Patterns in Sexual Behavior and STI Risk among MSM using ART to Treat or Prevent HIV

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Abstract

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Background: Men who have sex with men (MSM) face a disproportionately high burden of HIV. Recent advances in biomedical prevention of HIV such as treatment as prevention (TasP) and pre-exposure prophylaxis (PrEP) promise to improve the reach of HIV prevention efforts in MSM communities, but questions remain regarding the impact of these prevention methods on sexual behavior and STI risk. This dissertation investigated the impact of antiretroviral therapy (ART) on sexual behavior and STI risk among newly HIV-infected MSM and transgender women (TW) in Lima, Peru and among PrEP-using MSM in Seattle, WA.

Methods: This dissertation used data from MSM and TW participating in an expanded TasP study in Lima, Peru, to answer the question of whether ART use is associated with differences in sexual behavior and STI risk. In Aim 1, sexual behavior and STI incidence were compared between participants who had been randomized to receive ART either immediately or 24 weeks after diagnosis of early HIV infection. Two analyses were completed to answer the question of whether PrEP use is associated with changes in sexual behavior or increased risk of STIs. In Aim 2, data from the Public Health, Seattle & King County (PHSKC) STD Clinic was used to measure changes in sexual behavior after PrEP initiation. In Aim 3, data from the same clinic was used to compare STI incidence and time to first symptomatic STI among PrEP users to a propensity score-matched comparison group of non-users.

Results: In Aim 1, we found that while sexual risk behavior decreased in both study arms following HIV diagnosis, there was no difference in sexual behavior between the study groups. Incidence of bacterial STIs was high in both study arms, and participants randomized to receive ART after 24 weeks had higher incidence of chlamydia, but no difference in gonorrhea or syphilis incidence. In Aim 2, we found that 12 months after initiation of PrEP, MSM were more likely to report never using condoms and less likely to report unknown HIV-status partners compared to the PrEP initiation visit. There was no change in the number of sexual partners or reporting HIV-positive or HIV-negative partners. In Aim 3, we found that MSM using PrEP had higher incidence of chlamydia, gonorrhea, and early syphilis and faster time to first symptomatic STI compared to propensity score-matched PrEP non-users.

Conclusions: We observed decreased condom use and increased risk of bacterial STIs among HIV-negative PrEP users, no differences in sexual behavior associated with ART use among HIV-positive individuals, and overall high STI rates in both study populations. This work highlights the need for continued monitoring of sexual behavior in the changing context of biomedical HIV prevention and emphasizes the continued need for STI prevention, screening, and clinical care among high-risk MSM populations.

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Chapter 1: Introduction

Men who have sex with men (MSM) are disproportionately impacted by the HIV epidemic, both in the United States (US) and in Peru. In 2015, MSM accounted for 70% of all new HIV diagnoses among adults in the US and 86% of new infections among men (1), despite comprising only 4% of the US male population (2). The Centers for Disease Control and Prevention (CDC) estimates that the rate of new HIV infections among MSM ranges from 522 to 989 per 100,000, compared to 12 per 100,000 for other men (2). In Peru, prevalence of HIV among all adults is estimated to be 0.4%, while prevalence among MSM is 12%, with this subpopulation representing 56% of new infections (3–6). HIV prevalence among transgender women (TW) in Peru is even higher, at 30% (7,8). While condom use is effective at preventing both HIV and other sexually transmitted infections (STIs), a number of studies have found the proportion of MSM using this method to be below 50% (9–11), and increasing trends in condomless sex have been observed among MSM in many high income countries during the past decade (12–16). Contemporaneously, biomedical interventions involving the use of antiretroviral therapy (ART) to prevent HIV transmission are improving the efficacy and range of HIV prevention efforts.

There are currently two primary strategies of ART use for prevention. The first involves early initiation of ART in HIV-positive individuals, which reduces their HIV viral load to undetectable levels. This benefits them individually and also decreases the risk of onward transmission, an approach called “treatment as prevention” (TasP) (17). When used in serodiscordant couples, TasP can reduce HIV transmission by more than 90% when adherence is high (18,19), and recent studies conducted among serodiscordant MSM couples have shown no phylogenetically linked within-couple HIV transmissions during a combined 2181 couple-years of follow-up (20,21). Pre-exposure prophylaxis (PrEP), the use of ART by HIV-negative individuals to prevent HIV acquisition, has been shown to reduce risk of HIV acquisition in MSM by up to 92%

among highly adherent participants (22–25). As a result of the large body of evidence supporting the efficacy of TasP and PrEP, the World Health Organization (WHO) and the United States (US) Department of Health and Human Services (DHHS) recommend early initiation of ART in HIV-infected individuals regardless of disease stage and PrEP for HIV prevention in high risk communities (26–28).

The addition of these biomedical prevention methods to overall prevention strategies should increase the proportion of MSM protected from HIV, but TasP and PrEP do not protect against other STIs. Moreover, the possibility of risk compensation – the idea that an increase in risk behavior will follow the application of a method for risk-reduction (29,30) – in the context of ART for prevention has raised concerns that sexual behavior in high-risk populations will change in the presence of these new prevention methods, and in particular, that rates of condom use will decline (31–35). Changes in sexual behavior that may increase the risk of acquiring STIs could increase HIV risk as well, if HIV prevention strategies are not 100% effective. Optimization of both HIV and STI prevention efforts in MSM populations will require a better understanding of sexual behavior and STI risk in the context of scale up of ART as prevention.

This dissertation seeks to investigate changes in sexual behavior and STI rates among men who have sex with men (MSM) after they begin taking antiretroviral therapy (ART), either as treatment for HIV infection or to prevent HIV acquisition, by addressing three primary aims. The primary purpose of Aim 1 is to explore the impact of ART on sexual behavior and STI risk among HIV-positive MSM and TW. For this aim, described in Chapter 2, we used data from Peruvian MSM and TW participating in a randomized study of the timing of ART initiation to compare sexual behavior and STI incidence among participants using ART to those not using ART. Aims 2 and 3 focus on the impact of PrEP on sexual behavior and STI risk among HIV-negative MSM in King County. For these aims, described in Chapters 3 and 4, we used data

from MSM attending the Public Health, Seattle & King County (PHSKC) STD Clinic to measure changes in sexual risk behavior among MSM after PrEP initiation (Aim 2), and to test whether PrEP use is associated with increased risk of bacterial STIs (Aim 3). The overall objective of this research is to gain a better understanding of the impact of ART on sexual behavior among MSM, both in the context of early initiation of ART among HIV-positive MSM, and in the context of PrEP use for HIV prevention. Increasing our understanding of sexual behavior in the context of ART for prevention will allow us to develop better targeted interventions and strategies to address possible increases in risk, and elucidate opportunities for better implementation of biomedical HIV prevention programs.

Chapter 2. Sexual Behavior and STI Risk among Men who have Sex with Men and Transgender Women Participating in a Study of the Timing of Antiretroviral Therapy in Lima, Peru

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ABSTRACT

We assessed sexual behavior and risk of sexually transmitted infections risk among men who have sex with men (MSM) and transgender women (TW) participating in *Sabes*, a study of an expanded treatment as prevention strategy focused on early diagnosis and treatment of HIV infection in Lima, Peru. *Sabes* participants were tested monthly for HIV to identify acute or early infections, and HIV-positive participants were randomized to receive ART immediately (Immediate Arm) or after 24 weeks (Deferred Arm) during a 48-week follow-up period. Sexual behavior was assessed via computer-based questionnaire at randomization (baseline) and every 12 weeks thereafter. Participants were tested for urethral and rectal chlamydia and gonorrhea (via nucleic acid amplification tests) and for syphilis at baseline, 12, 24, and 48 weeks. We describe patterns of sexual behavior over the 48 week follow-up period, and compare sexual behavior and STI incidence between study arms. After randomization, 207 HIV-positive participants completed questionnaires and STI testing at 2 or more visits. Participants in both arms reported decreases in sexual risk behaviors after HIV diagnosis. We observed no between-arm differences in sexual behavior. Deferred Arm participants had higher incidence of chlamydia (Incidence Rate Ratio [IRR]: 2.33; 95% CI: 1.14 – 4.77), but not gonorrhea or syphilis. The overall high incidence of STIs reflects ongoing condomless sex among HIV-positive MSM and TW, highlighting the importance of regular STI screening and counseling to support consistent condom use among HIV-positive individuals at risk for STIs.

INTRODUCTION

In Peru, as in most of the world, men who have sex with men (MSM) and transgender women (TW) are at disproportionately high risk of HIV acquisition. While HIV prevalence in the general population of Peru is estimated to be less than 1%, prevalence among MSM and TW is an estimated 12% and 30%, respectively, with these subpopulations also representing a disproportionate percentage of new infections (5–8). The World Health Organization (WHO) recommends that antiretroviral therapy (ART) be initiated in all HIV-infected adults regardless of clinical stage of disease (26), and as soon as possible following diagnosis (27). These recommendations are due in part to substantial evidence that viral suppression resulting from initiation of and adherence to ART prevents onward transmission of HIV (18,21,26,36). Evidence from a number of observational studies conducted prior to the updated WHO recommendations showed that some MSM change their sexual behavior after HIV diagnosis to reduce behaviors associated with a high probability of onward transmission (37–43). Qualitative research suggests that these increases in protective behavior are primarily motivated by a desire to avoid infecting sexual partners (39). The majority of research studies exploring sexual behavior and STI risk by ART status have found either no association or lower sexual risk behavior and STI risk in ART users (44,45). It is unclear whether observed differences in behavior are due to ART use or to other baseline factors that differed between study groups such as HIV disease progression, and engagement in HIV-related clinical care, counseling, and prevention messaging. These studies were overwhelmingly conducted when recommendations for ART initiation depended on HIV disease stage, and as a result they are likely limited by differences in these factors between ART-users and non-users, which may have confounded observed associations between ART use and behavior. Further, the majority of these studies did not include MSM and TW, and data on the impact of ART on sexual behavior in these populations is lacking.

The Sabes study, which took place among MSM and TW in Lima, Peru, was a large study of an expanded treatment-as-prevention (TasP) strategy focused on early detection and treatment of HIV, conducted prior to WHO recommendations for immediate ART initiation. HIV-infected Sabes participants were randomized to receive ART either immediately after diagnosis or 24 weeks after diagnosis, providing a unique opportunity to measure the impact of ART initiation on sexual behavior and STI risk without the limitations of between-group differences in HIV disease progression or engagement in care. The primary objective of this analysis was to determine whether sexual behavior and STI risk differ by ART status, comparing Sabes participants receiving ART to participants not receiving ART. The secondary objective was to measure patterns of sexual behavior among participants in the Sabes study.

METHODS

Study Design, Setting, and Population

Data collection for this analysis took place within the Sabes study, the goals of which were to reduce HIV transmission by optimizing an early HIV detection strategy among Peruvian MSM and TW, and to explore the benefits of rapid linkage to care by comparing the impact of immediate versus deferred ART initiation. Sabes methods are described in detail elsewhere (46). Briefly, Sabes took place in three steps. In Step 1, persons who were assigned male sex at birth, age 18 years or older, reported at least one male sexual partner in the past 12 months, were unaware of their HIV status, and were at high risk for acquiring HIV were screened to identify HIV-negative individuals. High risk for HIV acquisition was defined as self-identification as a sex worker, or engaging in any of the following in the prior 6 months: anal sex with 5 or more male partners, no condom use during anal sex, having a sexual partner who was an HIV-positive man or TW, or having been diagnosed with an STI. Persons who had a sexual partner with newly diagnosed acute or recent HIV, and those with symptoms of acute retroviral syndrome were also eligible. In Step 2, HIV-negative individuals identified during screening

were enrolled in monthly HIV testing in order to identify incident cases of HIV. In Step 3, participants with acute (HIV seronegative, but positive for HIV RNA) or recent (HIV seropositive with a negative HIV test within 3 months) HIV infection were enrolled in a 48-week randomized study of immediate versus deferred ART. This analysis uses data collected during the Step 3 randomized study.

