Prev Sci (2017) 18:737–747
DOI 10.1007/s11121-017-0799-8

Risk Perception, Sexual Behaviors, and PrEP Adherence Among Substance-Using Men Who Have Sex with Men: a Qualitative Study

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Published online: 3 June 2017

Abstract The antiretroviral drug combination emtricitabine and tenofovir disoproxil fumarate (TDF/FTC) taken as pre-exposure prophylaxis (PrEP) is effective in preventing HIV infection, yet it also requires adherence and potentially decreases condom use. This study sought to examine these issues among a key population at risk of HIV infection, substance-using men who have sex with men (MSM). We conducted semi-structured interviews with an ethnically diverse sample of 30 young (aged 20–35) MSM prescribed PrEP within a large integrated healthcare system in San Francisco, who had reported recent drug use or hazardous drinking and one or more missed doses of PrEP. We explored participants' risk perception and sexual risk behavior, drug and alcohol use, and PrEP adherence in the context of substance use. Interviews were transcribed and coded using a directed content analysis approach to identify key categories and commonalities, and differences across participants. Salient subcategories included positive psychological effects of being on PrEP (e.g., decreased anxiety, feelings of empowerment), social effects (e.g., reduced HIV stigma), and reduction in overall perceptions of HIV risk. While overall reported use of condoms went down and many reported a brief period of increased condomless sex following PrEP initiation, others continued condom use with most of their sexual partners. Contextual factors influencing their decision to engage in condomless sex included how well they knew the partner and whether the partner was on PrEP or HIV antiretroviral treatment. Factors associated with poor adherence included disruptions in daily routine and use of alcohol and methamphetamine. PrEP-prescribing clinicians should support their patients in making informed decisions about condom use and identifying strategies to maximize adherence in the context of substance use.

Keywords Pre-exposure prophylaxis · PrEP · Adherence · Risk perception · Sexual behavior · Alcohol · Methamphetamine · Substance use

Introduction

The antiretroviral drug combination emtricitabine and tenofovir disoproxil fumarate (TDF/FTC) taken as pre-exposure prophylaxis (PrEP) can be highly effective in preventing HIV infection (Baeten et al. 2012; Grant et al. 2010; Liu et al. 2016; McCormack et al. 2016; Molina et al. 2015; Volk et al. 2015). PrEP has been widely promoted as a vital prevention strategy for individuals in at-risk groups, including men who have sex with men (MSM) who have recently engaged in condomless anal sex with a non-monogamous partner (Centers for Disease Control and Prevention 2014; Smith et al. 2015). Substance-using MSM may also be prime candidates for PrEP, as there is substantial evidence of less condom use and more sexual partners while under the influence of substances such as alcohol (Vosburgh et al. 2012; Woolf and Maisto 2009) and methamphetamine (Halkitis et al. 2013; Shoptaw and Reback 2006). PrEP may be a particularly useful HIV prevention strategy for substance-using MSM given

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that, unlike condom use, the timing of medication taking can be separated from the timing of substance use and sex.

However, PrEP also presents a set of unique challenges and potential behavioral consequences that require further elucidation among the populations that stand to benefit most from its use. In particular, adequate adherence to PrEP during periods of increased HIV risk is critical to sustaining its effectiveness (Donnell et al. 2014; Haberer et al. 2015) and avoiding the development of resistance (Abbas et al. 2011). Identifying and addressing the factors that contribute to suboptimal adherence may be especially important for MSM taking PrEP who also report illicit drug use or hazardous drinking (i.e., 5+ drinks in a day) (Dawson 2011). Previous research has shown that substance use may be associated with antiretroviral non-adherence among HIV-positive MSM (Azar et al. 2015; Hendershot et al. 2009; Hinkin et al. 2007); the same may hold true for MSM taking PrEP, as evidenced by a trend towards lower adherence with increased alcohol use among PrEP trial participants (Grant et al. 2014), as well as an association between drug/alcohol abuse diagnoses and PrEP discontinuation in clinical practice (Marcus et al. 2013).

Aside from suboptimal adherence, concerns have also been raised about possible changes in risk perception while taking PrEP and associated increases in condomless anal sex and sexually transmitted infections (STIs) (Cassell et al. 2006; Golub et al. 2010). Researchers have referred to this phenomenon as *risk compensation* or an increase in risk-taking behaviors triggered by a decrease in perceived risk (Hogben and Liddon 2008). While risk compensation was not observed in three large PrEP randomized controlled trials (Liu et al. 2013; Marcus et al. 2013; Mugwanya et al. 2013), these studies provided extensive prevention education, including promotion of continued condom use and intensive risk reduction counseling. Data from the few emergent studies of routine clinical practice suggest variable responses upon initiating PrEP, with a significant subset of PrEP users reporting decreased condom use (de Wit et al. 2015; Gibson et al. 2016; Parker et al. 2015; Volk et al. 2015), reflecting observed differences between trials and real-world PrEP implementation. Differences in evidence of risk compensation reported from PrEP clinical trials, demonstration projects, and routine clinical practice suggest that sexual decision-making and risk-taking behavior may be more complex in real-world situations where substance use and relational and other situational factors may exert more influence and repeated, intensive prevention messaging including condom promotion may be lacking.

