Differences in sexually transmitted infection risk comparing preexposure prophylaxis users and propensity score matched historical controls in a clinic setting

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Objective: The aim of this study was to determine whether MSM using preexposure prophylaxis (PrEP) are at a higher risk of bacterial sexually transmitted infections (STIs) than MSM not using PrEP.

Design: Secondary analysis of longitudinal STI data obtained from MSM attending an STD Clinic in Seattle, Washington, USA, October 2011–September 2017.

Methods: We identified patients obtaining PrEP through the STD Clinic, and used propensity score matching to select a historical group of similar patients not using PrEP for comparison. We linked patient data with STI surveillance data to compare the incidence of chlamydia, gonorrhoea and early syphilis, and time to first symptomatic STI among PrEP users and nonusers.

Results: Three hundred and sixty-five PrEP users who picked up prescriptions and returned for follow-up and 730 propensity score matched nonusers were included in the analysis. Adjusted incidence rate ratios (aIRRs) for chlamydia, gonorrhoea and early syphilis were 3.2 [95% confidence interval (95% CI): 1.9–5.3], 2.8 (95% CI: 1.7–4.6) and 2.9 (95% CI: 1.5 – 5.6), respectively, comparing PrEP users to nonusers. Time to first symptomatic STI was shorter among PrEP users (120 days, 95% CI: 77 – 171) than among nonusers (185 days, 95% CI: 163–256).

Conclusion: Among MSM on PrEP, we observed a higher incidence of STIs and faster time to first symptomatic STI than MSM not using PrEP. PrEP may be a contributing factor in increasing STI rates among MSM.

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Introduction

MSM are disproportionately impacted by HIV in the United States, accounting for 86% of new infections among men in 2016 [1]. Preexposure prophylaxis (PrEP) reduces the risk of HIV acquisition by up to 92% in MSM [2–4], is recommended by the Centers for Disease Control and Prevention (CDC) for HIV prevention among sexually active MSM [5] and is offered through a variety of clinical settings in the U.S. [6]. MSM are also

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disproportionately impacted by bacterial sexually transmitted infections (STIs), the rates of which have increased substantially in the past decade. MSM accounted for 62% of gonorrhoea cases and 68% of primary and secondary syphilis cases among men in 2017 [7]. Between 2013 and 2017, the rate of primary and secondary syphilis among MSM increased by 64% [7].

Recent clinical data indicate that MSM using PrEP have an increased frequency of condomless anal sex after PrEP initiation [8–13], leading to concerns that PrEP may be contributing to increasing rates of bacterial STIs among MSM. But observational studies have reported mixed results regarding the association of PrEP use and increased rates of bacterial STIs among MSM [14–19]. However, these studies are limited by the lack of a comparison group of PrEP nonusers [16,17,19], failure to account for ascertainment bias resulting from increased STI screening among PrEP patients [15] or failure to adjust for secular STI trends [14,15,18]. Thus, the impact of PrEP use on STI risk remains unclear.

Since 2014, the Public Health – Seattle & King County (PHSKC) STD Clinic has provided PrEP to patients at a high risk of HIV. We used PHSKC STD Clinic data from PrEP users and a propensity score matched historical comparison group of nonusers to assess the impact of PrEP use on STI rates among MSM in the Seattle area. The primary objective of this study was to determine whether MSM using PrEP are at a higher risk of bacterial STIs than MSM not using PrEP.

Materials and methods

Study design, setting and population

This study was a secondary analysis of data from a cohort of MSM who initiated PrEP through the PHSKC STD Clinic between October 2014 and September 2017. As per PHSKC and Washington State (WA) PrEP guidelines [20], the PHSKC STD Clinic provides PrEP to patients at a high risk for acquiring HIV. This includes MSM and transgender persons who have sex with men who report any of the following risk factors in the past 12 months: diagnosis of rectal gonorrhoea or early syphilis; use of methamphetamine or amyl nitrites (poppers); or exchanging sex for money or drugs. PrEP is also recommended for patients with HIV-positive sexual partners who are not virally suppressed, and is provided to all interested African–American and Latino MSM. STD Clinic clinicians evaluate all patients for PrEP eligibility at routine visits, and those who meet the recommended criteria are offered PrEP through the clinic. Patients not meeting recommended criteria who are interested in initiating PrEP are referred to community PrEP providers. Throughout the study period (2011–2017), PHSKC has recommended that all MSM meeting the high-risk criteria defined above test for HIV and STIs quarterly, and has offered text-message reminders to encourage this [21].

