

PrEP Persistence Among Key Populations in Ukraine: Analysis of Scaled PrEP Program Data from
October 2020 through February 2022

Olga Vitruk

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Committee:

Nancy Puttkammer

Lisa Manhart

Monisha Sharma

Program Authorized to Offer Degree:

Department of Epidemiology

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Olga Vitruk

University of Washington

Abstract

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Olga Vitruk

Chair of the Supervisory Committee:

Nancy Puttkammer

Department of Global Health

Background

While global HIV incidence has rapidly decreased during the last decade, Central and Eastern Europe have experienced a significant rise in new cases annually. Ukraine, located in Eastern Europe, has been one of the most ambitious in the region in implementing programs to combat HIV since 2017, including expanding access to PrEP among key populations starting in 2020. Little is known about persistence on PrEP in subpopulations accessing it in Ukraine.

Methods

Ukraine's PrEP program was implemented in 40 health care facilities in 11 high-burden regions in Ukraine. We analyzed data from program initiation on October 1, 2020 through February 23, 2022. A Sankey diagram was constructed to visualize times between the first four PrEP visits. We conducted a Kaplan-Meier analysis to estimate persistence time for each key group, stratifying by men who have sex with men (MSM), people who inject drugs (PWID), sex workers (SW), and discordant couples and other people vulnerable to HIV acquisition (DC/Other). We also evaluated whether persistence varied by sex

and age using the Kaplan-Meier method. We used a Cox regression, clustering by healthcare facility, to estimate hazard ratios for non-persistence by key group and sex, and adjust for age as a potential confounding factor.

Results

There were 2,033 clients newly starting PrEP with up to 510 days of observation. 65% of clients were males, with a median age of 35 years [IQR=29-42] and 35% were females with a median age of 37 years [IQR=31-43]. There were 51% DC/Other, 22% MSM, 22% PWID and 5% SW. The number of days between visits varied across clients and visit timepoints. Among clients returning to collect a 2nd PrEP prescription, 81% returned within 1-45 days after their previous visit, and 3% discontinued PrEP and then re-initiated after 106 days or more. Six-month persistence estimates were highest overall among PWID (28.9%; 95% CI: 23.4-35.7%), moderate in comparison among SW (18.5%; 95% CI: 11.1-30.8%) and DC/Other (12.7%; 95% CI: 10.0-16.0%), and dropped to nearly 0 among MSM (0.8%; 95% CI: 0.1-5.8%). Individuals aged 26 and above were slightly more likely to persist on PrEP longer than younger individuals and females were slightly more likely to persist on PrEP than males. PrEP persistence calculated using the Kaplan-Meier method differed significantly by key group and age ($p < 0.05$), but not by sex. In the Cox regression model, compared with the female DC/Other reference group and adjusted for age, female PWID had the lowest risk of PrEP discontinuation (adjusted HR [aHR] 0.59; 95% CI: 0.31-1.11) while male SW had the highest discontinuation risk (aHR 1.87, 95% CI: 0.57-6.11), although findings were not statistically significant.

Conclusion

PrEP persistence at 6 months was low with the majority of individuals discontinuing PrEP by 6 months. Further research examining barriers and facilitators of persistence by groups can inform interventions to increase PrEP persistence.

Introduction

While global human immunodeficiency virus (HIV) incidence has rapidly decreased during the last decade, Central and Eastern Europe (CEE) have experienced a significant rise in incidence (Gogenkin et al., 2023). Historically, this region had reported long-term low HIV prevalence; however, multiple factors and large-scale conflicts, such as the collapse of the former Soviet Union (USSR), challenged health systems and the socioeconomic environment. These factors contributed to a reported nearly 60% increase in annual new HIV infections between 2010 and 2015 in countries of the former USSR. In the years that followed, incidence continued to climb and was further facilitated by factors such as limited resources, stigma and harsh laws against key groups most affected (Gogenkin et al., 2023). The diverse political and economic environments of CEE countries have made addressing the epidemic in a unified way across the region challenging (Gogenkin et al., 2023).

Ukraine has the second largest population of people living with HIV (PLH) in Eastern Europe; 245,000 people were living with HIV as of 2021 (Vasylyev et al., 2022). HIV primarily affected people who inject drugs (PWID), mainly men, at the start of the epidemic. However, sexual transmission has been the main driver of Ukraine's epidemic since 2008 (Joint United Nations Programme on HIV/AIDS [UNAIDS], 2020). According to 2021 data, the epidemic is largely concentrated in several key populations with highest rates of HIV: These consist of approximately 87,000 sex workers (SW), 179,000 men who have sex with men (MSM), 350,000 PWID, 47,000 prisoners and 8,000 transgender people (UNAIDS). Geographically, the epidemic is concentrated in seven regions, with six of them in the Southern and Eastern parts of the country (UNAIDS, 2020) (Figure 1). In 2017, the country formally committed to the UNAIDS 90-90-90 Fast-Track targets and has achieved significant progress. Since 2017, multiple large-scale projects to accelerate HIV prevention and control efforts have been launched, many of which are funded by the United States President's Emergency Plan For AIDS Relief (PEPFAR), to target regions where burden is highest.

Current HIV prevention focuses on numerous combination approaches. A core approach has been oral pre-exposure prophylaxis of HIV (PrEP), consisting of daily oral TDF/FTC 300 mg/ 200mg, which is highly effective at reducing infections when used with high adherence (Baeten et al., 2012). In

Europe, PrEP was first introduced in France in 2016 and the roll-out has been slow yet steady overall, though inequalities in availability and access result in low coverage of people with the highest need (Gogenkin et al., 2023). PrEP was introduced in Ukraine in 2017 as part of a pilot project for MSM and transgender people, implemented by the International Public Health Alliance Charitable Foundation and funded by PEPFAR (UNAIDS, 2020). Due to the pilot project scope, PrEP was provided primarily to MSM starting in 2017. In addition to scaling up PrEP, Ukraine implemented new protocols for HIV testing and treatment in compliance with World Health Organization (WHO) guidelines (WHO, 2019). This included adding HIV screening as part of primary healthcare, and adopting a unified HIV/TB/Hepatitis approach to counter these epidemics concurrently, both starting in 2019 (UNAIDS, 2020). In 2021, over 5,700 people received PrEP, and Ukraine had the highest number of PrEP-offering centers (24 centers) among all CEE countries (Gogenkin et al., 2023). Ukraine has committed to achieving the 95-95-95 UNAIDS targets.

