retrospective cohort)	Chicago (USA)	44/2984 adults, 1.5%	32§	Chlamydia, gonorrhoea, and syphilis diagnoses (testing); number of sexual partners (self-report); consistent condom use (self-report)	28 months	Not reported	Conference abstract /poster	⊕ Very low
Van Damme *et al.*, 2012[52]	FEM-PrEP	RCT	Bondo (Kenya); Bloemfontein and Pretoria (South Africa); Arusha (Tanzania)	1062/4163*** women, 25.5%	23 (18 to 35)	Chlamydia, gonorrhoea, and syphilis diagnoses (cervical swabs and blood test); number of sexual partners (self-report); consistent condom use (self-report)	Up to 60 weeks (4-week intervals)	148/1062†††, 13.9%	Journal article	⊕⊕ Low
Wu *et al.*, 2018[53]	Taiwan Demonstration Project	Demonstration project	Taipei, Taoyuan City, Tainan City and Kaohsiung City (Taiwan)	11/302 adults, 3.6%‡‡‡	34.6 (31.7 to 43.6)	Syphilis diagnoses (lab tests); number of sexual partners (self-report); consistent condom use (self-report)	12 months (quarterly)	Not reported	Conference abstract/ poster	⊕ Very low

Abbreviations: AGYW: adolescent girls and young women; FSWs, female sex workers; RCT, randomised controlled trial

* Defined as cisgender women enrolled to, or using, daily PrEP. Total population screened may include male participants or HIV positive (subsequently not enrolled).

† Reported 52 early terminations by week 48; 37 of which were lost to follow-up, 15 were formal withdrawals (with reasons listed).

‡ During updated search, paper was published ahead of print; therefore, year of publication is after date of search

§ Includes all study participants (i.e. not only cisgender women).

** 156 FSWs were lost to follow up / had no exit visit. Study authors also reported 4 FSWs who withdrew from study.

†† One person excluded from analysis due to missing data.

‡‡ Study authors also report attrition regarding number of participants not followed due to administrative censorship (n=90) and withdrawals (n=135) by month 24.

§§ Calculated by VP

*** 4163 women screened; 2120 women underwent randomisation, of which 1058 were assigned placebo and 1062 PrEP.

††† Study authors also report PrEP users who discontinued early (n=59)

‡‡‡ 3 women were taking daily PrEP, 8 were taking on-demand and mixed PrEP

§§§ Study quality ranked as very low (⊕), low (⊕⊕), moderate (⊕⊕⊕) and very high (⊕⊕⊕⊕) quality.

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Table 2. Reported risk of bacterial STIs, among ciswomen PrEP users, at baseline and following PrEP initiation within included studies. Abbreviations: STI, sexually transmitted infection.

Study	STI diagnoses at baseline	STI diagnoses at follow-up	% change***	Rate (per 100 person years)
Blumenthal *et al.*, 2020[48]	STI infection (12/136, 8.8%)	Bacterial STIs (n=4)	-	5/100py (95% CI 2, 10)
Clement *et al.*, 2021[54]	-	1 or more new STIs (2/23, 8.7%)	-	
Delany-Moretlwe *et al.*, 2019[50]	Chlamydia (120/412, 29%)*	119/412, 28.9% (n=79: new infections)	-	29.6/100py (95% CI 24.3, 35.4)
	Gonorrhoea (33/412, 8%)*	48/412, 42.3% (n= 41: new infections)	+428.8%	11.8/100py (95% CI 8.7, 15.7)
	Reactive syphilis serology (8/412, 2%)*	-	-	-
Eakle *et al.*, 2017[44]	STI infections† (1/17, 5.9%)	**3 months** (0/3, 0%)	-100%	-
		6 months (0/3, 0%)	-100%	-
		9 months (0/2, 0%)	-100%	-
		12 months (0/5, 0%)	-100%	-
		15 months (0/0, 0%)	-100%	-
		18 months (0/0, 0%)	-100%	-
		21 months (0/0, 0%)	-100%	-
Giguère *et al.*, 2019[46]	STI infections‡ (39/249, 15.7%; 95% CI 11.8, 21.0)	**6 months** (8.4%; 95% CI 4.5, 15.5)	-46.5%	-
		12 months (13.2%; 95% CI 7.1, 24.4)	-15.9%	-
		18 months (8.6%; 95% CI 2.6, 28.0)	-45.2%	-
		24 months (2.1%; 95% CI 0.4, 10.2)	-86.6%	-
Gill *et al.*, 2019[49]	Curable STI infection§ (66/200, 33%)	-	-	52/100py
	Chlamydia (50/200, 25%)*	**6 months** 24/39, 62% new infections*	+148%	42/100py
	Gonorrhoea (22/200, 11%)*	**6 months** 10/13, 77% new infections*	+600%	14/100py
Maljaars *et al.*, 2017[47]	STI infections** (27/58, 46.6%)	**12 weeks** (19/54, 35.2%)	-24.5%	-
Stewart *et al.*, 2019[51]	Chlamydia (120/708, 17%)*	-	-	40/100py
	Gonorrhoea (56/708, 8%)*	-	-	12.3/100py
Tabidze *et al.*, 2018[45 ††]	All types of syphilis‡‡ (0%)	**1 year** (0%)	-	-
	Genital gonorrhoea (0%)	**1 year** (3.3%)	-	-
	Rectal gonorrhoea (9.1%)	**1 year** (0%)	-100%	-
	Pharyngeal gonorrhoea (4%)	**1 year** (3.6%)	-3.8%	-
	Genital chlamydia (13.5%)	**1 year** (6.7%)	-50.6%	-
	Rectal chlamydia (0%)	**1 year** (0%)	-	-
	Pharyngeal chlamydia (0%)	**1 year** (0%)	-	-

