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Reviewing PrEP's Effect on STI Incidence Among Men Who Have sex with Men—Balancing Increased STI Screening and Potential Behavioral Sexual Risk Compensation

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Abstract

Though pre-exposure prophylaxis (PrEP) can prevent HIV acquisition, it provides no protection against bacterial sexually transmitted infections (STIs). PrEP use may increase STI acquisition due to sexual risk compensation, but that could be counterbalanced by increased STI screening at regular PrEP visits. We conducted a literature search of studies with quantitative data published prior to March 2020, assessing sexual risk compensation or STI screening among men who have sex with men (MSM) before and after PrEP initiation. We identified 16 relevant publications. Changes in condom use were inconsistent across studies. Partner acquisition following PrEP initiation decreased in most studies, likely due to behavioral counseling. In publications comparing a PrEP arm to a non-PrEP arm, serodiscordance increased in the PrEP arm and decreased in the non-PrEP arm. STI screening among MSM was low within a month of PrEP initiation. Monitoring trends in sexual risk compensation and STI screening will be critical to understand PrEP's effects on STI burden.

Keywords

Sexually transmitted infections; PrEP; HIV; Men who have sex with men; Sexual risk compensation; STI screening

Introduction

Among the 37,832 persons who were newly diagnosed with HIV in the United States (U.S.) during 2018, 66% acquired HIV through male-to-male sexual contact, despite men who have

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sex with men (MSM) constituting less than 5% of the total U.S. population [1–3]. To combat HIV, particularly among MSM, the U.S. Food and Drug Administration approved tenofovir and emtricitabine for HIV pre-exposure prophylaxis (PrEP) in 2012, and in 2014, the Centers for Disease Control and Prevention (CDC) recommended PrEP for HIV prevention in MSM and other groups at risk for HIV acquisition [4, 5]. When taken daily, PrEP can reduce HIV acquisition by over 90% [4–7]. Though PrEP use has steadily increased, PrEP initiation among MSM remains low, with 35% of those eligible on PrEP in 2017 [8]. CDC recommends PrEP for MSM if they engaged in one or more of the following behaviors in the past six months: (1) a high number of male sexual partners, (2) anal sex with a man without a condom, (3) a bacterial sexually transmitted infection (STI), (4) a HIV-positive sexual partner, or (5) see themselves engaging in these behaviors in the future [5]. While PrEP protects against acquiring HIV, it does not protect against acquiring or transmitting other STIs [4, 5].

MSM on PrEP may change their sexual behaviors due to their perceived protection against HIV [9, 10]. Adjusting one's behaviors due to perceived protections, also known as risk compensation, is a general phenomenon not unique to sexual infection transmission: seatbelt use in rural areas has been lower than in urban areas due to fewer cars on the road; snowboarders have performed riskier maneuvers when using helmets [11, 12]. Individual level sexual risk compensation can take multiple forms. People may (1) use condoms less frequently, (2) acquire new sex partners more rapidly, (3) have sex more frequently, (4) shift from lower risk to higher risk types of sex (e.g. shifting from oral sex to anal sex) (5) shift from lower risk to higher risk sexual positions (e.g. shifting from insertive anal sex to receptive anal sex), (6) shift from lower risk to higher risk partners (e.g., shifting from seroconcordant partners to serodiscordant partners), or (7) some combination of these. Before PrEP was available, previous literature reviews documented how other HIV prevention strategies affected sexual risk compensation; they found decreased condom use and increased partner number after HIV prevention technologies such as highly active antiretroviral therapy (HAART), antiretroviral therapy (ART), topical microbicide, circumcision, or candidate vaccine were implemented [9, 10]. Risk compensation among PrEP users was a concern among two previous reviews; Hoornenborg et al. reported decreased risk compensation among PrEP clinical trials, where risk compensation may not have occurred as PrEP efficacy was not established [13]. A more recent review, by Traeger et al., conducted a qualitative assessment of behavioral changes, and reported evidence of increased condomless anal sex after PrEP initiation [14].

Sexual risk compensation after PrEP initiation could affect STI incidence, as HIV and STI acquisition transmission paths overlap [15, 16]. Additionally, at the population level, both HIV and STIs are influenced by similar network effects, since both can use sexual networks for diffusion [17]. Thus, when sexual risk compensation occurs after PrEP initiation, STI incidence may increase [13].

