Effects of Pre-exposure Prophylaxis for the Prevention of HIV Infection on Sexual Risk Behavior in Men Who Have Sex with Men: A Systematic Review and Meta-analysis

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HIV pre-exposure prophylaxis and risk compensation

Summary

This systematic review and meta-analysis of seventeen open-label studies published between 2014-2017 found that daily HIV pre-exposure prophylaxis use among men who have sex with men is associated with increased STI diagnoses and a likely increase in condomless sex.

ABSTRACT

Background: HIV pre-exposure prophylaxis (PrEP) is effective in reducing HIV risk in men who have sex with men (MSM). However concerns remain that risk compensation in PrEP users may lead to decreased condom use and increased incidence of sexually transmitted infections (STIs). We assessed the impact of PrEP on sexual risk outcomes in MSM.

Methods: We conducted a systematic review of open-label trials and observational studies published to August 2017 reporting sexual risk outcomes (STI diagnoses, condom use, number of sexual partners) in the context of daily oral PrEP use in HIV-negative MSM and transgender women. Pooled effect estimates were calculated using random-effects meta-analysis and a qualitative review and risk of bias assessment were performed.

Results: Sixteen observational studies and one open-label trial met selection criteria. Eight studies with 4388 participants reported STI prevalence and 13 studies with 5008 participants reported change in condom use. PrEP use was associated with a significant increase in rectal chlamydia (odds ratio [OR]=1.59; 95%CI 1.19-2.13; p=0.002; heterogeneity I^2=23%) and an increase in any STI diagnosis (OR=1.24; 95%CI 0.99-1.54; p=0.059; I^2=50%). The association of PrEP use with STI diagnoses was stronger in later studies. Most studies showed evidence of an increase in condomless sex among PrEP users.

Conclusion: Findings highlight the importance of efforts to minimize STIs among PrEP users and their sexual partners. Monitoring of risk compensation among MSM in the context of PrEP scale-up is needed to assess the impact of PrEP on the sexual health of MSM and to inform preventive strategies.

Keywords

Human immunodeficiency virus, pre-exposure prophylaxis, risk compensation, sexual behavior, sexually transmitted infections

INTRODUCTION

Ambitious HIV elimination targets set by the Joint United Nations Programme on HIV/AIDS (UNAIDS) focus on HIV testing and treatment scale-up and viral suppression among people living with HIV, but also on scale-up of primary prevention strategies in high risk groups [1]. To date, such prevention strategies have focused mostly on expanded access to risk reduction counselling, condoms, and needle and syringe exchange programs [2, 3]. More recently, the success of pre-exposure prophylaxis (PrEP) – daily drug regimens of tenofovir disoproxil fumurate (TDF) and emtricitabine (FTC) – in reducing HIV acquisition in trials among men who have sex with men (MSM) [4, 5], heterosexual couples [6] and people who inject drugs (PWID) [7], has led to recommendations for expanded access to PrEP as an additional prevention choice for people at risk of HIV [8]. More than 100,000 people were accessing PrEP at the end of 2016, most of them MSM in middle- to high-income countries, however UNAIDS estimates that three million people worldwide are eligible for PrEP [9].

Compelling research findings on the efficacy and effectiveness of PrEP in reducing HIV acquisition risk have led to the regulatory approval for the use of TDF/FTC for PrEP in countries such as the United States, Australia and the U.K. [10, 11], with the focus of research now shifting towards PrEP demonstration projects. There are more than 50 such projects currently ongoing, planned or completed internationally [12]. A key aim of demonstration projects is to provide evidence to inform policy and practice around PrEP, including examination of cost-effectiveness and recommendations for public subsidization. Demonstration projects also aim to address common uncertainties around

widespread PrEP implementation, including concerns over long-term toxicity, adherence, drug resistance and behavioral change [13].

Measuring changes in sexual behavior after commencing PrEP is a focus of many demonstration projects in light of concerns that PrEP may result in shifts towards more risky sexual behaviors – 'risk compensation' [14]. MSM accessing PrEP may 'compensate' for the protection afforded against HIV by having more condomless sex or increasing their number of condomless sex partners. Concern arises from the impact decreased condom use may have on sexually transmitted infection (STI) epidemiology or HIV transmissions when PrEP regimens are not adhered to. There are also concerns that the HIV prevention benefits of PrEP could be counteracted by a decline in the overall acceptability of condoms across populations at risk of HIV due to increased PrEP use [15]. Risk compensation has been explored previously among MSM in the context of other HIV biomedical prevention measures, such as non-occupational post-exposure prophylaxis (NPEP) and sero-discordant sex in the context of HIV treatment derived viral suppression (treatment as prevention or TasP), however no evidence for increased risk-taking behavior was found [16, 17].

While a recent review of PrEP studies found no evidence of risk compensation among PrEP users [18], this review consisted mainly of blinded trials, which do not offer realistic insights into risk compensation given participants were blinded to whether they were receiving PrEP or placebo drugs. In the context of a rapidly growing number of demonstration projects occurring in 'real-world' settings, we aimed to conduct a systematic review and meta-analysis and update the current body of evidence on PrEP use among MSM and its impact on STI diagnosis and sexual risk behavior outcomes.

