Title

Sexual Risk Behavior in Men who have Sex with Men in an Era of Pre Exposure Prophylaxis (PrEP) for HIV Prevention.

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Publication Date

2018

Peer reviewed|Thesis/dissertation

Sexual Risk Behavior in Men who have Sex with Men in an Era of Pre Exposure Prophylaxis (PrEP) for HIV Prevention

by

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DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

in

Nursing

in the

GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

[redacted]

Dedication and Acknowledgements

This dissertation is dedicated to all the people who have been instrumental in encouraging me to never give up. My mother, the strongest bravest woman I have the privilege to know and love; my father, who always encouraged me to take on life's challenges and think about the details later, I wish you were here today to see how far I have come; Mags, who has always been able to make me realize just how fortunate I am; L.B. for all the love and support and for keeping me laughing over the years; Meres for always believing I could do this and to all my friends and family who support me even if they don't understand what it is I am doing. Most importantly, to Jono, for showing me I am capable of so much more than I realize.

I would like to thank the many individuals who have supported me during my PhD journey. I would like to express my sincerest gratitude to my advisor, Dr. Carmen Portillo and my dissertation committee Drs. Cherrie B. Boyer and Glen-Milo Santos for sharing their knowledge, guidance, and time. I would also like to thank Dr. Bruce Cooper for all his support, patience and statistical education, Dr. Carol Dawson Rose, Dr. Cedric-Crouch and Dr. David Vlahov for their support throughout the PhD process. I would like to say a big thank you to Dr. Glenda Baguso for all the soup, library time, encouraging me to submit abstracts and explore educational experiences outside of my comfort zone; Dr. Ilufredo Tantoy for keeping it all in perspective with his kindness and support. To all the Magnet volunteers, front desk staff, support services staff, benefits navigators, nurses, nurse practitioners who on a daily basis make a positive impact on the lives of gay, bi, and trans men and women. To all the clients who graciously allowed

me to not only provide healthcare but were generous in supplying the data for this study.

I would like to acknowledge the funding sources for this dissertation NIH/NINR F31 NR016179-01A1 Grant 12049698, T32 NR07081 HIV/AIDS Nursing Care and Prevention Training Program (Portillo/Vlahov)Graduate Dean's Health Sciences Fellowship (GDHSF)Dissertation Award, School of Nursing Century Club Scholarship and Sigma Theta Tau International Alpha Eta Chapter Leadership Development Award.

Abstract

Background - Pre-exposure prophylaxis (PrEP) provides protection against HIV transmission but not against other sexually transmitted infections (STIs), which disproportionally affect men who have sex with men (MSM).This dissertation examines the association of PrEP initiation with subsequent patterns of condom use and STIs in MSM. A cohort of 525 MSM, 18 years and older, who self-identified as either high or low risk for HIV acquisition was followed for 13 months after initiating PrEP at a sexual health clinic in San Francisco.

Dissertation Aims - 1) Review the literature to examine if PrEP is associated with changes in risk behavior in MSM; 2) determine the reasons why MSM who self-identify as low risk for HIV request PrEP; and 3) determine how PrEP use affects condom use and STIs rates in MSM who self-identify as high risk for HIV.

Methods - A systematic literature review was completed. The cohort was followed over 13 months subsequent to initiating PrEP. Questionnaires were used to examine condom use and biological assays were used to measure the frequency and type of STIs. Frequencies and descriptive analyses were completed, and multilevel logistic regression modeling was used to predict associations of condom use and STIs before and after initiation of PrEP. Framework analysis was used to identify themes and to develop a descriptive understanding of why low-risk MSM initiated and remained on PrEP.

Findings - No conclusive evidence was found that PrEP use leads to increased sexual risk behaviors. Overall, condom use decrease peaked at ~ 6 months and returned to baseline rates at ~12 months. Disparities in condom use and STI rates were observed within sub-populations of MSM, and condom use was found to be influenced by perceived risk. In both the low- and high-risk cohorts, anal GC/CT and syphilis decreased and pharyngeal GC/CT either remained constant or increased. MSM do not use PrEP solely to replace condoms, rather PrEP provides, peace of mind, sexual pleasure and safety and security.

Conclusion - In order to improve sexual health for MSM PrEP, STI screening and condom use education should be tailored to meet differing needs of sub populations. Sexual health discussion should include education on substance use, transmission of pharyngeal GC/CT and how MSM perceive sexual risk. Further research is needed to assess when more intensive counselling regarding condom use would be beneficial, how MSM perceive sexual risk and ways to reduce pharyngeal infections.

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Chapter 1: Introduction to the Dissertation

Background

In the United States, men who have sex with men (MSM) continue to be heavily affected by Human Immunodeficiency Virus (HIV) and sexually transmitted infections (STIs)[1,2]. The introduction of pre-exposure prophylaxis (PrEP) into clinical practice in 2012 for HIV in the form of Truvada® (emtricitabine + tenofovir dispoproxil fumarate) revolutionized HIV prevention among MSM[3,4]. PrEP is a once-daily pill that is simple to use, has low toxicity and is 92-99% effective in reducing HIV risk [4,5] both as a daily regimen and as event based treatment[6-8]. MSM accounted for 81% of the 37,887 estimated HIV diagnoses in 2013 among all males age 13 years and older[9] and are thus a population appropriately targeted by public health messaging for PrEP initiation. While PrEP reduces the risk of HIV transmission it does not provide any protection against other STIs, which can only be prevented by consistent condom use, mutual monogamy or abstinence[10,11].

STIs continue to be a major public health issue and it is estimated that 19 million new infections occur annually in the US[12,13]. MSM are disproportionally affected by STIs, and while the rates of HIV are beginning to decrease, STI rates continue to escalate[14-16]. In San Francisco, the increase in gonorrhea, chlamydia and syphilis in the MSM population reflects the national rates. The uptake of PrEP has been greater than in other similar populations and decrease in HIV infections among MSM has been substantial[17]. This has led to fears that PrEP may be a catalyst for a new public health crisis caused by STIs[18].

These fears have an historical basis, in the late 1980's and early 1990's when STI rates decreased among MSM, and this was hypothetically attributed to the increase in condom use in order to prevent HIV infection, rather than the decrease in STI testing in MSM secondary to fear and stigmatization[19]. MSM who wished to participate in condomless sex at this time were judged as being irresponsible, or were fearful of death secondary to an AIDS diagnosis, and often did not come forward for HIV/STI testing until they were hospitalized. With the introduction of highly active antiretroviral therapy (HAART) for HIV in the mid 1990's STI rates began to increase among MSM, and this may have been in part due to increased testing secondary to accessing healthcare for the first time rather than an indication that condom use was decreasing[20]. The trend continued with the introduction of less toxic antiretroviral therapy (ART). Concurrently, the National HIV Behavioral Surveillance System reported an increase in condomless anal sex in MSM from 45% in 2005 to 57% in 2011[9] and there is a concern that the introduction of PrEP in 2012 may have accelerated this trend, leading to escalating STI rates. Fueling the belief that PrEP is decreasing condom use and in turn increasing STIs are reports of resistant strains of gonorrhea and chlamydia[21-23] with treatment failure rates for these infections between 13% and 21% in MSM[2,24,25], and the reemergence of ophthalmic, otic and neuro syphilis [1]. The continuing increase in STI reports in the era of PrEP use may also be in part due to MSM accessing healthcare for the first time, as PrEP protocols in clinical practice require frequent STI and HIV testing.[11,26,27] PrEP may also be decreasing fear of HIV leading to first time condomless sex[28], without consideration of other STIs. However, it is not yet established that PrEP is a cause of condom use decrease or STI increase in MSM[29,30].

The debate surrounding PrEP's effect on both condom use and STI rates has left many healthcare providers, community members and individual MSM confused about the effect PrEP may have on sexual risk behavior [31-33]. The reasons for this are complex as many healthcare providers report being ill-equipped to discuss sexual health or identify MSM who would benefit from PrEP, policy makers are concerned about costs, and MSM report feeling uncomfortable disclosing their sexual practices for fear of being labelled or judged[34-36] .

In order to assist healthcare providers and MSM in the decision making process regarding initiating PrEP, the Centers for Disease Control and Prevention (CDC) provided clear guidelines[37] and multiple tools have been developed to assess who is at HIV risk and who would benefit from PrEP. Nevertheless, PrEP continues to cause controversy regarding how to evaluate risk of HIV acquisition[38] and who should be assessing HIV risk—the individual, the community, the healthcare provider or the healthcare system [39,40].

In an era of pharmacological HIV prevention[41],(PrEP), with concurrent escalating rates of gonorrhea, chlamydia and syphilis in MSM it is crucial to understand the role PrEP plays in condom use behavior and STI rates over time in a real-world setting. The information generated by the dissertation will hopefully guide sexual health counselling and STI screening to promote and enable the success of PrEP programs locally, nationally and internationally. Data from the dissertation will inform practice to improve sexual health and provide a basis for future research to reduce sexual risk behaviors.

Theoretical Framework

The theoretical framework used for the dissertation relies on two theories that incorporate related and critical concepts on sexual behavior: Theory of Reasoned Action (TRA) [42] and Sexual Scripting Theory (SST) [43]. TRA provides insight into the beliefs and values that influence behavior and how social norms shape behavior [42,44]. SST subscribes that social norms influence sexual conduct and that sexual scripts, individually and in tandem, inform and guide peoples' sexual behaviors and provide meaning to what may be considered appropriate activities [43,45]. Decisions regarding sexual risk behaviors are influenced by what an individual believes are the accepted practices in the location or community [46,47]. TRA also posits that not only are intentions influenced by individuals' attitudes toward the behavior but also perceived social norms which support the behavior[48]. For, example, if the intent is not to get a STI then communication regarding STI status or condom use should occur. However, if the individual experiences a negative consequence, such as a partner refusing to continue the sexual act if STI status is discussed or condom use requested, the cost to the individual may outweigh the benefit, and the motivation to comply with social norms will become stronger than behavioral intent, even when the individual has a positive attitude towards STI discussion. If PrEP influences social norms such that condomless sex becomes acceptable, individuals may feel a social pressure to alter their condom use behavior, thus increasing their risk for contracting an STI. Additionally if PrEP alters the social norms related to condom use, it may alter an individual's sexual script, leading to a change in condom-use behavior, and potential exposure to an STI.

Overview of the Clinical Study

Approach

This longitudinal observational clinical cohort study of MSM who presented for PrEP at an urban community based, sexual health clinic open to all gay, bisexual and transgender men in San Francisco and the Bay Area. The clinic site has a harm reduction philosophy and many individuals attending the clinic are not engaged in any other form of healthcare. The clinic is also unique in that it is a nurse-run sexual health clinic and all services are free of charge. Data were collected on HIV, gonorrhea (GC), chlamydia (CT), syphilis, and condom-use patterns.

In October, 2014, the clinic conducted a feasibility study using the CDC guidelines for initiating PrEP in MSM. The study was open to MSM who were not in a mutually monogamous relationship with a partner who recently tested HIV-negative, and MSM who had had anal sex without a condom or been diagnosed with a STI in the past 6 months [49]. The study, which enrolled 75 participants, included assessments of acceptability, demand, implementation and practicality of the proposed PrEP program. Analysis of the data collected revealed the following: the age range was 20-68; 28% were Hispanic; 60% were Caucasian; 81% participants reported condomless anal sex as the reason for initiating PrEP; 30% had a STI at baseline; and the number of sex partners ranged from 2-100. The feasibility study also revealed the need for benefit navigators to be on site to help participants navigate the complexities of medication cost coverage.

Following the successful feasibility study, the clinic implemented the PrEP Health Program. Initially this continued to follow the CDC guidelines for initiating PrEP in MSM however, in order to better serve the community the program directors opted to also

include MSM who report 100% condom use or oral sex only. The rationale for including these seemingly low-risk individuals was that social desirability may cause under-reporting of risk behaviors [50], and if a client requests PrEP they should not feel pressured to disclose behavior. The final inclusion criteria were: age 18 and over (per FDA approval for PrEP); gay, bisexual or transgender; HIV negative; and seeking PrEP. The exclusion criteria included: renal disease; acute viral syndrome; high-risk HIV exposure in past 72 hours (any individual with a high risk exposure in past 72 hours was referred for non-occupational post-exposure prophylaxis (nPEP) for HIV); liver disease or hepatitis; osteoporosis; any uncontrolled chronic health condition; or abnormal complete metabolic panel. Individuals with Kaiser or Veterans Association insurance did not qualify for PrEP services at the clinic study site, as these institutions do not fill prescriptions from outside their systems. Participants received a prescription for Truvada at their baseline visit. Prescription co-pay cards were provided and a financial counselor was available to help individuals negotiate their healthcare plans.

Visits

Visits were scheduled at baseline and months 1, 4, 7, 10, and 13. Month 1 visit included completion of safety studies and to ensure the individual had started PrEP. Visits were scheduled along the same timeline for each participant, but due to individual fluctuations, for example rescheduled appointments, visits did not occur at the exact same time points but as close as possible.

Retention

Prescription refills for PrEP were only provided if the follow-up visits were completed, initially a one month supply and then 90 day supply, facilitating higher visit retention rates. Participants were contacted three days after their baseline visit by a benefits navigator to ensure they were able to obtain Truvada.

Analysis

The analysis of the cohort data was limited to patients who attended their first appointment to initiate PrEP at the clinic site between November, 2014, and May, 2015, and who completed the 13-month visit. All participants were required to complete baseline demographic, sexual risk and substance use questionnaires. Baseline laboratory studies included HIV antibody and viral load, hepatitis B antigen and hepatitis C antibody, STI screening and a complete metabolic panel. Nurse practitioners performed history and physical examinations and reviewed all tests results with the clients. At baseline visit, all clients received verbal and written education regarding how PrEP works, the importance of adherence to PrEP and the protection condoms provide against other STIs. Follow-up visits were scheduled one month after initiating PrEP, to monitor for adverse events and understanding of PrEP use, and then quarterly. At all follow-up visits, STI screening (anal, pharyngeal, and urethral GC/CT, HIV and syphilis) and safety studies (complete metabolic panel) were completed, medication adherence was reviewed and ways to improve adherence were discussed. At every follow-up visit, clients were asked if their condom use had decreased, increased or not changed since the last visit.

Of the 1,000 individual records reviewed, 525 had complete data. Reasons for excluding individual data records from the analysis included switching insurance, meaning the client was no longer able to access PrEP at the clinical site; moving out of the area; missing the 13-month visit; missing more than 3 visits; stopping PrEP and then re-enrolling at a later date (considered a new case); missing data regarding condom use; missing STI data; and incomplete chart notes at more than one visit. Information was recorded initially in standardized, written clinic notes but half way through the study the clinic changed to an electronic medical record. The same questions on the written forms were included in the electronic medical record to ensure the integrity of the program and provide a seamless transition for the clients. All biological samples were stored and transported according to Clinical Laboratory Improvement Amendments (CLIA)[51] regulations. STI results were obtained from printed laboratory reports. All data relevant to the study was stored in a separate, password-protected electronic database and data was cleaned before analysis using a statistical software package (STATA®14).

After frequencies and descriptive analyses were completed, multilevel logistic regression models were utilized to predict the associations of condom use change and STI rates before and after initiation of PrEP with the following variables: age[3], number of partners[52], HIV positive partner[3], unknown HIV status of partners[6], alcohol binging[53,54], sex while intoxicated[55], race[9,56], ethnicity[57] and health insurance status[58].

Power Analysis and Effect Size Estimation

Power for this study was estimated for a sample size of 400 to be .90 or larger, given that multiple comparisons would be carried out for each risk behavior, and with the knowledge that the sample size would be limited by the number that could be enrolled in the study. A Monte Carlo simulation with 1,000 repetitions was carried out with two different random number seeds. It was found that an effect size of −.2 (log of the odds) for a change could be detected with power above .90 allowing for 15% attrition.

Ethics Statement

Approval for this study was granted by from the Committee on Human Research at University of California, San Francisco and informed consent was provided at the baseline visits by the participants. Additionally, approval from the study site was obtained.

Purpose of Dissertation

The purpose of the dissertation is to fill a gap in knowledge regarding the effects of PrEP on condom use, STIs and sexual health in MSM, in order to inform practice and provide foundational work for the development of sexual health interventions.

Summary of the Papers

This dissertation comprises three separate studies with an overall focus on how PrEP is affecting sexual health in MSM. The first is a systematic review of the current literature, which was conducted in order to guide the research. The second is a mixed

methods study that followed a cohort of MSM using PrEP who identified as low risk for HIV. The third utilized multi-level modelling to estimate the change trajectory in condom use and STIs in a cohort of MSM who meet CDC criteria for PrEP over 13 months.