However, because PrEP users have regular medical check-ups with HIV testing every 3 months to receive a prescription, there is an opportunity for increased STI screening to act as a counterweight against potential sexual risk compensation. PrEP guidelines recommend STI screening every 6 months for MSM, and every 3 months for MSM reporting recurrent

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STIs [5, 16]. Increased STI screening can shorten the duration of asymptomatic infections, potentially resulting in decreased population levels of infection [16]. MSM STI screening rates were relatively low before 2010. Analysis of the National Survey of Family Growth estimated that 38.7% of sexually active MSM reported STI testing for any bacterial STI within the past 12 months between 2006 and 2010 [18]. Similar levels of syphilis testing in the past 12 months (38.0%) were found in 2008 from the National HIV Behavioral Surveillance (NHBS) [19]. Studies since then indicate STI screening may have increased in MSM. Two studies found increases in chlamydia testing (from 37.2% to 46.7%) [20], gonorrhea testing (from 38.0% to 47.3%) [20], and syphilis testing (from 40.0% to 49.0%) [19] between 2011 and 2014. However, these studies did not take PrEP status or frequency of testing into account, as there was no official CDC PrEP recommendation at the time of data collection [5]. It is unlikely that PrEP use would have had an impact on STI screening rates during the time these data were collected.

In this study, we reviewed literature assessing individual level sexual risk compensation after PrEP initiation and how rates of STI screening are affected by PrEP initiation in MSM. For each form of risk compensation, we generated measures of association and compared these measures across studies. This allowed us to describe how STI incidence in MSM might be affected by increased PrEP access and utilization and identify gaps in the literature related to PrEP's potential effects on STIs.

Methods

We conducted a search for literature examining either (1) risk compensation or (2) STI screening before and after PrEP initiation. We searched PubMed for publications that measured PrEP's effects on individual level sexual risk compensation or STI screening rates using specified search strings; we did not include conference abstracts or grey literature in our search (Fig. 1). We temporally limited this search to manuscripts published before March 1, 2020. We also required the study populations to be HIV-negative MSM on a daily regimen of PrEP. Publications examining risk compensation needed to report on participant behavior before and after PrEP initiation to be eligible for inclusion. Publications were not eligible if they only examined perceptions or acceptability of PrEP.

From the full set of publications identified by search strings, we first scanned the title and abstract to exclude publications. Then publications were examined in their entirety, to determine final inclusion. Within the risk compensation literature, we grouped publications based on the types of behaviors examined; some publications examined more than one outcome. Specific outcomes were summarized as either a proportion or rate at each time point. If publications compared behaviors among MSM on daily PrEP versus other frequencies of PrEP, we reported specific outcomes for MSM on daily PrEP only.

To extract all measures, we scanned for data from each publication's text, tables, and figures; Engauge Digitizer digitally extracted figure data [21]. A second co-author verified all data elements. If not already provided, we calculated multiplicative measures of association (either risk or rate ratios based on each study's design) using extracted data, along with associated 95% confidence intervals [22]. Finally, we plotted all measures of

associations to make comparisons across publications for each behavior. Further details of this process are available in supplementary materials.

Results

The literature search returned 385 publications. After review of title and abstract, 312 publications were excluded for lack of relevance, leaving 73 publications that received full text review. Of the 73 publications, 57 publications were excluded due to lack of quantitative results or lack of comparison between PrEP users/non-PrEP status; as a final check, we compared our list of publications to previous reviews to ensure our search did not exclude any peer-reviewed literature [13, 14]. Ultimately, 16 publications met our inclusion criteria [23–38] (Fig. 1). Of these publications, 14 examined different forms of risk compensation: all 14 examined condomless anal sex [23–36], 8 examined partner acquisition [23, 24, 26–28, 31, 33, 36], 4 examined serodiscordance [28, 31, 33, 34], and 3 examined frequency of sex [25, 26, 28]. Among these 14 publications examining risk compensation, 3 used a complex study design comparing sexual behaviors between MSM on daily PrEP and those not on PrEP; 3 types of sexual risk compensation were measured: condomless anal sex [34–36], sex partner acquisition [36], and serodiscordance [34]. The remaining 2 publications of the 16 publications examined STI screening [37, 38]. We found no publications examining the following outcomes: shifts in types of sex (e.g., shifting from oral sex to anal sex), types of partners (beyond serodiscordance), or duration of partnerships following PrEP initiation. Additionally, we did not find studies describing national level STI screening among MSM PrEP users, or national screening visit frequency over 12 months after PrEP initiation.

