AIDS PATIENT CARE and STDs
Volume 36, Number 7, 2022

DOI: 10.1089/apc.2022.0068

Open camera or QR reader and scan code to access this article and other resources online.

Long-Acting Injectable Human Immunodeficiency Virus Pre-Exposure Prophylaxis Preferred Over Other Modalities Among People Who Inject Drugs: Findings from a Qualitative Study in California

Angela R. Bazzi, PhD, MPH,[1,2] Chad J. Valasek, PhD,[1] Samantha A. Streuli, PhD,[1] Carlos F. Vera,[3] Alicia Harvey-Vera, PhD,[3] Morgan M. Philbin, PhD,[4] Katie B. Biello, PhD, MPH,[5] Alexis M. Roth, PhD, MPH,[6] Steffanie A. Strathdee, PhD,[3] and Heather A. Pines, PhD[1,7]

Abstract

People who inject drugs (PWID) have extraordinarily low uptake of human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP) despite high levels of need. Long-acting PrEP modalities hold promise for HIV prevention among PWID, but product preferences remain poorly understood. From September to November 2021, we conducted qualitative interviews with 28 HIV-negative, adult (≥18 years) PWID in San Diego County, CA, to explore their perspectives on daily oral PrEP pills and long-acting PrEP modalities (i.e., injections, implants, intravaginal rings, and broadly neutralizing antibodies), which we explained using standard scripts. Thematic analysis identified variations in PrEP modality interest and acceptability. We identified three key factors across the 28 interviews that appeared to influence PrEP modality preferences: perceived convenience of use, invasiveness, and familiarity (based on past experience). Overall, most participants preferred injectable PrEP over other modalities because they viewed injectable medications as convenient, noninvasive, and familiar. While injectable PrEP was recently approved for use in the United States and was most the acceptable PrEP modality in this sample, our findings suggest that intervention and implementation research is urgently needed to improve our understanding of strategies that could support access, uptake, and sustained adherence to longer-acting PrEP for PWID.

Keywords: pre-exposure prophylaxis, substance use, long-acting HIV prevention and treatment, intravenous, HIV prevention, cabotegravir, acceptability

Introduction

Human immunodeficiency virus (HIV) outbreaks among people who inject drugs (PWID), both domestically and internationally, illustrate how the ongoing opioid and polysubstance use epidemics are threatening decades of HIV prevention progress.[1–8] For the first time in decades, HIV incidence is increasing among PWID in the United States;[9] 7–10% of new HIV infections annually in the United States are attributed to injection drug use.[10,11] This increasing HIV transmission is due to sexual and injection-related behavioral risk factors,[10] which frequently co-occur in this population.[12] It is also due to drug supplies containing illicitly manufactured fentanyl,[13,14] which is associated with

[1]Herbert Wertheim School of Public Health, University of California, San Diego, La Jolla, California, USA.
[2]Department of Community Health Sciences, Boston University School of Public Health, Boston, Massachusetts, USA.
[3]Department of Medicine, School of Medicine, University of California, San Diego, La Jolla, California, USA.
[4]Department of Sociomedical Sciences, Mailman School of Public Health, Columbia University, New York, New York, USA.
[5]Departments of Behavioral & Social Sciences and Epidemiology, Brown University School of Public Health, Providence, Rhode Island, USA.
[6]Department of Community Health and Prevention, Drexel University School of Public Health, Philadelphia, Pennsylvania, USA.
[7]Division of Epidemiology and Biostatistics, School of Public Health, San Diego State University, San Diego, California, USA.

increased injection frequency and receptive syringe sharing.[15,16] Furthermore, the rising prevalence of psychostimulant use among PWID, which has been associated with sexual exposures, may be further exacerbating HIV transmission.[1,2]

San Diego County (SDC) is an Ending the HIV Epidemic (EHE) priority jurisdiction.[17] SDC has prevalent methamphetamine use[18] and, in recent years, has a rising proportion of new HIV diagnoses among PWID.[19] In fact, mirroring national trends, 5.2% of new HIV diagnoses in SDC from 2016 to 2020 were attributed to injection drug use,[20] up 30% from 3.9% from 2012 to 2016.[19] Furthermore, phylogenetic analyses of HIV-1 *pol* sequences from people living with HIV in SDC and Tijuana, Mexico—where HIV incidence is higher among PWID than in SDC—provide evidence of bidirectional cross-border transmission (i.e., linked HIV epidemics) and bridging between risk groups [e.g., PWID and men who have sex with men (MSM)] in the SDC-Tijuana border region.[21–24]

While the provision of sterile syringes, medications for opioid use disorder, behavioral interventions, and HIV testing services all help prevent HIV transmission among PWID,[25–27] access to these essential services remains limited in many regions and may have been further restricted during the COVID-19 pandemic.[8,28,29]

Antiretroviral pre-exposure prophylaxis (PrEP) as daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) has been available for adults in the United States since 2012, and for adolescents since 2018, and is effective and recommended for HIV prevention among at-risk PWID.[30,31] Despite the high proportions of PWID who have clinical indications for PrEP (e.g., 92% in one study),[12,32] awareness of PrEP is low (18.6% of PWID in SDC in 2018; national range, 6–54%) and very few have ever accessed it (only 0.4% of PWID in SDC; national range, 0–4%).[9] Low PrEP utilization in this and other at-risk populations has been attributed to multilevel barriers, including low PrEP knowledge, concerns over side-effects, insurance problems, limited health care engagement, and stigma.[33–40]

Furthermore, studies with providers have suggested less willingness to prescribe PrEP to PWID than to other populations, which may relate to assumptions about challenges with daily adherence.[41–44] Recent advances in biomedical HIV prevention, including long-acting PrEP modalities, could thus support PWID in effectively using PrEP.[45–47]

These advances include injectable cabotegravir administered every 8 weeks, which was superior to TDF/FTC in cisgender MSM and transgender and cisgender women in clinical trials.[48,49] Although PWID were excluded from efficacy trials of cabotegravir for PrEP,[50] nonhuman primate data suggest that injectable cabotegravir protects against intravenous challenge analogous to injection drug use.[51] Additional long-acting PrEP modalities at various stages in the development pipeline include monthly dapivirine vaginal rings,[52,53] injectable PrEP at 6-month intervals, annual subdermal implants,[54] and broadly neutralizing antibodies (bnAbs).[55] Injectable cabotegravir was approved by the US Food and Drug Administration in December, 2021 and the dapivirine vaginal rings received approval from the European Medicines Agency in July, 2020.[56–58]

Given these additional options, an improved understanding of preferences for various PrEP modalities among PWID could help inform interventions to increase PrEP utilization in this marginalized population and carry broader implications for EHE among PWID in the United States and beyond.