PrEP visit procedures at our clinic have been described previously [9]. Briefly, PrEP patients are tested for HIV and STIs at their initial visit, and are given a 3-month prescription for PrEP. They return 1 month after PrEP initiation, and then quarterly for clinical follow-up and monitoring, including HIV and STI testing. We included PrEP patients (PrEP users) in this analysis if they were HIV-negative MSM who initiated PrEP through the STD Clinic between October 2014 and September 2017, who picked up their initial 3-month prescription, and returned for their first follow-up visit at 1 month. Our comparison group (PrEP nonusers) was composed of HIV-negative MSM who attended the STD Clinic between October 2011 and September 2014 (the period prior to PrEP availability at the clinic), propensity score matched to PrEP users. Our rationale for this approach was twofold: First, our clinic provides PrEP to patients at a high risk for HIV acquisition, and a comparison group of current clinic patients who are not on PrEP would be at a lower risk of HIV and STI acquisition than current PrEP users. Second, although PrEP is widely available in King County, our data only include PrEP status for STD Clinic patients. With no way to ascertain PrEP status for MSM outside of the STD Clinic population, we chose to compare our PrEP patients to propensity score matched historical controls from our clinic.

Propensity score matching and comparison group formation

We used propensity score matching to select a group of comparison patients who were most similar to our PrEP users, in order to identify a group of patients who would have likely been on PrEP in our STD Clinic if it had been available at the time they attended the clinic. The goal of propensity score matching is to approximate the effect of randomization by balancing observed covariates between study groups. We included 62 variables in our propensity score model, related to PrEP eligibility, sexual behaviour, STI risk, recent STI diagnoses, demographic characteristics and reasons for visiting the clinic (Supplementary Table, http://links.lww.com/QAD/B488). Data for the propensity score model were from the initial PrEP visit for PrEP users, and from the first STD clinic visit between October 2011 and September 2014 for PrEP nonusers. We used descending, nearest-neighbour matching without replacement to select two matched PrEP nonusers for each PrEP user based on their propensity scores [22,23]. After matching, we graphically compared the distribution of propensity scores in both groups (Supplementary Figure, http://links.lww.com/QAD/B489), and used graphs of standardized differences to check covariate balance between groups. Standardized differences of 10% or less were judged to be negligible and indicate good covariate balance [24,25]. Covariates with standardized

differences greater than 10% were added to final outcome models one at a time, and any that caused an absolute change in effect size of greater than 5% were included as covariates in final adjusted outcome models.

Data sources, measures and data linkage

For both PrEP users and PrEP nonusers, we obtained data on clinic attendance, visit dates, PrEP status and prescription fills from STD Clinic electronic patient records. Data on bacterial STI diagnoses were obtained from the Public Health Issue Management System (PHIMS), the electronic STI surveillance system used in WA. This system is separate from STD Clinic patient records, and only captures positive STI test results. WA laws require laboratories and medical providers to report all cases of chlamydia, gonorrhoea and syphilis to local health authorities who subsequently provide data to the WA Department of Health via PHIMS. The PHIMS data included all positive STI laboratory tests reported in King County during the time frame under study, including anatomic site of infection and diagnosis date. Thus, we used PHIMS to identify all STIs diagnosed during the study period, including those diagnosed outside the STD clinic. We defined early syphilis as primary, secondary or early latent stage syphilis. As most cases of urethral gonorrhoea and primary and secondary syphilis among men are symptomatic, we defined symptomatic STIs as cases of urethral gonorrhoea or primary or secondary syphilis [26,27]. We obtained the data included in the propensity score model from STD Clinic electronic medical records, standardized, comprehensive intake forms filled out by patients at all clinic visits, and from PHIMS.

We matched STD Clinic visit data to PHIMS STI case report data to identify incident STIs diagnosed during the study period. We linked these two data sources on first name, last name and date of birth. Matching was performed using fastLink, a probabilistic record linking package for R [28]. FastLink utilizes a Felligi–Sunter probabilistic record linkage model with an expectation-maximization algorithm. We used the default Jaro–Winkler method to measure agreement for partial matches, and set the lower bound for posterior match probability to 0.85.

Sexually transmitted infection testing

Quarterly STI tests are recommended for all clinic PrEP patients [29], and are performed as part of routine clinical care. Patients are screened for chlamydia and gonorrhoea at each anatomic site (urethra, pharynx, rectum) based on reported exposure. Urine samples, and urethral, pharyngeal and rectal swabs were tested for gonorrhoea and chlamydia using nucleic acid amplification testing (APTIMA Combo 2; Hologic, Inc, Marlborough, Massachusetts, USA). Blood samples were tested for syphilis using a quantitative rapid plasma reagin (Beckton Dickinson, Franklin Lakes, New Jersey, USA) test, with confirmatory tests performed using *Treponema pallidum* particle agglutination assay (Fujirebio Inc., Tokyo, Japan). All cases of syphilis in King County are staged by a disease intervention specialist based on laboratory and clinical findings.

