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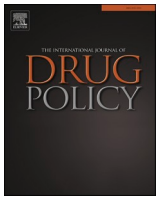

Research Paper

Low daily oral PrEP adherence and low validity of self-report in a randomized trial among PWID in Ukraine

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ABSTRACT

Background: The efficacy of daily oral pre-exposure prophylaxis (PrEP) in preventing HIV transmission among people who inject drugs (PWID) was demonstrated over a decade ago. However, only a few studies among PWID have since measured PrEP adherence using laboratory markers.

Methods: In this trial, we randomized recently injecting PWID in Kyiv, Ukraine, to receive daily oral TDF/FTC with or without SMS reminders. Enrollment and PrEP initiation took place at an HIV clinic. Subsequent visits at months 1, 3, and 6 were conducted at a community harm reduction center and included a structured interview, adherence counseling, PrEP dispensing, and dried blood spot collection. PrEP adherence was assessed using standard self-reported measures and TDF/FTC biomarkers.

Results: A total of 199 PWID (99 SMS, 100 No-SMS) were enrolled, of whom 24 % were women, with a median age of 37. At month 6, 79.4 % (158/199) of participants were retained, with 84 % (133/158) reporting opioid injection and 20 % (31/158) reporting stimulant injection in the past 30 days. 77 % (122/158) reported taking >95 % of PrEP doses in the past month, and 87 % reported taking the last dose within 2 days. Tenofovir diphosphate was detected in 17 % (28/158) of participants, and emtricitabine triphosphate was detected in 25 % (40/158). Only 3 % (5/158) had metabolite levels indicative of consistent PrEP uptake at 4+ doses per week. There was no association between the SMS intervention and TDF/FTC metabolite detection.

Conclusion: Adherence to daily oral PrEP among actively injecting PWID, without daily supervision or incentives, was extremely low, despite supportive counseling and SMS reminders. We also observed a high rate of discordance between self-report and classification by a validated biomarker of adherence. Given the scarcity of evidence and emerging data suggesting low oral PrEP adherence among PWID, additional implementation studies with TDF/FTC biomarkers are needed to study whether a sufficient level of adherence to daily PrEP is attainable among PWID, especially as long-acting injectable PrEP offers a promising alternative.

Introduction

Pre-exposure prophylaxis (PrEP) with tenofovir/emtricitabine (TDF/FTC) is an evidence-based intervention to reduce HIV transmission and a recommended component of integrated prevention approaches for populations at high risk of HIV. Large-scale trials have demonstrated the efficacy of the daily oral TDF/FTC regimen in men who have sex with men (MSM) (Grant et al., 2010), serodiscordant couples (Baeten et al., 2012), and people who inject drugs (PWID) (Choopanya et al., 2013). A recent meta-analysis, including six trials found a 75 % reduction in the rate of HIV acquisition among MSM (O Murchu et al., 2022). Despite the fact that injection drug use continues to drive HIV epidemics in many countries, only one large trial assessed PrEP efficacy among PWID. The Bangkok Tenofovir Study (BTS), conducted between 2005 and 2010, demonstrated a 52 % overall reduction of HIV risk (Choopanya et al., 2013), and an 84 % reduction among those with a high level of adherence (Martin et al., 2015).

This compelling evidence led to a rapid approval by regulatory

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agencies and the endorsement of PrEP as an effective prevention strategy for high-risk populations by the CDC in 2013 and the WHO in 2015 (World Health Organization, 2015). However, the enabling regulatory framework in many countries and the increasing body of evidence on PrEP efficacy do not necessarily translate into PrEP scale-up, particularly among PWID. Despite the notable acceptability and willingness in a range of settings (Mistler, Copenhaver & Shrestha, 2021), PrEP coverage remains low. For example, in the US, less than 1 individual per 1000 persons with opioid use disorder receives PrEP (Streed et al., 2022).

While recent evidence suggests that using oral PrEP before and after sexual encounters may provide sufficient protection for MSM (Molina et al., 2015), daily PrEP regimens remain the only option for other populations that have more frequent or unpredictable exposures. In these populations, adherence to the daily medication is the key factor for PrEP effectiveness, but it has been challenging in many settings (Amico et al., 2014). For example, in the iPrEx study among MSM, self-reported adherence was 51 %, while laboratory testing suggested it was only 41 % (Amico & Stirratt, 2014). In the BTS, the participants reported taking PrEP during 84 % of days on average, while TFV metabolites were found in 66 % (Choopanya et al., 2013). In an open-label extension of the BTS, PWID agreeing to start daily PrEP showed low overall adherence according to written diaries, with almost half (47 %) having less than 10 % adherence, and only 25 % had high (>90 %) adherence (Martin et al., 2017).

Accurate measurement of medication adherence is crucial in clinical trials and implementation studies. Laboratory testing for TFV/FTC metabolites in plasma, urine, or dry blood spot (DBS) samples has been used as a gold standard, with varying concordance between laboratory-based and self-reported adherence measures. In the iPrEX extension study among MSM, the positive predictive value of self-report (proportion of visits when the self-reported adherence was consistent with the drug concentration data) was high at 83 % (Amico et al., 2014). Conversely, in the FEM-PrEP trial among young women in Africa the positive predictive value was lower than 40 % for different self-reported measures of adherence and decreased over time (Agot et al., 2015). Besides the BTS, only two studies reported laboratory data on PrEP adherence among PWID, both with small sample sizes and less than 50 % retention at 6 months (Brokus et al., 2022; Roth et al., 2021).