Study	STI diagnoses at baseline	STI diagnoses at follow-up	% change***	Rate (per 100 person years)
Van Damme *et al.*, 2012[52]	Gonorrhoea (56/939, 6.0%)	**Week 60** (4.9%)	-18.3%	-
	Chlamydial infection (142/939, 15.1%)	**Week 60** (13.3%)	-11.9%	-
	Syphilis (21/1060, 2.0%)	-	-	-
Wu *et al.*, 2018[53§§]	Syphilis (0/11, 0%)	Syphilis (1/11, 9.1%)	-	-

* Numerator back-calculated by VP
† STIs recorded: genital ulcer disease, genital warts, herpes, vaginal candidiasis, vaginal discharge, abscess, pelvic inflammatory disease (PID). STI infection recorded = PID/Total STIs. Presented in original manuscript's supplementary file (see Table H).
‡ Positive tests for trichomoniasis (1/250, 0.4%), chlamydia (14/249, 5.6%), gonorrhoea (28/249, 11.2%)
§ Includes chlamydia, gonorrhoea and trichomoniasis.
** STIs tested: Herpes Simplex Virus-2, *Chlamydia trachomatis* and *Nesisseria gonorrhoeae*
†† Study authors contacted for further data as this was provided in a conference abstract/poster. Outcome is changes between year before and after PrEP start.
‡‡ Syphilis defined as primary and secondary, early latent and late latent.
§§ Study authors contacted for further data as this was provided in a conference abstract / poster. Data breakdown not provided by type of PrEP (n=3, daily; n=8, on-demand and mixed). Wu *et al.* includes all women on the study (n=11) and therefore includes on-demand dosage.
*** Percentage change calculation = [(follow-up % - baseline %) / baseline %] * 100

Incident infections during follow-up. Three studies calculated the incidence rate of chlamydia diagnoses at between 30 and 42 cases per 100 person-years[49–51]. In two studies of adolescent girls and young women, around two-thirds of chlamydia infections were incident, i.e., not present when PrEP started[49,50]. Furthermore, three studies that calculated the overall incidence rate of gonorrhoea infections reported these at 12–14 cases per 100 person-years[49–51]. In two studies of adolescent girls and young women, over three-quarters of gonorrhoea infections were incident[49,50]. Two studies reported subsequent syphilis diagnoses at follow-up; no syphilis was detected during follow-up by Tabidze *et al.*[45] and Wu *et al.*[53] reported one new case of syphilis among 11 ciswomen using PrEP (including on-demand or mixed dosage).

Synthesis of results: sexual behaviour

Analysis of reported behaviour showed inconsistent results, with no clear signal of increase in risk following PrEP initiation. Table 3 illustrates risks reported across the studies. Sexual partners were variably defined across the studies; some studies specified by the 'type' of sexual partner (e.g., casual, regular, main), with sex workers definitions of 'client' also specified (e.g., occasional, regular). Condom use also varied in definition across the studies in terms of 'consistency' or 'condomless sex acts.' All studies were based on self-reports; however, one study also explored the accuracy (underreporting) of reporting condomless sex by comparing self-reports against a biological assessment (vaginal swabs) which detected traces of prostate-specific antigen (PSA) and Y-chromosomal DNA (Yc-DNA) as biomarkers of recent semen exposure[46].