Statistical analysis and follow-up time calculation

We used Poisson regression to compare incidence of bacterial STIs between PrEP users and PrEP nonusers. PrEP users were followed from their first prescription fill through 90 days after their last PrEP clinic appointment. Nonusers were followed for 1 year from their first clinic visit between October 2011 to September 2014. We limited the follow-up period for the comparison group to 1 year to minimize the likelihood that nonusers who moved out of King County would accrue follow-up time but not contribute STI diagnoses to incidence calculations. Any incident diagnoses of chlamydia, gonorrhoea or early syphilis were counted as outcomes with one exception: a diagnosis of an STI that occurred just after another diagnosis of the same STI (21 days for chlamydia, 14 days for gonorrhoea, 28 days for early syphilis) was not counted. Because this resulted in a window after each STI diagnosis wherein additional cases could not be counted, we subtracted the relevant number of days from the denominator for each diagnosis (e.g. subtracted 21 days from the denominator for each chlamydia diagnosis). We ran separate Poisson regression models for each STI, symptomatic STIs in combination and each anatomic site of infection for chlamydia and gonorrhoea. We clustered by patient ID to account for 43 PrEP users who were also included in the comparison group. We adjusted models for secular STI trends by including a continuous variable for annual incidence of each STI (or site-specific STI) in the general MSM population in King County [30]; these data were obtained from the PHSKC STD Epidemiologist. Rectal gonorrhoea and early syphilis models were not adjusted for secular trends due to model instability arising from years with zero cases among study patients.

To account for ascertainment bias resulting from more frequent STI screening among PrEP users, we compared time to first symptomatic STI between PrEP users and nonusers using Kaplan–Meier survival analysis. For this analysis, PrEP users were followed from their first prescription fill date and PrEP nonusers were followed from their first clinic visit date, with follow-up time for both groups censored at the first diagnosis of urethral gonorrhoea or primary or secondary syphilis. We used a log rank test to compare median time to first symptomatic STI between the groups. We compared the cumulative probability of experiencing a symptomatic STI between the groups during 1 year of follow-up using a Kaplan–Meier failure curve.

We used Stata version 15.1 (College Station, Texas, USA) for all analyses. Two-sided statistical tests were performed

at a significance level of 0.05. This study was approved by the University of Washington Institutional Review Board.

Results

Between October 2014 and September 2017, 557 MSM were prescribed PrEP through the PHSKC STD Clinic. Ninety-one patients were excluded from this analysis because they did not pick up their first prescription, and a further 101 did not return for their first follow-up visit, leaving 365 PrEP users in our analytic sample. Of these, 15 initiated PrEP in 2014, 108 in 2015, 121 in 2016 and 121 in 2017. For each PrEP user in our analysis, we selected two propensity score matched PrEP nonusers, resulting in a comparison group of 730 patients. Of these, 79 had their initial clinic visit in 2011, 262 in 2012, 223 in 2013 and 166 in 2014. Among PrEP users, the median length of time on PrEP was 292 days [interquartile range (IQR): 117–561]. The two study groups were balanced in terms of age, race/ethnicity, PrEP eligibility criteria and sexual behaviour (Table 1). The mean age in both groups was 30 years. Half of each group was white, non-Hispanic, and approximately 15% were diagnosed with syphilis in the past year. Men in both groups had a mean number of five male sexual partners in the prior 2 months and three-quarters of men reported receptive anal sex in the past year.

The c-statistic for our propensity score model was 0.81. The distribution of propensity scores was similar in both groups (Supplementary Figure, http://links.lww.com/QAD/B489). Fifty-two of the 62 covariates included in the propensity score were balanced between the two groups (Supplementary Table, http://links.lww.com/QAD/B488). All 10 unbalanced covariates resulted in absolute changes in point estimates of less than 5% after inclusion in adjusted models, so none were included in final outcome models.

Table 2 provides incidence and adjusted incidence rate ratio (aIRR) of each STI, comparing PrEP users to PrEP nonusers. Among PrEP users, incidence of chlamydia, gonorrhoea and early syphilis was 45.2, 37.1 and 6.9 per 100 person-years, respectively. PrEP users had an approximately three-fold higher incidence rate than PrEP nonusers for chlamydia (aIRR: 3.2; 95% CI: 1.9–5.3), gonorrhoea (aIRR: 2.8; 95% CI: 1.7–4.6) and early syphilis (aIRR: 2.9; 95% CI: 1.5–5.6). STI incidence among PrEP users was highest for rectal chlamydia (38.0

Table 1. Characteristics of preexposure prophylaxis users and propensity score matched historical comparison patients (preexposure prophylaxis nonusers) at the time of their initial Public Health – Seattle & King County STD clinic visit (*N* = 1095).

