Clinical Infectious Diseases

MAJOR ARTICLE

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

Michael W. Traeger,[1,2] Sophia E. Schroeder,[1,3] Edwina J. Wright,[1,4,5,6] Margaret E. Hellard,[1,4,5] Vincent J. Cornelisse,[5,7,8] Joseph S. Doyle,[1,5,a] and Mark A. Stoové[1,4,a]

[1]Disease Elimination Program, Public Health Discipline, Burnet Institute, and [2]School of Population and Global Health, The University of Melbourne, Victoria, Australia; [3]Department of Clinical Sciences, Lund University, Malmö, Sweden; and [4]School of Public Health and Preventive Medicine, Monash University, [5]Department of Infectious Diseases, The Alfred and Monash University, [6]Peter Doherty Institute of Infection and Immunity, University of Melbourne, and [7]Central Clinical School, Monash University, Melbourne, and [8]Melbourne Sexual Health Centre, Carlton, Victoria, Australia

Background. Human immunodeficiency virus (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 studies published to August 2017 that reported sexual risk outcomes 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 1 open-label trial met selection criteria. Eight studies with a total of 4388 participants reported STI prevalence, and 13 studies with a total of 5008 participants reported change in condom use. Pre-exposure prophylaxis use was associated with a significant increase in rectal chlamydia (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.19–2.13) and an increase in any STI diagnosis (OR, 1.24; 95% CI, .99–1.54). 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.

Ambitious human immunodeficiency virus (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, as well as 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 counseling, 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 3 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 regulatory approval of the use of TDF/FTC for PrEP in countries such as the United States, Australia, and the United Kingdom [10, 11], with the focus of research now shifting toward PrEP demonstration projects. There are >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

Received 21 November 2017; editorial decision 15 February 2018; accepted 28 February 2018; published online March 2, 2018.

[a]J. S. D. and M. A. S. contributed equally to this work.

Correspondence: M. W. Traeger, Burnet Institute, 85 Commercial Rd, Melbourne, Victoria 3004, Australia (michael.traeger@burnet.edu.au).

Clinical Infectious Diseases® 2018;67(5):676–86

DOI: 10.1093/cid/ciy182

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 toward more risky sexual behaviors—"risk compensation" [14]. Men who have sex with men 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 and serodiscordant sex in the context of HIV treatment-derived viral suppression (treatment as prevention); however, no evidence for increased risk-taking behavior was found [16, 17].

Although 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 because 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, and nonblinded randomized controlled trials (RCTs); blinded studies were excluded to ensure measured outcomes were the result of the effects of perceived HIV protection offered by PrEP. Outcomes were compared over time between participants taking PrEP and participants not taking PrEP or changes were analyzed longitudinally in PrEP users. The following 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 the following (see Appendix 1 for full search strings):

1. HIV;
2. MSM (men who have sex with men, gay and bisexual 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, 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, were searched manually. Results were collated and titles and abstracts screened independently by 2 reviewers for relevance against the predefined eligibility criteria. For studies that reported at least 1 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 nonrandomized trials and observational studies. We assessed the methodological quality according to participant selection and control of confounding, and we assessed publication bias by constructing a funnel plot [22].

Data Extraction

Data were extracted and assessed independently by 2 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 (ORs) with 95% confidence intervals (CIs) 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 among 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 among 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 among subgroups. A 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 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 8 journal articles and 9 conference proceedings: 1 study was an RCT where participants were randomized to immediate or delayed PrEP; 1 was a nonrandomized 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, and all but 2 studies were undertaken in high-income countries. A total of 6671 (median, 268; range, 50–1603) participants were included, and length of follow-up ranged 3–18 months (median, 6 months). Age distribution was similar across studies, with a mean age of 34 years (range, 18–70 years). Although there was a possible sample overlap of 2 studies [34, 40], these studies reported different outcomes, which allowed both to be included in the qualitative review, but only 1 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 nonintervention group (see Supplementary Table 1 for list of excluded studies).

