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MAJOR ARTICLE

Interest in Long-Acting Preexposure Prophylaxis (PrEP) Among Men at Risk for Human Immunodeficiency Virus Who Use Methamphetamine Participating in a Daily, Oral PrEP Adherence Trial in San Francisco, California

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Background. Methamphetamine use is associated with increased risk for human immunodeficiency virus (HIV) and suboptimal adherence to daily, oral preexposure prophylaxis (PrEP). Long-acting PrEP is a promising HIV prevention method for people who use methamphetamine.

Methods. We conducted interviews with participants of a daily, oral PrEP adherence trial at their final visit. Participants were assigned male at birth and reported past-month methamphetamine use and past-year condomless sex with a partner with HIV or unknown status. We conducted a thematic analysis of interview transcripts to assess experiences with daily, oral PrEP and interest in long-acting PrEP.

Results. Of 23 participants, median age was 42 (interquartile range, 33–48) years, all were cisgender men, most were White (73%), and approximately half had been homeless or lived in a shelter in the past year (52%). The most common daily, oral PrEP adherence challenges were forgetting to take the medication, followed by not having the medication available and competing priorities. Most participants (91%) were interested in long-acting PrEP. A plurality (43%) preferred injection as the modality, 39% preferred a long-acting pill, and 17% an implant. Most concerns about long-acting PrEP regarded the implant, including the length of time drug is in the body and the insertion/removal procedure; frequent clinic visits were another concern.

Conclusions. Most participants who used methamphetamine were interested in and described barriers to daily medications that could be mitigated by long-acting PrEP. Injections were the most preferred modality, although long-acting oral PrEP alleviated concerns for some. Future research should assess optimization of long-acting PrEP delivery to this at-risk population.

Clinical Trials Registration. NCT04523519.

Keywords. adherence; HIV prevention; long-acting preexposure prophylaxis; methamphetamine; preexposure prophylaxis.

Methamphetamine use is associated with increased risk of human immunodeficiency virus (HIV) acquisition [1–4]. Despite elevated risk, uptake of preexposure prophylaxis (PrEP) for HIV prevention has been slow among people who use drugs (PWUD) in the United States (US) [5–7]. In the 2018 National HIV Behavioral Surveillance (NHBS) survey among people who inject drugs (PWID) in 23 US cities, only 1.1% reported PrEP use in the past year [8]. In San Francisco, where 75% of those with a PrEP indication received PrEP in 2021 [9], only 1.5% of PWID participating in the 2022 NHBS survey reported past-year PrEP use [5]. Among PWUD who do initiate PrEP, methamphetamine use can be associated with suboptimal adherence [10, 11]. Methamphetamine use, especially binge use, can result in "losing days" whereby someone may not recognize the passage of days, complicating adherence to a daily medication [12]. People who use methamphetamine may also have nontraditional, varying schedules, like sleeping during the day and being awake at night, which can make it challenging to attend medical appointments or keep a daily routine, impeding effective daily PrEP use [13, 14].

Long-acting PrEP agents, which do not require daily medication adherence, may be a promising HIV prevention strategy for people who use methamphetamine [15, 16]. Currently, bimonthly injectable cabotegravir is the only long-acting PrEP product approved for use by the US Food and Drug Administration

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(FDA). Recently, biannual lenacapavir injections showed efficacy among men who have sex with men (MSM), gender-diverse individuals, and cisgender women, and continue to be investigated for efficacy in other populations at risk for HIV [17, 18]. Long-acting oral pills and subcutaneous implants are under preclinical development [19–21].

We sought to better understand interest in long-acting PrEP and modality preference among men who use methamphetamine who were participating in a daily, oral PrEP trial. Considering that participants had enrolled in a PrEP trial, we expected high interest in long-acting PrEP. All participants in the parent study used methamphetamine and the majority had experienced homelessness. Therefore, we explored interest in long-acting PrEP in the context of methamphetamine use and homelessness. We expected that the nontraditional schedule that can be associated with methamphetamine use may contribute to challenges taking daily, oral PrEP [12, 13] and therefore increase interest in long-acting PrEP. We also anticipated that participants experiencing homelessness, who may have limited transit [22] and experience other structural barriers impeding access to health services [23], may prefer long-acting PrEP since they would need to attend fewer clinical visits over time and would not need to access a pharmacy for medications.

