Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

A Pilot Study

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PrEP for PWID in Ukraine

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LIST OF ABBREVIATIONS AND ACRONYMS

ACTG	AIDS Clinical Trials Group
AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
ART	Antiretroviral Therapy
ARV	Antiretroviral
AST	Aspartate transaminase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CBO	Community Based Organization
CCMT	Care Coordination Measurement Tool
CI	Confidence Interval
CPCQ	Client Perception of Coordination Questionnaire
CPK	Creatine phosphokinase
CPQA	Clinical Pharmacology Quality Assurance
CQR	Consensual Qualitative Research Method
CRF	Case Report Form
CTM	Care Transition Measure
DBS	Dried Blood Spot
EAE	Expedited Adverse Event
FTC	Emtricitabine
FTC/TDF	Emtricitabine/ Tenofovir Disoproxil Fumarate FTC-TP Emtricitabine Triphosphate
HCCQ	Health Care Climate Questionnaire
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
IRB	Institutional Review Board
MD	Medical Doctor
NIH	(United States) National Institutes of Health
PHC	Public Health Center

PLHIV	People Living with HIV
PrEP	Pre-Exposure Prophylaxis
QA/QC	Quality Assurance/ Quality Control
RNA	Ribonucleic Acid
SA	Substance Abuse
SAE	Serious Adverse Event
SDT	Self-Determination Theory
SOP	Standard Operating Procedure
STD	Sexually Transmitted Disease
STI	Sexually transmitted infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
SW	Social Worker
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
TFV	Tenofovir
TFV-DP	Tenophovir Diphosphate
TSRQ	Treatment Self-Regulation Questionnaire

PROTOCOL TEAM ROSTER

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Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

SCHEMA

Purpose:	To assess the acceptability and feasibility of PrEP for People Who Inject Drugs (PWID) in Kyiv, Ukraine with and without SMS facilitation.
Design:	An 24-week prospective randomized controlled trial of PrEP as usual versus PrEP with SMS facilitation
Population:	HIV-uninfected PWID at risk for HIV infection in Kyiv, Ukraine.
Study Size:	A total of 200 participants randomized 1:1 to experimental and control arms.
Study Regimen:	All participants will be offered once daily oral emtricitabine 200 mg / tenofovir disoproxil fumarate 300 mg (FTC/TDF) combined with SMS facilitation in the experimental arm.
Study Duration:	12 months including closeout activities. Preparatory phase is planned to take 2 months. Recruitment is anticipated to take place over a 2-month period. Each participant will be followed for a total of 6 months. Two months are included for data clean-up and closeout.
Primary Objectives:	To compare adherence to and persistence on daily PrEP prescribed as the fixed dose formulation to PWID randomized 1:1 to PrEP as usual or SMS-enhanced PrEP.
Secondary Objectives:	□ To describe patterns and attributes of PrEP adherence among participants (e.g., SMS intervention acceptance, substance use, sociocultural factors) □ To measure changes in injection and sexual risk taking behavior among study participants □ To describe client- and provider-level barriers to PrEP initiation and adherence
Study Sites:	□ Institute of Epidemiology and Infectious Diseases (Lavra) Clinic □ Club Eney Community Center

1.0 INTRODUCTION

1.1 Background and Prior Research

After a long decline, HIV epidemic among PWID in Ukraine is again showing signs of growth. In the two last rounds of national IBBS, prevalence in young PWID and overall is increasing. Needle and syringe programs (NSP) are a key strategy to prevent HIV among PWID, and Ukraine has reached the recommended level of coverage of 60%. It is evident that substantial increase in frequency of coverage is not feasible for a large number of PWID. Availability of opioid agonist therapy (OAT) also remains suboptimal at 4% of those with opioid dependence. Pre-exposure prophylaxis (PrEP) is a potential strategy to fill the gap in the prevention continuum for PWID in Ukraine and countries with similar epidemics.

PrEP with tenofovir/emtricitibine (TDF/FTC) is an evidence-based HIV prevention strategy recommended for key populations where HIV incidence exceeds 1%. In RCTs, it is effective in both men-who-have-sex (MSM) and people who inject drugs (PWID). PrEP administered ***daily*** with TDF/FTC was approved by the FDA with CDC[1] and WHO providing guidance on its use in MSM in 2012, and in PWID in 2014.[2] PrEP uptake, however, in these highest-risk subpopulations of MSM and PWIDs is low, and adherence to the daily medication regimen is the greatest barrier to scale-up for those who need it most.

PrEP efficacy in both MSM and PWID in RCTs reduces HIV transmission by ~50%. Adherence, however, is the key factor contributing to its success. For example, in the IPrEx study in MSM, self-reported adherence was 51%,[3] though dried blood testing (DBS) suggested it as being only 41%. Similarly, in the Bangkok Tenofovir Study (BTS),[4] self-reported adherence was 67%, though daily supervised monitoring confirmed only 49% adherence. [5] In the BTS, an open-label extension of 793 PWID, showed low overall adherence to daily PrEP; almost half (47%) had less than 10% adherence, but only 25% had high (>90%) adherence.[6] PrEP in the BTS was supervised daily at methadone clinics and during incarceration, and being incarcerated was independently associated with higher levels of adherence, suggesting that without daily monitoring, PrEP adherence in the community will likely be lower.[6] Moreover, subsets of MSM in PrEP trials had underlying substance use disorders, yet the efficacy of PrEP or adherence levels among them is unknown. In the BTS, all PWID on the trial were maintained on methadone and the analysis did not disaggregate efficacy or adherence for the subgroup that continued to inject. Consequently, it is crucial to better understand adherence to daily PrEP in subgroups of MSM and PWID with substance use disorders who have suboptimal adherence to PrEP, but who are the ones who likely need it most.

Adherence guidelines by the International Association of Physicians in AIDS Care describes adherence optimization strategies, including in key populations like patients with substance use disorders.[7] Though these guidelines do not include PrEP, recommendations for PrEP adherence are likely to apply. Short-messaging service (SMS) or text messaging is recommended, including from a systematic review of reviews that supports SMS use and recommends refinements in frequency and message content.[8] Another systematic review in patients with HIV confirmed the adherence benefits from using SMS and extended it to improvements in clinic attendance,[9] which is crucial for PrEP monitoring every three months. Moreover, while SMS works generally, two-way interactive and tailored reminders appear to be most beneficial, but can be burdensome to patients if too frequent.[10-14]

A survey of 400 PWID receiving chronic methadone maintenance assessed their ownership and usage frequency of various communication technologies, including cell phones and smart phones, and their acceptance of SMS.[15] Of these, 67% were still using drugs (mostly cocaine). Overall, 91.5% regularly used some form of cell phone with most (71.3%) of these having a smart phone. Over one third (35.2%) of participants had evidence of moderate to severe neurocognitive impairment, which is associated with lower adherence levels.[16] Reminders, including the use of SMS, is an integral strategy for addressing medication adherence in individuals with neurocognitive impairment.[17,18] High levels (72.3%) of interest were expressed for communicating using SMS, and was higher among those with neurocognitive impairment.[18]

An ongoing study to optimize medication adherence in HIV patients with cocaine use disorders used formative research to establish the procedures for monitoring adherence and tailoring the reminder messages using focus groups and beta testing. Integral to the SMS reminders is the frequency (patients indicated daily was optimal), the timing of the reminder (they wanted to set their own time of the day),

content (they preferred positive message frames that did not allude to HIV), and quantity (one additional reminder after the preferred time and they would like to set the delay in the reminder from 15 to 60 minutes).

1.2 Rationale

The proposed study is significant in that PWID contribute a significant proportion to ongoing HIV transmission in Ukraine, and little is known about possible adherence levels to PrEP. Moreover, given the documented challenges with medication adherence in active drug users, evidence-based and low cost strategies to optimize medication are urgently needed if PrEP is to be effective in this key population. The proposed study is innovative in that it uses an RCT design testing a promising adherence enhancement approach, and focuses on a target population of active drug users who were not fully examined for either efficacy or adherence in prior trials.

1.3 Participating Sites

The study is designed to evaluate PrEP adherence in the population at greatest risk for HIV acquisition in Ukraine, PWID. We will achieve efficiencies by situating the PrEP provision model within real-world community settings and draw on the expertise of clinicians that have already demonstrated expertise in working with PWID and other populations at high risk of HIV. Sites located in various parts of Kyiv and run by NGOs currently providing HIV prevention services to PWID were chosen due to their excellent access to the target group and experience in provision of various social and para-clinical services. The primary community sites will partner with HIV clinical facilities to enable necessary laboratory testing and medication provision.

1.4 HIV Seroconversion

Incident HIV infections on this study are expected to occur uncommonly, even in the at-risk study population. However, any participant experiencing an incident HIV infection offers the opportunity to assess the impact of the PrEP regimen. Consequently, these participants will discontinue study medication and will be carefully characterized with regard to their HIV RNA level, CD4 cell count and set points over time, as well as antiretroviral drug resistance, and other factors.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

- To compare adherence to and retention on daily PrEP prescribed as the fixed dose formulation to PWID randomized 1:1 to PrEP as usual or SMS-enhanced PrEP.

2.2 Secondary Objectives

- To describe patterns and attributes of PrEP adherence among participants (e.g., SMS acceptance, substance use, sociocultural factors)
- To measure changes in injection and sexual risk taking behavior among study participants
- To describe client- and provider-level barriers to PrEP initiation and adherence

2.3 Study Design (Quantitative Component)

The study is a hybrid type 2 implementation design at two sites partnering with local healthcare facilities. In a prospective randomized controlled trial, participants will be randomized 1:1 to PrEP prescribed as usual or PrEP with SMS adherence facilitation.

Participants will be followed up for up to 6 months after enrollment and will be assessed every month for key PrEP adherence measures.

2.4 Study Design (Qualitative Component)

The primary objective of the qualitative component is to provide a contextual understanding of the multi-

level barriers and facilitators in the initiation, acceptability, and adherence to PrEP for PWID. The qualitative data will provide relevant findings regarding the participants' overall impressions and experiences related to their study participation, including motivations for participating in the study, perceptions about PrEP, reasons that PWID choose to initiate or decline PrEP, and describing the most helpful and least helpful components of study/service uptake for PrEP provided in this study (e.g., experimental services provided such as SMS facilitation). The qualitative component will also describe the individual, cultural, institutional, and geographic-specific barriers and facilitators that influence PWID initiation, utilization and adherence to PrEP, including those critical factors that influence study participation and up-take of PrEP (e.g., substance use, socio-economic indicators, culturally specific psychosocial stressors related to stigma). Importantly, the study will also assess the providers' perspectives on PrEP utilization among PWID, and system-level barriers.

