Couples ART Adherence Intervention for PWID in Kazakhstan

National Clinical Trial (NCT) Identified Number: NCT03555396

Principal Investigator: Alissa Davis, PhD

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Version 3.1

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SMART Couples II
Stand-Alone Protocol

1. BACKGROUND

1.1. The fastest growing HIV epidemics globally are driven by injection drug use. Injection drug use is a major vector for HIV/AIDS in seven of 10 world regions, including Eastern Europe and Central Asia (EECA), southeast Asia, the Middle East, Latin America, and Appalachia and other rural areas in the U.S.[1,2] People who inject drugs (PWID) are disproportionately burdened by HIV, and in regions with HIV epidemics driven by injection drug use, HIV prevalence is over 40% among PWID.[3] HIV epidemics among PWID spread due to punitive drug laws, inadequate access to HIV care, and few available interventions.[3,4] As opioid epidemics continue to increase worldwide, more effective strategies are needed to reduce HIV transmission and HIV-related morbidities.[5] This proposal addresses the tremendous need for innovative ART adherence interventions for PWID that also provide attention to drug use issues among this population.

1.2. EECA has one of the fastest growing HIV epidemics in the world. EECA is the only region globally where both new HIV infections and HIV-related mortality are increasing.[6] New HIV infections in the region increased by 57% in 2015, while remaining static or declining in all other global regions.[6] This rapid increase is occurring in a setting of highly prevalent opioid injection.[6-8] In EECA countries, as in many other areas of the world, HIV+ PWID are not adequately treated, thereby undermining treatment as prevention strategies.[9] In Kazakhstan, the majority of people living with HIV (PLWH) are PWID (52%), and the majority of eligible HIV+ PWID are on ART (87%). However, only 27% of HIV+ PWID on ART are virally suppressed, indicating significant adherence challenges.[10] Studies on ART adherence interventions among HIV+ PWID in developing countries are limited,[1] which is problematic given large HIV epidemics among PWID in these countries.[3,11] Without evidence-based interventions (EBIs) to promote adherence among PWID an effective response to the HIV epidemic is unlikely. Given that the EECA has among the highest injection drug use rate and prevalence of HIV among PWID in the world,[3] the region is an optimal location to develop and adapt adherence EBIs for PWID. Moreover, low threshold interventions using mobile technology and dried blood spot (DBS) testing that are designed for low resource settings in EECA have potential to be implemented and scaled up in resource-constrained rural areas in the U.S. and other countries experiencing heroin epidemics.

1.3. ART adherence is critical to achieving viral suppression and reducing the spread of HIV. Because HIV+ PWID are from high-risk social networks, improving adherence to ART may reduce sexual and parenteral transmission of HIV to the broader community.[1] Although some physicians are reluctant to prescribe ART to PWID,[1,12-15] studies have found that HIV+ PWID can reach similar levels of ART adherence found among PLWH who have never used illicit drugs, particularly with social support and methadone maintenance treatment.[1,16] Evidence indicates that the simultaneous combination of ART adherence interventions with linkage to opioid substitution therapy (OST) and needle-exchange programs has a joint effect and provides more positive clinical outcomes and a greater reduction in HIV transmission than individual strategies alone.[1,17-19] In this project we will integrate referrals to OST and needle-exchange programs into our adapted couple-based adherence intervention.

1.4. New biological assays that measure ART drug levels can provide an objective adherence measure in a clinical setting and could be a useful tool in ART adherence interventions for PWID. ART drug levels in blood provide direct evidence of drug ingestion, but the short plasma half-lives of parent drugs (often hours) results in only an assessment of very recent adherence, thus limiting their applicability in clinical settings. Tenofovir (TFV) is a nucleoside analog that is used in common ART regimens. TFV is phosphorylated in cells to TFV-diphosphate (TFV-DP), which has a longer plasma half-life than the parent drug[20] and reflects longer term drug exposure (adherence).[20-23] Dr. Anderson has developed an assay for TFV-DP using DBS, which are easily collected in low resource settings. Furthermore, he is developing a point-of-care (POC) version of the assay that would allow rapid assay of samples collected by clinic providers or pharmacists.[24,25] Such an assay may provide early warning of viremia and be the basis for clinical feedback for earlier intervention to prevent viral rebound and development of resistant virus. In the proposed project, we will test the feasibility and acceptability of sample collection in AIDS Center clinics in Kazakhstan and will interview HIV+ PWID and healthcare providers about strategies for and acceptability of collecting samples in other community and health system venues.