METHODS

The systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines for reporting systematic reviews [19]. The review protocol was registered prospectively (PROSPERO registration number 2017:CRD42017059674).

Eligibility Criteria

We included studies of HIV-negative MSM and transgender women (TGW) taking PrEP to reduce their risk of HIV infection and restricted the review to studies prescribing once-daily oral PrEP. We included longitudinal observational studies, open-label clinical trials or non-blinded RCTs; blinded studies were excluded to ensure measured outcomes were the result of the effects of perceived HIV protection offered by PrEP. Outcomes were either compared over time between participants taking PrEP and participants not taking PrEP or changes were analyzed longitudinally in PrEP users. The below outcomes were included as measures of risk compensation:

1. Diagnoses of newly acquired bacterial STIs, including chlamydia, gonorrhea and early syphilis infection, measured at baseline and follow-up visit;
2. Proportion of participants self-reporting condomless anal sexual intercourse, defined as any condomless anal sex or inconsistent condom use;
3. Number of self-reported condomless anal sex partners, defined as the number of condomless anal sex partners where the participant was the receptive or insertive partner; and
4. Number of self-reported anal sex partners regardless of condom use.

All outcomes were compared from baseline to time of longest follow-up. Studies were excluded if they measured beliefs about PrEP use rather than actual PrEP use. Studies were also excluded if they reported predicted future behavior rather than actual change in behavior.

Search Strategy

We conducted a search up to 15 August 2017 of three online databases; Medline and EMBASE, both using Ovid, and Web of Science. Search strings included medical subject headings and free text relating to (see Appendix 1 for full search strings):

1. HIV;
2. MSM (men who have sex with men, GBM, gay men);
3. Pre-exposure prophylaxis (PrEP, Truvada, tenofovir, TDF, emtricitabine);
4. Sexual risk (condom use, unsafe sex, unprotected sex, sexual partners, risk compensation, risk behavior); and
5. STIs (sexually transmitted infections, chlamydia, gonorrhea, syphilis)

No restrictions were made on language or date of publication. Reference lists of all relevant studies were searched manually, as well as abstracts from the International AIDS Society Conference, International AIDS Conference and annual Conference on Retroviruses and Opportunistic Infections over the past 5 years. Results were collated and titles and abstracts screened for relevance independently by two reviewers against the pre-defined eligibility criteria. For studies that reported at least one outcome of interest in the abstract, full texts were obtained and assessed to confirm eligibility. In instances of multiple publications reporting data from the same cohort, the most recent period of study for the relevant outcome(s) was included.

Risk of Bias Assessment

Quality and risk of bias assessment were conducted on included studies using aspects of the Cochrane Risk of Bias Tool [20] for randomized trials and the Newcastle-Ottawa Scale [21] for non-randomized trials and observational studies. We assessed the methodological quality according

to participant selection and control of confounding and assessed publication bias by constructing a funnel plot [22].

Data Extraction

Data were extracted and assessed independently by two reviewers using a standardized form to collate the following study characteristics and outcomes:

1. study design and comparison used;
2. location and date of study;
3. sample size;
4. length of follow up;
5. participant demographics (including the proportion classified as MSM or TGW, age, ethnicity);
6. outcome measures (including specific definitions of each outcome reported); and
7. main findings.

Any disagreements were resolved by consensus, and study authors were contacted via email to obtain missing data or further information where needed.

Statistical Analysis

Due to high clinical heterogeneity between measures of sexual behavior across studies, a meta-analysis was not feasible for prevalence of condomless sex, number of condomless partners or number of sexual partners and was only conducted for change in STI diagnoses. As such, we conducted a qualitative synthesis of the sexual behavior outcomes without a meta-analytical synthesis.

Effect sizes for STI outcomes were calculated using odds ratios with 95% confidence intervals by categorizing participants into binary variables for exposure (PrEP or no-PrEP) and outcome (STI diagnosis). Odds ratios measured change in STI positivity rather than STI incidence to maintain consistent metrics across studies and ensure the maximum number of studies were included in the data synthesis. Where odds ratios and confidence intervals were not included in published studies they were calculated from prevalence data reported in manuscripts or provided by authors. Random effects meta-analyses were conducted to calculate within-study pooled estimates for specific STI outcomes where available data were disaggregated across infection type or anatomical site and also to calculate across-study pooled estimates. Pooling of STI outcomes within studies was considered appropriate on the basis of high levels of multiple STI infections among participants [23]. Statistical heterogeneity between studies was assessed by calculating an I^2 and χ^2 statistic, with a χ^2 significance level of 0.10 and $I^2 > 50\%$ considered moderate or high levels of heterogeneity [24].

Subgroup analyses were performed to identify causes of heterogeneity between studies by stratifying studies by date of final data collection, sample size, location, participant demographics and length of follow-up. Median values for study date, sample size and length of follow-up were chosen as cut-offs to distribute studies evenly between subgroups. Sensitivity analysis was performed to assess robustness of findings. All statistical analyses were performed using Stata software (Version 14.1 for Mac; StataCorp, College Station Texas).