The International Training and Education Center for Health (I-TECH) is a PEPFAR partner providing Ukraine with support and technical assistance (TA) to improve the HIV care cascade, with the goal of achieving the 95-95-95 targets. I-TECH has been working with Ukraine since 2011 to broadly improve service provision for PLH, and in 2020-2022 it provided TA with a particular focus on 40 hospitals and clinics in 11 regions of Ukraine to scale up and improve PrEP programs (Figure 1). This initiative was supported with funding from the Health Resources and Services Administration (HRSA) under PEPFAR and with guidance from the US Centers for Disease Control and Prevention (CDC). As is the case in all PEPFAR supported programs, PrEP is provided to clients cost-free (PEPFAR, 2021). I-TECH's TA expanded PrEP reach among SW, MSM, PWID, Discordant Couples (DC), and other people vulnerable to HIV acquisition.

Figure 1 Map of Ukraine with 11 oblasts containing 40 healthcare facilities included in the program highlighted in yellow, with number of facilities per oblast indicated



Studies evaluating PrEP persistence in other settings show that persistence is generally short, with 50% or more of users discontinuing within 6-12 months (Laborde et al., 2020). While national data indicates that PrEP uptake has been increasing steadily since it was first introduced in Ukraine in 2017, there is no existing information regarding persistence in this setting. How long clients typically take PrEP is important to understand as this translates to added protection from acquiring HIV. The goal of our analysis was to estimate PrEP persistence rates in key population groups and see if rates varied by sex and age in Ukraine from 2020 through 2022. We also sought to identify characteristics of people who did not continue/persist on PrEP in order to target assistance to those individuals.

Methods

Study Design and Setting

We analyzed data from Ukraine's scaled PrEP program from October 1, 2020, when I-TECH began providing technical assistance in 40 healthcare facilities to scale up PrEP, through February 2022 when Russia invaded Ukraine.

The standard operating procedure (SOP) for Ukraine's PrEP program follows international guidelines and requires clients to be screened for HIV infection and complete other PrEP screening procedures before being eligible to initiate PrEP. Upon receiving PrEP, clients are to be counseled regarding risk reduction, importance of sexually transmitted infection (STI) testing, PrEP adherence and adherence strategies, detecting acute infection, PrEP side effects, and family planning methods. Initially a 30 days' supply of PrEP is to be prescribed and a subsequent visit should be scheduled approximately one month later.

After the one-month post PrEP initiation visit where clients obtain their first PrEP refill, clients are asked to come for consultation and medication refill every 3 months thereafter, and enough medication is dispensed at each visit to last the client until their next visit. In practice, however, there have been variations in SOP compliance, with providers prescribing 30-90 day supplies of medication between visits even at the onset of PrEP usage. HIV testing, acute HIV infection screening, PrEP adverse effects assessments, PrEP adherence counseling, and other STI and health assessments are conducted at each visit. All client and visit information is recorded on the client's medical card and in the Information System for Socially Significant Diseases (IS-SSD), Ukraine's electronic health record system. If clients are diagnosed with HIV, this is recorded and they receive HIV antiretroviral therapy (ART) in place of PrEP.

A secondary analysis of medical record data was conducted for 2,033 clients seen at 40 ART sites in 11 high-priority regions with high HIV incidence. The regions or oblasts are located in central, southern and eastern Ukraine (Figure 1).

Study Participants

We included new PrEP users (defined as those who had not taken PrEP before enrollment), initially seen at one of the 40 program facilities, 18 through 70 years old, and members of the following key risk groups: SW, PWID, and MSM, DC, and other people vulnerable to HIV acquisition. Current gender was not collected during the timeframe of this analysis, so it was not possible to know whether people were transgender.

Data collection

Birthdate, sex, behavioral risk factor or key group type, and treatment facility were collected by health facility staff for all clients upon program entry. Dates of consultations with infectious disease specialists, PrEP issuance and HIV testing were recorded. The dataset was constructed by I-TECH Ukraine staff using monthly extracts provided by the Public Center of the Ministry of Health of Ukraine (PHC) using secondary data from the IS-SSD and facility-level PrEP program registers.

Data Analysis

A Sankey diagram was constructed to visualize the number and percentage of clients returning 0-45, 46-75, 76-105, or >105 days after their prior PrEP visit, or not returning at all. Understanding refill frequencies helped us determine the persistence definition for our primary analysis.

The key groups (MSM, PWID, SW, and DC/Other) were our primary exposure and persistence on PrEP was our primary outcome. Persistence was defined by refilling PrEP medications within 75 days of the previous visit. We also examined persistence by sex and age groups (18-25, 26-45, and 46-70 years).

Our primary analysis was a time-to-event analysis to estimate the proportion of the population persisting on PrEP six months following PrEP initiation. We also stratified by key group, sex and age categories, constructing a Kaplan-Meier curve to estimate persistence time for each group. We used a Cox regression to compare the probability of discontinuing PrEP for key groups while adjusting for sex and age, clustering on healthcare facilities.

Variable Classification

Standard registration procedures in HIV clinics in Ukraine are not always accurate in identifying stigmatized groups such as MSM or PWID, which underestimates the proportion of cases attributed to these groups (Dumchev et al., 2020). For this reason, we classified people into key groups based on both pieces of data available regarding their group membership: examination code and group type. Group types were assigned by health workers at the time of PrEP enrollment and included SW, DC, MSM, PWID, and other people vulnerable to HIV acquisition. Examination codes represented the client's reason

for testing for HIV, and included more granular categories than the group type variable, including pregnant people, people who had heterosexual contacts with PLH, people with symptoms of sexually transmitted infections, people who had unprotected sexual contacts with casual sexual partners, and other people vulnerable to HIV acquisition such as those released from prison or experiencing homelessness. We considered both data elements and upcoded clients to PWID, MSM, or SW categories (groups associated with the greatest vulnerability to HIV acquisition, with vulnerability descending by order listed) if there was evidence for this classification in either group type or examination code. For most clients, this led us to consider the group type variable as the primary variable when assigning them to a group. However, the exam code was referenced to re-assign the fourteen women who were coded as MSM per the group type (thirteen into DC/Other and one into SW). One male client that was classified as MSM per the group code who had an exam code indicating PWID was assigned to PWID. We classified clients with recorded group types of DC and those with other heterosexual relationships into the DC/Other group. The examination code was not available for 1.1% of clients while the group code was available for all clients, therefore no one was coded as missing in group membership.