Individual Risk Compensation

Overall, evidence of individual level sexual risk compensation was inconsistent (Table 1). Most publications used a simple study design where MSM reported sexual behaviors before and after PrEP initiation (Fig. 2). Other publications used a more complicated study design where MSM in PrEP and non-PrEP study arms were followed longitudinally (Fig. 3). Notably, all publications provided behavioral risk counseling at regular intervals.

Changes in condomless anal sex following PrEP initiation showed inconsistent risk compensation (Fig. 2a). Publications operationalized comparisons of condomless anal sex at the end of the study to the beginning of the study in two different ways: (1) a rate ratio of condomless anal sex and (2) a risk ratio of the proportions of MSM reporting any condomless anal sex during a time frame (ranging from 1 to 3 months). All four publications that measured the rate of condomless anal sex found increases following PrEP initiation, three of which were significant [23–26]. Three out the seven publications that measured condomless anal sex as a proportion found significant increases following PrEP initiation [27–29]. One of these three publications, Vuylsteke et al. further distinguished between casual and anonymous partners, finding similar increases in condomless anal sex following PrEP initiation regardless of partner type (results not shown) [27]. The remaining four publications, all of which measured condomless anal sex as a proportion, found non-significant changes after PrEP initiation [30–33]. It should be noted that two of the publications that did not find significant changes in condomless anal sex after PrEP initiation

were PrEP efficacy trials [32, 33]. The largest magnitude of effect reported a more than doubling of the rate of condomless anal sex (Rate ratio = 2.14, 95% CI (2.01, 2.28)) [23]. Studies other than the PrEP efficacy trials found increases in condomless anal sex after PrEP initiation.

Unlike condomless anal sex, significant changes in partner acquisition indicated decreased risk compensation—after PrEP initiation MSM reported significantly fewer partners in three of seven publications [23, 31, 33]. While all seven publications operationalized partner acquisition in a similar way by measuring the number of anal sex partners in the past 1 to 3 months, only six reported results in a way that allowed us to compare rate ratios (Fig. 2b) [23, 24, 26, 28, 31, 33]. The remaining publication compared median number of partners before and after PrEP, finding non-significant changes over time (results not shown) [27]. The largest magnitude of effect reported a 27% decrease in the rate of partner acquisition (Rate ratio = 0.73, 95% CI (0.69, 0.76)) following PrEP initiation [30].

Serodiscordance decreased following PrEP initiation in two [31, 33] out of three publications (Fig. 2c) [28, 31, 33]. In other words, fewer MSM reported sex with known HIV positive sex partners in the past 3 months after PrEP initiation compared to the 3 months before PrEP initiation. Serodiscordance was operationalized in these publications as the proportion reporting any known HIV positive sex partner in the past 3 months. This result was only significant in Grinsztejn et al. (Risk ratio = 0.78, 95% CI (0.67, 0.92)) [31].

Three publications examined frequency of sex, measured by rates of total, receptive, and insertive anal sex before and after PrEP initiation (Fig. 2d) [25, 26, 28]. The overall rate of anal sex did not significantly change after PrEP initiation in both publications examining total sex acts [25, 26]. Newcomb et al. found a non-significant increase in receptive anal sex (rate ratio = 1.27, 95% CI (1,1.61)) that was accompanied by a non-significant decrease in the rate of insertive anal sex (rate ratio = 0.89 95% CI (0.68,1.16)) [25]. Montaño et al. found no changes in receptive anal sex (risk ratio = 1.01, 95% CI (0.95,1.08)) or insertive (risk ratio = 1.00, 95% CI (0.93,1.08)) after PrEP initiation [28]. This indicates that PrEP did not increase sexual activity overall, nor did it significantly affect the rates of sexual activity when stratified by sexual position.