RESULTS

Included Studies

Six hundred and ninety six citations were found and 36 full texts reviewed; 17 studies [25-41] published from 2014 to 2017 met inclusion criteria and were included in the review (search results are shown in Figure 1). Included studies were from eight journal articles and nine conference proceedings; one study was a randomized controlled trial where participants were randomized to immediate or delayed PrEP; one was a non-randomized open-label extension of a double-blind

clinical trial; and 15 were longitudinal cohort studies (Table 1). Eleven studies were conducted in the United States with all but two studies being undertaken in high-income countries. A total of 6671 (median, 268; range, 50–1603) participants were included and length of follow-up ranged from 3 to 18 months (median = 6 months). Age distribution was similar across studies with a mean age of 34 years (range = 18–70 years). Despite a possible sample overlap of two studies [34, 40], these studies reported different outcomes allowing both to be included in the qualitative review while only one publication was included in the data synthesis. Reasons for exclusion included mixed populations where data were not disaggregated by MSM status, perceived change in risk behavior outcomes, blinding of participants and no comparison period of the non-intervention group (see Supplementary Table 1 for list of excluded studies).

Sexually Transmitted Infections

Eight studies that included 4388 participants reported STI positivity at baseline and follow-up visits and were included in the meta-analysis. The pooled odds ratio [OR] for any STI diagnosis was 1.24 (95% confidence interval [CI]: 0.99–1.54; p=0.059) (Figure 2). Statistical heterogeneity across studies was moderate (I^2=50%; $\chi 2$, p=0.052). PrEP use was associated with significantly increased odds of any rectal STI diagnosis (OR, 1.39; 95% CI: 1.03–1.87, p=0.029) and rectal chlamydia diagnosis (OR, 1.59; 95% CI: 1.19–2.13, p=0.002). PrEP use was also associated with statistically non-significant increases in syphilis (OR, 1.12; 95% CI: 0.86–1.47; p=0.408), chlamydia (OR, 1.23; 95% CI: 1.00–1.51, p=0.051) and gonorrhea (OR, 1.13; 95% CI: 0.78–1.64; p=0.515) infection from any anatomical site (Table 2).

Date of study influenced the association between PrEP use and STI diagnosis, with studies whose final data collection was from 2016 onwards giving a pooled odds ratio of 1.47 (95% CI: 1.05–2.05; p=0.024) for any STI diagnosis. Heterogeneity remained moderate (I^2=47%) for these studies. The likelihood of increased STI diagnoses was not affected by study sample size and participant

demographics were similar across all studies in the meta-analysis. Sensitivity analysis showed omission of any one study from the meta-analysis had little effect on the overall pooled estimate (see Supplementary Figure 1).

Sexual Behavior

Thirteen studies that included 5008 participants measured change in self-reported sexual behavior in response to PrEP. Table 3 shows a summary of findings from included studies. Measures of risk compensation reflected our included outcomes; proportion of participants reporting any condomless sex and number of condomless anal sex partners, however other indicators of risk compensation were common. Studies also examined the change in HIV-seropositive or HIV-unknown partners and most measured differences in outcomes for insertive or receptive anal intercourse. Some subgroup analyses were performed within studies, with differences in risk compensation noted in a few subgroups.

None of the studies found a significant increase in the proportion of MSM reporting any condomless sex from baseline to follow-up. However, across studies there was evidence of an increased proportion of participants reporting; condomless receptive anal sex with 10 or more partners [35]; condomless sex with an HIV-positive or HIV-unknown partner [36, 41]; and never using condoms during anal sex [37]. Only one study reported a significant decrease in the proportion reporting condomless receptive sex over time; however, this study was the first open-label PrEP study and findings may reflect the effectiveness of safe-sex counselling prior to later PrEP normalization. There was also no difference in change in condom use between PrEP and non-PrEP arms in this study [29]. Longitudinal modeling adjusting for age and ethnicity found an increase in the mean number of condomless anal sex partners among MSM in an American cohort from baseline to six months but no change in total number of partners, suggesting a decrease in condom use over time [38]. An Australian demonstration project found a decrease in frequency of condom use with regular

and casual partners over one year of follow-up among cohort participants [32]. Two studies reported decreased condom use among between 25% and 41% of study participants [39, 40]. Four studies reported the mean number of anal sex partners regardless of condom use [29, 33, 35, 38], with none finding a significant increase due to PrEP use. One study found 11% of participants reported an increased number of total partners from baseline to six months [40]. No studies reported a difference in outcomes for TGW compared to MSM.

Quality Assessment

Levels of bias were classified as moderate across studies (see Supplementary Tables 2 & 3 for risk of bias assessment). Participation bias was likely due to specific participant eligibility criteria in most studies; cohorts were not necessarily representative of the general MSM population. All studies were at risk of reporting bias as sexual behavior outcomes relied on self-reporting. Participant retention was mixed but relatively high overall; 13 of 17 studies had retention higher than 75% (retention >90% in eight studies) at final follow-up. The one RCT adjusted for disproportionate frequency of STI screening between groups [35]. A funnel plot indicated no evidence of publication bias (Supplementary Figure 2).