METHODS

Study Sample

The parent study was a randomized controlled trial evaluating video directly observed therapy plus contingency management to support daily, oral PrEP adherence in San Francisco, California (the PRIME study). Eligible participants were HIV negative, 18–65 years old, assigned male at birth, proficient in English, and either interested in initiating PrEP or had initiated it within the past 6 months and reported suboptimal adherence. All participants reported methamphetamine use at least 4 of the past 30 days and had a positive urine drug screen for methamphetamine during screening. Participants also reported condomless anal or insertive vaginal/frontal sex in the past 12 months with a partner who had HIV or was of unknown status.

Eligible participants were enrolled and followed for 24 weeks with visits every 6 weeks. At enrollment, participants were randomized to video directly observed therapy plus contingency management with integrated next step counseling (iNSC) [24] compared to iNSC alone. At the final visit, a subset of participants was invited to participate in an interview about their experience taking daily, oral PrEP and interest and preferences for long-acting PrEP. We conducted interviews until we reached thematic saturation. We aimed to have diversity with respect to age, race/ethnicity, sexual orientation, PrEP adherence, and treatment assignment among interviewees. This study was approved by the University of California, San Francisco's Human Research Protection Program (#20-31575) and registered with ClinicalTrials.gov (NCT04523519).

Interview Procedures

Interviews were conducted in person or remotely by trained qualitative interviewers following a semi-structured interview guide. Participants provided verbal informed consent. We audio recorded interviews and transcribed them using an official transcription service (www.rev.com). All transcripts were reviewed for accuracy against the recording before being thematically coded.

Long-Acting PrEP Questions

We described different long-acting PrEP modalities, including bimonthly and biannual injections, an implant that could last up to 1 year, and a weekly or monthly pill as potential, future prevention options. Participants were then asked if they would be interested in long-acting PrEP if it was approved, if they would prefer long-acting PrEP to daily, oral PrEP, and which long-acting PrEP product they would prefer. Once bimonthly cabotegravir received FDA approval, we described its known efficacy.

Other Measures

At baseline in the parent study, participants were asked to complete a self-administered survey using REDCap [25, 26], which asked about demographic characteristics (age, birth sex, gender, race, ethnicity), history of homelessness, methamphetamine use (frequency, route of administration), and PrEP history. At follow-up visits, participants were asked to report their daily PrEP use using a timeline followback (TLFB) approach [27]. The TLFB asked if participants had used PrEP since their last visit and, for those who had, we reviewed a calendar with the participant and recorded which days the participant had used PrEP since their last visit. We used anchor dates (eg, birthdays, holidays) to help the participant remember their PrEP use over the recall period.

Analysis

The analytical team included 3 authors (V. M. M., E. P., X. LM), who analyzed the data using a thematic analysis framework [28]. We first familiarized ourselves with the data by reading initial transcripts. Then we met before coding to develop an a priori codebook of the major themes in the interview guide and those that arose from familiarizing themselves with the study data. We then coded 2 interviews together and refined the codebook based on those discussions. Each of the 21 remaining interviews was individually coded by 2 coders. Each pair of coders reviewed 7 of the same interviews. During coding, the team met weekly and updated the codebook to reflect emerging themes and code application [29]. We reviewed the transcripts coded earliest and applied any codes that emerged

during the coding process as appropriate. After coding, we reconciled any discrepancies between each pair of coders. The final coded transcripts were analyzed for salient and recurring themes regarding barriers using daily, oral PrEP and interest and preferences for long-acting PrEP products. We first searched for themes, then reviewed them, and finally defined and named them for the qualitative report. All analyses were done using ATLAS.ti (version 23).

RESULTS

Among 31 participants who completed a final visit in the parent study, we interviewed 23 between November 2021 and April 2024. Interviews were completed within 28 days of the final study visit. Ten participants (43%) were randomized to the intervention and 13 (57%) to counseling alone. The median age was 42 (interquartile range, 33–48) years, all participants were cisgender men, and most were White (73%) (Table 1). Approximately half had been homeless or lived in a shelter in the past year (52%). Of the 22 participants who provided data at baseline, all had used methamphetamine at least weekly in the past 3 months, with 14 (63%) using it every day and 14 (63%) injecting methamphetamine. Most reported hearing of PrEP before the study (14 [61%]), of whom few had reported taking it previously (3 [21%]). As selected, participants reported varying adherence levels. Two had discontinued PrEP during follow-up. Using TLFB data, over the past 30 days 1 had not taken any PrEP, 5 took it every day, and the remaining 15 took between 3 and 29 pills.