PrEP persistence was defined as the time period that a client continued to fill PrEP prescriptions without encountering an interruption or failure event. A failure event (e.g., discontinuing PrEP) was defined as the first instance of a 75 day or greater gap between recorded prescription refills. Our dataset lacked information on how much PrEP medication was dispensed at each visit, and included only the dates of observed visits. We established the 75-day time frame assuming a 60-day refill window plus a 15-day buffer period. We based our definition on a 60-day PrEP supply (rather than a 30 or 90 day supply), to avoid systematically over or under-estimating persistence in absence of information about actual amounts of medication dispensed. For clients that experienced failure events, time on PrEP was calculated as the number of days between their initial prescription and their last refill prior to failing, plus 37 days (the midpoint of the expected 75-day return window). For clients that received a positive HIV test, the date of positive test was their failure date (without addition of any days to calculate their persistence time). For clients who did not experience failure events, time in days was calculated as the number of days between the initial prescription and the administrative censor date of February 23rd, 2022. This was

the day before the Russian invasion of Ukraine, and allowed us to focus on PrEP persistence in the absence of the complex effects of war.

Sensitivity Analysis

Sensitivity analyses with varying persistence definitions were conducted using failure definitions of gaps greater than 45 or greater than 105 days, rather than 75 days (primary definition). Persistence time calculations included addition of the midpoint to the number of days between first prescription and first failure, in the same way that the primary analysis calculations were done (i.e. 22 days added for the 45 day definition and 52 days for the 105 day definition). Analyses were completed in R version 4.2.3 and the Sankey diagram was made using SankeyMATIC.

Results

Demographic Information

We identified 2,033 total first-time PrEP users, of whom 65% were males and 35% were females (Table 1). Males had a median age of 35 years [IQR=29-42] and females had a median age of 37 years [IQR=31-43]. Our sample population consisted of 51% DC/Other, 22% MSM, 22% PWID and 5% SW.

Table 1 Characteristics of clients aged 18-70 years enrolled in PrEP program between October 1 2020 through February 23 2022 in 40 health facilities in 11 high HIV-burden regions in Ukraine*

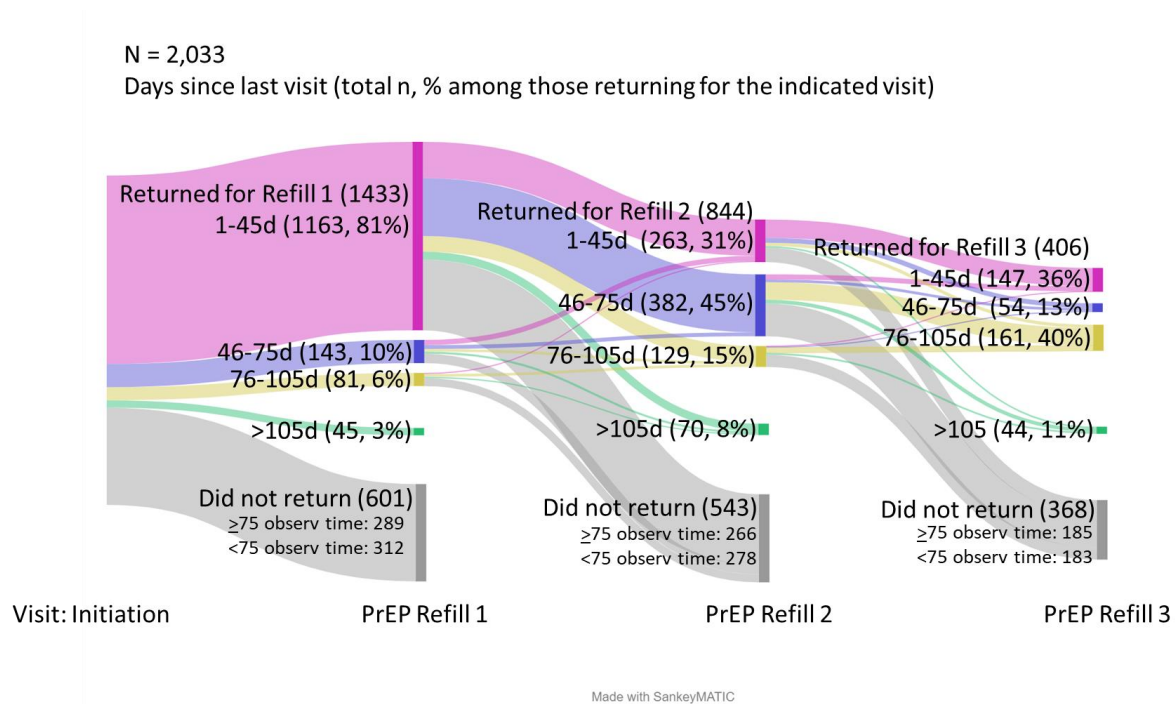
	DC/Other 1042 (51%)	MSM 453 (22%)	PWID 437 (22%)	SW 101 (5%)	Total 2,033
Males	486 (47%)	453 (100%)	364 (83%)	9 (9%)	1312
Age (years) Median [IQR]	37 [32-45]	30 [23-38]	36 [32-41]	35 [30-40]	35 [29-42]
18-25 years	45 (4%)	157 (35%)	18 (4%)	1 (1%)	221
26-45 years	328 (31%)	235 (52%)	301 (69%)	6 (6%)	870
46-70 years	113 (11%)	61 (13%)	45 (10%)	2 (2%)	220
Females	557 (53%)	NA (0%)	73 (17%)	92 (92%)	722
Age (years) Median [IQR]	37 [32-43]	NA	35 [31-39]	34 [25-44]	37 [31-43]
18-25 years	58 (6%)	NA (0%)	4 (1%)	25 (25%)	87
26-45 years	395 (38%)	NA (0%)	64 (15%)	47 (47%)	507
46-70 years	103 (10%)	NA (0%)	5 (1%)	20 (20%)	128