	PrEP users (*N* = 365)		PrEP nonusers (*N* = 730)		
Characteristic	*N*	%	*N*	%	*P*
Age (Mean, SD)	30.6	8.7	30.1	8.6	0.33
Race/Ethnicity[a]					
White, non-Hispanic	183	50.1	390	53.4	0.11
Black/African–American, non-Hispanic	25	6.8	43	5.9	
Hispanic	90	24.7	137	18.8	
Asian/Pacific Islander, non-Hispanic	41	11.2	76	10.4	
Mixed Race/Other, non-Hispanic[b]	14	2.7	42	4.7	
Unknown, non-Hispanic	12	3.3	42	5.8	
PrEP eligibility criteria[c]					
Rectal gonorrhoea diagnosis in the past year[d]	108	29.6	221	30.3	0.82
Early syphilis diagnosis in the past year[d]	58	15.9	106	14.5	0.55
Methamphetamine use in the past year	36	9.9	81	11.1	0.53
Popper use in the past year	175	47.9	313	42.9	0.11
Sex work in the past year[e]	11	3.0	21	2.9	0.90
Number of male sexual partners[f] (Mean, SD)	5.0	11.9	5.3	8.5	0.74
Sexual behaviour in past 12 months					
Receptive anal sex	272	74.5	565	77.4	0.29
With HIV-positive partner	46	12.6	81	11.1	0.46
With HIV-negative partner	233	63.8	502	68.8	0.10
With unknown status partner	91	24.9	169	23.2	0.51
Insertive anal sex	261	71.5	550	75.3	0.17
With HIV-positive partner	70	19.2	147	20.1	0.71
With HIV-negative partner	240	65.8	519	71.1	0.07
With unknown status partner	98	26.8	196	26.8	1.0

PHSKC, Public Health – Seattle & King County; PrEP, preexposure prophylaxis; SD, standard deviation.
[a]Categories for race/ethnicity are mutually exclusive.
[b]Other includes self-reported other race and Native American and Alaskan Native.
[c]PrEP eligibility in the PHSKC STD Clinic; categories are not mutually exclusive.
[d]Includes diagnosis at current visit.
[e]Sex work is defined as giving or receiving money or drugs in exchange for sex.
[f]Self reported, in prior 2 months.

Table 2. Incidence of bacterial sexually transmitted infections among preexposure prophylaxis users and nonusers attending the Public Health – Seattle & King County STD clinic (2011–2017), *N* = 1095.

STI	PrEP users (*N* = 365) Incidence, per 100 person-years	Nonusers (*N* = 730) Incidence, per 100 person-years	IRR	95% CI	aIRR[a]	95% CI
Chlamydia	45.2	14.4	3.1	2.4–4.2	3.2	1.9–5.3
Rectal	38.0	10.4	3.7	2.6–5.1	3.7	1.9–7.3
Urethral	7.4	3.7	2.0	1.1–3.6	2.2	1.1–4.5
Pharyngeal	3.8	2.5	1.6	0.8–3.2	1.6	0.7–3.8
Gonorrhoea	37.1	17.7	2.1	1.6–2.8	2.8	1.7–4.6
Rectal	20.7	9.8	2.1	1.5–3.0	2.1[b]	1.5–3.0
Urethral	9.9	6.1	1.6	1.0–2.6	1.5	0.6–4.1
Pharyngeal	16.2	9.2	1.8	1.2–2.5	2.0	1.1–3.5
Early syphilis[c]	6.9	2.3	2.9	1.5–5.6	2.9[b]	1.5–5.6
Symptomatic[d]	13.1	7.3	1.8	1.2–2.7	2.4	0.9–6.3

aIRR, adjusted incidence rate ratio; CI, confidence interval; IRR, incidence rate ratio; PrEP, preexposure prophylaxis.
[a]Models for incidence rate ratios are clustered by patient ID and adjusted for the annual incidence for each STI among all MSM in King County, for each year in 2011–2017 to account for secular STI trends, unless otherwise specified.
[b]Models adjusted for secular STI trends were unstable due to zero cases among study patients in some years. Models for rectal gonorrhoea and early syphilis are clustered by patient ID, but not adjusted for annual MSM incidence.
[c]Includes primary, secondary and early latent.
[d]Includes urethral gonorrhoea and primary and secondary syphilis.

per 100 person-years) and rectal gonorrhoea (20.7 per 100 person-years), which were both significantly higher than among PrEP nonusers. Incidence of urethral gonorrhoea, pharyngeal chlamydia and symptomatic STIs (urethral gonorrhoea and primary/secondary syphilis) was higher among PrEP users than nonusers, though not statistically significantly. Adjustment for secular trends in STI incidence had a minimal impact on IRRs.

The median time to first symptomatic STI among PrEP users was 120 days (95% CI: 77–171), compared with 185 days among PrEP nonusers (95% CI: 163–256; log-rank $P < 0.01$). The cumulative probability of experiencing a symptomatic STI by the end of 1 year of follow-up was nearly twice as high among PrEP users compared with PrEP nonusers (12 vs. 7%, respectively; Fig. 1).