Methods

Study design and sample

We conducted a qualitative study with SDC-based participants in the ongoing, binational ''La Frontera'' cohort study of HIV, hepatitis C virus (HCV), SARS-CoV-2, and overdose outcomes among PWID in the SDC-Tijuana border region. As previously described,[59] La Frontera recruited PWID using street outreach between October 2020 and June 2021 and administered baseline behavioral assessments using computer-assisted personal interviewing.[60] Eligibility criteria included living in the SDC-Tijuana border region, being ≥18 years old and reporting past-month injection drug use. For this qualitative study, we drew from La Frontera baseline data to purposively sample sociodemographically diverse participants residing in SDC who were HIV-negative, but at risk for HIV (based on self-reported sexual and injection behaviors).[61,62]

La Frontera staff approached participants during routine street-based outreach encounters to briefly explain the qualitative study and connect interested participants to our qualitative interviewers. We obtained verbal informed consent and provided $20 cash compensation for participation. Institutional Review Boards of the University of California, San Diego, and Xochicalco University reviewed and approved all study protocols using the expedited review process.

Data collection

From September to November 2021, a lead qualitative investigator and two trained interviewers conducted in-person or video conference-based interviews in English or Spanish, depending on participants' preferences. Immediately before qualitative interviews, we administered brief surveys assessing sociodemographics (Table 1). Next, we used a semi-structured interview guide informed by our past research and relevant literature.[33,63–67] Open-ended questions and specific probes explored perspectives on daily oral PrEP pills and long-acting PrEP injections, implants, intravaginal rings, and bnAbs. Before open-ended questions, we explained modalities using standard scripts and infographics developed based on available data for each modality.[64,67] Interviewers recorded detailed notes using a structured template with fields for key topics from the interview guide and emergent findings.

All interviews were audio recorded and professionally transcribed (and translated into English, as needed, by a trained, bilingual member of the study team). We reviewed transcripts for quality and to identify potential themes, which we discussed in weekly meetings. After determining through these meetings that additional data collection would be unlikely to yield new findings regarding product preferences, we ceased recruitment and interviewing.[68]

Data analysis

Following a collaborative codebook development process, three interviewers independently reviewed interviewer notes and selected transcripts to develop potential codes and definitions, which were compiled into a preliminary codebook.[69,70] Next, we independently tested preliminary codes on another selection of transcripts, meeting to review

Table 1. Characteristics of Interview Participants ($N=28$)

Variable	n *(%)*
Age in years, mean (standard deviation)	42 (12.4)
Hispanic or Latino	20 (71.4)
Gender identity	
Cisgender man	19 (67.9)
Cisgender woman	9 (32.1)
Sexual orientation	
Heterosexual/straight	25 (89.3)
Bisexual	3 (10.71)
Years of education, mean (standard deviation)	12 (3.2)
Currently unhoused	17 (60.7)
Perceived risk of HIV	
More likely to get HIV than other PWID in this city	5 (17.9)
HIV testing history	
Ever tested	23 (82.1)
Tested in the past year	8 (28.6)
Tested in the past 3 months	1 (3.6)
Sexual health and behaviors (past 6 months)	
Any sexual intercourse	17 (60.7)
Any regular partners	9 (32.1)
Never used condom with regular partner	4 (44.4)
No condom used at last sex with regular partner	5 (55.5)
Any casual partners	11 (39.3)
No condom used at last sex with casual partner	7 (63.6)
Any sex work clients	2 (7.1)
Any partners living with HIV	17 (60.7)
Any alcohol use before or during sex	4 (14.3)
Any drug use before or during sex	17 (60.7)
Overdose history	
Ever	17 (60.7)
Past 6 months	8 (28.6)
Fentanyl use (past 6 months)	
Smoked, inhaled, snorted, or vaped fentanyl	10 (35.7)
Injected fentanyl by itself	5 (17.9)
Injection behaviors (past 6 months)	
Injected drugs multiple times per day	18 (64.3)
Used a syringe that you knew/suspected had been used by someone else	14 (50.0)
Divided up drugs with someone else using a syringe	14 (50.0)
Used a cooker, cotton, or water with someone or after someone else	15 (53.4)
Bought drugs that came in an already prepared syringe	6 (21.4)

HIV, human immunodeficiency virus; PWID, people who inject drugs.

code application and refine the codebook as needed. We repeated this process several times until reaching consensus on a final codebook. A lead analyst (C.J.V.) then applied codes to transcripts using NVivo (v12). Through weekly meetings, we discussed coding progress and potential themes. In-depth, thematic analysis for this article then involved synthesizing relevant codes (e.g., for HIV risk behaviors and perceptions, PrEP knowledge and interest, and each PrEP modality) to identify PrEP modality interest and key acceptability considerations. We selected representative quotes to illustrate key findings, presented with age and sex characteristics.

Results

Sample characteristics

Among 28 participants, the mean age was 42 years (standard deviation: 12.4 years); 19 (67.9%) identified as male [9 (32.1%) as female], and 20 (71.4%) identified as ''Hispanic or Latino'' (Table 1). Seventeen (61%) were currently unhoused. In the past 6 months, most had injected drugs multiple times per day ($n=18$; 64.3%) and half had used syringes ($n=14$; 50%) or other injection preparation equipment ($n=15$; 53.4%) that had already been used by someone else. Half of participants reporting injecting drugs in the past 6 months using syringes from a syringe exchange program. Seventeen participants (60.7%) reported having any sexual intercourse in the past 6 months, with 32.1% and 39.3% reporting sex with regular and casual sex partners, respectively.