Step 3 participants were randomized in a 1:1 ratio to initiate ART either immediately (Immediate Arm) or after 24 weeks (Deferred Arm). Participants were not blinded to randomization arm. After enrollment, participants returned for follow-up visits every 12 weeks. Questionnaires were administered via computer-assisted self-interview (CASI) at enrollment (week 0) and every 12 weeks thereafter. Participants were tested for chlamydia, gonorrhea, and syphilis at weeks 0, 12, 24, and 48. Participants were included in this analysis if they were diagnosed with either acute or recent HIV, were randomized to either the Immediate or Deferred study arms, and completed the questionnaire and STI testing during at least two study visits.

Data Sources and Measures

Data on demographic characteristics and sexual behavior were obtained from questionnaire responses. Participants completed CASIs at weeks 0, 12, 24, 36, and 48. The enrollment CASI included questions about demographic characteristics, including age, gender identity, race, and socioeconomic status. All CASIs included a series of questions about sexual behavior in the prior 30 days, including type of anal sex partners (main, casual, transactional), condom use behavior with each type of partner, and substance use during or immediately prior to anal sex. Data on partner type was collected as yes/no for each type of partner, while data on condom use were collected using 5-point Likert scales ranging from always to never. Condom use variables were recoded into binary categories of “100 percent of the time” versus “less than 100 percent of the time” for this analysis.

Data on sexually transmitted infections included STI type (chlamydia, gonorrhea, syphilis), test date, and anatomic site of infection for chlamydia and gonorrhea (rectal, urethral), and were obtained via laboratory tests described below. Participants were tested for chlamydia, gonorrhea, and syphilis at enrollment, and at weeks 12, 24, and 48 of follow-up. Urine samples and rectal swabs were collected from participants and tested for chlamydia and gonorrhea via nucleic acid amplification testing, using the APTIMA Combo 2 Assay (Hologic Gen-Probe Inc. San Diego, CA). Incident cases of chlamydia and gonorrhea were defined as positive tests occurring after either a prior negative test, or after a prior positive test with evidence of treatment of the prior case. Syphilis testing was conducted using a rapid plasma reagin test (RPR Quicktest, Stanbio, Boerne, TX), with positive results confirmed using a *Treponema pallidum* particle agglutination assay (DR0530, TPHA Test, Oxoid Limited, Basingstroke, UK). Incident cases of syphilis were defined as cases with RPR $\geq$ 16 dilutions and positive TPHA result occurring after a prior negative test, or a four-fold increase in RPR titer following a prior positive test.

Statistical Analysis and Follow-up Time Calculation

We compared demographic characteristics, sexual behavior, and STI diagnoses between the two arms at enrollment using ANOVA for normally distributed continuous variables, Wilcoxon rank-sum for skewed distribution continuous variables, and Fisher's exact test for categorical and binary variables.

We used two methods for comparing sexual behavior between the two study arms. First, we used Poisson regression with robust standard errors to calculate prevalence ratios (PR) and corresponding 95% confidence intervals (CI) comparing each sexual behavior between the arms at 24 weeks, the time point at which the two study arms had differed by ART status for the maximum length of time, and at which we expected a resulting maximum difference in behavior. When analyzing cross-sectional data with common, binomial outcomes, Poisson regression with

robust standard errors approximates the relative risk better than logistic regression (47). Separate Poisson models were utilized for each behavior. Participants were included in the model for each behavior if they responded to the question about that behavior in the Week 24 CASI.

For our second behavioral analysis, we used generalized estimating equations (GEE) to model changes in sexual behavior over time. We used separate models for each behavior, comparing behavior at 12, 24, 36, and 48 weeks to behavior reported at enrollment, and comparing behavior between arms at each time point. We used an exchangeable correlation structure and robust standard errors for all models. Number of male sexual partners was modeled using a Poisson distribution and all other behaviors were modeled using log-binomial distributions. Time was included as a dummy variable, measured by study visit (0, 12, 24, 36, or 48 weeks), and an interaction term for time and study arm was included to account for differences in longitudinal patterns of behavior by arm. Participants were excluded from models for individual behaviors if they did not respond to the question about that behavior at any of their visits.

We used Poisson regression with robust standard errors to compare incidence of chlamydia, gonorrhea, and syphilis between the study arms during the first 24 weeks of follow-up, during which ART status differed between the two study arms. We ran separate Poisson models for each STI, and each anatomic site of infection for chlamydia and gonorrhea. Incident cases of chlamydia, gonorrhea, and syphilis were identified as described above. Cases of each STI that were diagnosed at the visit immediately after a diagnosis of the same STI with no evidence of treatment in between were not counted as incident infections. In these instances, the length of time between the two positive tests was subtracted from the total follow-up time for that participant, to account for the period of time between visits during which the participant was not at risk for an incident case of that STI. Due to concerns that differences in STI incidence during follow-up might result from differences in STI prevalence at enrollment, a sensitivity

analysis was performed in which Poisson regression models were re-run after excluding participants who were diagnosed with STIs at baseline.

All analyses were intent-to-treat. Two-sided statistical tests were performed at a significance level of 0.05. We used Stata version 13.1 (College Station, TX, USA) for all analyses. This study was approved by the institutional review boards of Asociación Civil Impacta Salud y Educación, Asociación Vía Libre, and the Fred Hutchinson Cancer Research Center.

RESULTS

During the study period (2013-2017), 216 Sabes participants were diagnosed with early or acute HIV, and randomized to either the Immediate or Deferred study arms. Of these, 207 participants had complete CASI and STI data at 2 or more study visits and were included in our analytic sample, 99 in the Immediate Arm and 108 in the Deferred Arm. The two groups were balanced in terms of demographic characteristics, sexual behavior, and STIs measured at enrollment (Table 1.1). The mean age in both study arms was 27 years, and most participants were cisgender MSM. At enrollment, almost half of participants reported having had a main partner in the prior 30 days, and over half reported having had at least one casual partner. Condom use with all partner types was similar between arms at enrollment. A higher, but not statistically significant, proportion of Deferred Arm participants were diagnosed with STIs at enrollment. Participants in both arms had the same median number of visits (5), and length of follow-up time (336 days).

Sexual Behavior

Participants in both study arms reported increases in protective sexual behavior after HIV diagnosis (Figure 1.1). The proportion of participants who reported 100% condom use with both main and casual partners doubled during follow-up. The number of recent male anal sex

partners and the proportion of participants reporting drug or alcohol use immediately prior to or during anal sex fell during follow-up. Aggregate changes in behavior were observed by the 12-week visit, and were largely sustained throughout the 48-week follow-up period. The proportion of participants in each arm reporting each sexual behavior at 24 weeks, and comparisons of behavior between the two arms at 24 weeks is included in Table 1.2. There were no differences in the proportion of participants reporting any sexual behavior between arms. In longitudinal models, while protective behavior in both arms increased in comparison to baseline, there were no differences in sexual behavior between study arms (Supplementary Tables 1.1 & 1.2).

Sexually Transmitted Infections

Among Deferred Arm participants, incidence of chlamydia, gonorrhea, and syphilis was 59.6, 36.4, and 6.0 per 100 person-years, respectively (Table 1.3). Deferred Arm participants had over 2-fold higher incidence of chlamydia compared to Immediate Arm participants (IRR: 2.33; 95% CI: 1.14 – 4.77), but no significant differences in gonorrhea or syphilis incidence. Results of sensitivity analyses excluding participants who were diagnosed with STIs at enrollment did not differ from the results of the primary analysis, with a two-fold higher incidence of chlamydia among Deferred Arm participants (IRR: 2.16; 95% CI: 1.00 – 4.66), and no differences in gonorrhea or syphilis incidence (not shown).

DISCUSSION

In this randomized study of timing of ART initiation among Peruvian MSM and TW, we observed no differences in sexual behavior between the study arms at enrollment, or after the first 24 weeks of follow-up during which ART status differed between the arms. Longitudinal models similarly showed no differences in patterns of behavior between arms, although marked and sustained changes in behavior likely to reduce the risk of HIV transmission were observed

in the cohort as a whole. Taken together, these results suggest that HIV diagnosis was the primary motivator for changes in sexual behavior, while ART initiation had little overall impact.

Our behavioral findings are consistent with studies of the impact of HIV diagnosis on sexual behavior. Several observational studies have documented reductions in HIV risk behavior after diagnosis, including decreases in number of sexual partners (38,39,42,43), increases in overall condom use (42,43), and declines in condomless sex with unknown status (38), and HIV-negative partners (41). These behaviors were sustained over periods of months to years, depending on study and follow-up time. Our behavioral findings are somewhat inconsistent with prior studies of the impact of ART on sexual behavior. Studies on this topic have been summarized in two systematic reviews published prior to the updated WHO recommendations for universal treatment and the scale up of TasP and undetectable equals untransmissible (U=U) programs. One review, conducted by Zakher and colleagues, found that overall, ART use was not associated with increased HIV risk behavior, although some studies included in the review found that ART use was associated with reduced risk behavior (45). Similarly, a review and meta-analysis by Doyle and colleagues found lower pooled odds of both condomless sex (odds ratio [OR]: 0.73; 95% CI: 0.64 – 0.83) and STI diagnoses (OR: 0.58; 95% CI: 0.33 – 1.01) among persons using ART compared to those not using ART (44). Our between-arm behavioral results indicated no differences in sexual behavior by ART use, although we did observe decreased risk of chlamydia among participants using ART, similar to the Doyle analysis. The concurrent impacts of engagement in HIV treatment and associated ongoing HIV prevention messaging among people on ART, including regular clinical monitoring and counseling, may have resulted in more opportunities to reinforce prevention messaging among ART users compared to non-users. This may account for observed differences in sexual behavior between groups. Because our participants were randomized to receive or not receive ART, and were engaged in the same clinical care and counseling through the study regardless

of ART status, there were no differences in HIV disease progression or engagement with HIV-related care, counseling, and prevention between our ART and non-ART groups.

Despite the lack of observed differences in behavior by study arm, participants in the Deferred Arm had more than two-fold higher incidence of chlamydia than Immediate Arm participants, and this difference persisted even after the exclusion of participants diagnosed with chlamydia at enrollment. It is not clear what accounts for the disparity in our behavioral and biologic outcomes for this STI. Chlamydia was the most commonly diagnosed of the three STIs, so it is possible that the lower number of observed outcomes for gonorrhea and syphilis models resulted in a lack of power to detect differences in these two STIs. Conversely, it is possible that overall STI risk in the two arms did not differ, as results for gonorrhea and syphilis were not significant.

The overall high incidence of STIs in this study population after HIV diagnosis suggests ongoing condomless sex, despite self-reported increases in condom use during follow-up. Viral load suppression, which vastly reduces the risk of HIV transmission, is not an immediate consequence of ART initiation, and sexual risk behavior can result in HIV transmission in the gap between ART initiation and HIV viral load suppression. Participants received strong and consistent messaging about the importance of continuing to use condoms due to the high risk of transmission during the acute phase of HIV infection. That STI incidence overall was so high in spite of this messaging and concomitant self-reported increases in condom use may be cause for concern, and supports the importance of public health messaging regarding the continued use of condoms during the weeks after ART initiation.