Sexually Transmitted Infections

Eight studies that included a total of 4388 participants reported STI positivity at baseline and follow-up visits and were included in the meta-analysis. The pooled odds ratio for any STI diagnosis was 1.24 (95% CI, .99–1.54; $P = .059$) (Figure 2). Statistical heterogeneity across studies was moderate ($I^2 = 50\%$; $\chi 2$, $P = .052$). Pre-exposure prophylaxis use was associated with significantly increased odds of any rectal STI diagnosis (OR, 1.39; 95% CI, 1.03–1.87; $P = .03$) and rectal chlamydia diagnosis (OR, 1.59; 95% CI, 1.19–2.13; $P = .002$). Pre-exposure prophylaxis use was also associated with statistically nonsignificant increases in syphilis (OR, 1.12; 95% CI, .86–1.47; $P = .41$), chlamydia (OR, 1.23; 95% CI, 1.00–1.51; $P = .051$), and gonorrhea (OR, 1.13; 95% CI, .78–1.64; $P = .515$) 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 onward giving a pooled odds ratio of 1.47 (95% CI, 1.05–2.05; $P = .02$) for any STI diagnosis. Heterogeneity remained moderate ($I^2 = 47\%$) for these

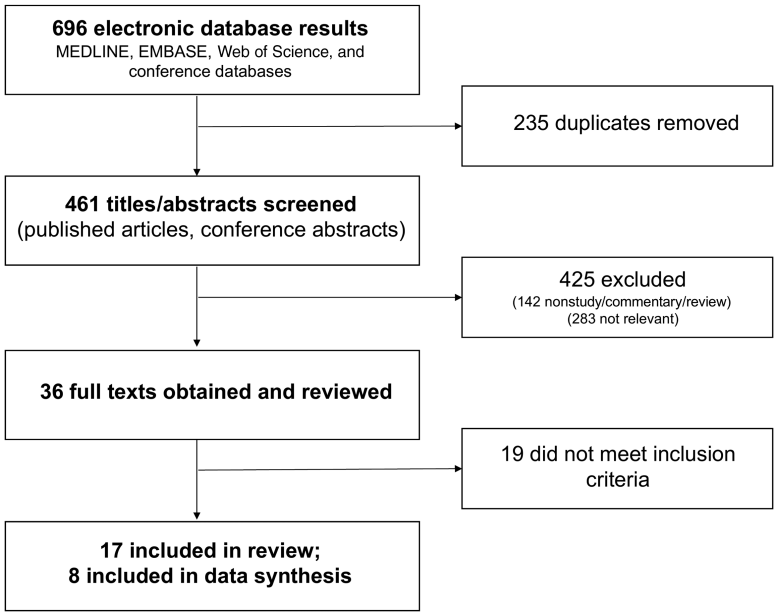

Figure 1. Schematic diagram of search results and screening process.

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 1 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 partners [35], condomless sex with an HIV-positive or HIV-unknown partner [36, 41], and never using condoms during anal sex [37]. Only 1 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 counseling 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 a US cohort from baseline to 6 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 1 year of follow-up among cohort participants [32]. Two studies reported decreased condom use among 25%–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 6 months [40]. No studies reported a difference in outcomes for TGW compared with MSM.

Quality Assessment

Levels of bias were classified as moderate across studies (see Supplementary Tables 2 and 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 because sexual behavior outcomes relied on self-reporting. Participant retention was mixed but relatively high overall; 13 of 17 studies had retention >75% (retention >90% in 8 studies) at final follow-up. The 1 RCT adjusted for disproportionate frequency of STI screening between groups [35]. A funnel plot indicated no evidence of publication bias (Supplementary Figure 2).

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, USA	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][a]	Kaiser Permanente North California	Prospective cohort	Before PrEP	July 2012	USA	972	98% Male
McCormack et al 2016 [35]	PROUD	Immediate vs delayed RCT	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 and 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][a]	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

Abbreviations: MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; RCT, randomized controlled trial; TGW, transgender women.

[a]Studies may contain overlapping cohorts.