At baseline, the average number of sexual partners differed between studies (range: 0.7, 22.9). Consistent condom use at baseline ranged from 33% to 100%. Only three studies[44–46] provided data on sexual behaviour at both baseline and follow-up. Eakle *et al.*[44] describe an increase in the mean number of casual sexual partners [0.7 (SD=1.1) to 1.5 (SD=1.3)] and occasional clients [17.5 (SD=21.8) to 25.0 (SD=22.1)] in the past seven-days, when comparing baseline to 12-months after PrEP initiation. They report a decrease in the mean number of regular clients [22.9 (SD=21.1) to 10.7 (SD=9.4)] in the past seven-days, when comparing baseline to 12-months after PrEP initiation[44]. Tabidze *et al.*[45] describe a non-significant increase in median number of sexual partners from two to six following 12-months PrEP use (P=0.18).

Generally, consistent condom use was unchanged or improved. One study[46] reported a significant reduction in unprotected sex after 12 months, compared to baseline (27.2% to 18.1%, P=0.04). Two studies[45,47] found no change and Eakle *et al.*[44] had insufficient data due to loss to follow-up.

Quality assessment

Overall, the quality of evidence was very low[41]. Nine studies (81.8%) scored very low and two studies (18.2%) low quality when using the GRADE assessment. Firstly, the sample size of ciswomen using daily PrEP in four of the studies[45,47,53,54] was small (range: 3–98) which will have resulted in imprecise measurements. Secondly, high loss to follow-up (ranging from 13.9% to 90.8%) of participants was reported in most studies (n=6), introducing substantial risk of bias. Thirdly, the presentation of data limited the ability to determine any significant changes to risk. For instance, Maljaars *et al.*[47] did not stratify behaviour outcomes by gender, therefore it is not possible to determine whether any changes in condom use are influenced by gender.

Table 3. Self-reported risk (including sexual partners, consistent condom use), among PrEP users, at baseline and following PrEP initiation within included studies*.

Study	Number of sexual partners at baseline [mean (SD)]	Number of sexual partners at follow-up [mean (SD)]	Consistent condom use at baseline	Consistent condom use at follow-up
Blumenthal *et al.*, 2020[48]	Number of sex partners in past 3 months [Median (IQR)]: 1 (1-3)	-	-	-
Delany-Moretlwe *et al.*, 2019[50]	Primary sex partner (346/412, 84%)†	-	Never or rarely use condoms (144/412, 35%)†	-
Eakle *et al.*, 2017[44]	Casual partner in past 7-days [0.7 (1.1)]	**3 months** [3 (3.2)]	Casual partner in past 7-days (14/22, 64%)	**3 months** (5/6, 83%)
		6 months [1 (1.5)]		**6 months** (4/7, 57%)
		9 months [1.4 (1.1)]		**9 months** (5/5, 100%)
		12 months [1.5 (1.3)]		**12 months** (3/4, 75%)
	Occasional client in past 7-days [17.5 (21.8)]	**3 months** [13.9 (13.2)]	Occasional client in past 7-days (181/181, 100%)	**3 months** (78/78, 100%)
		6 months [23.2 (32.4)]		**6 months** (54/54, 100%)
		9 months [24.7 (31.9)]		**9 months** (38/40, 95%)
		12 months [25 (22.1)]		**12 months** (33/33, 100%)
	Regular client in past 7-days [22.9 (21.1)]	**3 months** [12.9 (10.3)]	Regular client in past 7-days (179/180, 99%)	**3 months** (80/82, 98%)
		6 months [8.3 (7.9)]		**6 months** (58/59, 98%)
		9 months [9.1 (8.9)]		**9 months** (49/50, 98%)
		12 months [10.7 (9.4)]		**12 months** (31/31, 100%)
	-	-	Main partner in past 7-days (47/144, 33%)	**3 months** (25/62, 40%)
				6 months (13/41, 32%)
				9 months (14/34, 41%)
				12 months (7/27, 26%)
Giguère *et al.*, 2019[46]	-	-	Weighted prevalence of unprotected sex in last 2 days (69/254, 27.2%; 95% CI 22.3, 33.2)	**6 months** (18.4%; 95% CI 12.9, 26.3)
				12 months (18.1%, 95% CI 11.8, 27.6; *P*=0.04)
				18 months (30.3%; 95% CI 15.5, 59.1)
				24 months (34.2%; 16.6, 70.5; *P*=0.42)
			Weighted prevalence of unprotected sex in last 14 days (53.6%; 95% CI 47.7, 60.1)	**6 months** (45.8%; 95% CI 38.3, 54.8)
				12 months (48.6%; 95% CI 39.8, 59.5, *P*=0.36)
				18 months (49.0%; 95% CI 34.3, 69.9)
				24 months (38.7%; 95% CI 18.4, 81.4; *P*=0.49)
Maljaars *et al.*, 2017[47]	-	-	Inconsistent condom use (44/58, 75.9%)	Data unavailable - not stratified by gender
			Condom use during last sexual act (39/58, 67.2%)	Data unavailable - not stratified by gender