*PWID = People who inject drugs, MSM = Men who have sex with men, SW = Sex workers, DC/Other = Discordant couples and other people vulnerable to HIV acquisition; NA: No individuals in this group

Frequency of PrEP Prescription Refills

The number of days between visits varied across clients and visits 1 through 4, from 1 - 377 days (results not shown). Most clients that returned for their first PrEP refill returned within 45 days after initiation (81% among those with a first refill visit), while the largest share with a second PrEP refill visit returned within 46-75 days after their first refill visit (45% among those with a second refill visit) (Figure 2). A small percentage of clients discontinued PrEP and then re-initiated after 106 days or more after visits 1-3 (3%, 8%, 11%, respectively). Among 217 people that returned for their fourth refill, 49% completed this visit within 1-45 days, 7% within 46-75 days, and 29% within 76-105 days of their third refill (results not shown). Among 52 returning for a sixth refill, 71% completed this visit within 1-45 days, 6% within 46-75 days, and 8% within 76-105 days of visit 6 (results not shown). These calculations include all clients returning for their fourth and sixth refills, regardless of time between prior visits or prior episodes of stopping and restarting PrEP.

Figure 2 Number and percentage of clients in Ukraine returning 0-45, 46-75, 76-105, >105 days, or not returning at all, since their prior PrEP refill visit. Those who returned >105 days after the prior visit likely stopped and then restarted PrEP. Clients that did not return were broken down by those with ≥ 75 days observation time and those with <75 days before administrative censoring. Percentages shown are calculated from the total number of clients returning for that visit (i.e. excluding those that did not return at all from the percentage calculation).



Legend for horizontal lines (“nodes”) and connections between nodes (“links”):

- Pink: Clients that returned within 45 days (from previous visit) for visit indicated
- Blue: Clients that returned within 46-75 days (from previous visit) for visit indicated
- Yellow: Clients that returned within 76-105 days (from previous visit) for visit indicated
- Green: Clients that returned after >105 days (from previous visit) for visit indicated
- Gray: Clients that did not return (from previous visit) for visit indicated

Persistence Estimates and Hazard Ratios

Overall persistence at 6 months was 14.2% (95% CI: 12.1-16.6%) in our primary analysis using a 75-day (after the previous refill) definition of failure time (Figure 3). For the sensitivity analysis, we constructed Kaplan Meier curves according to varied definitions of discontinuation. We estimated PrEP persistence using a more conservative assumption regarding failure time (45 days after the last refill) and a more liberal assumption definition (105 days after the last refill). Defining PrEP discontinuation after 45 days, the six-month persistence estimate for the 45 day definition was 5.7% (95% CI: 4.3-7.4%), whereas the six-month persistence estimate was 41.9% (95% CI: 39.0-45.0%) when we defined PrEP discontinuation as occurring after 105 days.

Persistence at 6 months was highest overall among PWID (28.9%; 95% CI: 23.4-35.7%) (Table 2). Persistence dropped to nearly 25% by 3 months among SW and then plateaued slowly at 6 months (18.5%; 95% CI: 11.1-30.8%) (Figure 4). The lowest persistence estimates at 6 months were among DC/Other and MSM; persistence for DC/Other declined to 12.7% by 6 months (95% CI: 10.0-16.0%) while persistence for MSM consistently declined to 0.8% by this time (95% CI: 0.1-5.8%) . The Kaplan-Meier curve for 18–25-year-olds versus 26-70 year olds demonstrates that individuals in the older age group were slightly more likely to persist on PrEP longer (Figure 5). Females were slightly more likely to persist on PrEP longer than males (Figure 6). Median persistence estimates also followed these trends, with lowest values observed among MSM and SW (Figure 7). Differences by key group and age were statistically significant ($p < .05$), while differences by sex were not.

Table 2 Kaplan Meier persistence estimates at 6 months for clients aged 18–70 years who initiated PrEP between October 1 2020 through February 23 2022 across 40 health facilities in Ukraine*

	DC/Other 1042 (51%)	MSM 453 (22%)	PWID 437 (22%)	SW 101 (5%)
Total (N=2,033)	12.7 (10.0-16.0)	0.8 (0.1-5.8)*	28.9 (23.4-35.7)	18.5 (11.1-30.8)
Males	13.1 (9.5-18.1)	0.8 (0.1-5.8)*	27.6 (21.8-34.9)	33.3 (13.2-84.0)*
Age groups				
18-25	15.0 (5.6-39.9)*	3.0 (0.5-17.8)*	35.3 (16.6-75.1)	-
26-45	10.2 (6.4-16.2)	-	28.0 (21.9-35.9)	50 (22.5-100)*
46-70	22.0 (13.7-35.1)	-	23.3 (10.6-51.4)*	-
Females	12.3 (8.8-17.1)	NA	36.2 (23.2-56.4)*	18.0 (10.3-31.4)*
Age groups				
18-25	9.9 (2.8-35.2)*	NA	-	-
26-45	14.8 (10.5-20.8)	NA	36.1 (22.4-58.1)	23.6 (12.9-43.1)
46-70	3.2 (0.6-18.7)*	NA	40.0 (13.7-100)*	28.3 (13.5-59.3)

*PWID = People who inject drugs, MSM = Men who have sex with men, SW = Sex workers, DC/Other = Discordant couples and other people vulnerable to HIV acquisition

NA: No individuals in this group

- 0 individuals at risk at 6 months

* 1-5 individuals at risk 6 months

gray background initial sample size ≤ 20

Figure 3 Kaplan Meier curves for clients in Ukraine displaying probability of persistence on PrEP for sensitivity analyses of discontinuation definitions of 45 days and 105 days, as compared to the main analysis.