1**.5. A couple-based intervention holds promise for improving ART adherence among PWID.** Access to social support from intimate partners is critical in ART adherence among HIV+ PWID.[26-30] Yet most HIV interventions focus on individuals as a unit of change, ignoring couple dynamics and the important role that partners play in risk behaviors and HIV treatment engagement and adherence.[31,32] Couple-based interventions have several advantages over individual approaches, including: 1) promoting mutual responsibility in protecting each other from HIV transmission and/or improving each other's health and ART adherence; 2) highlighting the relationship context and its connection to HIV acquisition and disease progression; and 3) creating a safe environment to discuss sensitive topics, such as sexual concurrency, needle-sharing, and medication

adherence.[32] Project Renaissance (R01DA022914; PI: El-Bassel), a couple-based HIV and overdose prevention intervention for PWID, was effective in reducing HIV acquisition, HIV risks, and overdose.[33] Intervention effectiveness and high retention achieved in this study demonstrate the feasibility of conducting couple-based adherence intervention research among PWID in Kazakhstan.

In focus groups conducted with 58 HIV+ PWID in Kazakhstan, participants cited partner support as a key facilitator of ART adherence.[34] Participants stated that intimate partners provided needed support for dealing with their HIV status in a context where many of them are rejected by their families and experience high levels of stigma and discrimination for being HIV+ and a PWID from the community and healthcare providers as well.[34] Despite the desire for a couple-based approach, there is only one couple-based ART adherence EBI (SMART Couples), but it has not yet been adapted for PWID. The proportion of prescribed doses taken within a specified time window, as measured by MEMS Cap, was significantly greater among the intervention participants than control participants at 3 months (change score b = -13.17, p=.028).[35] The four-session SMART Couples intervention was designed to improve ART adherence among HIV+ patients by intervening with both the patient and his/her primary partner in order to foster support from the partner to achieve optimal adherence.[35-37] While the intervention was shown to be effective in increasing the proportion of prescribed doses taken, its effects were short-lived.[35] Therefore, we propose to strengthen this promising and well-developed intervention to make it more relevant for PWID by integrating other existing efficacious adherence intervention strategies for PWID (i.e., directly observed therapy, drug risk reduction components)[38,39], incorporating linkage to opioid substitution therapy (OST), and adding new biomedical tools that provide an objective measure of adherence and may provide greater utility in a clinical setting than current adherence monitoring tools (i.e., electronic monitoring devices). The adaptation of an existing, efficacious couple-based adherence intervention strategy for PWID, combined with the integration of efficacious individual-level adherence strategies (i.e., directly observed therapy (DOT)) modified for couples and the incorporation of linkage to drug treatment services and needle-exchange programs could substantially improve adherence among HIV+ PWID, especially in resource constrained settings. Additionally, measuring adherence over time through the use of a mobile app and through new biomedical strategies to measure adherence (i.e., dried blood spot (DBS) tests) could provide a more objective measure of adherence, allowing earlier detection of adherence problems and more timely intervention.

2. STUDY AIMS

AIM 1: Adapt and refine the SMART Couples intervention and identify augmentative intervention strategies guided by the collaborative intervention planning framework[40] to create an integrated, couple-based ART adherence intervention for HIV+ PWID and their treatment support partners.

AIM 2: Pilot test the resulting couple-based intervention among 66 heterosexual PWID couples in Kazakhstan through a randomized control trial (RCT) to assess the safety, feasibility and acceptability of the intervention and obtain preliminary estimates of adherence outcomes (e.g. electronic monitoring devices, self-reported adherence, viral load) in the intervention arm versus standard of care.

3. STUDY RATIONALE

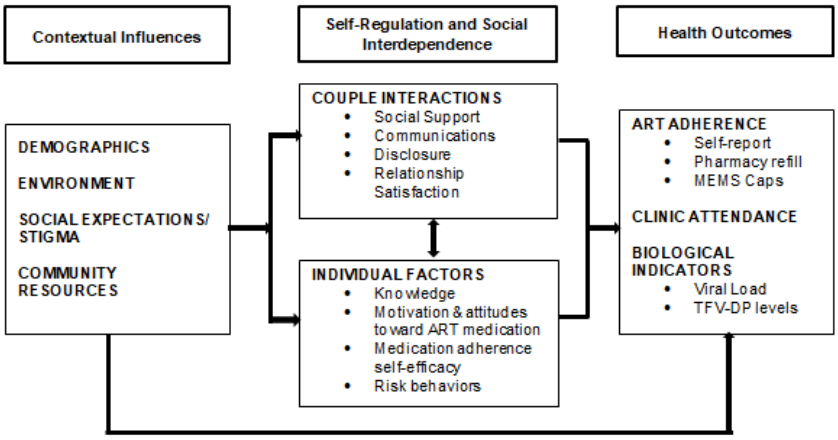
Only 27% of HIV+ PWID on ART in Kazakhstan are virally suppressed, indicating significant adherence challenges.[10] Studies on ART adherence interventions among HIV+ PWID in developing countries are limited,[1] which is problematic given large HIV epidemics among PWID in these countries.[3,11] ART adherence is critical to achieving viral suppression and reducing the spread of HIV. Without evidence-based interventions (EBIs) to promote adherence among PWID an effective response to the HIV epidemic is unlikely. The adaptation of an existing, efficacious couple-based adherence intervention strategy for PWID, combined with the integration of efficacious individual-level adherence strategies (e.g., the incorporation of linkage to drug treatment services and needle-exchange programs) could substantially improve adherence among HIV+ PWID, especially in resource constrained settings such as Kazakhstan.

