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Optimizing the Delivery of HIV Pre-Exposure Prophylaxis (PrEP): An Evaluation of Risk Compensation, Disengagement, and the PrEP Cascade

by

J. Carlo Hojilla, RN, MSN

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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Nursing

in the

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of the

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[redacted]

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J. Carlo Hojilla

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Optimizing the Delivery of HIV Pre-Exposure Prophylaxis (PrEP): An Evaluation of Risk Compensation, Disengagement, and the PrEP Cascade

J. Carlo Hojilla, RN, MSN

Introduction

To inform the optimal implementation of HIV pre-exposure prophylaxis (PrEP), we conducted three studies that evaluated serodisclosure, identified correlates of PrEP disengagement, and characterized the PrEP cascade of care.

Methods

Study 1 examined the association of PrEP use with participant non-disclosure and lack of knowledge of partner HIV status in the iPrEx Open Label Extension (OLE). Study 2 examined the effects of stimulant use and binge drinking (i.e., ≥5 drinks on one occasion) on PrEP disengagement in a nested case-cohort in OLE. PrEP disengagement was defined as failure to show for a follow-up visit or tenofovir drug levels <700fmol/punch. Study 3 characterized the PrEP cascade (i.e., seeking services, initiating PrEP, and retention in care) and identified predictors of non-retention among those who started PrEP in a clinic-based cohort of men who have sex with men in San Francisco.

Results

We analyzed data from 1,184 participants in Study 1. PrEP use was not significantly associated with non-disclosure or lack of knowledge of partner status in adjusted analyses (*p*-values≥.16). However, relationship characteristics were significantly associated with both outcomes. Of the 330 MSM and transgender women included in Study 2, 16% used stimulants and 22% reported binge drinking in the previous three months. Stimulant users had more than 5-fold greater odds of PrEP disengagement (adjusted odds ratio [aOR]=5.24, 95% CI [1.64-16.76]). Binge drinking

was not significantly associated with PrEP disengagement after adjusting for stimulant use and baseline confounders (aOR=0.78 [0.33-1.88]). Of the 344 men who sought PrEP services in Study 3, 268 (78%) initiated PrEP. Cost was the most commonly cited reason for not starting. Among patients who initiated PrEP, cumulative incidence of non-retention at 13 months was 38%. Men with an STI diagnosis at enrollment had a 79% greater rate of non-retention (adjusted hazard ratio [aHR]=1.79 [1.06-3.01]).

Conclusion

We found no evidence to suggest that PrEP use is associated with non-disclosure or not knowing partner status. Comprehensive prevention approaches that enhance uptake, reduce stimulant use, and support PrEP adherence and persistence are needed to address the heightened risk of HIV infection of those who use stimulants and those with STI diagnoses.

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Chapter 1: Introduction

HIV pre-exposure prophylaxis (PrEP) is a biomedical prevention strategy, in which individuals who are HIV-negative but at high risk for infection are started on an antiretroviral regimen prior to exposure. Daily oral PrEP using tenofovir disoproxil fumarate (TDF) or the co-formulated drug, emtricitabine-TDF (FTC-TDF), was shown to reduce the risk of HIV infection in various populations, including men who have sex men (MSM), heterosexual men and women, and injection drug users (Baeten et al., 2012; Choopanya et al., 2013; Grant et al., 2010; Thigpen et al., 2012). In the US, MSM are disproportionately affected by HIV, accounting for 63% of all incident cases in 2014 (Centers for Disease Control and Prevention, 2016). In the seminal iPrEx study, Grant et al. (Grant et al., 2010) demonstrated that daily PrEP use is associated with up to 96% protective efficacy (Anderson et al., 2012). Subsequent studies in MSM corroborated these findings after demonstrating an 86% relative reduction in risk (McCormack et al., 2015; Molina et al., 2015). However, the relative novelty of PrEP has raised concerns on how it might displace existing risk reduction behaviors and how it can be effectively implemented in high-priority populations.

This dissertation establishes the groundwork for a program of research that centers on the optimal implementation of biomedical HIV prevention strategies, like PrEP. It focuses on two overarching objectives that address clinically relevant questions. The first is to evaluate HIV serodisclosure in the context of PrEP. Serodisclosure is a process that involves informing sex partners of one's HIV status (Obermeyer, Baijal, & Pegurri, 2011) to help raise awareness of HIV risk, encourage individuals to seek out regular testing, destigmatize HIV through open communication, and facilitate informed sexual decision making and sexual negotiation (Horvath, Nygaard, & Simon Rosser, 2010; Obermeyer et al., 2011; Smith, Rossetto, & Peterson, 2008). It is also a critical prerequisite to risk reduction strategies like seropositioning and serosorting. There is uncertainty on how PrEP might contribute to risk compensation where individuals

abandon well-established risk reduction efforts, like serodisclosure, because of a decrease in perceived risk.

The second objective of this dissertation is to characterize the “PrEP cascade” and identify determinants of PrEP disengagement. The cascade is a framework that can be used to identify gaps in the care continuum. It includes seeking services, initiating PrEP, retention in care, and adherence (Kelley et al., 2015; Liu et al., 2012; Nunn et al., 2017). The optimal public health benefit of PrEP is posed as being contingent on effective engagement at each step of the PrEP cascade (Liu et al., 2012). Although we know from existing literature that interest and uptake of PrEP is high among MSM (Chan et al., 2016; Grant et al., 2014; Liu et al., 2016; Volk et al., 2015), there is a scarcity of data that describe the PrEP cascade in real world clinical settings. Further, existing studies are unable to clearly elucidate reasons for PrEP disengagement. A significant proportion of individuals either discontinue or fail to adhere to the regimen shortly after initiation even in the absence of side effects and continued risk for HIV(Grant et al., 2014). Among all individuals who elected to start PrEP in iPrEx OLE, 53% had disengaged from the regimen by the first month of follow-up (Glidden et al., 2015), and by the third month, over 60% had disengaged (Grant et al., 2014). PrEP disengagement refers to individuals failing to to show for a follow-up visit or having tenofovir drug levels consistent with sub-optimal dosing (i.e., <4 doses per week). Uncovering factors associated with disengagement is critical because almost every instance of acute HIV seroconversion in the context of PrEP occurred during periods of inadequate PrEP use or when the regimen was prematurely discontinued (Grant et al., 2014; Liu et al., 2016; Molina et al., 2015).

In the HIV treatment literature, stimulant and heavy alcohol use are well-established correlates of treatment non-adherence and non-retention among HIV-positive persons (Carrico et al., 2011; Hinkin et al., 2007). However, it is unclear to what extent these factors are associated with disengagement in the context of PrEP where individuals are HIV-seronegative

but are at high-risk for acquiring the disease. Accounting for the possible contribution of stimulant and alcohol use are especially important because of the high prevalence of these behaviors among MSM (Cochran, Ackerman, Mays, & Ross, 2004; Stall et al., 2001) and their well-documented association with risky sexual behavior (Koblin et al., 2006; Ostrow et al., 2009; Santos et al., 2013).

Specific Aims

Aim 1: Identify baseline factors associated with participant non-disclosure and lack of knowledge of partner status. The first study is a cross-sectional analysis that identifies the association between baseline characteristics and HIV serodisclosure in a cohort of MSM and transgender women enrolled in the iPrEx Open Label Extension (OLE)(Grant et al., 2014). Surveys conducted among MSM have suggested that PrEP could lead to a reduction in HIV risk perception (Brooks et al., 2012; Golub, Kowalczyk, Weinberger, & Parsons, 2010; Grov, Whitfield, Rendina, Ventuneac, & Parsons, 2015) that, in turn, might cause PrEP users to view discussions on HIV status with sex partners as unnecessary (Gorbach et al., 2004; Rönn, White, Hughes, & Ward, 2014). However, there are limited data that explore HIV status communication among HIV-negative MSM and transgender women taking PrEP. We hypothesize that participants taking PrEP are less likely to disclose and ask partners about their HIV status compared to those that are not taking PrEP.

Aim 2: **Identify risk factors of PrEP disengagement among MSM in an open label cohort**. The second study is a longitudinal analysis that identifies the association of biomarker-confirmed stimulant use and self-reported heavy alcohol use with PrEP disengagement in a subcohort of MSM in iPrEx OLE. Disengagement is operationally defined as failure to show for a scheduled follow-up visit or the sub-optimal adherence to the drug (i.e., tenofovir concentration in dried blood spots [DBS] <700 fmol/punch). Literature suggests that a significant proportion of

MSM either discontinue or fail to adhere to PrEP shortly after initiation despite the absence of side effects and continued high-risk for HIV. In the HIV treatment literature, stimulant and problematic alcohol use are well-established correlates of treatment non-adherence and non-retention in care for HIV-positive persons but it is unclear to what extent these factors are associated with disengagement in the context of PrEP. We hypothesize that PrEP disengagement will be higher among persons with positive biomarkers of stimulant use and those that report heavy alcohol use than those without such markers and reports.

Aim 3: Identify prognostic indicators for discontinuation in care among MSM enrolled in a clinic-based cohort. The final aim builds upon the research described above by using longitudinal data to characterize the PrEP cascade (i.e., seeking services, initiating PrEP, and retention in care) and identify predictors of non-retention in care among patients who start PrEP.