Three publications used a more complex study design, where MSM were followed longitudinally, but were stratified into PrEP and non-PrEP arms. This study design allowed researchers to separate the effects of being on PrEP from the concomitant behavioral risk counseling (Fig. 3). In two of these publications, all participants knew their true PrEP status [34, 35]. However, in the third, participants did not know their true PrEP status as this was a randomized controlled trial examining the efficacy of PrEP, and the measure of effect was based on perceived PrEP status [36]. All three publications examined condomless anal sex (Fig. 3a). One publication stratified change in condomless anal sex by sexual position among PrEP and non-PrEP arms [34]. In Milam et al. condomless receptive anal sex in the PrEP arm increased significantly (rate ratio = 1.25, 95% CI (1.19,1.31)) before and after PrEP initiation, while it remained unchanged in the non-PrEP arm during the same time period [34]. In contrast, condomless insertive anal sex significantly decreased in both arms. In the two publications examining the risk of overall condomless anal sex, the risk ratios decreased

similarly in both arms [35, 36]. Only Marcus et al. examined sex partner acquisition, finding a significant decrease in both arms (Fig. 3b) [36]. Finally, only Milam et al. examined serodiscordance; MSM in the PrEP arm reported a significant increase in HIV-positive partners in the past month (rate ratio = 1.22 95%CI (1.10, 1.35)) while those in the non-PrEP arm reported a significant decrease (Fig. 3c) [34].

STI Screening

We found two publications describing STI screening by PrEP status among MSM. One described STI screening within one month of PrEP initiation [37], and the other described STI screening over 12 months [38]. In the first publication, Schumacher et al. used medical records to retrospectively describe STI screening at PrEP initiation and at 6 and 12-month follow-up among MSM in Baltimore City; they found that 43.1% (95% CI 34.7%,48.8%) of MSM were screened at all sites for chlamydia, gonorrhea, and syphilis within one month of PrEP initiation as recommended by CDC [5]; screening decreased to 28.2% (95% CI 22.2%, 34.2%) at 6 months, and 41.5% (95% CI 33.0%, 50.0%) and at 12 months after PrEP initiation [37]. In the second publication, Menza et al. used NHBS survey venue-based sampling to examine annual screening in 2017 in Portland, Oregon [38]. Among MSM not reporting PrEP use, 59.7% (95% CI 53.4%,60.0%) reported receiving any STI screening in the past 12 months; whereas, among MSM reporting PrEP use in the past 12 months, 92% (95% CI 86.3%,97.7%) reported receiving any STI screening in the past 12 months. Both publications also reported rectal chlamydia and gonorrhea testing rates: 55.9% (95% CI 50.2%,61.6%) of MSM on PrEP within one month of PrEP initiation [37], compared to 69.3% (95% CI 59.7%,78.9%) of MSM on reporting PrEP use in the past 12 months and 25.7% (95% CI 20.1%,31.3%) of MSM not on PrEP in the past 12 months [38].

Discussion

Only fourteen publications examining individual level sexual risk compensation after PrEP initiation were found in the literature and results were inconsistent. For example, some publications examining condomless anal sex found significant increases after PrEP initiation [22–24, 26–29], while others found non-significant changes [25, 30–33]. In contrast, all publications examining partner acquisition with significant results found decreases after PrEP initiation [23, 31, 33]. No publications examined other types of sexual risk compensation such as type of sex, sexual partnership duration, and sexual mixing beyond serodiscordance changed after PrEP initiation. In addition, we found gaps in the literature examining national STI screening trends among MSM on PrEP and national frequency estimates of STI screening within a year of PrEP initiation.

Three publications used a complex study design where sexual behavior changes were described longitudinally in PrEP and non-PrEP arms. These multi-armed studies are uniquely suited to describe the interaction of behavioral risk counseling and PrEP initiation. In these studies, changes in condom use and partner acquisition were similar in both arms, indicating that PrEP may not affect behaviors in these samples or behavioral risk counseling might have an impact on behavior change [34–36]. However, this did not hold true for serodiscordance: MSM not on PrEP reported fewer HIV positive partners whereas MSM on

PrEP had sex with more HIV positive partners, who may be at increased risk for STI acquisition [16], once they receive protection from HIV acquisition PrEP [34].