Although changes in risk perception may contribute to decreased condom use, there have also been several studies noting the psychosocial benefits of taking PrEP, including reduced anxiety around sex, increased intimacy, increased feelings of empowerment, and decreased stigma towards HIV-positive individuals (Brooks et al. 2011; Grant and Koester 2016). While the primary and secondary public health aims of PrEP are biological (i.e., for individuals at high risk to remain HIV negative and thus not transmit the virus to partners), the tertiary psychological and social outcomes need to be fully understood to inform PrEP dissemination, adherence support, and STI prevention efforts, particularly among high-risk populations such as substance users that experience disproportionate rates of stigma, discrimination, and mental health problems among substance-using MSM (Halkitis et al. 2013; Meyer 2003; Storholm et al. 2015). It is important for clinicians to understand the positive psychosocial aspects of taking PrEP in this population as well as the potential for decreases in condom use and the impact of illicit drug use or hazardous drinking on PrEP adherence. Such knowledge will inform future interventions aimed at improving adherence and lead to improvements in routine patient care.

PrEP can be effective in preventing HIV infection and has potential psychosocial benefits, yet medication adherence, concerns about risk compensation, and the impact of substance use remain to be key implementation challenges. Thus, the objectives of the current qualitative study were to better elucidate (1) changes in risk perception and sexual behavior, (2) adherence and its relationship to substance use, and the (3) psychosocial impact of taking PrEP among substance-using MSM prescribed PrEP as part of routine clinical practice.

Methods

Study Setting

This study was conducted at Kaiser Permanente San Francisco (KPSF), an urban medical center within a large integrated healthcare system that provides comprehensive medical services to over 175,000 adult residents of San Francisco. At KPSF, patients who may be good candidates for PrEP or who express interest in PrEP are referred to a specialized PrEP program housed within HIV Specialty Care Services, where PrEP is provided by HIV-trained physicians (Volk et al. 2015). This clinic has been administering PrEP for several years and has seen increasing demand as the potential benefits of PrEP become more widely known (Volk et al. 2015).

Participants and Procedures

This study was conducted using a sample of 30 young PrEP-taking MSM, all of whom reported missed doses of PrEP and recent hazardous drinking or illicit drug use. We chose these selection criteria in order to examine potential relationships between drug and alcohol use and suboptimal adherence. KPSF patients aged 18–35 who identified as MSM and were prescribed TDF/FTC as PrEP were contacted via email by a

PrEP clinician at KPSF (co-author JEV) to assess interest in participating in an interview to discuss their experiences of taking PrEP. Interested participants were instructed to contact the lead investigator (author ES) for eligibility screening. Given their disproportionately high risk of HIV acquisition (CDC 2016), Black and Latino MSM were oversampled (16.7 and 23.3%, respectively) as compared to Asian and White men (20.0 and 40.0%, respectively) in order to ensure adequate representation in the study since the population of Black and Latino men (6.1 and 15.1%, respectively) is significantly less than the population of Asian and White men (33.3 and 48.5%, respectively) in San Francisco County (U.S. Census Bureau 2010). Thirty-five participants who met the eligibility criteria for inclusion [they were biologically male, reported hazardous drinking (i.e., 5+ drinks in a day) and/or using illicit substances (other than marijuana) during the past 3 months (Humeniuk et al. 2010), used PrEP for at least 3 months, and reported missing at least 1 day of their PrEP medication during the prior 6 months (or since initiation if <6 months)] were invited to participate in the study. Participants received a $50 gift card for participation. Thirty-five eligible participants were screened and invited to participate in the study. Five either declined to participate or did not show up to the interview, yielding a final interview sample of 30 participants.