Study	Number of sexual partners at baseline [mean (SD)]	Number of sexual partners at follow-up [mean (SD)]	Consistent condom use at baseline	Consistent condom use at follow-up
Tabidze *et al.*, 2018[45] ‡	Median = 2	**12 months** (median=6, *P*=0.18)	Never/sometimes using condoms (77.78%)	**12 months** (75%, *P*=0.32, effect sample size = 8)
Van Damme *et al.*, 2012[52]	Partners in past week (mean = 1.0, median = 1, range = 0-6)	-	Sex without condom in past week (mean = 1.9, median = 1, range = 0-25)	-
Wu *et al.*, 2018[53] §	0 regular sexual partners (1/11, 9.1%)	-	Consistent condom use in past 3-months (6/11, 54.5%)	-
	0–3 regular sexual partners (9/11, 81.8%)			
	≥4 regular sexual partners (1/11, 9.1%)			
	0 casual sexual partners (6/11, 54.5%)			
	0–3 casual sexual partners (3/11, 27.3%)			
	≥4 casual sexual partners (2/11, 18.2%)			

* Some included studies did not provide follow-up data but are presented here to provide context when interpreting findings
† Numerator backcalculated by VP
‡ Study authors contacted for further data as this was provided in a conference abstract / poster. Outcome is changes between year before and after PrEP start.
§ Study authors contacted for further data as this was provided in a conference abstract / poster. Data breakdown not provided by type of PrEP (n=3, daily; n=8, on-demand and mixed).

Discussion

We found no consistent evidence that PrEP use increased the risk of ciswomen acquiring bacterial STIs, with some studies indicating that it may be associated with reduced risk. This aligns with similar findings in MSM and transgender women, described in observational studies[16,24], demonstration projects[21,22,25], pilot studies[23] and RCTs[1–3]. Additionally, our review found no clear evidence that PrEP use results in an increased likelihood of engaging in an action that can make ciswomen more vulnerable to acquiring an STI. We found that adolescent girls and young women in sub Saharan Africa have a high prevalence and incidence of bacterial STIs (particularly chlamydia and gonorrhoea) which is linked to higher vulnerabilities based on age-disparate sex, transactional sex, gender norms and lifetime gender-based violence[55–58].

Increasingly diverse methods of PrEP (including delivery and dosage) provide an increasingly personalised approach to HIV prevention[7]. Our review focussed on oral PrEP however, other methods for HIV prevention include the vaginal ring (either dapivirine or tenofovir), which has been found to be an acceptable method among women, with high continuation rates seen in both observational studies and randomised controlled trials (RCTs)[59–62] as well as injectable PrEP[63]. The HPTN 084 study found 8-weekly injections of long-acting PrEP (cabotegravir) to be 89% more effective (HR 0.11; 95% CI 0.01, 0.31) among ciswomen in sub-Saharan Africa than the daily, oral PrEP (tenofovir/emtricitabine)[63].

Strengths and limitations

To our knowledge, this is the first exploration of this research question in this population group. While the included studies had widely varying methods, they all followed participants for at least three months. We used a systematic approach to critically summarise and review the limited literature that currently exists on this topic. There are several limitations; firstly, despite an extensive literature search, we found few studies examining STI risk following PrEP initiation which contrasts with the evidence on PrEP efficacy. Our review did not include studies using other modalities of PrEP (e.g., injectable, vaginal ring); therefore, we are unable to draw conclusions on whether different modalities effect STI risk or changes in or changes in sexual behaviour and would need separate studies to review these relationships. Secondly, several of the included studies were very small and all were assessed as 'low' or 'very low' quality. We also did not search specific clinical trials registers for trials conducted in Africa (e.g., the South African Clinical Trials Register (SANCTR) or Pan African Clinical Trials Registry (PACTR)) which may have introduced a publication bias relating to population setting. Thirdly, there is marked variability in the measurement of STI outcomes (specifically timing, types, and composite endpoints)

and sexual behaviour risk, which are essential to interpret patterns and causal pathways of STI acquisition to guide public health interventions. For instance, STI diagnoses varied across studies and are likely to have been influenced by attrition bias; notably in the FEM-PrEP study[52], where less than half of participants had a pelvic examination which would then confirm the self-reported data on risk. Finally, there were high numbers of loss to follow-up (range: 14%–91%) across studies; for instance, Wu *et al.*[53] explained that loss to follow-up was influenced by women who could not afford or were unwilling to pay for PrEP as participants were only offered a maximum of 105 pills for a year.