3.0 STUDY POPULATION

The study will enroll 200 eligible HIV-uninfected PWID, 100 at each site. Participants will be selected for the study according to the criteria specified below. They will be recruited, screened and enrolled as described in Section 3.3. Issues related to participant retention and withdrawals from the study are described in Sections 3.4 and 3.5, respectively.

3.1 Inclusion Criteria

Individuals who meet all of the following criteria are eligible for inclusion in this study:

- 18 years of age or older
- No prior HIV diagnosis (self-report)
- Recent injecting drug use, defined as self-report of any type of drug injection and presence of visible injection marks verified by recruiting staff
- Able and willing to sign the informed consent, assessed by consenting staff
- Willing to provide locator information in accordance with the Study Operating Procedures (SOP)
- Have a mobile phone able to receive short messages (SMS).

3.2 Exclusion Criteria

PWID who meet any of the following criteria will be excluded from this study:

- Any reactive or positive HIV test at Screening
- Any reactive or positive HBsAg test at Screening
- Serum creatinine < upper limit of normal (ULN) and calculated creatinine clearance of at least 60 mL/min by the Cockcroft-Gault formula where:
    - eCcr in mL/min = [(140 – age in years) x (actual body weight in kg)] / (72 x serum creatinine in mg/dL)
- Planning to move out of the area or to travel for more than 3 months during the study follow-up period
- Unwilling to adhere to study procedures
- Use of ARV drugs (PrEP or PEP) in the last 60 days prior to anticipated enrollment by self-report
- Prior history of a gastrectomy, colostomy, ileostomy, or any other procedure altering the gastrointestinal tract or drug absorption (provided by self-report, or obtained from medical history or records)
- Any condition, that in the opinion of study staff, would make participation in the study unsafe, or interfere with achieving the study objective

Any person who cannot provide informed consent will be excluded from participation in the project. Staff conducting screening will be trained to identify participants who cannot provide appropriate informed consent. If it is determined that the inability to provide informed consent is due to a temporary/situational factor (e.g., intoxication), these persons will be given the opportunity to reschedule their enrollment appointment as appropriate. All participants will be afforded the same protections.

3.3 Recruitment Process

The study team will develop a SOP on recruitment that is specific to the PWID community. The participants may be recruited using a variety of methods, including referral from harm reduction programs, HIV testing sites, community outreach, and personal referrals. Outreach workers will disseminate information about the study, will provide oral descriptions of the study to prospective participants, and will encourage potential participants to participate in screening activities at the local study site. Potential participants will also be informed that they should pass the information on to other individuals if the study does not apply to them. No scripts or printed materials will be used for recruitment. Recruitment will be conducted at each site separately until the target sample size is reached.

3.4 Participant Retention

Once a participant enrolls in this study, the study sites will make every effort to retain him/her for 6 months of follow-up to minimize possible bias associated with loss-to-follow-up. The study team recognizes that PWID represent a heterogeneous population requiring multiple methods to meet their needs, and also recognizes the importance of interacting with the participants in a culturally competent manner. A basic philosophy of the retention strategy is that follow-up begins at recruitment and is a priority at every visit. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, with re-emphasis at each study visit.
- Thorough explanation of the importance of both study arms (intervention and standard of care) to the overall success of the study.
- Collection of detailed locator information at the Screening visit, with active review and updating of this information at each subsequent visit.
- Use of appropriate and timely visit reminder mechanisms.
- Visit calendars, flyers or other handouts will be offered at enrollment to assist with retention.
- Mobilization of trained outreach workers or “tracers” to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to build trust and increase awareness about substance use treatment and HIV/AIDS.

3.5 Participant Withdrawal

Regardless of the participant retention methods just described, participants may voluntarily withdraw from the study for any reason at any time. The Investigator also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Principal Investigator and study clinician. Study staff will record the reason(s) for all withdrawals from the study in participants’ study records.

4.0 STUDY PRODUCT CONSIDERATIONS

4.1 Study Product Formulation/Content/Storage

FTC/TDF is a fixed dose combination tablet containing 200 mg of emtricitabine (FTC) and 300 mg of tenofovir disoproxil fumarate (TDF) in each tablet.

FTC/TDF study tablets must be stored at 25°C, with excursions permitted to 15°C-30°C. FTC/TDF tablets must be stored in the original container. Each container is packaged with a child-resistant screw cap and contains a silica gel to protect the product from humidity.

FTC/TDF 200mg/300 mg is available as Tenof-EM®, a medication registered by the MoH of Ukraine for treatment of HIV-1 infection and for PrEP to reduce the risk of sexually acquired HIV-1 in adults at high risk. Further information on Tenof-EM® is available in the current package insert.

4.2 Study Product Regimen, Administration, and Duration

Once enrolled, all participants who agree to initiate FTC/TDF study product will be directed to take one FTC/TDF 200mg/300mg (Tenof-EM®) tablet orally once daily with or without food for up to 52 weeks.

The participant can decide to initiate FTC/TDF administration at any time after enrollment and week 48 of the study treatment period. Once initiated, the study participant may also decide to discontinue taking FTC/TDF study product at any time during the 52 week study treatment period. For participants who decide to initiate PrEP at or after Week 48, partnerships will be established as applicable with community partners in order to provide adequate clinical care and follow-up.

4.3 Study Product Supply and Acquisition

Emtricitabine (FTC) 200 mg/tenofovir disoproxil fumarate (TDF) 300 mg study product tablets are manufactured and provided by Hetero Healthcare, Ltd. FTC/TDF 200mg/300 mg study product will be available through the Kyiv City AIDS Center on general terms.

5.0 STUDY PROCEDURES

An overview of the study visits and procedures schedule is presented in Appendix I and has been written in concordance with current WHO guidelines for PrEP administration. In addition, all providers will be required to follow MOH requirements for the initiation of Tenof-EM for PrEP. Presented below is additional information on visit-specific study procedures. Detailed instructions to guide and standardize all study procedures across sites will be provided in the SOPs.

5.1 Pre-screening

Pre-screening procedures will be conducted by outreach workers and other team members who have access to the target population. The outreach workers will contact potential participants by phone or personally and briefly tell them about the opportunity to participate in a research study.

Pre-screening and screening visit procedures

1. Briefing

All potential participants will be informed of the opportunity to participate in the research study. Those who express interest will be informed about the main criteria (emphasizing the HIV-negative status) and rapid HIV testing requirement. If the individual is interested in the study, he will be instructed on where and when the Enrollment visit will take place. A reminder card will be provided. All interested subjects will be referred or accompanied to the clinical study site. Individuals who are not eligible will be informed that they do not meet the requirements of the study and, if necessary, will be referred for appropriate medical services.

5.2 Enrollment Visit

The enrollment visit will take place at a clinical facility designated as a PrEP provider for the study. All procedures will be conducted by the research/intervention staff in close collaboration with the clinical staff. A participant is considered enrolled at the point in time when all enrollment visit procedures are complete.

The following procedures are included in the Enrollment visit (actual sequence may differ).

Administrative and Behavioral Evaluations/ Procedures (research staff)

1. Eligibility Screening

Eligibility screening will consist of a brief interview using the Screening Form with the study staff. It will contain basic demographic and HIV risk information.

2. Informed consent

Prior to screening, every potential participant demonstrating interest in study participation will have to sign the Informed Consent Form (See Appendix III). Consent procedure will be performed by a study staff member responsible for recruitment. In more details, the consent procedure is described in Section 8.

3. Randomization

   Consenting participants will be randomized using the functionality in REDCap participant database using a pre-defined allocation schedule stratified by site.

4. Locator information

   After signing the ICF, the participant will provide his contact information. Staff members will assure participants that the detailed follow-up information will be deleted if they are not enrolled in the study.

5. Behavioral and psychosocial survey

   Structured interviews will be administered by an experienced interviewer using the questionnaire designed by study team (Appendix II). Baseline and follow-up questionnaires will not differ in content. Interview data will be directly entered into the online version of the participant questionnaire at the REDCap platform.

Intervention provision (intervention staff)

6. Assess participant's readiness for PrEP adherence

   PNs will use a PrEP readiness tool to assess key predictors of PrEP adherence.

7. PrEP discussion

   PrEP Education will be provided at each study visit to participants by PrEP Navigators with the option to start/continue, stop, or abstain from usage. A manual will be created for all sites to follow when discussing PrEP with participants based on safety and efficacy language found in the ICF under "Study Purpose".

8. Autonomy supportive adherence counseling

   Adherence counseling will be provided to all participants who initiate PrEP at each study visit starting at the enrollment visit. The counseling makes use of self-determination theory that is designed to facilitate the client's integration of PrEP usage into his health behavioral routines and support the client in making his own decisions regarding adherence[27,28]. Counseling will include the development of client-centered strategies to support the consistent daily adherence of PrEP. This counseling is delivered one-on-one by PrEP navigators during the study visits. The counseling will also include reminders not to share the medication and to contact project staff with questions about product use.

   After each counseling session, the PN will fill out the Care Coordination Measurement Tool (CCMT).

9. PrEP Navigation and study product supply

   After the brief PrEP discussion, PNs will ensure that each study participant has received the first supply of the medication for one month.

10. SMS reminder customization

    The experimental group participants will complete a SMS customization tool, setting key parameters for the intervention (frequency, timing, wording).

11. SMS reminder test

    After setting the SMS intervention parameters, a sample message will be delivered to the participant to test the procedure.

12. HIV/ STI behavioral risk-reduction counseling, provision of prevention supplies

    Brief risk reduction counseling will be provided to all participants at each visit. These counseling sessions will reinforce the role of consistent use of clean syringes and condoms in HIV/STI prevention, as well as other strategies such as addiction treatment. The overall goal will be to supplement PrEP counseling by supporting participants to adopt or continue risk-reduction practices. Prevention supplies, including clean syringes and condoms will be offered at each visit. Participants will be also provided with information about opioid agonist treatments, and referred to the preferred clinic if necessary.

Clinical Evaluations/ Procedures (clinical staff)

13. Medical history including but not limited to co-morbidities, concomitant medications, HIV risk history

    The clinician will evaluate medical history of the participant to verify the absence of potential contraindications and drug interactions for PrEP.

14. Symptom-driven physical exam

    If any physical or mental symptoms will be expressed by the participant, the clinician will conduct an exam to diagnose the condition and provide appropriate referrals if needed.