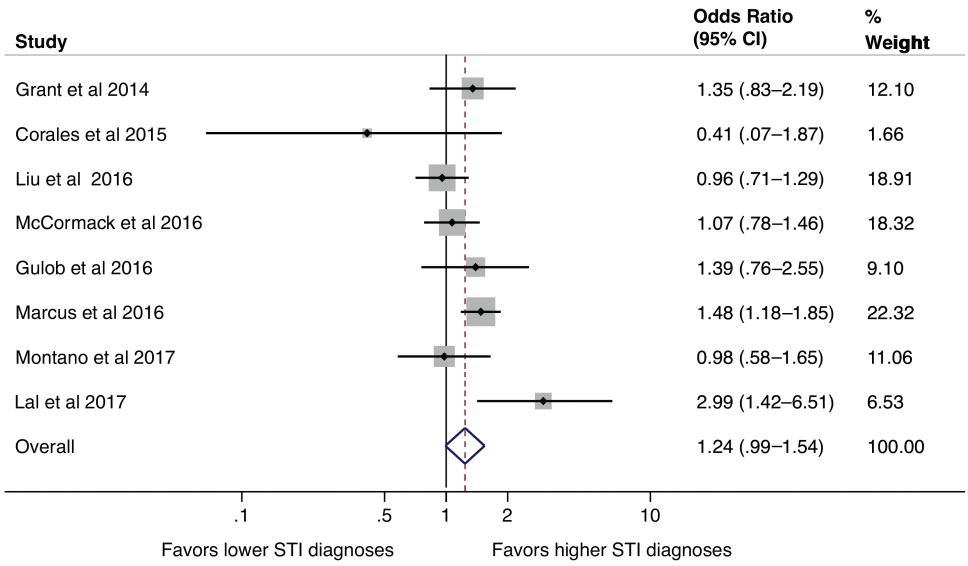

Figure 2. Random effects meta-analysis of effects of pre-exposure prophylaxis on sexually transmitted infection diagnosis. Abbreviations: CI, confidence interval; STI, sexually transmitted infection.

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

Variable	No. of Studies	Odds Ratio (95% CI)	*P* Value	Heterogeneity χ^2 test (I^2)
Overall	8	1.24 (.99–1.54)	.06	0.052 (50%)
Comparison				
Control group	2	1.15 (.88–1.49)	.31	0.430 (0%)
Before PrEP	6	1.27 (.93–1.74)	.14	0.025 (61%)
Follow-up ≥ 12 mo	3	1.45 (.91–2.30)	.12	0.007 (80%)
Follow-up < 12 mo	3	1.08 (.72–1.61)	.72	0.349 (5%)
Sample size				
<300	4	1.34 (.73–2.44)	.35	0.055 (61%)
>300	4	1.20 (.96–1.50)	.12	0.102 (52%)
Date of last follow-up				
Before 2016	4	1.05 (.86–1.27)	.66	0.452 (0%)
From 2016	4	1.47 (1.05–2.05)	.02	0.128 (47%)
Location				
US	5	1.16 (.88–1.53)	.30	0.097 (49%)
Non-US	3	1.47 (.90–2.42)	.13	0.048 (67%)
Outcome assessment				
Infection[a]				
Syphilis	6	1.12 (.86–1.47)	.41	0.602 (0%)
Chlamydia[a]	5	1.23 (1.00–1.51)	.051	0.701 (0%)
Rectal	4	1.59 (1.19–2.13)	.002	0.272 (23%)
Urethral	3	0.96 (.61–1.51)	.86	0.890 (0%)
Pharyngeal	2	0.93 (.53–1.62)	.80	0.354 (0%)
Gonorrhea[a]	5	1.13 (.78–1.64)	.52	0.004 (74%)
Rectal	4	1.21 (.78–1.88)	.40	0.174 (40%)
Urethral	3	1.61 (.45–5.78)	.47	0.030 (72%)
Pharyngeal	3	1.20 (.88–1.64)	.26	0.327 (11%)
Site[a]				
Rectal	6	1.39 (1.03–1.87)	.03	0.012 (66%)
Urethral	5	1.11 (.64–1.92)	.71	0.316 (15%)
Pharyngeal	3	1.13 (.79–1.60)	.51	0.227 (33%)

Abbreviations: CI, confidence interval; PrEP, pre-exposure prophylaxis.