Our results should be interpreted with caution due to the changing landscape of ART as prevention. This study was conducted prior to the updated WHO recommendations regarding TasP and the current UNAIDS undetectable equals untransmissible (U=U) campaign. While some study participants may have been aware that HIV transmission risk is decreased in individuals on ART, they did not receive consistent messaging about the efficacy of TasP as

part of the study. In the current global context of U=U messaging the impact of ART initiation on sexual behavior may differ from what we observed in the Sabes study. The Opposites Attract Study, which examined TasP among MSM serodiscordant couples in Brazil, Australia, and Thailand found that among HIV-negative Australian participants, perceiving their partner's viral load to be undetectable was associated with increased condomless anal sex (48).

Our results should be interpreted in light of several limitations. First, our self-reported data on sexual behavior is subject to social desirability bias. While we attempted to mitigate the impact of this source of bias by using CASIs for data collection, it is possible that some level of bias persists in our data, and that this bias may differ between the study arms. Second, prior research in this population indicates that there are behavioral differences between MSM and TW (49), but due to the small number of TW in our study population we were unable to conduct separate analyses with this subgroup. Third, generalizability of these results to other MSM and TW populations is uncertain due to our study population's frequent contact with clinicians and research staff, and to the fact that study participants were selected for their high risk of HIV acquisition. Finally, a small number of participants in the Deferred Arm of our study broke randomization and were started on ART earlier than 24 weeks due to decline in CD4 count to below 350 or clinical symptoms that met criteria for ART initiation. The inclusion of these participants in our intent-to-treat analysis may have attenuated our effect size, and it is possible that we have underestimated the observed difference in STI risk between study arms as a result. However, the primary strength of our randomization is that there were no differences in baseline characteristics including disease progression, health, and engagement in care between the arms at baseline, and our intent-to-treat analysis preserves this strength.

Our study had a number of strengths. Most importantly, randomization of participants to either receive ART immediately or 24 weeks after HIV diagnosis enabled us to measure the impact of ART on behavior without between-group differences in HIV disease progression or engagement in care, a limitation of prior studies on this topic. This ensured that any differences

in sexual behavior between the arms were a result of ART initiation rather than baseline differences between ART users and non-users. In addition, follow-up was consistent between arms after randomization, with the same median length of follow-up time and number of study visits in both arms. Finally, questionnaire data and STI testing were standardized for both arms, and STI testing took place at all planned visits regardless of the presence or absence of symptoms.

In summary, we found that HIV-positive Peruvian MSM and TW in both randomization arms increased sexual behavior likely to protect their sexual partners from HIV acquisition during the year after diagnosis, indicating the powerful behavioral influence of knowledge of HIV status. Our results suggest that lower rates of risk activity seen in persons on ART in earlier studies are likely due to higher exposure to counseling and other clinical services. Our data were collected prior to the widespread appreciation of U=U and thus it is perhaps not surprising that the sexual behavior of those on ART did not differ from those not on ART. However, despite reductions in reported risk behavior, participants in both arms reported substantial levels of risk. STI rates were high, without a clear and consistent difference between arms, which reflects ongoing condomless sex among HIV-positive MSM and TW after HIV diagnosis, and highlights the importance of regular STI screening as a fundamental component of HIV patient care. The data presented reflect the landscape prior to the widespread understanding that U=U. While the evidence regarding the impact of ART initiation on sexual behavior in the new context of U=U is limited thus far, these results underscore both the need for continued counseling to support consistent condom use both to prevent HIV transmission in persons on ART prior to full viral load suppression and to reduce STI transmission in fully suppressed HIV-positive individuals, and the increased importance of regular STI screening for MSM communities who may be using condoms less.

Table 1.1. Characteristics of Sabes Participants at the Time of Their Enrollment Visit (N=207)

	Deferred (N=108)		Immediate (N=99)		
Demographic Characteristics	**N**	**%**	**N**	**%**	**p-value**
Age (Mean, SD)	26.7	6.8	27.7	7.2	0.28[a]
Gender					
Cis Man	89	82.4	83	83.8	0.85[c]
Transgender Woman[b]	9	8.3	6	6.1	
Not Reported	10	9.3	10	10.1	
Education					
High School or Less	36	33.3	20	20.2	0.13[c]
Some Technical School or University	38	35.2	35	35.4	
Complete Technical School, University, or Higher	28	25.9	35	35.4	
Not Reported	6	5.6	9	9.1	
Sexual Behavior					
Number of Anal Sex Partners, Prior 3 Months (Med, IQR)	3	1, 6	3	1, 5	0.66[d]
Main Partner, Prior 30 Days	48	47.5	46	51.7	0.66[c]
Frequency of Condom Use during Anal Sex with Main Partner[e]					
Less than 100%	39	81.2	31	67.4	0.16[c]
100%	9	18.8	15	32.6	
1+ Casual Partners, Prior 30 Days	63	61.8	55	59.8	0.88[c]
Frequency of Condom Use during Anal Sex with Casual Partners[f]					
Less than 100%	39	61.9	34	61.8	1.00[c]
100%	24	38.1	21	38.2	
Rec'd Money/Goods/Etc for Anal Sex, Prior 30 Days	17	15.9	18	18.9	0.58[c]
Frequency of Condom Use with Transactional[g] Partners[h]					
Less than 100%	11	64.7	9	50.0	0.50[c]
100%	6	35.3	9	50.0	
Drug/Alcohol Use Before/During Anal Sex, Prior 30 Days	20	19.6	21	22.6	0.73[c]
Clinical Characteristics					
CD4 Count (Med, IQR)	401	283, 542	431	269, 576	0.78[d]
Viral Load (Med $\log_{10}$ copies/ml, IQR)	5.8	5.2, 6.6	6.1	5.2, 6.8	0.33[d]
Sexually Transmitted Infections					
Chlamydia Infection[i]	20	19.8	13	13.7	0.34[c]

Gonorrhea Infection[j]	17	16.7	9	9.6	0.21[c]
Syphilis Infection[k]	3	3.4	3	3.5	1.00[c]

SD: Standard Deviation; Med: Median; IQR: Inter-quartile range
[a]Groups compared using ANOVA
[b]Includes participants assigned male at birth who identified in questionnaire as transgender woman or female
[c]Groups compared using Fisher's exact test
[d]Groups compared using Wilcoxon rank-sum
[e]Of the participants who reported main partners (Immediate=46; Deferred=48)
[f]Of the participants who reported casual partners (Immediate=55; Deferred=63)
[g]Transactional sex is defined as receiving money, gifts, alcohol, drugs, clothing, food, transportation, or lodging in exchange for anal sex
[h]Of the participants who reported transactional sex partners (Immediate=18; Deferred=17)
[i]Out of 95 participants in the Immediate Arm and 101 participants in the Deferred Arm who were tested for chlamydia at their Enrollment visit and contributed follow-up time to analysis
[j]Out of 94 participants in the Immediate Arm and 102 participants in the Deferred Arm who were tested for gonorrhea at their Enrollment visit and contributed follow-up time to analysis
[k]Out of 86 participants in the Immediate Arm and 89 participants in the Deferred Arm who were tested for syphilis at their Enrollment visit and contributed follow-up time to analysis

Table 2. Sexual Behavior at 24 Weeks, Comparing the Deferred Arm to the Immediate Arm (N=195[a])

	Deferred (N=100)		Immediate (N=95)				
Behavior	**Med**	**IQR**	**Med**	**IQR**	**IRR**	**95% CI**	**p-value**
Number of Anal Sex Partners, Prior 3 Months	1	1, 3	1	1, 3	0.95	(0.52, 1.74)	0.86
	N	**%**	**N**	**%**	**PR**	**95% CI**	**p-value**
Main Partner, Prior 30 Days	40	40.0	43	45.3	0.90	(0.66, 1.23)	0.51
100% Condom Use with Main Partner[b]	26	65.0	33	76.7	0.85	(0.64, 1.12)	0.25
1+ Casual Partners, Prior 30 Days	44	46.3	44	47.3	0.98	(0.72, 1.33)	0.89
100% Condom Use with Casual Partners[c]	34	77.3	36	81.8	0.94	(0.76, 1.17)	0.60
Transactional Sex[d] Prior 30 Days	11	11.0	11	11.6	0.95	(0.43, 2.09)	0.90
100% Condom Use with Transactional Partners[e]	8	72.7	9	81.8	0.89	(0.56, 1.42)	0.62
Drug/Alcohol Use Before/During Anal Sex, Prior 30 Days	10	10.6	8	8.6	1.24	(0.51, 3.00)	0.64

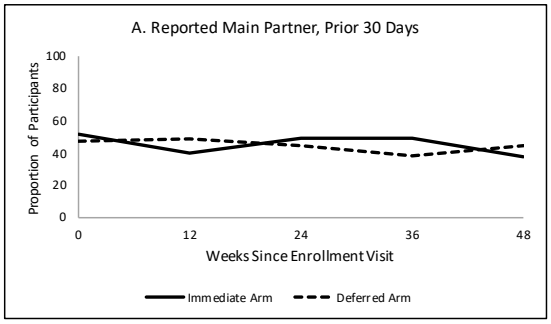
Med: Median; IQR: Inter-Quartile Range; IRR: Incidence Rate Ratio; PR: Prevalence Ratio; 95% CI: 95% Confidence Interval
[a]Due to skip patterns and response rates to individual questions, sample sizes for each behavioral model vary slightly
[b]Of the participants who reported Main Partners (Immediate=43; Deferred=40)
[c]Of the participants who reported Casual Partners (Immediate=44; Deferred=44)
[d]Transactional sex is defined as receiving money, gifts, alcohol, drugs, clothing, food, transportation, or lodging in exchange for anal sex
[e]Of the participants who reported Transactional Partners (Immediate=11; Deferred=11)

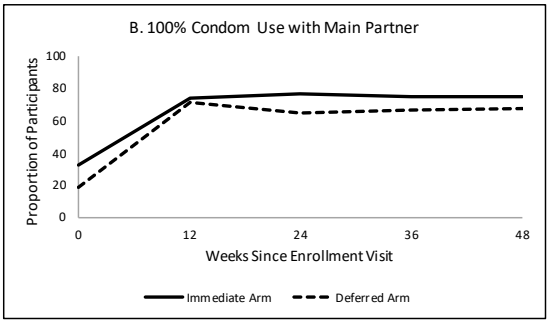
Table 1.3. Incidence of Bacterial STIs among Sabes Study Participants in the Immediate and Deferred Study Arms (N=207)

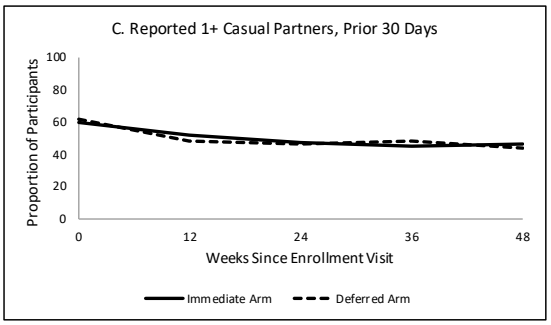
STI	Deferred Arm Incidence, per 100 person-years	Immediate Arm Incidence, per 100 person-years	IRR	95% CI	p-value
Chlamydia	59.6	25.6	2.33	(1.14, 4.77)	0.02
Rectal	48.6	25.6	1.90	(0.91, 3.98)	0.09
Urethral[a]	12.6	0	--	--	--
Gonorrhea	36.4	28.1	1.29	(0.62, 2.68)	0.49
Rectal	21.4	28.1	0.76	(0.33, 1.74)	0.52
Urethral	14.6	2.3	6.44	(0.80, 51.6)	0.08
Syphilis	6.0	11.0	0.55	(0.13, 2.25)	0.40