Numerous interventions have been proposed to improve individual adherence to daily oral PrEP. These interventions range from individual counseling, structured behavioral interventions, and motivational interviewing to technology-based solutions of varying interactivity, including 1- and 2-way text messaging, mobile phone apps, and websites (Garrison & Haberer, 2021). Text messages (SMS) were shown to improve adherence to ART (Mbuagbaw et al., 2015) and to have some benefit for PrEP among MSM (Moore et al., 2018; Serrano et al., 2023). A number of PrEP adherence enhancement studies for PWID are underway (Bazzi et al., 2023).

It has been more than a decade since the seminal BTS trial was published, and the reasons for systematic exclusion of PWID from subsequent trials evaluating new PrEP approaches are unclear (Brody, Taylor, Biello & Bazzi, 2021). Very few studies reported adherence to PrEP among PWID (Mistler, Copenhaver & Shrestha, 2021), and even fewer assessed laboratory markers (Brokus et al., 2022; Roth et al., 2021). Yet, despite the paucity of PrEP research among PWID and the limitations of the BTS (Miller et al., 2013), the advocacy for continued scale-up remains strong, with some authors calling for an "aggressive expansion" of PrEP for PWID (Streed et al., 2022).

The present study aimed to address this research gap, by evaluating PrEP adherence using self-reported and laboratory-based measures in the context of a randomized implementation trial testing the effectiveness of a tailored SMS reminder system in a sample of community-recruited PWID.

Methods

Study setting

Ukraine has one of the largest HIV epidemics in Eastern Europe (UNAIDS, 2018). The epidemic continues to be driven by injection drug use, which is responsible for at least half of newly detected cases (Dumchev et al., 2020). Among 355,000 estimated PWID (Sazonova, Duchenko, Kovtun & Kuzin, 2019), HIV prevalence in 2020 reached 20.3 %, and incidence was estimated at 1.1/100 person-years (Titar et al., 2021). According to the 2020 biobehavioral survey conducted in 12 cities, ART coverage among PWID tested positive for HIV was 53 %, and viral load <1000 cp/ml was found in 82 % of those on ART (Dumchev et al., 2023). The present study was conducted in Kyiv - Ukraine's capital city with an estimated 33,700 PWID (Sazonova, Duchenko, Kovtun & Kuzin, 2019), 16.6 % of whom live with HIV (Titar et al., 2021).

PrEP programs in Ukraine started in 2018 with support from PEPFAR. The number of clients in 2020 reached 2258, 2 % of whom were PWID. The proportion of PWID steeply increased to 14 % of 5711 total clients in 2021 (Public Health Center of the MoH of Ukraine, 2022).

Study population and procedures

This implementation study was designed as a two-arm randomized trial with 1:1 allocation to experimental (SMS facilitation) and control arms. The target sample size was determined based on feasibility considerations while providing adequate precision in measurement of adherence and persistence on PrEP. The participants were recruited by outreach workers at geographically diverse mobile and stationary harm reduction sites. Eligibility criteria for pre-screening included being at least 18 years old, no self-reported HIV positivity, injection drug use in the past 30 days confirmed by presence of injection marks, possession of a mobile phone, willingness to participate in the study and take PrEP medications daily, and ability to sign informed consent.

Eligible candidates were referred to the study clinical site (Clinic of the Institute of Epidemiology and Infectious Diseases). During the recruitment visit, all candidates completed the following procedures: verification of eligibility criteria; informed consent; rapid test for HIV; rapid test for HBsAg; venous blood sample collection for creatinine.

Participants who tested negative on rapid tests and provided consent were enrolled in the study. The site physician then conducted initial counseling, prescribed a daily oral TDF/FTC 300/200 mg regimen, dispensed the first 30-day supply of medication, and observed the first pill being taken. Once PrEP was initiated, participants were randomly assigned to either the SMS or No-SMS arms and completed a baseline interviewer-administered questionnaire using REDCap electronic data capture tools hosted at the Ukrainian Institute on Public Health Policy (Harris et al., 2019). Additionally, participants assigned to the SMS arm filled out an SMS customization form.

Candidates who screened positive for HIV or HBsAg were referred to the clinic staff for the necessary services. After obtaining the results of creatinine testing (2–3 days after enrollment), participants with elevated creatinine levels were contacted by the clinic staff. They were advised to discontinue PrEP immediately and attend the clinic for further consultation.

In accordance with community recommendations obtained during the protocol design phase, subsequent visits at months 1, 3, and 6 were conducted at a harm reduction community site rather than the clinic. The clinic staff delivered and dispensed PrEP medications, conducted brief assessments of PrEP adherence and supportive counseling with participants. A two-month supply of PrEP medication was dispensed at month 1, and a three-month supply at month 3. The experimental arm participants had an option to customize the SMS reminders. All participants completed a structured survey, were tested using rapid tests for HIV at months 3 and 6, and provided DBS samples. Additional telephone

brief adherence counseling sessions (up to 15 min) were conducted with all participants at months 2, 4, and 5. The complete schedule of study evaluations and procedures is provided in Supplementary Table S1. Missing visits at months 1 and 3 did not lead to exclusion. For each fully completed study visit (baseline, months 1, 3, and 6) participants received monetary compensation equivalent of $8. No incentives were offered for PrEP adherence.

