AIDS and Behavior
https://doi.org/10.1007/s10461-024-04285-3

ORIGINAL PAPER

Long-acting Injectable PrEP Interest and General PrEP Awareness among People who Inject Drugs in the San Diego-Tijuana Border Metroplex

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Accepted: 27 January 2024

Abstract

Long-acting injectable HIV pre-exposure prophylaxis (LAI-PrEP) could help overcome multilevel challenges to HIV prevention for people who inject drugs (PWID), including those in the binational San Diego-Tijuana metroplex. Yet, general PrEP awareness and interest in LAI-PrEP remain underexplored among PWID. From 2020 to 2021, 562 HIV-negative PWID in San Diego and Tijuana completed surveys assessing general PrEP awareness and interest in oral and LAI-PrEP. Modified Poisson regression examined factors associated with general PrEP awareness. Multinomial logistic regression assessed factors associated with interest in both oral and LAI-PrEP, oral PrEP only, LAI-PrEP only, or neither. General PrEP awareness was low (18%) and associated with experiencing unsheltered homelessness (adjusted prevalence ratio [APR] = 1.50, 95% confidence interval [CI]: 0.96–2.33), past 6-month fentanyl injection (APR = 1.53, 95% CI: 1.04–2.25), and transactional sex (APR = 1.71, 95% CI: 1.06–2.76). Interest in oral PrEP only was most common (44%), followed by LAI-PrEP only (25%) and neither (16%). Compared to the odds of being interested in LAI-PrEP only, the odds of being interested in oral PrEP only were lower among those who were stopped by police (AOR = 0.38, 95% CI: 0.22–0.65), reported past 6-month fentanyl injection (AOR = 0.33, 95% CI: 0.20–0.56), polydrug use (AOR = 0.48, 95% CI: 0.27–0.86), injecting multiple times daily (AOR = 0.26, 95% CI: 0.14–0.46), receptive syringe use (AOR = 0.30, 95% CI: 0.19–0.49), and higher perceived HIV risk (AOR = 0.24, 95% CI: 0.15–0.39). Interest in LAI-PrEP was more common among PWID reporting social and structural factors that could interfere with oral PrEP adherence, suggesting LAI-PrEP implementation could increase PrEP coverage among those most vulnerable to HIV.

Keywords HIV prevention · People who inject drugs · Injection drug use · Pre-exposure prophylaxis

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Published online: 06 February 2024

Introduction

Despite making up less than 1% of the world's population [1], people who inject drugs (PWID) bear a significant burden of HIV infection [2]. This remains true in the San Diego, United States, and Tijuana, Mexico binational metroplex, where HIV infection among PWID is disproportionately high and increasing [3, 4]. For example, in the period from 2016 to 2020, there was a 30% increase in injection-related HIV diagnoses from the prior period (2012–2016) in San Diego County [3, 4], and it is estimated that by 2029 over 50% of new HIV infections in Tijuana will be among PWID [5]. Given the proximity of the two cities and their location on major drug trafficking routes into the United States [6], bidirectional cross-border travel and substance use are common [7, 8]. Recent phylogenetic analyses of HIV-1 *pol* sequences from people living with HIV in San Diego and Tijuana also suggest that there are frequent HIV migration events between the two cities [8]. HIV prevention interventions that disrupt HIV migration between San Diego and Tijuana are therefore imperative to ending the HIV epidemic on both sides of the border.

Pre-exposure prophylaxis (PrEP) is a promising HIV prevention strategy that is underutilized among PWID globally. Though oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC) was approved for PrEP by the U.S. Food and Drug Administration (FDA) in 2012 and was recently integrated into Mexico's national HIV prevention strategy [9–11], very few PWID are aware of PrEP, and even fewer have ever accessed it [12–14]. Despite large proportions of PWID in the United States reporting behaviors consistent with clinical indications for PrEP [15], this community faces multilevel barriers to PrEP awareness and uptake, including provider stigma and hesitation to discuss PrEP [14, 16, 17]. Also, PWID face transportation and insurance challenges, and competing priorities that could interfere with PrEP access and adherence [14, 18–21].

Newer, longer-acting PrEP formulations could be more responsive to the needs of PWID but remain understudied in this community [22–24]. For example, long-acting injectable cabotegravir for PrEP (LAI-PrEP), given every 8 weeks, was approved for use in the United States in 2021 among persons with sexual risk for HIV following efficacy trials with cisgender men who have sex with men (MSM) and transgender and cisgender women [25, 26]. Although PWID were excluded from these trials and current LAI-PrEP recommendations [27], it is hypothesized that LAI-PrEP will be more effective than oral TDF/FTC in preventing injection-related HIV transmission among PWID due to its longer duration of action and partial protection provided even after discontinuation [28, 29]. However, it is unclear how LAI-PrEP will impact PrEP interest, uptake, and persistence among PWID in the context of the multilevel barriers to PrEP use faced by this community.