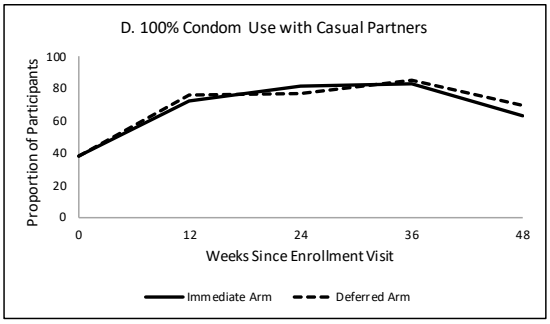
IRR: incidence rate ratio.
CI: Confidence interval
Note on sample size: Participants were dropped from individual models if they had no observed time-at-risk. Sample sizes for each STI are below.
Chlamydia models: Immediate Arm N=99, Deferred Arm N=105
Gonorrhea models: Immediate Arm N=97, Deferred Arm N=107
Syphilis model: Immediate Arm N=99; Deferred Arm N=108
[a]No cases of urethral chlamydia in Immediate Arm between weeks 0 and 24

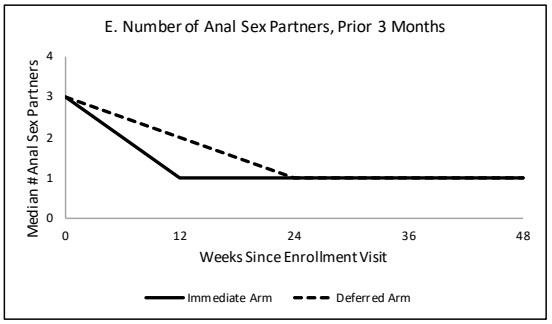
Figure 1.1. Proportion of Sabes Participants Reporting Sexual Behaviors at Each Follow-Up Visit, by Randomizaton Arm

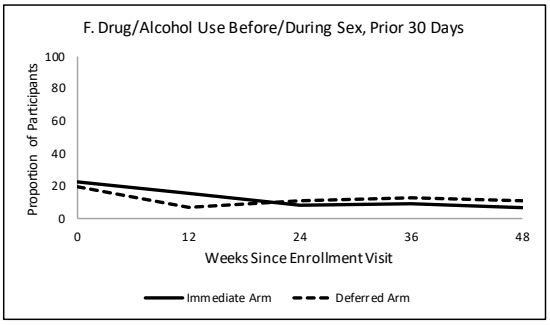












Supplementary Table 1.1. Risk of Reporting Sexual Behaviors at Each Follow-up Visit by Study Arm, Comparing Each Visit to Enrollment

		12 Weeks		24 Weeks		36 Weeks		48 Weeks	
Behavior	**N[a]**	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Number of Anal Sex Partners, Prior 3 Months									
Immediate Arm	207	0.67	(0.45, 0.99)	0.64	(0.41, 1.00)	0.72	(0.52, 1.02)	0.76	(0.52, 1.12)
Deferred Arm		0.68	(0.53, 0.88)	0.52	(0.37, 0.75)	0.56	(0.40, 0.79)	0.52	(0.38, 0.70)
	N	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Main Partner, Prior 30 Days									
Immediate Arm	206	0.78	(0.61, 0.99)	0.92	(0.72, 1.17)	0.92	(0.72, 1.19)	0.71	(0.53, 0.94)
Deferred Arm		0.89	(0.70, 1.12)	0.94	(0.75, 1.18)	0.83	(0.62, 1.10)	0.90	(0.67, 1.21)
100% Condom Use with Main Partner									
Immediate Arm	154	2.16	(1.41, 3.30)	2.26	(1.44, 3.54)	2.26	(1.42, 3.59)	2.19	(1.39, 3.44)
Deferred Arm		3.42	(1.94, 6.03)	3.11	(1.72, 5.64)	3.19	(1.74, 5.82)	3.36	(1.87, 6.05)
1+ Casual Partners, Prior 30 Days									
Immediate Arm	206	0.90	(0.71, 1.13)	0.80	(0.64, 0.99)	0.78	(0.62, 0.99)	0.79	(0.61, 1.01)
Deferred Arm		0.80	(0.64, 0.97)	0.74	(0.57, 0.95)	0.77	(0.61, 0.97)	0.69	(0.53, 0.90)
100% Condom Use with Casual Partners									
Immediate Arm	171	1.82	(1.27, 2.60)	2.03	(1.43, 2.89)	2.05	(1.45, 2.90)	1.62	(1.11, 2.36)
Deferred Arm		2.04	(1.41, 2.96)	2.11	(1.48, 3.00)	2.26	(1.61, 3.15)	1.78	(1.22, 2.60)
Transactional Sex[b] Prior 30 Days									
Immediate Arm	207	0.40	(0.21, 0.74)	0.65	(0.38, 1.11)	0.53	(0.29, 0.96)	0.64	(0.39, 1.07)
Deferred Arm		0.97	(0.66, 1.44)	0.70	(0.43, 1.14)	1.10	(0.76, 1.59)	0.84	(0.54, 1.33)
100% Condom Use with Transactional Partners									
Immediate Arm	56	0.35	(0.09, 1.28)	1.64	(0.87, 3.09)	1.39	(0.69, 2.76)	1.60	(0.91, 2.84)
Deferred Arm		1.54	(0.77, 3.05)	1.94	(0.93, 4.06)	1.94	(1.08, 3.46)	2.01	(0.98, 4.13)
Drug/Alcohol Use Before/During Anal Sex, Prior 30 Days									
Immediate Arm	207	0.74	(0.46, 1.21)	0.40	(0.21, 0.77)	0.42	(0.23, 0.75)	0.32	(0.15, 0.66)
Deferred Arm		0.35	(0.17, 0.72)	0.52	(0.26, 1.04)	0.62	(0.36, 1.04)	0.51	(0.27, 0.99)

IRR: Incidence Rate Ratio; CI: Confidence Interval; RR: Relative Risk

[a]Participants were excluded from individual models if they did not respond to the question about that behavior at any of their visits

[b]Transactional sex is defined as receiving money, gifts, alcohol, drugs, clothing, food, transportation, or lodging in exchange for anal sex

Supplementary Table 1.2. Risk of Reporting Sexual Behaviors at Each Follow-up Visit, Comparing the Deferred Arm to the Immediate Arm

	Enrollment		12 Weeks		24 Weeks		36 Weeks		48 Weeks	
Behavior	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**	**IRR**	**95% CI**
Number of Anal Sex Partners[a]										
Immediate Arm		1		1		1		1		1
Deferred Arm	1.13	(0.68, 1.89)	1.03	(0.64, 1.65)	0.81	(0.46, 1.44)	0.77	(0.48, 1.26)	0.68	(0.41, 1.11)
	RR	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**	**RR**	**95% CI**
Main Partner										
Immediate Arm		1		1		1		1		1
Deferred Arm	0.92	(0.69, 1.22)	1.14	(0.82, 1.60)	1.03	(0.73, 1.44)	0.90	(0.61, 1.31)	1.27	(0.84, 1.93)
100% Condom Use with Main Partner										
Immediate Arm		1		1		1		1		1
Deferred Arm	0.62	(0.31, 1.22)	1.59	(0.78, 3.22)	1.37	(0.65, 2.90)	1.41	(0.66, 3.01)	1.54	(0.73, 3.22)
1+ Casual Partners										
Immediate Arm		1		1		1		1		1
Deferred Arm	1.04	(0.83, 1.31)	0.88	(0.64, 1.20)	0.93	(0.66, 1.30)	0.98	(0.71, 1.36)	0.88	(0.61, 1.27)
100% Condom Use with Casual Partners										
Immediate Arm		1		1		1		1		1
Deferred Arm	0.93	(0.59, 1.47)	1.12	(0.67, 1.89)	1.04	(0.63, 1.71)	1.10	(0.68, 1.78)	1.10	(0.64, 1.87)
Transactional Sex[b]										
Immediate Arm		1		1		1		1		1
Deferred Arm	0.85	(0.46, 1.57)	2.45*	(1.18, 5.10)	1.07	(0.52, 2.21)	2.08*	(1.03, 4.17)	1.31	(0.66, 2.59)
100% Condom Use with Transactional Partners										
Immediate Arm		1		1		1		1		1
Deferred Arm	0.73	(0.34, 1.58)	4.40	(1.00, 19.3)	1.18	(0.45, 3.12)	1.40	(0.57, 3.44)	1.25	(0.50, 3.14)
Drug/Alcohol Use Before/During Anal Sex										
Immediate Arm		1		1		1		1		1
Deferred Arm	0.90	(0.53, 1.54)	0.47	(0.20, 1.13)	1.31	(0.50, 3.38)	1.48	(0.67, 3.27)	1.62	(0.61, 4.33)

IRR: Incidence Rate Ratio; CI: Confidence Interval; RR: Relative Risk
Immediate Arm is the reference group in all models
Participants were excluded from individual models if they did not respond to the question about that behavior at any of their visits
[a]Number of anal sex partners is in prior 3 months; all other behaviors are in prior 30 days
[a]Transactional sex is defined as receiving money, gifts, alcohol, drugs, clothing, food, transportation, or lodging in exchange for anal sex
*p<0.05

Chapter 3. Changes in Sexual Behavior and STI Diagnoses among MSM Initiating PrEP in a Clinic Setting

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Compliance with Ethical Standards

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.
For this type of study formal consent is not required.

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Previous Presentations
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Abstract: We examined changes in sexual behavior and sexually transmitted infection (STI) prevalence among 183 men who have sex with men (MSM) initiating pre-exposure prophylaxis (PrEP) at an STD Clinic in Seattle, WA. We used generalized estimating equations to measure changes in sexual behavior during PrEP use, and linked PrEP patient data with STI surveillance data to compare the prevalence of chlamydia, gonorrhea, and early syphilis in the periods prior to and during PrEP use. Reporting never using condoms in the prior 30 days increased (adjusted relative risk=1.46; 95% confidence interval: 1.13, 1.88) at 12 months after PrEP initiation compared to the initial PrEP visit. Reporting unknown status partners in the prior 30 days decreased at 12 months compared to the initial PrEP visit, but there was no change in number of sexual partners or reporting HIV-positive or HIV-negative partners. The percentage of patients diagnosed with any STI while using PrEP (49.2%) was higher than the percentage diagnosed in the 12 months prior to PrEP use (35.0%), likely driven in part by increased STI screening during PrEP use. Among MSM on PrEP, we observed decreases in condom use, and a higher prevalence of STIs during PrEP use compared to prior to PrEP initiation.