    Laboratory Evaluations/Procedures (clinical staff)

15. HIV testing

    HIV testing will be conducted according to the current HIV testing guidelines by trained staff, with pre- and post-test counseling. According to Ukrainian legislature, HIV diagnosis cannot be made at any setting other than an accredited governmental HIV lab. Therefore, a positive result of rapid testing (regardless of the number of confirmatory runs) will be explained to a subject as preliminary and insufficient to definitively confirm HIV infection, which can be done at specialized health care institutions. As specified in the National HTC guidelines, post-test counseling will provide all details on where the confirmatory testing can be done, and appropriate referrals will be provided.

    Participants who test HIV positive will be withdrawn from the study at this point.

16. HBsAg testing

    Testing for Hepatitis B is needed because the drugs used in Tenof-EM® can also be used to treat hepatitis B virus and taking Tenof-EM® now might result in less effective treatments for hepatitis B. Testing will be done using a venous blood sample with test kits available at the clinic. Participants positive for HBsAg will be excluded from the study and will be provided appropriate counseling.

17. Blood collection for creatinine test with subsequent calculation of creatinine clearance

    To verify eligibility, participants will provide a venous blood sample for the creatinine test. Routinely, the test results will be available within 3 days. Considering the low expected prevalence of elevated creatinine levels, PrEP will be dispensed at the same visit before the creatinine test result is available. If an elevated level is detected, the participant will be contacted, instructed to discontinue PrEP medication and invited for an interim visit to the clinician for a thorough assessment of renal function and possible reasons for elevated creatinine.

18. DBS storage for pharmacology testing

    DBS samples will be processed and stored for all participants; testing may be limited to a subset of these samples. DBS will be stored at -20° C within 24 hours of collection and shipped in bulk to a centralized laboratory on dry ice for testing. TDF will be quantified with a validated liquid chromatography tandem mass spectrometry method.[22,24]

5.3 Month 1, 3 and Month 6 (exit visit)

At months 1 and 3, the participants will visit the clinical site to complete the assessments and receive the medication supply for next two (at month 1) three (at month 3) months. At month 6, participants will not receive medication as a part of the study, but will be referred to other available PrEP providers in Kyiv. The following procedures will be included.

- Verify locator information
- Behavioral and psychosocial survey
- Self-reported study product adherence assessment
- PrEP discussion
- PrEP Navigation and study product supply
- Autonomy supportive adherence counseling
- SMS reminder customization

- HIV/ STI behavioral risk-reduction counseling, provision of prevention supplies
- Medical history including but not limited to co-morbidities, concomitant medications, HIV risk history
- Symptom-driven physical exam
- AE Assessment
- HIV rapid test – at months 3 and 6.
- DBS storage for pharmacology testing
- Urine storage for substance use testing

The exit visit will include all procedures for Month 3, except for PrEP provision and related counseling and SMS customization.

5.4 Months 2, 4, 5

Monthly assessments between the PrEP dispensing visits (Enrollment and 3-month) will be conducted by research staff **by telephone**. The following procedures will be included.

- Review and update locator information
- Self-reported study product adherence assessment

Self-reported PrEP adherence for all participants will assessed using both a visual analogue scale (VAS) and a new 3-item self-report measure. The VAS is empirically validated, consistently under-reports adherence, but effectively measures a "difference" in adherence that changes in response to an intervention. The 3-item adherence self-report scale showed good psychometric characteristics and good construct validity when compared with an drug monitoring standard.[26] Two self-report adherence measures are often recommended.

- PrEP discussion
- Autonomy supportive adherence counseling
- SMS reminder customization

Experimental arm participants will have an opportunity to change the parameters of the SMS reminders.

- HIV/ STI behavioral risk-reduction counseling

After the standard risk-reduction counseling, the participants will be invited to visit the harm reduction site to receive supplies.

5.5 Interim Visits

Interim visits may occur at any time during the project and may be conducted at the clinic or at the affiliated community sites. Interim visits may occur for one or more of the following reasons: 1) Medical reasons (e.g., a client may want to discuss barriers to adherence not related to side effects; client may require an interim visit related to a priority health issues; client may require STD/HIV screening); 2) Reasons related to an adverse event for example, intolerable side effects; 3) Other reasons the participant may request. In general, participants requesting interim visits should contact their PN for triage. The PN will make a recommendation to the client on whether an interim visit is indicated or whether an alternate plan is warranted.

When interim visits in response to participant reports of AEs are completed, the physician, physician's assistant or nurse practitioner member of the clinical team will clinically assess the reported event and provide appropriate medical care or make appropriate referrals. Participants with symptoms suggestive of acute HIV-infection syndrome will receive diagnostic testing to attempt to elucidate the cause of the syndrome, including HIV testing that includes testing for HIV RNA. Study medication will be stopped immediately if any HIV test is reactive or positive. All interim visits will be documented in the client's clinical/study records. All interim clinical visits identified in the health information exchange from client's primary or other health care provider (when applicable) will also be noted in the client's clinical/study records and on applicable CRFs.

5.6 Initiating or Starting PrEP after the Enrollment Visit

For any participant who has not taken PrEP or PEP in the past 60 days, PrEP may be restarted at Month 3 visit, after confirming PrEP eligibility according to the following Screening Visit parameters:

- HIV testing
- HBsAg testing
- Blood collection for creatinine test with calculation of creatinine clearance

5.7 Premature Study Discontinuation

Participants may voluntarily withdraw from the study for any reason at any time. Site Coordinators may, with the approval of the PI withdraw participants before their scheduled termination visit to protect their safety, and/or if participants are unable or unwilling to comply with study procedures. Participants also may be withdrawn if the study sponsors, government or regulatory authorities, or site IRBs terminate the study prior to its planned end date. Study staff will record the reason(s) for all withdrawals in participants' study records. The Month 6 visit schedule should be followed when possible, in the event that a participant chooses to withdraw from the study. If a participant chooses to withdraw, data collected from this participant will be deleted and will not be used for analysis. In all other cases, participant information will be used for analysis.

5.8 Qualitative Methods

All individual interviews and focus groups will be conducted by trained study staff. Interviewers will probe for indicators of the selected qualitative domains as well as for themes that emerge during the individual interviews/ focus groups. The interviews/ focus groups will be digitally audio-taped and transcribed verbatim for qualitative data analyses by a professional transcription service. Interviews/ focus groups will be conducted at a location identified by study staff to assure adequate privacy and confidentiality. Participants will be provided with a separate reimbursement for participation in the individual interview. All identifying information will be removed from the transcripts, and only the research team and the transcribers will have access to the audio interview data. Audio recordings of interviews will be destroyed after the analyses are complete. Consensual Qualitative Research methods will be used to analyze the qualitative data.

5.8.1 Individual Semi-Structured Interviews with Participants

The research team will conduct individual semi-structured interviews with approximately six participants that initiated PrEP at each site. The objective of the individual interviews is to ascertain information about factors that serve as facilitators and barriers in the initiation, acceptability and adherence of PrEP. Three interviews at each site will be conducted between Enrollment and Month 3 visit, and three between Month 3 and Month 6.

Each interview will last approximately 30 to 60 minutes in length among participants who are recruited for and consent to this component of the study. A qualitative interview guide will be developed to address two primary domains (1) factors that facilitate the initiation, acceptability and adherence of PrEP and (2) factors that serve as barriers in the initiation, acceptability and adherence of PrEP.

5.8.2 Individual Semi-Structured Interviews with Clinical Providers

The research team will conduct individual semi-structured interviews with all physicians involved in PrEP provision in the study. The objective of the individual interviews is to ascertain information about factors that serve as facilitators and barriers in the initiation, acceptability and adherence of PrEP among PWID. The interviews will be conducted after completion of all Month 3 visits. Each interview will last approximately 30 to 60 minutes in length. A qualitative interview guide will be developed to address the following domains: (1) factors that facilitate the initiation, acceptability and adherence of PrEP and (2) factors that serve as barriers in the initiation, acceptability and adherence of PrEP, (3) resources that were available at the clinic, and (4) discussion of what could have improved their ability to provide care.

5.8.3 Focus Groups with PrEP Navigators

The research team will conduct one focus group with all PNs at the end of the study to elicit feedback on

what resources they believe were necessary to optimally implement a PrEP program. Each focus group will last approximately 60 to 90 minutes in length. A focus group guide will be developed to address the following domains: (1) resources that were available at the clinic (2) resources that were available in the community, (3) resources that were not available during the course of the study, (4) feedback on the uptake and potential of the SMS reminder intervention, and (5) discussion of what could have improved their ability to provide care. The PN team will be consented for the focus group immediately prior to the conduct of the focus group and after all participants have completed the study.

5.9 Participants who have Suspected or Confirmed HIV at Screening or During the Study

In the case of suspected HIV infection at the Screening visit, HIV status will be confirmed using local HIV testing guidelines. Participants who have a reactive or positive HIV test at Screening are not eligible for enrollment, even if subsequent testing indicates that they are not HIV infected.

Participants who have a reactive HIV test result at a follow-up visit will be instructed to discontinue their study medication immediately. According to Ukrainian legislature, HIV diagnosis cannot be made in any setting other than an accredited governmental HIV lab. Therefore, a positive result of rapid testing (regardless of the number of confirmatory runs) will be explained to a subject as preliminary and insufficient to definitively confirm HIV infection, which can be done at specialized health care institutions. As specified in the National HTC guidelines, post-test counseling will provide all details on where the confirmatory testing can be done, and appropriate referrals will be provided.

Any participant who is found to have confirmed HIV infection after Enrollment will be followed at all scheduled visits as described in Appendix I. HIV-infected participants will be followed to contribute information regarding HIV outcomes after PrEP exposure (including viral set point), and to comply with expectations of communities.

HIV-infected participants will also be able to continue receiving assistance in securing HIV medical care, Participants who acquire HIV infection during the study will be asked to provide releases of information that will allow study counselors to consult with providers of HIV medical care to coordinate case management, and to implement other strategies intended to help participants to be retained in medical care and to adhere to treatment regimens. These activities will be logged in PN counselor charts.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Close cooperation between the Investigators, clinical and research teams will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner. The team will have regularly scheduled conference calls during the period of study implementation, and additional ad hoc calls will be convened if required.

The study site Coordinators are responsible for continuous close monitoring and management of AEs. Sites are required to follow the detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol and for alerting the Principal Investigator if unexpected concerns arise.