The SMS reminders could be customized in terms of frequency (1–7 days per week, 1–4 times per day), timing (any desired time), and content (using pre-defined standard options or custom, mentioning HIV, PrEP, medications, or generic). The messages were delivered using an automated service.

At the study exit visit at month 6, participants who were willing to continue PrEP were provided with an additional 30-day supply of medication and were referred to a preferred clinical site offering PrEP services.

Laboratory procedures and outcomes

Blood samples from finger stick were spotted onto Whatman 903 Protein Saver cards, dried at room temperature for at least 2 h, but no more than 24 h, and then stored in $a - 70$ °C freezer. DBS samples were stored for nearly two years until June 2022, when they could be safely transported to a US-based laboratory.

Tenofovir diphosphate (TFVdp) and emtricitabine triphosphate (FTCtp) metabolites were measured using previously published, validated liquid-chromatography tandem mass spectrometry methods, with the lower limit of quantification at 100 fmol/punch (Schauer et al., 2018).

The primary outcomes of interest were defined as quantifiable vs. below the limit of quantification (BLQ) level of TFVdp, to reflect PrEP uptake over the past 4–6 weeks, and FTCtp, to reflect a dose within the preceding 48 h (Castillo-Mancilla et al., 2016). The secondary outcomes were defined using thresholds of (1) 700 fmol/punch for TFVdp to reflect taking an average of 4 or more doses/week (a minimum target for effective PrEP in men) over the past 2–3 months (Grant et al., 2014), and (2) 200 fmol/punch for FTCtp to reflect taking an average of 4 or more doses/week over the past 1–2 weeks (Devanathan et al., 2023).

Survey measures

The structured surveys at baseline, months 3 and 6, were administered by a skilled interviewer with long-term experience in PWID studies. The survey included questions on socio-demographic characteristics, substance use and treatment history, HIV risk behaviors and risk perception, PHQ-9 instrument for depression screening, barriers to PrEP uptake, satisfaction with PrEP, and PrEP adherence. The adherence assessment included the three-item screener with Visual Analog Scale (Wilson et al., 2016), and two questions related to perceived confidence in future uptake (Table 1).

Statistical analysis

Baseline participant characteristics were summarized using descriptive statistics. Pearson chi-square test and Fisher's exact test (for variables with expected counts below 5) were used to test for baseline differences between the study arms.

Concordance between self-reported and laboratory-based adherence measures at 3- and 6-month visits was assessed using positive predictive values (PPV) and Cohen's kappa statistic.

Associations between the primary outcomes of interest (quantifiable levels of TFVdp and FTCtp) and potential correlates, including the experimental condition, were tested using multi-level generalized linear mixed models to account for within-subject correlation between 3- and 6-month assessments. Individual models were constructed for each covariate, and three multivariable models (for quantifiable levels of TFVdp, FTCtp, and either of the two) included key sociodemographic characteristics as well as variables that were hypothesized to affect adherence. All models included the participant ID as a random effect and the visit number (3 or 6) as a fixed effect.

All analyses were done using R version 4.0.5 (R Core Team, 2020).

Table 1
Self-reported adherence measures and corresponding variables.

	Type	Questions with Possible Responses	Recoding for analysis
1	Ability	Please rate your ability to take your study medications every day in the past month. 1 Very poor, 2 Poor, Fair, 3 Good, 4 Very Good, 5 Excellent	Dichotomous (1–3), (4–5)
2	Percent taken	Please click on the line below at the point showing your best guess about how much of your study medication you took as recommended over the past month. 0–100 %	Dichotomous (0–95 %), (>95 %)
3	Frequency	Thinking about your experiences with the study pills over the past month, about how much of the time did you take your study drug as recommended? 1 All of the time, 2 Most of the time, 3 Half of the time, 4 Some of the time, 5 None of the time	Dichotomous (1), (2–5)
4	Recency	When was the last time you took PrEP medications? Date	Categorical (0–1 days), (2–7 days), (8+ days)
5	Perceived continuation	How likely are you to continue PrEP in the next month? 1 Absolutely impossible, 2 Very unlikely, 3 Unlikely, 4 Not sure, 5 Likely, 6 Very likely, 7 Absolutely likely	Dichotomous (1–5), (6–7)
6	Perceived competence	I feel confident in my ability to use PrEP daily, as recommended. 1 Not at all true, 2 Not true, 3 A little, 4 Somewhat true, 5 True, 6 Very true, 7 Absolutely true	Dichotomous (1–5), (6–7)

Compliance with ethical standards

The study was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments. All participants provided written informed consent. The protocol was reviewed and approved (reference #2020–009–02) by the IRB#1 of the Ukrainian Institute on Public Health Policy (FWA #00,015,634).

Results

Participant recruitment took place between July 15 and September 23, 2020. Of the 207 potential participants that visited the clinical site, 1 was excluded for failure to confirm recent drug injecting, 6 for positive HBsAg, and 1 for positive HIV test. Of the remaining 199, 99 were randomized to the SMS group and 100 to No-SMS (Fig. 1).

Ten participants were terminated from the study due to elevated creatinine, consent withdrawal or moving to another city. One participant tested positive for HIV at month 3 and was referred for diagnosis confirmation and treatment. Retention in the study was 78.9 % (157/199) at month 3 and 79.4 % (158/199) at month 6. Follow-up was completed in March 2021.