Key Words: Men Who Have Sex With Men; HIV; Pre-Exposure Prophylaxis; Sexually Transmitted Infections; Sexual Behavior

INTRODUCTION

Men who have sex with men (MSM) are disproportionately impacted by HIV in the United States (US), accounting for 86% of new infections among men in 2016 (1). Pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition in MSM by over 85% among highly adherent participants (2–4) and is now being offered routinely in many clinical settings in the US (5). The possibility of risk compensation – an increase in risk behavior following the application of a method for risk reduction – raises concerns that there will be increases in condomless sex or number of sexual partners in populations using PrEP, (6–8) which could facilitate the transmission of sexually transmitted infections (STI). Most evidence describing PrEP risk compensation comes from clinical trials of PrEP efficacy and open-label studies, which have found no evidence of increases in high-risk behavior (2,3,9). However, new data from clinic-based studies shows decreased condom use and increases in some STIs among MSM using PrEP, suggesting that risk compensation may occur outside of the context of research settings (10–12). Further, increasing bacterial STI rates in the US have reinforced concerns regarding risk compensation among MSM on PrEP. The rate of primary and secondary syphilis among men has increased 70% during the past 5 years, with an estimated 58% of cases occurring among MSM (13). While much of this increase predated widespread adoption of PrEP, it may be that PrEP is an important factor driving changes in sexual behavior and associated increases in STI rates among MSM.

The Public Health – Seattle & King County (PHSKC) STD Clinic provides PrEP to patients at high risk for HIV, and collects robust sexual behavior data from PrEP patients at each clinical visit. This setting provides an opportunity to examine changes in sexual behavior and STI risk before and after the implementation of PrEP among a clinic-based population of MSM. The primary objectives of this study were to determine whether and how MSM change their sexual behavior after initiating PrEP and to examine STI diagnoses among MSM on PrEP. We hypothesized that there would be no change in number of male sexual partners or sexual

position, but that MSM would be more likely to report HIV-positive and unknown status partners, and less likely to use condoms while taking PrEP. We further hypothesized that the prevalence of all STIs would be higher during PrEP use compared to the period prior to PrEP use.

METHODS

Study Design, Setting and Population

This study was a secondary analysis of longitudinal data from a cohort of MSM who initiated PrEP through the PHSKC STD Clinic between October 2014 and April 2017. Per PHSKC and Washington State (WA) PrEP guidelines (14) the PHSKC STD Clinic has provided PrEP to patients at high risk for acquiring HIV since October 2014. This group includes transgender persons who have sex with men and MSM who report any of the following risk factors in the past 12 months: diagnosis of rectal gonorrhea or early syphilis; use of methamphetamine or amyl nitrites (poppers); or exchanging sex for money or drugs. PrEP is also recommended for patients who are in ongoing sexual relationships with HIV-positive partners who are not virally suppressed. STD Clinic clinicians evaluate patients for PrEP eligibility, and those who meet the recommended criteria are offered PrEP through the clinic.

At the PrEP initiation visit, patients complete a behavioral questionnaire by computer-assisted self-interview (CASI), are tested for HIV and STIs, and are given a PrEP prescription. Clinic staff verify the initial prescription fill. Patients return one month after PrEP initiation, then quarterly for clinical follow up and monitoring. At quarterly visits patients are tested for HIV and STIs, complete behavioral questionnaires, and receive new 3-month prescriptions for PrEP. If patients are unable to attend a follow-up appointment in person, STD Clinic clinicians can call in one 30-day prescription refill. Clinic staff attempt to determine reason for PrEP discontinuation for all patients who stop attending follow-up appointments or stop using PrEP. Patients are categorized as lost to follow-up if clinic staff are unable to reach them after three attempts.

PrEP patients were included in this analysis if they initiated PrEP during the study period, and completed a questionnaire during their initial visit and at least one follow-up visit. If patients stopped and re-started PrEP during the study period, the longest series of completed questionnaires was used. This study was approved by the University of Washington Institutional Review Board.

Data Sources and Measures

Patients complete a CASI at PrEP initiation and at quarterly follow-up visits. The CASI queries patients on aggregate sexual behavior with male partners during the prior 30 days. Data collected in the CASI include number of male sexual partners, partner HIV status (HIV-positive, HIV-negative, unknown status), sexual role (insertive, receptive) by partner HIV status, and condom use by partner HIV status and sexual role. Data on sexual role and partner HIV status are collected as yes/no, while data on condom use are collected as always/usually/sometimes/never. Condom use variables were recoded into binary categories of "ever" versus "never" for this analysis.

Data on age, race, and insurance status were obtained from electronic medical records. Data on bacterial STI diagnoses were obtained from the Public Health Issue Management System (PHIMS), the electronic STI surveillance system used in WA. WA laws require laboratories and medical providers to report all cases of chlamydia (CT), gonorrhea (GC), and syphilis to local health authorities who subsequently provide data to the WA Department of Health via PHIMS. Through PHIMS, we obtained data on all positive STI laboratory tests reported in King County. STI diagnosis (CT, GC, early syphilis (primary, secondary, or early latent)), anatomic site of infection, and diagnosis date were obtained from PHIMS, and linked to PrEP patients via deterministic matching by last name and date of birth.

HIV and STI Testing

Quarterly HIV and STI tests are recommended for all patients obtaining PrEP through the clinic, and are performed as part of routine clinical care. Patients are screened for CT and GC at each anatomic site (urethra, pharynx, rectum) based on reported exposure. Urine samples, and urethral, pharyngeal, and rectal swabs were tested for GC and CT using nucleic acid amplification testing (APTIMA Combo 2, Hologic, Inc, Marlborough, MA). Blood samples were tested for syphilis using a qualitative rapid plasma reagin test, with confirmatory tests performed using *Treponema pallidum* particle agglutination assay and, as needed, enzyme-linked immunosorbent assay (EIA). All cases of syphilis in King County are assigned stages by a disease intervention specialist based on laboratory and clinical findings. Blood samples were tested for HIV using a fourth-generation antigen/antibody test (BioRad GS HIV Combo Ag/Ab EIA, Hercules, CA). At the initial visit, patients are also tested using an INSTI rapid antibody test (BioLytical Laboratories, Richmond, BC).

Statistical Analysis

To examine behavioral trends, we used generalized estimating equations (GEE) to model changes in self-reported sexual behavior over time. Separate models were developed for each behavior. We identified age, race, and insurance status *a priori* as confounders, and included them in all models. Time was included as a continuous variable, measured in days since initial questionnaire. Quadratic and cubic time variables were initially included in all models to test for non-linear changes in behavior, but were left out of final models if they were not statistically significant. Number of male sexual partners was modeled using a Poisson distribution with exchangeable correlation structure, to obtain adjusted incidence rate ratios (aIRR) comparing each time point to the time point immediately prior. All other behaviors were modeled using log binomial distribution with exchangeable correlation structure, to obtain the adjusted relative risk (aRR) and corresponding 95% confidence interval (CI) of reporting each behavior at each time point compared with the time point immediately prior. Patients were

included in the analysis even if they did not complete the CASI at all visits, but were dropped from individual models if they did not report a behavior at any of their visits. Adjusted IRR (for number of male sexual partners) and aRR (all other behaviors) were calculated for 3-month, 6-month, 9-month, and 12-month time points compared to the initiation visit.

To explore possible increases in STI diagnosis among PrEP patients before and after PrEP initiation, we examined the burden of bacterial STIs in three distinct time periods: (1) during the 12 months prior to PrEP initiation not including the 30 days just prior to PrEP initiation (i.e., prevalent STIs); (2) during PrEP use, beginning 30 days after initiation visit through 90 days after the last in-person visit (i.e., incident STIs); and at the time of PrEP initiation, defined as 30 days prior through 30 days after the PrEP initiation visit (to capture prevalent infections that occurred around the time of PrEP initiation). STIs diagnosed within 30 days of PrEP initiation were separated to ensure that STIs acquired prior to PrEP use (that were diagnosed during PrEP initiation) did not contribute to the proportion of STIs diagnosed during PrEP use. For each time period, we calculated the proportion of patients with at least one STI diagnosis. This calculation was repeated for each STI. We used paired t-tests to compare mean number of STIs diagnosed per patient before and after PrEP initiation.

We used Stata version 13.1 (College Station, TX, USA) for all analyses. Two-sided statistical tests were performed at a significance level of 0.05.

RESULTS

Between October 2014 and April 2017, 376 MSM were evaluated for PrEP through the PHSKC STD Clinic. Forty-two patients were excluded because they did not complete CASIs at their initial visit; an additional 138 were excluded because they had initial CASIs but no follow-up data. Of the remaining 196 patients, 93% (183 patients) had complete behavioral data available at their initial visit and at least one follow-up visit and are included in this analysis. The mean number of PrEP clinic visits for these 183 patients was 4.1 (standard deviation (SD): 2.2

visits). The mean length of time between the initial CASI and last CASI was 335 days (SD: 210 days). Of the 183 patients, 134 had a visit at 3 months, 110 had a visit at 6 months, 87 had a visit at 9 months, and 63 had a visit at 12 months. The mean age of these 183 men was 31.2 years (SD: 8.9). Half the patients were white, non-Hispanic, and almost 60% were on private insurance (Table 2.1).

Sexual Behavior

The proportion of participants reporting each sexual behavior during the 30 days prior to initial PrEP visit are included in Table 2.1. The majority of participants reported anal sex with HIV-negative partners, and the proportion reporting anal sex with HIV-positive or unknown status partners was 22.5% and 39.0%, respectively. At the initial visit, 13.8% of patients reported never using condoms, regardless of sexual role or partner HIV status. The mean number of male sexual partners reported at the initial visit was 4 (SD: 3.7).

The absolute proportion of patients reporting anal sex with HIV-negative and HIV-positive partners remained unchanged during 12 months of follow-up, while the proportion reporting sex with unknown status partners decreased to 11% at 12 months. There were no changes in the absolute proportion of patients reporting receptive anal sex during the 12-month follow-up period, or in the proportion reporting insertive anal sex. The absolute proportion of patients reporting never using condoms overall increased to a high of 22% at 9 months and declined to 16% at 12 months. Absolute proportions in other categories of condom use followed a similar pattern of increasing through 9 months, after which the proportion appeared to level off or decrease slightly for never using condoms during receptive anal sex, and during anal sex with HIV-positive and HIV-negative partners.

There was no statistically significant change in the mean number of male sexual partners reported in the past 30 days over the follow up period (Table 2.2). MSM were no more likely to report either HIV-positive or HIV-negative partners during PrEP use, though the

adjusted relative risk of reporting partners of unknown HIV status was 0.41 (95% CI: 0.29, 0.57) at the 12-month visit compared to the initial visit. MSM were no more likely to report insertive or receptive anal sex at 12 months compared to PrEP initiation. The adjusted relative risk of reporting never using condoms overall at 12 months after PrEP initiation compared to the initial visit was 1.46 (95% CI: 1.13, 1.88), with similar trends in those with HIV-positive and HIV-negative partners. We also observed increases in never using condoms for receptive anal sex (aRR=1.56; 95% CI: 1.23, 1.98) and insertive anal sex (aRR=1.32; 95% CI: 1.01, 1.72) at 12 months compared to the initial visit. This finding was similar when we stratified by partner HIV status and sexual role (data not shown).

Bacterial STIs

Half the patients were diagnosed with an STI around the time of PrEP initiation (Table 2.3). A higher percentage of patients were diagnosed with any STI in the period during PrEP use (49.2%) than the period prior to PrEP use (35.0%). Over half of patients were diagnosed with an STI within 30 days of PrEP initiation visit. There were only slight differences in the proportion of patients with urethral GC comparing these periods. The proportion diagnosed with primary and secondary syphilis was lower in the period during PrEP use compared to before. A higher proportion of patients were diagnosed with CT during PrEP use compared to before PrEP use, which is driven primarily by a high proportion of incident rectal CT diagnoses during PrEP use. There were no MSM in our clinic diagnosed with HIV while on PrEP.