Five (55.5%) of those with regular partners did not use condoms at last sex with those partners, while 7 (63.6%) of those with casual partners did not use condoms at last sex with those partners. Seventeen (60.7%) reported using drugs before or during sex in the past 6 months. Eight (28.6%) had been tested for HIV in the past year, and only one (3.6%) had been tested for HIV in the past 3 months. None had ever been prescribed PrEP.

HIV risk perceptions and PrEP knowledge before the study

Most participants in our sample were ''not too worried'' about acquiring HIV because they were not sexually active, were in monogamous relationship, did not share syringes, or only gave syringes away rather than accepting used syringes from others. Several explained that their HIV risk had decreased over time, with one transitioning out of injection drug use, and another explaining, ''I'm not looking for different girls every night anymore.'' However, a few participants acknowledged that ''anything can happen'' when experiencing drug-related withdrawal or obtaining syringes from other people who ''say they're new [syringes], but you never know.''

A couple of participants used discarded syringes found on the street, which was not concerning for one 31-year-old man who was ''pretty sure HIV dies real quick.'' Only a few participants perceived themselves to be at high HIV risk, which they attributed to sharing syringes or other injection equipment (e.g., cookers, rinse water), spending time in environments they perceived to be high risk (e.g., ''there are many sexual diseases in Tijuana''), or engaging in condomless sex with ''dates'' for higher prices. One 31-year-old woman who shared syringes and engaged in sex work said, ''The fact is, I'm risking a lot here. I know that. And I have a feeling everybody knows someone who's infected with HIV.''

Although PrEP has been approved for nearly a decade, most participants had little to no accurate PrEP knowledge before their interviews, with several expressing surprise or concern upon learning that an HIV prevention medication

existed (e.g., ''I'm surprised I didn't know about that''; ''Jesus, that's the first I've heard about it''). Several others conflated PrEP with postexposure prophylaxis (e.g., ''the pill taken for 30 days or something''), newer HIV treatment medications, or medications for opioid use disorder (e.g., ''the injection for opiate addicts''). Several had vague awareness of PrEP from advertisements, but could not elaborate on what it was (e.g., ''I just heard that there is a new medication, Truvada'').

Several others had heard about PrEP from presentations in drug rehabilitation centers or conversations with friends, with one 46-year-old man, asking, ''Is that the one for prostitutes?'' The only two participants with accurate knowledge about PrEP explained that it was ''so you don't catch AIDS if you're exposed to it,'' or ''if your partner has HIV.''

Acceptability of various PrEP modalities

When asked about various PrEP modalities, the following three considerations emerged as the primary drivers of indivdiuals' PrEP product preferences: (a) convenience of use (including relative ease of access), (b) invasiveness (i.e., perceived risk of bodily harm or side effects), and (c) familiarity (often based on past experiences with other medications). Of note, some participants rated multiple modalities equally without expressing a clear preference for one over another. A few participants were not interested in any form of PrEP due concerns about medication side effects, like one 35-year-old man who generally ''avoid[ed] the whole western medicine thing.'' Nevertheless, these three key considerations for PrEP product preferences are described in the context of each modality below.

Daily oral PrEP.

Most participants not only viewed daily oral PrEP as inconvenient due to the difficulty of daily medication adherence, but also viewed pills as noninvasive and highly familiar. For example, a participant who preferred daily oral PrEP over the other modalities explained, ''because you take it and it's out of the way, and you don't feel the prick of the needle; it's just easy and it don't hurt.'' A few participants saw daily oral PrEP pills as convenient based on their experience taking other daily medications (e.g., birth control pills) successfully. Participants suggested that convenience could be improved by making this modality highly accessible.

Options included providing refills *at least* ''once a month,'' and assistance with replacement prescriptions if belongings were lost or stolen or if individuals had to resort to selling their prescriptions. A couple of participants also suggested providing additional information about ingredients and function of the medication to alleviate potential concerns.

Long-acting injectable PrEP.

Participants viewed long-acting injectable PrEP as highly convenient, familiar, and generally noninvasive, making this modality the most acceptable overall. Many participants described it as highly convenient because it seemed ''quick'' and ''a lot easier'' than daily oral PrEP pills since it did not require adherence and lasted longer (e.g., ''you just get the shot and you're covered''). One 31-year-old woman explained her preference for injectable over daily oral PrEP, saying, ''To keep it real, with [my] addiction, I'm not responsible…I know I'm going to forget to take pills, so yeah, I'll go for the shot.'' Of note, to further increase convenience, several participants mentioned that they would be more inclined to use long-acting injectable PrEP if it could be offered within syringe service programs.

Participants also described injections as a familiar modality, including a 44-year-old man who had used other injectable medications (e.g., ''Since I'm always taking shots, I trust it…it seems comfortable; it's in my comfort zone''). Most participants also rated injectable PrEP as relatively noninvasive, particularly because it could be injected into muscle as opposed to veins, which several participants described as too damaged or difficult to find due to their injection drug use.

A minority of participants expressed concerns about the safety and tolerability of long-acting injectable PrEP. One 25-year-old woman who was more interested in injectable PrEP than the other modalities was still concerned about the possibility of ''something going wrong'' like having a ''bad reaction [to] a vaccine, your skin can get red or swollen, and it hurts.'' Based on her experience with long-acting contraception, a 40-year-old woman said, ''I feel like any side effects would probably be more severe. When I did birth control shots every 3 months, the side effects were pretty noticeable.''