DISCUSSION

In this review of seventeen open-label studies use of pre-exposure prophylaxis was associated with increased diagnoses of STIs in men who have sex with men. The effect was greatest for rectal infections for both chlamydia and overall STI diagnoses, and rates of repeat STI diagnoses among participants during follow-up were high. When appraising evidence for risk compensation, it is important to take into consideration when the studies were conducted with respect to any changing attitudes towards PrEP. Despite early uptake of PrEP being slow and the initial stigma surrounding PrEP, most notably in the United States [42], PrEP use is now increasing in the US [43] and others

have reported increasing knowledge of and willingness to use PrEP among MSM over the past five years [44, 45]. Our finding of a greater increase in STI diagnoses in more recent studies and in studies with longer follow-up time suggest increasing trust in the HIV protective effect of PrEP and potentially a normalization of PrEP for HIV prevention over time. Key differences in stages of normalization of PrEP between studies may influence outcomes such as risk compensation. This is reflected in the most recent study included in our meta-analysis from Australia, where an internationally unprecedented rate of enrolment has since been observed in large demonstration projects in Sydney and Melbourne [46].

Although changes in self-reported sexual risk behavior varied across study populations, most instances reflected an increased number of different condomless partners or a decrease in overall condom use, rather than a change in proportion of men engaging in any condomless sex. The finding that no studies reported a significant increase in the proportion of MSM participating in any condomless sex most likely reflects a study population where many participants were not previously using condoms 100% of the time. We note however the variations in evidence for risk compensation between subgroups engaging in different levels of sexual risk behavior [33, 38], as well as evidence of MSM transitioning from inconsistent condom use to never using condoms [37]. These findings suggest that risk compensation is most prominent among MSM already engaging in behaviors that place them at risk of HIV and support risk-based guidelines for PrEP [10].

A previous meta-analysis on the association between PrEP use and STIs among MSM found that MSM enrolled in PrEP studies were between 11.2 and 44.6 times more likely to be diagnosed with an STI versus MSM enrolled in cohort studies without PrEP [49]. Greater effect sizes in this meta-analysis reflect methodological differences to our own, such as comparing STI incidence between different populations. Although the previous meta-analysis was limited in its analysis due to heterogeneous populations and differences in STI testing frequencies, its findings suggest MSM who

enroll in PrEP studies have a greater baseline STI risk compared to MSM who do not. This is consistent with early experiences of PrEP programs in the US where MSM initiating and continuing to use PrEP were more likely to engage in condomless sex, be the receptive partner during sex and report sex with an HIV-positive person than those who do not use PrEP [47, 48].

Our inability to conduct a meta-analysis on behavioral outcomes due to differences in metrics of condom use and the period over which they were measured, indicates that defining clear and meaningful measures of sexual behavior in PrEP research is crucial. As risk compensation is exhibited differently among PrEP users, future research should ensure the collection of data on a wider range of sexual behaviors and report within-participant changes, as opposed to proportional changes across the whole cohort. More descriptive reporting of other sexual risk behaviors, such as participation in group sex and the viral load of HIV-positive partners, may further enhance our understanding of individuals' behavioral responses to PrEP use and how trends in STIs will be affected. Future research should also explore the effects of increases in STI testing due to increased PrEP access on STI epidemiology in MSM. Decreases in condom use may be counteracted by the benefits accrued from the early diagnosis and treatment of STIs in the context of PrEP use.

While this is the first systematic review of risk compensation in the context of real-world PrEP demonstration studies, several limitations of our review must be acknowledged. First, STI positivity was only reported in studies as aggregated data at baseline and post-PrEP follow-up, making it impossible to calculate odds ratios that account for the paired samples and dependency of outcomes, leading to underestimated standard errors and narrower confidence intervals. Secondly, the lack of individual-level and demographical data limited our understanding of the individual circumstances in which sexual behavior changed due to PrEP use. Third, due to differences in outcome measures of STIs (i.e. prevalence versus incidence) we were unable to include some studies in the data synthesis. In such cases, we made efforts to contact authors, however were unable to obtain additional data for

all studies. Fourth, studies in this review involved PrEP protocols that included safe-sex counselling and comprehensive STI screening, which may lead to an underestimate in the magnitude of risk compensation associated with PrEP use outside of a study environment. Finally, lack of control data in observational studies makes it difficult to attribute changes in sexual behavior to PrEP use alone, with unmeasured or unanalyzed confounders potentially affecting results.