Interviews

After obtaining informed consent, the lead author conducted semi-structured interviews ranging from 48 to 73 min (M = 66.5 min, SD = 8.2) in a private office at KPSF. The qualitative component was designed to elicit the experiences and perspectives of the participants in their own terms and words (Corbin and Strauss 2008). Interviews explored participants' conceptualization of experiences, meanings, norms, contexts, interpersonal communication, relationships, and daily routines that could be expected to significantly impact risk perception, sexual behavior, substance use, medication adherence, and psychological and biological adaptation to PrEP. Specific questions focused on participants' reasons for taking PrEP; changes in risk perception; experiences with STIs; changes in frequency of condom use, number of partners, or sexual positioning; substance use; experiences with missed doses; psychological changes (e.g., anxiety reduction); willingness to have HIV-positive sexual partners; and experiences of stigma. Interviews were conducted with a conversational flow, encouraging the participants to elaborate on each question in their own words and probing deeper, as needed, to clarify vague or unclear responses and to elicit more nuanced and elaborate responses to the inquiries. Interviews were recorded using secure digital audio devices and professionally transcribed. Immediately following the interview, participants were administered the National Institute on Drug Abuse (NIDA)-Modified ASSIST V2.0 to assess for current substance use and asked to complete a sexual behavior questionnaire including items assessing PrEP adherence. Study procedures were approved by the Kaiser Permanente Northern California and University of California San Francisco Institutional Review Boards.

Data Analysis

Demographic, substance use, sexual behavior, and PrEP adherence data were examined descriptively. Qualitative data analyses were informed by adapted aspects of grounded theory (Corbin and Strauss 2008) that incorporated directed content analysis (Potter and Levine-Donnerstein 1999) in areas of sexual risk-taking behavior, substance use, and adherence. Transcribed interviews were reviewed to identify primary coding categories as well as subcategories within each topic area. Identified coding categories and subcategories were organized into a formal code book that was refined until agreed upon by the coding team. Transcripts were then divided and coded by two members of the study team, and six transcripts (20%) were randomly selected and independently coded by both coders. The coding team reviewed both coded versions of these transcripts for consistency, resulting in good inter-rater agreement (k = 0.94) between coders. Inter-rater discrepancies were discussed by the coding team until consensus was obtained.

Results

Characteristics of Participants

Participants ranged in age from 20 to 35 years (M = 27.5, SD = 3.9; Table 1). The majority of participants (60.0%) were non-White, and two participants reported primary relationships with HIV-positive partners. The average length of time on PrEP was 10.7 months, with a range of 4 to 24 months. The average number of self-reported missed doses over the past 3 months was 5.5 (SD = 5.8; i.e., <1 per week), with a range from 1 (<1 per week) to 24 (approximately 2 per week); none reported dosing consistent with fewer than 4 doses per week, the number of doses needed to achieve high protection (Anderson et al. 2012; Grant et al. 2014). The majority of participants (86.7%) reported engaging in condomless anal sex during the 30 days prior to interview, with the number of condomless sex partners ranging from 0 to 15 partners (M = 3.7, SD = 3.5). Fifty-nine percent of anal sex encounters in the month prior to the interview were reported to be condomless.

Fourteen participants (46.7%) reported engaging in anal sex with an HIV-positive sex partner during the 30 days prior to interview, with the number of HIV-positive partners ranging

Table 1 Characteristics of substance-using young adult MSM taking PrEP ($N = 30$)

Characteristic	*N* (%)
Sociodemographic	
Age	
20–24	6 (20.0)
25–29	15 (50.0)
30–35	9 (30.0)
Gender	
Male	30 (100.0)
Sexual orientation	
Gay	29 (96.7)
Bisexual	1 (3.3)
Race/ethnicity	
Asian/Pacific Islander	6 (20.0)
African-American	5 (16.7)
Latino	7 (23.3)
White	12 (40.0)
Education	
High school graduate	4 (13.3)
Enrolled in college	5 (16.7)
College degree	14 (46.7)
Enrolled in graduate school or graduate degree	7 (23.3)
Sexual behavior (during the last 30 days)	
Engaged in condomless anal sex	26 (86.7)
Engaged in anal sex with HIV+ partner in the last 30 days	14 (46.7)
Engaged in anal sex with HIV-status unknown partner in the last 30 days	8 (26.7)
Total number of anal sex partners	
0–1	4 (13.3)
2–3	9 (30.0)
4–5	7 (23.3)
6–7	3 (10.0)
8+	7 (23.3)
Total number of condomless anal sex partners	
0–1	8 (26.7)
2–3	11 (36.7)
4–5	5 (16.7)
6–7	2 (6.7)
8+	4 (13.3)
Substance use (during the last 3 months)	
Hazardous drinking[a]	29 (96.7)
Cocaine	17 (56.7)
Methamphetamine	6 (20.0)
Poppers[b]	21 (70.0)
MDMA	13 (43.3)
GHB	7 (23.3)
Ketamine	10 (33.3)
Prescription stimulant misuse	6 (20.0)
Prescription opioid misuse	4 (13.3)
PrEP use	
Length of time on PrEP (months)	
3–6	8 (26.7)
7–9	9 (30.0)
10–12	7 (23.3)
15–17	1 (3.3)
18+	5 (16.7)
Number of days missed PrEP (last 90 days)	
0–1	10 (33.3)
2–3	5 (16.7)
4–5	2 (6.6)
6–7	7 (23.3)
8+	6 (20.0)