To address this aim, data were abstracted from the medical records of 348 patients seen between November 2014 and August 2015 at a nurse-led sexual health clinic in the Castro district of San Francisco. All individuals screened for PrEP services during this time period were included in the analysis. Patients were eligible for PrEP if they were at least 18 years of age, HIV-negative, identified as a man who has sex with men or as a transgender male, lived in the San Francisco Bay Area, and had no medical contraindications to PrEP (e.g., renal disease, liver disease). Eligible patients had follow-up visits scheduled one month after PrEP was prescribed and quarterly thereafter. This study followed patients for up to 13 months. We hypothesize that self-reported stimulant use and heaving drinking will be significantly associated with non-retention in care.

Theoretical Framework

Outcomes expectancy theory (Oei & Baldwin, 1994) and myopia theory (Steele & Josephs, 1990) provide broad theoretical frameworks from which the aims of the dissertation are addressed. Outcomes expectancy theory posits that individuals engage in specific behaviors based on the expectation that these acts would achieve a desired outcome, like sexual pleasure, relaxation, or an escape from the cognitive load imposed by social norms around safer sex (Jones, Corbin, & Fromme, 2001). The first aim delves into the beliefs of participants regarding PrEP and how these perceptions influence serodisclosure. Although the data are limited in its ability to thoroughly examine PrEP-related expectancies, it allows us to glean important insights to inform future studies that can directly estimate the effects of PrEP-related expectancies on behavior. Aims two and three identify potential predictors of PrEP disengagement and evaluate the effects heavy drinking and stimulant use. Myopia theory provides a theoretical understanding of how these behaviors affect decision-making by shifting cognitive processing from long terms goals (e.g., staying HIV-negative) to more immediate rewards (e.g., sexual pleasure).

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Chapter 2

HIV serodisclosure among men who have sex with men and transgender women on HIV pre-exposure prophylaxis

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ABSTRACT

HIV pre-exposure prophylaxis (PrEP) might lead individuals to view serodisclosure as unnecessary. We examined the prevalence of non-disclosure and lack of knowledge of partner status in a global cohort of men who have sex with men (MSM) and transgender women (TW) enrolled in the iPrEx Open Label Extension (OLE). We calculated prevalence ratios by fitting a logistic model and estimating predicted probabilities using marginal standardization. Prevalence of non-disclosure and lack of knowledge of partner status were highest in Thailand (73% and 74%, respectively) and lowest in the USA (23% and 37%, respectively). In adjusted analyses, PrEP use was not significantly associated with non-disclosure or lack of knowledge of partner status. Apprehensions about patients changing serodisclosure behaviors should not preclude the provision of PrEP. We also found that relationship characteristics were significantly associated with both outcomes. Risk reduction counseling provided in conjunction with PrEP should address dyadic factors to help patients develop feasible strategies to reduce HIV risk.

INTRODUCTION

HIV pre-exposure prophylaxis (PrEP) using oral emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) has been shown to reduce the risk of HIV transmission in sexually active adults, including men who have sex with men (MSM) and transgender women (TW) (1-4). In September 2015, the World Health Organization (WHO) released guidelines supporting expanded access to PrEP services for those at substantial risk for HIV (5). However, PrEP's relative novelty has raised concerns about the impact it might have on existing risk reduction strategies, like serodisclosure and seroadaptive behaviors.

HIV serodisclosure is a process that involves informing others of one's HIV status (6). Considering that HIV transmission largely occurs in the context of a serodiscordant partnership where one person is HIV-viremic and the other is not, there has been substantial public health effort to encourage communication of HIV status between partners (7-10). Serodisclosure can help raise awareness of HIV risk, encourage individuals to seek out regular testing, destigmatize HIV through open communication, and facilitate informed sexual decision making and sexual negotiation (6,11,12). Accurate HIV serodisclosure is also a critical prerequisite to the effectiveness of various seroadaptive behaviors, such as serosorting or seropositioning, that are widely used among MSM and TW (13-15).

Surveys conducted among MSM have suggested that PrEP could lead to a reduction in HIV risk perception (16-18) that, in turn, might cause PrEP users to view discussions on HIV status with sex partners as unnecessary (19,20). PrEP should be viewed as a complement to other risk reduction strategies (21), so it is important to understand how its use might impact crucial behaviors like serodisclosure and asking partners about their status. To our knowledge, there have been no previous studies that have explored HIV status communication among HIV-negative MSM and TW taking PrEP. To address this gap, we sought to identify in an open label PrEP cohort what factors are associated with non-disclosure and lack of knowledge of partner status. We tested the null hypothesis that PrEP use had no effect on serodisclosure.

METHODS

Participants and Procedures

The current study is a secondary analysis of data from the iPrEx open label extension (iPrEx OLE), described in detail elsewhere (2). Briefly, participants were enrolled from three previous randomized clinical trials conducted at 11 sites across Brazil, the Andes (Ecuador and Peru), South Africa, Thailand, and the United States (USA). Participants were male sex at birth, reported having anal sex with men, were at least 18 years of age, and must have participated in a previous PrEP clinical trial. The study enrolled participants between June 2011 and June 2012, and followed participants for up to 72 weeks. All participants provided informed consent and the iPrEx OLE study protocol was approved by institutional review boards at each site and by relevant regulatory agencies in each country.

At enrollment, all eligible HIV-negative participants were offered daily oral FTC-TDF PrEP. Participants who opted to not take PrEP remained in the study and had the opportunity to start the regimen at any visit during the first 48 weeks of follow-up. Visits were scheduled at 4, 8, and 12 weeks after enrollment, and every 12 weeks thereafter. Since data for this analysis was gathered in the broader context of a PrEP open label study, we limited our inquiry to a cross-sectional examination of demographic and relationship characteristics obtained at baseline and serodisclosure data collected at the 12-week visit. These timepoints provided the most complete information. This also allowed us to objectively determine which participants were using PrEP based on plasma tenofovir levels that were measured within the first 12 weeks. Adherence during this timepoint was found to be highly predictive of subsequent adherence (22).

Measures

Relationship characteristics

Participants were asked to report detailed information on up to three sex partners in the last three months using computer-assisted self-interview (CASI). For each sex partner, participants were queried on what best describes the type of relationship they have with that individual (i.e., sexual and emotional, sexual only, transactional) and how long the participant knew the partner before having sex (i.e., minutes or hours, days or weeks, months or years).

Non-disclosure and lack of knowledge of partner status

For each partner, participants were asked whether or not they serodisclosed (i.e., "Does partner A know that you are HIV-negative"). Responses were coded as non-disclosure if participants responded "No" or "Don't know." Participants were also asked if the partner had ever tested positive for HIV. A response of "Don't know" indicated a lack of knowledge of partner status. Less than 5% of data on disclosure (n=94) and knowledge of partner status (n=112) were missing at the 12-week follow-up visit .

PrEP Use and beliefs on effectiveness of PrEP

Blood samples were tested for plasma tenofovir levels within 12 weeks of starting PrEP to quantify drug adherence. Of those who reported at least one sex partner in the last three months, 54% (644/1,184) had detectable drug and were coded as being "On PrEP – Detectable." Participants who elected to start PrEP but had plasma drug levels below level of quantification (244/1,184) were coded as "On PrEP – Undetectable." Those that never started the regimen (281/1,184) were coded as being "Off PrEP." Less than 2% (15/1,184) of those who elected to start PrEP and had reported at least one recent sex partner did not have their drug levels quantified. Participants were also asked to rate on a 10-point scale how well they believed PrEP works at preventing HIV. A score of one indicated that they believed PrEP was not effective at all, five meant it was effective half the time, and 10 indicated that they believed PrEP is effective all of the time.

Statistical Analyses

The two outcomes of interest were participant non-disclosure and lack of knowledge of partner HIV status reported at the 12-week follow-up. Using a directed acyclic graph (23,24), we hypothesized *a priori* the relationships between demographic factors (age, education, gender), study region, baseline relationship characteristics (relationship status, relationship type, time partner known before sex), PrEP use (off PrEP, on PrEP – undetectable drug, on PrEP – detectable drug), and our two outcomes of interest (non-disclosure and lack of knowledge of partner status). These covariates were evaluated individually in bivariate analyses and as a predictor set using logistic regression, accounting for the repeated observations within participants. Following estimation of the logistic model, we calculated prevalence ratios by estimating predicted probabilities using marginal standardization (25). Confidence intervals were estimated using the delta method (26,27). Interaction terms between PrEP use, relationship type, and time before first sex with partner were statistically uninformative (data not shown). Statistical significance was set at $p<0.05$ and analyses performed using Stata 14 (28).

RESULTS

Study Population

The iPrEx OLE cohort included 1,603 HIV-negative individuals; 286 (18%) reported no sex partners in the last three months at their 12-week follow-up and 133 (8%) declined to answer. The final analysis was limited to the 1,184 who reported having at least one recent sex partner. Median age at baseline was 30 years, most were MSM (90%), single, divorced, or widowed (53%), and had completed secondary education or less (53%).

At their 12-week follow-up, participants provided information on a total of 2,382 partners, most of whom were described as casual partners based primarily on a sexual relationship (55%). A small number were reported as clients or transactional sex partners (5%).

Approximately 26% of partners were known to participants only within minutes or hours before their first sexual encounter. Participant demographics and relationship characteristics are summarized in Table 1.