CONCLUSION

This is the first review of risk compensation among MSM using PrEP that includes findings from demonstration projects and open-label extension studies implemented since the regulatory approval of PrEP. Study findings suggest that STIs increase after participants commence PrEP. Of particular interest is the increase in anorectal STIs, suggesting an increase in condomless receptive anal intercourse after participants commence PrEP. It was difficult to analyze an overall effect on sexual behavior change, as studies did not adopt standardized measures. But taken together, the included studies suggest that PrEP use is associated with a decline in condom use for anal sex, especially among MSM already using condoms inconsistently. These findings highlight the importance of ongoing efforts to control the spread of STIs among PrEP users and their sexual partners. Our findings support ongoing education to encourage the judicious use of condoms for anal sex; routine testing and comprehensive treatment of high-prevalence STIs seen among MSM, including syphilis, chlamydia and gonorrhea as part of PrEP programs; and further research to assess novel biomedical strategies to prevent bacterial STIs, such as antibiotic pre-exposure and post-exposure prophylaxis [50], and the use of antiseptics [51, 52]. PrEP is being positioned as an integral tool in reducing new HIV infections among MSM in country-level and global prevention strategies, and responses to emerging trends in risk compensation need to be balanced against the considerable HIV transmission averted and the long-term prevention impact of greater PrEP coverage.

FUNDING

Burnet Institute acknowledges support from the Victorian Government Operational Infrastructure Fund. EJW, MEH, JSD and MAS acknowledge fellowship support from the National Health and Medical Research Council. VJC receives a stipend from the Research Training Program of the Australian Government's Department of Education and Training.

POTENTIAL CONFLICTS OF INTEREST

EJW, MEH, JSD and MAS declare research funding to their institute from Gilead Sciences. JSD and MEH declare research funding to their institute from Merck, AbbVie and Bristol Myers Squibb. EJW has received funding for consultancy and educational resources from ViiV and Merck, and research funding from Gilead Sciences, Abbott, Janssen Cilag and Boehringer Ingelheim. JSD has received honoraria from Gilead Sciences, Bristol Myers Squibb and Merck. VJC has received speaker's fees and conference assistance from Gilead Sciences, speaker's fees from MSD, and advisory board fees from ViiV. All other authors report no potential conflicts.

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TABLES

Table 1. Characteristics of Open-Label Pre-exposure Prophylaxis Studies Included in the Review

Study	Project / Clinic	Design	Comparison	Start Date	Country	Sample Size	Participants
Beymer et al, 2017 **[25]**	Los Angeles LGBT Centre	Retrospective cohort	Before PrEP	November 2015	USA	211	100% MSM
Colby et al, 2016 **[26]**	PrEP 30	Prospective cohort; demonstration project	Before PrEP	December 2015	Thailand	197	91% MSM 1% TGW
Corales et al, 2015 **[27]**	Trillium Health	Prospective cohort	Before PrEP	August 2012	USA	98	88% Male
Elsesser et al, 2015 **[28]**	Fenway Health	Prospective cohort	Before PrEP	November 2012	USA	50	100% MSM
Grant et al, 2014 **[29]**	iPrEX OLE	Prospective cohort; open label extension of RCT	No PrEP control group	June 2011	Brazil, Peru, Ecuador, South Africa, Thailand, U.S.	1603	89% MSM 11% TGW
Gulob et al, 2016 **[30]**	SPARK	Prospective cohort; demonstration project	Before PrEP	January 2014	USA	280	100% MSM or TGW
Hosek et al, 2017 **[31]**	Project PrEPare 2	Prospective cohort; demonstration project	Before PrEP	January 2013	USA	200	100% MSM
Lal et al, 2017 **[32]**	VicPrEP	Prospective cohort; demonstration project	Before PrEP	June 2014	Australia	114	99% MSM 1% TGW
Liu et al, 2016 **[33]**	DEMO project	Prospective cohort; demonstration project	Before PrEP	October 2012	USA	557	98% MSM 1% TGW
Marcus et al, 2016 **[34]** *	Kaiser Permanente North California	Prospective cohort	Before PrEP	July 2012	USA	972	98% Male

McCormack et al, 2016 **[35]**	PROUD	Immediate vs delayed randomised controlled trial	Delayed PrEP control group	November 2012	UK	544	100% MSM
Milam et al, 2015 **[36]**	CCTG 595	Prospective cohort	Before PrEP	January 2013	USA	268	100% MSM
Montano et al, 2017 **[37]**	Public Health – Seattle & King County	Prospective cohort	Before PrEP	September 2014	USA	218	100% MSM
Oldenburg et al, 2017 **[38]**	PrEP clinic in Providence, Rhode Island	Prospective cohort	Before PrEP	January 2013	USA	61	100% MSM
Thomas et al, 2016 **[39]**	Clinique médicale l'Actuel	Prospective cohort	Before PrEP	January 2011	Canada	322	97% MSM
Volk et al, 2015 **[40]** *	Kaiser Permanente San Francisco	Prospective cohort	Before PrEP	July 2012	USA	657	99% MSM
Zablotska et al, 2017 **[41]**	PRELUDE	Prospective cohort; demonstration project	Before PrEP	November 2014	Australia	317	97.5% MSM

*Studies may contain overlapping cohorts. Abbreviations: MSM, men who have sex with men; TGW, transgender women.