The literature review, presented in Chapter 2, analyzed the state of the evidence regarding the association of PrEP with condom use, STI incidence and change in sexual risk behaviors in MSM. A structured search of databases resulted in 142 potential citations, but only ten publications met inclusion criteria and underwent data abstraction and critical appraisal. An adapted Cochrane Collaboration domain based assessment tool was used to critically appraise the methodological components of quantitative studies, and the Mixed Methods Appraisal Tool (MMAT) was used to critically appraise qualitative and mixed-methods studies. This systematic review of the literature guided both the development of a clinical PrEP Health Program and the subsequent longitudinal analysis of changes in condom-use and STIs in a cohort of MSM using PrEP for HIV prevention.

The primary purpose of the mixed methods study presented in Chapter 3 was to illuminate the reasons why a self-identified group of MSM who reported as low risk for acquiring HIV initiate, remain on, or stop using PrEP. Low risk was defined as clients who, during intake and subsequent visits, reported 100% condom use or only engaging in oral sex. Participants completed a self-reported questionnaire at baseline, and open-ended questions on reasons for initiating, stopping or remaining on PrEP. A secondary purpose was to assess if a cohort of MSM who report low-risk was truly low risk for HIV acquisition and whether condom use and STI rates changed after initiation of PrEP over a 13-month period. HIV risk behaviors reported by clients on a brief self-report

screening questionnaire, self-reports of condom use change, and tests for biological markers of anal, pharyngeal and urethral gonorrhea and chlamydia (GC/CT), syphilis and HIV were analyzed.

The purpose of the final study, presented in Chapter 4, was to estimate the change trajectories in self-reported condom use and frequency of STIs (detected using biological assays) before and after initiating PrEP in a cohort of MSM over a 13 month period. Multilevel logistic regression models, including piecewise modelling, were used to predict the differences in condom use and STI acquisition before and after initiation of PrEP. Treating time as a categorical variable, baseline, (before initiation of PrEP) condom use and STIs were compared to subsequent responses after one month and then at 3 month intervals (after initiation of PrEP). This approach helped to account for associations among observations within clusters to make efficient and valid inferences. In addition, the associations between variables known to influence condom use or STI rates—age[3], number of partners[52], HIV positive partner[3], unknown HIV status of partners[7], alcohol binging[59], sex while intoxicated[55], race[9,56], ethnicity[57] and health insurance status[58] were tested.

The final chapter includes the discussion, limitations and conclusions of this dissertation.

Innovation

This dissertation is innovative in that the studies described were designed to investigate how PrEP affects condom-use behavior and STI rates in an established urban sexual health clinic that provides PrEP services only to MSM. Results from these

studies provide valuable information on potential disease prevention strategies and health promotion messages.

Implications for Nursing

Nurse researchers conduct studies in order to develop scientific nursing knowledge that informs public health messaging and clinical practice in order to improve the health of individuals and communities. This dissertation provides data which may support the importance of discussing condom use and sexual risk behavior and routine STI screening for all MSM regardless of disclosed risk behavior, in order to improve both individual and community health. This study may help shape condom-use promotion and STI prevention messages that are relevant over time to MSM initiating PrEP, not only in sexual health clinics but also in primary care.

Conclusion

In an era where HIV prevention methods are rapidly improving, changing the perceived threat of disability or death, preconceptions regarding PrEP's effect on condom use and STI rates need to be investigated. Information gathered in this dissertation fills a knowledge gap regarding MSM using PrEP for HIV prevention, and will guide sexual health interventions and STI screening in order to improve overall health and well-being.

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Chapter 2: Does Pre-exposure prophylaxis (PrEP) for HIV prevention in men who have sex with men (MSM) change risk behavior? A systematic review

Abstract

Background

Pre-exposure prophylaxis (PrEP) for HIV has been available since 2012. Even so, PrEP has not been widely accepted among healthcare providers and MSM some of whom are convinced that PrEP decreases condom use, and increases sexually transmitted infections (STIs).

Design

A systematic review of the state of the evidence regarding the association of PrEP with condom use, STI incidence and change in sexual risk behaviors in MSM. A structured search of databases resulted in 142 potential citations, but only ten publications met inclusion criteria and underwent data abstraction and critical appraisal.

Methods

An adapted Cochrane Collaboration domain based assessment tool was used to critically appraise the methodological components of each quantitative study, and the Mixed Methods Appraisal Tool (MMAT) was used to critically appraise qualitative and mixed-methods studies.

Results

Condom use in MSM utilizing PrEP is influenced by multiple factors. Studies indicate rates of STIs in treatment and placebo groups were high. PrEP did not significantly change STI rates between baseline and follow-up. Reporting of sexual risk improved when questionnaires were completed in private by clients. Our review found that PrEP may provide an opportunity for MSM to access sexual health care, testing, treatment and counselling services. We did not find any conclusive evidence that PrEP users increase sexual risk behaviors.

Conclusion

The perception among healthcare providers that PrEP leads to increased sexual risk behaviors has yet to be confirmed. In order to provide effective sexual health services, clinicians need to be knowledgeable about PrEP as an HIV prevention tool.

Relevance to Clinical Practice

In an era where HIV prevention methods are rapidly improving strategies for STI testing, treatment, counselling and prevention remain vital in order to improve health. All healthcare providers are uniquely positioned to promote sexual health through the dissemination of accurate information.

Introduction

The introduction of pre-exposure prophylaxis (PrEP) in 2012 for HIV in the form of Truvada® (emtricitabine + tenofovir dispoproxil fumarate) provided a new tool to help prevent HIV transmission. PrEP is a once-daily pill that is simple to use with low toxicity

and good efficacy in reducing the risk of HIV acquisition [1]. Event based dosing of PrEP—at least one pill 24 hours before and one pill 24 hours after sex—is an alternative dosing form in some countries [2]. Globally, it is estimated MSM have a 19.3-fold greater odds of becoming infected with HIV compared to the general population [3]. In light of this, MSM are a high risk population appropriately targeted for PrEP initiation.

The introduction of PrEP as an HIV prevention method is not without controversy and concern has been raised that it may lead MSM to think that they no longer need other preventive measures such as condoms [3,4]. The support for this concern is evidenced in qualitative PrEP studies which report 35%-60% of high-risk MSM believed that they would be less likely to use a condom if they were on PrEP [5-7]

While PrEP reduces the risk of HIV transmission it does not provide any protection against other sexually transmitted infections (STIs), which can only be prevented by consistent condom use, mutual monogamy or abstinence [1]. STIs disproportionally affect MSM and continue to escalate in this population [8]. The introduction of PrEP is viewed by many as fueling the recent upsurge in STIs [1,9]. STIs continue to be a major public health issue and it is estimated globally there are 357 million new cases a year [8]. Reports of STI treatment failure rates are between 13% and 21% in MSM, and different STIs have re-emerged with a vengeance such as resistant strains of gonorrhea and chlamydia, ophthalmic and otic syphilis, and even neuro syphilis [8,10].

In many cultures, MSM are unable to access sexual health services as homosexuality is illegal and in some cases punishable by death, leaving them at high risk for HIV acquisition[11]. Even when healthcare access is not an issue, medical

providers report being ill-equipped to discuss sexual health and are concerned that sexual risk behaviors, and in turn STI rates, will increase if they prescribe PrEP. Furthermore, PrEP for HIV prevention remains contentious because some medical providers fear they will be seen as condoning condomless sex [4]. In order to help medical providers prescribe PrEP, the World Health Organization (WHO) has published clear guidelines that recommend the use of PrEP in conjunction with condoms [1].

The increase in the apparent incidence of STIs among PrEP users may be related to STI testing required by PrEP protocols in clinical practice[12]. Historically, similar patterns occurred with the introduction of highly active antiretroviral therapy (HAART) for HIV in the mid 1990's. As STI rates began to rise among MSM presenting for HIV treatment, some researchers hypothesized that risk compensation, rather than increased testing during the HIV treatment process, was to blame[13]. In fact, the apparent rates of syphilis, rectal gonorrhea and chlamydia in MSM have been increasing since 2009—several years before PrEP was introduced to clinical practice—and rates continue to increase in countries were PrEP is not yet available[8,10]. This suggests that PrEP alone cannot account for the observed increase in STI rates among its users. It may instead be that programs targeting MSM for HIV/STI testing and treatment are actually the cause of the reported increase in STIs. Similarly, another biomedical intervention that had biases comparable to PrEP was the oral contraceptive pill, which many assumed would lead to adverse results and an increase in sexual risk behavior[14]. When the pill was first brought to market, it required a woman to be married. Later, when the pill could be prescribed for any woman regardless of marital status, gonorrhea diagnoses increased and the working theory was that the unintended

consequences were due to condomless sex, rather than more effective testing protocols for STIs [13] that were implemented at the same time. A parallel debate continues among healthcare providers, political entities and the MSM community whether PrEP is a direct link to decrease in condom use among MSM secondary to a decreased fear of being infected with HIV—just as it was feared the pill would lead to a decrease in condom use secondary to a decreased fear of becoming pregnant.

Aims

The purpose of this study was to review the literature on the association of PrEP use with condom use, STI incidence, and change in sexual behaviors, such as anal sex and number of partners in MSM. The research questions were:

1) How does PrEP use affect condom use in MSM?

2) How does PrEP use affect STI incidence in MSM?

3) How can transmission risks for HIV/STI (*e.g.*, type of anal sex, number of partners) be assessed in MSM using PrEP?

Methods

Design

An adapted Cochrane Collaboration domain based assessment tool was used to critically appraise the methodological components of each quantitative study [15], and the Mixed Methods Appraisal Tool (MMAT) [16] was used to critically appraise qualitative and mixed-methods studies. Qualitative and mixed-methods studies were included as they

are better suited for exploring the complexities of sexual risk perception, behavior change and attitudes towards new biomedical prevention tools [17].

Search Methods

A search of current PrEP literature, which utilized medical subject headings (MeSH) and keywords to identify studies of potential interest, was constructed with the aid of an expert librarian at the University of California San Francisco. Literature searches using PubMed, Embase, Medline, PsychINFO®, Web of Science®, CINHAL and Google Scholar were performed. Initially, the following MeSH search terms were entered into the PubMed database to determine if they were appropriate: sexual partners, sexual behavior, sexually transmitted infections, sexually transmitted diseases, sexual health, gay, bisexual, homosexual, sexual risk, sexual behavior, pre-exposure prophylaxis for HIV, syphilis, gonorrhea, chlamydia, anal sex, condom use, condomless sex, biomedical HIV prevention, risk compensation, harm reduction and risk reduction. The following MeSH search string was considered most appropriate: "Sexually Transmitted Diseases"[MeSH]) AND "Pre-Exposure Prophylaxis"[MeSH]) AND "Sexual Behavior"[MeSH]) AND "Homosexuality, Male"[MeSH].” The search was expanded by including sentinel research papers and secondary analyses of the body of work identified in the database search, and a review of meeting abstracts. Inclusion criteria for studies were as follows: 1) English language; 2) PrEP for HIV prevention; 3) included MSM and transwomen; and 4) discussion of STI rates or condom use during study. Exclusion criteria were: 1) studies that only described women, children or heterosexuals; 2) studies that describe pre-exposure prophylaxis for other diseases

(*e.g.* doxycycline for syphilis [18]; and 3) articles published prior to 2010 due to a paucity of data.

Search Results

The electronic database search generated 142 potential citations, published between January 2010 and January 2016, and another 3 were identified by searching for sentinel studies (IPERGAY, PROUD, iPrEx). All titles and abstracts were screened and reviewed by the first author and Dr. David Vlahov, who has authored a body of work on HIV, risk behavior and MSM. Initially there was a disagreement regarding the inclusion of qualitative and mixed method studies as they did not include STI screening data, but upon further review it was agreed the insights they provided into PrEP related change in condom use, STIs and capturing change in sexual practices were valuable. Figure 1 presents a flow diagram of the selection and review process. After inclusion and exclusion criteria were met, and systematic reviews, practice guidelines, editorials, meeting abstracts, meta-analyses, duplicates and unrelated articles were excluded, the final number was 10.

Results

Characteristics of the Studies

Table 2 displays the 10 reviewed studies, which were published between 2010 and 2016; three were randomized control trials (RCTs) [2,19,20], one began as an RCT but was changed to an open label trial [21], one was a community open label trial [22], one was a prospective cohort study [23], one was a survey [7], two were mixed methods [5,6] and one

was qualitative [24]. The RCTs and open label trials had Truvada provided by Gilead at no cost to the participants [2,20-22] The prospective cohort study was limited to individuals who accessed care through the Kaiser healthcare system. For that study, Truvada was not provided by Gilead and clients had a copayment toward drug cost between 30 and 50 USD [23]. Daily dosing of PrEP was used in 9 studies and event based dosing was used in one study [2].

Inclusion and Exclusion Criteria for the Studies

The methods and inclusion criteria varied considerably across these studies. The common elements extracted to facilitate comparisons included MSM age 18 or over who were HIV seronegative, condom use, sexual risk behavior and STI data. Definitions of sexual risk included condomless anal intercourse, (receptive or insertive) and at least one partner in the past 3, 6, or 12 months [5-7,19,20,22,24]. Terms used to describe the target population varied among the studies: four studies referred to MSM as men having sex with men and transgender persons[2,19,20,24], four studies only used the term MSM and did not refer to any other subgroups of people [6,7,23], one study used the term “gay and bisexual” [5] and three studies defined men who have sex with men as “male at birth” [19,20,23].Definitions of sexual risk varied as follows:

- Grant et al., (2010): unprotected anal receptive sex in past 12 weeks; any transactional sex in past 6 months; known HIV positive partner; any unprotected anal intercourse with partner of positive or unknown HIV status.

- Golub et al., (2010): instances of substance use with at least one incident of unprotected anal intercourse (insertive or receptive) with a casual or serodiscordant male partner in last 3 months.
- Hojilla et al., (2015): any condomless anal sex (insertive or receptive) with two or more male or transgender female partners in past 12 months.
- Brookes et al., (2012): HIV negative MSM in a serodiscordant relationship for 12 months or longer.
- Marcus et al., (2013): any condomless anal sex (insertive or receptive).
- Hoff et al., (2015): serodiscordant couples engaging in any anal sex (insertive or receptive) in past 3 months.
- Volk et al., (2015): risk assessed by primary care provider before referral to PrEP clinic.
- Molina et al., (2015): unprotected anal sex (insertive or receptive) with at least two partners in past six months.
- McCormack et al., (2015): previously attended one the 13 screening clinics and had been screened for HIV/STIs; anal intercourse (insertive or receptive) without a condom in previous 90 days and likely to have condomless anal intercourse (insertive or receptive) in next 90 days.
- Liu et al., (2015): condomless receptive anal sex with at least 2 male or transwomen partners; or at least 2 episodes of condomless anal sex (insertive or receptive) with at least 1 HIV infected partner; or sex with a male or transgender partner and being diagnosed with syphilis or anal GC/CT.

Exclusion criteria included medical contraindications to PrEP [2,19-24], not meeting risk criteria [5-7], and not agreeing to or not completing follow up visits [23,24]. Participant retention rates in studies where drug or placebo was provided were 72-78%, but over the course of all of the studies, response rates for behavioral measures decreased.

Race

Participants were recruited from multiple locations including Peru, Ecuador, Brazil, Thailand, South Africa, USA, Canada, France and the UK. Race was not clearly defined in all of the studies, with some not mentioning race or ethnicity and instead merely stating the site of the trial [2,19,20]. Therefore a comparison of differences in STI rates and condom use between races/ethnicities was not an element of review in this study.

Location

All of the studies were located in urban areas with high HIV prevalence rates among MSM (25-46%), such as San Francisco, New York, Miami, London, Paris, Montreal, Rio de Janeiro, Chang Mai and Cape Town [2,5-7,19-25].

Socioeconomic Status

Quantifying education status and income of participants across the studies was problematic due to studies having been conducted in 10 countries with differing educational structures and levels and differing definitions of income levels [2,5-7,19-25].

Age

The age range in the quantitative studies was 18-68, three studies reported mean ages which ranged from 25-37 years old [19,20,23], one study only provided a range of 18-45+ [22], and two studies reported a median age of 35 [2,21]. The quantitative survey study had a smaller age range of 18-49 with a mean of 29 [7]. In the mixed methods studies the age range was 19-71 with a median age of 36 [5,6]. The qualitative study that utilized a Framework Analysis had a range of 21-63 with a median age of 37 [24].