At baseline, median age was 37 years old, 24 % were women (Table 2), and 1 % were homeless, 19 % lived alone, and 57 % were either married or had a partner. Approximately a quarter (25 %) met the PHQ-9 criteria for moderate-to-severe depression. The most commonly used drugs were opioids (used by 95 % in the past 30 days, primarily

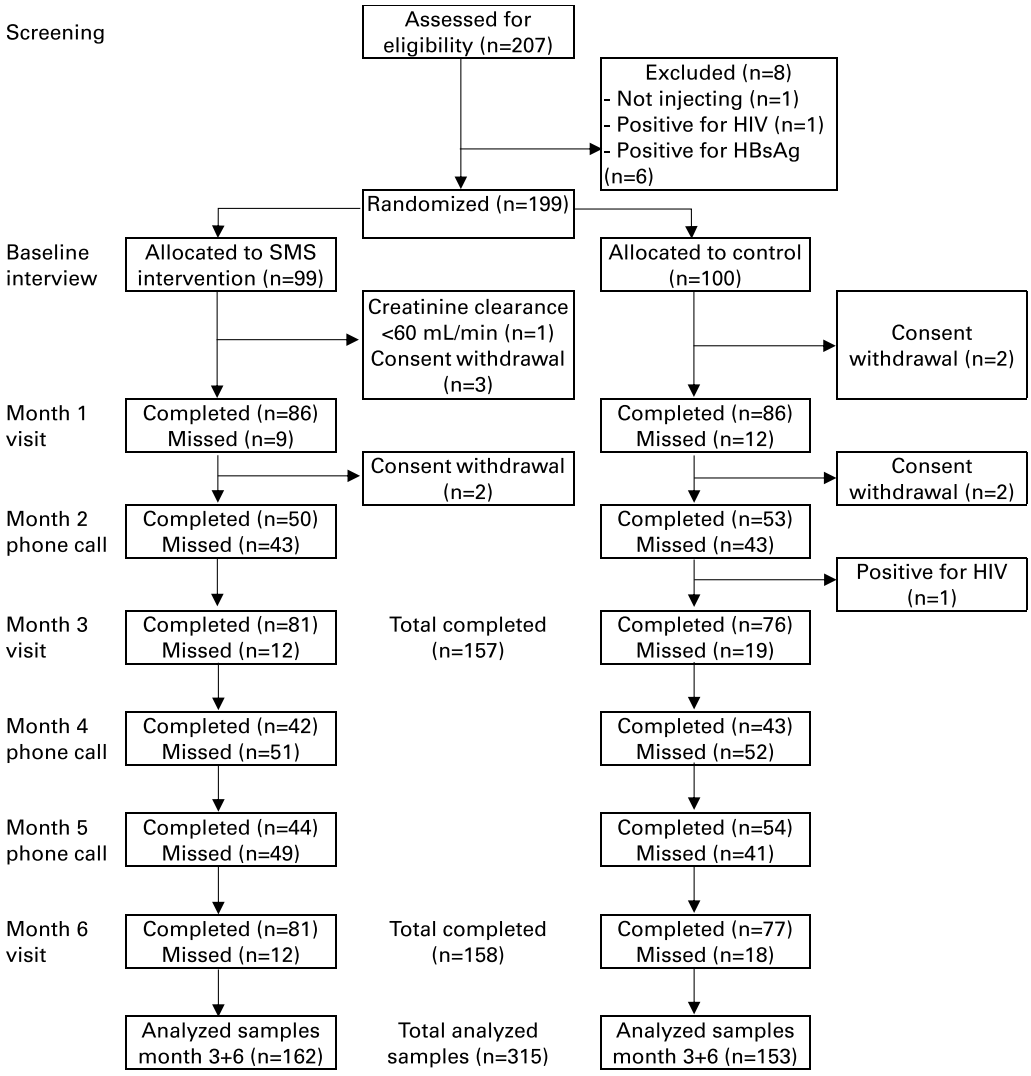

Fig. 1. CONSORT flow diagram.

illegally manufactured methadone), followed by other drugs (54 %, primarily antihistamines, commonly used as an adjuvant to opioids (Dumchev et al., 2009)), and stimulants (33 %, primarily amphetamine). There were no significant differences between the intervention arms at baseline, except for the injection use of "bath salts" (5 % in the SMS group and 16 % in No-SMS, $p = 0.022$, data not shown). Injection drug use in the past 30 days decreased to 84 % for opioids and to 20 % for stimulants at the last follow-up.

Participants expressed high confidence in their likelihood and ability to take PrEP. At baseline, 93 % were very confident that they would be taking it in the next month, and 96 % felt fully capable of taking it daily.

Self-reported adherence was consistently high across all measures at both follow-up visits: 92 % rated their ability in taking PrEP in the past month from good to excellent, 77–81 % reported taking more than 95 % of daily doses in the past month, and 76–87 % said they took a pill no more than a day before (Table 3).

However, the concordance between the self-report and the laboratory markers was extremely low. At month 3, forty participants (26 %) had quantifiable TFVdp level, and only 2 (1.3 %) exceeded the 700 fmol/punch threshold, reflecting average use of ≥4 doses/week in the past 2–3 months. Forty-one participant (26 %) had quantifiable FTCtp, suggesting medication intake in the past 48 h, and 30 (19 %) were above 200 fmol/punch, reflecting average use of ≥4 doses/week in the past 1–2 weeks. At month 6, 28 participants (17 %) had quantifiable TFVdp, and 7 (4 %) exceeded 700 fmol/punch, 40 (25 %) had quantifiable FTCtp, with 32 (20.3 %) exceeded 200 fmol/punch.