Participant non-disclosure

Table 2 depicts prevalence estimates of non-disclosure. Overall, participants reported not disclosing their HIV status to 39% of sex partners in the last three months. Non-disclosure varied considerably by study region. Notably, prevalence was highest in Thailand (73%) and lowest in the USA (23%). Regional differences remained statistically significant even after adjusting for demographic characteristics, relationship factors, and PrEP use.

In adjusted analyses, the prevalence of non-disclosure was not significantly different among participants on PrEP (aPR 1.10; 95% CI 0.85 – 1.35) and those with undetectable drug levels (aPR 1.03; 95% CI 0.76 – 1.29), compared to those off PrEP. We observed a higher prevalence of non-disclosure to casual (aPR 1.54; 95% CI 1.24 – 1.84) and transactional sex partners (aPR 2.03; 95% CI 1.44 – 2.62), compared to those whom participants felt an emotional and sexual connection. Similarly, participants were significantly more likely to not disclose their HIV status to partners whom they have known for only minutes or hours (aPR 1.62; 95% CI 1.33 – 1.92), compared to those whom participants have known for months or years before their first sexual encounter.

To further explore the relationship between PrEP use and non-disclosure, we restricted our analysis to only those who elected to start PrEP. We examined if those who did not disclose viewed PrEP to be more effective at preventing HIV than those that did. Median scores (*Mdn*= 7) were not significantly different (p=0.07) and suggest both groups equally viewed PrEP to be moderately effective.

Lack of knowledge of partner status

Participants reported not knowing the HIV status of approximately 57% of sex partners in the last three months. Regional differences were also substantial, with the highest prevalence in Thailand (74%), followed by Brazil (64%), and the Andes (63%). In the adjusted model, lack of knowedge of partner status was not significantly different among those on PrEP (aPR 1.08; 95% CI 0.91-1.24) and those with undetectable drug levels (aPR 1.14; 95% CI 0.95-1.34), compared to participants off PrEP (Table 3). Relationship characteristics were statistically significant predictors of not knowing partner status, as participants were more likely to not know the HIV status of casual partners (aPR 1.50; 95% CI 1.30-1.71) and transactional sex partners (aPR 1.62; 95% CI 1.30-1.95) compared to individuals whom participants had an emotional and sexual relationship. Participants were also more likely to not know the HIV status of partners whom they have known for only minutes or hours (aPR 1.27; 95% CI 1.11-1.42) and days or weeks (aPR 1.13; 95% CI 0.99 – 1.27) compared to those they have known for longer before first having sex. When we limited our analysis to only those that opted to start PrEP to evaluate any differences in perceived PrEP effectiveness, median scores were the same among those that reported knowing their partner status and those that did not (*Mdn*=7; *p*=0.2).

DISCUSSION

Our findings offer three important insights that may be particularly salient in the context of ongoing discussions about how PrEP can be effectively integrated into existing prevention frameworks and how it might impact longstanding efforts, like serodisclosure (29). Although not statistically significant, we found a possible trend suggesting a modestly higher prevalence of non-disclosure and lack of knowledge of partner status among PrEP users. However, when we examined participants' beliefs about the effectiveness of PrEP, we found that those that did not disclose and those that did not ask their partners about their HIV status viewed PrEP to be just as effective as those that did. This suggests that inflated perceptions of PrEP as a panacea are not driving these behaviors. We know from earlier studies (4,30,31) that PrEP adherence is

greater among those with higher risk for HIV so it is possible that persons opting to take PrEP are already less inclined to disclose or ask partners about their status. Most studies thus far have not observed substantial changes in behavior among PrEP users (30-34) but how this will play out in the future is unclear. As PrEP becomes more integrated and available in the broader community we need to track whether or not individuals will become more, less, or equally inclined to disclose and talk about HIV in the context of PrEP. Others have noted how PrEP has already started to change our understanding of traditional notions of "risk" and "safe" sex, so we may be in the midst of a shift where being either HIV-positive or negative may no longer be as relevant (35). Regardless, it is important to remember that PrEP is only one tool in a growing list of evidence-based risk reduction strategies, and apprehensions about patients changing behavior should not preclude the provision of PrEP.

Second, we observed substantive differences in the prevalence of non-disclosure and lack of knowledge of partner status across study regions. Prevalence for both were particularly high in Thailand, the Andes, and Brazil. These findings are consistent with previously reported data (36-38) and stress the need for greater work in identifying challenges and effective strategies to encourage mutual serodisclosure. Differences may reflect a complex array and interaction between structural barriers, such as the availability of testing services, and sociocultural factors, like attitudes towards disclosing or asking about sensitive topics particularly in the context of a sexual encounter, homophobia, and HIV stigma (36,39-42). A prerequisite of accurate disclosure is knowing one's status through testing but various reports have noted the low prevalence of HIV testing in these regions (43-46). Although participants received regular HIV testing as part of their participation in the study, the need to disclose or ask partners about their status may be irrelevant if there is a high likelihood that partners have not been tested anyway. This may partly explain why we observed a higher overall prevalence of lack of knowledge of partner status compared to non-disclosure. Additionally, the availability of internet and phone application-based social networks for finding sexual partners may also have

contributed to the variability across regions. Studies suggest that online social networks provide individuals a medium to disclose and negotiate sexual practices with relative ease and anonymity (47-49).

Lastly, the significant associations between relationship characteristics and discussions about HIV status underscore the importance of how dyadic factors influence HIV prevention efforts. The prevalence of non-disclosure and lack of knowledge of partner status were highest among casual (i.e., sexual only) and transactional sex partners, and among partners whom participants have known only briefly before their first sexual encounter (e.g., minutes or hours). These findings are consistent with studies among HIV-positive persons that suggest discussions about HIV status are largely influenced by the context of the individual's relationship with the partner (19,50,51). In one study, men reported that not knowing each other very well was a primary reason for not disclosing (52). Risk reduction counseling provided in conjunction with PrEP should take these dyadic factors into account to help patients develop feasible strategies to reduce their risk. There is emerging evidence that feelings of safety afforded by PrEP frequently fosters greater focus on relationships (53), which would lead to greater numbers entering close relations, which appear to provide a context for disclosure discussions.

These findings should be interpreted with the understanding of some limitations. The use of self-reported disclosure and knowledge of partner status may be prone to recall and social desirability bias. We attempted to limit this by using CASI, which may allow for more candid responses. Additionally, study sites were trained on strategies to foster a sex-positive, nonjudgmental environment to ensure participants felt they could provide honest responses to behavioral questions. There were also missing data related to our predictors and outcomes of interest. We conducted sensitivity analyses assuming various scenarios for participants that had missing data on PrEP use, disclosure, and knowledge of partner status. Differences in point estimates across all models were minor and not qualitatively meaningful (data not shown). Lastly, we were limited in our ability to measure relevant social and cultural constructs, like

stigma and homophobia, as well as event level variables, like drug and alcohol use. Future studies will need to incorporate these factors to more clearly understand the individual and societal level correlates of disclosure in this population.

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Table 1. Baseline demographic and relationship characteristics of HIV-negative participants who reported at least one sex partner at the 3-month follow-up visit (N = 1,184)

	Median	(range)
Demographics		
Age, in years	30	(19-70)
	n	(%)
Study Region		
Andes [a]	706	(60)
Brazil	153	(13)
South Africa	36	(3)
Thailand	44	(4)
USA	245	(21)
Gender		
MSM	1063	(90)
Transgender	121	(10)
Education		
Completed secondary or less	619	(52)
Post secondary	555	(47)
Relationship Status		
Single/Divorced/Widowed	586	(50)
In a primary relationship	512	(43)
Relationship Characteristics (n = 2,382 partners)		
Relationship type		
Sexual relationship only	1314	(55)
Sexual and emotional	612	(26)
Client/transactional sex	112	(5)
Time partner known before first sex		
Months or years	874	(37)
Days or weeks	632	(27)
Minutes or hours	616	(26)

[a] Andes includes sites in Ecuador and Peru

Table 2. Prevalence of non-disclosure by HIV-negative participants at 3-month follow-up visit

	Prevalence	Adjusted PR	(95% CI)	p-value
Study region				
USA	23%	Reference		
South Africa	30%	1.77	(0.84 – 2.71)	0.10
Brazil	38%	1.71	(1.11 – 2.32)	0.02
Andes	45%	1.95	(1.38 – 2.51)	0.001
Thailand	73%	3.19	(2.15 – 4.23)	<0.001
Relationship type				
Sexual and emotional	24%	Reference		
Casual/sexual only	42%	1.54	(1.24 – 1.84)	<0.001
Transactional	59%	2.03	(1.44 – 2.62)	<0.001
Time partner known before sex				
Months or years	32%	Reference		
Days or weeks	35%	1.12	(0.92 – 1.33)	0.24
Minutes or hours	46%	1.62	(1.33 – 1.92)	<0.001
PrEP use				
Off PrEP	42%	Reference		
On PrEP – undetectable drug	38%	1.03	(0.76 – 1.29)	0.83
On PrEP – detectable drug	40%	1.10	(0.85 – 1.35)	0.43

Adjusted for baseline age, education, gender, and relationship status
PR: prevalence ratio
CI: confidence interval
PrEP: pre-exposure prophylaxis

Table 3. Prevalence of lack of knowledge of partner status by participants at 3-month follow-up visit