Substance Use

Substance use, including intravenous drug use, was not measured consistently across studies, and thus it was not possible to draw conclusions about the associations between sexual risk behavior and substance use. For example, two of the RCT studies included methamphetamine, ecstasy and gamma-hydroxybutyrate [2,21], and another only measured alcohol use [20]. The open label study included amyl nitrite (poppers), erectile dysfunction drugs and heroin [22], and the prospective cohort study included cocaine and methamphetamine. The predominant finding was that substance use did not influence adherence to PrEP but how substance use influenced condom use and sexual risk behaviors varied [2,20-24].

Measurements of Risk Behavior

All of the studies collected individual risk behavior data by using multiple methods, including interviewer-administered questionnaires and surveys[5,19-21,26], secure email surveys[23], computer-assisted structured interviews[6,7,20] and data from daily

diaries[21]. Questions common across all studies included number of condomless anal receptive and insertive sex episodes, number of partners (both receptive and insertive anal with or without a condom) and intended or actual use of condoms since the last visit.

In one RCT study[20], in which baseline risk behavior was captured by computer-assisted self-interview (CASI) but follow up risk behavior was captured by in-person interview, study participants predominately reported no behavior change or a decrease in risk behavior. Similarly, the studies of Liu et al. (2016) and Marcus et al. (2013), which used in-person interviews only, revealed no behavioral change or less risk taking between baseline and follow up. In contrast, McCormack et al. (2015) used questionnaires completed in private and risk behavior was reported to have increased, while Molina et al. (2015), using CASI only, found either no change or an increase in reported risk behavior between baseline visits and follow up. The mixed methods and survey studies which utilized CASI also found that there was either no change or an increase in reported risk behavior between baseline and follow up[5-7]. One cohort study[23] found that participants responding to emails from healthcare providers reported no change in sexual risk, while participants responding to emails from non-healthcare providers reported increased sexual risk between baseline and follow up. Reliability for reporting risk during sexual activities has been shown to decrease over time[27]. To control for decreased risk reporting, daily diaries and monthly questionnaires were initiated in one RCT, but were subsequently abandoned due to a low response rate. In contrast, baseline and 12-month questionnaires, by paper and pencil or computer, in the same study yielded a higher response rate[21].

Condom Use Change

Condom use change associated with PrEP was variable throughout the studies reviewed. The data from the blinded RCTs showed either no change [2] or increased use of condoms and only a ~4% decrease in condomless anal sex after stopping the study [19,20]. Conversely, the open label and cohort trials reported an increase in the number of condomless receptive anal sex partners if on PrEP [22,23]. In the PROUD study [21], participants were randomized to begin PrEP either at the start of the study or after one year. Those who began on PrEP reported a larger increase in receptive anal sex without a condom with ten or more partners (21% vs. 12%; p=0.03, test for trend) at month 12 of the study. Participants also reported an increase of 14% in first time condomless receptive anal sex, however, there was no significant difference between placebo and PrEP groups, and therefore the authors did not consider this to represent a behavior change. This finding was also reflected in the secondary analysis of the iPrEx study: if a participant responded strongly believing he was taking PrEP the mean number of partners increased from 7.7 to 12.8 (p=0.04) [19]. Conversely, the open label and cohort trials reported an increase in the number of condomless receptive anal sex partners if on PrEP [22,23].

In the Golub et al. (2010) survey study the participants were told that PrEP was 80% effective against HIV and then asked what impact this would have on their condom use. Responses were dichotomized into, likely or not likely to decrease condom use on PrEP, with 35% of participants reporting that their condom use would likely decrease. In the Brooks et al. (2012) mixed methods study, in which PrEP

efficacy was presented as 92% effective against HIV, thematic content analysis revealed a perception that PrEP provided an alternative to condom use for HIV prevention. Neither the quantitative survey nor the mixed methods studies discussed the importance of adherence to medication in order to provide the proposed high levels of protection against HIV which may have influenced the overall results [5-7].

Decreased condom use had interesting associations with a number of other variables. For example, in the iPrEx study participants under 25 years of age were more likely to report condomless anal receptive sex at follow up than those age 25 or older [19,20]. Conversely, in the mixed methods studies older MSM were more likely to decrease condom use [5,6]. Situational factors, such as geographical location and place of sexual encounter also affected condom use change, with San Francisco participants reporting the greatest decrease in condom use compared to other locations [22], and encounters in bath houses more likely to involve condomless sex [24]. Decreased condom use was associated with certain relationship factors, for example, if an HIV negative partner were using PrEP, his HIV positive partner would feel more comfortable barebacking [6]. Other variables that showed associations with decreased condom use included mental health issues, such as depression [19,22]; perception of partners being low risk [24]; and socioeconomic factors, such as higher income and having a college degree [6,7]. Of note, substance use was found to decrease condom use [7,24] or have no effect on condom use change [21-23].

Sexually Transmitted Infections

In order to verify whether condomless sex had occurred, participants in certain studies were tested for biomarkers of GC/CT [2,21-23] and syphilis [2,19-22]. The biomarkers used were all validated and are currently used in practice. Treatment for STIs was provided per local guidelines in all studies. There was no significant difference in STI rates between participants on PrEP and those not on PrEP in the RCT studies [19-21].

Assessment and testing for STIs was completed at baseline in six studies, but how the information was collected was not uniform across the studies as shown in Table 1. Three-point testing for GC/CT (urethral, anal and pharyngeal) and syphilis was completed in four studies at baseline and every 12 weeks [2,21-23]. STI incidence was high in the studies that consistently screened for anal, pharyngeal, and urethral GC/CT, and syphilis. For example, two of the RCT studies found rectal GC/CT in 32-39% of participants [2,21] and syphilis infections ranged from 5 to 11% [21-23].

The iPrEx study only analyzed urethral GC/CT samples if leukocytes were present in the urine and urethral screening for asymptomatic urethritis occurred every 24 weeks. There were no anal biomarker tests for GC/CT and reporting relied on exam and self-reports of symptoms or exposure making syphilis the only STI with consistent biomarker testing [20]. STI rates were similar in treatment and placebo groups at all time points there were no significant between-group differences in the numbers of subjects with gonorrhea or chlamydia during follow-up. Syphilis cases decreased during follow up in both treatment arms (P trend < 0.001) [20]. The PROUD study also found no significant difference in STI rates between participants on PrEP and those not on PrEP despite participants on PrEP reporting increased number of partners and an increase in receptive anal sex [21]. Liu et al. (2016) found that 51% of participants were diagnosed

with one STI (CT,GC or syphilis) at baseline, with an initial decrease in rectal and pharyngeal GC/CT at 6 months followed by an increase at 12 months ($p < 0.05$) and a final overall STI positive rate similar to the baseline STI rate [22]. Two studies did not include baseline STI data [2,23] but found increases in STIs over time at multiple follow-up visits, specifically in anal GC/CT, despite no reported changes in number of partners and similar rates of condom use throughout.

The mixed methods studies did not collect STI data however, between 30-40% of participants discussed being concerned about STI risk if they decreased condom use secondary to being on PrEP [5,6]. Neither the survey study [7] nor the framework analysis included questions or data regarding STIs [24].

Impact of Risk Reduction Counselling on Behavior

All of the RCTs and open label trials provided risk reduction counselling at least on a monthly basis, as well as condoms and lubricant [2,20-22]. Only one study described implementing and training counsellors in the use of, a risk reduction model (RESPECT), and risk behaviors during that study did not change from baseline[2]. In contrast, in the Grant et al. (2010) blinded RCT where risk reduction counselling and HIV/STI tests were provided at the same visit, risk reporting decreased. In the prospective cohort study that implemented unspecified risk reduction counselling, reports of sexual risk increased from baseline[23]. Conversely, in the open label study number of anal sex partners decreased in a response to risk reduction counselling [22].

In the two mixed methods studies and the quantitative survey, participants did not receive any risk reduction counselling, condoms or lubricant because hypothetical

scenarios were used [5-7]. This may account for the reports of increased risk behaviors compared to the studies were risk reduction counselling was included.

In the qualitative study, participants received risk reduction counselling, condoms and lubricant at every visit. The analysis of counselling notes revealed that the risk reduction counselling provided to PrEP users included guidance on serosorting (having sex with HIV negative partners only), seroadaptation (asking sex partners their HIV status), and seropositioning (oral or insertive anal sex with HIV positive partners) and condom use. Counselling on the combination of these methods is reported to decrease sexual risk behaviors in this cohort [24].

Discussion

Our review found that offering PrEP services provides an opportunity for MSM to access sexual health care, testing, treatment and counselling that would not be accessed otherwise. Although STI rates were high in this population, we did not find any conclusive evidence that PrEP use leads to increased sexual risk behaviors. Counselling regarding condom use and STI testing at every encounter improved compliance and should be a fundamental component of PrEP services. Adherence to a PrEP regimen, whether daily dosing or event based, is vital to preventing HIV infection. STI testing should include extra-genital testing in MSM regardless of PrEP use, in order to prevent health deficits and onward transmission. In the studies reviewed, providing privacy for MSM to complete health questionnaires improved accurate risk reporting, which allows clinicians to address behaviors that increase the risk of HIV/STIs. Event based dosing of PrEP—at least one pill 24 hours before and one pill 24 hours after

sex—had a low adherence rate of 43%, and PrEP was only effective if a median of 15 or more pills per month were taken [2]. Clinicians should counsel MSM that protection against HIV acquisition is dependent on adequate levels of TDF-FTC in their system.

Measuring risk behavior is complex. Our review represents the first effort, to our knowledge, to synthesize evidence regarding the association of PrEP use among MSM with changes condom use, STI incidence and sexual risk behaviors. How PrEP effects condom use in MSM is challenging to interpret from the data available. All of the trials used self-report of condom use and the response rate was low. Regardless of response rate, validity of self-report is difficult to measure and is often influenced by the individual feeling compelled to report the "correct" answer [28]. This may explain why there was a 56 to 74% report of no change in condom use in the studies where participants were counseled to use condoms [2,19-24]. Furthermore, none of the studies included questions about condom use before PrEP initiation, making it impossible to assess if "no change" meant using or not using condoms. And paradoxically, two of the trials reported an increase in condom use without any significant changes in STI rates, further suggesting that self-report of condom use is methodologically unreliable.

STI biomarker analysis is a commonly used method for quantifying sexual risk behaviors such as condom use [29,30]. However, there are some behaviors for which biomarkers are ill-suited (*e.g.*, sexual frequency or needle sharing) [24,27,31]. From a research perspective, relying solely on self-reports or physiologic data limits our ability to understand the full-scope of the phenomena of sexual risk behavior. Understanding sexual risk behavior necessitates a highly complex framework to conceptualize every facet of the physiological, intellectual, emotional, situational, social, cultural, legal and

moral range of issues. In general, individuals consider sexual risk to equal a negative outcome, and within the MSM community for a long period of time the negative outcome was HIV acquisition. The ability to intervene clinically, with biomedical interventions such as PrEP, necessitates that healthcare providers have an understanding of how and why changes in sexual risk behaviors may occur. For example, Liu et al. (2016) noted that geographical location influenced a change in condomless receptive anal sex highlighting the need for clinicians to be aware of the accepted norms of sexual behavior in their communities when discussing PrEP.

The perception among healthcare professionals that PrEP will lead to increased risk behaviors [4,32] has yet to be confirmed. A number of the studies reviewed here did show high overall rates of STIs in MSM on PrEP or placebo (33-57%), yet none of them reported a significant change in STI rates between baseline and follow-up. In fact one study found no change over time in rates of rectal GC/CT despite participants reporting increased number of partners and increased receptive anal sex [21]. Furthermore, while there may be a perception that it is PrEP that leads to an increase in STI rates, many of the participants had never been tested for STIs before entering a PrEP study. The emergence of PrEP as an HIV prevention tool may increase STI testing and treatments in MSM and in turn help reduce onward transmission of STIs. Moreover, the STI rates in the studies are similar to current STI rates among MSM, regardless of PrEP status, as reported by the World Health Organization [8], making frequent STI counselling, testing and treatment a priority worldwide to prevent health deficits.

There is some evidence within the reviewed studies that risk compensation may occur on PrEP. There was a common theme that PrEP reduced the anxiety around

sexual acquisition of HIV [5-7,24], thus creating a perception among MSM that the need for condom use is eliminated. For example, many HIV seropositive partners expressed they would be comfortable engaging in condomless anal sex if their partner was on PrEP [5-7]. However, the influence of partners' preference not to use condoms was not measured in many of the studies, even though this has been found to have a significant influence on condom use [33]. Furthermore, a common finding was a change in sexual practice from being exclusively anally insertive, to experimenting with being anally receptive after PrEP initiation [2,20,21,23,24]. This willingness to experiment sexually may be attributed to a reduction in anxiety of HIV acquisition.

In order to capture risk behavior the studies made an effort to collect individual risk behavior using multiple methods that included, interviewer administered questionnaires [19,21,22], secure email survey [21,23], computer-assisted self-interview [6,7,20,21], daily diaries and paper and pencil questionnaires [21], and review of counselling notes [24]. In the studies reviewed herein, computer-assisted self-interviews (CASIs) produced better response rates than other methods used to capture sexual risk behavior. This is consistent with the literature that has shown higher rates of risk behavior reported in CASIs than in interviewer-administered questionnaires [34]. Participants questioned using CASI methodologies typically report number of partners and frequency of condomless sex more openly than those interviewed face-to-face, an observation that has been attributed to greater privacy for reporting socially sensitive behaviors[35] and socially acquiescent responses that occur with in-person interviews[36]. Behavior disclosure is often influenced by the desire to create a positive social image [37], which may have been reflected in the results of in-person interviews. Such social desirability influence may

explain why there was a decline in risk behavior reports in one RCT where the baseline behavior risk was captured by CASI but follow up risk behaviors were captured by in-person interviews [20].

The response rate for the secure email questionnaires was lower than for interviewer administered questionnaires, which may have been a consequence of the higher level of language and computer literacy required for email compared to interviewer administered questionnaires [31]. Where participants were required to respond to an email received from a healthcare provider the majority reported no change in sexual risk behavior [23], which may have been because this was perceived as being part of the medical record. None of the studies in this review included validity or reliability reports for the methods used to capture risk behavior. Such reports are unfortunately uncommon in sexual health research, even though suitable methodologies have been developed and tested [35].

Additionally, in the studies reviewed, representation of MSM under age 25, who are considered to be at greatest risk for HIV/STIs was low, 5%-30% [1]. Data from the RCTs reflected this finding [2,19-21] with the majority of participants being in their thirties. One might speculate that this was due to decreased risk awareness or a lack of information regarding new HIV prevention tools [38]. Barriers to younger PrEP users may include inexperience negotiating healthcare systems, reluctance to discuss sexual preferences with healthcare providers, fear of parents being informed, and cost [39]. For example, in the prospective cohort study [23], which was set in a large US healthcare institution, the mean age of participants was 37. One possible explanation for this is that, while other studies provided PrEP free of charge, the Volk et al. (2015) study

required a payment, which some younger MSM may not have been able to afford. Cost has been found to be a barrier to accessing PrEP and a barrier to adherence to other medications [40-42]. However, there are currently no data available outside of a study context regarding the effect of cost on adherence to PrEP. Volk et al. (2015) was also the only study requiring a primary healthcare provider determination of a need for PrEP. In contrast, screening in the other studies outside of a large healthcare system at "gay-friendly" sites merely required participants to state that they wanted PrEP. However, even at such gay-friendly sites, participation by those under 25 did not increase [2,20-22]. All of the studies included a HIV risk component in their inclusion criteria, which may have inadvertently alienated younger MSM. The low uptake of PrEP by young MSM has been identified in other studies and may be secondary to individuals not having established a gay identity, a misconception that PrEP is synonymous with promiscuity and a lack of insight into risk behavior within communities with high HIV prevalence [39,43]. Healthcare professionals should take these factors into consideration when interpreting the available PrEP data for younger MSM. In view of the fact that younger MSM are one of the populations in which HIV rates are increasing, this review suggests that neither an individual's ability to pay, nor a clinician's assessment of risk, should be prerequisites for access to PrEP.