Finally, a couple of participants' concerns appeared related to distrust of governmental and medical systems. For example, another 40-year-old woman explained, ''I always think the government is trying to inject us with something, so I'd rather just take the pills.'' Similarly, a 40-year-old man worried that injectable PrEP could be a covert way of administering COVID-19 vaccines, asking the interviewer, ''Okay, I'm just kind of exploring here, like, if it's a COVID vaccine?''

PrEP implants.

Most participants reacted negatively to the idea of PrEP implants due to unfamiliarity and perceived invasiveness. Many stated clearly and simply that they would not want PrEP implants, as one 57-year-old woman explained, ''I just don't want anything implanted in me.'' Another woman, aged 46 years, was also concerned that PrEP implants could be a covert means of implanting a governmental tracking chip, stating ''That's weird….what if they put a chip inside you at the same time?'' A minority of participants were not concerned about implants' invasiveness (e.g., ''I'm not worried about scars'') or viewed its potentially longer duration as more convenient than other modalities. For one 27-year-old man, the possibility that implants could be biodegradable increased his interest because, ''I wouldn't like [some]thing that has to be taken out of my arm later in the future, but the biodegradable thing sounds pretty neat.''

Broadly neutralizing antibodies.

Reactions to bnAbs were also largely negative, with most participants viewing the infusion process as inconvenient and invasive, especially when compared to injectable PrEP. As a 46-year-old man noted, ''I don't think I'd be interested in that at all…Just sitting, laying there, getting the drip…it's just not appealing.'' When asked how long they would be willing to wait during infusions, a couple of participants said several hours would be tolerable, while others stated that 1 h would be the longest acceptable duration.

Several participants worried about their venous access, with one 55-year-old man explaining, ''I don't have any veins, so they'd have a hard time even putting that on me, you know?'' The 40-year-old woman quoted above who worried about government involvement in injectable PrEP also asked, ''What if they try to sneak the [COVID] vaccine into the drip?'' In contrast, a couple of participants explained that bnAbs seemed slightly less invasive than implants and were more open to this modality based on their experience with other medication infusions (e.g., antibiotics, pain medications). This familiarity did not necessarily improve acceptability of bnAbs, however, as a 46-year-old woman who had participated in research studies involving infusions was still concerned about the invasiveness of this modality due to her lack of ''good veins.''

Intravaginal PrEP rings. Despite familiarity with intravaginal ring technologies for contraceptives, most female participants viewed this modality as inconvenient and invasive. As a 37-year-old woman stated, ''I just don't [use] anything like that. It's not for me, I just don't do that.'' Several participants were concerned about difficulty or discomfort inserting something intravaginally as well as what would happen during menstruation or sex while the ring is inserted. As one 46-year-old woman explained, ''When you have sex, you don't know if it's going to move around or stuff like that.''

While a couple of women said they would be more interested in this modality if it also contained medications to prevent pregnancy and sexually transmitted infections in addition to HIV, others wondered if intravaginal PrEP rings would be ineffective or less effective for PWID with injection-related HIV exposure. As one 31-year-old woman stated, ''Well, I inject drugs, so if I get HIV through that, [a vaginal ring] is not going to help.''

Discussion

In the context of increasing HIV transmission among PWID across the United States,[1–8] expanded access to evidence-based HIV prevention options is urgently needed. Understanding the acceptability of newer, long-acting PrEP modalities that reduce or eliminate the need for daily medication adherence is a first step to optimizing the public health benefits of PrEP among PWID,[45,46,71] a population underrepresented in biomedical HIV prevention research to date.[50] Through qualitative interviews with PWID in SDC, a jurisdiction where new HIV infections attributed to injection drug use increased 30% over the last decade,[19,20] we found that PrEP modality preferences depended on perceived product convenience, invasiveness, and familiarity.

While many participants were excited about the availability of the new HIV prevention options we described, they also expressed skepticism regarding some or all forms of PrEP. Our findings suggest that a range of PrEP options, accompanied by adequate product descriptions and education, will likely be needed to support HIV prevention efforts with this population.

Participants saw long-acting injectable PrEP as the most acceptable PrEP modality due to high perceived convenience, familiarity with long-acting injectable medications, and low perceived invasiveness. In a small number of previous studies, PWID also expressed interest in injectable PrEP, including in Cabell County, West Virginia, where 55.7% of PWID surveyed expressed interest in injectable PrEP (compared to 13.3% and 22.7% for bnAbs and implants, respectively).[72] A qualitative study with PWID in the US Northeast also identified acceptability of long-acting injectable PrEP relating to the reduced need to adhere to and safeguard medications.[63] While injectable PrEP indeed holds promise for overcoming these adherence challenges,[45,46] our current study highlights the importance of implementation considerations, as some participants commented on how delivery of injectable PrEP through particular venues (e.g., syringe service programs) could further increase access and convenience.

Furthermore, the lack of clinical trial data on safety and efficacy of cabotegravir for PrEP among PWID could leave many of patients' and providers' potential questions about safety, tolerability, side effects, and medication interactions (e.g., with direct acting antivirals for the treatment of HCV, methadone, or other drugs) unanswered.[50] Other studies found that some people with a history of injection drug use feared that injectable PrEP could serve as a trigger leading to a reoccurence of drug use.[71] Even if serious problems are unlikely to occur, additional data will likely be needed to guide patient-provider communication and decision-making around PrEP acceptance.[33]

While participants were less enthusiastic about the other HIV prevention modalities we described (implants, bnAbs, intravaginal rings), our findings underscore the need to understand and integrate PWID perspectives into product development and testing to increase acceptability and ultimate impact.[50] For example, while reactions to PrEP implants were largely negative, some participants were interested in their potentially longer durations of action and the possibility of biodegradable products, suggesting that effective messaging could support implant acceptability and uptake. Similarly, participants in an early trial of bnAbs had limited understandings of the modality, with some confusing bnAbs with HIV vaccines and cures,[73] underscoring the need for social and behavioral research on product education and messaging early in biomedical research agendas.

Finally, while intravaginal PrEP rings could hold promise for women who inject drugs and experience unique challenges to daily medication adherence,[74] the low acceptability of this modality among women in our study and others[72] echoes the need for early and sustained engagement of product end-users in the research and development process.