Due to the heterogeneity in study designs and outcome measures, it was not appropriate to conduct a meta-analysis, restricting our synthesis to a narrative review. Just over one-quarter (n=3/11, 27.3%) of the included studies reported sexual behaviour at follow-up and baseline, therefore we were unable to measure the full extent of this potential impact.

Study implications

Our findings suggest that, like previous reviews including MSM and transgender women, there is no evidence that ciswomen using PrEP have a changed risk of bacterial STIs; however, adolescent girls and young women in sub–Saharan Africa had very high prevalence of bacterial STIs at PrEP initiation. Overall, we found very limited and low-quality evidence, making it difficult to draw any solid conclusions. This highlights an important issue of gender data biases in clinical research design, conduct and reporting, and specifically HIV prevention trials[64–66]. Despite this, the provision of PrEP presents an opportunity to engage women in programmes to prevent and treat STIs, providing opportunities for sexual health promotion and advice[15,67,68]. This is particularly important for those populations of adolescent girls and young women in sub-Saharan Africa with a high burden of bacterial STIs[69,70].

Conclusions

Based on this review, there is insufficient evidence to show whether PrEP use is associated with increased STI diagnoses for ciswomen. Specifically, the quality of evidence from included studies were limited and emphasises a need for larger scale studies of cisgender women in different settings which also measure sexual behaviour including condom use and number of sexual partners at both baseline and during follow-up. We emphasise the need for larger PrEP studies with ciswomen using standard periods of follow-up that align with testing guidelines. We also suggest consistent definitions of STIs, stratification of data by gender identity and validated and standardised methods for measuring risk are used in these studies to provide more robust data to help inform PrEP implementation guidelines.

Data availability

Extended data

Zenodo: Extended data for 'Impact of daily, oral pre-exposure prophylaxis on the risk of bacterial sexually transmitted infections among cisgender women: a systematic review and narrative synthesis'. https://doi.org/10.5281/zenodo.5827582[41]

This project contains the following extended data:

- Additional file 1: PRISMA 2020 checklist.docx
- Additional file 2: Systematic review protocol.pdf
- Additional file 3: PICO criteria.docx
- Additional file 4: Search strategy.pdf
- Additional file 5: Standardised data extraction template.xlsx
- Additional file 6: GRADE assessment of included studies.docx

Reporting guidelines

Zenodo: PRISMA checklist for 'Impact of daily, oral pre-exposure prophylaxis on the risk of bacterial sexually transmitted infections among cisgender women: a systematic review and narrative synthesis'. https://doi.org/10.5281/zenodo.5827582[41]

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PubMed Abstract | Publisher Full Text | Free Full Text

60. World Health Organization: **WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection.** *WHO News.* 2021.
Reference Source

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PubMed Abstract | Publisher Full Text

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PubMed Abstract | Publisher Full Text | Free Full Text

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Reference Source

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PubMed Abstract | Publisher Full Text

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Reference Source

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PubMed Abstract | Publisher Full Text | Free Full Text

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PubMed Abstract | Publisher Full Text | Free Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 2

Reviewer Report 19 August 2022

https://doi.org/10.21956/wellcomeopenres.20061.r51990

✔ **Janey Sewell**
UCL Institute for Global Health, University College London, London, UK

All comments have been addressed concisely.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infection and population health, HIV.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 12 July 2022

https://doi.org/10.21956/wellcomeopenres.19303.r51243

✔ **Katherine Gill**
Desmond Tutu HIV Centre, University of Cape Town, Cape Town, South Africa

Thank you for the opportunity to review this paper. It's an important topic and a timely review. In general, I thought it was a well-written paper. I only have a couple of minor comments.

Introduction:

- Para1: Injectable PrEP is a promising option but seems misplaced here. Focus on oral PrEP and in the discussion you can briefly mention long acting PrEP.

- Para2: Understand what you mean by “syndemic” but don’t think it’s the appropriate term to use when describing HIV prevention. Maybe add that it is a theoretical relationship.