Table 2. Effect of Pre-exposure Prophylaxis (PrEP) Versus no PrEP on Sexually Transmitted Infection Diagnoses in Men Who Have Sex with Men

Variable	Number of Studies	Odds Ratio (95% CI)	*P* Value	Heterogeneity $\chi 2$ test (I^2)
Overall	8	1.24 (0.99 – 1.54)	0.059	0.052 (50%)
Comparison				
Control group	2	1.15 (0.88 – 1.49)	0.311	0.430 (0%)
Before PrEP	6	1.27 (0.93 – 1.74)	0.138	0.025 (61%)
Follow-up ≥ 12 months	3	1.45 (0.91 – 2.30)	0.119	0.007 (80%)
Follow-up < 12 months	3	1.08 (0.72 – 1.61)	0.721	0.349 (5%)
Sample size				
<300	4	1.34 (0.73 – 2.44)	0.345	0.055 (61%)
>300	4	1.20 (0.96 – 1.50)	0.116	0.102 (52%)
Date of last follow-up				
Before 2016	4	1.05 (0.86 – 1.27)	0.658	0.452 (0%)
From 2016	4	1.47 (1.05 – 2.05)	0.024	0.128 (47%)
Location				
U.S.	5	1.16 (0.88 – 1.53)	0.297	0.097 (49%)
Non-U.S.	3	1.47 (0.90 – 2.42)	0.128	0.048 (67%)
Outcome assessment				
Infection †				
Syphilis	6	1.12 (0.86 – 1.47)	0.408	0.602 (0%)
Chlamydia †	5	1.23 (1.00 – 1.51)	0.051	0.701 (0%)
Rectal	4	1.59 (1.19 – 2.13)	0.002	0.272 (23%)
Urethral	3	0.96 (0.61 – 1.51)	0.857	0.890 (0%)
Pharyngeal	2	0.93 (0.53 – 1.62)	0.797	0.354 (0%)
Gonorrhea †	5	1.13 (0.78 – 1.64)	0.515	0.004 (74%)
Rectal	4	1.21 (0.78 – 1.88)	0.397	0.174 (40%)
Urethral	3	1.61 (0.45 – 5.78)	0.467	0.030 (72%)
Pharyngeal	3	1.20 (0.88 – 1.64)	0.257	0.327 (11%)
Site †				
Rectal	6	1.39 (1.03 – 1.87)	0.029	0.012 (66%)
Urethral	5	1.11 (0.64 – 1.92)	0.709	0.316 (15%)
Pharyngeal	3	1.13 (0.79 – 1.60)	0.510	0.227 (33%)

†The total number of studies in these subgroup comparisons is greater than the total (n=8) because some studies reported multiple STI outcomes.

Table 3. Summary of Findings for Change in Self-Reported Sexual Behavior and Sexually Transmitted Infections in Men Who Have Sex with Men Using Pre-exposure Prophylaxis

Study	Sexual Behavior	Sexually Transmitted Infections
Beymer et al, 2017 LA LGBT Centre		• Significant within-participant increase in syphilis (p=0.01) and rectal chlamydia (p=0.02) between periods 1 year before and 1 year after initiating PrEP • Significant decrease in STIs overall between same periods (p=0.004) • No significant difference between same periods in urethral gonorrhea (p=0.77), rectal gonorrhea (p=0.63), pharyngeal gonorrhea (p=0.48) or urethral chlamydia (p=0.62)
Colby et al, 2016 PrEP 30	• Non-significant decrease in proportion reporting any CLAI from baseline (54.3%) to 6 months (50%) (p=0.197)	
Corales et al, 2015 Trillium Health	• Decrease in mean number of sexual partners in previous 3 months from baseline (4.1) to 6 months (3.3) *	• Non-significant decrease in proportion reporting any STI in the previous 6 months from baseline (7.4%) to 6 months (3.0%) (p=0.083)
Elsesser et al, 2015 Fenway Health	• Non-significant increase in mean number of CLAI acts in previous 3 months from baseline (13.6) to 6 months (18.6) (p=0.17) • Non-significant increase in proportion of sex acts in previous 3 months which were condomless from baseline (67.4%) to 6 months (69.4%) (p=0.71) • Non-significant increase in total number of sex acts in previous 3 months from baseline (20.3) to 6 months (24.2) (p=0.3)	
Grant et al, 2014 iPrEX OLE	• Significant decrease in proportion reporting CRAI from baseline (34%) to week 72 (25%) in PrEP arm (p=0.006) and from baseline (27%) to week 72 (20%) in non-PrEP arm (p=0.03) • No significant difference between PrEP and non-PrEP arms in the decrease of proportion reporting any CRAI (p=0.95), CIAI (p=0.56) or number of sex partners (p=0.64)	• Non-significantly higher syphilis incidence in PrEP arm (7.2/100 person-years) compared to non-PrEP arm (5.4/100 person-years) (HR=1.35, 95% CI=0.83-2.19)