4. STUDY DESIGN

4.1. Theoretical Framework. This study is guided by the integration of Behavior Exchange Theory (BET)[41] with Social Action Theory (SAT).[42] BET posits that couples in high satisfaction relationships will engage more frequently in behaviors perceived as positive or supportive by their partner than will couples in low satisfaction relationships.[41] SAT (the underlying theory of SMART Couples) posits that behavioral change is the result of self-regulation processes, social interdependence, and contextual influences.[42] Research on social support indicates that the availability of a trusted confidant is a critical factor determining whether people feel they are supported in coping with difficult challenges (i.e., HIV management, ART adherence).[42] The integration of BET with SAT allows us to analyze relationship satisfaction, self-regulation, and contextual influences to identify processes conducive to sustained support (see Figure 1 above). These theories suggest, and numerous studies indicate,[32,43-45] that people feel greater support for self-protective behaviors and more confident in their

ability to change if they and a trusted other are able to a) report mutual responsibility for each other's health, b) communicate about their relationship in a safe environment, and c) engage in collective goalsetting and monitoring activities. Manipulating these relationship capabilities in adherence interventions has the potential to effectively increase and sustain ART adherence and reduce risk behaviors (i.e., needle-sharing, drug use, sexual concurrency). This model guides my selection of research questions and methods.

Figure 1: Integrated Behavior Exchange and Social Action Theory



4.2. Study Design Overview.

In the pilot testing phase, 66 HIV+ PWID and their treatment support partners (n=66) will participate in a pilot randomized controlled trial (RCT) of the adapted couple-based intervention developed in the pre-trial phase of the study. Psychologists and intervention facilitators will be trained to deliver the adapted intervention remotely to assess safety, feasibility, acceptability, retention, and preliminary estimates of adherence to directly inform a future, full-scale R01 efficacy trial. Couples will be randomized to the intervention or standard of care (SOC) arms and assessed with repeated measures at four time-points on ART adherence, behavioral outcomes (i.e., drug use, sexual risk behavior), social support processes, and biological measures from baseline to 6 months post-intervention (see **Table 2** below). Electronic monitoring device (EMD) and weekly mobile app data will be collected throughout the intervention and follow-up periods. Due to COVID-19, all study procedures will be conducted remotely.

4.3. Study location and Recruitment Sites. HIV+ PWID will be recruited from the Almaty AIDS Center, which has 1,546 patients on ART, 660 of whom are PWID prescribed ART at least 6 months, 240 of whom are not virally suppressed.[46] Current AIDS Center patients on ART are 57.6% male and 42.4% female.[46] The AIDS Center does not currently provide any routine adherence intervention to patients, but recognizes ART adherence as a significant problem and is highly motivated to conduct research and intervention adaptation with us.

4.3.1. Recruitment and Eligibility Screening. Participants will be recruited from the Almaty City AIDS Center. An epidemiologist at the Almaty City AIDS center will review patient records to determine which patients potentially meet eligibility requirements. A list of potentially eligible patients will be given to nurses at the Almaty City AIDS Center. Nurses will call patients to inform them about the study and, for those who are interested, conduct eligibility screening with them. The nurse will obtain consent from eligible participants to be contacted by research staff and provide research staff with the contact information of eligible participants who have consented to be contacted.

Research staff will call eligible participants and explain the study verbally in detail, including the purpose of the study and the study procedures (including risks and benefits) and will answer questions to ensure that the patient understands what would be expected of her/him. The RA will then conduct confirmatory eligibility screening and informed consent. If the participant is eligible, the RA will send the participant a Qualtrics link to complete the baseline assessment. The RA will also obtain participant consent to review recent viral load test results from the AIDS Center and medical/research records. Potential participants will be told that participation in this study is completely voluntary and their decision whether or not to participate in this study or provide permission for screening will not affect any medical treatment they are receiving at the clinic or their participation in any other studies.

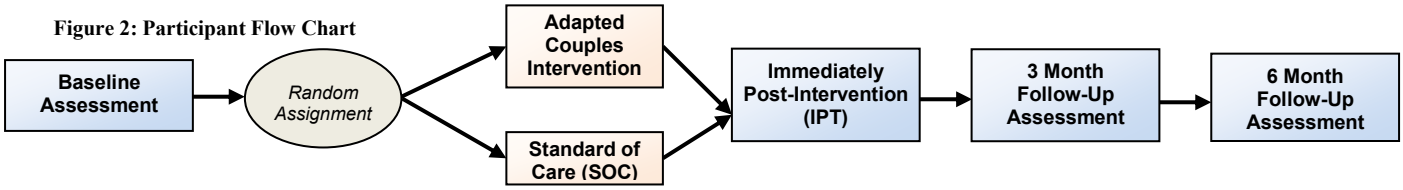
4.4. Inclusion/Exclusion Criteria

Participant inclusion criteria

We will recruit 66 dyads (n=132) to participate in a randomized control trial of the adapted couple-based intervention. We anticipate we will need to screen 450 individuals to obtain 66 eligible dyads (n=132). Dyads are eligible to participate if

(1) both partners are ≥18 years old,

(2) both identify each other as their intimate partner, family member, friend, or other person within their social network,



(3) the relationship has existed at least 3 months,

(4) both report feeling safe participating with their partner in the study,

(5) neither reports any severe physical or sexual violence perpetrated by the other partner in the past year,

(6) both are able to provide informed consent and follow study procedures, and

(7) both are fluent in Russian.