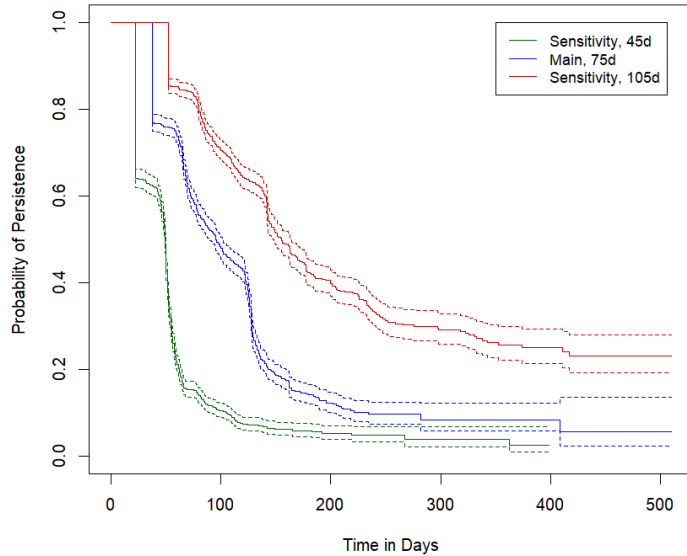
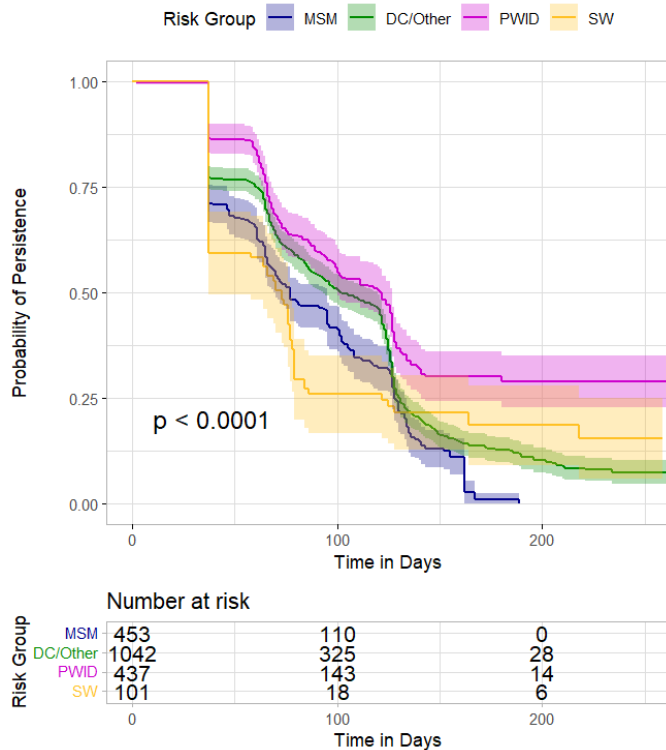
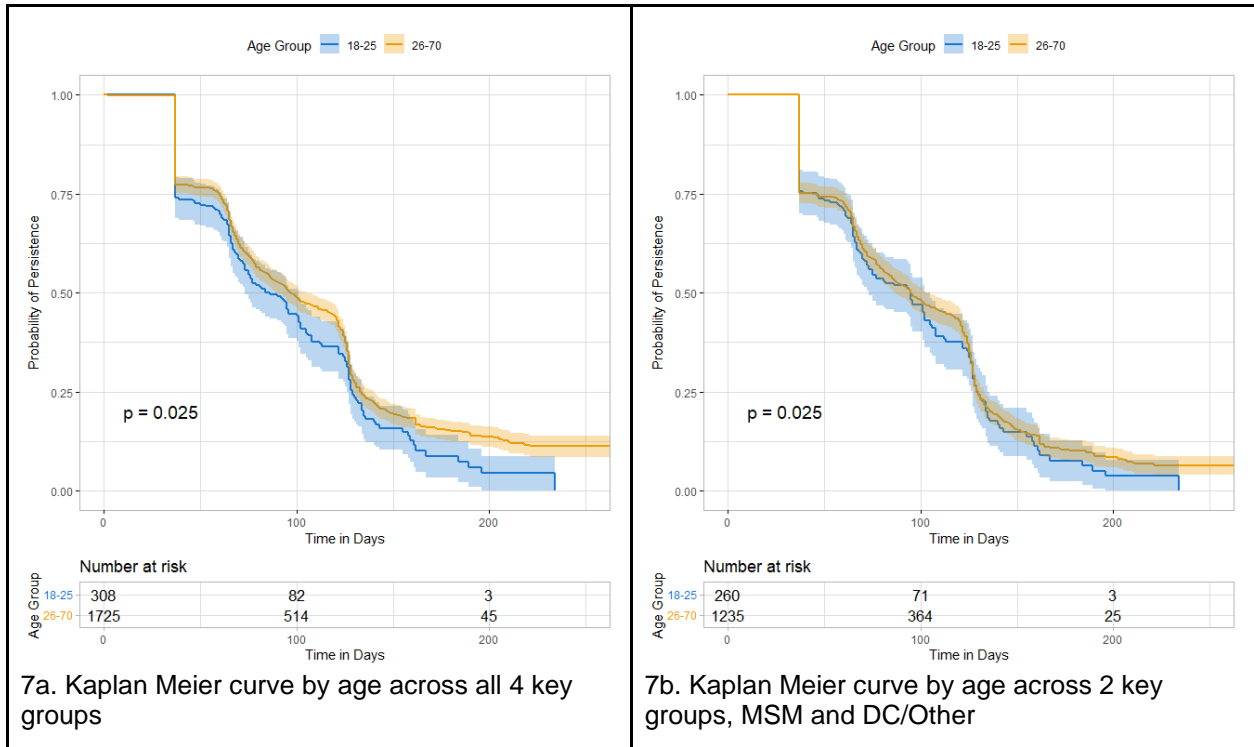


Figure 4 Kaplan Meier PrEP persistence curves for clients in Ukraine, by key population. Number at risk values are zero when all participants have failed or been administratively censored by the time point of interest. Curve is truncated at 250 days, after which there are fewer than 17 total individuals at risk*



*PWID = People who inject drugs, MSM = Men who have sex with men, SW = Sex workers, DC/Other = Discordant couples and other people vulnerable to HIV acquisition

Figure 5 Kaplan Meier PrEP persistence curves for clients in Ukraine, by 2 age groups. Graph 7a is among all four key groups. Graph 7b is among MSM and DC/Other, as the majority of clients in the 18-25 age group belonged to those two key groups. Curves are truncated at 250 days, after which there are fewer than 17 total individuals at risk.*



*MSM = Men who have sex with men, DC/Other = Discordant couples and other people vulnerable to HIV acquisition

Figure 6 Kaplan Meier PrEP persistence curves for clients in Ukraine, by sex. Curve is truncated at 250 days, after which there are fewer than 17 total individuals at risk.