With the goal to inform future PrEP implementation and dissemination strategies tailored to PWID, we aimed to understand general PrEP awareness and interest in oral PrEP and LAI-PrEP among PWID in the San Diego-Tijuana metroplex. More specifically, we examined whether PrEP awareness and interest are associated with social vulnerability (e.g., housing status, interactions with law enforcement), substance use and sexual behaviors (e.g., injection frequency, receptive syringe use, transactional sex), and perceived HIV risk, which we hypothesized may impact future PrEP interest, uptake, and persistence within this community.

Methods

Participants and Eligibility

This analysis used baseline data from *La Frontera*, a longitudinal study of HIV, Hepatitis C virus (HCV), and drug overdose outcomes in the context of binational drug markets in the San Diego-Tijuana metroplex. As previously described [30, 31], between October 2020 and October 2021, trained research staff used street outreach to recruit and screen individuals for the following eligibility criteria: ≥ 18 years of age, injecting drugs in the past month, and residing in San Diego, United States, or Tijuana, Mexico. Recruitment was conducted via a mobile outreach van, where staff approached potential participants in diverse settings, including streets, parks, shelters, motels, river canyons, and vacant lots where drug use visibly occurs or where prior research revealed a high geographic prevalence of drug use. At baseline, staff conducted HIV testing using the Miriad® HIV/HCV Antibody InTec Rapid Anti-HCV Test (Avantor, Radnor, PA) [32]. Individuals receiving reactive and indeterminate results underwent second rapid tests with Oraquick® HIV tests (Orasure, Bethlehem, PA) followed by confirmatory testing at the University of California, San Diego (UCSD) Center for AIDS Research laboratory [33]. This analysis was limited to participants testing HIV-negative at baseline. All participants provided written informed consent and received $20 USD as compensation. Institutional review boards at UCSD and Xochicalco University approved all study activities.

Data Collection

Previous research with PWID in the San Diego-Tijuana metroplex and the Collaborating Consortium of Cohorts Producing NIDA Opportunities (C3PNO) informed the

development of survey items [34, 35]. Trained, bilingual interviewers administered the following survey measures in English or Spanish using computer-assisted personal interviewing.

Outcomes of Interest

General PrEP awareness was measured using the question, "Before today, had you ever heard of HIV-negative people taking HIV medications or PrEP *before* being exposed to HIV to protect against HIV infection?" PrEP modality interest was measured by asking participants, "What kind of PrEP product would you be interested in taking?", with options including, (a) "A pill I need to take every day," (b) "An injection I need to get every two months," (c) "A vaginal gel I need to use before sex" (for women only), and (d) "None." We then categorized this outcome variable as "Oral PrEP only" (for participants who selected "a" only), "LAI-PrEP only" (for participants who selected "b" only), "Both Oral PrEP and LAI-PrEP" (for participants who selected "a" and "b"), and "Neither" (for participants who selected "d" only). Only one participant selected option "c" only and was excluded from this analysis.

Exposures of Interest

Location of Residence: Location of residence was required for entry into our study, which asked participants to specify their current country (United States or Mexico) and region (San Diego County, United States, or Tijuana, Mexico) of residence.

Social Vulnerability: Housing status was ascertained by the questions, "In the past 6 months, tell me if you have lived in or slept in any of the following places," and "In the past 6 months, which place did you sleep in most of the time?," for which we categorized responses into "unsheltered homelessness" (car, bus, truck or other vehicle, abandoned building, streets, beach, canal, or shooting gallery), "sheltered homelessness" (migrant worker's camp, asylum seekers shelter, shelter/welfare residence, workplace, deportee shelter/camp, rented room [hotel, motel or other rooming house], correctional institution [jail, prison, detention center], drug treatment center, medical care facility [hospital, hospice, or nursing home], or rented garage), and "not homeless" (own house or apartment, parent's house or apartment, spouse's/sexual partner's house or apartment, family's house or apartment, or friend's house or apartment). Initially, the *La Frontera* study assessed interactions with law enforcement by asking participants if they were stopped by law enforcement in Mexico in the past 6 months; this question was broadened to include being stopped by law enforcement in the United States approximately one month into the study. Therefore, law enforcement interaction data are missing for 108 participants who were San Diego residents and did not report past 6-month travel to Mexico at baseline during the first month of the *La Frontera* study.