In addition, the "index case" (partner initially recruited from AIDS Center) must

(1) be confirmed HIV+ by the AIDS Center,

(2) have been on ART at least 3 months,

(3) not be virally suppressed according to the AIDS Center standard (<500 copies/ml), and

(4) report injecting any drug in the past year.

"Partners" may be HIV- or HIV+ and may or may not be a PWID. Because dyad dynamics may depend on the sex of the "index case", women will be the "index case" in at least a third of dyads. If both partners meet eligibility criteria, both will provide consent, complete the baseline assessment, and be randomized to study arm.

Participant exclusion criteria

Individuals who do not meet inclusion criteria or who meet any of the following criteria will be excluded from the study.

(1) unable to provide informed consent,

(2) unwilling or unable to participate in study procedures,

(3) any condition that, in the opinion of the principal investigator and research staff, would make participation in the study unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives.

4.5. Study Enrollment. The Baseline Visit will be conducted remotely by phone or computer with participants. At the Baseline Visit, the participants will provide informed consent, be enrolled in the study, complete the baseline assessment through Qualtrics, and self-collect urine and hair samples (if HIV-positive), which will then be mailed to the GHRCCA research staff.

4.6. STUDY PROCEDURES

We will conduct an RCT pilot trial of the adapted couple-based intervention. 66 couples will be randomized into two arms – 33 couples into the intervention arm and 33 couples into standard of care (SOC). SOC consists of an appointment with an AIDS Center nurse at baseline and three and six months later. Under current SOC in Almaty, no behavioral intervention is provided. Participants obtain prescription refills and give blood for viral load and CD4 tests once every 6 months. Participants receive viral load and CD4 test results only by request, and adherence is generally not assessed. We anticipate the intervention will consist of 3 sessions over the course of one month. Participants in both arms will be assessed at 4 time points: baseline "pre-intervention", immediately post-intervention (IPI), 3-month follow-up, and 6-month follow-up. **Figure 2** illustrates participant flow through the study.

4.6.1. Baseline Visit (for all participants)

Baseline visits will be conducted remotely by phone/video call using video call platforms that are commonly used in Kazakhstan and available on participant phones or in-person in GHRCCA's field office. Prior to remote visits, an RA will mail a baseline kit to participants containing an electronic monitoring device (EMD), study phone, and materials to self-collect hair and urine samples. The following procedures/assessments will be performed at the baseline visit:

1. The RA will complete the **Locator Information Form**;

2. The RA will send the **Baseline Assessment** through Qualtrics;

3. The RA will set-up **electronic monitoring device (EMD)** and phone app with participants. The RA will instruct the participants on proper EMD use and conduct an EMD test to confirm that the device is working properly and is connected with the data server;

4. To ensure equal distribution between study arms by the sex of the "index case" and those on tenofovir-based regimens, a randomization list will be generated. The dyad will be **randomized** to an intervention arm; If the dyad is randomized to Standard of Care, they will be sent informational materials. If they are randomized to the intervention, they will be scheduled an intervention appointment with an intervention facilitator.

5. Participants will self-collect urine samples and hair samples to measure biological levels of medication adherence. These samples will be mailed to GHRCCA staff.

4.6.2. Intervention Visits (for participants in the intervention arm)
Intervention sessions will be conducted by phone/video call or in-person in the psychologist's office (post-COVID) at the AIDS Center. The following procedures/assessments will be performed at the intervention visits:

1. The intervention facilitator will verify the participants by name.

2. The intervention facilitator will request **informed consent** to audiotape the intervention session. If both members of the dyad consent, the intervention facilitator will mark that consent was given and the audiorecorder will be turned on.

3. The facilitator will explain the purpose and activities of the day's session. S/he will go over the EMD adherence data of HIV-positive participants and discuss adherence patterns and challenges with the dyad.

4. The facilitator will conduct the day's session with the dyad.

All intervention sessions (3 sessions per couple) must be completed within two months of when the first intervention session is conducted.

4.6.3. Immediately Post-Intervention (IPI) Visit (for all participants)
The IPI will be conducted by phone/video call or in-person in GHRCCA's field office (post-COVID). Prior to the visit, an RA will mail an IPI kit to participants containing materials to self-collect hair and urine samples. For in-person visits, participants will self-collect samples at the GHRCCA field office. The following procedures/assessments will be performed at the IPI visit:

1. The RA will verify the participants by the name on the record and update the **Locator Information Form**;

2. The RA will send the **IPI Assessment** through Qualtrics;

3. The RA will conduct an **EMD** test and will check in with the participant regarding EMD uses and resolve any issues;

4. Participants will self-collect urine samples and hair samples to measure biological levels of medication adherence. These samples will be mailed to GHRCCA staff.