Discussion

We found that, compared with MSM not using PrEP, PrEP users had a two to three-fold higher incidence of nearly all bacterial STIs, a higher incidence of symptomatic STIs, a 50% faster median time to first symptomatic STI and almost double the probability of experiencing a symptomatic STI during the first year of follow-up. These findings are consistent with recent data from our clinic showing increased frequency of

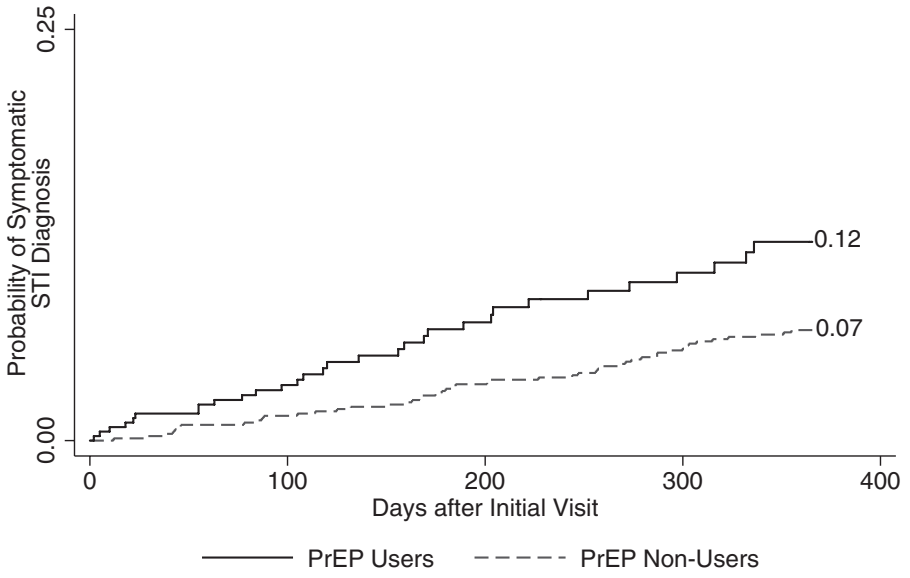

Fig. 1. Cumulative probability of symptomatic sexually transmitted infection diagnosis during the first year after initial clinic visit.

condomless sex among PrEP users [9], and support reports from prior studies of high STI incidence among PrEP users. Further, our findings suggest that PrEP use is associated with a higher risk of bacterial STIs independent of bias resulting from increased STI screening among PrEP users and secular trends.

Recent studies, including two meta-analyses of STI incidence among PrEP users, report incidence of bacterial STIs among PrEP users in the range of 38.0–56.7 per 100 person-years, 37.5–51.7 per 100 person-years and 9.1–14.5 per 100 person-years for chlamydia, gonorrhoea and syphilis, respectively [15–17,31]. Incidence of chlamydia and gonorrhoea among PrEP users in our study was similar, while incidence of early syphilis was slightly lower (45.2, 37.1 and 6.9 per 100 person-years, respectively). The majority of these studies did not include comparison groups of MSM not using PrEP [16,17,31]. However, the meta-analysis by Kojima *et al.* [15] compared pooled incidence estimates for MSM using PrEP and MSM not using PrEP from several studies of STI incidence among MSM.

In the meta-analysis by Kojima *et al.* [15], the pooled IRRs comparing STI incidence of PrEP users to nonusers, 11.2, 25.3 and 44.6 for chlamydia, gonorrhoea and syphilis, respectively [15], are substantially higher than those observed in our study. This is likely due to differences between our propensity score matched comparison group and the pooled comparison group of PrEP nonusers included in the meta-analysis. Most studies included in the meta-analysis did not include direct comparison of PrEP users and nonusers. Further, the studies included in the pooled incidence estimate for PrEP nonusers were extremely heterogeneous; studies included a wide range of behavioural criteria, some included HIV-positive men, and some dated back to 1998, when syphilis incidence was at its lowest point in the past 20 years. Secular trends in STI incidence, differences in screening frequency and differences in baseline sexual behaviour may have impacted the comparison of PrEP users and nonusers.

Two recent observational studies not included in the above meta-analysis used within-individual comparison to measure the impact of PrEP use on STI risk, comparing STI incidence during pre and post-PrEP initiation periods within the same group of participants [14,18]. Although their reported incidence during PrEP use is somewhat similar to our group of MSM using PrEP, Beymer *et al.* [14] observed decreases in incidence between the pre-PrEP and during-PrEP periods for all STIs except syphilis. However, their inclusion of STIs diagnosed at PrEP initiation in the pre-PrEP period may have contributed to their observation of decreases in incidence. We excluded STIs diagnosed at the initial visit from our incidence calculations. Nguyen *et al.* [18] similarly compared incidence of bacterial STIs among MSM using PrEP to the same group of MSM prior to PrEP use. In that study, only chlamydia was found to have higher incidence during PrEP use than before PrEP use (any site aIRR: 1.74; 95% CI: 1.02–2.96). In contrast, we observed a two to three-fold increase in incidence for most STIs included in our analyses.