- Para 3: Unprotected sex = condomless sex.

Methods:

- Search strategy: No reference made to an african Clinical trial register like the SANCTR or PACTR. This may have biased your results.

Results:

- Table 1: Please define the symbols under the study quality column.

Conclusions:

- Paragraph 4 - not sure what you mean by 27% of the studies reported risk

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?

Yes

Are the conclusions drawn adequately supported by the results presented in the review?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: HIV Prevention

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 25 Jul 2022

Vasiliki Papageorgiou, Imperial College London, London, UK

We thank both Janey Sewell (Reviewer 1) and Katherine Gill (Reviewer 2) for their supportive comments to help strengthen this article. We have detailed our comments below (point by point) with edits indicated using tracked changes in the manuscript file.

Comments:

Thank you for the opportunity to review this paper. It's an important topic and a timely review. In general, I thought it was a well-written paper. I only have a couple of minor

comments.

Introduction:

- Para1: Injectable PrEP is a promising option but seems misplaced here. Focus on oral PrEP and in the discussion you can briefly mention long acting PrEP.

- Para2: Understand what you mean by "syndemic" but don't think it's the appropriate term to use when describing HIV prevention. Maybe add that it is a theoretical relationship.

- Para 3: Unprotected sex = condomless sex.

Response/revisions

- We have split the two sentences here for clarity and have moved the sentence focussing on long-acting PrEP to the Discussion as suggested.
- We use the terminology stated in Gandhi *et al*. (2019) paper here referring to a 'syndemic' however agree that this is theoretical so have clarified here. We have also referred to causal relationships here to make this distinction clearer and added a new reference which reflects on the complexity of uncovering the causal pathway between PrEP use and STI risk:

  Stewart, J., Baeten, J.M. HIV pre-exposure prophylaxis and sexually transmitted infections: intersection and opportunity. *Nat Rev Urol* **19,** 7–15 (2022). https://doi.org/10.1038/s41585-021-00527-4

- We agree to and have made the suggestion highlighted.

Comments:

Methods:

- Search strategy: No reference made to an african Clinical trial register like the SANCTR or PACTR. This may have biased your results.

Response/revisions

- We agree that a need remains to highlight this potential bias, so we have included an additional sentence in the Discussion section.

Comments:

Results:

- Table 1: Please define the symbols under the study quality column.

Response/revisions

- We have added a footnote to Table 1 to explain the symbols for the GRADE assessment as well as clarifications for each study rating.

Comments:

Conclusions:

- Paragraph 4 - not sure what you mean by 27% of the studies reported risk

Response/revisions

- We have clarified this sentence in the 'strengths and limitations' section of the Discussion to highlight that this refers to changes in sexual behaviour at baseline and follow-up.

Competing Interests: None

Reviewer Report 10 June 2022

https://doi.org/10.21956/wellcomeopenres.19303.r50681

?

Janey Sewell
UCL Institute for Global Health, University College London, London, UK

Thank you for the opportunity to review this systematic review on the "Impact of daily, oral pre-exposure prophylaxis on the risk of bacterial sexually transmitted infections among cisgender women." Overall the manuscript is extremely clear and concise and presents a timely review of the evidence on the impact of PrEP on STI infections among cisgender women. I have just a few queries and clarifications as outlined below.

Introduction

The introduction clearly outlines the context and rationale for this review. Minor comments or clarifications required:

1. Paragraph 1: 'PrEP can be administered as a daily, oral tablet or long-acting injection' - I wonder if some explanation to demonstrate the distinctions with vaginal ring trials which would also help contextualise HIV prevention interventions in women, might be useful here or perhaps see point 3).

2. Paragraph 3 'For instance, an intended benefit of PrEP use is the freedom for people to have unprotected sex,' - does the term 'unprotected sex' mean condomless sex? It is important to define 'unprotected sex' in the context of PrEP use (offering protection against HIV) here.

3. Paragraph 6 '...however few trials have reported results specifically on ciswomen, despite accounting for almost half of new HIV infections in adults globally' - could the authors postulate as to why this is? is it (as described in the previous sentence) lack of representation within clinical trials? or fewer trials specifically aimed at women? This could also be where the distinction between PrEP trials and vaginal ring trials might land.

4. Paragraph 7 - acronyms for PrEP and STIs have already been defined in paragraph 1, I am not sure about the added value for defining again here. However, as in the first paragraph of the introduction, there has been a description of the long-acting injectable, cabotegravir, it would be worth clarifying that this review focuses on oral PrEP rather than injectable PrEP.