There are methodological concerns throughout all of the studies. For instance, the mixed methods and quantitative survey studies used hypothetical scenarios with a guaranteed 80% or greater protection against HIV without addressing participants' understanding of risk factors for HIV or STIs, making it difficult to extrapolate their findings to real world scenarios [5-7]. In addition, the reporting of certain measures of

sexual risk, such as frequency of anal sex, number of partners and drug use, were not consistent across the studies, making it difficult to draw inferences from these data on the effects of PrEP on risk behavior. Although all the studies included risk reduction counselling, only one study actually used a recognized risk reduction model [2].

In addition, the studies reviewed here were all potentially biased. For example, recall bias for sexual risk, which is influenced by the impact or meaning of an encounter [44], was not addressed in any of the studies. It is possible that not all sexual encounters were included in participants' reporting, and yet validity scales to adjust for recall bias during the statistical analyses were not included [31]. Recruitment bias is another potential problem [45]. The participants recruited into the studies were all interested in PrEP as a form of protection against HIV, implying a self-awareness of risk behavior that may not be found in the general MSM population.

Notwithstanding the methodological shortcomings described above, it is always more difficult to draw inferences from a collection of studies such as those reviewed here that have different designs, and that have different variables collected from different populations, in different places.

Conclusion

We are presently in an optimistic period of biomedical advances to prevent HIV [46]. However, in view of the gaps in the literature described herein, researchers must continue to investigate new ways to frame the discussion and messaging around STI prevention in a way that is meaningful to the individual, in order to reduce the social, physiological, psychological and financial burden of STIs.

Relevance to Clinical Practice

In an era where HIV prevention methods are rapidly improving, changing the perceived threat of disability or death, strategies for STI prevention and reducing sexual risk behavior cannot remain stagnant. Nurses, community health workers, doctors, outreach workers, social workers are all well positioned to promote sexual health through the dissemination of accurate information to the communities they serve, including marginalized MSM throughout the world.

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Figure 1. PRISMA Flow Chart

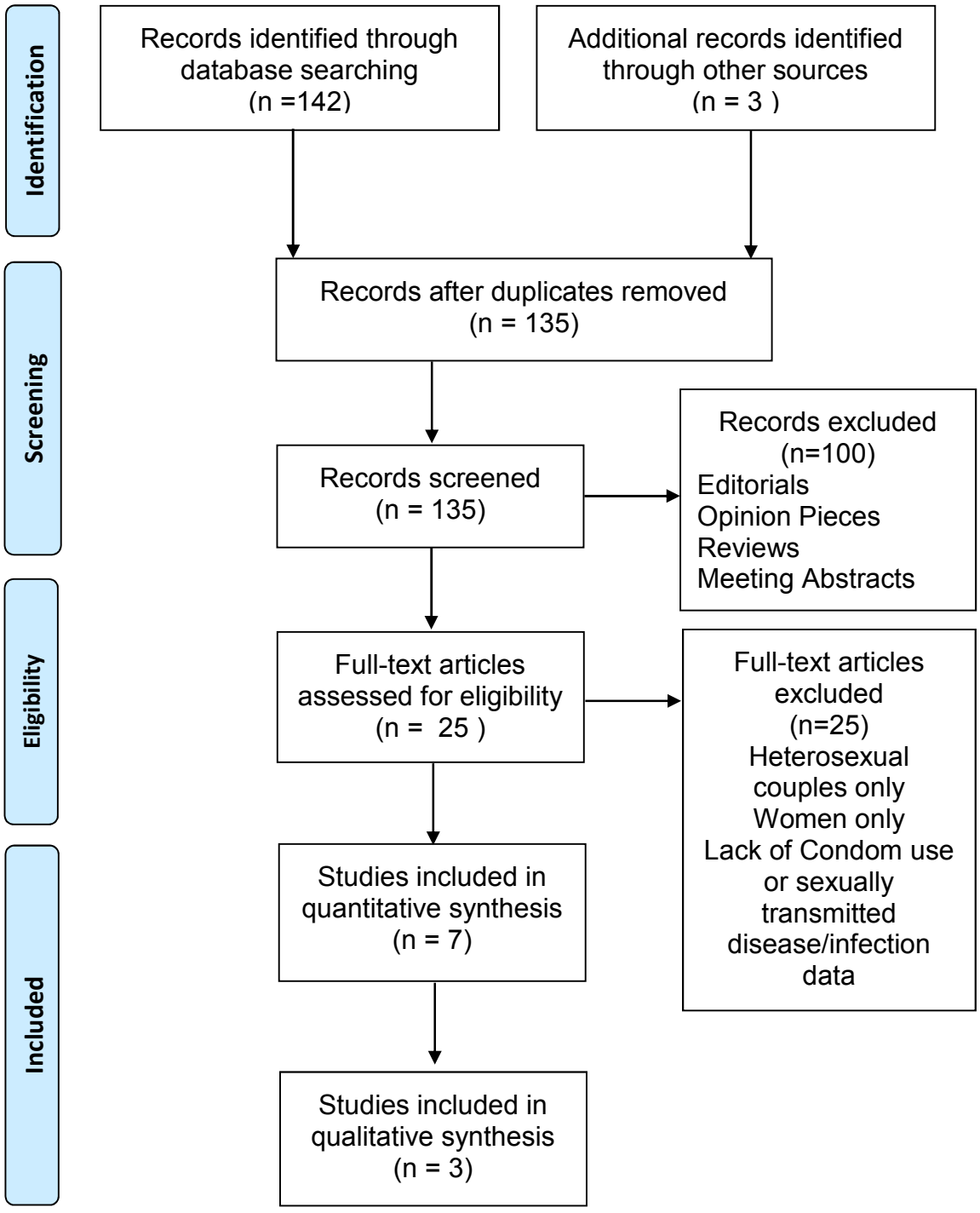

Table 1. Data collected and Methods of diagnosing STIs

Study	STI Data Collected	STI Diagnostic Methods
Grant et al., 2010	Warts, Herpes, Syphilis, Urine leukocyte esterase positive	Physical examination, Symptoms, Partner diagnosis, Biological markers
Marcus et al., 2013	Syphilis, GC/CT	Physical examination, Symptoms, Biological markers
McCormack et al., 2015	Syphilis, GC/CT, HCV	Biological markers
Molina et al., 2015	Syphilis, GC/CT, HCV, Herpes	Biological markers
Volk et al., 2015	Syphilis, GC/CT, HCV	Biological markers
Liu et al., 2016	Syphilis, GC/CT, Herpes	Biological markers

Table 2. Overview of Studies

Author	Grant	Golub	Brooks	Marcus	Molina	McCormack	Volk	Hojilla	Hoff	Liu
Year	2010	2012	2012	2013	2015	2015	2015	2015	2015	2016
N	2499	180	50	1743	400	544	657	26	219	557
Design	RCT	Quantitative Survey	Mixed Methods	RCT	Double Blind RCT	Open Label RT	Prospective Cohort Study	Framework Analysis	Mixed Methods	Open Label
Age	18-67	18-49	19-71	18-67	18-50+	29-43	20-68	21-63	19-71	18-45+
	Mean 27	Mean 29	Mean 37	Mean 25	Median 35	Median 35	Mean 37	Median 37	Median 36	
Participants	MSM or Trans-gender	MSM	Gay or Bisexual	MSM or Trans-gender	MSM or Trans-gender	MSM	MSM	MSM, Trans-gender	MSM	Male at Birth
Data Collection Methods	**Baseline:** CASI	ACAI	Interviewer Administered Survey	IAQ	CASI	Questionnaire	Secure Email Survey	Analysis of Counselling Notes	ACAI	IAQ
	Follow up: In-Person Interview		Grounded Theory	Biomarkers & Physical Exam	3-Point Testing	3-Point Testing	3-Point Testing		Grounded Theory	3-Point Testing
	Biomarkers & Physical Exam				Syphilis Testing	Syphilis Testing	Syphilis Testing			Syphilis Testing
Risk Reduction Counselling	Monthly for 6 Months, then Quarterly	n/a	n/a	Monthly	Monthly	Quarterly	Monthly or Quarterly	Monthly or Quarterly	n/a	Quarterly
STI Rates on PrEP	Syphilis: 13%	n/a	n/a	No Change	41%	50- 57%	50%	n/a	n/a	50.9%
Partners	↓	↔	↔	↑	↔	↑	↔	↑↓	↔	↓
Anal Sex	↓	↑	↑	↑	↔	↑	n/a	↑	↔	↓
Condom Use	↑	↓	↓	↑	↔	n/a	↔	↓	↓	↔
Dosing	Daily	Hypothetical Daily	Hypothetical Daily	Daily	Before & After Sex	Daily	Daily	Daily	Hypothetical Daily	Daily

3 point testing = GC/CT pharyngeal, anal and urethral. ↑ = increased, ↓ = decreased, ↔ = no change.

CASI = Computer assisted structured interview.

ACAI = Audio Computer assisted Interview. IAQ = Interview Assisted Questionnaire.

Chapter 3: Men Who Have Sex with Men (MSM) who self-identify as Low Risk for HIV requesting Pre Exposure Prophylaxis for HIV prevention (PrEP): A Mixed Methods Study

Abstract

This mixed methods study followed a cohort of MSM using PrEP, who reported 100% condom use or oral sex only, during clinical visits over 13 months. Participants completed a self-reported questionnaire at baseline, and open-ended questions on reasons for initiating, stopping or remaining on PrEP. Condom use change and bacterial sexually transmitted infections (STIs) were assessed at month 1, 4, 7, 10 and 13. Approximately 80% had one or more risk factors for HIV at baseline, despite reporting 100% condom use, including multiple partners, rectal STIs, syphilis and substance use. Themes for initiating PrEP included “added protection” and “peace of mind” and for those who remained on PrEP additional themes included “sexual pleasure” and “safety and security”. Condom use change occurred at months 1 and 7 and returned to 100% at month 13. STI rates declined over time. These findings provide information on reasons why MSM reporting low risk choose PrEP.

Introduction

In 2010, the iPrex study provided a major advance in HIV prevention, proving that pre-exposure prophylaxis for HIV (PrEP) in the form of Truvada® (emtricitabine + tenofovir dispoproxil fumarate), reduced HIV transmission in men who have sex with

men (MSM) by 92%.[1] Following this groundbreaking research other studies demonstrated that PrEP is 92-99% effective in preventing HIV infection in MSM.[2-4]

The introduction of this biomedical HIV prevention tool has caused much debate among healthcare providers, HIV advocacy groups and charities, and MSM regarding how it affects sexual risk behaviors, with some concerned it will decrease condom use, in turn increasing sexually transmitted infections (STIs) and others who believe it will decrease HIV risk without altering behavior.[5-8] These contrasting views have led to some confusion regarding who should be offered PrEP, often leaving clinicians unsure how and to whom they should provide PrEP services.[9] In order to assist clinicians, the Centers for Disease Control and Prevention (CDC).[10] and the World Health Organization (WHO) have published guidelines to identify individuals who would most benefit from PrEP.[11] The guidelines have led to the development of multiple tools designed to help clinicians predict risk of HIV acquisition in MSM[12-17] (see Table 1). The tools are useful only insofar as clients are comfortable disclosing their sexual risk factors and substance use. However, research studies have shown that self-reporting these behaviors to a clinician is often unreliable [18-21] because social desirability may cause individuals not to disclose their "real" behaviors.[22,23]

Sexual health is not only about preventing diseases, such as HIV; it is a complex topic that involves psychological, social, cultural and historical factors. [24-27] Specifically, for MSM in the US a spectrum of events have affected their sexual health including the belief that homosexuality was a sickness; the decriminalization of homosexuality; the impact of the AIDS crisis and the links between sex and death; the acceptance of same sex marriage; and the continued health and social disparities in MSM of color. [8] The

complexities of sexual health are not typically discussed during a routine health care encounter which may lead to the client or clinician to fail to recognize risk factors for HIV.[28]

By attempting to define HIV risk through prediction tools, clinicians may be unintentionally creating barriers that prevent MSM from accessing PrEP.[29,30] Classifying an individual as low risk solely on the basis of self-reported risk behaviors can be misleading to the individual. The consequence of falsely assigning low risk scores to MSM who are truly high risk for HIV acquisition is likely to be denial of PrEP as an HIV prevention tool which may lead to a preventable HIV infection or a subsequent high risk exposure to HIV requiring post-exposure prophylaxis (PEP).

The provision of PrEP to all MSM who request this new biomedical prevention tool continues to be controversial due to concerns that PrEP will increase sexual risk behavior and in turn reduce population level prevention benefits, decrease cost-effectiveness and increase STIs secondary to decreased condom use.[13,14,31-33] The tools developed for assessing HIV risk [1,3,4,34,35] and recommending PrEP to MSM vary greatly, which may lead conflicting advice regarding PrEP depending on which risk assessment tool is utilized (see Table 1). Moreover, the tools are dependent on the willingness of individuals to disclose risk behaviors, including alcohol and substance use. The reliance on MSM to reveal risk behavior leaves a paucity of information regarding MSM who do not report any HIV risk. Specifically, it is these types of gaps in knowledge that may leave clinicians with little or no information on how to proceed when an MSM seeking PrEP does not disclose any qualifying risk factors. To our

knowledge this is the first paper to explore why MSM who self-identify as low risk request PrEP.

Purpose

The primary purpose of this study was to explore the reasons why MSM who identify as low risk for acquiring HIV MSM initiate, stop or remain on PrEP. We also sought to assess the prevalence of misclassification in HIV risk perceptions and evaluate changes in condom use and STI acquisition after initiation of PrEP over a 13-month period.

Methods

Sample and Setting

This study is part of a larger nurse-led longitudinal PrEP Health Program open to gay, bisexual and transgender men in San Francisco and the Bay Area. Between November 2014 and May 2016, ~1,000 MSM were enrolled in the PrEP Health Program. Clients were included in this analysis if they were age 18 and over; gay, bisexual or transgender; HIV negative; and seeking PrEP; and identified as low risk for HIV acquisition defined as 100% condom use or only engaging in oral sex. Client informed consent was obtained and the study was approved by the clinic site and the University of California San Francisco Committee on Human Research.

Study Procedures

At the baseline visit, conducted by a nurse practitioner, a history and physical was completed, blood tests for HIV, hepatitis B and C, renal function, and syphilis were performed, and samples for pharyngeal, urethral and anal gonorrhea and chlamydia were collected. HIV risk behaviors (including substance use, number of partners, sex with HIV positive or HIV status unknown partners) were reported by clients on a brief self-report screening questionnaire. Follow up visits began one month after initiation of PrEP, in order to assess safety of the drug, and then continued quarterly thereafter. Follow up visits included biological samples for renal function, HIV, syphilis, gonorrhea and chlamydia, and a review of adherence to PrEP. Clients were also asked if their condomless sex had changed (more, less or the same), and what their reasons were for remaining on or discontinuing PrEP. HIV risk behaviors, self-reports of condom use change, and tests for biological markers of anal, pharyngeal and urethral gonorrhea and chlamydia (GC/CT), syphilis and HIV were analyzed. Each client was provided with an ID number in place of their name and medical record number and their visits history was logged in a database. The de-identified database revealed that 89 clients were self-identified as low-risk for HIV at the enrollment visit for PrEP. Of the 89 clients self-identified as low risk, three clients were ineligible to start PrEP due to medical contraindications that included osteogenesis imperfecta, abnormal renal function, uncontrolled diabetes and undiagnosed hepatitis B. Five clients declined PrEP after completion of the education and counselling provided stating they had a better understanding of sexual risk of HIV and no longer felt they needed PrEP. In total 89 provided reasons for wanting to initiate PrEP, 81 enrolled in the program and 59 remained on PrEP for 13 months.

Clients were followed over a 13-month period to assess STIs, condom use behavior change and the effect of PrEP on sexual health. HIV and STI prevention counselling was provided at each visit, based on a harm reduction model, and PrEP was provided regardless of HIV risk. Clinicians were informed of the results of the analysis after the clients had been in the study for one year in order to provide real-world charting.

We examined 81 distinct de-identified client charts for reasons for initiating and remaining on PrEP. Using a Framework Analysis to identify themes and develop a descriptive understanding of why low risk MSM initiated and remained on PrEP,[36] we examined 3-4 clinical notes per client. We analyzed risk behavior change using self-reported condom use change and testing for biological markers of GC/CT, syphilis and HIV.

Qualitative Analysis

The process of data analysis began with open coding to classify the data and capture nuances. The responses to “Reasons for Initiating or not Initiating PrEP”, “Reasons for stopping PrEP” and the follow up hand written responses to the question “What is PrEP doing for you?” were manually transcribed verbatim and then entered into a spreadsheet (Microsoft Excel, 2010), with entries listed by participant ID and time from baseline. From this spreadsheet of responses to the questions in the clinical notes themes were generated through an iterative process that involved repeated analysis of the raw data.