Differences between our study findings and those mentioned above are likely a result of two key methodological differences. First, propensity score matching allowed us to identify a comparison group as similar as possible to our PrEP users with respect to recent STI diagnoses, sexual behaviour, HIV risk and other characteristics likely associated with PrEP use. This resulted in a group of PrEP nonusers who were most likely to have been using PrEP if it had been available to them. Second, of the three studies above that compared PrEP users with nonusers, only one addressed the issue of ascertainment bias resulting from higher STI screening frequency among PrEP users. Nguyen *et al.* [18] adjusted their models for the number of screening visits in the pre and post-PrEP initiation periods. Lacking data on frequency of STI testing among PrEP nonusers, we investigated the impact of PrEP use on risk of urethral gonorrhoea and primary and secondary syphilis, which are most frequently symptomatic and result in care-seeking, using survival analysis to measure time to first symptomatic STI among PrEP users and nonusers. We chose to focus on symptomatic STIs because detection of these infections would be unlikely to be affected by an increase in screening frequency. Indeed, our hypothesis that PrEP users would experience faster time to first symptomatic STI was supported by our findings, which provide evidence that PrEP use is associated with an increased risk of symptomatic STIs independent of increased screening frequency. These approaches allowed us to address both the difficulty of comparison group formation and the possibility of ascertainment bias, two limitations that have been present in many past studies of PrEP use and STI risk.

This study has a number of strengths. First, to our knowledge, this is the first study of the impact of PrEP on STI risk to compare time to first symptomatic STI between PrEP users and nonusers as a means of addressing ascertainment bias. Second, we adjusted for secular trends by including annual incidence of each STI among MSM in King County, which we were able to measure due to robust and detailed STI surveillance data from PHIMS. Third, our use of propensity score matching approximates the effect of randomization, and allowed us to balance a large number of observed characteristics between study groups. Further, this method of comparison group formation enabled us to identify PrEP nonusers who were most likely to have been on PrEP if it had been available. Finally, access to case report data from our state STI surveillance system allowed more complete ascertainment of STI outcomes by enabling us to identify STIs diagnosed outside of our clinic.

Our results should be interpreted in light of several limitations. First, observed incidence among PrEP users and comparison of incidence between PrEP users and nonusers is likely to be impacted by ascertainment bias resulting from higher frequency of STI testing among PrEP users. Because we did not have data available on STI screening frequency for either group, we attempted to address this by including an analysis of the incidence of symptomatic STIs, and comparison of time to first symptomatic STI. Second, propensity score matching is predicated on the assumption that the covariates included in the propensity score model can predict likelihood of PrEP use. If incorrect, this assumption may have resulted in biased estimates of the impact of PrEP on STI risk. Third, we were unable to adjust all statistical models for secular STI trends. However, the incidence in the two propensity-score matched groups does suggest that the magnitude of the relative association would have been similar to that which was reported in the fully adjusted models. Further, it is possible that the inclusion of yearly STI incidence among the general population of MSM failed to completely adjust for secular STI trends. However, insofar as PrEP played an important role in increasing STI incidence in MSM, it is also possible that our adjustment for secular trends represents an overadjustment. Finally, the generalizability of these results to other MSM populations outside of Seattle is uncertain.

In summary, we observed an increased STI risk among PrEP users relative to nonusers. Incidence of bacterial STIs among MSM has been increasing over the past decade, both in King County and nationally [7,30], and evidence that PrEP may be contributing to these increases is troubling. However, our findings do not negate the tremendous success of PrEP as a tool for HIV prevention. In light of centrality of PrEP as an HIV prevention tool, new and creative STI prevention efforts among PrEP users are needed. Our results highlight the importance of ongoing screening and treatment of STIs among PrEP users. Because these are components of PrEP patient care, it may be that PrEP programmes can be leveraged to continue to engage MSM in more comprehensive STI prevention programmes in the future. The success of PrEP programmes may provide a unique opportunity to design and implement novel interventions to address increasing STI rates in this population.

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Conflicts of interest

All other authors declare that they have no conflict of interest.