5. At the participant's next regular AIDS Center visit, the nurse will obtain an additional **blood sample** to conduct dried blood spot sampling and measure levels of medication in the body

4.6.4. 3-month and 6-month Follow-Up Visits (for all participants)
Three- and six-month Follow-Up Visits will be conducted by phone/video call or in-person in GHRCCA's field office (post-COVID). The following procedures/assessments will be performed at the 3- and 6-month follow-up visits:

1. The RA will verify the participants by the name on the record and update the **Locator Information Form**;

2. The RA will send the **3-** or **6-month follow-up assessment** through Qualtrics;

3. At the **3-month** follow-up, the RA will conduct an **EMD** test and will check in with the participant regarding EMD uses and resolve any issues. At the **6-month** follow-up, the participant will mail the **EMD** back to the RA.

4. After the **6-month** follow-up, the RA will administer the Exit Interview;

4.6.5. Pilot study assessments. Participants in both arms will receive the same schedule of assessments. There will be four main repeated assessment occasions: baseline "pre-intervention", immediately post-intervention (IPI), 3-month and 6-month follow-up. The primary adherence outcome will be proportion of prescribed doses taken as measured by EMD. Study assessments will be delivered remotely through Qualtrics.

4.6.6. Electronic Monitoring Device (EMD) Data. We will continuously monitor EMD device openings. The EMD sends a signal to a secure website via cellular data networks whenever the device is opened as a proxy for ART adherence. If connection or SIM card problems prevent real-time monitoring, records and diagnostics are stored (up to 1 year) and uploaded to the server when a connection is re-established. The device can store a 30-day supply of medication. EMD-measured adherence will be operationalized as percentage of days/doses for which a device-opening signal was received in the past month. EMDs will be given to participants in both arms. Pills will be deposited into the EMD device, which will record every time the device is opened. EMD data will allow patients to see objective feedback of their adherence patterns, which could help them improve their medication adherence.

At the conclusion of the baseline visit, the RA will mail the participant an EMD device with instructions on how to fill the device, open it for dosing, and pair it with the app. The RA will call the participant to assist with troubleshooting and confirm that the EMD device is properly set up, that it is recognized by the EMD server, and that device openings are being recorded properly (date and time). If 7 days pass and the device is not seen at all on the server, the RA will call the participant to see if there are any device problems. At each study visit, the RA will ask if the participant is having any problems using the EMD.

4.6.7. Weekly app assessments on a mobile phone. Based on GHRCCA's previous studies, we anticipate that participants will own a smart phone. We will pay for all participants' data plans during the course of the study. Weekly assessment data will be collected once a week throughout the course of the study through an app which will be installed on participants' phones. Assessment items will focus on drug use in the past week, adherence to ART, social support, and relationship satisfaction.

4.6.8. Biological Sample Collection. DBS samples for TFV-DP assay. Dried blood spot (DBS) samples will be collected from HIV-positive participants at their regular AIDS Center visit to assess feasibility and acceptability of the biological collection process and measure biological levels of medication. A nurse will collect DBS samples by venipuncture, using a pipette to spot blood directly onto Whatman 903 ProteinSaver cards. The cards will be air-dried, individually packaged in a plastic bag with desiccant, and transferred to a -20 to -80°C freezer for storage. Only samples of participants on tenofovir-based regimens will be shipped to the US, allowing us to assess the feasibility and acceptability of storage and shipment processes.

Hair samples for ART levels. Participants will self-collect hair samples and mail them to GHRCCA staff. To collect hair samples, participants will need to cut a small thatch of hair (~50 strands of hair) close to the scalp from a bottom layer of their hair. Hair should be placed in a piece of tinfoil and inside a Ziploc bag labeled with their study ID. Participants will ship samples to GHRCCA staff, who will then batch ship samples to the US for testing, allowing us to assess biological measures of ART adherence over the past several weeks.

Urine samples for point-of-care ART urine tests. Participants will self-collect urine samples and mail them to GHRCCA staff. To collect urine samples, participants will need to pee in a cup labeled with their study ID. Upon receipt of urine samples, GHRCCA staff will conduct point-of-care urine tests according to manufacturer protocols. This will allow us to assess biological measures of ART adherence over the previous 48 hours.

4.6.8.1. Assays. DBS assays. All DBS samples from participants taking tenofovir-based regimens will be batch-shipped to a lab in the United States for assay after all participants complete the intervention period. DBS samples will be shipped to the University of Colorado on dry ice for analysis using Dr. Anderson's current validated assay for TFV-DP.[22] Hair assays. All hair samples from HIV-positive participants will be batch-shipped

to a lab in the United States for assay after all participants complete hair sampling. Hair samples will be shipped to the University of California-San Francisco for analysis using Dr. Gandhi's current validated assay for hair samples. Urine assays. All urine samples will be tested by GHRCCA research staff using UrSure's validated assay for urine samples.