Taken together with existing literature, our findings underscore how intervention and implementation research is needed to better support access, uptake, and persistence among PWID. Importantly, as in most other US jurisdictions,[9] PrEP knowledge was very low in our sample of PWID in SDC, despite daily oral PrEP being approved for adult use nearly 10 years before our interviews.[30,31] While a minority of participants in our sample had some accurate knowledge of PrEP, very few could explain what it was for, and knowledge of nonoral PrEP modalities was nearly nonexistent. Similar to findings from other studies with PWID,[33] this low level of PrEP awareness may have reduced participants' enthusiasm for PrEP in general.

We also identified specific concerns in a minority of participants that may reflect distrust in governmental and

medical systems. This included concerns that various PrEP modalities could be a covert means of governmental surveillance (e.g., by implanting ''chips'') or involuntary vaccine administration. In a previous study of La Frontera participants, over half were unwilling or hesitant to receive COVID-19 vaccines, which was independently associated with endorsing COVID-19 disinformation and obtaining most of their COVID-19 information through social media.[75] These findings suggest that further research is needed to explore the role of governmental and medical distrust in influencing the uptake of various PrEP modalities and prevention interventions.

In addition to improving PrEP knowledge, intervention and implementation research will also be needed to determine the optimal strategies for delivering PrEP to PWID. Research has identified multilevel barriers to PrEP access for PWID in the United States, including stigma in health care settings, providers' unwillingness to prescribe PrEP to this population, homelessness, and other structural factors.[33–37,43,44,76–78] These systemic problems will be equally significant for long-acting forms of PrEP, for which uptake and retention challenges will be critical.[49,79] Our data suggest that community-based PrEP delivery (e.g., through syringe service programs, mobile health services, or pharmacies) could increase accessibility and possibly trust in these modalities.

Considering the skepticism of medical interventions and pharmaceuticals in this population, research to identify, develop, and test a variety of PrEP delivery strategies and venues should engage PWID to ensure that findings are relevant for individuals in this population who frequently experience homelessness, poverty, and other structural challenges, and competing health needs relating to other infectious diseases and drug-related overdose.[37,80]

Our study had several limitations. First, several of the PrEP modalities we explored are still undergoing product development and testing, and the perceived acceptability and feasibility of hypothetical products may differ from actual barriers and facilitators of FDA-approved, available HIV prevention tools. Although we selected PrEP modalities and descriptions based on prior research,[33,63–66] alternative descriptions could lead to different findings regarding product preferences.[64,73] In addition, our inductive themes (convenience, invasiveness, and familiarity) are not all-inclusive of all PWID concerns about PrEP modalities. These considerations sometimes overlapped, and other considerations could also exist that were not captured in our study, underscoring the need for improved engagement of PWID in biomedical HIV prevention research.

Third, the generalizability of our findings may be limited due to its geographic focus and qualitative approach. Since PWID are an underreached population within the biomedical HIV prevention literature,[50] additional studies with PWID in this and other US regions (and using different sampling recruitment strategies) are needed to confirm or expand upon the findings presented here.

These limitations aside, our study suggests that long-acting injectable PrEP was preferred in our sample over daily oral PrEP and other long-acting modalities. Based on the three key considerations we identified, we argue that PrEP development research should engage PWID from the beginning as potential end users to obtain feedback on product convenience, invasiveness, and familiarity. The limited number of PrEP trials and implementation studies that included PWID suggests that their needs differ from those of other, less socially or structurally marginalized populations. Attention to the unique concerns and questions is warranted, especially as HIV incidence in this group is increasing, forewarning of a possible resurgence of HIV in a population whose prevalence was previously stable for decades.

In addition, across these ''next generation'' PrEP modalities, market research will be needed to optimize the clarity and cultural appropriateness of product descriptions and messaging; this is true for PWID and other high-risk groups for whom preferences, priorities, and access may differ. Tailoring efforts could help increase potential end users' comprehension of and ability to select the ideal HIV prevention tools for their circumstances. Finally, research will be needed to improve PrEP persistence and retention in care, which will have a unique set of challenges based on the specific constraints of different modalities.

Authors' Contributions

Conceptualization, Methodology, Supervision, Funding Acquisition: A.R.B., S.A.S., and H.A.P.; Software, Validation, Data curation: C.J.V.; Formal analysis, Writing—Original draft: A.R.B., C.J.V., and S.A.S.; Investigation: A.R.B. and C.J.V.; Resources and Project administration: C.F.V., A.H.V., and S.A.S.; Writing—Review and Editing: C.F.V., A.H.V., M.P., K.B.B., A.M.R., S.A.S., and H.A.P.

Ethics Approval

The University of California, San Diego, and Xochicalco University Institutional Review Boards approved all study protocols.

Consent to Participate

We obtained verbal informed consent before initiating any study activities.

Availability of Data and Material

The data that support the findings of this study are not publicly available but may be available upon reasonable request to the corresponding author.

Code Availability

Coded data are available upon reasonable request.

Author Disclosure Statement

K.B.B. received unrestricted research grants from Merck. All other authors report no conflicts or competing interests to declare.

Funding Information

This work was supported by the San Diego Center for AIDS Research (National Institute of Allergy and Infectious Diseases, grant P30AI036214) with additional support from the National Institute on Drug Abuse (grants R01DA051849, R01DA049644-S1, R01DA049644-02S2, K01DA043412, 3K01DA043412-04S1, T32DA023356, and R34MH124552) and the California HIV/AIDS Research Program (CHRP, grant OS17-SD-001).