Of 183 patients, 33 (18%) had at least one STI diagnosis both during the year prior to PrEP initiation and during PrEP use. Among all 183 patients there was a significant difference in mean number of STI cases diagnosed per person prior to PrEP use compared to during PrEP use (0.5 vs. 1.1; $p<0.001$). Among the 33 patients who were diagnosed with STIs both prior to and during PrEP use, the mean number of STI cases per person diagnosed prior to PrEP

initiation was also significantly lower than the mean number of STI cases per person diagnosed during PrEP use (1.5 vs. 2.6; p=0.002).

DISCUSSION

In this clinic-based population of MSM using PrEP in Seattle, we found decreases in condom use and in reporting of unknown status partners, but no change in sexual positioning, number of sexual partners, or reporting of HIV-positive or -negative partners. Half of the PrEP patients were diagnosed with a bacterial STI while on PrEP, and the proportion of patients with STIs during PrEP use was higher than prior to PrEP use. It is unclear whether this observed difference is a result of declining condom use or other factors such as an increase in the frequency of screening for STIs. There was an overall trend toward a greater number of STIs in the period during PrEP use, and the mean number of STIs was significantly higher for the sub-set of MSM diagnosed with STIs before and during PrEP use.

Our findings are consistent with both predicted and measured behavior change reported in recent studies of PrEP in clinics or clinic systems. Among MSM using PrEP at Kaiser Permanente San Francisco, 41% of PrEP users had decreased their condom use after 6 months of PrEP use (10) and among MSM using PrEP at an STD clinic in Providence, Rhode Island, the mean number of condomless anal sex partners increased from 2.0 at initial visit to 3.3 at 6 months, though there was no change in total number of sex partners (11). In our study, we similarly found a nearly 50% increase in condomless anal sex at 12 months compared to the initial visit and found similar increases in condomless anal sex for both receptive and insertive roles. Notably, our findings contradict several clinical trials and open-label studies that found no evidence of changes in sexual behavior among participants using PrEP (23,52,58,59). It is possible that the placebo-controlled nature of many of these trials, or uncertainty regarding the efficacy of PrEP at the time the trials were undertaken may have contributed to the absence of changes in sexual behavior observed in these studies.

We observed no change in the proportion of patients reporting HIV-positive or HIV-negative partners, but a steep decline in unknown status partners, which has not been reported in other studies. The latter finding could be either because PrEP-using MSM in our clinic are preferentially choosing sexual partners who know their own HIV status, or because they discuss HIV status with their partners more often after initiating PrEP. Additional research should be conducted to assess whether PrEP facilitates HIV serostatus discussions between sexual partners.

The proportion of patients with diagnosed STIs in our cohort differed somewhat from that reported by Marcus and colleagues' study of MSM on PrEP at Kaiser Permanente Northern California, which found that the percentage of participants with urethral GC and rectal CT doubled between initial visit and 12 months, from 0.9% to 2.5% and from 7.7% to 14.1%, respectively (12). Our results showed a similar relative increase in the proportion of participants with rectal CT (11.5% prior to PrEP vs. 29.0% during PrEP), but not urethral GC (8.2% vs. 9.3%, respectively). Further, findings from a PrEP demonstration project in Melbourne, Australia report the proportion of patients diagnosed with at least one STI during PrEP use ranged from 25-35% during months 3-12 of follow-up. The proportion of patients in our cohort that were diagnosed with at least one incident STI during follow-up was somewhat higher, at 50%.

Our hypothesis that the proportion of patients with STIs would be higher during PrEP use than before PrEP use was not supported for either GC or syphilis. We observed slight increases in the proportion of participants diagnosed with rectal GC and early syphilis during PrEP compared to the year prior to PrEP use, and a high proportion of patients diagnosed with these STIs within 30 days of PrEP initiation. However, rectal GC and early syphilis are criteria for PrEP initiation at our clinic, and pre-PrEP and peri-PrEP prevalence of these infections may be inflated as a result, potentially limiting the comparability of the pre- and during-PrEP time periods. We observed a higher prevalence of CT during PrEP use, which was primarily driven by a higher prevalence of rectal CT. Because rectal CT is most often asymptomatic, it is likely

that some proportion of this change is due to ascertainment bias resulting from increased testing frequency. Prevalence of urethral GC – which was essentially unchanged between the periods prior to and during PrEP use – is not among the eligibility criteria for receipt of PrEP in our clinic, and unlikely to be subject to ascertainment bias because it is usually symptomatic. Given the absence of change in proportion of patients with symptomatic STIs, it is likely that the overall higher prevalence of STIs during PrEP use is due in part to increased STI screening after PrEP initiation. Notably, we observed an increase in the mean number of STIs per patient during PrEP compared to the year prior to PrEP use, particularly among the subset of patients who experienced STI diagnoses both before and during PrEP use. However, in the absence of a control group for comparison, it is unclear whether this increase is due primarily to ascertainment bias resulting from increased testing, or a result of increases in condomless anal sex.

Our study had a number of strengths. First, our use of longitudinal data from a clinic population enabled us to study the effects of PrEP use on the sexual behavior of high-risk MSM in a non-research setting. Second, GEE models allowed for valid estimates of population-level regression coefficients despite variable length of time between clinic visits and varying length of follow-up. Third, our clinic's sexual behavior CASI is robust and includes information on condom use by partner HIV status and sexual role. Finally, access to data from our STI surveillance system enabled us to identify STI's diagnosed outside of the STD clinic for more complete ascertainment of incidence.

Our results should be interpreted in light of several limitations. First, per our clinic's eligibility criteria for initiating PrEP, MSM in this study are at higher risk for HIV and other STIs than the general MSM population. Therefore, these results may not be generalizable to the broader MSM population in Seattle or other locations. Second, the decrease in absolute proportion of patients reporting some sexual behaviors between 9 and 12 months may be an artifact of decreasing sample size. Third, while our results highlight the high rate of bacterial

STIs among MSM using PrEP, our lack of a comparison group makes it difficult to determine whether or not rates would have been high in the absence of PrEP use. Fourth, the fact that diagnoses of rectal GC or syphilis in the preceding 12 months are among the eligibility criteria for PrEP initiation in our clinic may have resulted in selection bias in the comparison of GC and syphilis diagnosis rates prior to versus during PrEP use. Further, increases in the prevalence of chlamydia during PrEP use should be interpreted with caution due to ascertainment bias resulting from increased testing frequency during PrEP use.

In summary, we found that MSM decreased their use of condoms following PrEP initiation. Further, both the proportion of patients diagnosed with STIs and the mean number of STIs per patient increased during PrEP use, although this was likely due in part to more frequent STI screening during PrEP use. In our clinic population, PrEP is functioning well as an HIV prevention tool; there were no new HIV diagnoses among MSM on PrEP during our observation period. However, even in the presence of decreasing HIV risk, behavioral changes that may increase risk of bacterial STIs are concerning. Incidence of bacterial STIs among MSM in the US have been increasing over the past decade, and STIs remain a substantial source of morbidity in this population (56,60,61). King County has seen a sizeable increase in the rates of syphilis among MSM since 1997, and incidence of both GC and CT in this population have also been steadily increasing since 2008 (62). Given our observed population-level decreases in condom use among MSM on PrEP, and the continued increases in bacterial STIs in the general population of MSM in King County, it is likely that PrEP use will be a factor contributing to rising rates of bacterial STIs among MSM in the future. Ongoing screening and treatment of STIs is both a necessary component of PrEP patient care, and a potential method for decreasing STI burden in this population in the face of decreasing condom use (63). As we continue to roll out PrEP programs targeting MSM at high risk for HIV, it will be increasingly important to evaluate ways in which we can use PrEP programs to engage MSM in sexual health and comprehensive STI prevention programs that do not focus solely on condom use.

Table 2.1. Characteristics of MSM Initiating PrEP at the PHSKC STD Clinic at the time of the initial PrEP visit (N=183)

Characteristic	N	%
Age (Mean, SD)	31.2	8.9
Race/Ethnicity		
White, non-Hispanic	102	55.7
Black, non-Hispanic	12	6.6
Hispanic	35	19.1
Other, non-Hispanic	34	18.6
Insurance Status		
Public/Patient Assistance[a]	76	41.5
Private	107	58.5
Sexual Behavior in Past 30 Days		
Number of Male Sex Partners (Mean, SD)	4.0	3.7
Receptive Anal Sex[b]	139	79.4
Insertive Anal Sex[b]	120	68.6
Any HIV+ Partners[c]	37	22.5
Any HIV- Partners[c]	149	90.1
Any Unknown Status Partners[c]	64	39.0
Never Used Condoms, Overall[c]	22	13.8
Never Used Condoms during Receptive Anal Sex[c]	20	15.0
Never Used Condoms during Insertive Anal Sex[c]	20	17.5
Never Used Condoms with HIV+ Partners[c]	7	18.9
Never Used Condoms with HIV- Partners[c]	23	15.4
Never Used Condoms with Unknown Status Partners[c]	7	11.0

[a]E.g. Medicaid or drug company patient assistance
[b]The denominator (n=175) is the number of patients who reported at least one sexual partner in the last 30 days.
[c]The denominator is the number of patients who responded to the question about that sexual behavior in the past 30 days. E.g. The denominator for "Never Used Condoms during Receptive Anal Sex" (n=133) is the number of patients who reported having receptive anal sex in the past 30 days.

Table 2.2. Risk of Reporting Sexual Behaviors at Each Follow-up Period among MSM on PrEP at PHSKC STD Clinic, Comparing Each Time Point to the Initial PrEP Visit[a]

		3 Months		6 Months		9 Months		12 Months	
Sexual Behavior	**N**	**aIRR**	**95% CI**	**aIRR**	**95% CI**	**aIRR**	**95% CI**	**aIRR**	**95% CI**
Number of Male Sexual Partners	183	1.01	(0.96, 1.05)	1.01	(0.93, 1.11)	1.02	(0.89, 1.17)	1.03	(0.86, 1.23)
Partner HIV Status		**aRR**	**95% CI**	**aRR**	**95% CI**	**aRR**	**95% CI**	**aRR**	**95% CI**
Any HIV-Positive Partners	181	1.01	(0.96, 1.06)	1.01	(0.91, 1.12)	1.02	(0.87, 1.19)	1.02	(0.83, 1.26)
Any HIV-Negative Partners	181	1.00	(0.98, 1.01)	0.99	(0.97, 1.02)	0.99	(0.95, 1.02)	0.98	(0.93, 1.03)
Any Unknown Status Partners	181	0.80	(0.74, 0.87)	0.64	(0.54, 0.76)	0.51	(0.40, 0.66)	0.41	(0.29, 0.57)
Sexual Position									
Receptive	182	1.00	(0.99, 1.02)	1.00	(0.97, 1.04)	1.01	(0.96, 1.06)	1.01	(0.95, 1.08)
Insertive	182	1.00	(0.98, 1.02)	1.00	(0.96, 1.04)	1.00	(0.94, 1.06)	1.00	(0.93, 1.08)
Never Uses Condoms[b]									
Overall	180	1.10	(1.03, 1.17)	1.21	(1.06, 1.37)	1.33	(1.10, 1.60)	1.46	(1.13, 1.88)
During Receptive Anal Sex	167	1.12	(1.05, 1.19)	1.25	(1.11, 1.41)	1.40	(1.17, 1.67)	1.56	(1.23, 1.98)
During Insertive Anal Sex	152	1.07	(1.00, 1.15)	1.15	(1.00, 1.31)	1.23	(1.01, 1.50)	1.32	(1.01, 1.72)
With HIV-Positive Partners	76	1.08	(1.00, 1.16)	1.16	(1.00, 1.36)	1.25	(1.00, 1.58)	1.35	(0.99, 1.84)
With HIV-Negative Partners	176	1.08	(1.02, 1.14)	1.16	(1.03, 1.30)	1.25	(1.05, 1.49)	1.34	(1.06, 1.70)
With Unknown Status Partners[c]	90	1.61	(1.13, 2.28)	2.07	(1.18, 3.65)	2.15	(1.10, 4.20)	1.80	(0.90, 3.58)

aIRR: Adjusted Incidence Rate Ratio
aRR: Adjusted Relative Risk
[a]All estimates from GEE models, adjusted for age, race, and insurance status
[b]The subcategories refer to the risk of reporting never using condoms with partners specific to each behavior category. E.g. for "During Receptive Anal Sex," this is the risk of reporting never using condoms with partners with whom the patient has engaged in receptive anal sex.
[c]Quadratic time included in this model