The study intervention, SMS reminders, did not appear to have a significant effect on PrEP adherence measured by biological markers (multivariable regression $p = 0.11$ for quantifiable TFVdp, and $p = 0.104$ for FTCtp, Table 4).

The positive predictive value of self-reported items versus quantifiable TFVdp was ≤28 % at month 3 and ≤20 % at month 6. For FTCtp, it was ≤31 % and ≤29 % at months 3 and 6, respectively, with little difference between the self-reported measures. Kappa statistics ranged from −0.09 to 0.12, indicating absence or very minor agreement between the measures (Table 3).

In the multivariable analysis of potential predictors of PrEP uptake, very few significant associations were found (Table 4). Self-reported injection risk behavior in the past 30 days (receptive syringe sharing, using pre-filled syringe, back-or front-loading, or container sharing) was associated with quantifiable FTCtp (aOR=3.4 [95 % CI 1.6–7.0]). History of overdose in the past 6 months decreased the odds of detecting FTCtp (aOR=0.1 [0.01–0.6]). No associations were found for quantifiable level of TFVdp.

Discussion

In this implementation trial among PWID in Ukraine we confirmed

Table 2
Participant characteristics by study arm in PrEP implementation trial among PWID in Ukraine.

		Total		Study arm					
				SMS		No SMS			
		N	%	N	%	N	%	Chi	Sig.
	Total	**199**		**99**		**100**			
Age category, years	<=30	22	11.1	12	12.1	10	10.0	F	0.974
	31–40	122	61.3	60	60.6	62	62.0		
	41–50	47	23.6	23	23.2	24	24.0		
	51 or more	8	4.0	4	4.0	4	4.0		
Gender	female	48	24.1	21	21.2	27	27.0	0.6	0.430
	male	151	75.9	78	78.8	73	73.0		
Residence	own or family	146	73.4	75	75.8	71	71.0	F	0.757
	rent or shared	51	25.6	23	23.2	28	28.0		
	other or homeless	2	1.0	1	1.0	1	1.0		
Employment	full-time	34	17.1	22	22.2	12	12.0	4.2	0.125
	part-time or temporary	109	54.8	53	53.5	56	56.0		
	unemployed	56	28.1	24	24.2	32	32.0		
Income, UAH/month	<=3000	53	26.6	24	24.2	29	29.0	1.4	0.696
	3001–8000	56	28.1	31	31.3	25	25.0		
	8001–20,000	78	39.2	39	39.4	39	39.0		
	20,000+	12	6.0	5	5.1	7	7.0		
Injection duration, years	<=10	50	25.1	23	23.2	27	27.0	3.3	0.192
	11–20	78	39.2	45	45.5	33	33.0		
	21 or more	71	35.7	31	31.3	40	40.0		
Family status	married or in partnership	113	56.8	55	55.6	58	58.0	0.0	0.838
	single, divorced, widowed	86	43.2	44	44.4	42	42.0		
Education	up to full high school	72	36.2	30	30.3	42	42.0	3.6	0.168
	college	77	38.7	44	44.4	33	33.0		
	university	50	25.1	25	25.3	25	25.0		
Living alone	no	162	81.4	80	80.8	82	82.0	0.0	0.973
	yes	37	18.6	19	19.2	18	18.0		
Depression (PHQ-9)	none or mild	89	44.7	44	44.4	45	45.0	0.0	0.979
	moderate	61	30.7	30	30.3	31	31.0		
	moderate-severe	49	24.6	25	25.3	24	24.0		
Injection frequency	never	0	0.0	0	0.0	0	0.0	F	0.721
	less than daily	112	56.3	54	54.5	58	58.0		
	daily or more	86	43.2	44	44.4	42	42.0		
Syringe sharing in 30 days	yes	41	20.6	23	23.2	18	18.0	0.5	0.461
	never	158	79.4	76	76.8	82	82.0		
Using pre-filled syringe in 30 days	no	162	81.4	82	82.8	80	80.0	0.1	0.741
	yes	37	18.6	17	17.2	20	20.0		
Back- or front-loading	no	189	95.0	96	97.0	93	93.0	F	0.331
	yes	10	5.0	3	3.0	7	7.0		
Container sharing	no	88	44.2	49	49.5	39	39.0	1.8	0.178
	yes	111	55.8	50	50.5	61	61.0		
Overdose in 6 months	no	165	82.9	82	82.8	83	83.0	0.0	1.000
	yes	34	17.1	17	17.2	17	17.0		
Severity of drug use	mild	69	34.7	36	36.4	33	33.0	0.3	0.874
	moderate	90	45.2	44	44.4	46	46.0		
	severe	40	20.1	19	19.2	21	21.0		
MOUD at present	no	171	85.9	86	86.9	85	85.0	0.7	0.713
	in public program	13	6.5	7	7.1	6	6.0		
	in private program	15	7.5	6	6.1	9	9.0		
Alcohol use in 30 days	no	55	27.6	25	25.3	30	30.0	0.3	0.555
	yes	144	72.4	74	74.7	70	70.0		
Cannabis use in 30 days	no	131	65.8	65	65.7	66	66.0	0.0	1.000
	yes	68	34.2	34	34.3	34	34.0		
Opioid injection use in 30 days	no	11	5.5	4	4.0	7	7.0	0.4	0.546
	yes	188	94.5	95	96.0	93	93.0		
Stimulant injection use in 30 days	no	134	67.3	71	71.7	63	63.0	1.3	0.246
	yes	65	32.7	28	28.3	37	37.0		
Other injection drug use in 30 days	no	92	46.2	44	44.4	48	48.0	0.1	0.718
	yes	107	53.8	55	55.6	52	52.0		
Had sex in 30 days	no	41	20.6	21	21.2	20	20.0	0.0	0.971
	yes	158	79.4	78	78.8	80	80.0		
Perceived HIV risk through injection	no	131	65.8	67	67.7	64	64.0	0.2	0.691
	yes	68	34.2	32	32.3	36	36.0		
Perceived HIV risk through sex	no	176	88.4	91	91.9	85	85.0	1.7	0.192
	yes	23	11.6	8	8.1	15	15.0		
Confidence in taking PrEP in the next month	will not or not sure	14	7.0	8	8.1	6	6.0	0.1	0.767
	sure will be taking	185	93.0	91	91.9	94	94.0		
Confidence in ability to take PrEP daily	not able or not sure	8	4.0	5	5.1	3	3.0	F	0.498
	fully able	191	96.0	94	94.9	97	97.0		