	Prevalence	Adjusted PR	(95% CI)	p-value
Study region				
USA	37%	Reference		
South Africa	48%	1.13	(0.50 – 1.76)	0.69
Brazil	64%	1.80	(1.41 – 2.19)	<0.001
Andes	63%	1.76	(1.39 – 2.12)	<0.001
Thailand	74%	2.01	(1.46 – 2.56)	<0.001
Relationship type				
Sexual and emotional	37%	Reference		
Casual/sexual only	63%	1.50	(1.30 – 1.71)	<0.001
Transactional	70%	1.62	(1.30 – 1.95)	<0.001
Time partner known before sex				
Months or years	50%	Reference		
Days or weeks	55%	1.13	(0.99 – 1.27)	0.06
Minutes or hours	59%	1.27	(1.11 – 1.42)	<0.001
PrEP use				
Off PrEP	59%	Reference		
On PrEP – undetectable drug	61%	1.14	(0.95 – 1.34)	0.16
On PrEP – detectable drug	55%	1.08	(0.91 – 1.24)	0.34

Adjusted for baseline age, education, transgender identity, and relationship status
PR: prevalence ratio
CI: confidence interval
PrEP: pre-exposure prophylaxis

Chapter 3

Stimulant use is associated with PrEP disengagement in men who have sex with men and transgender women

Keywords: pre-exposure prophylaxis, PrEP, HIV prevention, men who have sex with men, transgender women, iPrEx OLE

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ABSTRACT

This study evaluated the association of stimulant use and binge drinking with PrEP disengagement among men who have sex with men (MSM) and transgender women. We analyzed data from a case-cohort in the iPrEx Open Label Extension. Stimulant use and binge drinking (i.e, ≥5 drinks in one occasion) in the last three months were assessed at enrollment. PrEP adherence was measured using tenofovir drug levels in dried blood spots. PrEP disengagement was defined as failure to show for a follow-up visit or tenofovir drug levels <700 fmol/punch, corresponding to adherence <4/week. We modeled baseline predictors of PrEP disengagement at the 4-week follow-up visit. Data from 330 participants were analyzed. Baseline prevalence of stimulant use and binge drinking was 16% (52/330) and 22% (72/330), respectively. Overall, 53% (174/330) of participants disengaged by the 4-week follow-up. Approximately 62% (32/52) of stimulant users and 61% (44/72) of binge drinkers disengaged by the first month. In the adjusted model, stimulant users were over five times more likely to disengage than non-users (aOR 5.24; 95% confidence interval [CI] 1.64-16.76). Binge drinking was not significantly associated with PrEP disengagement after adjusting for stimulant use and baseline confounders (aOR 0.78; 95% CI 0.33-1.88). We found strong evidence to suggest that stimulant use is associated with PrEP disengagement. This underscores the need for comprehensive prevention strategies that include an assessment of potential barriers and interventions to enhance optimal PrEP engagement.

INTRODUCTION

The prevalence of stimulant and alcohol use is higher among men who have sex with men (MSM) and transgender women compared to all other US populations.[1-4] Methamphetamine, in particular, is the second leading substance of abuse globally.[5] MSM and transgender women who use stimulants and those with problematic patterns of alcohol use represent a significantly higher risk group because of these substances' association with HIV risk behavior.[6-10] HIV pre-exposure prophylaxis (PrEP) using oral emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) is a potentially ideal prevention strategy for this high priority population because of its demonstrated efficacy for reducing HIV infection.[11-15]

However, the optimal benefits of PrEP require engagement in care and sustained use throughout periods of risk, and there is uncertainty if stimulant and problematic alcohol use place individuals at greater risk for PrEP disengagement. Liu and colleagues[16] proposed the PrEP prevention cascade as a framework to understand individual and structural factors that potentially impact the public health implications of PrEP. To be effective, PrEP requires engagement at every step of the cascade, which includes seeking services, initiating FTC-TDF, continuing care during periods of risk through regular follow-up and medication refills, and adequate medication adherence.[17] The concept of PrEP disengagement specifically refers to steps in the prevention cascade related to adherence and retention in care.

Despite high interest and uptake of PrEP among MSM and transgender women,[12,18,19] a considerable proportion of individuals either discontinue or fail to adhere to the regimen shortly after initiation.[12,20] In several studies, all acute HIV seroconversions occurred exclusively during periods of inadequate PrEP use or when the regimen was prematurely discontinued,[12,13,21] highlighting the urgency for identifying factors associated with disengagement. Existing studies are unable to clearly elucidate reasons for PrEP disengagement in this population but psychosocial factors, like stimulant and heavy alcohol use, may be important drivers. This study

evaluates the hypothesis that stimulant and heavy alcohol use are significantly associated with PrEP disengagement in an open label cohort of MSM and transgender women.

METHODS

Study Participants

We analyzed data from a subset of participants who elected to start PrEP in the iPrEx Open Label Extension (OLE). The parent study is described in detail elsewhere.[22] Briefly, participants were enrolled at 11 sites across six countries (Brazil, Ecuador, Peru, South Africa, Thailand, and the US) between June 2011 and June 2012, and followed for up to 72 weeks. Visits were scheduled 4, 8, and 12 weeks after enrollment, and quarterly thereafter. Participants were male sex at birth, reported having anal sex with men, and were at least 18 years of age. The subset of participants included in this analysis were individuals in the case-cohort[23] nested within iPrEx OLE who provided consent for long term storage and testing of biological specimens. Cases were all individuals who became HIV-seropositive during follow-up. Controls were a site-stratified sample of HIV-negative participants who elected to start PrEP at enrollment.[12]

Study Procedures

At enrollment and at each subsequent visit, participants reported any stimulant and alcohol use in the last three months using computer-assisted self-interview (CASI). The stimulant use questionnaire was modified based on the study region to adapt to local terminology and included crack, cocaine, pasta basica (i.e., cocaine paste used in Brazil, Ecuador, and Peru), methamphetamine, methcathinone (in South Africa), and methylenedioxy-methamphetamine (MDMA). Binge drinking was defined as consuming 5 or more drinks on one occasion. Banked urine specimens collected at baseline were also tested for metabolites of

amphetamine, cocaine, and MDMA to validate CASI responses. Participants who reported no recent drug use but had positive urine tests were coded as having used stimulants.

The Center for Epidemiologic Studies Depression Scale (CES-D) was administered at baseline to capture any depressive symptomology in the previous 7 days.[69] The CES-D is a 20-item scale validated for use in English, Portuguese, Spanish, and Thai.[69-74] Standard clinical cutoffs were used to categorize CES-D scores: none-mild depression (0-15); mild-moderate depression (16-26); and severe depression (+27). The number of sex partners in the last three months was collected using an interviewer-administered questionnaire. PrEP adherence was measured by quantifying tenofovir drug levels in dried blood spots collected at each follow-up visit after PrEP dispensation.

The outcome of interest is PrEP disengagement. This was operationalized as a binary indicator that indexed either: 1) failure to show for a follow-up visit; or 2) tenofovir drug levels <700 fmol/punch, which corresponds to less than four doses of FTC-TDF per week.[24,25] Previous studies in MSM suggest that four doses per week is the minimum required to achieve optimal protection against HIV.[12,21,24] This study was approved by the Committee on Human Research at the University of California, San Francisco.

Statistical Analyses

Logistic models with probability weights to account for the case-cohort design were used to test baseline correlates of PrEP disengagement at the 4-week follow-up. We evaluated PrEP disengagement at the first follow-up as previous analysis had shown that participants who disengaged at this visit were unlikely to become optimally engaged in future visits.[17] Our predictors of interest were stimulant use and binge drinking. Relevant baseline confounders were identified using a directed acyclic graph (DAG).[26,27] Each predictor was modeled individually then as a predictor set. We tested for the possible interaction between stimulant use and binge drinking, stimulant use and CES-D score, and binge drinking and CES-D score, but

found no evidence of effect heterogeneity (p>0.05), so these terms were not included in the final model. All analyses were conducted using Stata 14.2.[28]

RESULTS

Sample Characteristics

Data from 330 participants were included in the analysis (Table 1). Median age at baseline was 29 years (range 19-70) and median number of partners was two (range 0-250). Most participants identified as MSM (89%), Latino or Hispanic (57%), and had completed secondary or post-secondary education (78%). Of the total, 16% (52/330) either self-reported using stimulants in the prior three months or had positive urine results. The most commonly used stimulants were crack, cocaine and pasta basica (42%) followed by methamphetamine and methcathinone (4%). Approximately 22% (72/330) reported binge drinking in the last three months. Nearly half (49%) of all participants reported engaging in condomless anal sex in the last three months.

PrEP Disengagement

Overall, 53% (174/330) of participants had disengaged by the first follow-up visit (i.e., week 4). Of those that disengaged, 79% (137/174) had drug levels that corresponded to less than four doses per week and 21% (37/174) failed to show for the visit. Approximately 62% (32/52) of stimulant users and 61% (44/72) of binge drinkers disengaged by the first month.