Prescription stimulant or opioid misuse = not taken as prescribed

MDMA methylenedioxyphenethylamine, *GHB* gamma-hydroxybutyric acid

[a] Five or more drinks in a given sitting

[b] Amyl nitrate

from 0 to 12 partners ($M = 1.3$, $SD = 2.4$). Eight participants (26.7%) reported engaging in condomless anal sex with an HIV-status unknown partner during the 30 days prior to interview, with the number of HIV-status unknown partners ranging from 0 to 10 partners ($M = 1.4$, $SD = 2.9$).

All but one participant (96.7%) reported hazardous drinking during the 3 months prior to interview. The majority of participants also reported use of cocaine (56.7%) and poppers (70%), while about half (43.3%) reported MDMA and one fifth (20.0%) reported methamphetamine during the 3 months prior to interview.

Overview of Qualitative Results

Qualitative content analyses revealed multiple salient subcategories among these MSM (Table 2). These categories, significant subcategories, and representative quotes are outlined below in order of the three study objectives: (1) changes in risk perception and sexual behavior, (2) adherence and its relationship to substance use, and (3) psychosocial impact of taking PrEP.

Changes in Risk Perception and Sexual Behavior

Decreased Condom Use

Although the frequency of condom use reported by participants varied greatly both before and after starting PrEP, 73% of participants reported a decrease in condom use after PrEP initiation:

"Okay. So, pre-PrEP, I would say that I had about maybe two to three unsafe sex incidents in one year. I think during PrEP, I've had about double, maybe six, per year. I don't know if I would be doing it anyways or if this an outcome of PrEP. But, at the same time I do know that the reality is it's happening, therefore I'm glad I am on PrEP." (API, 29 years old, 11 months on PrEP)

Many participants (40.0%) reported that they continued to use condoms with new or *unknown* partners and one participant reported that he continued to use condoms with all partners unless he was in a monogamous relationship. Twenty percent of participants reported that they discontinued the use of condoms all together as illustrated by the following quote:

"I was a condom user, a pretty regular one, almost like 100 percent of the time, until about a year ago. And then I - I think some of my regular [partners] started taking PrEP, and so I kind of stopped using condoms with them. And then once that - that's just kind of like the domino effect. Then I found myself in some situations where I wasn't using them with people that I didn't know. I never use a condom now, ever." (White, 31 years old, 6 months on PrEP)

Table 2 Changes in risk perception, sexual behavior, adherence, and sexual well-being among substance-using young-adult MSM taking PrEP ($N = 30$)

Category	Subcategory
Changes in risk perception and sexual behavior	Decreased condom use
	Partner sorting based on the use of PrEP
	STI attitudes and experiences
	"Honeymoon period" halted after STI
Adherence and relationship to substance use	Impact of substance use
	Factors that facilitate adherence
Psychosocial impact of taking PrEP	Enhanced sexual well-being
	Increased openness to HIV-positive partners
	Experience with and ability to combat PrEP-related stigma

PrEP pre-exposure prophylaxis, *STI* sexually transmitted infection, *HIV* human immunodeficiency virus

Partner Sorting Based on Use of PrEP

A few participants (16.7%) discussed either actively seeking out other partners who were also taking PrEP or deciding to engage in condomless sex only with partners taking PrEP, and they reported thinking that this method of *PrEP sorting* would further reduce their risk of HIV infection:

"It was someone that I was casually seeing, we'll call it. When it came down to the moment, things just sort of happened. We talked a little about our behaviors and our practices. They were on PrEP as well. Which probably influenced my decision. So yeah, then unprotected sex happened. I think that definitely is another factor, not just my own status and the fact that I'm on it, but also other people too." (API, 27 years old, 10 months on PrEP)

"Once I started taking PrEP, I feel that the handful of times that I did have sex while I was on PrEP. I do feel that it changed. If I did find out that the other person was also on PrEP, then we could engage in unprotected sex." (API, 28 years old, 10 months on PrEP)

STI Attitudes and Experiences

Eighty-seven percent of men brought up concerns about other STIs, including hepatitis C. In the following example, the participant suggested that pictures of other STIs should be placed on PrEP bottles to scare MSM taking PrEP into continuing to use condoms:

"Well, the concern really isn't, like, you know, HIV at this point because you're on PrEP, it's hepatitis, and I don't want that either. There's no magic drug for that one yet and I don't want that. So, instilling fear is pretty great. That should be slapped like the lung pictures on the cigarettes; that should be on every bottle. Like, you're going to get hepatitis if you don't bring a condom." (API, 27 years old, 6 months on PrEP)

Multiple participants (26.7%) discussed an increased concern about other STIs as a result of the sexual health education they received either from their PrEP providers or from becoming more informed as a result of doing research on PrEP. In the following example, a participant discussed how he wanted to reduce his level of condomless sex to protect himself from other STIs.

"There's hepatitis and there's all of this other stuff that, like, it's just - not necessarily stuff that I didn't know about, but now that I'm more informed about it, I'm not having unprotected sex ever again. Like, even while on this. Unless it's some sort of serious relationship. I think there's times that, I probably get wasted or whatever else on alcohol, and then, like, occasionally will forget." (White, 27 years old, 6 months on PrEP)

"*Honeymoon Period*" *Halted After STI*

Several participants (13.3%) discussed the experience of a honeymoon period or brief period of increased engagement in condomless sex with partners after first initiating PrEP. As one participant put it, "I'd say when I first started PrEP, it felt like a free for all" (Black, 35 years old). However, as the following quote illustrates, this was often halted by the experience of one or more STIs:

"When I first got on it, I was super horny to start having more bareback sex because it felt safer. And I did that for a while. Yeah, and that sort of like torpedoed my whole - I just wanted to have all the sex in the world. [And] I actually got sick. I got CMV - cytomegalovirus. It's related to mono, and is probably sexually transmitted. And I was having fever on and off for several months. Since thinking about that in combination with like getting sick [it], sort of ended my bareback bonanza." (White, 33 years old, 12 months on PrEP)

Adherence and Its Relationship to Substance Use

Impact of Substance Use

Among the 20% of participants who reported using methamphetamine, all reported experiencing a significant disruption in routine that negatively impacted their ability to take PrEP:

"You know, it was three weeks ago - or four - it was a number of weeks ago, on a weekend. And I was on a drug-fueled sex binge. Yeah. And day and night meant nothing. I wasn't on my phone. I was on my phone for other reasons. And that didn't matter. And the three reminders - I have one at 5:00, 6:00, and 7:00. Plus, it's on my Google calendar. So, I get three reminders. And so, I forgot two days in a row. And I think, even when I had done that before, I had not been so irresponsible." (White, 32 years old, 18 months on PrEP)

"I would say I have missed multiple days after using [methamphetamine] because I am just knocked out from tweaking." (White, 22 years old, 12 months on PrEP)

Another participant discussed how he lost a 3-month supply of PrEP when he was high on methamphetamine:

"It was a very bad, very, very bad scene. Like, I should not have been there. It was not good people, no good things going on. And at the time I had - this is how like messed up I was on meth. I had just come to Kaiser to get my PrEP. And I think it was my first three months' supply. And I had actually left it there because I was so messed up and I remember I brought a bag full of thousands of dollars' worth of pills. It was like, almost $2,900. Anyway, so I left my stuff there. And it was bad." (Latino, 32 years old, 18 months on PrEP)

Alcohol use was another substance reported to have a negative impact on participants' routine and subsequently their ability to take PrEP. Thirty percent of participants reported that alcohol had contributed to one or more missed doses of PrEP:

"Yeah, so it's not like I got drunk and I forgot. It's like I got drunk and I got out of my routine, and I did something I didn't expect to do, and then I didn't have the access to it that I might have when I was at home." (Latino, 28 years old, 24 months on PrEP)

"If I were day drinking, that would be, I think, another factor in me forgetting to take the medication. And then, even then, too, if I went out and I was drinking, and then I had taken drugs, and then the next day, on Sunday, I'm completely out of it, not in a good state of mind. Also, I would forget on Sunday, even if I were home all day on Sunday, I would not remember to take my medication." (API, 28 years old, 12 months on PrEP)

The following participant discussed how poly-substance use contributed to multiple days in a row of missed PrEP doses:

"Midnight, you know, and I get home and I might be drunk and high or whatever, and then fall asleep. And I would frequently - I mean I forget to set my alarm most times when I go out - I forgot - I forgot to take it, like I remember I forgot to take it once, and then the next day, and there was like three days, and I was like okay, I've got to do something different." (White, 31 years old, 6 months on PrEP)

Factors that Facilitate Adherence

Many participants reported that they came up with their own ways for remembering to take their PrEP medication each day. For example, 18 participants (60.0%) reported the use of memory techniques or devices to support PrEP adherence.