Table 1. Baseline Sociodemographic Characteristics and Preexposure Prophylaxis (PrEP) History of Men Who Use Methamphetamine Participating in a Daily, Oral PrEP Adherence Trial Who Completed an In-Depth Study Exit Interview (N = 23)

Characteristic	No.	(%)
Age y, median (IQR)	42	(34–49)
Gender		
Cisgender man	23	(100)
Transgender woman	0	(0)
Nonbinary	0	(0)
Race/ethnicity[a]		
Asian American	2	(8)
Black/African American	3	(12)
Native American/American Indian/Alaska Native	1	(4)
Native Hawaiian/Other Pacific Islander	0	(0)
White	19	(73)
Other	1	(4)
Ethnicity[b]		
Hispanic/Latine	2	(9)
Not Hispanic/Latine	20	(91)
Sexual orientation		
Gay	6	(26)
Straight/Heterosexual	6	(26)
Bisexual	6	(26)
Pansexual	1	(4)
Other	4	(17)
Highest level of education completed[b]		
High school/GED or less	11	(50)
Some college, associate's degree, or technical degree	10	(45)
College graduate or more schooling	1	(5)
Ever experienced homelessness or lived in a shelter		
Yes	22	(96)
No	1	(4)
Homeless or lived in a shelter in the past year		
Yes	12	(52)
No	11	(48)
Has health insurance		
Yes	19	(83)
No	4	(17)
Taken PrEP before study enrollment[b]		
Yes	3	(14)
No	17	(77)

Data are reported as No. (%) unless otherwise indicated. Abbreviations: GED, General Educational Development; IQR, interquartile range; PrEP, preexposure prophylaxis.

[a]All races are reported. Multiracial participants appear in >1 category.

[b]There is 1 missing value for ethnicity and 1 for the highest level of education completed. There are 3 missing values for PrEP use history.

Barriers to Daily, Oral PrEP

All participants identified at least 1 barrier to daily, oral PrEP adherence. The most common barrier was forgetting the medication, which was mentioned in 16 of the 23 interviews. Participants described their inconsistent schedules, including being up all night and sleeping in the day, as a reason why they would forget taking their daily, oral PrEP.

I: What made it harder for you to take PrEP during the study?

R: My room's messy and I misplaced the pills a couple of times for a couple of days at a time …. My schedule is really crazy. I'll be up all night and sleeping in the afternoon. It's just different all the time so it's hard to get a consistent cycle going on where you just, oh, I remember take this right before bed every night. I don't go to bed on purpose, it's by accident. It's some random time. (Cisgender man, 42 years old, White)

I: Was there anything that made it harder for you to take your PrEP?

R: There were a couple of days that I might've been using [methamphetamine] and then I crashed or something, and then I just sleep through a day and then I just forget. That was the main reason that I would forget. (Cisgender man, 33 years old, White)

Other barriers included not having the medication available and competing priorities, which were each discussed in 11 of the interviews, and side effects, which were mentioned by 8 participants. Barriers were similar across study groups. Participants

also described their experiences of homelessness and depression as reasons why they may miss taking their daily, oral PrEP.

I'm living day to day. It's kind of hard to remember to take PrEP …. Well, as far as me being homeless, I have a lot of other things to worry about that's more important that I prioritize over taking PrEP. (Cisgender man, 38 years old, Black/African American)

I would have days where life was getting in the way and I just couldn't function or I was having a bad day at work, things like that … I don't think a threat of death would've made me take the pill. (Cisgender man, 44 years old, White)

Interest in Long-Acting PrEP

Of the 23 individuals interviewed, 21 said they were interested in long-acting PrEP (91%). One participant who was not interested had experienced side effects with daily, oral PrEP and the other did not feel at risk for HIV anymore, so both were no longer interested in PrEP in general. The main reason participants were interested in long-acting PrEP was that it was easier to use than daily, oral PrEP because they would not need to remember to take a daily pill.

Because [long-acting PrEP] just makes everything that much easier. You don't have to take it every day. Just once, and then you don't have to worry about it. (Cisgender man, 44 years old, Asian American and White)

[Taking long-acting PrEP] would make it a lot easier to be on PrEP for me. To be home taking a pill everyday thing, I didn't really like it too much …. I wouldn't have to worry about taking a pill every day. It would be a lot less worry, I wouldn't worry too much about catching HIV or anything, because I would know I'm on, of course I was on PrEP. (Cisgender man, 39 years old, Black/African American)

I: Would you prefer [long-acting PrEP] over daily, oral PrEP?

R: Oh yeah, for sure …. Because I was forgetting to take the pills a lot … my day cycle is completely all over the place. Really hard to remember every day to take it. (Cisgender man, 42 years old, White)

PrEP Modality Preference

A plurality (43%) said injection was their preferred long-acting modality, 39% a long-acting pill, and 17% an implant. Interest was similar across study arms, although the long-acting pill was preferred by a larger proportion of the intervention group (60%) than the control group (23%). The most common themes that arose when participants were asked about their preferred long-acting PrEP modality were its duration of protection and the frequency of provider visits. The most common concerns regarded the implant. Participants also discussed their preferences regarding taking PrEP in their home (ie, a long-acting pill) or going to a clinic to receive long-acting PrEP.