SMS, Short Message Service; MOUD, medications for opioid use disorder; PHQ-9, patient health questionnaire, 9-item version; PWID, people who inject drugs; UAH, Ukrainian hryvnia.
"F" denotes that an expected count was below 5 and Fisher's exact test was used.

Table 3
Concordance between self-reported and laboratory markers of PrEP adherence.

		Month 3								Month 6							
		Total		TFVdp (quantifiable)			FTCtp (quantifiable)			Total		TFVdp (quantifiable)			FTCtp (quantifiable)		
		N Col%		N Row%		Kappa Sig.	N Row%		Kappa Sig.	N Col%		N Row%		Kappa Sig.	N Row%		Kappa Sig.
	Total	157		40	25.5		41	26.1		158		28	17.7		40	25.3	
Study arm	SMS	81	51.6	22	27.2		24	29.6		81	51.3	19	23.5		23	28.4	
	No SMS	76	48.4	18	23.7		17	22.4		77	48.7	9	11.7		17	22.1	
Gender	female	42	26.8	8	19.0		11	26.2		42	26.6	4	9.5		8	19.0	
	male	115	73.2	32	27.8		30	26.1		116	73.4	24	20.7		32	27.6	
Ability to take PrEP last month	poor to moderate	12	7.7	3	25.0	0.958	1	8.3	0.141	12	7.6	1	8.3	0.192	2	16.7	0.179
	good to excellent	144	92.3	37	**25.7**		40	**27.8**		146	92.4	27	**18.5**		38	**26.0**	
Percentage of doses taken last month	<=95 %	29	18.7	11	37.9	0.098	12	41.4	0.043	36	22.8	5	13.9	0.668	8	22.2	0.432
	>95 %	126	81.3	29	**23.0**		29	**23.0**		122	77.2	23	**18.9**		32	**26.2**	
Frequency of PrEP taking daily last month	not always	24	15.4	8	33.3	0.348	9	37.5	0.175	40	25.3	7	17.5	0.672	9	22.5	0.753
	always	132	84.6	32	**24.2**		32	**24.2**		118	74.7	21	**17.8**		31	**26.3**	
N of days since the last dose taken	8 or more	10	6.4	2	20.0	0.252	2	20.0	0.012	6	3.8	0	0.0	0.107	0	0.0	0.096
	2–7	28	17.8	5	17.9		2	7.1		14	8.9	0	0.0		0	0.0	
	0–1	119	75.8	33	**27.7**		37	**31.1**		138	87.3	28	**20.3**		40	**29.0**	
Confidence in taking PrEP in the next month	will not or not sure	6	3.8	1	16.7	0.614	1	16.7	0.591	23	14.6	3	13.0	0.044	8	34.8	0.118
	sure will be taking	151	96.2	39	**25.8**		40	**26.5**		135	85.4	25	**18.5**		32	**23.7**	
Confidence in ability to take PrEP daily	not able or not sure	6	3.8	1	16.7	0.614	1	16.7	0.591	3	1.9	0	0.0	0.304	0	0.0	0.296
	fully able	151	96.2	39	**25.8**		40	**26.5**		155	98.1	28	**18.1**		40	**25.8**	

FTCtp, emtricitabine triphosphate; TFVdp, tenofovir diphosphate. Bolded figures represent positive predictive values.

the feasibility of a community-based model of PrEP delivery but found a very low level of adherence to daily oral PrEP according to TFV/FTC metabolite quantification in DBS. The study intervention, SMS reminders, did not have a significant effect on PrEP adherence.