[a]The total number of studies in these subgroup comparisons is greater than the total (n = 8) because some studies reported multiple sexually transmitted infection 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	Project/Clinic	Sexual Behavior	Sexually Transmitted Infections
Beymer et al 2017 [25]	LA LGBT Centre	…	• Significant within-participant increase in syphilis ($P = .01$) and rectal chlamydia ($P = .02$) between periods 1 year before and 1 year after initiating PrEP • Significant decrease in STIs overall between same periods ($P = .004$) • No significant difference between same periods in urethral gonorrhea ($P = .77$), rectal gonorrhea ($P = .63$), pharyngeal gonorrhea ($P = .48$), or urethral chlamydia ($P = .62$)
Colby et al 2016 [26]	PrEP 30	• Nonsignificant decrease in proportion reporting any CLAI from baseline (54.3%) to 6 months (50%) ($P = .20$)	…
Corales et al 2015 [27]	Trillium Health	• Decrease in mean number of sexual partners in previous 3 months from baseline (4.1) to 6 months (3.3)[a]	• Nonsignificant decrease in proportion reporting any STI in the previous 6 months from baseline (7.4%) to 6 months (3.0%) ($P = .08$)
Elsesser et al 2015 [28]	Fenway Health	• Nonsignificant increase in mean number of CLAI acts in previous 3 months from baseline (13.6) to 6 months (18.6) ($P = .17$) • Nonsignificant increase in proportion of sex acts in previous 3 months which were condomless from baseline (67.4%) to 6 months (69.4%) ($P = .71$) • Nonsignificant increase in total number of sex acts in previous 3 months from baseline (20.3) to 6 months (24.2) ($P = .30$)	…
Grant et al 2014 [29]	iPrEX OLE	• Significant decrease in proportion reporting CRAI from baseline (34%) to week 72 (25%) in PrEP arm ($P = .006$) and from baseline (27%) to week 72 (20%) in non-PrEP arm ($P = .03$) • No significant difference between PrEP and non-PrEP arms in the decrease of proportion reporting any CRAI ($P = .95$), CIAI ($P = .56$), or number of sex partners ($P = .64$)	• Nonsignificantly higher syphilis incidence in PrEP arm (7.2/100 person-years) compared with non-PrEP arm (5.4/100 person-years) (HR, 1.35, 95% CI, .83–2.19)
Gulob et al 2016 [30]	SPARK	…	• Increase in STI positivity from baseline (11%) to 6 months (21%) followed by decrease to 12 months (13%)[a] • Increase in rectal STI positivity from baseline (9%) to 6 months (14%) followed by decrease to 12 months (10%)[a]
Hosek et al 2017 [31]	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)[a]
Lal et al 2017 [32]	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%) ($P < .001$) • Significant increase in incidence of any STI from baseline–3 mo (43.2/100 person years) to 3–12 mo (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 [33]	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%)[a] • Increase in mean number CRAI episodes in MSM from San Francisco from baseline (8.4) to 48 weeks (11.0)[a] • Significant decrease in mean number of anal sex partners in previous 3 months from baseline (10.9) to 48 weeks (9.3) ($P = .04$)	• Decrease in STI positivity from baseline (26.4%) to 24 weeks (17.8%) followed by increase at 48 weeks (25.5%)[a]
Marcus et al 2016 [34]	Kaiser Permanente North California	…	• Significant increase in urethral gonorrhea from baseline (0.9%) to 12 months (2.5%) ($P = .012$) • Significant increase in rectal chlamydia from baseline (7.7%) to 12 months (14.1%) ($P < .001$) • Nonsignificant 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%)