Duration of Protection

The most common characteristic that participants referenced when asked about their preferred long-acting PrEP agent was duration of protection. Most participants preferred the agent that had the longest duration of protection, regardless of modality (ie, injection, pill, or implant).

Basically, the more frequently you had to take [a long-acting PrEP modality], it was lower on the list one-by-one. So, the one that you take once a year would be the top of the list, and then the second one would be like every couple months, then the third one. The less I have to take it, the higher it is [on my list]. Regardless of how it's taken, if it's a pill or an injection. (Cisgender man, 42 years old, White)

For some participants, however, longer duration made the modality less preferable because they worried about not being able to stop the medication if they experienced side effects or changed their mind.

[Of the long-acting PrEP products described], the injection every couple of months … I think it gives you more of an option of whether you want to continue to take it or not. Instead of the year one, the implant, you're just stuck with it for a year. You don't have really much of a choice. (Cisgender man, 39 years old, Black/African American)

What if I started having side effects to it or something? … Then you can't turn it off, right?… [I would prefer PrEP] that you could get off, if you had to, immediately, because of the health risk or something like that. (Cisgender man, 44 years old, Asian American and White)

Frequency of Provider Visits

Among those who described interest in longer-acting agents, this preference was offset by the possibility of needing to go to a provider more frequently among some participants.

The length of time that [the implant] lasts [is appealing to me]… [but] it really depends also if … Do I have to go in and see the doctor for checkups to see if the implant hasn't moved or something? … If I had to go to the doctor every once in a while, to get checked up, I probably would change my decision. (Cisgender man, 28 years old, White)

Preference for At-Home Versus Clinic Administration

Being able to take a long-acting PrEP product at home was appealing to some participants who preferred a long-acting pill to the other modalities. Participants described not needing to go to a clinic as a positive characteristic of a long-acting PrEP pill. Reasons for not wanting to go to the clinic included the time it would take and transportation. However, other participants preferred to go into a clinic to receive their PrEP medication because they thought it would help them remain adherent.

> *I: You would prefer to take a pill if it was a long-acting pill?*
>
> *R: Right, because you could take that at home. You don't have to take it at the clinic, or you don't even have to go into the clinic. Whereas they have an injectable, they're going to meet with you at a clinic, which making an appointment could be a pain, or just getting transportation or whatever.* (Cisgender man, 42 years old, White)

> *I prefer the shot …. Because I know if I got a doctor's appointment, he's expecting me to be there. I don't usually let people down with appointments and times, and that would be another way to make sure that I took it because I wouldn't want to waste my doctor's time by not showing up, so I would definitely be there to take the shot.* (Cisgender man, 45 years old, White)

Concerns About Implants

The modality that raised the most concern was the implant. Aside from the concerns about the duration of the medication, participants also had concerns about the insertion and removal procedures. One participant described a negative experience with an implant for opioid use disorder, which resulted in his preference for injectable PrEP.

> *I had an implant before of buprenorphine addiction medication. I had trouble adhering to taking it every day … I actually still have [the implant] in my arm because I didn't want to get it taken out because it was so uncomfortable, so I'll go with the [PrEP] injection.* (Cisgender man, 24 years old, White)

One participant brought up a salient concern regarding implants among people who use methamphetamine. They were concerned about the safety of PrEP implants in people who use methamphetamine since methamphetamine can be associated with skin picking, usually from formication.

> *I wouldn't want something implanted in me that's not supposed to be there. Yeah, I'm not so sure how that would work out with meth addicts either. That does not sound like a good idea. Well, a lot of them tend to pick at their skin already. I could see potential problems there.* (Cisgender man, 41 years old, White)

Injection Drug Use Experience

While we did not explicitly ask participants how their route of methamphetamine use may impact their opinions about long-acting PrEP, a couple of participants discussed how experience injecting drugs impacted their preference. For 1 participant, it made the injection less appealing and for the other it made it more appealing.