References

1. Alpren C, Dawson EL, John B, et al. Opioid use fueling HIV transmission in an urban setting: An outbreak of HIV infection among people who inject drugs-Massachusetts, 2015–2018. Am J Public Health 2020;110:37–44.
2. Cranston K, Alpren C, John B, et al. Notes from the field: HIV diagnoses among persons who inject drugs—Northeastern Massachusetts, 2015–2018. MMWR Morb Mortal Wkly Rep 2019;68:253.
3. McCarthy M. Indiana declares health emergency in response to HIV outbreak. BMJ 2015;350:h1708.
4. Conrad C, Bradley HM, Broz D, et al. Community outbreak of HIV infection linked to injection drug use of oxymorphone—Indiana, 2015. MMWR Morb Mortal Wkly Rep 2015;64:443–444.
5. Adams J. HIV Outbreak in Indiana. N Engl J Med 2015; 373:1379–1380.
6. Golden MR, Lechtenberg R, Glick SN, et al. Outbreak of human immunodeficiency virus infection among heterosexual persons who are living homeless and inject drugs—Seattle, Washington, 2018. MMWR Morb Mortal Wkly Rep 2019;68:344.
7. Evans ME, Labuda SM, Hogan V, et al. Notes from the field: HIV Infection investigation in a rural area—West Virginia, 2017. MMWR Morb Mortal Wkly Rep 2018;67: 257–258.
8. Hershow RB, Wilson S, Bonacci RA, et al. Notes from the field: HIV outbreak during the COVID-19 pandemic among persons who inject drugs—Kanawha County, West Virginia, 2019–2021. MMWR Morb Mortal Wkly Rep 2022;71: 66–68.
9. U.S. Centers for Disease Control and Prevention. HIV Infection Risk, Prevention, and Testing Behaviors among Persons Who Inject Drugs—National HIV Behavioral Surveillance: Injection Drug Use, 23 U.S. Cities, Atlanta, GA: Centers for Disease Control and Prevention, 2018. 2020.
10. Spiller MW, Broz D, Wejnert C, et al. HIV infection and HIV-associated behaviors among persons who inject drugs—20 cities, United States, 2012. MMWR Morb Mortal Wkly Rep 2015;64:270–275.
11. U.S. Centers for Disease Control and Prevention. Fact Sheet: HIV Injection and Drug Use. Atlanta, GA: Centers for Disease Control and Prevention, 2015.
12. Edeza A, Bazzi A, Salhaney P, et al. HIV pre-exposure prophylaxis for people who inject drugs: The context of co-occurring injection- and sexual-related HIV risk in the U.S. Northeast. Subst Use Misuse 2020;55:525–533.
13. Massachusetts Department of Public Health. Data Brief: Opioid-Related Overdose Deaths among Massachusetts Residents. Boston, MA: Massachusetts Department of Public Health, 2019.
14. Gladden RM, O'Donnell J, Mattson CL, Seth P. Changes in opioid-involved overdose deaths by opioid type and presence of benzodiazepines, cocaine, and methamphetamine—25 States, July–December 2017 to January–June 2018. MMWR Morb Mortal Wkly Rep 2019;68:737.
15. Lambdin BH, Bluthenthal RN, Zibbell JE, Wenger L, Simpson K, Kral AH. Associations between perceived illicit fentanyl use and infectious disease risks among people who inject drugs. Int J Drug Policy 2019;74:299–304.
16. Taylor JL, Walley AY, Bazzi AR. Stuck in the window with you: HIV exposure prophylaxis in the highest risk people who inject drugs. Subst Abus 2019;40:441–443.
17. Fauci AS, Redfield RR, Sigounas G, Weahkee MD, Giroir BP. Ending the HIV epidemic: A plan for the United States. JAMA 2019;321:844–845.
18. Halkitis PN, Mukherjee PP, Palamar JJ. Longitudinal modeling of methamphetamine use and sexual risk behaviors in gay and bisexual men. AIDS Behav 2009;13:783.
19. County of San Diego Health and Human Services Agency Epidemiology and Immunization Services Branch. HIV/AIDS Epidemiology Report-2016. San Diego: County of San Diego Health & Human Services Agency, Public Health Services; 2017.
20. Wooten S. HIV Disease in San Diego County, 2020. Presentation on behalf of the HIV Epidemiology Unit, County of San Diego Health and Human Services Agency Public Health Services. In: Paper Presented at: SD CFAR EHE Scientific Working Group Meeting 2021; Virtual.
21. Mehta SR, Wertheim JO, Brouwer KC, et al. HIV Transmission networks in the San Diego-Tijuana Border Region. EBioMedicine 2015;2:1456–1463.
22. Vrancken B, Mehta SR, Avila-Rios S, et al. Dynamics and dispersal of local human immunodeficiency virus epidemics within San Diego and across the San Diego-Tijuana Border. Clin Infect Dis 2021;73:e2018–e2025.
23. Pines HA, Mehta SR, Abramovitz D, et al. Dynamics of HIV transmission between high-risk populations in Tijuana. In: Paper Presented at: Conference on Retroviruses and Opportunistic Infections (CROI) 2021; virtual.
24. Horyniak D, Wagner KD, Armenta RF, Cuevas-Mota J, Hendrickson E, Garfein RS. Cross-border injection drug use and HIV and hepatitis C virus seropositivity among people who inject drugs in San Diego, California. Int J Drug Policy 2017;47:9–17.
25. Aspinall EJ, Nambiar D, Goldberg DJ, et al. Are needle and syringe programmes associated with a reduction in HIV transmission among people who inject drugs: A systematic review and meta-analysis. Int J Epidemiol 2013;43:235–248.
26. Bernard CL, Owens DK, Goldhaber-Fiebert JD, Brandeau ML. Estimation of the cost-effectiveness of HIV prevention portfolios for people who inject drugs in the United States: A model-based analysis. PLoS Med 2017;14:e1002312.
27. Metzger DS, Donnell D, Celentano DD, et al. Expanding substance use treatment options for HIV prevention with Buprenorphine-Naloxone: HIV Prevention Trials Network 058 (HPTN 058). J Acquir Immune Defic Syndr 2015;68:554.
28. Glick SN, Prohaska SM, LaKosky PA, Juarez AM, Corcorran MA, Des Jarlais DC. The impact of COVID-19 on syringe services programs in the United States. AIDS Behav 2020;24:2466–2468.
29. Taylor JL, Ruiz-Mercado G, Sperring H, Bazzi AR. A collision of crises: Addressing an HIV outbreak among people who inject drugs in the midst of COVID-19. J Subst Abuse Treat 2021;124:108280.
30. Choopanya K, Martin M, Suntharasamai P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): A randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2013;381:2083–2090.
31. Chou R, Evans C, Hoverman A, et al. Preexposure prophylaxis for the prevention of HIV infection: Evidence report and systematic review for the US Preventive Services Task Force. JAMA 2019;321:2214–2230.
32. Earlywine JJ, Bazzi AR, Biello KB, Klevens RM. High prevalence of indications for pre-exposure prophylaxis