"I have a little week of pills that, you know, whenever it's empty, I refill it, and I keep it on my kitchen counter. And it's kind of, like, right there. I can't escape it." (White, 32 years old, 18 months on PrEP)

"Yeah. It's an alarm on my phone and it just pops up, it has a picture of a pill, it says take your damn pill, and I take it." (White, 24 years old, 8 months on PrEP)

A few participants (6.7%) discussed borrowing pills from their friends, roommates, and/or partners when they did not have access to their own:

"Because - well, for me it's easy too because most of my friends are on it. So, like, say I am at one of their - I'm at, like, someone's place and be like, oh, let me take one of yours and I'll swap you one of mine later." (API, 25 years old, 8 months on PrEP)

Psychosocial Impact of Taking PrEP

Enhanced Sexual Well-being

Twenty-eight participants (93%) reported a sense of relief and reduction in anxiety around having sex. Participants talked about being able to relax and not having to worry about getting HIV from either their casual or main partners:

"It's significantly changed my sex life because again, like I wasn't riddled with anxiety. I didn't have to look at a sexual partner [thinking] you could be the person that devastates my life. I never have to do that again. I never have to look my boyfriend in the face and freak out because the condom broke." (White, 26 years old, 9 months on PrEP)

Two participants (6.7%) discussed being in primary relationships with HIV-positive partners and having a reduction in fear of contracting HIV from their partners after starting PrEP. This participant felt that taking PrEP provided him with additional security should his virally suppressed partner forget to take some of his medication:

"It's been really great actually. I definitely have a lot less anxiety over sex. I guess I should say that I'm in a primary relationship, and I haven't had sex outside of it. But, my partner's HIV positive, and he takes his meds, but it's not something that I talk to him [about] on a regular basis. So, it's more of, I think

PrEP's giving me an added sense of security for myself." (Black, 32 years old, 8 months on PrEP)

Another participant discussed how he previously felt significant anxiety every time he had sex and got tested for HIV after all new sexual encounters. He reported feeling that with both PrEP and condoms, he felt more confident in his ability to stay healthy:

"I think prior to being on it I'd regularly – unless I was in a committed relationship – if I had hooked up with someone it was like, okay, no, immediately every single time you hook up with someone you come in and you get tested. And now, you know, between PrEP and condoms I feel much more comfortable in just trusting that I'm still healthy and not having – it's not like I had huge panic attacks or anything like that, but there was a little anxiety around it, you know?" (White, 25 years old, 6 months on PrEP)

The majority of participants (63.3%) also reported increased comfort and confidence as they felt more educated and empowered by the sense that they were proactively taking care of their sexual health. This lead to increased comfort in connecting with other men:

"I would say I feel like I know more and I'm taking steps to prevent contracting HIV. So, I feel a little bit more comfortable being sexual, and I feel like [PrEP] made me a little bit more comfortable connecting with guys physically." (Black, 33 years old, 7 months on PrEP)

Several participants (30.0%) also reported finding confidence in knowing that in addition to taking care of their own sexual health, they were also able to better protect their partners:

"I think it's made me feel more confident in my ability to take care of my own sexual health, to protect people that I'm with." (Latino, 29 years old, 6 months on PrEP)

Increased Openness to HIV-Positive Partners

Eighteen participants (60%) reported increased comfort and openness to dating and having sexual relationships with HIV-positive partners for the first time as a result of taking PrEP:

"For the first time, I considered dating somebody who had a different status. I just thought that any other status but negative was not okay for me to get close to or have sexual experiences with, because it was just me protecting my own health and I just didn't want to think about it or have that be an extra stress in my life, so I guess I - I would like to say that I wasn't too judgmental about different statuses and stuff, but I definitely became a lot more open-minded and, yeah, I met a really great guy that has a great heart." (White, 22 years old, 11 months on PrEP)

Experience with and Ability to Combat PrEP-Related Stigma

Only three participants (10.0%) discussed direct experience of being stigmatized by other men for taking PrEP, with some men reporting that partners assumed they were sexually promiscuous.