Injection and substance use behaviors: Past 6-month injection and substance use behaviors considered for this analysis included any fentanyl injection, polydrug use (using any two of the following: heroin, crack cocaine, fentanyl, ecstasy, PCP/Angel Dust, and methamphetamine; including simultaneous injection of crack and heroin, methamphetamine and crack, methamphetamine and heroin, and fentanyl and methamphetamine), injection frequency (injecting multiple times daily versus one time per day or less), and receptive syringe use (injected using a previously used syringe versus did not inject using a previously used syringe). We assessed alcohol use via the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) and defined current "hazardous alcohol use" as AUDIT-C scores ≥ 4 for men and ≥ 3 for women [36].

Sexual Behaviors: Past 6-month sexual behaviors included any sex (vaginal, anal, or oral sex), transactional sex (exchanging money, drugs, alcohol, shelter, food, transportation, or protection for sex), alcohol or drug use before or during sex, sex with an HIV-positive partner, and number of sexual partners.

Perceived risk of HIV: We measured perceived HIV risk via Likert-type responses (much more likely to much less likely) to the question, "Compared to other drug users in this city, how likely do you think you are to get (infected with) HIV/AIDS?" Participants were then classified as having "high perceived risk" (much more likely or a bit more likely) or "low perceived risk" (about the same, a bit less likely, or much less likely).

Other Relevant Covariates

Additional covariates relevant to our analysis included: age in years, sex assigned at birth (male or female), gender identity (man, woman, or transgender man [no participants reported being a transgender woman or other identity]), sexual orientation (heterosexual/straight, homosexual/gay/lesbian, bisexual, other), ethnicity (Hispanic or non-Hispanic), educational level (completed at least secondary school versus completed more than secondary school), incarceration history (ever in prison or never in prison), and previous and current PrEP use.

Statistical Analysis

First, we calculated descriptive statistics to characterize our sample by our outcomes of interest, general PrEP awareness and PrEP modality interest. Next, we examined the effect

of our exposures of interest—including location of residence, social vulnerability (i.e., housing status), injection behaviors (i.e., fentanyl injection, polydrug use, injection frequency, receptive syringe use), sexual behaviors (i.e., transactional sex, number of sexual partners, substance use before or during sex), and perceived HIV risk—on general PrEP awareness using modified Poisson regression with a robust variance correction to account for overestimation of error in approximating prevalence ratios [37–39]. Then, we used multinomial logistic regression to examine the effect of our exposures of interest on PrEP modality interest. Additional exposures of interest for our analysis of PrEP modality interest included general PrEP awareness and being stopped by law enforcement in the past 6 months, which could drive interest in LAI-PrEP over other modalities among PWID who may be concerned about police confiscating their belongings. For all regression analyses, we fit separate unadjusted regression models and separate adjusted regression models to examine each exposure-outcome relationship of interest. Based on *a priori* knowledge and existing literature, we constructed a directed acyclic graph (DAG) to depict known or plausible causal interrelationships among each exposure of interest, each outcome of interest, and other relevant covariates (Supplemental Fig. 1) [40]. For each exposure-outcome relationship of interest, we used the DAG to identify open, confounding paths between the exposure and outcome that must be closed to obtain an unconfounded estimate of the exposure-outcome relationship. We then selected variables that lie along those paths (i.e., confounders, see Table footnotes) for inclusion in adjusted regression models to close those paths and control for confounding specific to each exposure-outcome relationship of interest. For each exposure-outcome relationship of interest, the magnitude of the effect estimate and the range of values included in its confidence interval guided our interpretation [41, 42]. We developed all DAGs in DAGitty.net and conducted all statistical analyses in SAS 9.4 (SAS Institute, Inc.; Cary, NC).

Results

Sample Characteristics

Among a total of 562 participants, mean age was 43.1 years (standard deviation [SD]: 10.9). Most participants were assigned male sex at birth (74.4%), identified as men (74.2%), heterosexual/straight (93.2%), and Hispanic (70.8%), and resided in San Diego County (69.9%; Table 1). Large proportions of participants had ever been in prison (46.8%), were experiencing unsheltered homelessness (43.6%), and had been stopped by law enforcement in the past 6 months (37.6%). Past 6-month substance use behaviors related to HIV transmission were common, including fentanyl injection (23.8%), polydrug use (78.3%), injecting multiple times daily (68.2%), receptive syringe use (51.3%), and hazardous alcohol use (25.6%). Approximately half of participants reported having sex in the past 6 months (54.9%) with 11.9% reporting transactional sex in the past 6 months. Overall, less than one third of the sample (28.2%) perceived their risk of HIV to be higher than that of other PWID in their city.