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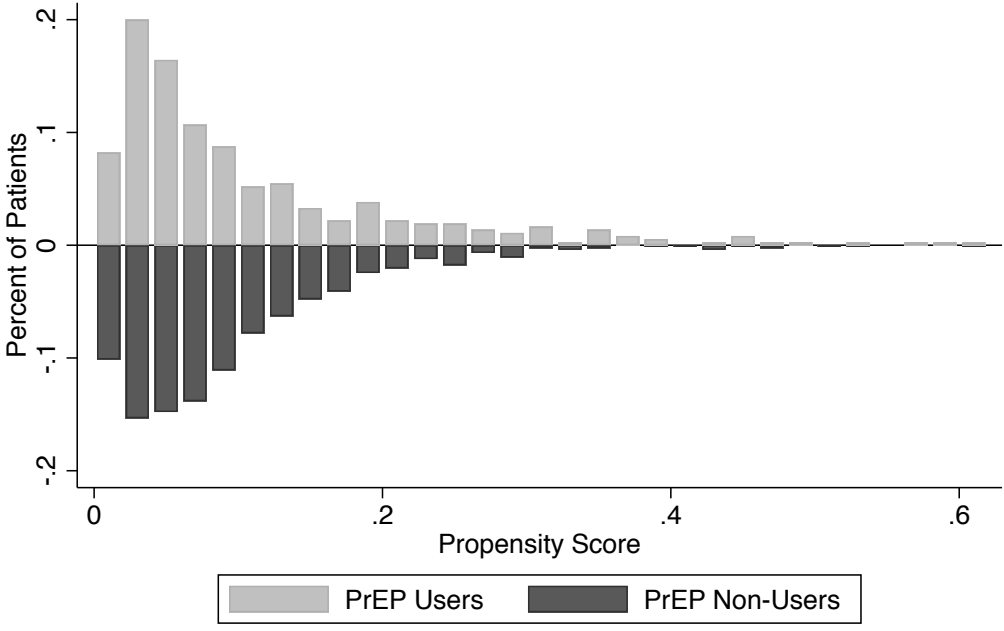
Supplementary Figure I. Distribution of Propensity Scores among PrEP Users and Non-Users



Supplementary Table 1. Standardized Differences for Propensity Score Covariates, Comparing PrEP Users and Propensity Score-Matched PrEP Non-Users at the Time of Their Initial PHSKC STD Clinic visit (N=1095)[a]

	PrEP Users (N=365)		PrEP Non-Users (N=730)			
Characteristic	**N**	**%**	**N**	**%**	**P-value**	**Standardized Difference**
Age (Mean, SD)	30.6	8.7	30.1	8.6	0.33	6.3
Race/Ethnicity[c]						
White, non-Hispanic	183	50.1	390	53.4	0.11	6.6
Black/African American, non-Hispanic	25	6.8	43	5.9		3.9
Hispanic	90	24.7	137	18.8		14.3
Asian/Pacific Islander, non-Hispanic	41	11.2	76	10.4		2.6
Mixed Race/Other, non-Hispanic[d]	14	2.7	42	4.7		9.0
Unknown, non-Hispanic	12	3.3	42	5.8		11.9
Visit Reason						
Symptoms	198	27.1	100	27.4	0.92	0.6
STI Screening	288	39.5	147	40.3	0.79	1.7
Positive STI Test	115	15.8	47	12.9	0.21	8.2
Partner has Symptoms or STI Diagnosis	212	29.0	109	29.9	0.78	1.8
Health Department Partner Services	18	2.5	12	3.3	0.43	4.9
Contact to Gonorrhea	62	8.5	37	10.1	0.37	5.7
Contact to Chlamydia	56	7.7	32	8.8	0.53	4.0
Contact to Syphilis	28	3.8	26	7.1	0.02	14.5
Symptoms						
Discharge	60	8.2	35	9.6	0.45	4.8
Painful Urination	60	8.2	38	10.4	0.23	7.5
Penile Discomfort	72	9.9	32	8.8	0.56	3.8
Genital Rash	83	11.4	29	7.9	0.08	11.6
Body Rash	64	8.8	23	6.3	0.15	9.3
Anorectal Discomfort	77	10.5	36	9.9	0.73	2.3
Testicular Discomfort	26	3.6	11	3.0	0.64	3.1
Other	82	11.2	38	10.4	0.68	2.6
Sexual Behavior[e]						
New Male Sex Partner, Prior 2 Months	513	70.3	258	70.7	0.89	0.9
Oral Sex, Receptive	575	78.8	286	78.4	0.88	1.0
Oral Sex, Insertive	584	80.0	284	77.8	0.40	5.4
Anal Sex, Receptive	565	77.4	272	74.5	0.29	6.7
With HIV-Positive Partner	81	11.1	46	12.6	0.46	4.7
Condom Use						
N/A	649	88.9	320	87.7	0.49	3.8
Always	23	3.2	8	2.2		5.9
Usually	23	3.2	12	3.3		0.8
Sometimes	16	2.2	14	3.8		9.6
Never	19	2.6	11	3.0		2.5
With HIV-Negative Partner	502	68.8	234	64.1	0.12	9.9
Condom Use						