They'd say, "Wow, you're on PrEP." "You're being slutty." "Oh, you're having a lot of unprotected sex, aren't you? I can't imagine that." "Unprotected sex is the worst thing that anyone can do." (API, 28 years old, 12 months on PrEP)

One participant opted to not include being on PrEP in online social networking profiles after witnessing stigma online towards those who take PrEP:

"I think it really is people – I mean, so, like, falling into, like, Scruff or Grindr, the apps. When people post that they're on PrEP and they put that out there, I think there's this really large stigma happening where people instantly associate, oh, you'll probably do bareback sex." (White, 22 years old, 15 months on PrEP)

Although the majority of participants reported that they did not experience PrEP-related stigma directly, several participants (26.7%) discussed feeling educated, empowered, and emboldened to take a stand against stigma and stereotypes around taking PrEP. An example of one participant's ability to push back against the stigma that he experienced directly follows:

"But if you want to cast aspersions onto me, I have no problem knocking those down. And that's one of those things where like information is power. I can sit back and just tell you fact. And you can throw whatever stigma you want, and be whatever attitude you have, that's you taking in information. I'm just going to give you information." (White, 26 years old, 9 months on PrEP)

Several participants (23.3%) also described feeling supported by family and/or friends. One participant described a particularly enthusiastic response from his mother and other adults in her generation when he told them he was taking PrEP:

"I find that people who are older, maybe a generation ahead of me, the gays know about it but the straight people who are a little older may not be familiar and they think it's really cool. My parents were alive in the 80's and saw everything go down, and, it's just such a game changer. Everyone's been super supportive. My mom was super supportive, everyone thought it was really cool and very impressive." (White, 25 years old, 6 months on PrEP)

Discussion

This study examined changes in risk perception and sexual behavior, adherence and its relationship to substance use, and the psychosocial impact of taking PrEP among

substance-using MSM prescribed PrEP. Qualitative findings suggest an overall decrease in condom use, some evidence of partner sorting based on PrEP use, and a wide variety of attitudes and experiences related to non-HIV STIs. Findings also provide qualitative insights into some of the unique challenges in PrEP adherence for MSM who report recent hazardous drinking and/or methamphetamine use. Finally, findings also suggest that there are likely complex psychological and social changes that occur in the context of PrEP use that can help us to elucidate a more comprehensive view of risks to adherence and for potential non-HIV STIs and, at the same time, provide insights into potential avenues for ongoing risk reduction interventions for substance-using MSM. For example, many of the participants in the current study reported decreased levels of fear and anxiety around having sex in general and stated that they felt that PrEP provided an *added layer of protection* against HIV (Brooks et al. 2015; Perez-Figueroa et al. 2015). While this finding might suggest some men are more likely to engage in more frequent condomless anal sex, participants often reported feeling more empowered taking PrEP and felt as though they were proactively taking care of their sexual health—i.e., getting regular HIV and STI testing, rapidly treating any STIs, and notifying partners of possible STI exposure.

While participants reported empowerment, they also reported increased risk-taking behavior, indicating that HIV risk perception may have shifted somewhat for these men overall since taking PrEP. Consistent with previous studies, we found that sexual decision-making was highly complex among these men post PrEP (Carlo Hojilla et al. 2016; Pines et al. 2014), involving the integration of information about both the added benefits and remaining risks. For example, while the majority of men interviewed in this study reported using condoms less frequently overall, some reported continued use of condoms with unknown or new partners. Consistent with previous findings suggestive of "biomed-matching," other men reported PrEP sorting—i.e., that they were more likely to select partners or to engage in condomless sex with partners, who were also on PrEP (Newcomb et al. 2016). However, participants reported that these additional prevention methods were often superseded in situations where decision-making was further impaired by drugs such as methamphetamine and/or hazardous drinking.

Many participants reported a newfound openness to dating HIV-positive men; two men were in primary relationships with HIV-positive partners and others reported increased willingness to date someone who was HIV-positive since starting PrEP. These findings suggest that PrEP may help to attenuate HIV-related stigma among some HIV-negative MSM and further reduce social barriers based on HIV status among HIV-positive and HIV-negative MSM. Finally, while the majority of men reported some change in their sexual behavior, either in the serostatus of their partners or in their willingness to engage in condomless sex, there were other men who reported no change in their sexual behavior, but simply a reduction in the level of anxiety they experienced around their existing sexual behavior. This was consistent with prior work suggesting that the reduction in HIV risk perception contributed to feelings of increased confidence and comfort about having sex in general (Brooks et al. 2011; Grant and Koester 2016).

While experiences of stigma and discrimination around taking PrEP were reported by a minority of participants, many participants reported feeling well equipped to confront such biases head-on. Some participants even reported feeling empowered to advocate for PrEP and to dispel assumptions made about their sexual behavior when they were confronted with stigma and discrimination. Overall, the participants in this study reported far more experiences of support from family, friends, and partners than direct experiences of stigma and discrimination. It is important to note that this may, in part, reflect the culture of San Francisco, which has relatively high levels of PrEP awareness and uptake (Volk et al. 2015) and that the support levels in other regions of the country might be lower.