Methods

The methods are transparent and comprehensible. It would be useful to expand on (in the 'Risk of Bias' section where GRADE is referred to) the four levels of evidence that are produced by a GRADE assessment and how these relate to the symbols in Table 1.

Results

The results are clearly presented. Some clarifications are needed.

1. It would be useful in the 'Study characteristics' section for the studies to be referenced as they have been throughout the rest of the results section.

2. Table 1 - it would be useful to know how the reported outcomes were collected - lab/clinician confirmed/diagnoses? self-reported?

3. Table 1 - GRADE symbols need to have been described in the Methods section so that this column is interpretable to anyone not familiar with GRADE.

4. Table 2 - column % change - please add (in the footnote or text) how this calculation was made.

5. Synthesis of results: sexual behaviour - are all these behaviours self-reported (assume so!)? - this should be made clear in this section.

6. Quality assessment. This section needs to be contextualised by outlining the scoring for GRADE as per the comment in the Methods section. A summary of how many studies scored ++, and how many scored +, would contextualise the first sentence 'Overall, the quality of evidence was low' - and (as 9/11 studies were assessed as '+' is it not more accurate to say that 'Overall, the quality of evidence was very low'?

Discussion

The discussion is succinct and describes the results clearly in light of the limited evidence. A few minor details to consider:

1. Strengths and limitations: 'Secondly, several of the included studies were very small and some of poor quality' - Table 1 would indicate that they were all of 'low' or 'very low' quality.

2. Paragraph 4: 'Just over one-quarter of the included studies reported risk at follow-up and baseline' - it is not clear what 'risk' refers to here.

Otherwise no further comments or recommendations.

Are the rationale for, and objectives of, the Systematic Review clearly stated?

Yes

Are sufficient details of the methods and analysis provided to allow replication by others?

Yes

Is the statistical analysis and its interpretation appropriate?
Yes

Are the conclusions drawn adequately supported by the results presented in the review?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infection and population health, HIV.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 25 Jul 2022

Vasiliki Papageorgiou, Imperial College London, London, UK

We thank both Janey Sewell (Reviewer 1) and Katherine Gill (Reviewer 2) for their supportive comments to help strengthen this article. We have detailed our comments below (point by point) with edits indicated using tracked changes in the manuscript file.

Comments:

Thank you for the opportunity to review this systematic review on the "Impact of daily, oral pre-exposure prophylaxis on the risk of bacterial sexually transmitted infections among cisgender women." Overall the manuscript is extremely clear and concise and presents a timely review of the evidence on the impact of PrEP on STI infections among cisgender women. I have just a few queries and clarifications as outlined below.

Introduction
The introduction clearly outlines the context and rationale for this review. Minor comments or clarifications required:

1. Paragraph 1: 'PrEP can be administered as a daily, oral tablet or long-acting injection' - I wonder if some explanation to demonstrate the distinctions with vaginal ring trials which would also help contextualise HIV prevention interventions in women, might be useful here or perhaps see point 3).
2. Paragraph 3 'For instance, an intended benefit of PrEP use is the freedom for people to have unprotected sex,' - does the term 'unprotected sex' mean condomless sex? It is important to define 'unprotected sex' in the context of PrEP use (offering protection against HIV) here.
3. Paragraph 6 '...however few trials have reported results specifically on ciswomen, despite accounting for almost half of new HIV infections in adults globally' - could the authors postulate as to why this is? is it (as described in the previous sentence) lack of representation within clinical trials? or fewer trials specifically aimed at women? This could also be where the distinction between PrEP trials and vaginal ring trials might

land.

4. Paragraph 7 - acronyms for PrEP and STIs have already been defined in paragraph 1, I am not sure about the added value for defining again here. However, as in the first paragraph of the introduction, there has been a description of the long-acting injectable, cabotegravir, it would be worth clarifying that this review focuses on oral PrEP rather than injectable PrEP.

Response/revisions

1. To highlight that our study focusses on oral PrEP only, we have moved detail on other modalities into the Discussion and have clarified that we are unable to draw conclusions on these methods (as a limitation). We have included more information on vaginal ring trials and other modalities of PrEP in the Discussion, including 4 additional references:

   Baeten JM, Palanee-Phillips T, Mgodi NM, Mayo AJ, Szydlo DW, Ramjee G, Mirembe BG, Mhlanga F, Hunidzarira P, Mansoor LE, Siva S. Safety, uptake, and use of a dapivirine vaginal ring for HIV-1 prevention in African women (HOPE): an open-label, extension study. The Lancet HIV. 2021 Feb 1;8(2):e87-95.