N/A	232	31.8	133	36.4		9.8
Always	107	14.7	32	8.8		18.4
Usually	192	26.3	97	26.6	0.017	0.6
Sometimes	123	16.8	75	20.5		9.5
Never	76	10.4	28	7.7		9.6
With Unknown Status Partner	169	23.2	91	24.9	0.51	4.2
Condom Use						
N/A	562	77.0	274	75.1		4.5
Always	46	6.3	13	3.6		12.7
Usually	45	6.2	37	10.1	0.006	14.5
Sometimes	41	5.6	31	8.5		11.2
Never	36	4.9	10	2.7		11.4
Anal Sex, Insertive	550	75.3	261	71.5	0.17	8.7
With HIV-Positive Partner	147	20.1	70	19.2	0.71	2.4
Condom Use						
N/A	585	80.1	295	80.8		1.7
Always	56	7.7	15	4.1		15.2
Usually	31	4.2	23	6.3	0.13	9.2
Sometimes	36	4.9	20	5.5		2.5
Never	22	3.0	12	3.3		1.6
With HIV-Negative Partner	519	71.1	240	65.8	0.07	11.5
Condom Use						
N/A	215	29.5	125	34.2		10.3
Always	107	14.7	42	11.5		9.3
Usually	197	27.0	85	23.3	0.06	8.5
Sometimes	119	16.3	76	20.8		11.6
Never	92	12.6	37	10.1		7.8
With Unknown Status Partner	196	26.8	98	26.8	1.0	0.0
Condom Use						
N/A	534	73.2	268	73.4		0.6
Always	49	6.7	14	3.8		12.9
Usually	61	8.4	37	10.1	0.12	6.1
Sometimes	49	6.7	33	9.0		8.6
Never	37	5.1	13	3.6		7.4
Female Sex Partner, Prior 12 Months	33	4.5	23	6.3	0.21	7.9
Female Sex Partner, Prior 2 Months	17	2.3	9	2.5	0.89	0.9
New Female Sex Partner, Prior 2 Months	13	1.8	6	1.6	0.87	1.1
Vaginal Sex, Female Partner, Prior 2 Months	13	1.8	8	2.2	0.64	2.9
Condom Use						
N/A	717	98.2	357	97.8		2.9
Always	3	0.4	2	0.5		2.0
Usually	2	0.3	1	0.3	0.98	0.0
Sometimes	4	0.5	3	0.8		3.3
Never	4	0.5	2	0.5		0.0
Oral Sex, Female Partner, Prior 2 Months						
Gave	14	1.9	8	2.2	0.76	1.9
Received	12	1.6	8	2.2	0.52	4.0
STI Diagnoses[f]						
Pharyngeal Gonorrhea	146	20.0	71	19.5	0.83	1.4

Urethral Gonorrhea	66	9.0	38	10.4	0.47	4.6
Rectal Gonorrhea	221	30.3	108	2.6	0.82	1.5
Pharyngeal Chlamydia	30	4.1	18	4.9	0.53	4.0
Urethral Chlamydia	48	6.6	29	7.9	0.4	5.3
Rectal Chlamydia	152	20.8	87	23.8	0.26	7.2
Early Syphilis	106	14.5	58	15.9	0.55	3.8
Presumptive NGU Diagnosis, Current Visit	33	4.5	17	4.7	0.92	0.7
HIV Risk Behaviors[g]						
Sex with Injecting Drug User	51	7	24	6.6	0.8	1.6
Sex with HIV-POSITIVE Partner	176	24.1	86	23.6	0.84	1.3
Sex with Transgender Person	20	2.7	5	1.4	0.15	9.7
Sex with Anonymous Partner	281	38.5	130	35.6	0.35	6
Sex with Partner from the Internet	441	60.4	224	61.4	0.76	2
Sex at Bath House	156	21.4	74	20.3	0.67	2.7
Injection Drug Use	23	3.2	12	3.3	0.9	0.8
Crack Cocaine Use	9	1.2	6	1.6	0.58	3.4
Erectile Dysfunction Drug Use	93	12.7	44	12.1	0.75	2.1
Popper Use	313	42.9	175	47.9	0.11	10.2
Methamphetamine Use	81	11.1	36	9.9	0.53	4
Exchange Sex[h]	21	2.9	11	3	0.9	0.8

PHSKC, Public Health – Seattle & King County; SD, standard deviation; NGU, non-gonococcal urethritis
[a]Bold denotes variables where any standardized differences are greater than 10%
[b]Standardized differences are reported as the absolute value of the standardized difference comparing the two groups
[c]Categories for race/ethnicity are mutually exclusive
[d]Other includes self-reported other race and Native American and Alaskan Native
[e]Self reported sexual behavior in prior 12 months, unless otherwise specified
[f]In prior 12 months, unless otherwise specified; includes diagnosis at current visit
[g]Selfreported, in prior 12 months
[h]Giving or receiving money or drugs in exchange for sex.