4.6.8.2. Biohazard Containment. As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the Centers for Disease Control and Prevention and the World Health Organization. The Almaty AIDS Center has extensive experience and authorization for the handling and containment of hazardous materials. AIDS Center staff complete regular safety training on exposure control, managing hazardous materials, and safe biospecimen collection, storage, and disposal. The University of Colorado Antiretroviral Laboratory has biosafety authorization for handling and containment of hazardous materials. Training is required within 6 months of hire and on an annual basis thereafter. Training includes Hazardous Chemical Waste Management and Bloodborne Pathogens Exposure Control Training for Research. Documentation is maintained in laboratory personnel records.

4.6.9. Medical Record Data. Almaty AIDS Center staff will provide research staff with limited electronic medical record data in order to determine participant eligibility and assess intervention outcomes. Electronic medical record data will be de-identified and assigned a unique study ID before they are provided to research staff. Almaty AIDS Center's Electronic HIV Case Management System (EHCMS) is a government-approved computer system for the collection, storage, transfer and analysis of epidemiological, laboratory and clinical data on all registered cases of HIV infection in Kazakhstan. Within this system, a file is created for each client who registers for treatment at the AIDS Center. All visits, tests, results and treatment information for each client are regularly entered by staff from the epidemiology and treatment department. Data extraction from this database will be done by AIDS Center staff who already have access to it. Data provided to GHRCCA research staff will be stripped of all PII identifiers. Data will be linked to participant study data through a unique study ID. Data extracted will include 1) HIV status, 2) PWID status, 3) Current ART regimen and ART regimens over the past year, 4) Length of time on ART, and 5) Viral load test results over the past year. Coded data will be entered into a password-protected file and sent via encryption to GHRCCA staff.

4.6.10. Quality control/intervention fidelity. To determine the extent to which the intervention is implemented as planned, we will use monitoring systems as in previous studies.[35,43,47,48] We will assess participant attendance, protocol adherence, and the integrity of implementation. We will audiotape all intervention sessions where participant consent is provided for quality assurance and supervision purposes. We will randomly select and review 20% of sessions in order to assess quality control and implementation fidelity.

4.6.11. Safety, Acceptability, Feasibility, Retention and Implementation Data. Intervention safety will be assessed through adverse event reporting by study and clinic staff and an exit interview asking about any negative experiences during the intervention. We will assess acceptability and feasibility of the adapted intervention and biological testing. Both partners will be assessed at the end of each intervention session on satisfaction and obstacles to participation. A brief survey will ask about participants' experiences with biological sample collection. We will track the number of participants retained in the study. For those who drop out, we will attempt to contact them to determine the reason. Staff will be asked questions about intervention delivery, specimen collection and challenges and facilitators of implementation.

4.6.12. Sample size and power considerations for the pilot RCT. We can estimate power for this study based on previous studies.[33,35] Based on Project Renaissance attrition rates,[33] we anticipate there will be no more than 10% attrition throughout the study. Power analyses were conducted with G*Power[49] (v3.1.0) using a repeated measures within-between ANOVA approach and α=.05. With 30 dyads per arm, we would have 80% power to detect a medium effect size (f=.15). Thus, we will recruit 66 couples and aim to have 60 for analysis.

4.7. DATA ANALYTIC PLAN

The primary purposes of a pilot study are to demonstrate safety, acceptability, and feasibility of methods and to determine important parameters with sufficient accuracy to allow reliable estimates of sample size, power, and detectable effects for a subsequent large-scale trial. Parameters include proportions for dichotomous endpoints (i.e. achieved 95% adherence over one-month); means and standard deviations for continuous endpoints (i.e. percentage of adherence over one month); and the spectrum of response profiles for longitudinal studies (i.e. adherence improvement or degradation). Thus, this pilot study aims to ensure that the parameters

for the larger trial are estimated as informatively as possible. We will estimate key study effect parameters with sample means and proportions together with 95% confidence intervals and test the primary null hypothesis at the two-sided level =.05.

5. DATA AND SAFETY MONITORING

The study will collect 5 distinct sources of data: (1) source documents (screening forms, informed consent, and participant contact information [locator form]); (2) assessment data (Baseline, Immediately Post Intervention, 3-month and 6-month Follow-Up Assessments, Biospecimen Acceptability Questionnaire, Self-Reported Adherence Questionnaire); (3) electronic monitoring device (EMD) data; (4) weekly mobile app data; and (5) biospecimen data (viral load test and dried blood spot samples).

Data from source 1 (source documents) will contain identifiable data and will be stored separately from all other data sources, which will only contain coded data. Consent forms from source 1 will be stored in a locked file cabinet in a locked office, and the locator form (which contains the link between patients and their unique PIDs) will be stored in a password protected file on a shared folder through Columbia University's Secure Data Enclave on an encrypted study computer stored in a locked office.