PrEP adherence

No more than 26 % of participants in our study had quantifiable levels of TFV/FTC metabolites, despite most self-reporting high adherence (taking ≥95 % of doses). In comparison, the quantifiable level of plasma tenofovir was found in 67 % of the main BTS trial participants who were tested at study exit (Choopanya et al., 2013), representing consistent uptake over an extended period of time. Some participants could take the medication intermittently, rendering the intervention sufficient to reduce the risk of HIV in the entire cohort. Such high level of adherence, compared to our study, may be explained by several important aspects of the BTS. First, it recruited participants at drug treatment centers, where the frequency of illicit drug use was relatively low: 63 % injected within 3 months before enrollment, and only 23 % injected at month 12 (Martin et al., 2014), while participants of our study were mostly out of treatment, injected in 30 days before baseline, and 85 % continued to inject at month 6. Drug injection frequency correlates with severity of addiction, which adversely affects treatment adherence through multiple mechanisms (Altice et al., 2010). Second, the BTS participants took PrEP under daily clinical observation on average 87 % of the time, which is a known method to ensure treatment adherence for a number of chronic conditions, and were incentivized for each visit. In our study only the first dose was observed, the rest were dispensed for take-home intake, and incentives were provided only for survey completion. Another difference is related to the time of adherence assessment – in the BTS the blood sample was obtained at the end of observation, which on average was 4 years, and importantly there was no obvious difference in seroconversion rates until after 3 years of observation, which may indicate delayed uptake within this population. In our study observation was limited to 6 months, and even though the numbers were small, we observed an increase in the number of participants with consistent adherence from 2 to 5 people over this short period, which may also reflect this trend towards delayed uptake.

To the best of our knowledge, since the BTS, only two published studies assessed PrEP adherence using biological markers among PWID. Both of these studies had small sample sizes and poor retention, which limits our ability to compare and interpret the low level of adherence observed in our study to existing evidence. In the Project SHE demonstration study among women who inject drugs, only three of 13 participants who provided samples at week 24 (of 74 who started PrEP) had detectable levels of TFV in urinalysis, and one had a level indicative of consistent adherence (Roth et al., 2021). In the ANCHOR study of people with opioid use disorder and HCV, of 29 participants who initiated PrEP, 13 were retained by week 24, 10 of those had detectable TFVdp level in DBS, and 6 had level associated with daily PrEP (Brokus et al., 2022). Combined, these findings suggest that PrEP adherence in PWID may vary, but low retention in both studies limits their generalizability.

Validity of self-report

A central finding in this study is the low validity of self-report of PrEP uptake among PWID: no more than 31 % of good-to-perfect self-reported adherence was confirmed by laboratory markers. This did not vary much across the four standard adherence questions as well as participants' confidence in their ability to take PrEP as prescribed. No more than 4 % of participants had TDFdp levels reflective of consistent PrEP use (4+ doses/week).

Concordance between the laboratory and self-reported adherence was not analyzed in the BTS, but the crude comparison of quantifiable tenofovir level in a subsample of participants (67 % [100/151]) (Choopanya et al., 2013) with self-report in the entire cohort (61 %

Table 4
Predictors of quantifiable levels of TDF/FTC metabolites in DBS (multivariable model results).

		TFVdp			FTCtp		
		beta	Sig	aOR (95 % CI)	beta	sig	aOR (95 % CI)
Study arm	SMS	*ref*					
	No SMS	−0.68	0.110	0.5 (0.2–1.2)	−0.56	0.104	0.6 (0.3–1.1)
Visit	month 3	*ref*					
	month 6	−0.67	0.060	0.5 (0.3–1.0)	−0.08	0.803	0.9 (0.5–1.7)
Gender	female	*ref*					
	male	0.63	0.222	1.9 (0.7–5.1)	0.13	0.752	1.1 (0.5–2.5)
Age category at baseline, years	<=40	*ref*					
	51 or more	−1.36	0.122	0.3 (0.0–1.4)	−0.28	0.642	0.8 (0.2–2.5)
Any injection risk in the past 30 days*	no	*ref*					
	yes	0.43	0.310	1.5 (0.7–3.5)	1.22	**0.001**	3.4 (1.6–7.0)
Overdose in 6 months	no	*ref*					
	yes	−1.79	0.104	0.2 (0.0–1.4)	−2.83	**0.016**	0.1 (0.0–0.6)
Injection frequency in the past 30 days	less than daily	*ref*					
	none	0.58	0.352	1.8 (0.5–6.0)	0.77	0.150	2.2 (0.8–6.2)
	daily or more	−0.27	0.545	0.8 (0.3–1.8)	−0.38	0.312	0.7 (0.3–1.4)
MOUD at present	no	*ref*					
	yes	−0.03	0.941	1.0 (0.4–2.3)	−0.15	0.691	0.9 (0.4–1.8)
Alcohol use in the past 30 days	no	*ref*					
	yes	0.71	0.112	2.0 (0.8–4.9)	0.58	0.108	1.8 (0.9–3.7)
Depression (PHQ-9)	none or mild	*ref*					
	moderate to severe	0.20	0.631	1.2 (0.5–2.7)	0.66	0.060	1.9 (1.0–3.8)
Confidence in taking PrEP in the next month	will not or not sure	*ref*					
	sure will be taking	0.36	0.629	1.4 (0.3–6.1)	−0.64	0.257	0.5 (0.2–1.6)

* Self-report of any of the four: receptive syringe sharing, using pre-filled syringe, back-or front-loading, or container sharing.
The multivariable generalized linear mixed models included all variables shown in the table as fixed effects and participant ID as a random effect. SMS, Short Message Service; MOUD, medications for opioid use disorder; PHQ-9, patient health questionnaire, 9-item version; DBS, dried blood spots; FTCtp, emtricitabine triphosphate; TFVdp, tenofovir diphosphate.

[1462/2413] taking PrEP at least 90 % of the time) (Martin et al., 2015) suggests that it was likely substantial. In the open-label extension of the BTS, self-reported adherence was much lower (39 % of adherent days on average compared to 84 % in the parent study), which the authors attribute to reduced incentives (Martin et al., 2017). Because of the absence of laboratory data in the extension phase the true level of adherence is unknown, but a large reduction indicates that a substantial number of participants accurately reported non-adherence. The validity of self-report was also low in the Project SHE (Roth et al., 2021), but relatively high in the ANCHOR study (Brokus et al., 2022), however the results may be biased by high attrition.