among people who inject drugs in Boston, Massachusetts. Am J Prev Med 2021;60:369–378.
33. Bazzi AR, Biancarelli DL, Childs E, et al. Limited knowledge and mixed interest in pre-exposure prophylaxis for HIV prevention among people who inject drugs. AIDS Patient Care STDS 2018;32:529–537.
34. Biello KB, Bazzi AR, Mimiaga MJ, et al. Perspectives on HIV pre-exposure prophylaxis (PrEP) utilization and related intervention needs among people who inject drugs. Harm Reduct J 2018;15:55.
35. Bazzi AR, Drainoni ML, Biancarelli DL, et al. Systematic review of HIV treatment adherence research among people who inject drugs in the United States and Canada: Evidence to inform pre-exposure prophylaxis (PrEP) adherence interventions. BMC Public Health 2019;19:31.
36. Biancarelli DL, Biello KB, Childs E, et al. Strategies used by people who inject drugs to avoid stigma in healthcare settings. Drug Alcohol Depend 2019;198:80–86.
37. Motavalli D, Taylor JL, Childs E, et al. ''Health Is on the Back Burner:'' Multilevel barriers and facilitators to primary care among people who inject drugs. J Gen Intern Med 2021;36:129–137.
38. Kota KK, Mansergh G, Stephenson R, Hirshfield S, Sullivan P. Sociodemographic characteristics of HIV preexposure prophylaxis use and reasons for nonuse among gay, bisexual, and other men who have sex with men from three US Cities. AIDS Patient Care STDS 2021;35:158–166.
39. Leech AA, Biancarelli D, Aaron E, et al. HIV pre-exposure prophylaxis for conception among HIV serodiscordant couples in the United States: A cohort study. AIDS Patient Care STDS 2020;34:295–302.
40. Tao J, Montgomery MC, Williams R, et al. Loss to follow-up and re-engagement in HIV pre-exposure prophylaxis care in the United States, 2013–2019. AIDS Patient Care STDS 2021;35:271–277.
41. Calabrese SK, Kalwicz DA, Modrakovic D, et al. An experimental study of the effects of patient race, sexual orientation, and injection drug use on providers' PrEP-related clinical judgments. AIDS Behav 2022;26:1393–1421.
42. Pleuhs B, Mistler CB, Quinn KG, et al. Evidence of potential discriminatory HIV pre-exposure prophylaxis (PrEP) prescribing practices for people who inject drugs among a small percentage of providers in the U.S. J Prim Care Community Health 2022;13:21501319211063999.
43. Edelman EJ, Moore BA, Calabrese SK, et al. Primary care physicians' willingness to prescribe HIV pre-exposure prophylaxis for people who inject drugs. AIDS Behav 2017;21:1025–1033.
44. Karris MY, Beekmann SE, Mehta SR, Anderson CM, Polgreen PM. Are we prepped for preexposure prophylaxis (PrEP)? Provider opinions on the real-world use of PrEP in the United States and Canada. Clin Infect Dis 2014;58:704–712.
45. Coelho LE, Torres TS, Veloso VG, Landovitz RJ, Grinsztejn B. Pre-exposure prophylaxis 2.0: New drugs and technologies in the pipeline. Lancet HIV 2019;6:e788–e799.
46. Biello KB, Mimiaga MJ, Valente PK, Saxena N, Bazzi AR. The past, present, and future of PrEP implementation among people who use drugs. Curr HIV/AIDS Rep 2021;18:328–338.
47. Cambou MC, Landovitz RJ. Challenges and opportunities for preexposure prophylaxis. Top Antivir Med 2021;29:399–406.
48. Delany-Moretlwe S, Hughes JP, Bock P, et al. Cabotegravir for the prevention of HIV-1 in women: Results from HPTN 084, a phase 3, randomised clinical trial. Lancet 2022;399:1779–1789.
49. Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. N Engl J Med 2021;385:595–608.
50. Brody JK, Taylor J, Biello K, Bazzi AR. Towards equity for people who inject drugs in HIV prevention drug trials. Int J Drug Policy 2021;96:103284.
51. Andrews CD, Bernard LS, Poon AY, et al. Cabotegravir long acting injection protects macaques against intravenous challenge with SIVmac251. AIDS 2017;31:461–467.
52. Baeten JM, Palanee-Phillips T, Brown ER, et al. Use of a vaginal ring containing dapivirine for HIV-1 prevention in women. N Engl J Med 2016;375:2121–2132.
53. Nel A, van Niekerk N, Kapiga S, et al. Safety and efficacy of a dapivirine vaginal ring for HIV prevention in women. N Engl J Med 2016;375:2133–2143.
54. Matthews RP, Zang X, Barrett S, et al. Next-generation Islatravir implants projected to provide yearly HIV prophylaxis. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 2021. Available at: https://ww2.aievolution.com/cro2101/index.cfm?do=abs.viewAbs&abs=2598 (Last accessed May 28, 2021).
55. Wagh K, van Gils MJ, Gristick H, Schommers P. Editorial: Novel concepts in using broadly neutralizing antibodies for HIV-1 treatment and prevention. Front Immunol 2021;12:823576.
56. World Health Organization. European Medicines Agency (EMA) approval of the dapivirine ring for HIV prevention for women in high HIV burden settings. 2020. Available at: https://www.who.int/news/item/24-07-2020-european-medicines-agency-(ema)-approval-of-the-dapivirine-ring-for-hiv-prevention-for-women-in-high-hiv-burden-settings (Last accessed May 28, 2021).
57. European Medicines Agency. Vaginal ring to reduce the risk of HIV infection for women in non-EU countries with high disease burden. 2020. Available at: https://www.ema.europa.eu/en/news/vaginal-ring-reduce-risk-hiv-infection-women-non-eu-countries-high-disease-burden (Last accessed May 28, 2021).
58. World Health Organization. WHO recommends the dapivirine vaginal ring as a new choice for HIV prevention for women at substantial risk of HIV infection. 2021. Available at: https://www.who.int/news/item/26-01-2021-who-recommends-the-dapivirine-vaginal-ring-as-a-new-choice-for-hiv-prevention-for-women-at-substantial-risk-of-hiv-infection (Last accessed May 28, 2021).
59. Strathdee SA, Abramovitz D, Harvey-Vera A, et al. Prevalence and correlates of SARS-CoV-2 seropositivity among people who inject drugs in the San Diego-Tijuana border region. PLoS One 2021;16:e0260286.
60. Heckathorn DD, Semaan S, Broadhead RS, Hughes JJ. Extensions of respondent-driven sampling: A new approach to the study of injection drug users aged 18–25. AIDS Behav 2002;6:55–67.
61. Johnson JC. Selecting Ethnographic Informants. Newbury Park, CA: Sage Publications; 1990.
62. Patton MQ. Qualitative Research and Evaluation Methods, 3rd ed. Thousand Oaks, CA: Sage Publications; 2002.
63. Biello KB, Edeza A, Salhaney P, et al. A missing perspective: Injectable pre-exposure prophylaxis for people who inject drugs. AIDS Care 2019;31:1214–1220.