All other data will be labeled only with the PID and will not contain any identifiable information. All data from source 2 (assessment data) will be collected electronically on password protected and encrypted tablets. Data on the tablets will be electronically transmitted to a secure, remote and HIPAA compliant server with partitioned and dedicated space for this study only, known as the 'study server'. Only authorized users will be able to log into the server to view and download data for analysis. The server will maintain an audit trail of all log-ins, edits, and log-outs. Data collected on the tablets can be recorded with or without an internet connection. When there is a connection, the data will be automatically uploaded to the secure study server that will require password authentication. When there is not an internet connection, the data will be cached on the tablet and automatically upload once an internet connection is established. The data will be automatically deleted from the tablet once the upload to the study server is complete and the server will send an automatic email to the project manager and PI indicating that new data have been uploaded. Access to the data collected on the tablets and stored on the study server will be limited to only those study personnel with data access rights. The project manager will monitor the study server weekly to ensure that the data collected and uploaded to the server are complete and to monitor for suspicious data activity.

Data from source 3 (EMD data) and source 4 (mobile app data) will be stored on remote, password protected secure servers and contain no personally identifiable information.

Data from source 5 (biospecimens) will be identified only by the unique PID. Viral load results will be entered into the AIDS Center electronic medical record by clinic staff once the sample is processed. AIDS Center staff will provide a GHRCCA RA with study participant viral load results. DBS results will be processed at the University of Colorado. Hair sample results processed at the University of California-San Francisco.

5.1. Quality Control and Quality Assurance. In collecting the vast majority of the study data electronically, we will be able to closely monitor the quality and completeness of the data in near-real time and strive to correct any mistakes before they are propagated. To ensure that the correct assessment and procedures are completed at each study visit, the data collection program will be programmed to include only the study assessments and procedures relevant to that visit. The data collection program will also require that all questions be answered or refused, and we will build in skip patterns and logic checks for values entered to ensure data quality and completeness. We will closely monitor each step of the specimen collection, transport, storage, and analysis process to ensure that all specimens are continuously accounted for and stored and transported in conditions that will ensure their integrity. The project manager and RA will conduct weekly checks to confirm that the number of specimens collected match the number of assessments completed, and that the number of assessments completed match the number of visits. The research nurse will conduct a weekly check to ensure that the short-term specimen storage conditions are appropriate (e.g., refrigerator and freezer are the correct temperature) and will make adjustments as necessary.

The RA will monitor EMD devices continuously throughout the study to identify those devices that have that have not been seen by the server in the last week. If after 7 days the device still is not seen at all on the server, the RA will call the participant to see if there are any problems with the device and troubleshoot. The RA will also

conduct an EMD test at each study visit to identify and trouble-shoot any potential problems with the device.

6. HUMAN SUBJECTS PROTECTIONS

6.1. Institutional Review Board/Ethics Committee

This protocol, informed consent form, recruitment materials, and other requested documents will be reviewed and approved by institutional review boards at Columbia University and Al-Farabi Kazakh National University. All study investigators and research staff affiliated with Columbia University will be covered by the Columbia University IRB. All research staff who are not affiliated with Columbia University will be covered by the Al-Farabi Kazakh National University IRB. Subsequent to initial review and approval, the IRBs will review the protocol at least annually. The PI will make safety and progress reports to the IRBs at least annually and after study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, changes in research activity, and all unanticipated problems involving risks to human subjects or others.

6.2. Informed Consent

Informed consent will be obtained from each study participant prior to conducting study-related procedures. The informed consent process will be conducted in Russian by the Research Assistant (RA). Participants will be told that participation in this study is completely voluntary and their decision whether or not to participate in the study will not affect any medical treatment they are receiving at the clinic or their participation in any other studies being conducted by Columbia University. All study procedures will be described and they will be told that all information will be kept confidential within the limits of the law. Additionally, in the informed consent form, there will be areas for the participant to give permission to contact them for future research studies. Giving permission for this activity is optional not required for participation in the study.

Once the study has been explained in detail, time will be given for participant questions. If the participant wants to join the study, she/he will provide informed consent by signing the informed consent forms. A signed copy will be stored securely in a locked file cabinet in a locked room.

6.3. Risks

Participants enrolled in the study may experience the following risks and discomforts. They will be informed of these potential risks prior to providing their informed consent.

The blood sampling procedures to obtain blood are standard clinic procedures, but have some minor risks. The participant may experience a small amount of pain at the needle-prick site, but this should be minimal. A small amount of bleeding under the skin may produce a hematoma (bruising), which should dissipate in a few days. Venipuncture risks will be minimized by use of sterile technique by a trained nurse. The site of needle-prick will be swabbed with alcohol to minimize the chance of infection and protected by a band-aid or cotton wool to minimize risk of infection and pain. Care will be taken to choose a different needle entry point at subsequent visits. We believe that the likelihood of pain from venipuncture will be small. In previous work among this population, none of the participants reported significant pain from blood sampling procedures and none developed infection as a result of venipuncture.