General PrEP Awareness

Less than one in five participants were aware of PrEP (17.6%) (Table 1), with little difference by location of residence (San Diego 18.6%; Tijuana 15.4%) (Supplemental Table 1). Only 2.1% of participants had ever used PrEP, and one was currently using PrEP (0.2%). After adjusting for potential confounders, the prevalence of PrEP awareness was higher among participants who reported experiencing unsheltered homelessness (adjusted prevalence ratio [APR] = 1.50, 95% confidence interval [CI]: 0.96, 2.33), fentanyl injection (APR = 1.53, 95% CI: 1.04, 2.25), and transactional sex (APR = 1.71, 95% CI: 1.06, 2.76) in the past 6 months (Table 2). The prevalence of general PrEP awareness was lower among participants who perceived themselves to be at higher risk for HIV than other PWID in their city (APR = 0.73, 95% CI: 0.47, 1.13).

PrEP Modality Interest

Most participants were interested in oral PrEP only (44.1%), followed by LAI-PrEP only (24.6%), no interest in either oral or LAI-PrEP (16.0%), and interest in both oral and LAI-PrEP (15.3%) (Table 1). While similar PrEP modality interest patterns were seen in each city, overall PrEP interest was slightly higher in Tijuana than in San Diego, with 21.9% of participants in San Diego reporting no interest in either oral or LAI-PrEP compared to only 2.4% of participants in Tijuana (Supplemental Table 2).

Compared to the odds of being interested in LAI-PrEP only, the odds of being interested in oral PrEP only were lower among those who reported unsheltered homelessness (adjusted odds ratio [AOR] = 0.77, 95% CI: 0.47, 1.26), being stopped by law enforcement (AOR = 0.38, 95% CI: 0.22, 0.65), fentanyl injection (AOR = 0.33, 95% CI: 0.20, 0.56), polydrug use (AOR = 0.48, 95% CI: 0.27, 0.86), injecting multiple times daily (AOR = 0.26, 95% CI: 0.14, 0.46), receptive syringe use (AOR = 0.30, 95% CI: 0.19, 0.49), and substance use before or during sex (AOR = 0.67, 95% CI: 0.41, 1.09) in the past 6 months (Table 3). Participants with higher perceived HIV risk (AOR = 0.24, 95% CI:

Table 1 Characteristics of HIV-negative PWID in the San Diego, United States, and Tijuana, Mexico binational metroplex ($N = 562$)

Characteristic	Total ($N = 562$) N (%)[a]
Sociodemographics	
Mean Age in Years (SD)	43.09 (10.92)
Sex Assigned at Birth	
Male	418 (74.38)
Female	144 (25.62)
Gender Identity	
Man	414 (74.19)
Woman	142 (25.45)
Transgender man	2 (0.36)
Sexual Orientation	
Heterosexual/Straight	524 (93.24)
Homosexual/Gay/Lesbian	8 (1.42)
Bisexual	29 (5.16)
Other	1 (0.18)
Ethnicity	
Hispanic	398 (70.82)
Non-Hispanic	164 (29.18)
Location of Residence	
City of Tijuana, Mexico	169 (30.07)
San Diego County, United States	393 (69.93)
Highest Level of Education Completed	
At least secondary school	234 (41.64)
More than secondary school	328 (58.36)
Incarceration History	
Ever in prison	263 (46.80)
Never in prison	299 (53.20)
Social Vulnerabilities	
Housing Status (past 6 months)	
Unsheltered homeless	243 (43.55)
Sheltered homeless	116 (20.79)
Not homeless	199 (35.66)
Stopped by Law Enforcement (past 6 months)	
Stopped by law enforcement	172 (37.55)
Not stopped by law enforcement	286 (62.45)
Injection and Substance Use Behaviors	
Fentanyl Injection (past 6 months)	
Injected fentanyl	134 (23.84)
Did not inject fentanyl	426 (75.80)
Polydrug Use (past 6 months)[b]	
Polydrug use	433 (78.30)
No polydrug use	120 (21.70)
Injection Frequency (past 6 months)	
Injected drugs multiple times per day	383 (68.15)
Did not inject drugs multiple times per day	179 (31.85)
Receptive Syringe Use (past 6 months)	
Injected using a previously used syringe	288 (51.25)
Did not inject using a previously used syringe	274 (48.75)
Alcohol Use (current)	
Hazardous alcohol use	144 (25.62)
No hazardous alcohol use	418 (74.38)
Sexual Behaviors	
Any Sex (past 6 months)[c]	