Sexual risk compensation theory suggests that MSM on PrEP might acquire sex partners more frequently due to perceived protections. However, the publications reported associations in the opposite direction. This could have occurred for multiple reasons. Information bias related to partner number could result from poor recall, social desirability, or stigma [39]. Another reason is that one of the criteria for PrEP is having multiple partners at PrEP initiation, which could decrease overtime if participants began steady partnerships. In addition, all participants in all publications received behavioral risk counseling throughout the trials, potentially preventing risk compensation from occurring.

Prior reviews of sexual risk compensation focused on two types of sexual risk compensation: condom use and number of partners [9, 10, 13, 14]. Our study differed in three keyways. First, we only examined HIV-negative MSM receiving PrEP. Second, we quantified the results from previous studies in a way that they could be easily compared to one another through risk and rate ratios. Third, we documented additional types of sexual risk compensation such as changes in partner type (serodiscordance), frequency of sex, type of sex, and sexual position. We considered these types of sexual risk compensation because PrEP's indirect effects on non-HIV STI transmission dynamics are complicated and they could be detrimental, beneficial, or context specific [40]. On the detrimental side, increases in rates of condomless anal sex might increase STI transmission; whereas acquiring fewer partners and getting screened for STIs more frequently might decrease transmission. Other behaviors' effects on transmission dynamics are context specific, meaning they could either increase or decrease transmission depending on the context [41].

Because the changes driven by PrEP are complicated and countervailing, mathematical modeling is necessary to predict how PrEP use might affect STI burden. One previous modeling publication addressed this issue [42]. Jenness et al. weighed potential decreases in condom use against potential increases in STI screening to predict how STI incidence might change with PrEP initiation and found that the benefits of increased screening of those on PrEP would likely outweigh the detriments of decreased condom use, unless PrEP uptake is quite low, or condom use becomes nearly absent. Additionally, Jenness et al. found that at high levels of PrEP coverage (i.e., > 60% of those eligible being enrolled) chlamydia and gonorrhea incidence could be reduced by > 30–50%, assuming condom use is only halved. However, the model assumed that 100% of MSM initiating PrEP received STI screening semi-annually. Our review suggests that this was too high: annual rectal STI screening in Portland was only 69% [38] and semiannual screening for rectal chlamydia and gonorrhea at PrEP visits in Baltimore was between 43%–55% [37]. While this prior modeling publication considered two types of changes induced by PrEP, it ignored many others such as partner acquisition, serodiscordance, and rates of sex after PrEP initiation. The impact of these behavioral changes on STI incidence are most difficult to predict without the use of a mathematical model. By quantifying changes before and after PrEP initiation of condomless anal sex, partner acquisition, serodiscordance, and sex act frequency, our review compiles additional inputs that may aid future mathematical modeling. Despite not being able to find data at this time on changes in types of sex, types of partners, or duration of partnerships,

modelling may still be a useful tool to examine how risk compensation might affect transmission of STIs.

Our review highlights the scarcity of literature examining all types of sexual risk compensation. This is partially driven by these publications being focused on HIV rather than STIs. For example, though oral sex is an important transmission route for some STIs, it is unlikely to transmit HIV readily [5, 16]; thus, absence of shifts in types of sex from oral sex to anal sex in the literature is expected. Another limitation is that PrEP for HIV obtained U.S. approval in 2012; therefore, PrEP was still novel in many of these studies. In addition, PrEP knowledge and acceptability are still disseminating and shifting [8, 43]. Some of the publications in our study were placebo-controlled trials that established PrEP efficacy, and the results in terms of risk compensation should be interpreted cautiously [32, 33, 36]. Risk compensation theory relies on a person believing they are receiving protection from a risk outcome, in this case HIV; these studies are more likely to show no evidence of behavior change following PrEP initiation since participants on PrEP may not have perceived any protection from HIV. Our study was also limited to those on daily PrEP use, as recommended by CDC [5]; however, other PrEP regimens such as on-demand and event driven PrEP dosages are emerging and efficacy is being determined [26–28, 30]. These alternative PrEP use patterns likely are less effective at preventing HIV [5]. As a result, behaviors may continue to change, and future research will be needed to monitor evolving behaviors following PrEP initiation. A final limitation is the generalizability of the results from the publications we have summarized. It is unclear how well clinical trial and community-based results reflect the real clinical practices. For example, because risk-counseling was also provided to all study participants during these studies, changes in sexual behaviors might be different outside of controlled trials.