A sub-group of the Protocol Team, including the Principal Investigator, Clinical Consultant, and Co-Investigators will serve as Study Monitoring Committee (SMC). The SMC provides support to site clinicians regarding individual participant clinical management (toxicity management, clinical holds of study drug, study drug re-challenge, permanent discontinuations, etc.). The Site Coordinators will prepare routine study conduct and safety reports for the SMC, which will meet by conference call approximately monthly and will review safety data during a closed meeting. More frequent or ad hoc reviews of safety reports may be conducted by the SMC as needed. A recommendation to stop the trial may be made by the SMC at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made to discontinue the study product in all participants, the PI will notify the Site Coordinators and the responsible IRB expeditiously.

6.2 Adverse Event (AE) Reporting

Adverse events (AE) are defined as any untoward medical occurrence experienced by participants during the study, and may or may not have a causal relationship with the treatment. Information regarding all AEs regardless of seriousness or severity will be recorded in the participant's source files. Grade 3 and higher adverse events and all creatinine AEs will be recorded on study CRFs. All SAEs must be reported on AE Log CRF. All AEs that result in a clinical hold or permanent discontinuation of study product are reported on AE Log CRF regardless of grade. Grade 3 and higher clinical AEs will be referred to a study clinician at the time of the visit.

All critical laboratory values will be reported as applicable per site SOPs. Participants who are not present at the study site at the time a laboratory AE requiring retesting or follow-up is identified will be followed as deemed clinically appropriate. With appropriate permission of the participant, and whenever possible, records from non-study medical providers related to untoward medical occurrences will be requested and required data elements will be recorded on study CRFs and/or in the participant's medical chart. All AEs regardless of severity will be followed clinically, until the AE resolves or stabilizes as per the appropriate toxicity algorithm. AEs will be assessed for all participants, regardless if they continue PrEP or not, after enrollment through the final study visit.

6.3 Serious Adverse Events

Serious adverse events (SAEs) will be defined per CFR 312.32 guidelines, as AEs occurring at any dose that:

- Result in death;
- Are life-threatening adverse events;
- Require inpatient hospitalization or prolongation of existing hospitalization;
- Result in persistent or significant disability/incapacity; or
- Are congenital anomalies/birth defects.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the participant or require medical or surgical intervention to prevent one of the outcomes listed above.

Note: All SAEs must be reported on the AE Log CRF.

6.3.1 Grading System

All AEs will be graded using the DAIDS AE Grading Table, Version 1.0, December 2004 (Clarification dated August 2009) and the DAIDS Addendum 2 - Male Genital Grading Table, which are available at http://rsc.tech-res.com/safetyandpharmacovigilance/. Grade 1 creatinine toxicity will be determined by either the DAIDS AE Grading Table OR Grade 1 as defined by creatinine > 1.5x the participant's baseline serum creatinine, whichever is higher."

6.3.2 Assessment of Relationship to Study Agent

The relationship of all AEs to FTC/TDF will be assessed per the package insert and investigator's brochure for FTC/TDF, and clinical judgment of the investigator. The relationship categories that will be used for this study are related and not related, as defined in the Manual for Expedited Reporting of Adverse Events to DAIDS (Version 2.0, dated January 2010) which is available at http://rsc.tech-res.com/safetyandpharmacovigilance/.

6.4 Reporting Requirements for this Study

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 (or latest version) of the DAIDS EAE manual, will be used for this study. The study agents for the purposes of SAE reporting are part of a fixed dose combination tablet: emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF).

The SAE reporting period for this study is per the DAIDS EAE manual and continues from enrollment of a trial participant to the end of trial follow-up for that participant. All reportable SAEs occurring during the study reporting period will be reported to the principal investigator in an expedited manner, within three reporting days of site awareness of the events (see definition in Appendix D of the DAIDS EAE Manual).

Reporting requirements for the local IRB will also be followed.

6.5 Social Harms Reporting

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result. For example, participants could be perceived as being HIV-infected or at high risk for HIV infection and be treated unfairly or have problems being accepted by their families and/or communities. Social harms that are judged by the PI/designee to be serious or unexpected will be reported to the responsible site's IRB at least annually, or according to its individual requirements.

Social harms will be collected and reported on CRFs during regular visits. In the event that a participant reports social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant, and/or referral to appropriate resources for the safety of the participant. Each site will provide such care and counseling in accordance with standardized guidance in the SOP.

6.6 Toxicity Management

The site clinician has the discretion to hold FTC/TDF at any time if s/he feels that continued medication use would be harmful to the participant or interfere with treatment deemed clinically necessary according to the judgment of the investigator. Clinical or laboratory abnormalities that require follow up will be documented, and the research associate or clinician will contact the participant to schedule an interim visit for follow-up and/or repeat laboratory testing. All participants reporting an adverse event will be followed clinically until the occurrence resolves (returns to baseline grade, defined as grade at enrollment) or stabilizes or an effective referral to local health care providers is accomplished.

6.6.1 Discontinuation of Study Medication

Grades 1 or 2

Continue FTC/TDF at the discretion of the site investigator.

Grade 3

FTC/TDF may be continued at the discretion of the site investigator if a Grade 3 toxicity is considered to be unrelated to the study medication. Study medication will be temporarily withheld if Grade 3 toxicity is considered to be related to the study medication. After a Grade 3 toxicity returns to Grade 1, the participant can be reintroduced to medication after consultation with the site investigator, DAIDS Medical Officer, and other members of the CMC. If a Grade 3 toxicity recurs and is considered to be related to study medication, FTC/TDF will be permanently discontinued.

Grade 4

For all Grade 4 laboratory-identified or clinical toxicities, FTC/TDF will be withheld unless it is determined to be not related. If a Grade 4 laboratory toxicity is not confirmed by repeat testing, it should be managed per algorithm for the new toxicity grade. Participants with Grade 4 AEs will be followed until the event resolves to baseline or stabilizes. Study drug may be restarted in the event of the resolution of a Grade 4 AE back to Grade 1, after consultation with the site investigator, DAIDS Medical Officer, and other members of the CMC. If the toxicity recurs to Grade 3 or higher after FTC/TDF is restarted and is considered to be related to FTC/TDF, the study medication will be permanently discontinued.

6.6.2 Creatinine Elevations

For creatinine elevations >1.5-fold above baseline creatinine (at screening), serum creatinine will be repeated as soon as possible, preferably within 7 days. Participants who fail to have a confirmed test within two weeks of receiving the initial result should be permanently discontinued from use of the study drug and the CMC should be notified. FTC/TDF will be held for confirmed creatinine elevations >1.5-fold

above baseline until creatinine returns to <1.3-fold above baseline, at which point the participant may be re-challenged with FTC/TDF after consultation with the site investigator. Clinicians may re-test creatinine levels more often (i.e., weekly) should they choose; however, after the initial re-test approximately 7 days later, it is not required per protocol to re-test serum creatinine until the next scheduled study visit. If serum creatinine rises again to >1.5-fold above baseline when drug is restarted, the CMC must be notified and FTC/TDF should be permanently discontinued and the participant will be monitored as deemed clinically appropriate in consultation with the CMC until level returns to baseline (screening value) or stabilizes.

6.6.3 Creatinine Clearance

- Estimated CrCl< 60 mL/min

  If the calculated creatinine clearance is <60mL/min, it should be confirmed ideally within approximately one week of the receipt of the results.

  Discontinue study drug temporarily. Participants who fail to have a confirmed test within two weeks of receiving the initial result should be permanently discontinued from use of the study drug and the CMC should be notified.

- Confirmed CrCl<60 mL/min

  If the calculated creatinine clearance is confirmed to be <60 mL/min, the study drug must be temporarily discontinued. As previously stated, participants who fail to have a confirmed test within two weeks of receiving the initial result should be permanently discontinued from use of the study drug and the CMC should be notified. The participant will be monitored as deemed clinically necessary in consultation with the CMC until level returns to baseline (screening value) or stabilizes.

  Temporarily discontinue study drug (unless the participant does not return for repeat testing within approximately two weeks).

- Re-testing result is ≥60 mL/min

  If re-testing yields a result ≥60 mL/min, the Investigator may re-start study drug use, and follow creatinine clearance over time as deemed clinically necessary.

6.7 Concomitant Medications

With the exception of medications listed as prohibited (see below, this section), enrolled study participants may use concomitant medications during study participation. All concomitant medications, including prescribed and over-the-counter preparations, vitamins and nutritional supplements, recreational drugs and herbal preparations reported within 45 days prior to confirmation of eligibility for study enrollment and throughout the course of the study will be recorded on the CRF designated for that purpose. Medications used for the treatment of AEs that occur during study participation will also be recorded on applicable study CRFs. Participants who begin taking any medication during the trial that is listed as an exclusionary medication at Screening will temporarily discontinue study drug. Study drug may be resumed if no exclusionary medication has been taken in the last 4 weeks, if serum creatinine is within 1.3-fold above baseline, and if HIV testing is non- reactive/negative.

Should participants report use of any of the following medications, they will be required to discontinue use of study drug: interleukin therapy, medications with significant nephrotoxic potential (including but not limited to amphotericin B, aminoglycosides, cidofovir, foscarnet and systemic chemotherapy), and medications that may inhibit or compete for elimination via active renal tubular secretion (including but not limited to probenecid).

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is an open-label, two-site, two-arm, prospective, randomized controlled trial that aims to assess the initiation, acceptability, safety, and feasibility of daily PrEP for PWID in Ukraine with or without SMS reminder intervention. HIV-uninfected PWID aged 18 and over and at risk for HIV infection will be

recruited and enrolled. Each participant will be offered daily PrEP and followed up to 6 months.

Participants will be followed at the specified study time points and will be evaluated for side effects, adherence, risk behavior and HIV-seroconversion.

Primary Endpoints: The primary endpoint of this study is the adherence to PrEP.

PrEP adherence

Adherence will be assessed via self-report (VAS and 3-item screener) and TDF concentration in DBS samples. TDF will be quantified with a validated liquid chromatography tandem mass spectrometry method.

PrEP persistence

PrEP persistence is defined as the time from PrEP start to PrEP discontinuation. A PrEP discontinuation is considered to have occurred if a participant self-reported to miss the PrEP doses for 30 or more consecutive days, for reasons other than a medication hold instituted by a clinician.

Secondary Endpoints: The secondary endpoints of this study include the following:

Injection and sexual risk-taking behavior

Injection and sexual risk-taking behaviors will be measured by the survey performed at baseline and then at follow-up visits.

Reasons PWID choose to initiate and discontinue PrEP

The baseline and follow-up surveys will assess the main reasons for agreeing to start PrEP and stopping it (if stopped during the study period). The quantitative data will be supplemented by acquiring information about core reasons for initiating or refusing PrEP, based on the individual interview qualitative data from participants.