Quantitative Data Analysis

Self-reported condom use change, laboratory STI test results, behavioral questionnaire responses and reasons for not starting or stopping PrEP were entered into the spreadsheet. Paper charts were reviewed in order to confirm and verify the data. The de-identified results were entered into a statistical software package (Stata Statistical Software: Release 14, StataCorp, 2015) and descriptive statistics and bivariate analyses Chi–square and Fishers Exact were completed. Multilevel logistic regression analyses were completed to determine associations between condom use change and STIs risk behaviors and demographics reported by clients.

Results

The 81 clients who enrolled in the PrEP program had a mean age of 37 (range 22-71, SD 12), 83% identified as non-Hispanic (of whom 82% identified as white, 17% identified as Asian Pacific Islander, 5% identified as Middle Eastern and 3% identified as Black) and 17% identified as Hispanic. The mean number of partners (at baseline) in the past 12 months was 10 (range 0-100, SD 17.5). None of the clients reported perceived stigma related to PrEP use. Of the 81 clients who enrolled in the PrEP program 59 (66%) remained on PrEP for one year.

Reasons for PrEP Initiation

The main theme that emerged for wanting to initiate PrEP in all the clients (89/89) was the perception that they were being given an “Added protection against HIV acquisition.” Clients noted wanting “as many tools as possible to prevent HIV”, “an extra layer of protection” and “added protection in case a condom breaks”. The second theme

that emerged was a desire to have “Peace of mind” illustrated by clients voicing “peace of mind I am protected against HIV” and “PrEP provides peace of mind about HIV”. Thus, whether an illusory or actual benefit, being on PrEP provided self-identified low-risk MSM with further mental comfort and ease.

Reasons for Remaining on PrEP

At the four-month visit, the theme “Added protection against HIV acquisition” (81/81) continued, with clients stating that they now felt “100% covered against HIV” when using a combination of PrEP and condoms. The theme “Peace of mind” also persisted with many clients (59/81) noting “decreased anxiety about HIV infection during sex” and “a decreased fear of sex leading to HIV”. A third theme emerged that was related to “Sexual pleasure”, with many clients (44/81) reporting feeling “more secure and comfortable sexually” and “being able to relax and enjoy sex”.

Twenty-two clients stopped using PrEP between months four and seven and they commonly reported “not feeling the need for the extra protection against HIV”. Their reasons included that the education regarding HIV and STI transmission they received during their PrEP visits informed them adequately and they now believed they were not at risk of HIV, if, for instance, they were insertive only and always used condoms. Alternatively, they noted being on PrEP had not changed their sexual desires, for example, experimenting with receptive or condomless sex. Of the clients who reported stopping PrEP at seven months only two did so because they felt it had been the “cause” of their decreased condom use.

At month seven, the themes of “Added protection against HIV acquisition”, “Peace of mind” and “Sexual pleasure” persisted in the 59 clients who remained on PrEP. Clients described “feeling protected against HIV”, “able to relax during sex with partners” and “feeling good about sex”. No other themes emerged at this stage.

The same themes were reported by all clients at the thirteen-month visit, and a new theme emerged of “Safety and security” (50/59). Clients reported “no longer worrying about HIV after sex”, “no longer [being] fearful of HIV after sex”, “feeling more sexually secure due to an extra layer of protection against HIV” and that PrEP “makes sex safer” and allows them “to be safe and feel good about sex”.

Prevalence of Low Risk Misclassification

Although these clients presented as low risk during the baseline clinical encounter, a subsequent self-report questionnaire revealed certain risk behaviors that are known to be related to HIV acquisition. Overall, 80% of MSM who presented as low risk had reported at least one HIV-related risk behavior (i.e., high risk MSM misclassified as low risk). These behaviors included sex while intoxicated (n = 33, 38%), sex with a person of unknown HIV status (n = 25, 28%), injecting drugs (n = 1, 1%), and consuming 5 or more alcoholic drinks at one sitting (n = 36, 40%). Among other drug use, ecstasy (n = 10, 11%) and poppers (n = 14, 16%) were the most commonly used. There was an association between increase in number of partners and sex with a partner of unknown HIV status (Fisher’s exact p-value = 0.006). Being intoxicated during sex was also associated with an increase in the number of partners (Chi^2: p = 0.048). There were no statistical differences in age. Multilevel logistic regression analysis did

not reveal any associations with condom use or testing positive for STI and age, race, ethnicity, substance use, partners HIV status, partner of unknown HIV status or number of partners.

Changes in Sexual Risk Behaviors

Clients were asked by the clinician if their condom use had increased, decreased or not changed since their last visit. We found that increase in condomless sex occurred at month 1 (n = 11, 12%) and peaked at month 7 (n = 20, 22%). Condomless sex decreased at month 10 (n = 5, 6%). At month 13, 52 clients (92%) reported 100% condom use. The seven participants (8%) who reported not using condoms at month 13 all reported being in mutually monogamous relationships with a partner who was HIV positive.

Bacterial STI data laboratory results were accessed from the clinical charts and are summarized in Table 2.

Before initiating PrEP all clients were HIV and HCV negative, while 14% of clients were positive for any bacterial STI (7% pharyngeal GC/CT, 6% rectal GC/CT and 1% syphilis). At month 1, 16% of clients were positive for any bacterial STI (4% pharyngeal GC/CT, 1% rectal GC/CT and 11% syphilis). At month 4, 4% of clients were positive for any bacterial STI (2% pharyngeal GC/CT, 1% rectal GC/CT and 1% syphilis). At month 7, 19% were positive for any bacterial STI (3% pharyngeal GC/CT, 1% rectal GC/CT and 15 % syphilis). At month 13, 12% were positive for any bacterial STI (11% pharyngeal GC/CT and 1% syphilis). There were no new rectal, urethral GC/CT, HIV or HCV infections at month 13.

Discussion

In this mixed methods study, we found that MSM initiated and continued PrEP for a variety of reasons related to added protection against HIV, peace of mind, safety and security and sexual pleasure and also observed that large proportion of high-risk MSM perceive themselves to be at low-risk for HIV. Our findings highlight the important role that PrEP plays in allowing MSM who self-identify as low risk for HIV to be psychologically free from the constant fear of acquiring HIV and gain peace of mind as they move through their daily lives. Moreover, our findings demonstrate that PrEP improves sexual pleasure, decreases fear and anxiety and leads to a sense of well-being, which is an integral part of healthy sexuality.[37]

The majority of participants who self-identified as low risk for HIV acquisition during their clinical visit were actually found to be at high risk for HIV when their responses on the risk behaviors questionnaire were analyzed. Non-disclosure of these risks during the clinical visit may be due to multiple reasons, including a client's lack of understanding of risk, social desirability, discomfort in discussing risk behaviors with a health care provider, fear of being judged and a concern of how disclosing risk factors may affect their health insurance.[18,38,39] This study also affirms previous research findings that MSM do not understand what it means to be high risk due to misconceptions of risk factors for HIV and STIs.[40,41] The confusion regarding risk factors may be in part due to the varying tools for assessing risk (see Table 1), lack of clinician training and bias as to who may need to be informed of, or be at risk for, HIV/STI[42,43].

Research shows that, for MSM who have lived with the threat of HIV, the fear and anxiety surrounding sex can trigger risk behaviors such as alcohol or substance use, which in turn can lead to multiple partners and incorrect use of condoms [44-46]. This study cohort had a 40% rate of drinking five or more alcoholic drinks at one sitting, a 10% ecstasy use rate and a 16% rate of using poppers. If, as reported by this cohort, providing PrEP allows MSM to feel more in control of preventing HIV it may, in turn, decrease other risk behaviors, such as alcohol or substance abuse.[47-49] Further research is needed into the overall sense of well-being PrEP provides and the effect it has on substance use behaviors in order to advance our knowledge base regarding the role PrEP may have in decreasing alcohol and substance use.

The study findings do not support the perception among certain healthcare professionals, HIV advocacy groups and charities and MSM that PrEP leads to increased risk behaviors and more STIs. [9,50-52] After thirteen months on PrEP, every participant who was not in a mutually monogamous relationship reported 100% condom use, rectal GC/CT and syphilis had decreased, and there were no new HIV, hepatitis C or urethral GC/CT infections.

The study findings do support the need for more thorough STI screening in MSM requesting PrEP. Before initiating PrEP many of the MSM in this cohort reported they had not been previously tested for anal or pharyngeal GC/CT either because they had not reported risk factors, or they had only been offered urethral CT/GC testing. The reasons cited in the current research for urethral testing only in primary care include lack of discussion regarding sexual practices, lack of provider knowledge regarding STI screening and the belief that obtaining rectal and pharyngeal testing is costly and time

consuming.[53-56] In this cohort, although there were no urethral GC/CT infections over 13 months, at baseline there were 6% rectal and 7% pharyngeal GC/CT infections. Therefore, had only urethral testing been completed, treatment for actual GC/CT infection would not have been initiated leading to further health complications and increased onward transmission.

Albeit small, there was evidence of an increase in pharyngeal GC/CT from 7% at baseline to 11% at month 13. Even though consistent condom use for insertive or receptive anal sex was reported, condom use for oral sex was not reported and may have been the reason pharyngeal GC/CT continued to rise. This reflects the current trend of increase in pharyngeal GC/CT in MSM [57-59] and indicates the need for ongoing clinical education for clients regarding STI transmission.

While syphilis rates increased from 1% at baseline to 11% at month one, this may be explained by the lack of instrument sensitivity and specificity of the current test used (Venereal Disease Research Laboratory (VDRL)) during early syphilis stages resulting in false negatives at baseline. The spike in syphilis at month 7 (15%), is similar to what is occurring at the national level with more syphilis rates being reported among MSM[60]. Although the rise in syphilis infections at month 7 was also when clients reported the greatest decrease in condom use, and expressed less fear of contracting HIV secondary to PrEP use, syphilis can be transmitted by skin to skin contact regardless of condom use[61]. These findings indicate a need to educate MSM regarding the transmission of syphilis.

Syphilis and rectal GC/CT infections dropped to 1% at month 13. “Safety and security” and “Added protection against HIV acquisition” were the predominant themes

at this time point with many clients commenting that PrEP provided an “extra layer” of protection. This could be attributed to the repetition of STI and condom use counselling at clinic quarterly visits or alternatively the acquisition of an STI at month 7 may have led to a return to baseline condom use.

Early detection and treatment of STIs benefit MSM at a community level by preventing onward transmission leading to a significant decline in STIs over the following decade. This study suggests that quarterly STI testing including pharyngeal, anal and urethral sites with prompt treatment and education are vital components in overcoming the current STI epidemic in MSM[62] and should remain an integral part of PrEP provision.[3,34,35]

This study offers insights into PrEP use in low risk MSM attending a gay-friendly clinic in San Francisco. The clients at the clinic are demographically comparable to the overall MSM population in California, but it is acknowledged that the data may not be generalizable to other settings.

There is also potential for improvement in the baseline questionnaire and subsequent sexual risk counselling. For, example, the participants reporting 100% condom use at baseline did not state how or when condom use was initiated, as they were not asked during the visit. This is important because correct use of condoms is vital in protecting against STIs.[61,63] Furthermore, condomless sex increased from 0% at baseline to a peak of 22% at month 7 but decreased to 8% at month 13, which is consistent with other PrEP studies [2,3,34], which report first time condomless sex or decrease in condom use at ~6 months after initiating PrEP. Together these results may indicate a period when more intensive counselling condom use would be beneficial. The

reasons for not using condoms discussed in the literature include personal or partner desire to experience condomless sex, feelings of intimacy related to condomless sex, situational effects and social norms.[64-66]

The overall rate of MSM identifying as low risk was 8%, which is similar to another study in which 11% of MSM initiating PrEP did not report condomless sex.[67] In this study, prior to initiating PrEP, 60% of the cohort reported (on the questionnaire) greater than 10 partners in past six months, which would have made them high risk for HIV acquisition on the available HIV risk tools (Table 1) yet this information was not disclosed to a clinician during the PrEP intake visit. Non-disclosure of number of sexual partners during a clinical visit further emphasizes the need to provide sexual health education to all MSM.

The self-reported condom-use, which is known to be unreliable[68], may have been subject to social desirability bias in this study. For example, although the criteria for low risk were 100% condom use or oral sex only, 5% of clients reported an increased use of condoms at month 1. Furthermore, certain participants continued to self-identify as low risk for HIV despite evidence to contrary, such as when diagnosed with anal GC/CT and/or syphilis infections. This may have been secondary to social desirability bias during reporting, misunderstanding of the question or documentation errors in the chart. Generally, however, clients in this study appeared to speak frankly about sexual risk, as demonstrated by a willingness to discuss their feelings about PrEP with clinicians. This may have been influenced by repeat visits in a clinic supportive of a culture that allows organic and candid conversations to develop. Moreover, the use of biological-marker assays and frequent screening to diagnose STIs (acknowledging that not all STIs will be

captured as participants may be treated elsewhere and that not all condomless sex leads to a STI) provided an objective measure of risk before and after PrEP initiation.

Additionally, an urban sexual health clinic that serves an MSM population may imply a sampling bias towards individuals wanting to initiate PrEP. Such individuals could be considered more likely to engage in sexual risk behaviors and thus there may be more STIs diagnosed than the general MSM population. Indeed, many of the participants initially came to the clinic for HIV testing or STI treatment and were unaware of PrEP until they met with an HIV counsellor.

Conclusion

Given the discordance between perceived and actual HIV/STI risk, this study highlights the importance of clinicians providing PrEP and STI education for all MSM. It also validates previous research that low risk MSM do not accurately perceive their sexual risks. Clinicians should be prepared to discuss healthy sexuality and provide appropriate testing, treatment, and counselling including HIV/STI prevention methods in order to improve the overall health of all MSM. While PrEP can provide emotional and psychological security against acquisition of HIV, and thereby improve sexual pleasure, misconceptions regarding STI transmission and HIV risk remain. Utilizing tools to estimate risk during a clinical visit may unintentionally exclude MSM who either do not perceive themselves to be at risk for HIV or STIs or are not willing to discuss risk behavior. In order to prevent HIV/STI transmission, clinicians need to promote sexual health in all MSM through discussion and education on risk behaviors, PrEP, condom use, sexual pleasure, and HIV/STI transmission with quarterly testing to include extra

genital screening. These services need to be in place so that advances in HIV prevention are not surpassed by challenges in the control and management of bacterial STIs.

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Table 1. PrEP Tools

Menza et al., 2009 1) Race/ethnicity 2) Age 3) Diagnosis or history of an STI at baseline 4) Methamphetamine or nitrites use, prior 6 months 5) Prior year ≥ 10 male sex partners 6) Prior year receptive, non-concordant unprotected anal sex	**Smith et al., 2012** 1) Age 2) Number sex partners, prior 6 months 3) Number receptive anal sex episodes, prior 6 months 4) Number sex partners who were HIV positive 5) Number insertive anal sex episodes with an HIV+ man, prior 6 months 6) Methamphetamine use, prior 6 months 7) Nitrites use, prior 6 months
CDC, 2014 1) Any anal sex without condoms (receptive or insertive) in past 6 months 2) Any STI diagnosed or reported in past 6 months 3) Is in an ongoing sexual relationship with an HIV-positive male partner 4) Intravenous drug use	**Chen and Dowdy, 2014** 1) What percent of the time do you use condoms when having anal sex including both receptive (bottom) and insertive (top)? 2) What percent of the time are you the insertive partner (top) when having anal sex? 3) On average, how many times per month do you have anal sex? 4) Are you in a monogamous relationship with an HIV positive partner? 5) What is the HIV prevalence in your community? (uses CDC HIV prevalence estimates for the individual's current residence, but if left blank the national average of 19% is used)
World Health Organization, 2015 1) Priority for populations with an HIV incidence of about 3 per 100 person-years or higher. 2) PrEP should be an additional prevention choice in a comprehensive package of services that also includes HIV testing, counselling, male and female condoms, lubricants, ARV treatment for partners with HIV infection, voluntary medical male circumcision and harm reduction interventions for people who use drugs	**Ross et al., 2016** 1) Age 2) Number sex partners, prior 6 months 3) Number receptive anal sex episodes, prior 6 months 4) Number. sex partners who were HIV positive 5) Number. insertive anal sex episodes with an HIV+ man, prior 6 months 6) Methamphetamine use, prior 6 months 7) Nitrites use, prior 6 months
Hoenigl et al., 2016 *Over past 12 months* 1) Condomless receptive anal intercourse (CRAI) with HIV-infected partner 2) Combination CRAI plus ≥ 5 male partners 3) ≥ 10 male partners Bacterial STI	**Beymer et al., 2017** 1) Age 2) History of any STI 3) Condom use during receptive anal sex, last partner 4) Race/ethnicity, last partner 5) Age difference, last partner 6) Number sex partners, last 3 months 7) Intimate partner violence 8) Ecstasy use, prior 12 months 9) Methamphetamine use, prior 12 months 10) Nitrites use, prior 12 months

Table 2. Bacterial STI rates

	Pharyngeal GC/CT	Rectal GC/CT	Syphilis
Baseline	7%	6%	1%
Month 1	4%	1%	11%
Month 4	2%	1%	1%
Month 7	3%	1%	15%
Month 13	11%	0%	1%

Chapter 4: Condom Use and Sexually Transmitted Infections in a Longitudinal Cohort of MSM utilizing PrEP Services in a Nurse-Led Community Clinic

Abstract

Background

PrEP for HIV prevention has led to controversy over how it will affect condom use and sexually transmitted infections (STIs) in MSM. We examined the associations between PrEP, condom use change and STIs in a longitudinal cohort.