> *[I would prefer a weekly pill over an injection] because I've been an IV user for over 35 years, and I am trying to get away from that.* (Cisgender man, 48 years old, Native American and Central American)

> *I: Why are you interested in the injection specifically?*
>
> *R: Because I'm already used to the point. I'm already used to injecting some drugs. So, once you do, because I've been doing it for 10 years, it's just a prick.* (Cisgender man, 37 years old, White)

DISCUSSION

In a sample of people assigned male at birth who use methamphetamine and were enrolled in a daily, oral PrEP adherence trial, the vast majority were interested in long-acting PrEP (91%). The most common characteristic of long-acting PrEP that appealed to participants was not needing to remember to take a daily pill. In a national sample of MSM using daily, oral PrEP, using illicit drugs in the past year and taking 15 or fewer PrEP doses in the past 30 days were both associated with being willing to switch to long-acting PrEP [30]. Long-acting PrEP may be particularly appealing to PWUD, especially in the context of suboptimal adherence.

There was heterogeneity in modality preference, with injection preferred. Preference was mostly driven by duration of protection and frequency of provider visits. Longer-acting products and ones that required fewer provider visits were more appealing. A systematic review of 62 studies of perspectives on long-acting PrEP also found a high level of interest in long-acting PrEP, preference heterogeneity, and interest in products that last longer [31]. A US national study of >1000 MSM found that 10% fewer participants found long-acting PrEP acceptable when the frequency of injections changed from every 3 months to monthly [32]. Fewer and shorter provider visits have also been reported as a driver of modality preference in other US PrEP studies [33, 34]. While a plurality of participants in this study preferred injectable PrEP (43%), the proportion that preferred a long-acting pill (39%) was similar. Lower interest in a long-acting pill in the present study could reflect the lack of an approved and available long-acting oral PrEP product. If a

long-acting oral PrEP agent becomes available, it may be an optimal prevention strategy for people at risk for HIV who use methamphetamine since it would have long duration and require fewer clinic visits than other PrEP modalities.

While more participants were interested in longer duration products, some found longer duration to be a concern, especially with regards to an implant that could last up to 1 year. Other studies have reported a higher level of interest in implantable PrEP than we saw in our sample [35, 36]. People who use methamphetamine may be particularly hesitant to use a PrEP implant because of experiences of paranoia [37] or the potential of skin picking, typically resulting from formication [38]. Participants in this study were concerned about not being able to stop PrEP if they experienced side effects or changed their mind, as well as the insertion and removal procedures of the implant. While interest in the implant has been higher in other settings, similar concerns regarding lack of control and the insertion and removal procedure have also been reported [33, 39].

More than half of the sample had experienced homelessness in the past year, and homelessness was described as a barrier to adherence. The instability of homelessness and difficulty retaining medications has been shown to be a barrier to daily, oral PrEP adherence in other settings [40–42]. Long-acting PrEP may be particularly important for PrEP adherence among people who use methamphetamine who experience homelessness. Considering the challenges people who experience homelessness may have attending appointments due to experiences of stigma, competing priorities, limited transit, and unstable schedules [13, 14, 43–45], long-acting PrEP programs that reach people who experience homelessness should pair the medication injections with appropriate supportive PrEP navigation services for visit adherence [46, 47].

This study has limitations. We interviewed a small sample of men who use methamphetamine who had enrolled in a daily, oral PrEP trial. Consistent with our hypothesis, interest in long-acting PrEP was high. However, interest may be lower in settings of men who use methamphetamine at risk for HIV who are not already engaged in PrEP programs. We also only enrolled participants in 1 US city, where PrEP uptake among PWUD has been slow. In other environments where PrEP uptake has been more successful among PWUD, findings may be different. All participants were cisgender men, and most were White. Our results may not be generalizable to other settings and populations. While all but 1 interview was done after the FDA approval of bimonthly cabotegravir injections for PrEP, the other long-acting agents were still under research and not approved for use. Interest in these modalities may be different in a setting of known efficacy and FDA approval. In addition, we did not explore all potential characteristics of PrEP agents that are under development (eg, a biodegradable implant), which could impact preferences.

We found a high level of interest in long-acting PrEP in a cohort of men taking daily, oral PrEP who use methamphetamine. Participants described barriers to daily, oral PrEP adherence that could be mitigated by long-acting PrEP. Providing long-acting PrEP to people who use methamphetamine at risk for HIV, especially those with suboptimal daily, oral PrEP adherence or housing instability, should be a priority. We found varying levels of interest in different long-acting PrEP modalities. Some of these preferences may be associated with drug use (eg, injection, experiencing hallucinations). As more long-acting PrEP options become available, providers should assess how methamphetamine use may impact PrEP preferences to best tailor long-acting PrEP delivery and reduce any chance of harm. It is evident that people who use methamphetamine have varying preferences, and a broad array of choices will be key to effectively reduce HIV risk with long-acting PrEP among this population at elevated risk.

Notes

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