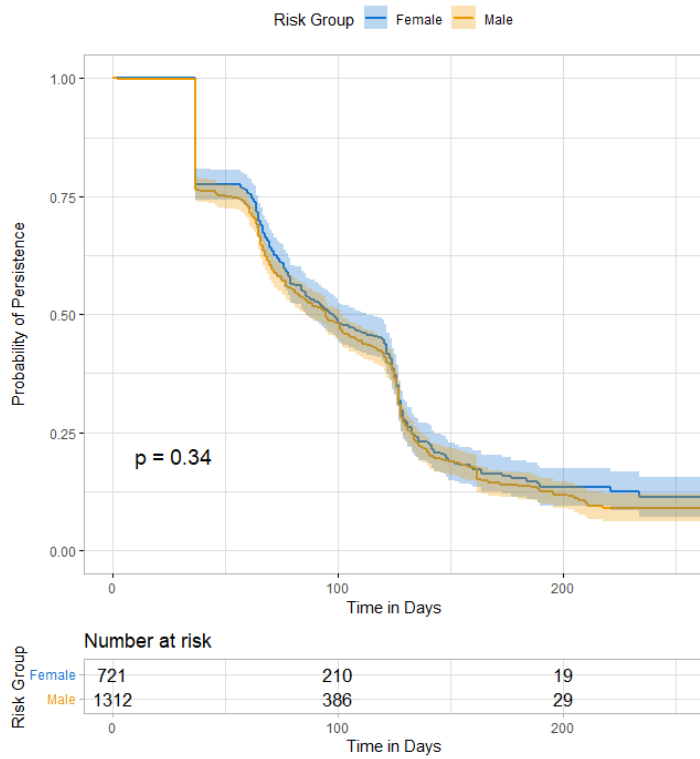
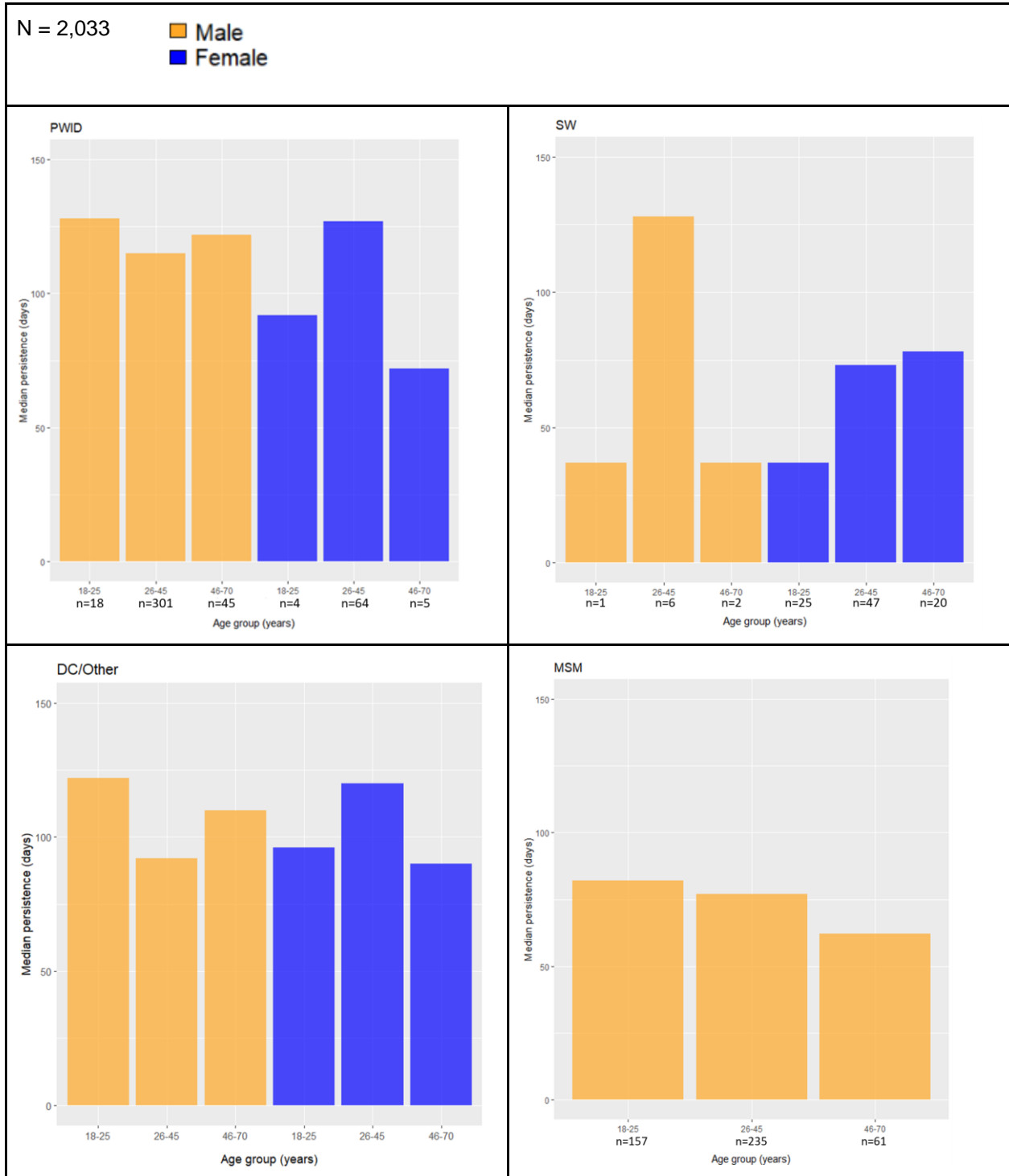


Figure 7 Bar charts showing median PrEP persistence estimates, derived using the Kaplan Meier method, for clients in Ukraine.