Table 2.3. The Proportion of MSM Initiating PrEP Diagnosed with STIs before and after PrEP Initiation, PHSKC STD Clinic (N=183)

	12 Months Prior to PrEP Initiation		At PrEP Initiation (+/- 30 Days)		During PrEP Use[a]	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Number of STIs per Patient	0.52	0.84	0.72	0.82	1.11	1.62
	N	**%**	**N**	**%**	**N**	**%**
Any STI	64	35.0	95	51.9	90	49.2
Chlamydia	28	15.3	36	19.7	62	33.9
Gonorrhea	41	22.4	67	36.6	58	31.7
Syphilis (1º, 2º, Early Latent)	16	8.7	21	11.5	17	9.3
Syphilis (1º, 2º)	13	7.1	15	8.2	8	4.4
Anatomic Site						
Pharyngeal Gonorrhea	13	7.1	33	18.0	34	18.6
Rectal Gonorrhea	27	14.8	51	27.9	32	17.5
Urethral Gonorrhea	15	8.2	12	6.6	17	9.3
Pharyngeal Chlamydia	5	2.7	3	1.6	8	4.4
Rectal Chlamydia	21	11.5	29	15.8	53	29.0
Urethral Chlamydia	11	6.0	6	3.3	15	8.2

[a] Mean time on PrEP = 13 Months

Chapter 4. Differences in STI Risk Comparing PrEP Users and Propensity Score-Matched Historical Controls in a Clinic Setting

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Previous Presentations

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ABSTRACT

Objective: To determine whether men who have sex with men (MSM) using pre-exposure prophylaxis (PrEP) are at higher risk of bacterial sexually transmitted infections (STIs) compared to MSM not using PrEP.

Design: Secondary analysis of longitudinal STI data obtained from MSM attending an STD Clinic in Seattle, WA, 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, gonorrhea, and early syphilis, and time to first symptomatic STI among PrEP users and non-users.

Results: 365 PrEP users who picked up prescriptions and returned for follow-up and 730 propensity score-matched non-users were included in the analysis. Adjusted incidence rate ratios (aIRR) for chlamydia, gonorrhea, and early syphilis were 3.2 (95% confidence interval [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 non-users. Time to first symptomatic STI was shorter among PrEP users (120 days, 95% CI: 77 – 171) compared to non-users (185 days, 95% CI: 163 – 256).

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

Key Words: Men Who Have Sex With Men; HIV; Pre-Exposure Prophylaxis; Sexually Transmitted Infections

INTRODUCTION

Men who have sex with men (MSM) are disproportionately impacted by HIV in the United States, accounting for 86% of new infections among men in 2016 (1). Pre-exposure prophylaxis (PrEP) reduces the risk of HIV acquisition by up to 92% in MSM (22,23,50), is recommended by the Centers for Disease Control and Prevention (CDC) for HIV prevention among sexually active MSM (64), and is offered through a variety of clinical settings in the US (51). MSM are also disproportionately impacted by bacterial sexually transmitted infections (STIs), the rates of which have increased substantially in the past decade. MSM accounted for 62% of gonorrhea cases and 68% of primary and secondary syphilis cases among men in 2017 (65). Between 2013 and 2017, the rate of primary and secondary syphilis among MSM increased by 64% (65).

Recent clinical data indicates that MSM using PrEP have an increased frequency of condomless anal sex after PrEP initiation (53,54,66–69), 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 (55,70–74). However, these studies are limited by the lack of a comparison group of PrEP non-users (55,72,73), failure to account for ascertainment bias resulting from increased STI screening among PrEP patients (71), or failure to adjust for secular STI trends (70,71,74). 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 high risk of HIV. We used PHSKC STD Clinic data from PrEP users and a propensity score-matched historical comparison group of non-users 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 higher risk of bacterial STIs compared to MSM not using PrEP.

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. Per PHSKC and Washington State (WA) PrEP guidelines (57) the PHSKC STD Clinic provides PrEP to patients at 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 gonorrhea 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 (75).

PrEP visit procedures at our clinic have been described previously (67). Briefly, PrEP patients are tested for HIV and STIs at their initial visit, and are given a 3-month prescription for PrEP. They return one 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 one month. Our comparison group (PrEP non-users) 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 high risk for HIV acquisition, and a comparison group of current clinic patients who are not on PrEP would be at 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 behavior, STI risk, recent STI diagnoses, demographic characteristics, and reasons for visiting the clinic (Supplementary Table). Data for the propensity score model was from the initial PrEP visit for PrEP users, and from the first STD clinic visit between October 2011 and September 2014 for PrEP non-users. We used descending, nearest-neighbor matching without replacement to select two matched PrEP non-users for each PrEP user based on their propensity scores (76,77). After matching, we graphically compared the distribution of propensity scores in both groups (Supplementary Figure), 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 (78,79). 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 non-users, 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, gonorrhea, 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. Since most cases of urethral gonorrhea and primary and secondary syphilis among men are symptomatic, we defined symptomatic STIs as cases of urethral gonorrhea or primary or secondary syphilis (80,81). 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 (82). 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.

STI Testing

Quarterly STI tests are recommended for all clinic PrEP patients (83), and are performed

as part of routine clinical care. Patients are screened for chlamydia and gonorrhea at each anatomic site (urethra, pharynx, rectum) based on reported exposure. Urine samples, and urethral, pharyngeal, and rectal swabs were tested for gonorrhea and chlamydia using nucleic acid amplification testing (APTIMA Combo 2, Hologic, Inc, Marlborough, MA). Blood samples were tested for syphilis using a quantitative rapid plasma reagin (Beckton Dickinson, Franklin Lakes, NJ) test, with confirmatory tests performed using *Treponema pallidum* particle agglutination assay (Fujirebio Inc. Tokyo). 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 non-users. PrEP users were followed from their first prescription fill through 90 days after their last PrEP clinic appointment. Non-users were followed for one year from their first clinic visit between October 2011 to September 2014. We limited the follow-up period for the comparison group to one year to minimize the likelihood that non-users who moved out of King County would accrue follow-up time but not contribute STI diagnoses to incidence calculations. Any incident diagnoses of chlamydia, gonorrhea, 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 gonorrhea, 28 days for early syphilis) was not counted. Because this resulted in a window after each STI diagnosis where 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 gonorrhea. 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 (62); these data were obtained from the PHSKC STD Epidemiologist. Rectal gonorrhea 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 non-users using Kaplan-Meier survival analysis. For this analysis, PrEP users were followed from their first prescription fill date and PrEP non-users were followed from their first clinic visit date, with follow-up time for both groups censored at the first diagnosis of urethral gonorrhea 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 one year of follow-up using a Kaplan-Meier failure curve.

We used Stata version 15.1 (College Station, TX, 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 non-users, 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 behavior (Table 3.1). 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 5 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 3.1). Fifty-two of the 62 covariates included in the propensity score were balanced between the two groups (Supplementary Table 3.1). All ten 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 3.2 provides incidence and aIRR of each STI, comparing PrEP users to PrEP non-users. Among PrEP users, incidence of chlamydia, gonorrhea, 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 compared to PrEP non-users for chlamydia (aIRR: 3.2; 95% CI: 1.9 – 5.3), gonorrhea (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 per 100 person-years) and rectal gonorrhea (20.7 per 100 person-years), which were both significantly higher than among PrEP non-users. Incidence of urethral gonorrhea, pharyngeal chlamydia, and symptomatic STIs (urethral gonorrhea and primary/secondary syphilis) was higher among PrEP users than non-users, though not statistically significantly so. Adjustment for secular trends in STI incidence had minimal impact on IRRs.

The median time to first symptomatic STI among PrEP users was 120 days (95% CI: 77 – 171), compared to 185 days among PrEP non-users (95% CI: 163 – 256; log-rank p-value <0.01). The cumulative probability of experiencing a symptomatic STI by the end of one year of follow-up was nearly twice as high among PrEP users compared to PrEP non-users (12% vs. 7%, respectively; Figure 3.1).

DISCUSSION

We found that, compared to 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 condomless sex among PrEP users (67), and support reports from prior studies of high STI incidence among PrEP users. Further, our findings suggest that PrEP use is associated with 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, gonorrhea, and syphilis, respectively (71–73,84). Incidence of chlamydia and gonorrhea 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 (72,73,84). However, the meta-analysis by Kojima and colleagues compared pooled incidence estimates for MSM using PrEP and MSM not using PrEP from several studies of STI incidence among MSM (71).

In the Kojima meta-analysis, the pooled IRRs comparing STI incidence of PrEP users to non-users, 11.2, 25.3, and 44.6 for chlamydia, gonorrhea, and syphilis, respectively (71), 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 non-users included in the meta-analysis. Most studies included in the meta-analysis did not include direct comparison of PrEP users and non-users. Further, the studies included in the pooled incidence estimate for PrEP non-users were extremely heterogeneous; studies included a wide range of behavioral 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 behavior may have impacted the comparison of PrEP users and non-users.

Two recent observational studies not included in the above meta-analysis used within-subjects 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 (70,74). While their reported incidence during PrEP use is somewhat similar to our group of MSM using PrEP, Beymer and colleagues observed decreases in incidence between the pre-PrEP and during-PrEP periods for all STIs except syphilis (70). 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 and colleagues similarly compared incidence of bacterial STIs among MSM using PrEP to the same group of MSM prior to PrEP use (74). In that study, only chlamydia was found to have higher incidence during PrEP use compared to 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 behavior, HIV risk, and other characteristics likely associated with PrEP use. This resulted in a group of PrEP non-users 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 to non-users, only one addressed the issue of ascertainment bias resulting from higher STI screening frequency among PrEP users. Nguyen and colleagues 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 non-users, we investigated the impact of PrEP use on risk

of urethral gonorrhea 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 non-users. 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 non-users 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 non-users 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 non-users 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 do 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 over adjustment. Finally, the generalizability of these results to other MSM populations outside of Seattle is uncertain.

In summary, we observed increased STI risk among PrEP users relative to non-users. Incidence of bacterial STIs among MSM have been increasing over the past decade, both in King County and nationally (62,65), 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 programs can be leveraged to continue to engage MSM in more comprehensive STI prevention programs in the future. The success of PrEP programs may provide a unique opportunity to design and implement novel interventions to address increasing STI rates in this population.