Table 1 (continued)

Characteristic	Total ($N=562$) N (%)[a]
Had sex	308 (54.90)
Did not have sex	253 (45.10)
Mean Number of Sexual Partners (past 6 months) (SD)	4.78 (43.40)
Transactional Sex (past 6 months)[d]	
Transactional sex	67 (11.94)
No transactional sex	494 (88.06)
Substance Use Before or During Sex (past 6 months)[e]	
Used substances before or during sex	294 (52.41)
Did not use substances before or during sex	267 (47.59)
Sex with an HIV Positive Partner (past 6 months)	
Had sex with an HIV positive partner	9 (1.60)
Did not have sex with an HIV positive partner	552 (98.40)
Perceived Risk of HIV[f]	
Low perceived risk	400 (71.81)
High perceived risk	157 (28.19)
PrEP Related Variables	
General PrEP Awareness	
Not aware of PrEP	463 (82.38)
Aware of PrEP	99 (17.62)
PrEP Use (Ever)	
Never used PrEP	550 (97.86)
Ever used PrEP	12 (2.14)
PrEP Use (Current)	
Not currently on PrEP	561 (99.82)
Currently on PrEP	1 (0.18)
PrEP Modality Interest	
No interest in PrEP	90 (16.01)
LAI-PrEP only	138 (24.56)
Oral PrEP only	248 (44.13)
Interested in both LAI-PrEP and oral PrEP	86 (15.30)

[a] Percentage (%) values may not add up to 100% due to rounding; Total column Ns may not sum to total due to missing values

[b] Defined as using any two of the following: heroin, crack cocaine, fentanyl, ecstasy, PCP/Angel Dust, and methamphetamine; including simultaneous injection of crack and heroin, methamphetamine and crack, methamphetamine and heroin, and fentanyl and methamphetamine

[c] Defined as vaginal, anal, or oral sex

[d] Transactional sex refers to exchanging something of value (such as money, drugs, alcohol, shelter, food, transportation, or protection) for sex

[e] Defined as using any substance, drugs or alcohol, before or during sex

[f] Originally asked as "Compared to other drug users in this city, how likely do you think you are to get (infected with) HIV/AIDS?"; Participants who responded that they were much more likely or a bit more likely were classified as having "high perceived risk" while participants who responded that they were about the same, a bit less likely, or much less likely were classified as having "low perceived risk"

Abbreviations: PWID = people who inject drugs; SD = standard deviation; PrEP = HIV pre-exposure prophylaxis; LAI = long-acting injectable

Table 2 Associations between general PrEP awareness and location of residence, social vulnerabilities, injection and substance use behaviors, sexual behaviors, and perceived risk of HIV among HIV-negative PWID in the San Diego, United States, and Tijuana, Mexico binational metroplex ($N = 562$)

	APR (95% CI)[a]
Location of Residence	
City of Tijuana, Mexico	0.83 (0.55, 1.25)
Social Vulnerabilities	
Housing Status (past 6 months)[b]	
Unsheltered homeless	1.50 (0.96, 2.33)
Sheltered homeless	0.82 (0.51, 1.30)
Not homeless	Ref
Injection and Substance Use Behaviors (past 6 months)	
Injected fentanyl[c]	1.53 (1.04, 2.25)
Polydrug use[c,d]	1.50 (0.88, 2.54)
Injected drugs multiple times per day[e]	1.01 (0.66, 1.53)
Receptive syringe Use[e]	0.83 (0.57, 1.21)
Sexual Behaviors (past 6 months)	
Any transactional sex[e,f]	1.71 (1.06, 2.76)
Number of sexual partners[g]	1.00 (0.99, 1.01)
Any substance use before or during sex[h,i]	1.14 (0.77, 1.68)
Perceived Risk of HIV	
More likely to get HIV[j,k]	0.73 (0.47, 1.13)

[a] APR (95% CI) = Adjusted prevalence ratio and 95% confidence interval from multivariable Poisson regression models with robust error variance correction

[b] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, and incarceration history

[c] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, and housing status (past 6 months)

[d] Defined as using any two of the following: heroin, crack cocaine, fentanyl, ecstasy, PCP/Angel Dust, and methamphetamine; including simultaneous injection of crack and heroin, methamphetamine and crack, methamphetamine and heroin, and fentanyl and methamphetamine