A positive side effect of interacting with PrEP providers on a more frequent basis and becoming more informed about PrEP and sexual health was that participants reported having increased awareness of other STIs. It should be noted that these interactions with providers took place in the context of an HIV specialty clinic, which is not provided in all locations. When it came to risk perception for other STIs, the responses exhibited a much greater level of variation, with some men reporting little to no concern regarding non-HIV STIs, and others reporting increased worry about contracting other STIs and potential increases in prevalence of other STIs in the community as a result of reduced condom use among PrEP users. While some men reported concerns about other STIs as a motivator for continued condom use, other men reported that they were less concerned about other *treatable* STIs. Finally, there were some participants who reported having returned to condom use after a brief honeymoon period of condomless sex were halted by one or more STIs. These responses speak to the high degree of individual variation in changes in both risk perception and behavior post PrEP.

A major focus of the interviews with these substance-using MSM was to determine the extent to which hazardous drinking (i.e., five or more drinks in a day) or the episodic use of other drugs impacted PrEP adherence. Consistent with studies examining antiretroviral adherence among substance-using HIV-positive MSM (Azar et al. 2010; Ellis et al. 2003; Moore et al. 2012; Reback et al. 2013), the use of alcohol and methamphetamine was reported to be associated with missed doses of PrEP. Further, the men who reported methamphetamine use reported forgetting to take PrEP for multiple days—often in the context of having sex with multiple partners, when therapeutically protective doses of PrEP are likely

to be most important. This finding highlights the need for ongoing research that focuses on the development of customizable risk reduction counseling and other behavioral interventions that focus on improving PrEP adherence among substance-using MSM, especially MSM using methamphetamines and/or alcohol. Such interventions might include discreet carry-cases or keychain cases for keeping PrEP pills handy when away from home, setting recurring phone reminders, and/or providing blue dot stickers to place on wallet, cigarette lighters, and/or cell phones to serve as memory aids during times of protracted substance use.

It is also important to consider the possible impact of methamphetamine, alcohol, and other substances on future dosing schedules that may evolve along with PrEP medications. For example, event-driven or on-demand PrEP dosing may be particularly challenging for persons using substances for protracted periods of time as they may have a higher likelihood of missing the most critical dosing periods—i.e., immediately prior to and in the days following sex (Molina et al. 2015). Conversely, long-acting injectable versions of PrEP may be particularly indicated for substance-using MSM as bimonthly or quarterly injections may be more feasible than taking daily pills (Landovitz et al. 2016). Future work should continue to elucidate the impact of episodic substance use on emerging delivery methods for PrEP.

It is noteworthy that although participants in this study reported that substances such as methamphetamine and hazardous drinking interfered with PrEP adherence, none reported dosing consistent with fewer than four doses per week, the number of doses needed to achieve high protection during anal sex (Anderson et al. 2012; Grant et al. 2014). This suggests that substance-using MSM are strong candidates for PrEP, and while providers should work with substance-using patients to develop customizable risk reduction interventions to maximize adherence, they should not hesitate to prescribe PrEP to this population that stands to benefit greatly.

Certain study limitations should be acknowledged. These findings were drawn from an exploratory qualitative interview study with a relatively small sample of substance-using MSM. Participants were recruited from a large integrated healthcare system and may not be representative of substance-using men recruited from other venues (e.g., community-based clinics, substance abuse treatment programs). The results may also be specific to the larger San Francisco community where PrEP awareness and use is relatively high compared with other regions. While many of these findings may not generalize to non-substance-using populations, they underscore the importance for ongoing work aimed at maximizing adherence for substance-using MSM, who comprise a key target group for PrEP-based HIV prevention (Centers for Disease Control and Prevention 2014).

In summary, this study examined the experiences of young MSM taking PrEP and factors associated with sexual risk behavior, substance use, and adherence. Overall, the participants' accounts of missed doses in relation to their drug or alcohol use highlight the importance of proactively developing methods to ensure adequate adherence, especially during periods of substance use and increased sexual risk-taking behavior. This qualitative study provides additional evidence that there are potential psychological and social benefits of taking PrEP (e.g., reduced anxiety around sex, reduced stigma towards HIV-positive MSM), in addition to a reduced risk of HIV infection.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they no conflicts of interest.

Funding The study received support with grant numbers P50DA009253, T32 DA007250, R03DA043402, U01AA021997, and K01AI122853.

Ethical Approval All study protocols and procedures involving human subjects were approved by the Institutional Review Boards of both the University of California, San Francisco and Kaiser Permanente Division of Research and were performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed Consent We obtained informed consent from all participants included in this study.

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