Table 3. Continued

Study	Project/Clinic	Sexual Behavior	Sexually Transmitted Infections
McCormack et al 2016 [35]	PROUD	• Overall trend for increase in number of different CRAI partners from baseline to 12 months • Significantly higher proportion of participants reporting CRAI with >10 partners in the immediate arm (21%) than in the delayed arm (12%) ($P = .03$) • No difference between immediate and delayed arms in total number of sex partners at 12 months ($P = .57$)	• Higher proportion diagnosed with any STI in immediate arm (57%) than in delayed arm (50%) (AOR, 1.07; 95% CI, .78–1.46) ($P = .74$) • Nonsignificant increase in odds of chlamydia (AOR,[a] 1.27; 95% CI, .89–1.80; $P = .27$) and syphilis (AOR,[a] 1.29; 95% CI, .79–2.10; $P = .39$) • Nonsignificant decrease in odds of gonorrhea (AOR,[b] 0.86; 95% CI, .62–1.20; $P = .46$) • No difference between arms in rectal infections (AOR,[b] 1.00; 95 CI, .72–1.38; $P = .99$)
Milam et al 2015 [36]	CCTG 595	• Nonsignificant increase in mean number of CRAI acts in previous month from baseline (1.79) to 24 weeks (2.58) ($P = .06$) and mean number of CIAI acts in previous month from baseline (2.47) to 24 weeks (2.52) ($P = .06$) • Significant increase in mean number of HIV-positive partners in previous month from baseline (0.89) to 24 weeks (1.13) ($P < .05$)	…
Montano et al 2017 [37]	Public Health – Seattle and King County	• Significant increase in proportion reporting never using condoms from baseline (10.3%) to 9 months (24.2%) ($P = .005$) • Nonsignificant increase in proportion reporting sex with HIV-positive partners from baseline (29.5%) to 9 months (30.6%) ($P = .60$)	• Increase in proportion reporting chlamydia infection during the 12 months prior (17%) to 12 months after (37%) PrEP initiation[a] • Increase in gonorrhea from 12 months prior (24%) to 12 months after (34%) PrEP initiation[a] • Decrease in syphilis from 12 months prior (19%) to 12 months after (9%) PrEP initiation[a]
Oldenburg et al 2017 [38]	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, .09–2.53; $P = .035$) • Increase in CLAI partners was greater in participants reporting <1 partner in previous 3 months at any time point; mean increase of 1.63 (95% CI: −.19, 3.45) from baseline to 6 months ($P = .08$) • Nonsignificant increase in mean number of sex partners in previous 3 months from baseline (4.9) to 6 months (5.7)[a] • Nonsignificant increase in mean number of oral sex partners in previous 3 months from baseline (6.4) to 6 months (6.6)[a]	…
Thomas et al 2016 [39]	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 ($P = .02$)	…
Volk et al 2015 [40]	Kaiser Permanente San Francisco	• 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 [41]	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%) ($P < .01$) • No change in proportion reporting CLAI in previous 3 months	…

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval; CIAI, condomless insertive anal intercourse; CLAI, condomless anal intercourse; CRAI, condomless receptive anal intercourse; HIV, human immunodeficiency virus; HR, hazard ratio; IRR, incidence rate ratio; MSM, men who have sex with men; PrEP, pre-exposure prophylaxis; STI, sexually transmitted infection.

[a] *P* value not reported

[b] Adjusted for number of screens.

DISCUSSION

In this review of 17 open-label studies, use of pre-exposure prophylaxis was associated with increased diagnoses of STIs in MSM. 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 toward 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 United States [43], and knowledge of and willingness to use PrEP among MSM has increased over the past 5 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 among 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 enrollment 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 among 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 11.2–44.6 times more likely to be diagnosed with an STI versus MSM enrolled in cohort studies without PrEP [47]. Greater effect sizes in this meta-analysis reflect methodological differences, such as comparing STI incidence among 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 with MSM who do not. This is consistent with early experiences of PrEP programs in the United States, 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 [48, 49].

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. Because 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.

Although 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. Second, the lack of individual-level and demographic data limited our understanding of the individual circumstances in which sexual behavior changed due to PrEP use. Third, because of differences in outcome measures of STIs (ie, prevalence vs incidence), we were unable to include some studies in the data synthesis. In such cases, we made efforts to contact authors; however, we were unable to obtain additional data for all studies. Fourth, studies in this review involved PrEP protocols that included safe-sex counseling 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.

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 because 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 PrEP and post-exposure prophylaxis [50] and the use of antiseptics [51, 52]. Pre-exposure prophylaxis 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.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Financial support. Burnet Institute acknowledges support from the Victorian Government Operational Infrastructure Fund. E. J. W., M. E. H., J. S. D., and M. A. S. acknowledge fellowship support from the National Health and Medical Research Council. V. J. C. receives a stipend from the Research Training Program of the Australian Government's Department of Education and Training.