Incident HIV-seroconversions and characteristics

HIV testing will be performed with confirmation if necessary at all study visits.

Adverse events

Measurement of AEs will be graded via the DAIDS Toxicity Grading System determined by review of reported adverse events (clinical and laboratory) during the study.

7.2 Sample Size Consideration

A total sample size of 200 PWID participants will be recruited into the study. Each participant will be enrolled to receive daily PrEP with Navigation for at least 6 months. Half of them will be randomized to receive SMS reminders.

For the PrEP adherence endpoint, the adjacent table lists the two-sided 95% confidence intervals for the true percentage of the PrEP adherence rates for the PWID who actually receive PrEP, assuming a 10% to 20% loss-to-follow-up (e.g. including those lost due to incarceration) during the 6-month period. For example, if the PrEP acceptance rate is 50% and an observed adherence rate is 67%, then there is 95% chance that the range 58%-76% will contain the true PrEP adherence rate.

Table: 95% Confidence Intervals for the True PrEP Adherence Rate Given by Possibly Observed PrEP Adherence Percentages

PrEP Persistence Rate	PrEP Adherence Rate	95% CI for True PrEP Adherence Rate	
		10% LTFP*	20%LTFP*
33% (low)	33%	(22%, 44%)	(21%, 45%)
	50%	(38%, 62%)	(37%, 63%)
	67%	(56%, 78%)	(55%,79%)
	33%	(24%, 42%)	(23%, 43%)
	50%	(40%, 60%)	(39%, 60%)

50% (moderate)	67%	(58%, 76%)	(57%,77%)
67% (optimistic)	33%	(25%, 41%)	(25%,41%)
	50%	(42%, 58%)	(41%,59%)
	67%	(59%, 75%)	(59%.75%)

*LTFP: Loss-to-Follow-up

7.3 Data Analysis

7.3.1 Primary Analyses

PrEP adherence

For binary outcome of high levels of PrEP adherence (defined as TDF >=700 fmol/punch), generalized estimating equation models (GEE)[27,28] with binomial distribution will be built to account for correlation in repeated measurements occurring in the same participant. Intervention assignment, time, interaction between time and intervention assignment and any other confounders will be included as covariates. The analysis will be done for repeated measure for both 3 and 6 months. As an alternative analytical plan for assessing the impact of the two intervention arms on adherence to PrEP, continuous version of adherence will be analyzed by using repeated-measures analysis with same set of covariates as the binary outcome and percent change in adherence between different assessment points will be estimated and compared between intervention assignment using linear contrast statement in SAS PROC MIXED. For the above mentioned model, Covariance structure will be selected based on the fit statistics (i.e., AIC, BIC etc.).

There are several strategies by which the PrEP adherence will be measured. We will utilize Spearman correlation coefficients, scatterplots and Kappa statistics to assess associations between the biomedical (TDF concentrations in red blood cells measured via DBS)[20-23] and self-report measures (VAS: visual analogue scale[25] and 3-item assessment[26]).

PrEP persistence

Kaplan-Meier plots will be used to characterize time to first discontinuation, as well as time to restarting PrEP among discontinuers, both overall and by age, education, and risk group. Intervention assignment, time, interaction between time and intervention assignment and any other confounders will be included as covariates. Among those continuing on PrEP, we will consider the medication possession ratio, defined as the number of tablets dispensed divided by the number of days between visits, a measure that performed best as an indicator of drug exposure in the iPrEx study.

7.3.2 Secondary Analyses

Analyses for secondary objectives will be mostly descriptive. Line listings as well as summary descriptive statistics including means, medians, and proportions with 95% exact or asymptotic confidence intervals as appropriate at each visit, will be used for the following secondary objectives. Specifically,

- Use GEE or random effects models to describe longitudinal patterns and their correlates of PrEP adherence among participants (e.g.: substance use, sociodemographics, sociocultural factors, risk practices and incarceration)
- To describe side effects and adverse events of PrEP among participants in the PrEP demonstration project. AEs will be tabulated, overall and by grade. For any reasonably common AEs (> 20 events), exploratory analyses will be conducted to assess correlates of the AE, including demographics and duration and patterns of PrEP use, within the limits imposed by the small expected number of events.
- Describe and produce summary plots for longitudinal changes in sexual risk-taking behavior among study participants
- List and summarize reasons PWID choose to initiate or decline PrEP
- List and summarize HIV seroconversions and characteristics of the infection(s) (e.g., viral set point, drug resistance patterns) in participants who initiated PrEP

- Use Kappa-statistics to assess agreement of adherence under different measures.

7.3.3 Qualitative Data Analyses

Qualitative data analyses will be conducted on an ongoing basis in collaboration with data collection. Thematic coding will be used to analyze the data from the individual interviews based on a grounded theory approach. The Consensual Qualitative Research Method (CQR) will be used by the study team to analyze the data. The CQR method provides a reliable, systematic, and rigorous method in conducting qualitative data analyses - recognizing the importance of context, incorporating an inductive analytic process, using a team and making decisions by consensus, using auditors, and verifying results by systematically checking against the raw data. The key elements of conducting qualitative data analyses using the CQR method include: (1) develop and code domains, (2) construct core ideas, and (3) develop categories to describe consistencies across cases (cross analysis).

8.0 HUMAN SUBJECTS CONSIDERATIONS

The protocol, ICF, participant education and recruitment materials, and other documents and any subsequent modifications will also be reviewed and approved by the Institutional Review Board (IRB) at the Ukrainian Institute on Public Health Policy (Kyiv, Ukraine).

The Investigator will make safety and progress reports to the IRB within three months of study termination or completion. These reports may include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others.

8.1 Informed Consent

Written informed consent will be obtained from each study participant, including both quantitative and qualitative components. Three separate ICFs will be developed for the main study participation (Appendix IIIa), in-depth interviews with participants (Appendix IIIb), and interviews/ focus groups with providers and PrEP Navigators (Appendix IIIc). In addition, the main study participants will be asked to provide a separate written informed consent for their blood specimens to be stored after the end of the study for possible future testing.

For all three procedures, the informed consent forms will be read aloud to each eligible participant by a project team member. All questions that respondents may have will be adequately clarified and explained to them. Potential participants will be informed that their participation in the intervention is completely voluntary and that they have a right to withdraw their consent forms and stop their participation in the study at any time. Refusal or withdrawal from the study at any time will have no effect on the participant's access to health facilities or HIV-related care and treatment, or their employment. Participants will be informed that any information that they disclose during the course of the study will be considered confidential (i.e., no personal identifiers will be used and only aggregated information across all participants will be reported). Participants will have the potential risks and benefits of the study explained to them as well. For all candidates, understanding of the essential parts of the document will be assured by asking questions to verify their knowledge of the study procedures. If a candidate agrees to participate in the study, the candidate, or a witness if a candidate is illiterate, will document provision of informed consent by signing on the consent form. Unsigned copy of consent forms will be offered to the participants

8.2 Potential risks

As part of this study, participants will be asked to undergo HIV counseling and testing, provide information about their drug use, provide contact information, and take PrEP medication. Drawing blood for HIV rapid test involves minimal risk, including the possibility of local trauma and infection. Participants will be asked questions about sensitive topics such as drug use. It is possible that some individuals may experience discomfort from taking part in these study activities.

There is a potential risk for participants who are found to be HIV-infected to become distressed after receiving their test results.

Participation in HIV prevention, and PrEP in Ukraine is not associated with any punitive or social risks with the exception of common stigma attached to drug use. This study does not increase the risk of stigma associated with drug use or HIV for participants.

Taking PrEP medication may lead to adverse events or side effects, described in detail in Section 6.

8.3 Protection Against Risks

Participation in the study is completely voluntary and confidential. The unique identifier code, linking all study records is based on information provided by participants verbally, and no documents are requested. It is not possible to identify a person using this code. Contact information will be requested to allow invitation for follow-up assessments, and this information will be kept strictly confidential (see below). Mobile phone numbers in Ukraine in most cases are not personally identifiable information, because prepaid numbers are not linked to any contract or personal registration data.

The study personnel will explain to participants that the information collected in the study may be accessed by the law enforcement entities only in case of an individualized request with regard to an open criminal case.

As part of the informed consent procedure, all potential participants will be instructed that they do not have to disclose personal information which they are uncomfortable sharing and that they can withdraw from the study at any time.

Participants will receive names and contact information of the organizations conducting the study, as well as other study team members, on their copy of the informed consent form. It will be explained to the participant that they may contact anyone on the list if they have any questions or comments regarding the study, if they suffered in any way due to their participation/failure to participate in the study. The participants will be informed that they may refuse to answer any questions that make them feel uncomfortable and that participation in the intervention is voluntary. Absolutely no information on any participants of the study will be given to other participants.

To minimize psychological risk, the recruitment into the study will be done by a trained social worker, and interview will be conducted by a trained interviewer. The interviews will be carried out face-to-face and there will be no additional persons in the room during the interview except the interviewer and respondent. HIV testing and counseling (HTC) will be performed in designated rooms, which meet the privacy requirements set in the national HTC guidelines. Pre-test counseling will be carried out before HIV testing. Participants with HIV positive test results will be informed that final diagnosis will only be given after confirmation testing by the AIDS center laboratory and referred for additional testing. There is a potential risk for participants who are found to be HIV-infected to become distressed after receiving their test results. Study staff is trained to provide HIV post-test counseling to persons newly diagnosed with HIV. Study staff will also be equipped to refer participants who need additional counseling and assistance to community resources, including referrals for HIV care and treatment. Pre- and post-test counseling will be provided by qualified staff only.

All adverse events will be managed as described in Section 6.

8.4 Incentives

Pending IRB approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. The reimbursement amounts will be specified in the study informed consent forms.

8.5 Confidentiality

All study-related information will be stored securely at the study sites and in the main office. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, and study data-collection, process and administrative forms will be identified by a coded number to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored with restricted access according to local SOP. All local databases will be secured with password-protected access systems.

Participant study information will not be released without the written permission of the participant, except as necessary for monitoring by the Sponsor, government and regulatory authorities, and/or site IRBs.

8.6 Protocol Deviations

All protocol deviations, new/unexpected findings and changes to the study environment will be documented and immediately reported to the in-country study team who will then notify the Sponsor. If necessary, a formal report will be sent to the appropriate IRBs. Reporting of such incidents will be the responsibility of the Principal Investigators of this study. Any discussions, issues, and complaints related to the study will be reviewed promptly to ensure close monitoring of the impact of the study on participants. Appropriate action will be taken to resolve or deal with all issues accordingly.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory Specimens

As described in Section 5, rapid HIV test will be done during the Screening visit to confirm the HIV-negative status of the participant. The rapid test will be done using test kits routinely by the community centers providing HIV prevention services, by the study nurse.