In the adjusted model, stimulant use was significantly associated with PrEP disengagement (Table 2). Stimulant users were over five times more likely to disengage at the first 4-week follow-up compared to non-users (adjusted odds ratio [aOR] 5.24; 95% confidence interval [CI] 1.64-16.76). Binge drinking was significantly associated with PrEP disengagement in univariate analysis (OR 1.97; 95% CI 1.05-3.68) but the effect was attenuated and lost statistical significance after adjusting for stimulant use and baseline confounders (aOR 0.78; 95% CI 0.33-1.88). Being transgender was also associated with higher odds of disengagement,

but this effect was not statistically significant in the adjusted model (aOR 1.18; 95% CI 0.28-5.06). STI diagnosis at baseline, total number of partners in the last three months, and depressive symptoms in the prior seven days were not significantly associated with PrEP disengagement. We also found no statistically significant linear trend for total number of partners (p=0.65) and CES-D score (p=0.57) in the multivariate model.

DISCUSSION

We found strong evidence to suggest that stimulant use is associated with PrEP disengagement. This finding is consistent with reports in the HIV-treatment literature where stimulant use is a well-established correlate of non-adherence and non-retention in care among HIV-positive persons.[29,30] We observed an association between binge drinking and PrEP disengagement in the univariate model, but this effect lost statistical significance and was considerably diminished after controlling for stimulant use and baseline characteristics.

Our findings are in contrast with results from other PrEP studies[13] (also J.C.H, unpublished data, 2017) that found no association between stimulant use and disengagement. Indeed, in the US PrEP Demonstration Project, Liu et al.[13] found a trend suggesting that participants reporting amphetamine use were more likely to optimally adhere to PrEP than non-users (OR 1.88; 95% CI 0.85-4.18). One possible reason for this difference is our use of a composite variable that indexed not just amphetamines but other stimulants found to be associated with poor adherence.[31,32] Cocaine was the most commonly used drug in our sample (13%) and the prevalence of amphetamine use was relatively low (4%). Further, we utilized urine biomarkers to validate the responses of those who denied any recent drug use. This helped identify individuals that may have otherwise been misclassified.

Regardless, reports of any stimulant use should not preclude patients with known risk factors from either accessing or being offered PrEP. Analysis by Buchbinder et al.[33] demonstrated that providing PrEP to MSM and transgender women who use stimulants would

require the lowest number needed to treat (NNT) among all transmission risk groups to prevent one HIV infection (NNT = 12). To achieve its maximum public health impact, PrEP delivery needs to target subgroups that have the highest rates of HIV incidence. Further, MSM and transgender women who report substance use behaviors already face considerable barriers to care.[34-39] PrEP can be an opportunity to link these individuals into care to address unmet healthcare needs and mitigate existing disparities.[40-42]

Our findings support the need to provide PrEP as part of a comprehensive package that includes an assessment of potential barriers and interventions to enhance optimal engagement. Although more work is needed to identify effective strategies that can mitigate PrEP disengagement in stimulant-using MSM and transgender women, existing models used in the other contexts have shown promising findings. Studies[43,44] have demonstrated the efficacy of contingency management in supporting medication adherence among methamphetamine-using MSM taking post-exposure prophylaxis (PEP) and those in HIV treatment. Future studies can build upon our findings to evaluate how we can effectively adapt this strategy for delivering PrEP in high-priority populations.

This study has several limitations. First, self-reported responses may have been prone to recall and social desirability biases, particularly for sensitive topics like drug and alcohol use. We attempted to mitigate misclassification by using urine biomarkers of stimulant use to validate participant responses. Future studies may benefit from using novel markers of problematic drinking, like phosphatidylethanol.[45] Further, we were unable to differentiate between frequent and episodic stimulant and alcohol use, which may affect disengagement differently. Second, we acknowledge that transgender women are a distinct group of individuals that do not necessarily share the same psychosocial contexts as MSM. Our study was not sufficiently powered to detect differences between these groups. Future studies will need to examine transgender women separately to clearly elucidate factors associated with PrEP disengagement in this population. Third, we included depressive symptomology as a baseline confounder

because of its documented association with problematic drug and alcohol use and non-adherence.[46,47] We utilized standard clinical CES-D cutoffs that have been validated in US populations but the scale has been shown to perform differently for different populations.[48] Lastly, we were unable to control for other potentially relevant factors, like stigma and social support, so residual confounding is possible.

Despite these limitations, our study provides an important contribution to the field. We examined clinically-relevant psychosocial factors and identified stimulant use as one of the main drivers of PrEP disengagement in this high-priority population. Our findings underscore the need for a comprehensive approach to prevention that combines PrEP with behavioral interventions to mitigate disengagement and optimize its public health benefit.

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Table 1. Baseline demographics and participant characteristics[^]

	Median	(Range)
Age	29	(19 - 70)
Total number of partners in last 3 months	2	(0 - 250)
	N	(%)
Study region		
Andes[†]	165	(50)
Brazil	68	(21)
South Africa	19	(6)
Thailand	18	(5)
United States	60	(18)
Gender		
MSM[±]	295	(89)
Transgender women	35	(11)
Latino or Hispanic	187	(57)
Education		
Less than secondary	71	(22)
Completed secondary	106	(32)
Post-secondary	152	(46)
Baseline CES-D[◊] score		
< 16	237	(72)
16-26	63	(19)
≥ 27	29	(9)
Stimulant use in the last 3 months[•]		
Crack/cocaine/pasta basica	43	(13)
MDMA	3	(1)
Methamphetamine/tik/methcathinone	12	(4)
Binge drinking[»]	72	(22)
Condomless anal sex in the last 3 months	161	(49)

[^]Proportions may not add to 100% due to rounding or missing data

[†]Includes sites in Ecuador and Peru

[±]Men who have sex with men

[◊]Center for Epidemiologic Studies Depression Scale

[•] Based on self-reported use and urine metabolites

[»] ≥5 drinks in one occasion

Table 2. Baseline correlates of PrEP disengagement at the 4-week follow-up.

	OR	(95% CI)	aOR	(95% CI)
Stimulant use in the last 3 months	1.85	(0.97 - 3.51)	5.24	(1.64-16.76)
Binge drinking in the last 3 months	1.97	(1.05 - 3.68)	0.78	(0.33-1.88)
Transgender	3.09	(1.33 - 7.16)	1.18	(0.28-5.06)
STI diagnosis	0.74	(0.32-1.72)	0.23	(0.03-2.06)
Total number of partners in the last 3 months				
0-1 partners	Ref	-	Ref	-
2-3 partners	0.89	(0.51 - 1.55)	1.01	(0.38-2.70)
≥ 4 partners	0.88	(0.50 - 1.57)	1.27	(0.45-3.63)
CES-D score				
< 16	Ref	-	Ref	-
16-26	0.55	(0.31 - 0.99)	0.60	(0.21-1.75)
≥ 27	1.08	(0.48 - 2.44)	1.42	(0.42-4.73)

Multivariate model also controlled for study region, age, education, and Latino ethnicity. Disengagement is defined as tenofovir levels <700 fmol/punch based on dried blood spots (DBS) at the 4-week follow-up visit or failure to show for the 4-week follow-up visit. DBS drug levels reflect adherence in the prior month. Stimulant use includes crack, cocaine, pasta basica, methamphetamine, methcathinone, and MDMA. Binge drinking is ≥ 5 drinks on one occasion. The Center for Epidemiologic Studies Depression (CES-D) scale captures depressive symptoms in the prior 7 days. All predictors were assessed at the baseline visit, prior to the start of PrEP. We found no statistically significant linear trend for total number of partners (p=0.65) and CES-D score (p=0.57) in the multivariate model.

Chapter 4

An evaluation of the PrEP cascade and correlates of non-retention in care in a clinic-based cohort of men who have sex with men (MSM)

Keywords: HIV/AIDS, pre-exposure prophylaxis, PrEP, adherence, PrEP cascade, men who have sex with men, MSM, stimulant use, alcohol use

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Abstract

Background: Addressing the pre-exposure prophylaxis (PrEP) cascade is crucial to optimize its clinical and public health benefits. This study characterized key steps of the PrEP cascade (i.e., seeking services, initiating PrEP, and retention in care) and identified predictors of non-retention among those who started PrEP.

Methods: Between November 2014 and August 2015, men who have sex with men (MSM) were enrolled in a PrEP clinic in San Francisco. PrEP initiation was verified at the 1-month follow-up. Non-retention was defined as failure to return within 30 days of a scheduled follow-up after initiating PrEP without evidence of transferring care.

Results: In total, 344 patients sought PrEP services. Most (95%) reported condomless sex and 14% were diagnosed with an STI. At enrollment, half reported binge drinking (50%) and one-fourth (27%) reported stimulant use. Of those who sought PrEP services, 268 (78%) initiated PrEP. Cost was the most commonly cited reason for not starting. Among patients who initiated PrEP, cumulative incidence of non-retention at 13 months was 38%. Men with an STI diagnosis at enrollment had a 79% greater rate of non-retention (adjusted hazard ratio [aHR]=1.79, 95% CI [1.06-3.01]). Binge drinking (aHR=1.07 [0.73-1.57]) and stimulant use (aHR=1.00 [0.64-1.56]) were not associated with non-retention.

Conclusions: Barriers to PrEP initiation among MSM are multifactorial, and cost remains a key concern. Non-retention is also prevalent. Although some PrEP discontinuations may be appropriate, expanded efforts are needed to support retention of those with STI diagnoses such as syphilis that increase risk for HIV seroconversion.