[e] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), and fentanyl injection (past 6 months)

[f] Transactional sex refers to exchanging something of value (such as money, drugs, alcohol, shelter, food, transportation, or protection) for sex

[g] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), and transactional sex (past 6 months)

[h] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), transactional sex (past 6 months), and number of sexual partners (past 6 months)

[i] Defined as using any substance, drugs or alcohol, before or during sex

[j] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), transactional sex (past 6 months), number of sexual partners (past 6 months), and substance use before or during sex (past 6 months)

[k] Originally asked as "Compared to other drug users in this city, how likely do you think you are to get (infected with) HIV/AIDS?"; Participants who responded that they were much more likely or a bit more likely were classified as having "high perceived risk" while participants who responded that they were about the same, a bit less likely, or much less likely were classified as having "low perceived risk"

Abbreviations: PWID = people who inject drugs; PrEP = HIV pre-exposure prophylaxis

Table 3 Associations between PrEP modality interest and location of residence, social vulnerabilities, injection and substance use behaviors, sexual behaviors, perceived risk of HIV, and general PrEP awareness among HIV-negative PWID in the San Diego, United States, and Tijuana, Mexico binational metroplex ($N = 562$)

	No Interest in PrEP ($n = 90$) AOR (95% CI)[a]	Oral PrEP Only ($n = 248$) AOR (95% CI)[a]	Interested in both ($n = 86$) AOR (95% CI)[a]
Location of Residence			
City of Tijuana, Mexico	0.08 (0.03, 0.24)	1.15 (0.75, 1.77)	0.43 (0.23, 0.82)
Social Vulnerabilities			
Housing Status (past 6 months)[b]			
Unsheltered homeless	1.74 (0.91, 3.32)	0.77 (0.47, 1.26)	2.01 (1.04, 3.87)
Sheltered homeless	2.89 (1.17, 7.13)	2.20 (1.16, 4.18)	3.34 (1.42, 7.83)
Not homeless	Ref	Ref	Ref
Stopped by law enforcement (past 6 months)[c]	0.74 (0.35, 1.58)	0.38 (0.22, 0.65)	0.17 (0.08, 0.38)
Injection and Substance Use Behaviors (past 6 months)			
Injected fentanyl[d]	0.86 (0.46, 1.62)	0.33 (0.20, 0.56)	0.40 (0.21, 0.78)
Polydrug use[d,e]	0.92 (0.41, 2.07)	0.48 (0.27, 0.86)	0.34 (0.17, 0.69)
Injected drugs multiple times per day[f]	0.42 (0.21, 0.82)	0.26 (0.14, 0.46)	0.50 (0.25, 1.01)
Receptive syringe Use[f]	0.48 (0.26, 0.89)	0.30 (0.19, 0.49)	0.16 (0.08, 0.30)
Sexual Behaviors (past 6 months)			
Any transactional sex[f,g]	0.62 (0.20, 1.96)	1.47 (0.75, 2.89)	0.24 (0.06, 0.89)
Number of sexual partners[h]	1.00 (0.98, 1.01)	0.98 (0.96, 1.00)	0.99 (0.95, 1.03)
Any substance use before or during sex[i,j]	0.39 (0.21, 0.72)	0.67 (0.41, 1.09)	0.56 (0.31, 1.03)
Perceived Risk of HIV			
More likely to get HIV[k,l]	0.22 (0.10, 0.46)	0.24 (0.15, 0.39)	0.17 (0.08, 0.36)
General PrEP Awareness			
Not aware of PrEP[m]	1.09 (0.52, 2.27)	0.65 (0.37, 1.17)	0.36 (0.15, 0.87)

[a] AOR (95% CI) = Adjusted odds ratio and 95% confidence interval from multivariable multinomial logistic regression models where the PrEP modality interest reference category is LAI-PrEP only ($n = 138$)

[b] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, and incarceration history

[c] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, and housing status (past 6 months)

[d] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, and housing status (past 6 months)

[e] Defined as using any two of the following: heroin, crack cocaine, fentanyl, ecstasy, PCP/Angel Dust, and methamphetamine; including simultaneous injection of crack and heroin, methamphetamine and crack, methamphetamine and heroin, and fentanyl and methamphetamine

[f] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), and fentanyl injection (past 6 months)

[g] Transactional sex refers to exchanging something of value (such as money, drugs, alcohol, shelter, food, transportation, or protection) for sex