Potential conflicts of interest. E. J. W., M. E. H., J. S. D., and M. A. S. declare research funding to their institute from Gilead Sciences. J. S. D. and M. E. H. declare research funding to their institute from Merck, AbbVie, and Bristol Myers Squibb. E. J. W. has received funding for consultancy and educational resources from ViiV and Merck and research funding from Gilead Sciences, Abbott, Janssen Cilag, and Boehringer Ingelheim. J. S. D. has received honoraria from Gilead Sciences, Bristol Myers Squibb, and Merck. V. J. C. 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 of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. UNAIDS. 90-90-90: An ambitious treatment target to help end the AIDS epidemic. Geneva, Switzerland: Joint United Nations Programme on HIV/AIDS, **2014**.
2. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: why individual, structural, and combination approaches are needed. Lancet **2010**; 376:285–301.
3. Malekinejad M, Parriott A, Blodgett JC, et al. Effectiveness of community-based condom distribution interventions to prevent HIV in the United States: a systematic review and meta-analysis. PLoS One **2017**; 12:e0180718.
4. Grant RM, Lama JR, Anderson PL, et al.; iPrEx Study Team. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. N Engl J Med **2010**; 363:2587–99.
5. Molina JM, Capitant C, Spire B, et al; ANRS IPERGAY Study Group. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. N Engl J Med **2015**; 373:2237–46.
6. Baeten JM, Donnell D, Ndase P, et al; Partners PrEP Study Team. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. N Engl J Med **2012**; 367:399–410.
7. Choopanya K, Martin M, Suntharasamai P, et al; Bangkok Tenofovir Study Group. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet **2013**; 381:2083–90.
8. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva, Switzerland: World Health Organization, **2015**.
9. UNAIDS. Maximizing the potential of a new HIV prevention method: PrEP. Available at: http://www.unaids.org/en/resources/presscentre/featurestories/2016/november/20161101_PrEP. Accessed 7 June 2017.
10. Wright E, Grulich A, Roy K, et al. Australasian society for HIV, viral hepatitis and sexual health medicine HIV pre-exposure prophylaxis: clinical guidelines. J Virus Erad **2017**; 3:168–84.
11. Centers for Disease Control and Prevention. Preexposure prophylaxis for the prevention of HIV infection in the United States—2014: a clinical practice guideline. Atlanta, Georgia: US Public Health Service, **2014**.
12. AIDS Vaccine Advocacy Coalition. Ongoing and planned PrEP demonstration and implementation studies. Available at: https://www.avac.org/resource/ongoing-and-planned-prep-demonstration-and-implementation-studies. Accessed 7 June 2017.
13. World Health Organization. PrEP demonstration projects: a framework for country level protocol development. Geneva, Switzerland: World Health Organization, **2013**.
14. Blumenthal J, Haubrich R. Risk compensation in PrEP: an old debate emerges yet again. Virtual Mentor **2014**; 16:909–15.
15. Holt M, Murphy DA. Individual versus community-level risk compensation following preexposure prophylaxis of HIV. Am J Public Health **2017**; 107:1568–71.
16. Martin JN, Roland ME, Neilands TB, et al. Use of postexposure prophylaxis against HIV infection following sexual exposure does not lead to increases in high-risk behavior. AIDS **2004**; 18:787–92.
17. Doyle JS, Degenhardt L, Pedrana AE, et al. Effects of HIV antiretroviral therapy on sexual and injecting risk-taking behavior: a systematic review and meta-analysis. Clin Infect Dis **2014**; 59:1483–94.
18. Fonner VA, Dalglish SL, Kennedy CE, et al. Effectiveness and safety of oral HIV preexposure prophylaxis for all populations. AIDS **2016**; 30:1973–83.
19. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med **2009**; 6:e1000100.
20. Higgins JP, Altman DG, Gøtzsche PC, et al; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ **2011**; 343:d5928.
21. Reeves BC, Deeks JJ, Higgins JPT, Wells GA. Chapter 13: Including non-randomized studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, **2011**. Available at: http://handbook-5-1.cochrane.org/chapter_13/13_including_non_randomized_studies.htm. Accessed 1 June 2017.
22. Stern JM, Simes RJ. Publication bias: evidence of delayed publication in a cohort study of clinical research projects. BMJ **1997**; 315:640–5.
23. Van den Noortgate W, López-López JA, Marín-Martínez F, Sánchez-Meca J. Meta-analysis of multiple outcomes: a multilevel approach. Behav Res Methods **2015**; 47:1274–94.
24. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ **2003**; 327:557–60.
25. Beymer M, Weiss R, Devost M, Flynn R, Bolan R, Landovitz R. Does pre-exposure prophylaxis use lead to a higher incidence of sexually transmitted infections? A case-crossover study of men who have sex with men in Los Angeles, California. In: Program and abstracts of the 9th IAS Conference on HIV Science, Paris, France, **2017**.
26. Colby D, Kongkabpan M, Teeratakulpisarn S, **et al**. Safety and efficacy of tenofovir disoproxil fumarate plus emtricitabine for HIV pre- exposure prophylaxis in Thailand. In: Program and abstracts of the Asia Pacific Conference on AIDS and Co-infections, Hong Kong, **2016**.
27. Corales R, Holt S, Chen SR, et al. PrEP in the real world: implementation of PrEP in a medium-sized city Community Health Clinic. In: Prgoram and abstracts of the 8th IAS Conference on HIV Pathogenesis Treatment and Prevention, Vancouver, Canada, **2015**.
28. Elsesser SA, Biello KB, Taylor SW, Tomassilli JC, Safren SA, Mayer KH. Absence of sexual behavioral disinhibition in a PrEP adherence trial: considerations for medical providers who prescribe PrEP for men who have sex with men (MSM). In: Program and abstracts of the 8th IAS Conference on HIV Pathogenesis Treatment and Prevention, Vancouver, Canada, **2015**.