At Enrollment, a venous blood sample will be collected to perform the creatinine test. The specimen will be collected at the clinical sites and processed at the local site laboratories (LL).

At Enrolment, Month 3 and 6 visits, DBS samples will be collected for pharmacology testing. Both samples will be stored in a -20° C freezer at the LL. The specimens will be analyzed in batches at the end of the study, and will not be used for adherence counseling during this study. Data from individual study participants will not be returned to study sites or study participants. TDF will be quantified with a validated liquid chromatography tandem mass spectrometry method.[22,24] The specimens of participants who do not consent to long- term storage and additional testing will be destroyed at the end of the study.

Each study site will adhere to standards of good clinical laboratory practice, and SOP for specimen management including proper collection, processing, labeling, transport, and storage of specimens to the LL.

10.0 DISSEMINATION AND REPORTING

10.1 Notifying Participants of Study Findings

Written material summarizing the findings from this study will be made available to participants and study staff upon completion of the study. The exact type of material is to be determined; usual forms of written communication targeting PWID in Ukraine are posters and brochures.

10.2 Dissemination of Study Findings

The study findings will be disseminated through presentations and publications in peer reviewed journals and other publications. Reports will be disseminated to an international audience, as well as to national and local HIV prevention planning groups who may use the findings to assist in the creation of HIV prevention activities. The UIPHP publications and presentations policy will be utilized.

In-country data and country-specific information will be made available to national policy-makers, organizations, and implementing partners as soon as possible. Study staff will be notified of the findings upon their presentation or publication. Any formal presentations at conferences or scientific publications will follow UIPHP procedures for publications and presentations.

APPENDIX I - SCHEDULE OF EVALUATIONS AND PROCEDURES

	Pre-screening	Enrollment	Month 1, 3	Month 2,4,5 (by phone)	Month 6 (exit)	Interim visits
Administrative and Behavioral Evaluations/ Procedures						
Pre-screening	x					
Eligibility screening and demographic information		x				
Informed Consent, randomization		x				
Locator information		x	x	x		x
Behavioral and psychosocial survey		x	x		x	
Initial PrEP adherence readiness assessment (PN)		x				
Self-reported study product adherence assessment (PN)			x	x	x	x
Individual Interview for selected participants						x
Staff Focus Group (after all participants complete						x
Intervention provision						
PrEP Discussion		x	x	x	x	x
Autonomy Supportive Adherence Counseling		x	x	x		x
PrEP Navigation and study product supply		x	x			x
SMS reminder customization[1]		x	x	x		x
SMS reminder[1]		x	xx	xx		
HIV/ STI behavioral risk-reduction counseling		x	x		x	x
Provision of prevention supplies		x	x		x	x
Clinical Evaluations/ Procedures						
Medical history including medications		x				
Symptom-Driven Physical Examination		x				
Laboratory Evaluations/Procedures						
HIV screening testing		x	x[2]		x	
HBsAg testing		x			x	
Renal function tests (creatinine)		x				
Calculated creatinine clearance		x				
DBS storage for possible Pharmacology testing		x	x		x	

1 Experimental arm only.
2 Month 3 only

APPENDIX II – SURVEY BATTERY AND OTHER FORMS

Forms filled by the PNs:

- Initial PrEP adherence readiness assessment
- Care Coordination Measurement Tool

Forms filled by the interviewer:

- PrEP Adherence (visual analog scale [VAS] and 3-item screener, additional block for those who discontinue)
- Client Perception of Coordination Questionnaire (24-items)
- Health Care Climate Questionnaire (15-items/ 5-item short form)
- Care Transition Measure (15-items/ 3-item short form)
- Health Care Climate Questionnaire
- Perceived HIV risk and severity
- Depression scale
- Perceived Competence for PrEP Use
- PrEP Self-Regulation Questionnaire
- PrEP/PEP Awareness
- Satisfaction with PrEP provision, medicines
- Side effects (at baseline – anticipation of SEs, at follow-up impact of SE on adherence)
- Sexual and injection risk behavior (n days injected, n days shared equipment, n days of sex, n days sex without condoms, n partners [of them PLWH])
- Social support (do you plan to tell anyone, have you told anyone, did he help, if did not – why?)
- Stigma (related to PrEP, ARV, PWID)
- Substance use inventory (short)
- Use of reminders (what type of reminders you use)

Detailed description of selected instruments:

PrEP Adherence Self-Regulation Questionnaire (15-items)

We will use a modified version of the Treatment Self-Regulation Questionnaire (TSRQ) to assess participants' reasons for using PrEP if self-determined—whereby higher self-determination scores reflect greater internalization of the target behavior and increased likelihood of adherence[32]. The TSRQ uses a 7-point Likert scale and has been modified in previous studies to address adherence to antiretroviral medication33 and other specific health behavior targets such as diet and exercise[29]. The TSRQ was shown to have adequate internal consistency with alphas ranging from (.85 to .93) across several studies.

Health Care Climate Questionnaire (15-items/ 5-item short form)

The HCCQ uses a 7-point Likert scale to assess the degree to which participants perceive their clinical team to be autonomy supportive[27]. Higher scores indicate greater perceived autonomy support. The HCCQ uses the concept of autonomy support, from self-determination theory, to characterize the client-centeredness of clinical environments, hypothesizing that autonomy-supportive (client-centered) clinical environments facilitate self-determined motivation for the adoption of target health behaviors[30,34]. The α coefficient for the internal

consistently of the HCCQ is > 0.90.

Client Perception of Coordination Questionnaire (24-items)

We will use the CPCQ to measure the client's perspective whether the care they received over time was client-centered and coordinated between health care providers[35]. The CPCQ demonstrated good internal consistency (α= 0.92). CPCQ has six subscales with alphas ranging from 0.31 to 0.86. We will use the four subscales with good internal consistency and adapt them for structure of the C4 model: (1) acceptability of care coordination, (2) receipt of self-perceived needed care, (3) perception of clinical care provider, (4) perception of psychosocial care provider. This reduces the item count from 31 to 24. While the CPCQ is the longest measure within the battery, it exhibited high completion rates (>95%) in the study in which it was developed[35].

Care Transition Measure (15-items/ 3-item short form)

The Care Transition Measure (CTM) uses 4-point Likert scale to assess quality of transition from hospital care to community-based care or home[37]. CTM will be adapted to assess client-centered transition from PrEP management in the C4 model to community-based clinical supervision of PrEP. The CTM demonstrated high-internal consistency and reliability, and adequate convergent validity with a validated measure[38] of client-perception of the quality of hospital discharge/transfer process. Spearman inter-item correlations were between 0.35 and 0.75 which indicate that the scales and conceptually similar but are not measuring identical constructs.

The following items will be collected on a CRF whenever care coordination is performed:
Care Coordination Measurement Tool (CCMT)

We will measure the activities involved in providing client-centered care coordination for PrEP using a modified version of the CCMT. The CCMT was developed based on national expert panel recommendations for care coordination measurement[18]. Among the items capture on the CCMT include: (1) client complexity level, (2) focus of the encounter (e.g., clinical/medical, legal, mental health, referral management, social service), (3) type of coordination needed, (4) services/activities rendered, (5) time-spent on coordination activities, and (6) outcome of coordination. The CCMT is designed for use by all personnel involved in a particular client-centered care coordination evolution and has been successfully used in previous studies[26,36]. The CCMT will allow us to obtain robust characterizations of care-coordination encounters for use in addressing our secondary objectives.

APPENDIX III - SAMPLE INFORMED CONSENT FORMS

SAMPLE MAIN STUDY CONSENT FORM

Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

Protocol Version 1.0 April 24, 2020

Main Study Informed Consent Version 1.0

Study Sponsor: The Global Fund to Fight AIDS, Tuberculosis, Malaria.

PRINCIPAL INVESTIGATOR: Kostyantyn Dumchev

PHONE: +38 044 222-6271

INTRODUCTION

You are being asked to take part in a research study that will help us design a new and better way to prevent the spread of HIV (human immunodeficiency virus, the virus that causes AIDS) among people who inject drugs.

This study is sponsored by the Global Fund to Fight AIDS, Tuberculosis, Malaria and conducted in Kyiv, Ukraine by the Ukrainian Institute on Public Health Policy (UIPHP). The person in charge of the study at this site is Kostyantyn Dumchev.

Before you can make an informed decision about whether to take part in this study, you should understand the possible risks and potential benefits of being in this study. That process is called informed consent.

This informed consent document gives information about the study that will be discussed with you. This consent form might contain some words that are not familiar to you. Please ask us to explain anything that you do not understand before you sign this form. Once you understand the study, and if you agree to take part, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary. You do not have to take part in any of the tests or procedures in the study.
- There may be no direct benefits for you if you participate in this study.
- There may be some risks with taking part in the study.
- You may decide not to take part in the study, or you may decide to leave the study at any time without losing your regular medical care.
- You are asked to tell the study staff about any other studies you are taking part in or thinking of taking part in. This is very important for your safety.

PURPOSE OF THE STUDY

The main purpose of this study is to see how willing people who inject drugs (PWID) are to take PrEP and how consistently they are able to take one tablet at approximately the same time during each day of the week, and what that experience is like for them. Additionally, we will test whether text message reminders are able to help taking these medications regularly.

Taking medications to prevent becoming HIV infected is sometimes called "pre-exposure prophylaxis" or "PrEP." The drug being used for PrEP in this study is called Tenof-EM®. Tenof-EM® is commonly used to treat HIV infection. Tenof-EM® is a tablet that has two drugs in it. These drugs are called "emtricitabine" and "tenofovir". Tenof-EM® is generally safe when used as treatment for HIV. Tenof-EM® is not a cure for HIV or AIDS. When given together with other drugs, Tenof-EM® may help to prevent or delay AIDS in people with HIV. In 2015, the World Health Organization (WHO) approved oral PrEP using Tenof-EM for prevention of HIV in adult men and women who are at risk of getting HIV. The WHO recommended daily dosing of Tenof-EM. Whether PWID are adherent to a daily dosing strategy (taking one tablet at approximately the same time during each day of the week) is being evaluated in this study. **You have to agree to take PrEP (Tenof-EM®) to be in this study.**

Providing PWID with Tenof-EM for PrEP has been found to reduce the risk of HIV infection by approximately 44%. Other examinations of study data suggest that it can be as high as 92% effective when taken daily. How well PrEP does at preventing HIV depends a lot on people actually taking PrEP daily and when people take it less than that it is not as effective.