Despite limitations, we examined the emerging literature describing how PrEP initiation might affect individual level sexual risk compensation. While PrEP is an invaluable tool to fight the HIV epidemic, it is also likely to affect STI burden. This could affect STIs either beneficially or detrimentally long term, but currently available data and mathematical models are inadequate to make this prediction with great certainty. PrEP provides a unique opportunity to MSM to conduct regular behavioral health counselling and STI testing every 3 months at regularly scheduled PrEP visits. Future publications need to measure not only whether MSM are tested for STIs, but also how frequently they are tested and report subsequent STI incidence, as this might be the primary beneficial effect of PrEP on STI burden. This will require some future PrEP studies to have a stronger STI focus. As PrEP coverage increases, regular STI counselling and screening and other interventions to PrEP users could lead to overall improvements in sexual health at both the individual and population levels.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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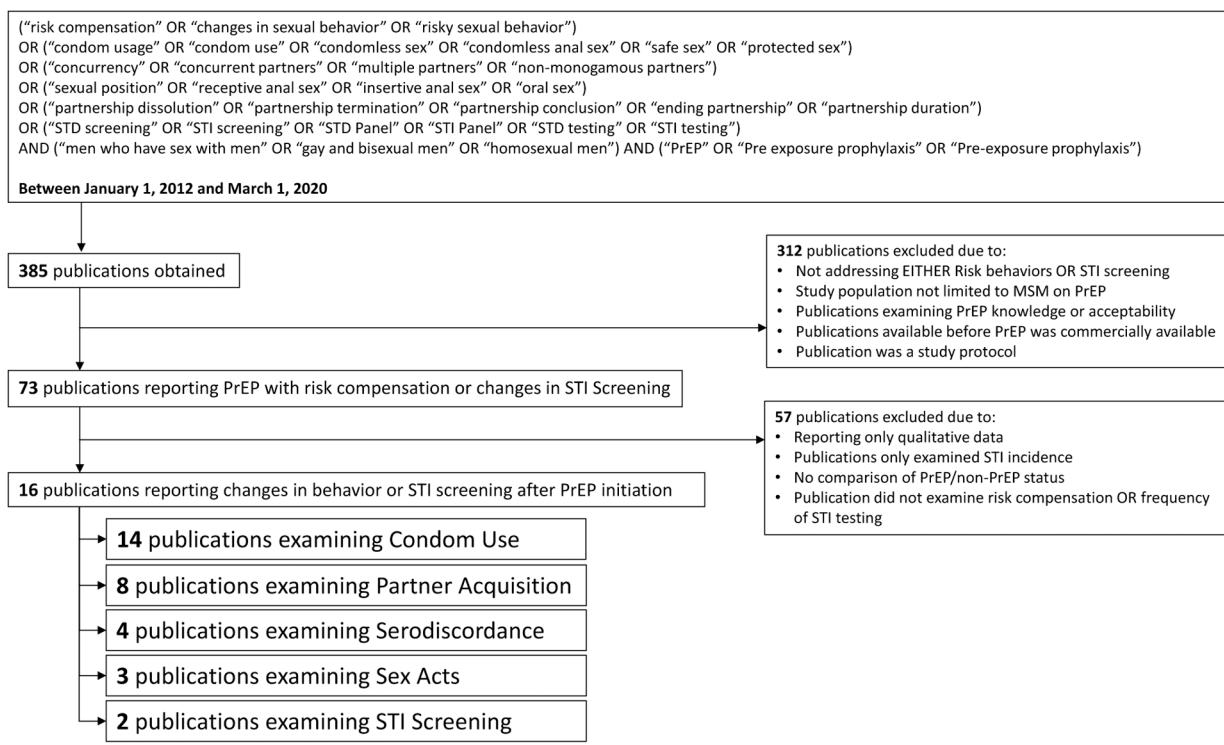
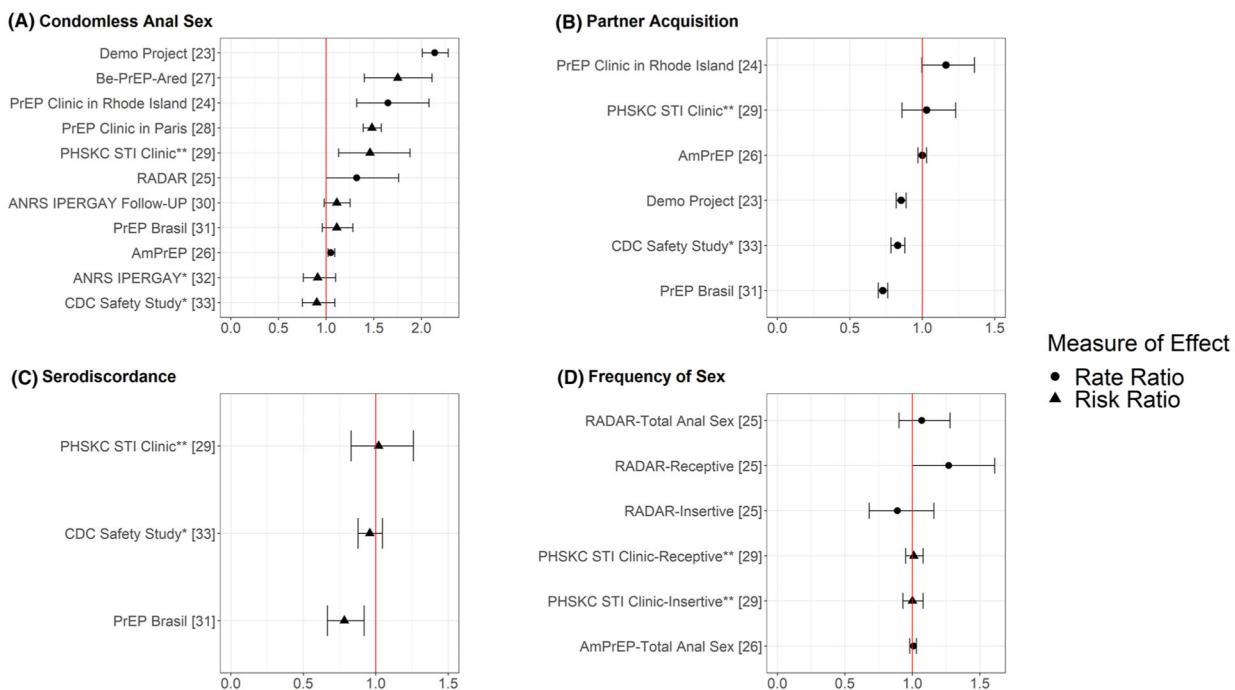
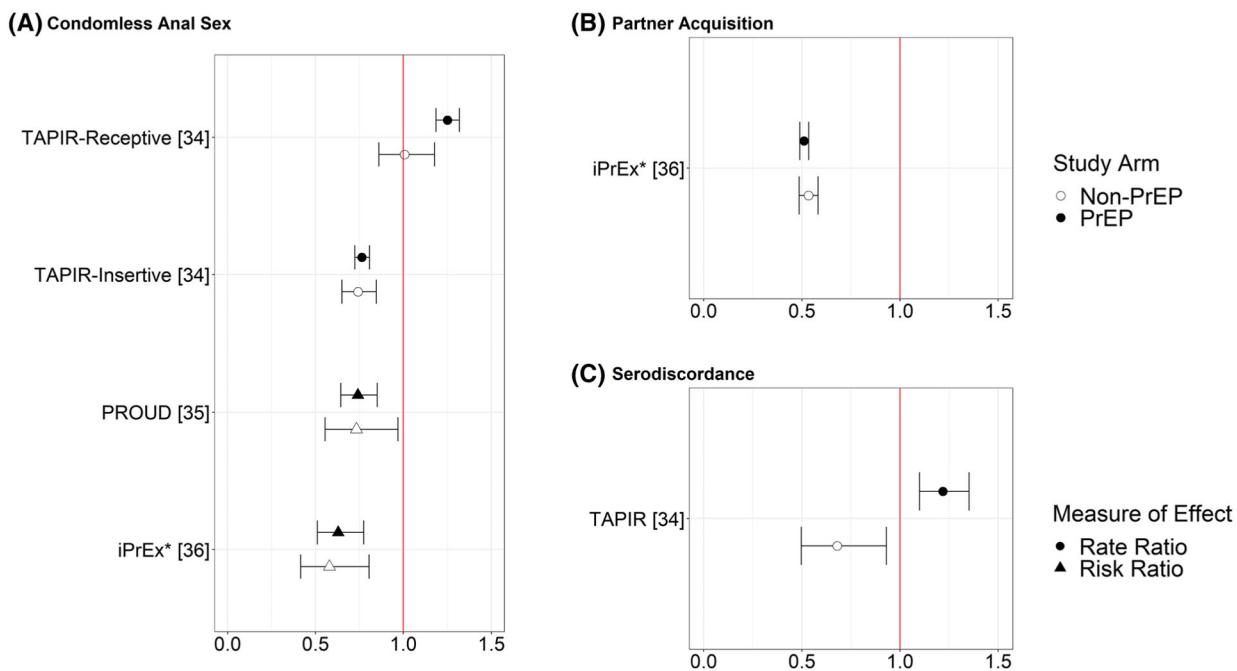