29. Grant RM, Anderson PL, McMahan V, et al; iPrEx study team. Uptake of pre-exposure prophylaxis, sexual practices, and HIV incidence in men and transgender women who have sex with men: a cohort study. Lancet Infect Dis **2014**; 14:820–9.
30. Gulob SA, Pena S, Boonrai K, Douglas N, Hunt M. STI data from community-based PrEP implementation suggest changes to CDC guidelines. In: Program and abstracts of the Conference on Retroviruses and Opportunistic Infections (CROI), Boston, Massachusetts, **2016**.
31. Hosek SG, Rudy B, Landovitz R, et al; Adolescent Trials Network (ATN) for HIVAIDS Interventions. An HIV preexposure prophylaxis demonstration project and safety study for young MSM. J Acquir Immune Defic Syndr **2017**; 74:21–9.
32. Lal L, Audsley J, Murphy DA, et al; VicPrEP Study Team. Medication adherence, condom use and sexually transmitted infections in Australian preexposure prophylaxis users. AIDS **2017**; 31:1709–14.
33. Liu AY, Cohen SE, Vittinghoff E, et al. Preexposure prophylaxis for HIV infection integrated with municipal- and community-based sexual health services. JAMA Intern Med **2016**; 176:75–84.
34. Marcus JL, Hurley LB, Hare CB, et al. Preexposure prophylaxis for HIV prevention in a large integrated health care system: adherence, renal safety, and discontinuation. J Acquir Immune Defic Syndr **2016**; 73:540–6.
35. McCormack S, Dunn DT, Desai M, et al. Pre-exposure prophylaxis to prevent the acquisition of HIV-1 infection (PROUD): effectiveness results from the pilot phase of a pragmatic open-label randomised trial. Lancet **2016**; 387:53–60.
36. Milam J, Jain S, Moore D, et al. Risk compensation among men who have sex with men (MSM) in Southern California following the initiation of pre-exposure prophylaxis (PrEP). In: Program and abstracts of the 8th IAS Conference on HIV Pathogenesis Treatment and Prevention, Vancouver, Canada, **2015**.
37. Montano MA, Dombrowski JC, Barbee LA, Golden MR, Khosropour CM. Changes in sexual behavior and sti diagnoses among msm using Prep in Seattle, WA. In: Program and abstracts of the Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, Washington, **2017**.
38. Oldenburg CE, Nunn AS, Montgomery M, et al. Behavioral changes following uptake of HIV pre-exposure prophylaxis among men who have sex with men in a clinical setting. AIDS Behav **2017**. doi: 10.1007/s10461-017-1701-1.
39. Thomas R, Galanakis C, Vezina S, et al. PrEP in Montreal: Good adherence, no seroconversion and no evidence of risk compensation. J Sex Med **2016**; 13:S165.
40. Volk JE, Marcus JL, Phengrasamy T, et al. No New HIV infections with increasing use of HIV preexposure prophylaxis in a clinical practice setting. Clin Infect Dis **2015**; 61:1601–3.