Table 3.1. Characteristics of PrEP Users and Propensity Score-Matched Historical Comparison Patients (PrEP non-users) at the Time of Their Initial PHSKC STD Clinic visit (N=1095)

	PrEP Users (N=365)		PrEP Non-Users (N=730)		
Characteristic	**N**	**%**	**N**	**%**	**p-value**
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 Gonorrhea Diagnosis in Past Year[d]	108	29.6	221	30.3	0.82
Early Syphilis Diagnosis in Past Year[d]	58	15.9	106	14.5	0.55
Methamphetamine Use in Past Year	36	9.9	81	11.1	0.53
Popper Use in Past Year	175	47.9	313	42.9	0.11
Sex Work in 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 Behavior 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; 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 3.2. Incidence of Bacterial STIs among PrEP Users and Non-Users attending the PHSKC STD Clinic (2011 – 2017), N=1095

STI	PrEP Users (N=365) Incidence, per 100 person-years	Non-Users (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
Gonorrhea	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

IRR: Incidence Rate Ratio
aIRR: adjusted incidence rate ratio.
CI: Confidence interval
[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 gonorrhea 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 gonorrhea and primary and secondary syphilis

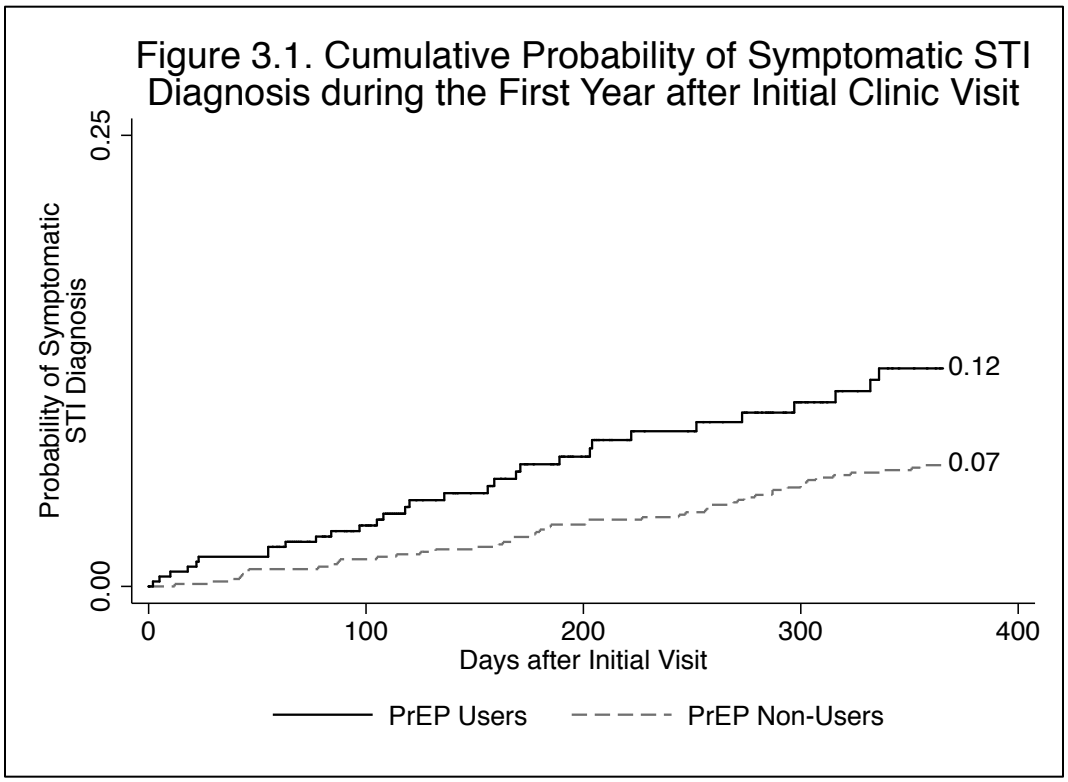


Figure 3.1. Cumulative Probability of Symptomatic STI Diagnosis during the First Year after Initial Clinic Visit
Probability of Symptomatic STI Diagnosis
0.25
0.00
0.12
0.07
0
100
200
300
400
Days after Initial Visit
PrEP Users
PrEP Non-Users

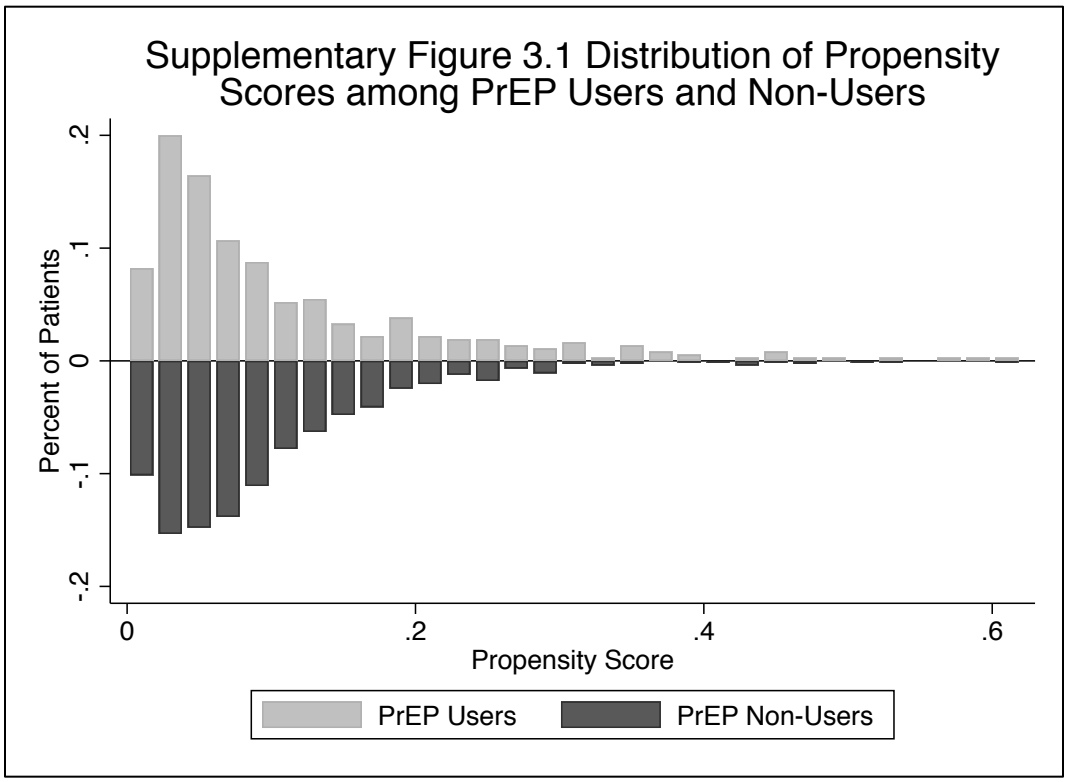
Supplementary Table 3.1. Standardized Differences for Propensity Score Covariates, Comparing PrEP Users and Propensity Score-Matched PrEP Non-Users at the Time of Their Initial PHSKC STD Clinic visit (N=1095)[a]

	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.


Supplementary Figure 3.1 Distribution of Propensity Scores among PrEP Users and Non-Users
Percent of Patients
-.2
-.1
0
.1
.2
0
.2
.4
.6
Propensity Score
PrEP Users
PrEP Non-Users

Conclusion

The research presented in this dissertation contributes to the growing body of evidence regarding the impact of ART on sexual behavior and STI risk among MSM. The primary goals of this work were to describe the impact of ART as prevention on sexual behavior and STI risk both in the context of early ART initiation among HIV-positive MSM and TW and in the context of PrEP use among HIV-negative MSM. To address these goals, Aim 1 characterized sexual behavior and STI risk among MSM and TW participating in a treatment as prevention study, comparing behavior and STI incidence among participants randomized to receive ART either immediately after HIV diagnosis or 24 weeks later. The results of this analysis showed that while participants in both study arms reported decreased sexual risk behavior after HIV diagnosis, behavior did not differ between randomization arms. We observed an overall high incidence of bacterial STIs and higher incidence of chlamydia among participants randomized to deferred ART initiation. These results indicate ongoing condomless sex in this population despite self-reported increases in condom use after HIV diagnosis, highlighting a continuing high risk for STIs.

Both Aims 2 and 3 focused on the impact of PrEP on sexual behavior and STI risk among MSM. For Aim 2, we estimated changes in sexual behavior among MSM initiating PrEP at the PHSKC STD Clinic, comparing self-reported sexual behavior during follow-up to that reported at the time of PrEP initiation. The results of this analysis showed that MSM decreased their condom use following PrEP initiation. For Aim 3, we compared STI incidence and time to first symptomatic STI among PrEP users to a group of propensity score-matched non-users to determine whether PrEP users were at higher risk for bacterial STIs. The results of this analysis showed that PrEP users had higher incidence of chlamydia, gonorrhea, and early syphilis compared to non-users and that they experienced a faster time to first symptomatic STI. Taken together, these results

suggest that PrEP use may contribute to both decreasing rates of condom use and increasing STI rates among MSM.

This dissertation highlights the importance of continued monitoring of sexual behavior in the era of ART as prevention. It is perhaps unsurprising that the sexual behavior of participants on ART did not differ from participants not on ART in Aim 1, given that this trial was conducted prior to widespread adoption of U=U messaging, nor that self-reported protective behavior increased after HIV diagnosis. However, the behavioral and STI results reported in this aim both point to ongoing sexual risk behavior. While the behavioral results reported in Aim 2 show an increase in condomless sex rather than a decrease as seen in Aim 1, the results from these two aims are thematically similar in that they both reflect ongoing sexual behavior that increases the risk of STI acquisition. Indeed, STI incidence observed in Aims 1 and 3 was similarly high among both PrEP-using MSM in King County and among HIV-positive MSM and TW in Lima. This observed high incidence of STIs is troubling given that over the past two decades increasing awareness among MSM that ART reduces HIV transmission risk has coincided with population-level increases in condomless anal sex (85). There is no doubt that PrEP and TasP are highly effective means of preventing HIV, and evidence of risk compensation does not constitute a reasonable argument for limiting access to these prevention methods. However, this continuing high risk of STIs is both cause for concern, and an opportunity for improvement.

For a time, the primary methods for avoiding HIV and other STIs overlapped almost completely; among sexually active individuals, condom use has long been an integral component of HIV and STI prevention. Condom use was declining prior to widespread scale up of TasP and PrEP (12–16). If condom use rates continue to decline in the context of new biomedical HIV prevention methods which are not effective against STIs, public health practitioners will be increasingly unable to rely on STI control as a byproduct of HIV prevention. The divergence of methods of

HIV prevention from methods of STI prevention provide a new impetus, and potential new opportunities, for STI prevention, management, and control.

Biomedical HIV prevention in the form of TasP/test and treat and PrEP offers opportunities to engage high-risk MSM in more comprehensive sexual health care. This research identified, in two disparate locations, high STI rates among MSM at risk for HIV acquisition. The high rates of bacterial STIs both among newly HIV-positive MSM and TW and among HIV-negative MSM on PrEP noted in these studies suggests that closer engagement of these populations in HIV care and prevention may be an opportunity to reach and intervene with those most at risk for bacterial STIs. These results highlight the continued importance of incorporating STI prevention, screening, and treatment into HIV prevention and HIV clinical care.

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