Gulob et al, 2017 SPARK		• Increase in STI positivity from baseline (11%) to 6 months (21%) followed by decrease to 12 months (13%) * • Increase in rectal STI positivity from baseline (9%) to 6 months (14%) followed by decrease to 12 months (10%) *
Hosek et al, 2017 Project PrEPare 2		• Decrease in incidence of any STI from first 24-week period of follow-up (76.5/100 person-years) to second 24-week period of follow-up (61.0/100 person-years) *
Lal et al, 2017 VicPrEP	• Significant decrease in mean Likert score of condom use with regular partners in the previous 3 months (1-never, 2-sometimes, 3-half the time, 4-most of the time, 5-always) from baseline (2.0) to 12 months (1.5) • Significant decrease in mean Likert score of condom use with casual partners in the previous 3 months from baseline (3.1) to 12 months (2.4)	• Significant increase in STI positivity from baseline (12.3%) to 12 months (29.5%) (P<0.001) • Significant increase in incidence of any STI from baseline-3mths (43.2/100 person years) to 3mth-12mth (119.8/100 person years), IRR = 2.77 (95% CI: 1.52-5.56) • Significant increase between same periods for gonorrhea (IRR=7.19; 95% CI=1.87-61.33), chlamydia (IRR=2.25; 95% CI=1.01-5.92) and rectal STIs (IRR=2.94; 95% CI: 1.41-7.08)
Liu et al, 2016 DEMO Project	• No change in proportion reporting any CRAI from baseline (65.5%) to 48 weeks (65.6%) • Increase in proportion of MSM from San Francisco reporting any CRAI from baseline (71.3%) to 48 weeks (75.7%) * • Increase in mean number CRAI episodes in MSM from San Francisco from baseline (8.4) to 48 weeks (11.0) * • Significant decrease in mean number of anal sex partners in previous 3 months from baseline (10.9) to 48 weeks (9.3) (p=0.04)	• Decrease in STI positivity from baseline (26.4%) to 24 weeks (17.8%) followed by increase at 48 weeks (25.5%) *
Marcus et al, 2016 KPNC		• Significant increase in urethral gonorrhea from baseline (0.9%) to 12 months (2.5%) (p=0.012) • Significant increase in rectal chlamydia from baseline (7.7%) to 12 months (14.1%) (p<0.001) • Non-significant increases between baseline and 12 months in rectal gonorrhea (4.6%-6.9%), pharyngeal gonorrhea (6.2%-8.4%), pharyngeal chlamydia (2.1%-2.3%) and urethral chlamydia (2.8%-2.9%)

		• No change in syphilis from baseline (2.1%) to 12 months (2.1%)
McCormack et al, 2016 PROUD	• Overall trend for increase in number of different CRAI partners from baseline to 12 months • Significantly higher proportion of participants reporting CRAI with more than 10 partners in the immediate arm (21%) than in the delayed arm (12%) (p=0.03) • No difference between immediate and delayed arms in total number of sex partners at 12 months (p=0.57)	• Higher proportion diagnosed with any STI in immediate arm (57%) than in delayed arm (50%) (AOR=1.07; 95% CI: 0.78-1.46) (p=0.74) • Non-significant increase in odds of chlamydia (AOR*=1.27; 95% CI: 0.89-1.80) (p=0.27) and syphilis (AOR*=1.29; 95% CI: 0.79-2.10) (p=0.39) • Non-significant decrease in odds of gonorrhea (AOR†=0.86; 95% CI: 0.62-1.20) (p=0.46) • No difference between arms in rectal infections (AOR†=1.00; 95 CI: 0.72-1.38) (p=0.99)
Milam et al, 2015 CCTG 595	• Non-significant increase in mean number of CRAI acts in previous month from baseline (1.79) to 24 weeks (2.58) (p=0.056) and mean number of CIAI acts in previous month from baseline (2.47) to 24 weeks (2.52) (p=0.058) • Significant increase in mean number of HIV+ partners in previous month from baseline (0.89) to 24 weeks (1.13) (p<0.05)	
Montano et al, 2017 Public Health – Seattle & Kings County	• Significant increase in proportion reporting never using condoms from baseline (10.3%) to 9 months (24.2%) (p=0.005) • Non-significant increase in proportion reporting sex with HIV+ partners from baseline (29.5%) to 9 months (30.6%) (p=0.6)	• Increase in proportion reporting chlamydia infection during the 12 months prior (17%) to 12 months post (37%) PrEP initiation * • Increase in gonorrhea from 12 months prior (24%) to 12 months post (34%) PrEP initiation * • Decrease in syphilis from 12 months prior (19%) to 12 months post (9%) PrEP initiation *
Oldenburg et al, 2017 PrEP Clinic in Rhode Island	• Significant increase in mean number of CLAI partners in the previous 3 months from baseline (2.0) to 6 months (3.3); mean increase = 1.31 (95% CI: 0.09-2.53) (p=0.035) • Increase in CLAI partners was greater in participants reporting <1 partner in previous 3 months at any time point; mean increase = 1.63 (95% CI: -0.19, 3.45) from baseline to 6 months (p=0.078) • Non-significant increase in mean number of sex partners in previous	