Methods

We analyzed data from 436 MSM who received PrEP services at a community based clinic over 13 months. Demographic, sexual risk and substance use behavior questionnaires were completed at baseline. At each visit, clients reported their condom use and were tested for HIV, syphilis and gonorrhea and chlamydia (GC/CT). Condom use change, STIs and sociodemographic reports were analyzed using multilevel modeling.

Results

Baseline condomless sex was high (77%), but decreased significantly at the Month 1 visit and remained below baseline over time. Condom use decreased in MSM who were white or had an HIV positive partner, and increased in older MSM and those having sex while intoxicated. Overall, anal GC/CT declined significantly from 27% to 5% and syphilis declined from 8% to 5%. Groups at higher risk of anal GC/CT and syphilis

included Hispanics and clients reporting sex with HIV positive partners or sex while intoxicated. Pharyngeal GC/CT remained consistent throughout at ~14% and those with HIV positive partners and those without health insurance had increased odds in testing positive.

Conclusion

Overall STIs and condomless sex did not increase in this cohort of MSM using PrEP. There were disparities between different groups of MSM indicating that programs need to be tailored to the individual's needs, rather than the traditional one-size-fits-all approach.

Introduction

The introduction of pre-exposure prophylaxis (PrEP) in 2012 revolutionized HIV prevention for men who have sex with men (MSM) [1-3]. However, this biomedical advance has led to controversy regarding the affect it will have on condom use and sexually transmitted infection (STI) rates [4,5]. PrEP is thought to be a cause of decreased condom use in MSM leading to a change in perceived community norms that condoms are not needed when PrEP is being used[6]. This phenomenon, known as condom migration, occurs when perceived protection from one prevention method (e.g., PrEP) eliminates, or reduces, the use of a second method (e.g., condoms) [7-9]. However, evidence of condom migration emerged before the US Food and Drug Administration approval of PrEP in 2012, with the National HIV Behavioral Surveillance System reporting an increase in condomless anal sex in MSM from 45% in 2005 to 57% in

2011[10], and currently it is estimated only 30% of MSM use condoms[11]. Condom use change was not observed in the iPrEX[12], IPERGAY[13,14], PROUD[15] or open label PrEP studies[16], yet qualitative research studies reported condom use decrease that ranged between 30 and 60% and varied by age, race, substance use, health insurance and HIV status of partners[17-19]. Adding to the controversy is the high overall prevalence of STIs among MSM in PrEP studies, ranging between 40 and 57%[13,15,16]. Additionally, STIs in MSM have been steadily rising since 2009[20], and currently in the US there is an STI epidemic disproportionally affecting MSM [21]. If initiating PrEP does cause further condom migration and the rates of STIs continue to escalate in MSM using PrEP there is the potential for the benefits of PrEP to be undermined by a worsening STI epidemic. However, the counseling on using condoms in conjunction with PrEP included in the current guidelines[22] may potentially lessen condom migration. Furthermore, recommended STI testing in the PrEP guidelines [23], including at extra-genital sites (anal and pharyngeal), may decrease STIs among PrEP users through early detection and treatment. It remains unclear whether condom migration and the disproportionate increase of STIs in MSM are influenced by PrEP, underscoring the need to assess the relationship between PrEP, condom use change and STI acquisition.

The purpose of this study was to identify the influence PrEP has on condom use and sexually transmitted infections and examine their association with sociodemographic factors over time in a community-based nurse-led PrEP program. To our knowledge this is the first study to evaluate the relationship between PrEP use, condom use and STI acquisition in a nurse-led PrEP program.

Methods

Setting and Sample

The clinical cohort comprised of 800 MSM, 18 years and older, who initiated PrEP between November, 2014 and May, 2015, and who were followed over 13 months while receiving PrEP services at a nurse-led clinic providing sexual health services to all men who identified as gay, bisexual or transgender in San Francisco. The study duration allowed for a follow-up visit for safety monitoring one month after PrEP initiation followed by four quarterly visits. All study procedures were approved by the Institutional Review Board of the University of California San Francisco (IRB Study #: 16-9026)

Clients were included in this research if they were male, self-identified having sex with a man, and met the CDC's criteria for PrEP initiation, which included reporting an HIV-positive partner, more than one sexual partner whose HIV status is negative or unknown, reporting anal sex without a condom, and a diagnosis of anal gonorrhea and/or chlamydia (GC/CT) and/or syphilis in the past 6 months[23]. Exclusion criteria for PrEP were based on CDC guidelines[22] and included renal disease, liver disease (including chronic hepatitis B and hepatitis C), osteoporosis, uncontrolled diabetes, pregnancy, acute viral syndrome, high risk HIV exposure less than 72 hours prior to enrollment, abnormal screening test results not explain by a comorbid condition, and any medical conditions contraindicated with PrEP use.

Measures

At baseline, all clients completed self-administered, standardized questionnaires to assess demographic information, sexual risk, and substance use behaviors. The questionnaires were initially completed using pen and paper, and as the clinical services developed, computer-based surveys were introduced. Baseline laboratory measures included HIV antibody and viral load, hepatitis B antigen and hepatitis C antibody, STI screening and a complete metabolic panel. Nurse practitioners performed history and physical examinations and reviewed tests result. At the baseline visit, all clients verbally asked if they used condoms always, sometimes or never and received verbal and written education material regarding how PrEP works, the importance of adherence to PrEP, and the protection that consistent and correct condom use provides against the acquisition of STIs. Follow-up visits were scheduled one month after initiating PrEP then quarterly thereafter to monitor for adverse events. At all follow-up visits, STI screening (anal, pharyngeal, and urethral GC/CT, HIV and syphilis) and PrEP safety assessments (complete metabolic panel) were completed, medication adherence was reviewed and strategies discussed to improve adherence. In addition, clients were asked by a nurse if their condom use had decreased, increased or not changed since the last visit.

Treatment of STIs

Clients who acquired STIs during the study period were documented and treated at the clinical site, based on CDC treatment guidelines[24]. Subsequent GC/CT infections in the same anatomical site were considered new independent events. New syphilis infections were defined as the first reactive serological response of an rapid plasma regain (RPR) or venereal disease research laboratory (VDRL) following at least one

non-reactive result, or any change in titer response that was at least four-fold greater than the previous screening.

Statistical Analysis

Statistical analysis was performed using Stata/SE 14[25]. Means and standard deviations for continuous variables, and frequencies and percentages for categorical variables, were calculated for all the study variables (see Table 1). Based on a review of the literature, covariates known to influence condom use or STI rates are age[26], number of partners[27], HIV positive partner[26], unknown HIV status of partners[12], alcohol binging[28,29], sex while intoxicated[30], race[10,31,32], ethnicity[33] and health insurance status[34]. These same variables were used and tested to determine whether they were similarly associated in the current data.

Multilevel ordinal logistic regression analyses were used to test the odds of moving one point up on a scale from never use to sometimes/always use condoms at each assessment after baseline. First, unconditional models were examined to estimate the best-fitting change trajectory; followed by examination of linear and quadratic change trajectories for condom use. Additionally, a piecewise model was examined to test the change from intake (before starting PrEP) to the first assessment following PrEP initiation at month 1, and then from month 1 to the last assessment at month 13.

At baseline, rectal GC/CT and/or syphilis were recorded as these infections are given as reasons to initiate PrEP in MSM per CDC recommendations[22]. From month 1 onwards, pharyngeal and urethral GC/CT testing was added. Urethral GC/CT was subsequently eliminated from the analysis as the rate was less than 2%. For any rectal

GC/CT and/or syphilis (STI2), and for pharyngeal GC/CT, multilevel logistic regression analysis was used to estimate changes over time. First, as with condom use, unconditional models were constructed to estimate the best-fitting change trajectories for STI2 and pharyngeal GC/CT. Linear and quadratic change trajectories for testing positive for STI2 or pharyngeal GC/CT were examined. Finally, for STI2 a piecewise model was examined to test the change from the intake visit to the first assessment following PrEP initiation and over time.

We determined the use of multi-level modelling because it allows for a flexible yet comprehensive approach to the analysis of longitudinal data and helps to account for associations among observations within clusters to make valid inferences. These models enabled separation of multiple aspects of change in order to provide trajectories of change in condom use and STIs.

After identifying the best fitting growth trajectories for condom use, STI2 and pharyngeal GC/CT, conditional models were fit to examine the association between status at intake with each of the covariates (age, number of partners, HIV positive partners, unknown status of partners, alcohol binging, sex while intoxicated, race, ethnicity and health insurance status) and change over time. For all analyses, a two-sided p-value of < 0.05 was considered statistically significant.

Multilevel ordinal logistic regression was employed to examine change over time in condom use, and multilevel logistic regression was employed to examine change over time in testing positive for STI2 or pharyngeal GC/CT, using unconditional models (i.e., no predictors except time). Following the analysis for the unconditional model for each of the outcomes, conditional models were estimated to test the association of

covariates with each outcome. The two conditional models examined were for condom use and STI2. First, the association of each covariate with initial condom use status reported and a positive STI2 test at the intake visit was estimated. Second, the association of each covariate with the change trajectories was examined by testing cross-level interactions (time by covariate). The same two conditional models were examined for pharyngeal GC/CT, however baseline was at the month 1 visit because pharyngeal testing was not recorded at the intake visit before PrEP initiation.

There was a meaningful difference between the reports from baseline (before PrEP initiation) to the first visit after PrEP initiation (Piece 1), compared to subsequent responses over time (Piece 2). Therefore, the change in condom use and testing positive for ST12 from the PrEP intake visit to the first follow up visit after initiating PrEP is different than the change that occurred from the first follow up visit after PrEP initiation to the end of data collection. The trajectory from baseline to the first follow up visit represents the effect of the intervention (PrEP initiation, condom use counselling), while the trajectory from the first follow up visit to the final visit represents a "maintenance" period. In the multilevel models, time was treated as a piecewise effect with the two pieces of the trajectory representing these two effects. The trajectories for the two pieces of time were tested as separate effects in the same model.

Results

A total of 436 clients in the PrEP program met the criteria for analysis. Reasons for exclusion included missing data from baseline questionnaires, baseline condom use change reports or STI data; moving out of the area; transferring care; and stopping

PrEP and then reenrolling at a later date. The clinic changed from paper charts to electronic records during the study period and because of this some clients had duplicate records and therefore those clients were excluded. A number of clients were excluded because they did not meet the CDC-defined risk behavior for initiating PrEP. The number of transgender clients was low and as such were not included in the analysis.

As shown in Table 1, the majority of clients were white (70%), non-Hispanic (89%) and insured (59%); 80% were under 45 (range 21-72, mean 36, SD 10); mean number of sexual partners was 16 (range 1-150); 32% reported sex with a partner of unknown HIV status; and 6% reported sex with a HIV positive partner. Reports by clients included a variety of substance use (49%), alcohol binging (44%) (> 5 drinks at one sitting), and sex while intoxicated (32%). Adherence to PrEP, defined as not missing more than 3 doses in the prior 7 days, was 68% at month 1, increased to 84% at month 4, 86% at month 7, and decreased to 72% at month 10 and to 70% at month 13.

Condom Use

Condom use change over time in this cohort (see Table 1), is illustrated in Figure 1. Moving one point up the ordinal scale represents an increase in frequency of condom use and moving one point down the ordinal scale represents a decrease in frequency of condom use. In the unconditional model, the odds of moving one point up the ordinal scale was 2.4 times greater at the first follow up visit (Piece 1), compared to the visit before PrEP initiation, and then decreased by 8% for each additional month over time

(Piece 2). As illustrated in Figures 1 and 2, had we only looked at the curvilinear trajectories we would not have observed that the greatest change was during the period between initiating PrEP and the first follow up visit.

The results for all the covariates in the piecewise models for condom use are displayed in Table 2. There was no association between age and condom use before PrEP initiation, nor was age associated with change in condom use from baseline to the first follow-up assessment, although there was a weak but significant increase in the odds of moving one point higher on the condom use scale over Piece 2 for each additional year of age. Before PrEP initiation, for each additional sexual partner reported, the odds of moving one point up the condom use scale was reduced 2.5%, however, there was no association between the number of sexual partners reported and change in condom use over the Piece 1 or Piece 2 trajectories. Among clients who reported HIV positive sexual partners, the odds were 64.55 times greater that the client would be one point higher on the condom use scale before PrEP initiation, compared to those who did not report HIV positive partners. Further, clients with HIV positive partners reported a 47.6% lower odds of moving one point higher on the condom use scale from baseline to first follow-up, and 16.2% lower odds of moving one point higher on the scale for each additional month of the maintenance period. Clients who had sexual partners of unknown HIV status before they initiated PrEP had a 69% lower odds of being one point higher on the condom use scale than those who did not have sexual partners of unknown HIV status, yet, unknown HIV status of partners was not associated with change in condom use over Piece 1 or Piece 2. Before PrEP initiation, clients who reported alcohol binging had a 54% lower odds of being point higher on the

condom use scale than those who did not binge, but there was no association between alcohol binging and change in condom use over Piece 1 or Piece 2. Those who reported sex while intoxicated had a 77% lower odds of being one point higher on the condom use scale before PrEP initiation than those who did not report sex while intoxicated. There was no association between having sex while intoxicated and change in condom use from baseline to the first follow-up. However, the odds of moving one point higher on the condom use scale were 1.1 times greater for those who reported sex while intoxicated for each month across the maintenance period. Race (white vs. non-white) was not associated with reports of condom use at baseline or with change in condom use over Piece 1. However, non-whites had 8% lower odds of moving one point higher on the condom use scale during the maintenance period, compared to whites. Ethnicity and health insurance status were not associated with condom use at baseline or with change in condom use over time.

Sexually Transmitted Infections

Anal GC/CT and/or Syphilis (STI2)

Changes in STI2 rates were observed in this study (see Table 3), and are illustrated in Figure 3. In the unconditional model, the odds of testing positive for anal GC/CT and/or syphilis were 78% lower at the first follow up visit compared to the visit before PrEP initiation, but there was no effect over time.

The results for all the covariates in the piecewise model for STI2 are displayed in Table 4. There was no association between STI2 and reporting sex with HIV positive partners before PrEP initiation, however, in the conditional model, from baseline to the

first follow up assessment, the odds of testing positive for ST12 were 8.9 times greater compared to those who did not report sex with HIV positive partners. There was no association between STI2 and reporting sex with HIV positive partners over time. In the unconditional model, ST12 and reporting sex while intoxicated were not associated. In the conditional model, those clients who reported sex while intoxicated at baseline had lower odds of ST12, but at the first follow up assessment they had 2.7 increased odds of testing positive for ST12 compared to those who did not report sex while intoxicated. There was no association between reporting sex while intoxicated and ST12 over time. In the unconditional model, clients' ethnicity was not associated with STI2. In the conditional model, those who were non-Hispanic had a 53% lower odds of testing positive for ST12, however there was no association between ethnicity and ST12 over the Piece 1 or Piece 2 trajectories. Age, number of partners, unknown HIV status of partners, alcohol bingeing, race and health insurance status were not associated with STI2 at baseline or over time.