   World Health Organization. WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection. WHO News. January. 2021.

   Nel A, Van Niekerk N, Van Baelen B, Malherbe M, Mans W, Carter A, Steytler J, Van der Ryst E, Craig C, Louw C, Gwetu T. Safety, adherence, and HIV-1 seroconversion among women using the dapivirine vaginal ring (DREAM): an open-label, extension study. The Lancet HIV. 2021 Feb 1;8(2):e77-86.

   Griffin JB, Ridgeway K, Montgomery E, Torjesen K, Clark R, Peterson J, Baggaley R, van der Straten A. Vaginal ring acceptability and related preferences among women in low-and middle-income countries: a systematic review and narrative synthesis. PloS one. 2019 Nov 8;14(11):e0224898.

2. As also suggested by reviewer 2, we have decided to clarify the wording here as condomless sex rather than ‘unprotected sex’.

3. We have included additional information here about the exclusion of pregnant, breastfeeding and women of childbearing potential from PrEP trials – and reference:

   Davey DL, Bekker LG, Bukusi EA, Chi BH, Delany-Moretlwe S, Goga A, Lyerly AD, Mgodi NM, Mugo N, Myer L, Noguchi LM. Where are the pregnant and breastfeeding women in new pre-exposure prophylaxis trials? The imperative to overcome the evidence gap. The Lancet HIV. 2022 Jan 25.

4. We have removed the acronyms as suggested and made it clearer that this review focuses on oral PrEP.

Comments:

Methods
The methods are transparent and comprehensible. It would be useful to expand on (in the 'Risk of Bias' section where GRADE is referred to) the four levels of evidence that are produced by a GRADE assessment and how these relate to the symbols in Table 1.

Response/revisions
We agree that additional information on how the GRADE tool is used would be helpful for readers so have included additional information about how to interpret ratings/assessment, including a new reference:

Schünemann HJ, Higgins JP, Vist GE, Glasziou P, Akl EA, Skoetz N, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. In: *Cochrane Handbook for Systematic Reviews of Interventions*. Version 6.3. 2022. https://training.cochrane.org/handbook/current/chapter-14

Comments:
Results
The results are clearly presented. Some clarifications are needed.

1. It would be useful in the 'Study characteristics' section for the studies to be referenced as they have been throughout the rest of the results section.

2. Table 1 - it would be useful to know how the reported outcomes were collected - lab/clinician confirmed/diagnoses? self-reported?

3. Table 1 - GRADE symbols need to have been described in the Methods section so that this column is interpretable to anyone not familiar with GRADE.

4. Table 2 - column % change - please add (in the footnote or text) how this calculation was made.

5. Synthesis of results: sexual behaviour - are all these behaviours self-reported (assume so!)? - this should be made clear in this section.

6. Quality assessment. This section needs to be contextualised by outlining the scoring for GRADE as per the comment in the Methods section. A summary of how many studies scored ++, and how many scored +, would contextualise the first sentence 'Overall, the quality of evidence was low' - and (as 9/11 studies were assessed as '+' is it not more accurate to say that 'Overall, the quality of evidence was very low'?

Response/revisions
1. We have added references to clarify which studies we are referring to here.

2. We have added how reported outcomes were collected for each study.

3. Agreed. We have added a footnote to Table 1 to explain the symbols for the GRADE assessment as well as clarifications for each study rating.

4. Percentage change calculation added as a footnote.

5. We have added a sentence in the opening paragraph of the “synthesis of results: sexual behaviour” section to clarify how this was measured across studies. We have also added detail in Table 1 under outcome column.

6. We have added a sentence outlining the number of studies which scored very low and low quality with the GRADE assessment in this sub-section.

Comments:

Discussion

The discussion is succinct and describes the results clearly in light of the limited evidence. A few minor details to consider:

1. Strengths and limitations: 'Secondly, several of the included studies were very small and some of poor quality' - Table 1 would indicate that they were all of 'low' or 'very low' quality.
   Paragraph 4: 'Just over one-quarter of the included studies reported risk at follow-up and baseline' - it is not clear what 'risk' refers to here.

Otherwise no further comments or recommendations.

Response/revisions

1. We have amended this sentence to match the wording of the GRADE assessment.
2. We have clarified this sentence in the ‘strengths and limitations' section of the Discussion to highlight that this refers to changes in sexual behaviour at baseline and follow-up.

Competing Interests: None