*PWID = People who inject drugs, MSM = Men who have sex with men, SW = Sex workers, DC/Other = Discordant couples and other people vulnerable to HIV acquisition

In our multivariable Cox Regression model including key group, sex, and age, age was not a strong predictor of persistence (adjusted HR [aHR] 1.00, 95% CI: 0.99-1.01) (Table 3). Compared with the female DC/Other reference group, female PWID had a 41% lower risk of PrEP discontinuation (aHR 0.59; 95% CI: 0.31-1.11) while male PWID had a 25% lower risk of discontinuation (aHR 0.75; 95% CI: 0.44-1.25). All other groups had higher discontinuation risk as compared to the reference group, the highest being among male SW at 87% greater risk (aHR 1.87, 95% CI: 0.57-6.11). Estimates were not statistically significant.

Table 3 Cox Proportional Hazard Models of PrEP discontinuation for clients in Ukraine, by key group, sex and age

N = 2,033	Adjusted Hazard Ratio (95% Confidence Interval)	P-Value
Key Population, Sex		
DC/Other, Female	REF	REF
DC/Other, Male	1.06 (0.90-1.25)	0.480
MSM, Male	1.32 (0.85-2.06)	0.210
SW, Female	1.28 (0.57-2.87)	0.542
SW, Male	1.87 (0.57-6.11)	0.299
PWID, Female	0.59 (0.31-1.11)	0.102
PWID, Male	0.75 (0.44-1.25)	0.264
Age	1.00 (0.99-1.01)	0.744

*PWID = People who inject drugs, MSM = men who have sex with men, SW = Sex workers, DC = Discordant Couples

Discussion

Clients had low persistence on PrEP, consistent with the global literature on PrEP persistence. Overall, PWID had the highest persistence compared to other key groups. People belonging to the DC/Other, SW, and MSM groups all showed signals of elevated discontinuation relative to PWID. Male clients were slightly less likely to persist than females, though looking at sex by key group rather than across all groups is likely a more effective way to interpret the effect of sex on persistence. People aged 18-25 were slightly less likely to persist than those aged 26 and above. Results from our Cox regression comparing persistence by key group adjusting for age were not statistically significant. This might be due

to our low sample size which did not provide sufficient power to detect differences among groups. Further studies with larger sample sizes are needed to answer this question. By clustering on healthcare facilities in the Cox model, we may have made a conservative assumption about the non-independence of clients served within the same facility, leading to a lack of statistical significance for our findings. Persistence estimates were very sensitive to the discontinuation definition used; If clients typically received a one-month PrEP supply then persistence was much lower, and on the contrary if clients typically received a three month supply then persistence was much higher. Importantly, the effectiveness of PrEP in preventing and reducing HIV incidence hinges on adherence. PrEP refill visit frequency varied greatly among clients.

To our knowledge, our study is the first to examine PrEP persistence in Ukraine and assess PrEP persistence in routine care settings in Eastern Europe. The effectiveness of Ukraine's PrEP program depends not only on persistent use, but also on high uptake among those at greatest risk of HIV. PrEP uptake in Ukraine has been increasing steadily with over 5,711 people using PrEP in 2021 (UNAIDS, 2021). This is a substantial number considering PrEP was first available in Ukraine in 2017 only to a pilot cohort of MSM and transgender people (UNAIDS, 2020). Ukraine's HIV index testing program consistently refers sexual and needle-sharing partners of clients newly diagnosed with HIV to PrEP services, but other efforts may be needed to expand access to PrEP. Uptake is complicated by systemic factors such as provider uncertainty regarding at what point the probability of acquisition is high enough to start clients on PrEP. Uptake is also strained by individual level factors such as depression, substance use and lack of support from family and sexual partners, with effects on PrEP adherence and persistence varying between each person, population and setting (Haberer et al., 2023).

Only a third of the clients in our analysis were women, indicating they may have lower uptake. This was surprising given that the absolute numbers, prevalence and incidence rates of HIV among women and men in Ukraine are very similar (UNAIDS, 2021). As campaigns in Ukraine have primarily focused on MSM and also PWID, most of whom are men, women have not been the focus of many PrEP information campaigns, which could result in less awareness about PrEP among women generally, and may explain why only about a third of clients in our analysis were female. This is further supported by a

study that found that a general lack of information about PrEP was the main barrier for PrEP use among women in Ukraine and across other countries in Europe (Moseholm et al., 2021). Interventions geared toward women could increase their uptake and persistence.

While the increasing PrEP uptake in Ukraine is encouraging, it is additionally important to know how long people stay on PrEP as this is more indicative of their protection from acquiring HIV. Across different countries and settings, PrEP persistence is generally short, with 50% or more of users discontinuing within 6-12 months (Laborde et al., 2020). Our study found that with a failure definition of >75 days, approximately 50% of all clients discontinued PrEP after just 3 months, which is a very short persistence time. The low observed persistence in MSM was unexpected given that MSM have been a primary focus of PrEP campaigns in Ukraine longer than other groups. They were the target pilot population when PrEP was introduced in the country in 2017, and multiple NGOs have focused testing, treatment and condom distribution efforts specifically toward MSM since 2003 (Trickey et al., 2022; UNAIDS, 2020). Intense stigma and discrimination facing sexual minorities in Ukraine is likely a barrier to consistency of health services for MSM (Buliga et al., 2020).

Many PrEP users globally have achieved adherence during periods of potential HIV exposures via event-driven PrEP use, such as taking two pills within 24 hours of a sexual encounter, and then one pill per day the following two days (Haberer et al., 2023). A 2016 study that elicited preferences of PrEP administration in MSM in Ukraine, before PrEP was available in the country, found that more people would be inclined to take PrEP if administration was event-driven, as compared to daily PrEP. The study also found that MSM were slightly more inclined to take PrEP if it was administered via injection (Dubov et al., 2018). The results of this study indicate that taking a daily pill may be challenging for some people, thus making persistence difficult. Though we are not able to distinguish clients on event-driven versus daily PrEP in the data, it is possible that some clients were adhering to this less-frequent administration pattern.