1. Introduction

Emtricitabine-tenofovir disoproxil fumarate (FTC-TDF) was approved by the US Food and Drug Administration for the prevention of HIV infection in July 2012. The modality, called HIV pre-exposure prophylaxis (PrEP), is a biobehavioral prevention strategy with demonstrated efficacy for reducing risk of HIV infection in various high priority populations, including men who have sex with men (MSM) (Choopanya et al., 2013; Grant et al., 2014; Grant et al., 2010; Liu et al., 2016; McCormack et al., 2016). In the US, MSM are disproportionately affected by HIV, accounting for 63% of all incident cases in 2014 (Centers for Disease Control and Prevention (CDC), 2016). Stimulant use and unhealthy alcohol use (i.e., >5 drinks in one occasion) are recognized as two of the most important drivers of HIV infection in this population because of their well-documented association with condomless anal intercourse (Baliunas, Rehm, Irving, & Shuper, 2010; Colfax et al., 2010; Degenhardt & Hall, 2012; Ostrow et al., 2009; Santos et al., 2013; United Nations Office on Drugs and Crime, 2014). In the Multicenter AIDS Cohort Study (MACS), stimulant use was associated with a nearly three-fold increase in risk for HIV seroconversion. The use of stimulants in combination with any other sex-drug (i.e., poppers and erectile dysfunction medications) was associated with more than an eight-fold greater rate of HIV seroconversion (Ostrow et al., 2009). In two large studies of HIV-negative MSM, risk for HIV seroconversion was nearly two times greater among binge drinkers compared to those who did not report unhealthy alcohol use.

The updated National HIV/AIDS Strategy for 2020 highlighted the role of PrEP as a key strategy to help dramatically reduce new rates of HIV infection among those at highest risk (Office of National AIDS Policy, 2015). Although initial uptake of PrEP in clinical settings was low, recent reports suggest that implementation and patient uptake are increasing (Chen, Snowden, McFarland, & Raymond, 2016; Cohen et al., 2015; Liu et al., 2016; Volk et al., 2015).

However, realizing the optimal public health benefits of PrEP will require effective engagement at each step of the PrEP cascade.

The PrEP cascade is a framework for identifying gaps in the continuum of care and involves a series of steps that includes seeking services, initiating PrEP, and retention in care (Kelley et al., 2015; Liu et al., 2012; Marcus et al., 2016; Nunn et al., 2017). The cascade provides measureable benchmarks from which we can evaluate the implementation of PrEP programs and develop interventions to optimize engagement. However, data that characterize the steps of the cascade in real-world clinical settings outside of demonstration projects are sparse. Further, the availability of literature that identify potential prognostic indicators of non-retention in care are limited. Stimulant and unhealthy alcohol use are well-known challenges to retention in care in the HIV treatment literature (Carrico et al., 2011; Hinkin et al., 2007), but little is known about how these behaviors impact care engagement in the context of PrEP. To address these gaps in knowledge, we documented the PrEP cascade in a community-based clinic serving MSM, and examined the association of stimulant use and binge drinking on non-retention in care.

2. Methods

2.1 Participants and Procedures

We abstracted the medical records of all consecutive patients who were screened for PrEP eligibility between November 2014 and August 2015 at a nurse-led community clinic that provides free sexual health services to MSM and transgender men. Patients either self-referred or were offered PrEP by clinicians because of known risk factors (e.g., recent diagnosis of sexually transmitted infection [STI]). Eligibility for PrEP included 18 years of age or older; identify as gay, bisexual, or a transgender male; live in the San Francisco Bay Area; and be

HIV-seronegative. Patients with renal disease, liver disease, osteoporosis, acute viral syndrome, a recent high risk HIV exposure (i.e., <72 hours from enrollment), uncontrolled diabetes, abnormal screening serology (e.g., elevated serum creatinine), or those that were pregnant were ineligible to receive PrEP. At each visit, patients were tested for HIV, syphilis, rectal gonorrhea, and rectal chlamydia. A prescription for PrEP was provided upon request, even in the absence of apparent HIV risk (e.g., denied engaging in condomless sex), given that risk behaviors are sometimes underreported. Follow-up visits were scheduled one month after enrollment and quarterly thereafter. We collected patient data up until patients reached their month 13 of follow-up. Since the clinic allowed a 30-day grace period for rescheduling missed appointments, this timepoint did not necessarily equate to 13 calendar months.

Two members of the research team abstracted data from medical records using a standardized data collection instrument. Clinicians and the clinic director were consulted to clarify any ambiguous entries in the notes. The study was approved by the University of California, San Francisco Committee on Human Research.

2.2 Measures

2.2.1 Demographic and sexual risk characteristics. Demographic information and sexual risk behavior reported at the enrollment visit were abstracted. Patients complete a self-administered questionnaire during their clinical intake. The form assesses relevant risk behaviors in the last 12 months, including condomless sex, sex with an HIV-positive partner, needle sharing, sex while high or intoxicated, sex with an unknown serostatus partner, and the total number of sex partners. At each visit, patients are tested for sexually transmitted infections (STI), including rectal gonorrhea, rectal chlamydia, and syphilis in addition HIV testing.

2.2.2 Drug and alcohol use. As part of their clinical intake, patients report any drug use in the last 12 months, including use of injection drugs, cocaine, crack, ecstasy, poppers, GHB, ketamine, or methamphetamine. Stimulants are a category of drugs that include cocaine, crack, ecstasy, and methamphetamine. Any recent binge drinking, defined as drinking five or more alcoholic beverages on one occasion in the last 30 days was also recorded as part of the clinical intake.

2.2.3 Initiation of PrEP and non-retention in care. PrEP initiation was verified at the 1-month follow-up visit. Those that did not return for their first follow-up were coded as not having started PrEP. Per clinic protocol, patients are provided a 30-day prescription refill after missing a follow-up visit to avoid any lapses in medication coverage while they are rescheduled. As such, non-retention was operationalized as failure to return within 30 days of a scheduled follow-up after initiating PrEP without evidence of transferring care. When noted in the medical record, we abstracted the reasons for why patients did not return for their follow-up visit or why they discontinued PrEP.

2.3 Statistical Methods

Descriptive statistics were used to characterize patients who sought PrEP services and those that initiated PrEP. PrEP uptake was calculated as the number of patients who returned for their 1-month follow-up divided by the total number who ever sought PrEP. The cumulative incidence of non-retention at 13 months of follow-up (i.e., 390 days) was estimated using the Kaplan-Meier estimator (Kaplan & Meier, 1958). Differences in the cumulative incidence of non-retention across strata of stimulant use and binge drinking were tested using the log-rank test of equality. Cox proportional hazard regression with robust standard errors to account for within-patient clustering was used to identify factors associated with time to first disengagement event

(Andersen & Gill, 1982). Covariates were analyzed individually and as a predictor set for their association with non-retention in care. We tested for the interaction of stimulant use and binge drinking with STI at baseline. The result was not statistically significant and added no meaningful effect so the interaction term was excluded in the final model. Models were checked for conformity with assumptions, including linearity and proportionality. All tests of significance were 2-sided and *p*-values <0.05 were considered statistically significant. Analyses were conducted using Stata 14 (College Station, TX).

3. Results

Table 1 shows a total of 344 patients who sought PrEP services during the study period. The median age was 31 (range 18-70) and the median number of sex partners in the last 12 months was 10 (range 1-100). Most identified as MSM (99%), White (65%), and non-Hispanic (74%). Approximately 208/344 (60%) reported using drugs in the last 12 months at their enrollment visit, of whom 130/208 (63%) reported using stimulants. The most widely used drug was poppers (46%) followed by ecstasy (30%) and cocaine (25%). Half of all patients reported binge drinking in the last 30 days and slightly over half (59%) reported having sex while either high or intoxicated. Nearly all patients who were screened for PrEP reported engaging in condomless anal sex in the last 12 months (95%) and a sizeable proportion reported having sex with an unknown serostatus partner (31%). At enrollment, 40/344 (12%) were diagnosed with rectal gonorrhea or rectal chlamydia and 10/344 (3%) tested positive for syphilis.

Of the 344 patients who were evaluated for PrEP, 76 did not return for their first month follow-up (Fig. 1). Of these, 23 (30%) did not start PrEP because of issues with cost. This includes individuals who were unable to access PrEP because they did not complete their application to qualify for drug assistance programs. Eight (2%) were not enrolled because of abnormal labs values; seven (2%) declined PrEP; three (1%) sought PrEP elsewhere; and three (1%) were not eligible for services at the clinic. A small number (2/76) started PrEP but

immediately discontinued the regimen due to side effects and did not return for their first month follow-up.

Among those that did not initiate PrEP, 14/76 (18%) were diagnosed with rectal gonorrhea, rectal chlamydia, or syphilis, 71/76 (93%) reported having condomless sex, 23/76 (30%) reported using stimulant in the last year, and 39/76 (51%) reported binge drinking in the last month. The demographic characteristics and sexual risk behaviors of those who did not start PrEP and were excluded from the final analysis were not significantly different from those who remained engaged at month one of follow-up (p>0.05; data not shown).

Among patients who initiated PrEP, median follow-up time was 389 days (range 112-488), generating 86,231 person-days of follow-up. The overall cumulative incidence of non-retention at 13 months was 38%. Reasons documented in the medical record for non-retention are summarized in Fig. 1. Of the 126 who were not retained in care, 28 (22%) presented to the clinic at a later date to restart PrEP.