The concordance between PrEP self-report and biomarkers was analyzed in a number of non-PWID studies, with varying results. Among MSM, strong correlation was found in the open-label extension of iPrEX (83 % positive predictive value) (Amico et al., 2016), and TAPIR study (correlation coefficient >0.2)(Blumenthal et al., 2019), but was low in TRUST-PrEP (correlation coefficient ranging from 0.02 to 0.2) (Adeyemi et al., 2023) and ATN-123 (kappa between 0.2 and 0.3) (Baker et al., 2018). Among young women in the FEM-PrEP, the exceptionally high self-report of taking PrEP on at least 6 of the previous 7 days at 95 % of the visits was confirmed in as few as 38 % of cases (Agot et al., 2015), leading to the early termination of the trial.

Relatively few studies examined the reasons for inaccuracy of PrEP self-report. The qualitative sub-study of FEM-PrEP indicated that the main reason for over-reporting of PrEP use was the fear of being terminated from the trial (Corneli et al., 2015). In our study, we did not penalize participants for reporting non-adherence to PrEP, which was explicitly stated in the consent form and reiterated before the interviews, nevertheless we cannot fully exclude this factor. We hypothesize that the main reason for over-reporting adherence in our study was the social desirability bias, which is particularly prevalent among PWID (Latkin et al., 2016; Rao, Tobin, Davey-Rothwell & Latkin, 2017). It is also likely to compromise the validity of self-report on ART adherence in this population (Kerr et al., 2008). Interestingly, in the 2020 bio-behavioral survey of PWID in Kyiv, 5.2 % admitted taking PrEP after being explained what it was (Titar et al., 2021). Given the estimated population size and the total number of PrEP clients in that period, this represents a major over-reporting, which may also result from the presumed social desirability of this behavior among PWID.

Predictors of PrEP adherence

In our study we found no significant associations between potential predictors and longer-term PrEP intake indicated by quantifiable TFVdp, and only two variables associated with recent PrEP intake measured by FTCtp. Self-reported injection risk (any of the four behaviors assessed in the study) was positively associated with recent PrEP intake, suggesting that episodes of high-risk exposure may have triggered PrEP use to reduce the risk. The negative association between recent PrEP intake and overdose in the past 6 months was an unexpected finding that warrants further investigation.

Limitations

In addition to the key strengths of our study, being the use of laboratory measures of PrEP uptake and relatively large sample size (the largest since the BTS), several important limitations should be acknowledged. The participants were recruited mostly as clients of harm reduction programs and the visits were conducted at a harm reduction site, which could lead to a perception of low injection risk and additional protection from PrEP being unnecessary. The study interviews were conducted during the study visits in conjunction with PrEP dispensing and intensive adherence counseling. Despite being done by different staff, it could strengthen the social desirability bias.

Conclusion

Major policy makers and funders are actively supporting and prioritizing the expansion of PrEP for PWID (American Psychological Association, 2020; Shaw et al., 2023). Substantial resources are invested in the implementation research (i.e. on awareness, feasibility, provider attitudes, and supportive interventions) on PrEP among PWID. Yet these recommendations and the overall enthusiasm are based on the assumption of universal effectiveness derived from a single clinical trial.

The results of the Bangkok Tenofovir Study, although compelling, are limited in terms of generalizability as it involved mostly former PWID, and adherence was strongly boosted by incentivized daily supervision – a model that is hardly feasible for the majority of PWID. Our study findings suggest that adherence to daily oral PrEP in actively injecting out-of-treatment PWID may not be attainable in real-world settings, even if supported with intensive counselling and SMS reminders.

These results urge for a critical review of the existing evidence and programmatic guidance on PrEP among PWID. More trials using laboratory markers are needed to verify whether daily PrEP is an option for mainstream HIV prevention programs for PWID. The emerging long-acting PrEP formulations hold promise in overcoming the adherence concerns and confirming PrEP as a viable strategy alongside other evidence-based prevention interventions, but their feasibility and efficacy are yet to be tested in PWID populations.

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Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval

The authors declare that they have obtained ethics approval from an appropriately constituted ethics committee/institutional review board where the research entailed animal or human participation.

The protocol was reviewed and approved (reference #2020–009–02) by the IRB#1 of the Ukrainian Institute on Public Health Policy (FWA #00,015,634).

The authors declare that the work reported herein did not require ethics approval because it did not involve animal or human participation.

CRediT authorship contribution statement

Kostyantyn Dumchev: Conceptualization, Methodology, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Marina Kornilova:** Conceptualization, Funding acquisition, Investigation, Writing – review & editing. **Olena Makarenko:** Project administration, Writing – review & editing. **Svitlana Antoniak:** Methodology, Writing – review & editing. **Mariia Liulchuk:** Resources, Writing – review & editing. **Mackenzie L. Cottrell:** Resources, Writing – review & editing. **Olga Varetska:** Funding acquisition, Supervision, Investigation, Writing – review & editing. **Olga Morozova:** Methodology, Supervision, Validation, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

According to the data sharing policy of the Alliance for Public Health, the data obtained from this study cannot be made publicly available due to privacy or ethical restrictions. However, it can be provided upon a reasonable request, which should be directed to office@aph.org.ua.

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Supplementary materials

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