Fig. 1.
Search terms for publications examining risk compensation or STI screening

**Fig. 2.**

Individual level sexual risk compensation after PrEP initiation among studies with only a PrEP arm. Participants reported **a** condomless anal sex, **b** partner acquisition, **c** serodiscordance, and **d** sex acts at baseline and throughout PrEP trial. Rate ratios and confidence intervals were calculated comparing risk behaviors at baseline and final phase of trial. Risk ratios were used if rate ratios were unobtainable. Significance was assessed at $p < 0.05$. Sexual risk compensation varied in terms of measure and risk behaviors

**Fig. 3.**

Individual level sexual risk compensation among studies comparing MSM in PrEP and non-PrEP arms. Participants reported **a** condomless anal sex, **b** partner acquisition, and **c** serodiscordance at baseline and throughout the trials. Rate ratios and confidence intervals were calculated and plotted for PrEP and non-PrEP arms. The rate ratios compared behaviors at baseline and trial conclusion. Significance was assessed at $p < 0.05$. *This study was a randomized control trial establishing PrEP efficacy and the effect of PrEP on risk compensation should be interpreted cautiously

Summary of risk compensation studies retrieved from the literature search

Table 1

Publications comparing MSM at beginning and end of studies						
Author	Study name	Study length	Condomless anal sex	Partner acquisition	Serodiscordance	Sex act frequency all sex acts
Liu et al. [23]	Demo Project	48 Weeks	+	—	—	—
Oldenburg et al. [24]	PrEP Clinic in Rhode Island	24 Weeks	+	—	—	—
Newcomb et al. [25]	RADAR	72 Weeks	—	—	—	—
Hoomenborg et al. [26]	AmPrEP	96 Weeks	+	—	—	—
Vuyisike et al. [27]	Be-PrEP-Ared	108 Weeks	+	—	—	—
Noret et al. [28]	PrEP Clinic in Paris	52 Weeks	+	—	—	—
Montaño et al. [29]	PHSKCSTI Clinic **	48 Weeks	+	—	—	—
Molina et al. [30]	ANRS IPERGAY Follow Up	72 Weeks	—	—	—	—
Grinsztejn et al. [31]	PrEP Brasil	48 Weeks	—	—	—	—
Sagaron-Teyssier et al. [32]	ANRS IPERGAY *	104 Weeks	—	—	—	—
Liu et al. [33]	CDC Safety Study *	52 Weeks	—	—	—	—

Publications comparing MSM at beginning and end of studies in arms: PrEP vs Non-PrEP						
Author	Study name	Study length	Study arm	Condomless anal sex	Condomless receptive anal sex	Condomless insertive anal sex
Milam et al. [34]	TAPIR	24 Weeks	PrEP	+	—	—
			Non-PrEP	—	—	—
Grant et al. [35]	PROUD	72 Weeks	PrEP	—	—	—
			Non-PrEP	—	—	—
Marcus et al. [36]	iPrEX *	48 Weeks	PrEP	—	—	—
			Non-PrEP	—	—	—

† Significant increase

— Significant decrease

Non-Significant change

* This study was a randomized control trial establishing PrEP efficacy, and the effect of PrEP on risk compensation should be interpreted cautiously

** The data from this study was abstracted through adjusted measures rather than crude measures