The cumulative incidence of non-retention at 13 months among stimulant users was 43% compared to 34% among non-users (p=0.51) and 42% among binge drinkers compared to 33% among those who denied unhealthy alcohol use (p=0.53). Survival distributions are presented in Fig. 2. In the multivariate Cox proportional hazards model (Table 2), men who were diagnosed with an STI at baseline had nearly double the rate of non-retention (adjusted hazard ratio [aHR] 1.79; 95% confidence interval [CI] 1.06-3.01). Stimulant use (aHR 1.05; 95% CI 0.69-1.58) and binge drinking (aHR 1.06; 95% CI 0.71-1.57) were not significantly associated with non-retention in care.

4. Discussion

This study is among the first to characterize the PrEP cascade in a clinic-based cohort of MSM on PrEP and examine the effects of simulant use and binge drinking on retention in care. We observed high uptake among individuals who sought PrEP services at the clinic, consistent

with what others have reported previously (Chan et al., 2016; Cohen et al., 2015; Volk et al., 2015). However, structural barriers to access, like cost, remain challenging for many patients. Despite the availability of PrEP navigators at the clinic who helped patients access insurance and drug assistance programs, a sizeable proportion (22%) did not initiate PrEP. Although a recent report by Chan et al. (Chan et al., 2016) that examined PrEP programs at three community clinics in Rhode Island, Mississippi, and Missouri found that drug cost was a not a significant barrier to accessing PrEP, the financial burden of the regimen posed a considerable challenge for those without insurance coverage. Other studies have also documented providers' and patients' hesitation on starting PrEP because of cost (Brooks et al., 2011; Calabrese et al., 2016; Cohen, Liu, Bernstein, & Philip, 2013; King et al., 2014; Sowicz, Teitelman, Coleman, & Brawner, 2014; Volk et al., 2015).

Approximately 53% of patients whom we verified had started PrEP were retained in the program at the end of the study period. It is important to note that some of the patients (6%) that were not retained were individuals who had entered mutually monogamous relationships and were, thus, no longer appropriate for PrEP. Most of the patients (77%) who were not retained did not have documented reasons for why they did not come back to the clinic, so it is possible that some may have moved away, transferred care to another provider, or selected a different HIV prevention method. Further, many of the patients (22%) that were coded as not retained eventually returned to the clinic at a later date to restart PrEP. This is perhaps reflective of the seasonality of HIV risk, which describes how behaviors can vary over time and how individuals go in and out of risk (Grant & Glidden, 2016; Haberer et al., 2015; Hojilla et al., 2015). All of these situations can be considered appropriate discontinuations of PrEP from the clinic's service.

We found that STI diagnosis at baseline was independently associated with a higher rate of non-retention. This is of particular concern because STI diagnoses like syphilis significantly increase the risk of HIV seroconversion (Solomon et al., 2014). A possible explanation for this

association might be that patients diagnosed with any STI during routine screening are more likely to be offered PrEP by clinicians than those that do not test positive. These individuals may feel less motivated to stay in the program, have lower perceived risk, or have more urgent psychosocial issues (e.g. housing, food security) than those who self-referred. Expanded efforts like resource navigation or motivational enhancement interventions (e.g., motivational interviewing, conditional cash transfers) may be needed to enhance retention among patients with these risk factors (Parsons et al., 2016).

Although stimulant use and binge drinking are known correlates of disengagement in the HIV-treatment literature (Carrico et al., 2011; Hinkin et al., 2007), this was not apparent in our sample. We failed to observe any statistically significant difference in rates of non-retention across groups. Others have reported similar findings from open label studies (Grant et al., 2014; Liu et al., 2015), but our findings are among the first characterize these associations using clinical data. A possible hypothesis is that persons who use stimulants or engage in heavy drinking may be more aware of how these behaviors can lead to greater risk taking so they are more inclined to adhere to PrEP to mitigate their risk. PrEP users have previously described the regimen as an added layer of protection (Hojilla et al., 2015) and recent observational studies found that PrEP uptake and adherence were higher among persons who exhibited greater risk for acquiring HIV (Grant et al., 2014; Liu et al., 2016). It is also important to recognize the current clinical context where PrEP roll-out is in its early stages and most individuals seeking PrEP are early adopters. These individuals are likely a select group that are well-informed and well-motivated. A recent qualitative report described the ambivalence of some providers in prescribing PrEP to persons who have issues with substance use (Spector, Remien, & Tross, 2015). Our findings add to the growing literature that suggest the provision of PrEP should not be withheld because of concerns surrounding stimulant and alcohol use behavior.

This study has several limitations. First, we are unable to fully evaluate reasons for non-retention so misclassification of our outcome is possible. Migration between residences and

insurance plans is high in this population, and such migrations make it impossible to fully evaluate whether loss to follow-up is appropriate or not. Additionally, our reliance on data collected as part of routine clinical practices limits our ability to fully evaluate any changes in patients' risk behaviors so some discontinuations may have been appropriate due to changing risk. Drug use was captured using a questionnaire that asked patients about behaviors in the last year so we were unable to clearly characterize problematic and recreational drug use. Lastly, it is important to recognize that persons who seek out PrEP likely already have positive health behaviors and may be more aware and willing to take on the requirements of a PrEP regimen. Future studies will need to better distinguish between episodic and frequent drug and unhealthy alcohol use using objective biomarkers, as well as identify appropriate PrEP discontinuations.

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Table 1. Baseline characteristics of HIV-negative patients screened for PrEP (N=344)

	Median	(range)
Age, in years	31	(18-70)
Number of sex partners in the last 12 months	10	(1-100)
	N	(%)*
Sexual orientation		
MSM	342	(99)
Unsure	2	(1)
Race		
White	225	(65)
Asian/Other	69	(20)
African-American	10	(3)
Ethnicity		
Non-Hispanic or Latino	253	(74)
Latino	88	(26)
Any binge drinking in the last 30 days^	172	(50)
Any drug use in the last 12 months	208	(61)
Drug type		
Poppers	158	(46)
Ecstasy	103	(30)
Cocaine	85	(25)
GHB	41	(12)
Ketamine	35	(10)
Methamphetamine	20	(6)
IDU	4	(1)
Crack	1	(<1)
Sex while high or intoxicated	203	(59)
Sex with unknown serostatus partner	106	(31)
Diagnosed with rectal gonorrhea/chlamydia	40	(12)
Diagnosed with syphilis	10	(3)
Condomless anal sex	327	(95)
HIV-positive partner	120	(35)

PrEP = pre-exposure prophylaxis
MSM = men who have sex with men
* Proportions may not add to 100% due to missing data
^ ≥ 5 drinks in one occasion
GHB = gamma hydroxybutyrate
IDU = injection drug use
STI = sexually transmitted infection (i.e., rectal gonorrhea, rectal chlamydia, or syphilis)

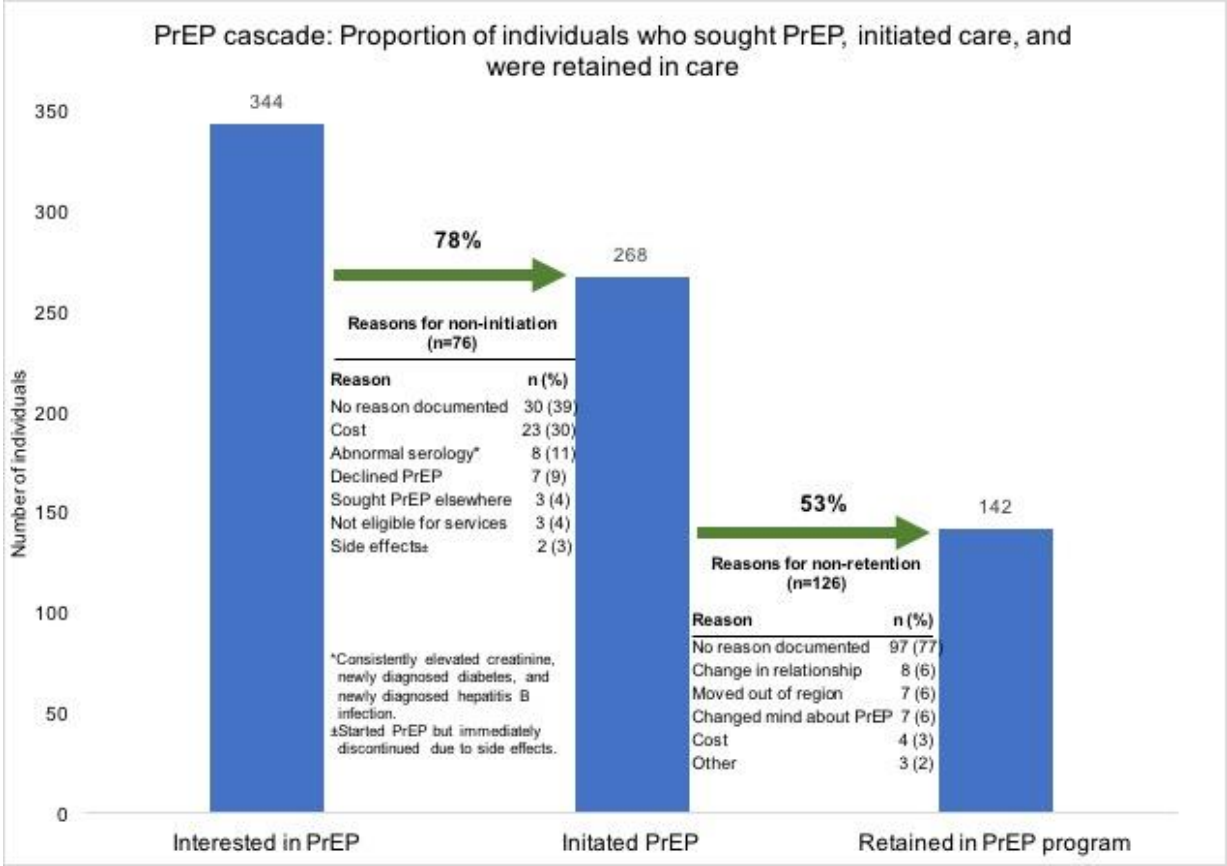


Figure 1. The pre-exposure prophylaxis (PrEP) cascade at a community-based clinic serving men who have sex with men (MSM). Of those who sought PrEP services, 268 (78%) initiated PrEP. Cost was the most commonly cited reason for not starting PrEP. Among those who initiated PrEP 142 (53%) were retained in the program at the end of follow-up.