Pharyngeal GC/CT data was collected from months 1 to 13, and remained consistent throughout at ~14%. In the conditional models, for each additional sexual partner there was a small but significant increased odds of a positive pharyngeal GC/CT result (OR 1.007, CI 1, 00-1, 01, p=0.05). Among clients who reported HIV positive partners there was a 1.96 increased odds of testing positive for pharyngeal GC/CT compared to those who did not report HIV positive partners (CI 1.13-3.36, p=0.015). There was a 31% decreased odds in testing positive for pharyngeal GC/CT if a client had health insurance compared to those who did not have health insurance (CI 0.516-0.93, p=014).

Discussion

In this study of MSM who self-identified as high risk for HIV acquisition and initiated PrEP, we observed significant changes in condom use and STI rates during follow-up. Baseline condomless sex was high (77%) but by using a piecewise model we were able to identify a significant increase in condom use after the initial PrEP visit that remained below baseline levels over time. We also identified specific risk groups that had significantly greater reductions in condom use and may benefit from more intense counselling. For example, condom migration was higher in MSM of color, and younger MSM were less likely to increase their condom use compared to older MSM over time. This is consistent with current research that shows in MSM using PrEP, condom use decision-making is affected by perceived risk, fluctuating risk behaviors[19,35] and a desire for intimacy[19,36,37]. There are also policy implications given that young MSM and MSM of color report that public health messaging does not target them [1,38] and there is a paucity of condom-use education programs targeting MSM who binge drink.

There were no new HIV infections over the study period despite a fluctuating PrEP adherence rate between 68% and 86%. Furthermore, anal GC/CT declined significantly from 27% to 5% and syphilis declined from 8% to 5%, which differs from recent studies where these infections either remained constant or increased [2,3,12,13,15]. The piecewise model identified groups at higher risk of anal GC/CT and syphilis, which included clients reporting sex with HIV positive partners, Hispanic clients and clients who reported sex while intoxicated. The rates in Hispanic MSM mirrored national trends[24], which supports the criticism that current public health messaging around HIV

and STIs is not relevant to this population[26,27,39-41]. Clients reporting sex with HIV positive partners may have in the past prevented STIs through condom use, therefore increasing STI testing in HIV positive MSM and offering partner STI testing services before initiating PrEP may help reduce STI rates.

Pharyngeal GC/CT infections remained constant at ~14% over time, which is higher than rates previously reported in MSM attending sexual health clinics[42,43] and were higher in clients without health insurance despite no change their condom use. Previous research[44] has found that insured MSM are more likely to be tested for pharyngeal GC/CT than uninsured, however, unlike most providers, the clinical site in the present study provides free services to all MSM regardless of insurance, which may help to explain these observations.

Limitations

This study included MSM who met high-risk criteria for HIV attending a sexual health clinic with a harm reduction philosophy, for gay, bisexual and transgender MSM in a predominately white, gay area in San Francisco. The number of MSM of color in this study was low and yet health disparities were still detected in this group. In order to more effectively provide services to MSM of color, a second clinic, in a multi-ethnic area has been opened. Younger MSM (18-21 years old) were not represented in this study because they typically access services at a nearby MSM adolescent clinic, and thus the study findings may not be transferable this age group. It is recognized that this analysis did not evaluate PrEP adherence and the effect on STI rates or condom use. A further limitation is the lack of data regarding urethral GC/CT secondary to the clinic's policy of

collecting urethral specimens only if the client was symptomatic or requested testing. Finally, social desirability is a consideration whenever questionnaires are used to assess behavior. In the present study, risk behavior reporting via questionnaire was generally high, however, certain high risk behaviors may have been under reported. For instance, there were no reports during the entire study of needle use or opiate use.

Conclusion

This study indicates that condom migration among PrEP users may be more complex than simply replacing one method of protection against HIV (condoms) with another (PrEP). The disparities between different high risk groups of MSM revealed by this study highlights the need to design PrEP programs that include STI testing and condom use education tailored to the individual's needs, rather than the traditional one-size-fits-all approach.

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Table 1. Demographics and baseline risk behaviors San Francisco PrEP Program Cohort (N = 436)

Characteristics	Mean (min, max, SD)
Age in years	36 (21, 72, 10)
Number of sex partners in last 6 months	16 (1, 150, 18)
Characteristics	**N (%)***
Gender	
Male	436 (100)
Ethnicity	
Hispanic	92 (21)
Non-Hispanic	343 (78)
Race	
White	303 (69)
Asian Pacific Islander	46 (10)
Middle Eastern	10 (2.5)
Black	9 (3)
Native American	4 (1)
Multiple	29 (7)
Other	35 (8)
Number of partners^	
0-2	37 (8)
3-5	68 (16)
6-10	139 (32)
11-20	106 (24)
21-30	46 (11)
31-150	40 (9)
Insurance status^	
Any	177 (41)
None	259 (59)
Sex with person of unknown HIV status^	
Yes	134 (32)
No	287 (68)
HIV positive partner^	
Yes	25 (6)
No	411(94)
Sex while intoxicated	
Yes	136 (31)
No	299 (69)
Alcohol binge (> 5 drinks at one sitting)	
Yes	193 (44)
No	243 (56)
Substance Use^	
Ecstasy	113 (26)
Cocaine	84 (19)
GHB	73 (17)
Poppers	70(16)
Speed	43(10)
Crack	7 (2)
Opiates	0 (0)

*Percentages may not add up to 100% due to rounding

^Assessed at Baseline

Table 2. Condom Use Unconditional Piecewise Model

	OR	z	SE	95% CI	p-value
Piece 1	2.40	4.72	0.446	1.67-3.45	**0.000**
Piece 2	0.92	-5.36	0.014	0.89-0.95	**0.000**

Table 3. Condom Use Conditional Piecewise Models

Covariate		OR	z	SE	95% CI	p-value
Age						
Model 1	(Baseline)	1.040	2.56	0.016	1.00-1.07	0.011
Model 2	(Piece 1)	0.989	-0.60	0.185	0.95-1.10	0.546
	(Piece 2)	1.007	5.02	0.001	1.00-1.01	**0.000**
Number of partners						
Model 1	(Baseline)	0.975	-2.81	0.008	0.95-0.99	**0.005**
Model 2	(Piece 1)	1.011	0.82	0.137	0.98-1.03	0.415
	(Piece 2)	1.000	0.48	0.009	0.98-1.00	0.634
HIV+ partners						
Model 1	(Baseline)	64.55	6.11	44.04	16.94-245	**0.000**
Model 2	(Piece 1)	0.524	-3.71	0.042	0.11-0.25	**0.000**
	(Piece 2)	0.838	-3.15	0.047	0.01-0.23	**0.002**
Unknown HIV status						
Model 1	(Baseline)	0.313	-3.35	0.108	0.16-0.62	**0.001**
Model 2	(Piece 1)	1.095	0.21	0.470	0.47-2.54	0.832
	(Piece 2)	1.051	1.53	0.345	0.98-1.12	0.127
Alcohol bingeing						
Model 1	(Baseline)	0.462	-2.45	0.146	0.25-0.86	**0.014**
Model 2	(Piece 1)	1.163	0.40	0.443	0.55-2.45	0.689
	(Piece 2)	1.024	0.79	0.031	0.96-1.08	0.428
Sex while intoxicated						
Model 1	(Baseline)	0.226	-4.35	0.077	0.11-0.44	**0.000**
Model 2	(Piece 1)	1.450	0.41	0.654	0.59-3.51	0.410
	(Piece 2)	1.096	0.01	0.368	1.03-1.17	**0.006**
Race						
Model 1	(Baseline)	1.895	1.70	0.713	0.91-3.96	0.089
Model 2	(Piece 1)	1.437	0.39	0.599	0.63-3.25	0.385
	(Piece 2)	0.923	0.02	0.313	0.86-0.98	**0.018**
Ethnicity						
Model 1	(Baseline)	0.732	0.42	0.281	0.35-1.55	0.417
Model 2	(Piece 1)	0.722	-0.70	0.337	0.29-1.80	0.486
	(Piece 2)	0.982	-0.50	0.360	0.91-1.05	0.618
Health Insurance						
Model 1	(Baseline)	1.097	0.29	0.349	0.58-2.05	0.771
Model 2	(Piece 1)	0.606	-1.31	0.232	0.29 -1.28	0.191
	(Piece 2)	0.969	-1.04	0.029	0.91-1.03	0.299

Two separate models are shown for each covariate. The association of the covariate with condom use at baseline is shown first, separated by a line from model two which tests of the cross-level interaction of the covariate with the two pieces for time. Piece 1 trajectory = effect from baseline to the first visit after initiating PrEP, and Piece 2 trajectory = effect from the first visit after initiating PrEP through to the final assessment at 13 months.

Table 4. STI2 (Anal GC/CT and/or Syphilis) Unconditional Piecewise Piece Model

	OR	z	SE	95% CI	p-value
Piece 1	0.223	-8.62	0.038	0.16-0.31	**0.000**
Piece 2	1.003	0.17	0.018	0.97-1.04	0.866

Table 5. STI2 Conditional Piecewise Piece Models

Covariate		OR	z	SE	95% CI	p-value
Age						
Model 1	(Baseline)	0.994	-0.96	0.007	0.98-1.00	0.339
Model 2	(Piece 1)	1.006	0.36	0.017	0.97-1.04	0.719
	(Piece 2)	1.000	0.28	0.002	0.97-1.00	0.780
Number of partners						
Model 1	(Baseline)	1.001	0.40	0.003	0.99-1.01	0.692
Model 2	(Piece 1)	1.009	1.07	0.009	0.99-1.03	0.284
	(Piece 2)	0.999	-0.84	0.001	0.99-1.00	0.401
HIV+ partners						
Model 1	(Baseline)	0.862	-0.49	0.260	0.48-1.55	0.622
Model 2	(Piece 1)	8.879	2.42	8.011	1.51-52.06	**0.016**
	(Piece 2)	0.968	-0.46	0.068	0.84-1.11	0.642
Unknown HIV status						
Model 1	(Baseline)	0.927	-0.51	0.137	0.69-1.24	0.610
Model 2	(Piece 1)	1.792	1.51	0.693	0.83-3.82	0.131
	(Piece 2)	1.054	1.36	0.041	0.98-1.13	0.172
Alcohol bingeing						
Model 1	(Baseline)	0.914	-0.66	0.124	0.70-1.19	0.510
Model 2	(Piece 1)	1.667	0.14	0.579	0.84-3.29	0.140
	(Piece 2)	0.984	0.66	0.357	0.92-1.06	0.659
Sex while intoxicated						
Model 2	(Baseline)	0.295	-4.31	0.836	0.17-0.51	**0.000**
Model 2	(Piece 1)	2.685	2.44	1.086	1.21-5.93	**0.015**
	(Piece 2)	1.086	1.52	0.041	0.98-1.14	0.127
Race						
Model 1	(Baseline)	1.115	0.49	0.179	0.81-1.53	0.496
Model 2	(Piece 1)	0.719	-0.75	0.314	0.31-1.69	0.451
	(Piece 2)	1.076	1.67	0.472	0.98-1.17	0.094
Ethnicity						
Model 2	(Baseline)	0.475	-2.88	0.123	0.29-0.79	**0.004**
Model 2	(Piece 1)	1.448	0.92	0.581	0.66-3.18	0.356
	(Piece 2)	1.061	1.33	0.471	0.97-1.16	0.183
Health Insurance						
Model 1	(Baseline)	1.069	0.49	0.147	0.82-1.40	0.624
Model 2	(Piece 1)	0.968	-0.09	0.338	0.49-1.92	0.926
	(Piece 2)	1.036	0.95	0.039	0.96-1.11	0.344

Two separate models are shown for each covariate except for “sex while intoxicated” and “ethnicity”, only the second model is shown, because the test of the covariates at baseline are significant in the second model when the cross-level interactions are tested, but the associations of the two variables with STI2 at baseline in the first model are not significant.

Figure 1

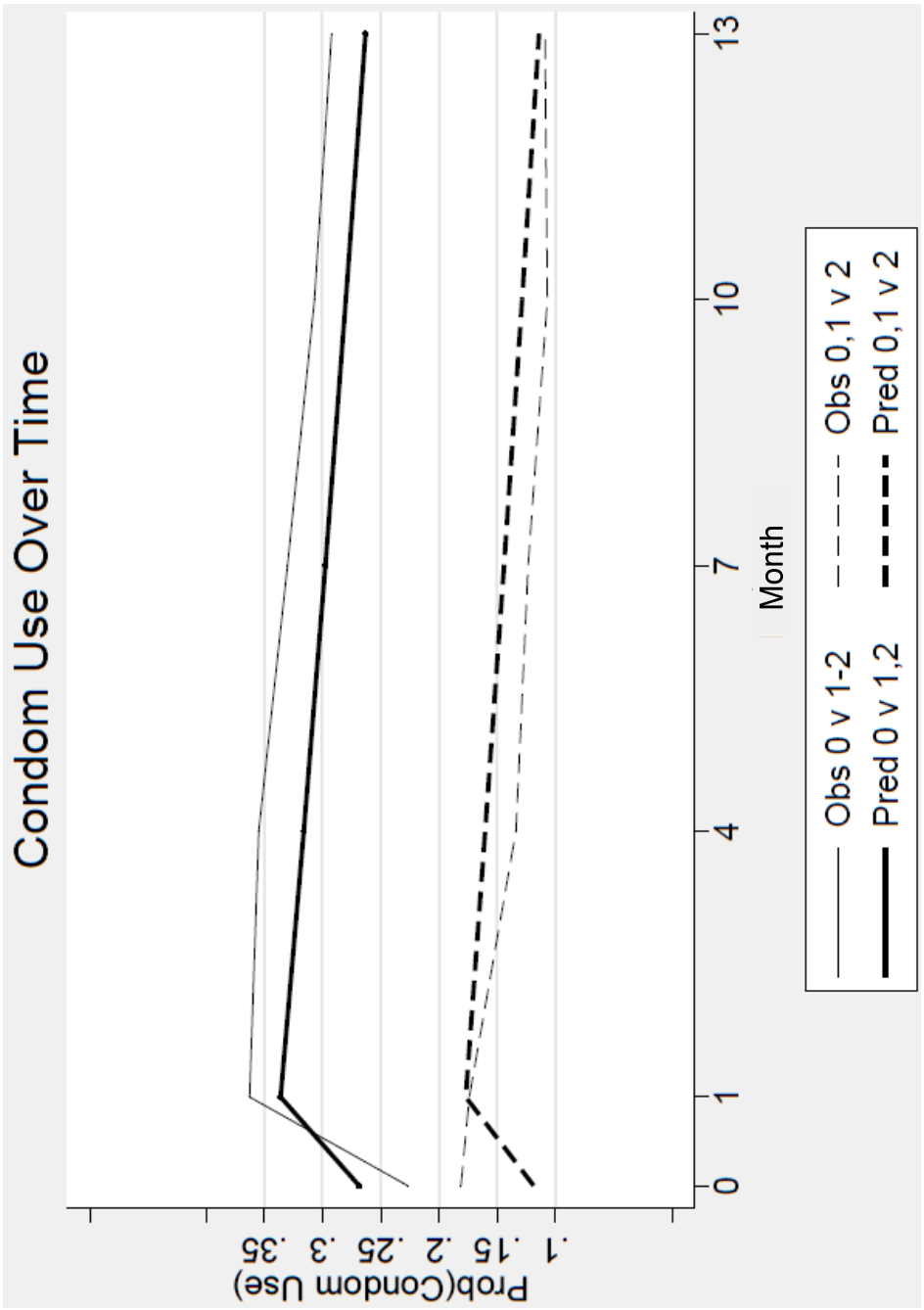

Figure 1 illustrates the unconditional piecewise model of the occurrence of condom use change over time. The first curve illustrates the proportion of clients who moved one point from never to sometimes or always use condoms. The second curve represents the clients who moved one point from never or sometimes to always use condoms. These predicted probabilities can be compared with the observed responses at each time point to determine how well the estimated trajectories match the observed responses.