[h] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), and transactional sex (past 6 months)

[i] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), transactional sex (past 6 months), and number of sexual partners (past 6 months)

[j] Defined as using any substance, drugs or alcohol, before or during sex

[k] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), transactional sex (past 6 months), number of sexual partners (past 6 months), and any substance use before or during sex (past 6 months)

[l] Originally asked as "Compared to other drug users in this city, how likely do you think you are to get (infected with) HIV/AIDS?"; Participants who responded that they were much more likely or a bit more likely were classified as having "high perceived risk" while participants who responded that they were about the same, a bit less likely, or much less likely were classified as having "low perceived risk"

[m] Adjusted for location of residence, age, ethnicity, sex assigned at birth, education, incarceration history, housing status (past 6 months), fentanyl injection (past 6 months), transactional sex (past 6 months), number of sexual partners (past 6 months), any substance use before or during sex (past 6 months), and perceived risk of HIV.

Abbreviations: PWID = people who inject drugs; PrEP = HIV pre-exposure prophylaxis; LAI = long-acting injectable

0.15, 0.39) and no prior PrEP awareness (AOR = 0.65, 95% CI: 0.37, 1.17) also had lower odds of being interested in oral PrEP only compared to LAI-PrEP only.

Discussion

To inform future PrEP implementation and dissemination strategies tailored to PWID, we examined general PrEP awareness and interest in oral and LAI-PrEP among HIV-negative PWID in the San Diego-Tijuana metroplex, where binational HIV transmission threatens HIV prevention efforts in the United States and Mexico. We found that approximately one in seven participants in San Diego and one in eight in Tijuana had previously heard of PrEP. This low level of PrEP awareness is consistent with a growing body of research with PWID [23, 43, 44], and may be explained by the limited marketing of PrEP to PWID communities [13, 23] as well as perceptions among some prescribers that PWID may not be ideal candidates for daily oral PrEP [14, 16, 45–47].

In our unique binational sample, participants who had recently injected fentanyl, had transactional sex, and were experiencing unsheltered homelessness were more likely to be aware of PrEP, suggesting that PrEP information may be reaching some PWID experiencing elevated social and structural vulnerability to HIV. It is also possible that clinicians or other "PrEP champions" who work with this community have provided PrEP education to some at-risk PWID based on their knowledge of potentially elevated HIV risk from fentanyl use [48, 49], homelessness, transactional sex, mental health comorbidities, and other sources of social and structural vulnerability [50, 51]. We also found that participants in our sample who perceived themselves to be at higher HIV risk were less likely to be aware of PrEP. Consistent with prior research [22, 52], this finding suggests that individuals may have a limited understanding of HIV transmission risk, highlighting the need for improved HIV and PrEP education in low-threshold clinical and non-clinical settings that are accessible to PWID. Syringe services programs (SSPs), which routinely provide HIV prevention education to PWID, could be ideal settings for efforts to rapidly disseminate PrEP education and address misperceptions regarding individuals' HIV risk [53–55]. Educational efforts through SSPs could also leverage the social networks of PWID, particularly those who already engage in the distribution of harm reduction supplies (e.g., sterile syringes, naloxone) and PrEP information to their peers [56].

Despite the limited prior PrEP awareness we identified, after interviewers explained PrEP (generally, and then for oral and LAI modalities), over three quarters of participants in San Diego and almost all PWID in Tijuana expressed interest in some form of PrEP, an observation that aligns with other studies identifying high interest in and willingness to use PrEP among PWID regardless of prior awareness [14, 18, 23, 43, 57]. Among those expressing interest in some form of PrEP in each city, interest in oral PrEP only was most common, followed by interest in LAI-PrEP only, and then interest in both LAI-PrEP and oral PrEP. These findings are consistent with studies with PWID in India and the United States where more participants preferred daily oral PrEP to LAI-PrEP [58, 59]. However, our findings stand in contrast to those from a small qualitative study of PrEP preferences among San Diego residents enrolled in *La Frontera* that found stronger interest in LAI-PrEP, which participants described as more convenient, familiar, and less invasive than other PrEP modalities (including daily oral PrEP, implants, and vaginal rings) [22]. It is possible that different methods of explaining LAI-PrEP to study participants and the greater amount of time allowed in qualitative interviews for participants to ask questions and contemplate available options contributed to these divergent findings. With greater time to describe the potential benefits of LAI-PrEP, such as its promise for overcoming adherence challenges, including storing medications or coping with PrEP-related stigma [22, 60, 61], it seems likely that evidence-informed messaging could facilitate interest in LAI-PrEP and other longer-acting formulations among PWID [60].