There are multiple interventions that might increase both uptake and persistence in Ukraine. The coformulation of emtricitabine and tenofovir is used for HIV treatment and prevention so oftentimes PrEP use is associated with having HIV, especially when the same facility provides both PrEP and ART

(Haberer et al., 2023). In recent years, Ukraine embarked on an ambitious healthcare reform to make previously hard-to-access specialized care accessible through primary care. Starting in 2019, family physicians began screening for HIV as part of basic primary healthcare (UNAIDS, 2020). Family doctors are an existing touchpoint in the medical system for many potential PrEP clients, and expanding this model by allowing them to prescribe PrEP would streamline linkages into care, and provide an entry into the medical system for some, especially young men. This model has been successful in other countries (Haberer et al., 2023). Because access and stigma are barriers to PrEP uptake in Ukraine, PrEP clients who do not have HIV may be more inclined to seek PrEP from a facility that does not focus solely on HIV care. PrEP uptake and adherence may also be improved by delivery locations being integrated with locations already interacting with key populations. For example, in their study eliciting preferences of PrEP administration in Ukrainian MSM in 2016, Dubov et al. suggested that NGOs providing services to the LGBT community should offer PrEP (2018). Visits and prescriptions over telehealth could also make PrEP more accessible and increase persistence. The addition of mobile clinics offering PrEP has increased PrEP coverage and persistence in other countries, and may be effective in Ukraine as well (Haberer et al., 2023). These interventions may facilitate both PrEP access and persistence, ultimately addressing the issue that we observed in our study where uptake steadily increased but persistence was low. This finding could indicate that people are going out of their way to initiate PrEP but unable to keep engaging with the care needed to stay on PrEP if it is inaccessible or inconvenient.

Suggestions for future research include exploring whether persistence is correlated with visit frequency. Conversations with I-TECH Ukraine staff informed us that providers may have adjusted and become more adherent to SOP-mandated visit patterns as the program matured. We observed a trend toward shorter intervals between visits, rather than longer intervals (90 day intervals) as instructed in the SOP, among people with more visits. It is possible that the short visit intervals among clients completing a great number of visits causally contributed to longer persistence, however. One study found that more frequent interactions with providers promoted adherence in adolescents in the United States (Tanner, 2020). In Ukraine, more frequent visits for PrEP might help overcome unease about using PrEP or reinforce the adoption of the new behavior of taking daily PrEP. Another study in Ukrainian MSM found that across nine possible PrEP delivery programs in their survey, participants were more interested in

taking PrEP if the program included the most demanding evaluation at the initial visit before starting PrEP, as compared to the least demanding and moderately demanding evaluations. The most demanding evaluation included safer sex counseling while the others did not. Authors believe the intensive evaluation lessened some of the participants' unease about taking PrEP (Dubov et al., 2018). It is possible that other groups felt similar unease about this medication and might prefer more thorough medical care (including more intensive and frequent consultations) as they take PrEP, which could impact both uptake and persistence.

Our study is the first to examine PrEP persistence in Ukraine, and our findings contribute to the limited amount of literature on PrEP persistence within Ukraine and among routine care settings in CEE countries. Our exploratory analysis identified potential characteristics of PrEP clients that may not continue on PrEP, among those already disproportionately vulnerable to HIV acquisition. The persistence definition we used included a reasonable time window during which clients were most likely adhering to their PrEP regimen and persisting on PrEP.

There were several limitations to our analysis. First, our analysis focused on approximately the first year and half following implementation with a limited sample size. The sample size for SW was particularly low, and they are a closed group that is hard to reach for specialized medical care. As part of a national sample, 21.3% of SW stated that they avoid health care due to stigma and discrimination, in comparison to 10.3% of PWID and 6.3% of MSM (UNAIDS, 2021). By conducting a similar analysis with a larger sample size in the future, the trends we observed may achieve statistical significance. Second, information on the amount of medication clients received was not collected. Objective monitoring strategies of SOP adherence and persistence will be made easier if the amount of medication is known. Third, we may have observed an artificially smaller proportion of clients in the SW, MSM and/or PWID groups, as some may have registered under DC/Other groupings due to associated stigma. This could have biased the group-specific estimates of PrEP persistence in unpredictable ways (e.g. if MSM individuals were grouped with DC/Other, this may have artificially lowered the average 6 month persistence time among DC/Other, while if SW or PWID were grouped with DC/Other, this may have artificially raised the average 6 month persistence time among DC/Other). Fourth, current gender identity

was not collected and our analysis does not assess transgender clients separately, despite their vulnerability to HIV acquisition. Lastly, although persistence measured by PrEP refill dates is a reasonable proxy for adherence, information regarding pill taking would more closely reflect whether clients had protection from acquiring HIV. Alternative PrEP adherence measures include pill counts, taking pharmacological samples, and self-report, all of which are a better measure than the refill dates available in our study (Haberer et al., 2023; Rao et al., 2022). Though clients were counseled by providers on taking PrEP daily to achieve protection, we do not have sufficient information to determine whether clients may have been following event-driven PrEP usage guidelines. Our inability to distinguish event-driven PrEP could lead to us underestimating persistence and overestimating discontinuation.

We identified sub-groups of key populations already disproportionately vulnerable to HIV acquisition who appear less likely to continue on PrEP. Given the limited information on PrEP persistence in Ukraine overall, further exploring the trends we identified using more robust outcome measures (e.g., adherence measured by pill counts) is recommended to establish programmatic priorities. We also recommend in-depth qualitative studies of barriers and facilitators to persistence among MSM, SW, and DC/Other to understand why they have low PrEP persistence. The findings in our study, coupled with qualitative studies, may bolster interventions that Ukraine plans to test to improve PrEP retention, such as PrEP access through family doctors and via telemedicine, that tailor messages and target groups with lower PrEP persistence. Though this analysis of the pre-2022 war data was conducted after the war outbreak, Ukraine remains ambitious about combating HIV and continues to implement novel, evidence-based approaches even in the context of war. Our findings help identify which populations to allocate efforts towards, with implications across Ukraine and other countries in CEE countries that have similar cultural and health systems, such as Poland and Moldova.

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