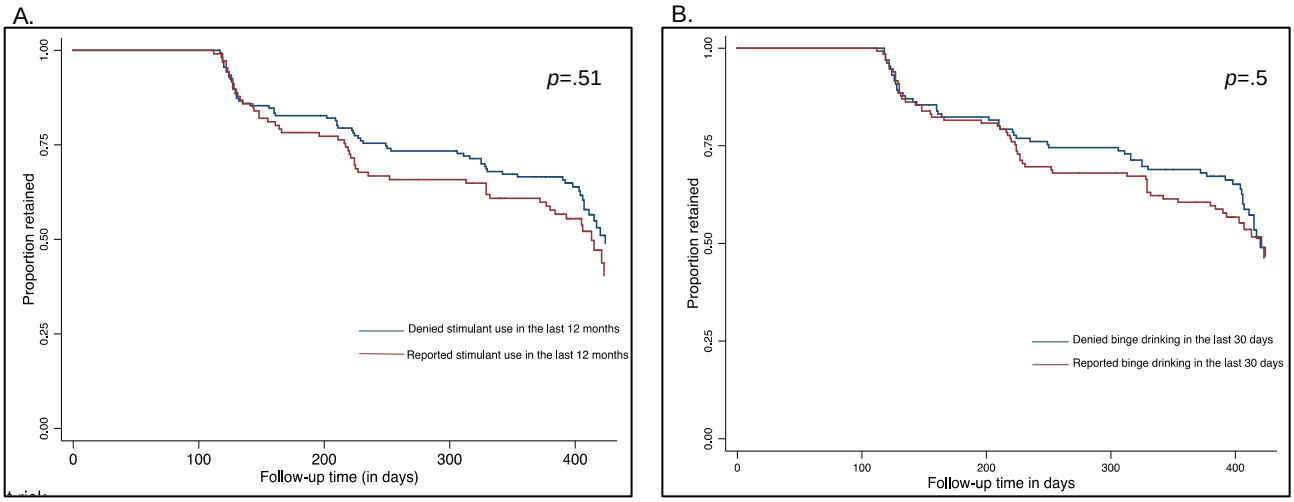


Figure 2. Non-retention over time by stimulant use (A) and binge (B) among patients who initiated PrEP.

Table 2. Cox proportional hazard regression models assessing predictors of non-retention among patients who initiated PrEP.

	Unadjusted Hazard Ratio	(95% CI)	Adjusted Hazard Ratio	(95% CI)
Age (10 years)*	0.79	(0.64 – 0.98)	0.77	(0.60 – 0.98)
Latino	1.23	(0. 82 – 1.85)	1.26	(0.80 – 1.99)
Number of partners	1.00	(0.99 – 1.01)	0.99	(0.98 – 1.01)
STI diagnosis at enrollment±	1.71	(1.04 – 2.78)	1.79	(1.06 – 3.02
Stimulant use	1.13	(0.79 – 1.61)	1.05	(0.69 – 1.58)
Binge drinking^	1.12	(0.79 – 1.60)	1.06	(0.71 – 1.57)

* For every 10-year increase in age
± STI = sexually transmitted infection (i.e., rectal gonorrhea, rectal chlamydia, or syphilis)
^ ≥ 5 drinks in one occasion

Chapter 5

Conclusion

The aims of this dissertation were to identify baseline factors associated with participant non-disclosure and lack of knowledge of partner status (Study 1); identify risk factors of PrEP disengagement among MSM in an open label cohort (Study 2); and identify prognostic indicators for discontinuation in care among MSM enrolled in a clinic-based cohort (Study 3).

Results of Study 1 suggest that PrEP use is not associated with either non-disclosure or not knowing a partner's HIV status. We also found no statistically significant difference in expectancies regarding PrEP effectiveness across groups of individuals who disclosed and asked partners about their HIV status and those that did not. These findings add to the growing literature suggesting that PrEP use is not associated with risk compensation (Grant et al., 2014; Hojilla et al., 2015; Liu et al., 2016; Marcus et al., 2013; McCormack et al., 2016). The results of this study also suggest that disclosing one's HIV status and asking partners about theirs may be primarily influenced by relationship characteristics. Factors like closeness with a sexual partner and the length of time that an individual has known a partner prior to their first sexual encounter have been previously described as important correlates of serodisclosure (Gorbach et al., 2004; Przybyla et al., 2013; Simon Rosser et al., 2008).

The key clinical insights of this study are twofold. First, concerns about risk compensation should not preclude patients from accessing PrEP. It is important for clinicians to remember that PrEP is only one tool in a growing list of evidence-based risk reduction strategies. Men in the US PrEP Demonstration Project described PrEP as an added layer of protection and the type of prevention strategy they used varied depending on the context (e.g., condoms with anonymous partners, mutual disclosure among established partners) (Hojilla et al., 2015). Second, the significant associations between relationship characteristics and discussions about HIV status underscore the importance of how dyadic factors influence HIV

prevention efforts. Interventions to mitigate HIV risk should account for these dyadic factors to provide feasible strategies tailored to the unique contexts of each patient's relationships.

In Study 2, we found strong evidence to suggest that stimulant use is associated with PrEP disengagement (i.e., missing a scheduled follow-up visit or adherence <4 doses per week). However, when we examined the effect of stimulant use and binge drinking on retention in care in a clinic-based cohort (Study 3), we found no significant associations. Rather, we noted how barriers to PrEP initiation and retention in care were multifactorial. The cost of PrEP was a predominant theme in patient self-reported reasons for not returning for their first follow-up visit. We also found that STI diagnosis at baseline (i.e., rectal gonorrhea, rectal chlamydia, and syphilis) was significantly associated with non-retention in care among those who started PrEP. The effect of STI at baseline was not statistically significant in Study 2.

There are several possible reasons for these contrasting results. We validated stimulant use responses by testing urine samples collected at baseline in Study 2. Participants who denied any recent drug use in their CASI responses were coded as having used stimulants if their baseline urine sample tested positive for stimulant metabolites. In Study 3, we relied on responses collected using a self-administered questionnaire completed during each patient's intake. Though the questions were informative, they were not designed for the purposes of a study and were inadequately specific (e.g., patients were asked about drug use in the last 12 months). Our use of urine biomarkers in Study 2 helped minimize misclassification. It is possible that effect estimates in Study 3 were attenuated because of misclassification or because of unmeasured confounding.

The iPrEx OLE case-cohort was comprised of a site stratified sample of participants that was reflective of the overall composition of the parent study. Most participants in iPrEx OLE were in South America, particularly the Andes (i.e., Ecuador and Peru). Whereas Study 3 was based at a sexual health clinic in the Castro District of San Francisco. Differences in culture,

social factors, and structural barriers across these settings are apparent. It is possible that factors driving PrEP disengagement vary based on the individual's broader social context.

Lastly, it is important to recognize that PrEP was provided at no cost in iPrEx OLE and health insurance was not a factor to accessing services. The study likely attracted a broader array of individuals, including those with problematic patterns of drug use. The setting for Study 3 was a community sexual health clinic that provided free to low-cost care, but patients were still required to pay some amount for their medication or access medication assistance programs. It is likely that persons who sought out PrEP at the clinic already had positive health behaviors and were more aware and willing to take on the requirements of a PrEP regimen.

Results from Study 3 may be more reflective of the factors that drive non-retention in care in the current clinical context where PrEP roll-out is in its early stages and most individuals seeking PrEP are the early adopters. These individuals are likely a select group that are well-informed and well-motivated. The more relevant factors to address for these individuals may be structural barriers like cost and insurance coverage. Over time, as PrEP roll-out expands and services are offered more broadly, we will likely see trends similar to what we observed in the iPrEx OLE cohort.

Our results underscore the need for comprehensive prevention strategies that include an assessment of potential barriers and interventions to enhance optimal engagement. PrEP should not be withheld from patients with known HIV risk factors who report stimulant use. Creative approaches to enhance retention and adherence, like contingency management (Carrico et al., 2016; Landovitz et al., 2012), have been tested in other contexts and may be adapted to support PrEP implementation. Findings from this dissertation form the foundation for postdoctoral work that will further identify and validate prognostic indicators of PrEP disengagement, and test interventions to optimize PrEP implementation in substance-using MSM.

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