41. Zablotska I, Vaccher S, Bloch M, et al. No HIV infections despite high-risk behaviour and STI incidence among gay/bisexual men taking daily pre-exposure prophylaxis (PrEP): the PRELUDE demonstration project. In: Program and abstracts of the 9th IAS Conference on HIV Science, Paris, France, **2017**.
42. Liu A, Cohen S, Follansbee S, et al. Early experiences implementing pre-exposure prophylaxis (PrEP) for HIV prevention in San Francisco. PLoS Med **2014**; 11:e1001613.
43. Mera R, Magnuson D, Trevor H, Bush S, Rawlings K, McCallister S. Changes in truvada (TVD) for HIV pre-exposure prophylaxis (PrEP) utilization in the United States: (2012–2016). In: Program and abstracts of the 9th IAS Conference on HIV Science, Paris, France, **2017**.
44. Voetsch AC, Heffelfinger JD, Begley EB, Jafa-Bhushan K, Sullivan PS. Knowledge and use of preexposure and postexposure prophylaxis among attendees of minority gay pride events, 2005 through 2006. J Acquir Immune Defic Syndr **2007**; 46:378–80.
45. Frankis J, Young I, Flowers P, McDaid L. Who will use pre-exposure prophylaxis (PrEP) and why? Understanding PrEP awareness and acceptability amongst men who have sex with men in the UK—a mixed methods study. PLoS One **2016**; 11:e0151385.
46. Lockwood J, Asselin J, Mak A, et al. Health systems and study design features permitting rapid enrolment of individuals at high-risk of HIV acquisition into a pre-exposure prophylaxis study in Melbourne, Victoria, Australia. In: Program and abstracts of the 9th IAS Conference on HIV Science, Paris, France, **2017**.
47. Kojima N, Davey DJ, Klausner JD. Pre-exposure prophylaxis for HIV infection and new sexually transmitted infections among men who have sex with men. AIDS **2016**; 30:2251–2.
48. Chan PA, Glynn TR, Oldenburg CE, et al. Implementation of preexposure prophylaxis for human immunodeficiency virus prevention among men who have sex with men at a new england sexually transmitted diseases clinic. Sex Transm Dis **2016**; 43:717–23.
49. Cohen SE, Vittinghoff E, Bacon O, et al. High interest in preexposure prophylaxis among men who have sex with men at risk for HIV infection: baseline data from the US PrEP demonstration project. J Acquir Immune Defic Syndr **2015**; 68:439–48.
50. Molina JM, Charreau I, Chidiac C, et al. On demand post exposure prophylaxis with doxycycline for MSM enrolled in a PrEP trial. In: Program and abstracts of the Conference on Retroviruses and Opportunistic Infections (CROI), Seattle, US, **2017**.
51. Fairley CK, Hocking JS, Zhang L, Chow EP. Frequent transmission of gonorrhea in men who have sex with men. Emerg Infect Dis **2017**; 23:102–4.
52. Chow EPF, Walker S, Hocking JS, et al. A multicentre double-blind randomised controlled trial evaluating the efficacy of daily use of antibacterial mouthwash against oropharyngeal gonorrhoea among men who have sex with men: the OMEGA (Oral Mouthwash use to Eradicate GonorrhoeA) study protocol. BMC Infect Dis **2017**; 17:456.