While more participants generally preferred oral PrEP, nearly a quarter expressed interest in LAI-PrEP only, and these participants appeared to be more socially and structurally vulnerable. Specifically, compared to those who preferred oral PrEP only, those who preferred LAI-PrEP only were more likely to experience unsheltered homelessness and be stopped by law enforcement, engage in injection- and sexual-behaviors known to increase HIV risk, have higher perceived HIV risk, and not possess prior general PrEP awareness. Limited research in the United States has revealed similar associations between LAI-PrEP interest and HIV-related transmission risk behaviors; for example, a study in West Virginia identified associations between injection-related HIV risk, prior sex work, and sexual minority identity with preferences for injectable PrEP [59], and among PWID in three U.S. cities, recent injection drug use was strongly associated with LAI-PrEP acceptability [23]. Taken together, these findings suggest that PWID experiencing social vulnerability through homelessness, interactions with the police, or other structural barriers to safe medication storage and adherence may be most interested in LAI-PrEP [22, 60–62]. Ultimately, our findings highlight the need to increase awareness of longer-acting PrEP modalities among PWID and the importance of additional efforts to provide affordable housing and other structural

interventions for PWID to ensure that adherence to PrEP (especially oral PrEP) is not undermined.

Limitations

The results of this study should be interpreted considering several limitations. First, the unique geographic context of our study and our relatively small sample size of PWID from Tijuana, Mexico, limits generalizability and may have implications for our ability to detect site differences. In particular, we acknowledge that the low awareness seen in our sample, particularly in Mexico, may be due to PrEP's limited availability at the time of data collection. Now that PrEP has continued to be rolled out in Mexico, awareness may be higher than seen here. Second, our survey measures relied on self-report and recall of sensitive, criminalized, and socially stigmatized behaviors. Third, while we used DAGs to identify and mitigate confounding bias, we cannot draw direct causal conclusions from these cross-sectional data. Finally, though our results shed light on factors associated with preferences for LAI-PrEP only, we did not assess reasons for specific preferences or explore the acceptability of additional biomedical HIV prevention modalities (e.g., vaginal rings, implants, broadly neutralizing antibodies), as some qualitative research has explored [22]. Additional research is needed to understand the extent to which PWID may be interested in these additional longer-acting PrEP modalities and why they may better engage this community.

Conclusions

As one of the few studies to directly examine factors associated with interest in oral and LAI-PrEP within a large sample of PWID, we found that, despite having low PrEP awareness, individuals in both San Diego and Tijuana were generally interested in either form of PrEP. Individuals who were socially and structurally vulnerable to HIV (e.g., interactions with law enforcement) were more likely to prefer LAI-PrEP over oral PrEP. Our findings suggest that efforts to improve PrEP implementation for PWID in the San Diego-Tijuana metroplex may benefit from enhanced HIV and PrEP education including education on multiple PrEP modalities, particularly for PWID experiencing social and structural vulnerability. Further research needs to be conducted to better understand what is driving interest in LAI-PrEP and how it can be most effectively implemented to reach PWID.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10461-024-04285-3.

Acknowledgements The authors gratefully acknowledge the *La Frontera* study team and participants in the San Diego-Tijuana metroplex where data were collected. We also thank staff at Genayltye and Fluxergy, and the Center for AIDS Research at UC San Diego for assistance interpreting laboratory results.

Author Contributions Conceptualization, Methodology, Funding acquisition: A.R.B., S.A.S., and H.A.P.; Data validation and curation: W.H.E., I.A., and H.A.P.; Data analysis: W.H.E. and H.A.P.; Original manuscript draft: W.H.E., A.R.B., H.A.P.; Resources and project administration: C.F.V., A.H.V., M.G.R., and S.A.S. All authors contributed to the interpretation of results, manuscript revisions, and approved the final manuscript.

Funding 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 R01DA049644-S1, R01DA049644-02S2, K01DA043412, 3K01DA043412-04S1, and T32DA023356), and the California HIV/AIDS Research Program (CHRP; grant OS17-SD001). The funders had no role in the decision to write and publish this manuscript or in the interpretation and presentation of findings.

Data Availability Data are available upon reasonable request to the Principal Investigator of *La Frontera*, Dr. Steffanie Strathdee (sstrathdee@health.ucsd.edu).

Declarations

Competing interests We declare no conflicts of interest.

Ethics Statement Institutional review boards at UCSD and Xochicalco University approved all study activities.

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