Figure 2

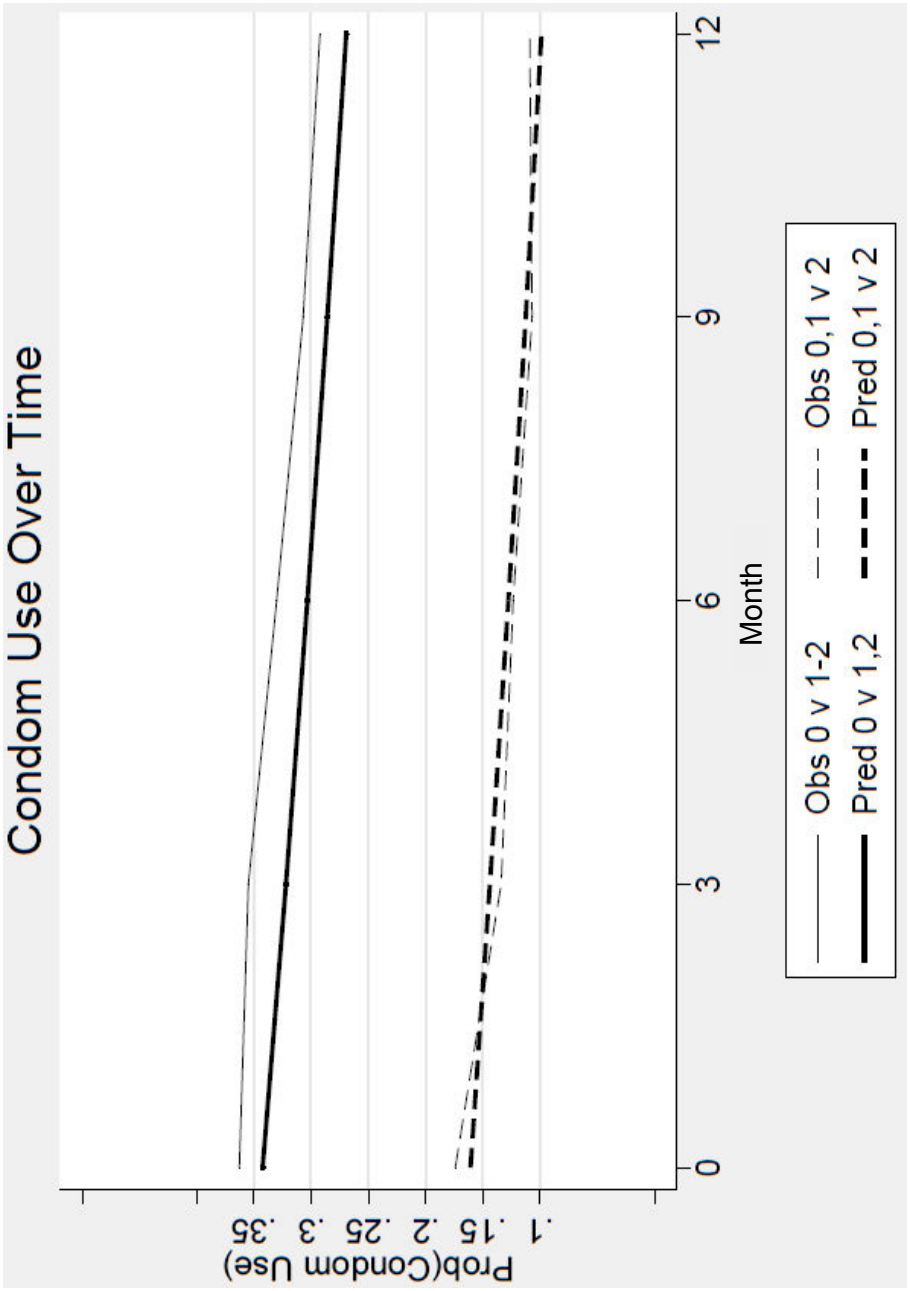

Figure 2 illustrates the unconditional curvilinear trajectory of the occurrence of condom use change over time. The first curve illustrates the proportion of clients who moved one point from never to sometimes or always use condoms. The second curve represents the clients who moved one point from never or sometimes to always use condoms. These predicted probabilities can be compared with the observed responses at each time point to determine how well the estimated trajectories match the observed responses.

Figure 3

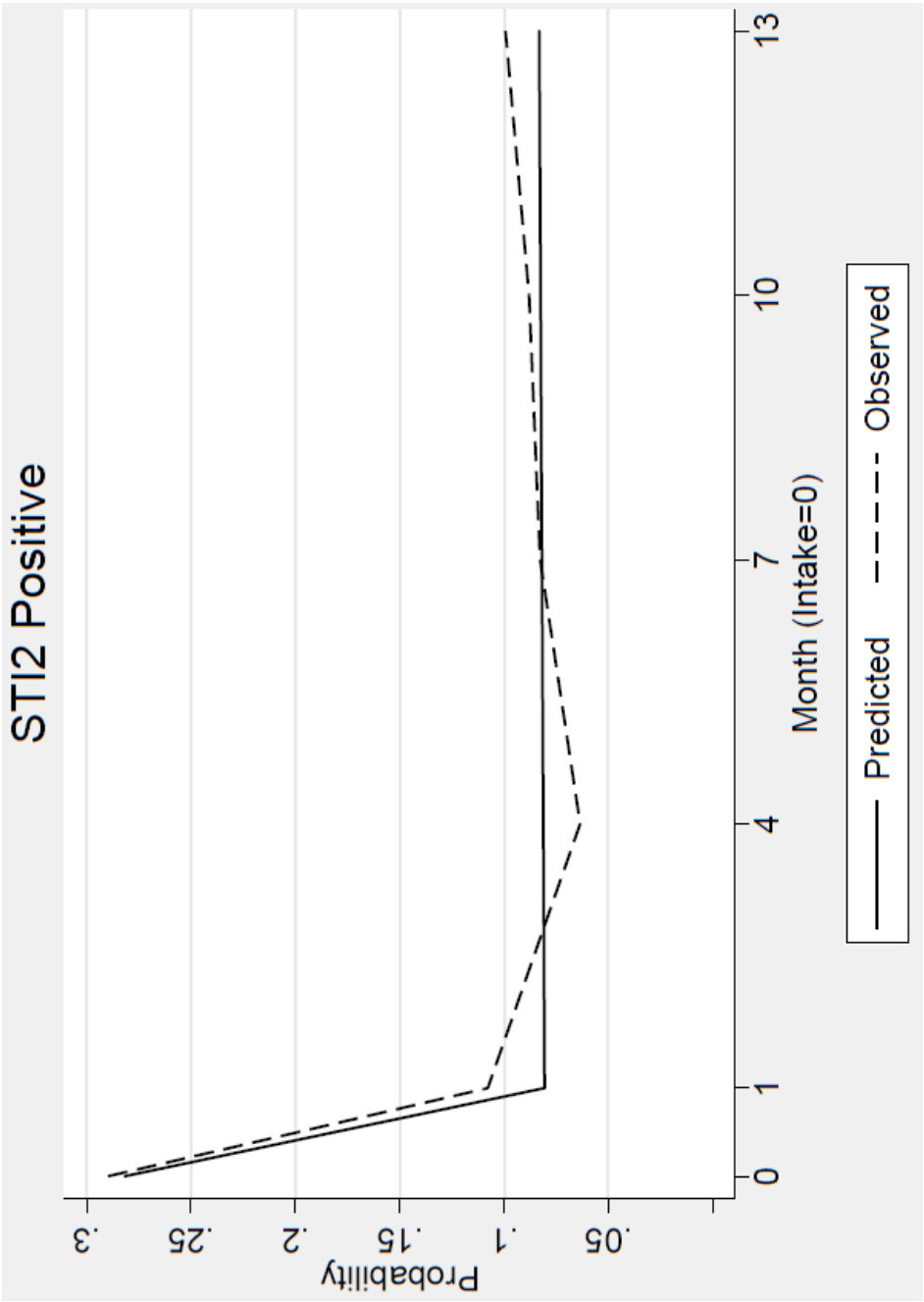

Figure 3 illustrates the piecewise observed and predicted probability over time for having a positive test for anal GC/CT and/or syphilis. These predicted probabilities were compared with the observed responses at each time point to determine how well the estimated trajectories matched the observed responses.

Chapter 5: Conclusions, Implications for Clinical Practice and Implications for Future Research

Summary of the Research Papers

The purpose of the review presented in Chapter 2 was to provide a foundation for the dissertation research through a systematic analysis of the current literature regarding PrEP use in MSM and its effect on condom use and STIs. Although STI rates were high in the populations studied, there was no conclusive evidence that PrEP use led to an increase in STIs. The effect of PrEP on condom use change in the quantitative studies was inconclusive however the qualitative studies reported a hypothetical decrease in condom use. Overall condom use in MSM utilizing PrEP was found to be complex and influenced by perceived risk, social norms, desire for intimacy and lack of STI transmission knowledge. Moreover, sexual risk was defined inconsistently across the studies, making it difficult to draw inferences from the data on the effects of PrEP on risk behaviors. Finally, research gaps regarding MSM who identify as low risk requesting PrEP and risk behaviors among PrEP users in real-world clinical settings were identified, providing a basis for the clinical research analysis in Chapters 3 and 4.

The mixed method study presented in Chapter 3 addressed the current gap in knowledge regarding the reasons why MSM who identify as low risk for HIV request PrEP. Overall, MSM in this study perceived a certain level of emotional and psychological security against acquisition of HIV and a decrease in fear and anxiety. The majority of participants who self-identified as low risk for HIV acquisition during their clinical visit were actually found to be at high risk for HIV when their responses on the

risk behaviors questionnaire were analyzed. This indicates that utilizing the currently available tools (see Chapter 3 table 1) to estimate risk during a clinical visit may unintentionally exclude MSM who either do not perceive themselves to be at risk for HIV or STIs or are not willing to discuss risk behavior. Before initiating PrEP many of the MSM in this cohort reported they had not been previously tested for anal or pharyngeal GC/CT either as they had not reported risk factors, or they had only been offered urethral CT/GC testing. Although there were no urethral GC/CT infections in this cohort over 13 months, at baseline there were 6% rectal and 7% pharyngeal GC/CT infections. Yet if only urethral testing been completed, treatment for actual GC/CT infection would not have been initiated leading to further health complications and increased onward transmission. Albeit small, there was evidence of an increase in pharyngeal GC/CT from 7% at baseline to 11% at month 13 indicating the need for ongoing clinical education for clients regarding STI transmission. Finally, a decrease in condom use and an increase in syphilis rates occurred at month 7 after PrEP initiation, which is similar to findings in the literature reviewed in Chapter 2, indicating intensified counselling may be needed at this point to reduce overall STI rates in MSM.

This study highlights critical issues that merit consideration by clinicians and researchers alike, particularly how to phrase questions regarding HIV/STI risk. Clients visiting the clinical site were not asked about their perception of risk, and instead the PrEP program included a low risk category to allow all MSM to access PrEP services. Furthermore the increase in STIs and decrease in condom use at month 7 indicates a need for understanding how risk perception changes over time. The question that should be asked in order to understand the perspective of MSM who are seen in clinical

settings is: Do you perceive yourself as low or risk for HIV? This question would provide an opportunity not only for discussing STI/HIV transmission but also for educating individuals who are unaware that their behaviors are putting them at risk of STIs and HIV. Furthermore, asking this question at each visit would help identify when an individual may erroneously believe they are not at risk of HIV/STIs and when more intensive counselling and education regarding HIV/STI transmission is necessary.

The purpose of the study presented in Chapter 4 was to examine how initiation and continued use of PrEP influenced subsequent patterns of condom use and STIs in a group of MSM self-identified as high risk for HIV acquisition who had access to free PrEP services at a nurse-led sexual health clinic over a 13 month period. This study revealed baseline condomless sex was high (77%) and a piecewise model identified a significant increase in condom use after the initial PrEP visit. Condomless sex did not return to baseline levels over the course of the study, indicating that routine condom use discussion did help to prevent further decrease in condom use. The piecewise model also identified risk groups that may benefit from more intense condom use counselling, for example, increase in condomless sex was higher in MSM of color, younger clients, and clients who reported alcohol binging. Furthermore, implementing routine STI testing at every visit decreased anal GC/CT significantly from 27% to 5% and syphilis from 8% to 5% over 13 months. The piecewise model further revealed that clients reporting sex with HIV positive partners, Hispanic clients and clients who reported sex while intoxicated were more at risk of these STIs. Pharyngeal GC/CT infections remained constant at ~14% over time and were higher in clients without health insurance.

The disparities in condom use and STI acquisition between groups of high risk MSM identified by this study provide valuable information for clinicians and researchers to consider when designing and implementing STI/HIV prevention programs. In particular, this study highlights the importance of such factors as geographical location and community buy-in, and the need to address alcohol and substance use as part of a sexual health discussion in order to improve condom use while intoxicated. Just as in the case of the low risk group, this study of high risk MSM demonstrated that condom use change in connection with PrEP is more complex than simply replacing one method of protection against HIV (condoms) with another (PrEP). Similar to the low risk group was the persistent pharyngeal GC/CT infections indicating that further research into how MSM perceive pharyngeal infections, their transmission, prevention, treatment options and how to provide appropriate education is urgently needed to thwart a potential public health crisis.

In summary, the findings from the study in Chapter 4 illustrate the same concern in the literature, that PrEP would lead to increases in condomless sex over time was not established in either low or high risk MSM cohorts in a real world setting. Overall, decrease in condom use was minimal and condomless sex did not increase over time, indicating that PrEP is not influencing the current STI public health crisis. Furthermore, the findings demonstrate that regular testing and treatment for STIs provided by a PrEP program does reduce anal GC/CT and syphilis, but reducing pharyngeal infections remains a challenge. This body of work also highlights that those currently at greatest risk of STI and HIV infection, MSM of color and younger MSM, are not accessing PrEP services. Moreover, if PrEP is providing a level of emotional and psychological security

against acquisition of HIV, it is vital that PrEP programs include education regarding STI transmission in order to prevent an erroneous belief there is not a risk of other STIs. Sexual health services, including condom use discussion, STI education, genital and extra-genital testing and treatment need to be provided with PrEP programs so that advances in HIV prevention are not surpassed by challenges in the control and management of bacterial STIs.

Implications for Clinical Practice

PrEP is an effective tool to prevent HIV infection. This study demonstrates routine visits to target STI testing and condom use discussion reduces syphilis and anal GC/CT rates over time and prevents an increase in condomless sex. The persistent rate of pharyngeal GC/CT indicates a need to integrate routine pharyngeal screening, treatment and transmission education into practice in order to prevent onward transmission of GC/CT. As PrEP access expands, the importance of routinely screening for STIs and messaging around STI risk reduction strategies including condom use in conjunction with PrEP must not be forgotten. The information from this dissertation provides a body of knowledge to assist healthcare providers in implementing not only PrEP services but also sexual health services generally for all MSM.

Implications for Future Research

Research is needed on MSM from underrepresented communities utilizing PrEP for HIV prevention, such as adolescent MSM, MSM of color, and MSM who use or inject drugs, to establish whether PrEP is related to condom use change, STI risk perception,

and changes in STI rates in these populations. Repeating the studies in these populations would provide much needed information for clinicians to tailor their services in order to meet the differing needs of the communities they serve. In light of the high rates of pharyngeal GC/CT infections in MSM regardless of their risk perception, further research into understanding pharyngeal GC/CT transmission and whether it differs within different MSM populations would provide valuable information in order to educate MSM on risk reduction strategies and in turn decrease the community prevalence of STIs. A larger study, including genital and extra-genital STI screening, of MSM who believe they are low risk for HIV/STI acquisition would identify deficits in risk awareness and provide information for STI/HIV prevention messaging. Moreover, it would help identify those who are unaware of their HIV risks and may benefit from PrEP.

While there may be a perception that PrEP leads to more STIs, many of the participants in both the low and high risk cohorts had never been tested for STIs before initiating PrEP. The high baseline STI rates in both cohorts were similar to those among MSM in the rest of the US, regardless of PrEP status, as reported by the CDC [1]. Moreover, anal GC/CT and syphilis decreased in both the low and high risk cohorts in Chapter 3 and 4 suggesting PrEP programs that include quarterly STI testing, as a form of prevention, may actually help reduce community prevalence of STIs.

The nurse-run clinic that helped to support the dissertation research is an example of how the nursing profession provides preventative services to improve the health of marginalized individuals and communities. Nursing and nursing research have been at the forefront of disease prevention, health promotion and the protection of

human rights[2]. Even before the introduction of medications to treat diseases such as tuberculosis and HIV, nurses alleviated suffering and advocated for the health of individuals and communities[3] in order to improve health. In the era of PrEP for HIV prevention, nurse researchers are pivotal to investigating new ways to improve STI prevention messaging and behavioral strategies that can be tailored to MSM from differing communities and backgrounds to reduce the current escalating trends in STI rates. This collaboration of research and practice will enable the nursing profession to continue to be at the forefront of providing and advocating for sexual health care, in turn improving health for all MSM.

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