It is important that all study participants try to take the tablets each day and preferably at the same time. If you cannot do this, you need to tell the study staff you are having difficulty taking the tablets. If you are having problems taking the tablets, or have concerns, or have decided not to take the tablets for personal reasons, please tell us. Telling us about your experience allows us to understand the most acceptable way to design and implement PrEP programs for PWID. **Stopping taking PrEP will not exclude you from the study, you will have an opportunity to complete study assessments and to restart PrEP if willing to do so.**

About 200 people will take part in this study. The study is conducted only in Kyiv. People in the study will be asked to take part in the study for a total of 6 months starting from the date of first PrEP use.

STUDY PROCEDURES

Enrollment visit: The first study visit is called the enrollment visit. The enrollment visit will take up to 1.5 hours. **It will take place at the Lavra clinic**.

At first, we will ask you a few questions about your health, current medications and personal life to see if you are eligible to participate. You should answer these questions truthfully.

Next, we will do a finger prick to perform rapid tests for HIV and hepatitis B virus. Study staff will inform you of the results as soon as they are available. If you test positive for HIV you **will not** be able to join because in this case you will need treatment for HIV and not prophylaxis like PrEP. We will refer you for confirmatory testing in the nearest available facility. If you test positive for Hepatitis B, you **will also not be able** to take part in the study because the drugs used in Tenof-EM can also be used to treat hepatitis B virus and taking Tenof-EM now might result in less effective treatments for hepatitis B. We will refer you for consultation and treatment for Hepatitis B.

If you are eligible and agree to participate, you will continue with the study procedures. They start with random assignment (like the flip of a coin) to one of the two study groups. One group will receive PrEP, counseling by a social worker and SMS reminders via mobile phone. Another group will receive PrEP and counseling without SMS reminders. Random assignment is done automatically using a computer program and cannot be manipulated by anyone.

After randomization, you will need to complete the following procedures.

We draw ~10 mL of blood from your vein to test your kidney function, using a creatinine test. Results of this test will be available in about 3 days. You will start PrEP without waiting for the results of this test. If they show an elevated level of creatinine, this will mean that your kidneys may not function properly to remove PrEP medications from your body. This is a rare event, and does not pose any immediate risk to your health. If this happens, you will be informed by the study staff that you should discontinue taking PrEP, and will be referred for medical consultation. Another test from this sample will be done to confirm the result of the HIV rapid test and confirm that you do not have it.

Additionally, we will store some of your blood from this sample as Dried Blood Spots for other possible tests related to this study. These tests include testing to measure the levels of Tenof-EM® or any other HIV treatment medications that may be in your body and may not be done for a year or more after you have had your last study visit. The results will not be reported back to you or the study staff.

You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. Please remember that this information will only be used to locate you for the project sessions or interviews. The phone number will also be used to deliver SMS reminders, if you happen to be in that study group. We will not share this information with anyone else. This information will be kept in a secure place. If you are not willing to give us this information, you should not agree to be in this study.

We will ask you questions about your past medical history and what medications you are currently taking and provide you with a physical examination focused on any current health problems that you report. After that, a physician will file a medical chart for you and will prescribe you PrEP medications. You will not need to present your ID or other documents for that. A social worker ("PrEP Navigator") will help you obtain your **first supply of PrEP medications for 1 month**. It is important that you do not share your medications with anyone else, as it may harm them.

Next, you will be asked to complete an interview, using a computer or a tablet, with assistance from a study staff. The questions will ask about your age and background, your experience with health care, whether or not you have been recently incarcerated or are on parole, which drugs (legal and illegal) you take, and your sexual practices. This information does not include your name and will not be seen by study staff, police, or health departments. The information will be sent via a secure link to the main study database with only your Participant Identification Number with it.

The PrEP Navigator will also ask you several questions about your readiness to take PrEP. After that he will talk with you to explain details about what it is, what it does, and how it should be taken. You will discuss approaches that can help you take it regularly in order to achieve the desired effect – to protect you from HIV.

If you get into the group that will receive SMS reminders, you will complete a short questionnaire about how and what reminders you wish to receive. We will also send you a test message to

ensure that your phone can receive SMS from us.

The PrEP Navigator will also talk to you about protecting yourself and your partner(s) from HIV and other diseases passed during sex (sexually transmitted infections, or "STIs"). We will offer you clean syringes, condoms, other materials and counsel you on how to use them safely.

Month 1 and 3: Two next study visits will take place approximately 1 and 3 months after Enrollment. These visits will last about 1.5 hours. You will have a 2-week window to meet with the study staff. The visits will take place **at the Club Eney community center**.

During these visits, you will undergo approximately the same procedures as during the Enrollment visit. We will verify your contact information. You will complete an interview on a computer or tablet, with approximately the same questions regarding your experience with health care, injection or sexual behaviors, drug use, and about your experience with taking PrEP.

The PrEP Navigator will ask you how regularly you are taking PrEP, and again discuss with you all questions related to PrEP and will provide you with the next supply of PrEP medications. At Month 1, you will receive medications that should last for two months, until the Month 3 visit. At Month 3, you will receive a 3-month supply that should last until Month 6. You will also receive counseling on how to take it properly, and discuss what can help you with that. Regardless of whether or not you are taking Tenof-EM®, study staff will develop a plan of care and support that may include referral to health care services or people to help you with other needs you may have, such as mental health issues, housing, or drug or alcohol use. You will be able to modify the gschedule and content of the SMS reminders, if you will receive them.

We will also do a finger prick to collect a Dried Blood Spot sample for future testing. At Month 3, we will conduct a rapid HIV test.

If you would have stopped taking PrEP before the visit, you will be offered to restart it. However, **restarting will not be mandatory to continue in the study**. Screening procedures may need to be repeated at any study visit to confirm your eligibility to restart PrEP. If you decide to start PrEP at any visit and it has been more than 45 days since you have had laboratory tests done you will need to return to have laboratory tests repeated prior to initiating PrEP.

Month 6: The Month 6 visit will be the final visit for this study. It will also be conducted at Club Eney, and will take up to 1 hour. It will include a questionnaire with the same questions you will answer at Months 1 and 3, HIV and Hepatitis B rapid tests, Dried Blood Spot collection.

You will not receive another supply of PrEP medications from this study. If you will be willing to continue taking PrEP, we will refer you to the available providers of PrEP in Kyiv. Regardless of whether or not you are taking Tenof-EM®, study staff will develop a plan of care and support that may include referral to health care services or people to help you with other needs you may have, such as mental health issues, housing, or drug or alcohol use. You will receive standard HIV risk reduction counseling and will be offered prevention supplies such as syringes and condoms.

Month 2, 4, 5: Between the study visits, we will **contact you by phone** to ask you how you are doing with taking PrEP. The PrEP Navigator will call you using the number you provided, and ask you questions about how regularly you are taking PrEP and whatever problems you might have. You will also have a chance to discuss what may help you to take it more regularly. If you will receive SMS reminders, you will be able to modify them if needed.

Note: For any study visit, staff may need to draw additional blood as part of evaluation of abnormal test results or to confirm test results

What if your blood shows that you have HIV?

At Enrollment, Month 3 and 6, we will conduct HIV testing. At any visit, if the result indicates you may have been infected with HIV, we will arrange to confirm the test result. If the positive result is confirmed, we will also refer you for HIV treatment and care.

If this happens at Enrollment, you will not be able to continue with the study. If this happens at Month 3, we will ask that you stop taking the study medication (Tenof-EM®) but will invite you for the Month 6 visit. At Month 6 we will also advise you to stop taking PrEP, if you were planning to do so, and will refer to HIV treatment and care.

RISKS AND/OR DISCOMFORTS

Blood Draws

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases you may faint. There is also a slight chance of infection when blood is drawn. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns.

Confidentiality

We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn that you are part of this study and they may think that you are infected with HIV or are at high risk for infection with HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends and community.

Sensitive questions

The questions we will ask you about your sexual behavior may make you feel uneasy. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time.

Drug resistance

If you become infected with HIV, there is a risk that the HIV you have become infected with could become "resistant" to Tenof-EM®. This may then mean that you may not be able to be treated with Tenof-EM® nor the drugs which are combined together to make Tenof-EM® (Tenofovir and Emtricitabine). Viral drug resistance to these drugs can also cause cross resistance (meaning your virus is also resistant to other drugs as well as the drugs in Tenof-EM ®) to more commonly used drugs such as Lamivudine (3TC). Your doctor would need to perform a blood test to see if there is any evidence of resistance to Tenof-EM® and if there is, prescribe different drugs which are used to treat HIV infection.

Study Drug Side Effects

Tenof-EM® may have side effects, some of which are listed below. Please note that this list does not include all the side effects seen with this drug. This list includes the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional Tenof-EM® side effects, please ask the medical staff at your site. It should be noted that these are the risks that are seen in HIV positive people taking these medications. It is not known if these side effects will occur as often and it could be that some of these side effects might be more or less serious in HIV negative people.

The following side effects have been associated with the use of Tenof-EM®:

- Allergic reaction. Participants should report the following symptoms to the site medical doctor immediately should they arise:
- Fever
- Rash
- Upset stomach
- Vomiting,
- Loose or watery stools
- Abdominal pain
- Achiness
- Shortness of breath
- A general feeling of illness
- A potentially serious swelling of the face, lips, and/or tongue
- Runny nose
- Gas
- Itching
- Headache
- Dizziness
- Depression
- Increased cough
- Shortness of breath
- Generalized weakness or tiredness
- Abdominal pain
- Upset stomach (nausea) or vomiting
- Loose or watery stools
- Muscle pain and muscle weakness
- Inability to sleep, unusual dreams
- Skin darkening of the palms and/or soles
- Abnormal liver function tests, which could mean liver damage
- Increases in pancreatic enzyme (substances in the blood), which could mean a problem with the pancreas
- Inflammation or swelling and possible damage to the pancreas and liver
- Increased triglycerides, which may result in fatty deposits under the skin
- Increased creatine phosphokinase (CPK), which could mean muscle damage
- Worsening or new kidney damage or failure
- Bone pain and bone changes such as thinning and softening which may increase the risk of breakage
- Lactic Acidosis, which could result in unexplained weight loss, stomach upset, nausea, vomiting, fatigue, weakness, and shortness of breath
- Weight Loss

Other Possible Risks

In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers immediately.