	3 months from baseline (4.9) to 6 months (5.7) * • Non-significant increase in mean number of oral sex partners in previous 3 months from baseline (6.4) to 6 months (6.6) *	
Thomas et al, 2016 Clinique médicale l'Actuel	• Increased risk behavior (defined as less condom use, more partners) after 3 months of PrEP use was observed in 25% of participants; 43% reported no change and 32% reported a decrease in risk behavior (p=0.018)	
Volk et al, 2015 KPSF	• Condom use decreased in 41%, was unchanged in 56% and increased in 3% from baseline to 6 months in subset of 188 participants asked about behavior • Number of partners increased in 11%, was unchanged in 74% and decreased in 15% from baseline to 6 months in subset of 188 participants asked about behavior	• Cumulative incidence for any STI after 6 months was 30% (95% CI: 26%–35%). After 12 months cumulative incidence for any STI was 50% (95% CI, 43%–56%)
Zablotska et al, 2017 PRELUDE	• Significant increase in proportion reporting CLAI with HIV-positive/unknown-status casual partners in the past 3 months from baseline (80.0%) to 12 months (91.1%) (p<0.01) • No change in proportion reporting CLAI in previous 3 months	

*P-value not reported †Adjusted for number of screens.

Abbreviations: STI, sexually transmitted infection; CLAI, condomless anal intercourse; CRAI, condomless receptive anal intercourse; CIAI, condomless insertive anal intercourse; IRR, incidence rate ratio; HR, hazard ratio; AOR, adjusted odds ratio; MSM, men who have sex with men; CI, confidence interval.

FIGURE LEGENDS

Figure 1. Schematic diagram of search results and screening process.

Figure 2. Random effects meta-analysis of effects of pre-exposure prophylaxis on sexually transmitted infection diagnosis. Abbreviations: CI, confidence interval; STI, sexually transmitted infection.

Figure 1.

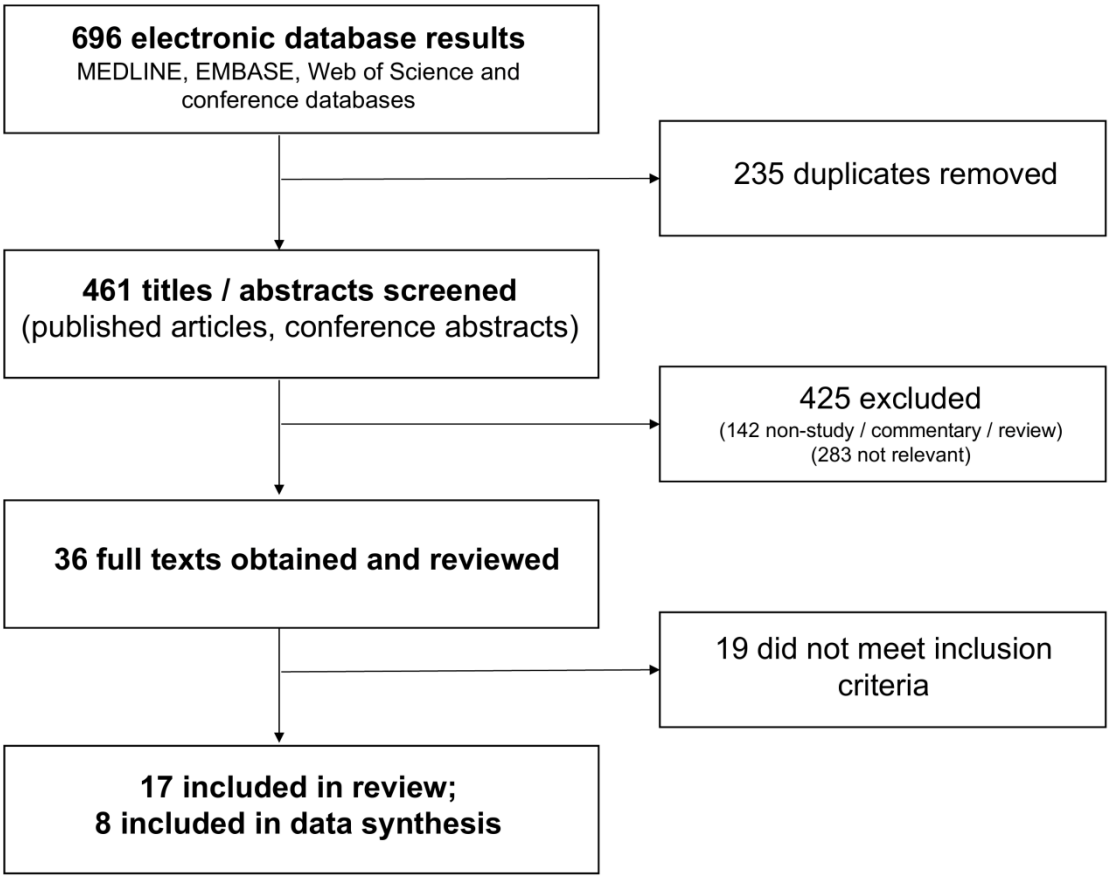

Figure 2.