64. Biello KB, Valente PK, Lin WY, et al. PrEParing for NextGen: Cognitive interviews to improve next generation PrEP modality descriptions for young men who have sex with men. AIDS Behav 2022;26:1956–1965.
65. Rael CT, Martinez M, Giguere R, et al. Transgender women's concerns and preferences on potential future long-acting biomedical HIV prevention strategies: The case of injections and implanted medication delivery devices (IMDDs). AIDS Behav 2020;24:1452–1462.
66. Philbin MM, Bergen S, Parish C, et al. Long-acting injectable ART and PrEP among women in six cities across the United States: A qualitative analysis of who would benefit the most. AIDS Behav 2022;26:1260–1269.
67. Biello KB, Hosek S, Drucker MT, et al. Preferences for injectable PrEP among young U.S. cisgender men and transgender women and men who have sex with men. Arch Sex Behav 2018;47:2101–2107.
68. Guest G, Bunce A, Johnson L. How many interviews are enough? Field Methods 2016;18:59–82.
69. DeCuir-Gunby JT, Marshall PL, McCulloch AW. Developing and using a codebook for the analysis of interview data: An example from a professional development research project. Field Methods 2010;23:136–155.
70. MacQueen KM, McLellan E, Kay K, Milstein B. Codebook development for team-based qualitative analysis. CAM J 2016;10:31–36.
71. Philbin MM, Parish C, Bergen S, et al. A qualitative exploration of women's interest in long-acting injectable antiretroviral therapy across six cities in the women's interagency HIV study: Intersections with current and past injectable medication and substance use. AIDS Patient Care STDS 2021;35:23–30.
72. Schneider KE, White RH, O'Rourke A, et al. Awareness of and interest in oral pre-exposure prophylaxis (PrEP) for HIV prevention and interest in hypothetical forms of PrEP among people who inject drugs in rural West Virginia. AIDS Care 2021;33:721–728.
73. Valente PK, Wu Y, Cohen YZ, Caskey M, Meyers K. Behavioral and social science research to support development of educational materials for clinical trials of broadly neutralizing antibodies for HIV treatment and prevention. Clin Trials 2021;18:17–27.
74. Roth AM, Tran NK, Felsher M, et al. Integrating HIV preexposure prophylaxis with community-based syringe services for women who inject drugs: Results from the project SHE demonstration study. J Acquir Immune Defic Syndr 2021;86:e61–e70.
75. Strathdee SA, Abramovitz D, Harvey-Vera A, et al. Correlates of coronavirus disease 2019 (COVID-19) vaccine hesitancy among people who inject drugs in the San Diego-Tijuana Border Region. Clin Infect Dis 2021. [Epub ahead of print]; DOI: 10.1093/cid/ciab975.
76. Degenhardt L, Mathers B, Vickerman P, Rhodes T, Latkin C, Hickman M. Prevention of HIV infection for people who inject drugs: Why individual, structural, and combination approaches are needed. Lancet 2010;376:285–301.
77. Milloy M-J, Montaner J, Wood E. Barriers to HIV treatment among people who use injection drugs: Implications for 'treatment as prevention'. Curr Opin HIV AIDS 2012;7:332–338.
78. Wood E, Kerr T, Tyndall MW, Montaner JS. A review of barriers and facilitators of HIV treatment among injection drug users. AIDS 2008;22:1247–1256.
79. Marzinke MA, Grinsztejn B, Fogel JM, et al. Characterization of human immunodeficiency virus (HIV) infection in cisgender men and transgender women who have sex with men receiving injectable cabotegravir for HIV prevention: HPTN 083. J Infect Dis 2021;224:1581–1592.
80. Reddy A, Lester CA, Stone JA, Holden RJ, Phelan CH, Chui MA. Applying participatory design to a pharmacy system intervention. Res Social Adm Pharm 2019;15:1358–1367.

Address correspondence to:
Angela R. Bazzi, PhD, MPH
Herbert Wertheim School of Public Health
University of California, San Diego
9500 Gilman Drive
MTF 265E (Mail Code 0725)
La Jolla, CA 92161
USA

E-mail: abazzi@health.ucsd.edu