BENEFITS

We will test you for HIV infection three times in this study. The counseling you get during this

study may help you to avoid HIV and other sexually-transmitted infections. If you become HIV infected, we will refer you for care and/or treatment. At the screening visit we will also check if you have hepatitis B infection. If needed, we will refer you for hepatitis B treatment. At every visit you will receive syringes and condoms free of charge.

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

NEW INFORMATION

You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the medication may be causing bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT

- You may be withdrawn from the study without your consent if any of the following occur:
- You are unable or unwilling to follow all of the study procedures or instructions.
- You could be harmed by continuing to take tablets.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- You are not able to attend visits or complete all of the study procedures.
- Other reasons, as decided by the study staff.

If you skip the Month 1 or Month 3 visit, you will not be withdrawn from the study, and will be invited for the next visit at the scheduled time.

ALTERNATIVES TO PARTICIPATION

If you choose not to take part in this study, it will have no effect on your access to regular services at this facility. There may be other studies at this facility in which you may be eligible to participate.

Tenof-EM (TDF+FTC) may be available from other places in Kyiv (including Kyiv City AIDS center) at no charge for people who are at risk of HIV. Also, there are many other places where you can go for HIV counseling and testing and HIV prevention services (free syringes and condoms), including at the Club Eney community center. We may tell you about other places if you wish.

COSTS TO YOU

There will be no cost to you for study related visits, study products, physical examinations, laboratory tests, or other procedures.

REIMBURSEMENT

If you are eligible and complete all study procedures, for your time, effort, and travel to and from the research sites you will receive 250 UAH for the Enrollment visit, 300 for Month 1 visit, 350 UAH Months 3 and 400 UAH for Month 6 visits (maximum total of 1300 UAH). The compensation is provided after all visit procedures are complete.

CONFIDENTIALITY

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Study records that identify you may be released to other parties or entities, only if you give your written permission or in case of a court order in as defined by law. However, your study records that do not contain personal information may be reviewed by various agencies that have a legal right to do so, such as the sponsor of the study (Alliance for Public Health), the UIPHP Institutional Review Board (IRB), study staff, study and monitors. Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

RESEARCH-RELATED INJURY

The study staff will ask you questions about your health at every study visit. If you have any health problems between visits, please contact the study staff. If you are injured as a result of the study procedures, please contact the Coordinator at the phone number indicated below, and the UIPHP will organize emergency care for your injuries. You will not have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the study sponsor.

You do not give up any legal rights by signing this consent form.

PROBLEMS OR QUESTIONS

About this study or in case of a study-related emergency, contact:	About your rights as a research subject, contact:
Olena Makarenko,	Iryna Pykalo,
Study Coordinator	Chair of Institutional Review Board
+38-093-328-9017	+38 044 222 62 71
4 Malopidvalna Str. Of. 6	4 Malopidvalna Str. Of. 6

Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

Protocol Version 1.0 April 24, 2020

Main Study Informed Consent Version 1.0

Signature page

If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to enroll into this study, please sign your name or make your mark below.

_____	_____	_____
Participant's Name (print)	Participant's Signature and Date	PTID

For staff: I have explained the purpose of the study to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

_____	_____
Study Staff Conducting Consent (print)	Study Staff Signature and Date and Time

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the purpose, procedures, risks and benefits of the study and has voluntarily accepted to participate in this study.

For those placing thumbprint only: I attest that the participant who states that his/her name is _____ has placed his/her thumbprint on this consent form of his/her own free will on this day _____.

_____	_____
Witness' Name (print)	Witness's Signature and Date

SAMPLE QUALITATIVE INDIVIDUAL INTERVIEW INFORMED CONSENT FOR SELECTED STUDY PARTICIPANTS

Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

Protocol Version 1.0 April 24, 2020

Individual Interview Informed Consent Version 1.0

Study Sponsor: The Global Fund to Fight AIDS, Tuberculosis, Malaria.

PRINCIPAL INVESTIGATOR: Kostyantyn Dumchev

PHONE: +38 044 222-6271

INTRODUCTION

You have been invited to have an individual interview with a study interviewer to discuss your participation in the "PrEP for PWID" study. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study. We would like to talk with you about topics such as healthcare, HIV/STI testing, and your community. We also are interested in learning about your thoughts and opinions about PrEP, including your experiences if you are taking PrEP. PrEP means Pre Exposure Prophylaxis. People take PrEP or medications to help prevent them from becoming infected with HIV. We hope that the information learned from this study will help us to better understand the health needs of People who inject drugs (PWID).

WHAT WILL HAPPEN DURING THIS PART OF THE STUDY?

If you decide to be in this study, you will be asked to have a 60 to 90 minute interview with a study interviewer. The interview will be at a location identified by study staff to assure adequate privacy and confidentiality. The information that you share during the interview will be treated confidentially. There will be no cost to you for participation.

During the interview, you will talk with a study counselor about different questions like:

- Please tell me about your experiences with the study so far?
- What do you think are the HIV prevention needs of People who inject drugs in your community?
- What is your experience with PrEP so far?
- What did or did not help you taking PrEP?

The interview will be recorded to help us get the best understanding possible from the interview. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. Your name or any other identifying information about yourself that you mention during the interview will not be associated with your responses. All identifying information will be removed from the transcript. These recordings will be destroyed after all analysis is completed.

You will receive 300 UAH for your time and effort with the interview.

Your participation in this interview is voluntary. You are not required to participate in this interview in order to remain in the rest of the study. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions.

Please also understand that you may stop your participation completely at any time. For example, if any of the questions make you upset either you or the interviewer may stop the interview at any time. You will also be provided with contact and referral information if any of the questions raise issues that you would like to talk about at a later time. You will not lose any of the regular benefits of your regular medical care at the Lavra clinic or prevention services at Club Eney.

WHAT ARE THE POTENTIAL BENEFITS?

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS?

To minimize any discomfort and to protect your privacy, the interview will take place in a private area that will allow you to speak comfortably without being overheard. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop the interview completely, at any time. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

HOW WILL YOUR PRIVACY BE PROTECTED?

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Study records that identify you may be released to other parties or entities, only if you give your written permission or in case of a court order in as defined by law. However, your study records that do not contain personal information may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (Alliance for Public Health), the UIPHP Institutional Review Board (IRB), study staff, study and monitors. Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

PROBLEMS or QUESTIONS:

About this study or in case of a study-related emergency, contact:	About your rights as a research subject, contact:
Olena Makarenko,	Iryna Pykalo,
Study Coordinator	Chair of Institutional Review Board
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Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

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Individual Interview Informed Consent Version 1.0

Signature page

If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to enroll into this study, please sign your name or make your mark below.

_____	_____	_____
Participant's Name (print)	Participant's Signature and Date	PTID

For staff: I have explained the purpose of the study to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

_____	_____
Study Staff Conducting Consent (print)	Study Staff Signature and Date and Time

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the purpose, procedures, risks and benefits of the study and has voluntarily accepted to participate in this study.

For those placing thumbprint only: I attest that the participant who states that his/her name is _____ has placed his/her thumbprint on this consent form of his/her own free will on this day _____.

_____	_____
Witness' Name (print)	Witness's Signature and Date

SAMPLE FOCUS GROUP INFORMED CONSENT

Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

Protocol Version 1.0 April 24, 2020

Study Staff Informed Consent Version 1.0

Study Sponsor: The Global Fund to Fight AIDS, Tuberculosis, Malaria.

PRINCIPAL INVESTIGATOR: Kostyantyn Dumchev

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INTRODUCTION

You have been invited to take part in an individual interview or a focus group or with other staff from the "PrEP for PWID in Ukraine" study. The interview or the focus group will be led by a trained and experienced interviewer. We are interested in learning about your thoughts, opinions, and experiences with being a part of the study, including talking with you about the PrEP model that is being used in the study. We hope that the information learned from this study will help us to better understand the health needs of People who inject drugs (PWID).

WHAT WILL HAPPEN DURING THIS PART OF THE STUDY?

If you decide to be in this study, you will be asked to participate in a 60 to 90 minute individual interview or a focus group with a trained and experienced interviewer.

All staff related to PrEP provision and counseling in the study will be asked to participate in the interview or the focus group. The questions will include (1) resources that were available at the clinic (2) resources that were available in the community, (3) resources that were not available during the course of the study, (4) feedback on the uptake and potential of the SMS reminder intervention, and (5) discussion of what could have improved their ability to provide care.

The interview or the focus group will be at a location identified by study staff to assure adequate privacy and confidentiality. The information that you share during the focus group will be treated confidentially.

The interview or the focus group will be recorded to help assure that we get the best understanding possible from each focus group. This recording will be used to make a written transcript of the interview. The recording and transcript will only have a Participant ID number. Your name or any other identifying information about yourself that you mention during the interview or the focus group will not be associated with your responses. All identifying information will be removed from the transcript. These recordings will be destroyed after all analysis is completed.

You will receive 300 UAH for your time and effort with the interview.

Your participation in this interview or the focus group is voluntary. You are not required to participate in this interview or the focus group in order to remain employed for this study. Although we

hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time. If you choose not to participate in the discussion or refuse to answer any of the questions, you will not lose any of the benefits of your regular employment.

WHAT ARE THE POTENTIAL BENEFITS?

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections.

WHAT ARE THE POSSIBLE RISKS OR DISCOMFORTS?

As noted, to minimize discomfort and to protect your privacy, the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

HOW WILL YOUR PRIVACY BE PROTECTED?

To help assure that we get the best understanding possible from the interview your answers will be recorded. After the interview is finished, the recording will be typed (called a transcript) by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript. The recording will be destroyed after all analysis is completed.

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Study records that identify you may be released to other parties or entities, only if you give your written permission or in case of a court order in as defined by law. However, your study records that do not contain personal information may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (Alliance for Public Health), the UIPHP Institutional Review Board (IRB), study staff, study and monitors. Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

PROBLEMS or QUESTIONS:

About this study or in case of a study-related emergency, contact:	About your rights as a research subject, contact:
Olena Makarenko,	Iryna Pykalo,
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Implementation of HIV Pre-Exposure Prophylaxis (PrEP) among People Who Inject Drugs (PWID) in Ukraine

Protocol Version 1.0 April 24, 2020

Study Staff Informed Consent Version 1.0

Signature page

If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to enroll into this study, please sign your name or make your mark below.

_____	_____	_____
Participant's Name (print)	Participant's Signature and Date	PTID

For staff: I have explained the purpose of the study to the volunteer and have answered all of his/her questions. To the best of my knowledge, he/she understands the purpose, procedures, risks and benefits of this study.

_____	_____
Study Staff Conducting Consent (print)	Study Staff Signature and Date and Time

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