6.4. Adverse Events

Serious adverse events include death, a life-threatening event, or an event resulting in hospitalization, prolongation of hospitalization, and disability. Serious adverse events, regardless of whether or not they are study-related, will be reported to the Columbia University IRB and the IRB at the study site serving the participant. Other adverse events include breaches of confidentiality (both intentional – e.g., mandated reporting of suicidal/homicidal participants – and unintentional), and non-life threatening psychological distress, arrest by the police and violence. The PI and research staff will closely monitor adverse events. The research team is aware that the study sample is likely to experience some adverse events, though unlikely to be study-related, due to their status in Kazakhstani society, their current or past history of law-breaking activity (e.g., use of or selling of illegal drugs), and the high levels of service needs. Drawing upon past GHRCCA studies, the research team designed an adverse event form.

Study staff will identify, manage and document all adverse events. These events may be identified by RAs, the Project Manager, or other staff, or they may be reported by participants. The procedures used to track, report, and examine adverse events are described below.

1) After an adverse event is reported/detected, the study staff member who identified the event will complete an Adverse Event Report form. The report form will include the date, description of the event, duration, severity, measures taken to ameliorate the adverse event, and disposition-related information (e.g., time spent providing referrals and type of referral). The report form will be reviewed and signed by the project manager, Dr. Davis, and Dr. El-Bassel, who will be responsible for ensuring that appropriate actions have been taken.
2) Drs. Davis and El-Bassel will consult with the Project Manager and any involved staff to ascertain whether the event was related to participation in the study and to ensure that an adequate response is provided to the participant. This will be followed by submission of a report to the IRBs at Columbia University and the Al-Farabi Kazakh National University.
3) In the event that a participant withdraws from the study or the PI decides to discontinue a participant due to an adverse event, the participant will be monitored by the Project Manager and the PI via ongoing status assessment until (a) a resolution is reached or (b) the event is determined to be unrelated to the study intervention.

Every two months, the research team from Columbia University and GHRCCA will review all adverse event data to date to determine if systematic trends exist among adverse event data to warrant changes to study protocols and procedures. Any proposed changes will be reviewed with staff at the study site, and, if needed, an external consultant (e.g., other senior investigators conducting federally-funded research on drug abuse). Approval for changes in study protocol or materials will then be obtained from the IRBs at Columbia University and the Kazakhstan School of Public Health. After approval, the NIDA Project Scientist will be notified, and changes will also be reported in the annual progress report submitted to NIDA.

6.4.1. Psychological distress. Participants may experience psychological distress resulting from the assessment questions. Using strategies established in our previous studies, the following steps will be taken to minimize the risk of psychological distress resulting from assessment questions.

1. Participants will be informed that the assessments include questions about sensitive behaviors (e.g., mental health, drug use, sexual behaviors, non-adherence), and that they can decline to answer any questions with which they are uncomfortable.

2. Procedures for emergency and nonemergency situations will involve the RA interviewer informing the project manager and PI of any such incidents of distress so that s/he can monitor compliance with distress-related protocol.

3. Participants who experience mild to moderate distress will be referred to the AIDS Center mental health staff for counseling. We will be able to make immediate referrals as needed to health care providers.

6.4.2. Unintended disclosure. Although it is possible that use of mobile apps or having electronic monitoring devices might also result in inadvertent disclosure of HIV status, we have had no such incidents in a current study (R01-MH09557; PI: Remien; NYPSI IRB# 6451) with over 450 participants using an electronic monitoring device for a 12-month period. Moreover, other colleagues who have used mobile apps or electronic monitoring devices in multiple sites with hundreds of patients have also not had any reported unintended disclosures (Altice, Haberer personal communication). We will take steps to minimize inadvertent disclosure of HIV status from receipt of text message reminders by keeping the text message simple and without any identifying and/or status related information.

6.4.3. Confidentiality breach. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study, or information collected by the study, could become known to others, and that participants may experience stigmatization or discrimination as a result. We will take the following steps to protect against the risk of a confidentiality breach.

1. All data, including biosamples, assessments, EMD output, and participant files will be labeled only with study identification numbers, and no participant names will be attached to study data.

2. The participant "key" linking study identification numbers with participant names will be kept by the project manager in a password-protected file on a password-protected and encrypted computer. Only the project manager and authorized research staff will have access to this “key”. Personal information including participant’s name, address and phone number will be stored separately from research data.

3. Electronic data files will be password protected and stored on a secure study server, which requires authentication to access.

4. All paper research data will be kept in locked file cabinets and will be available only to research staff directly involved in this project and institutional personnel for the purpose of routine audits.

5. All study staff will receive training on procedures to protect participant confidentiality and will take all required courses and certification tests. Participants will be told that all data are confidential within the limits of the law.

6.5. Alternatives
Participation in the study is voluntary and participants may withdraw from the study at any time. There are no alternatives to participation. Participants are free not to participate or to withdraw at any time. Their treatment will not be affected in any way, and they may still continue to attend the clinic.

6.6. Benefits
Study participants will receive no direct benefits from participating in this study. The potential benefit to science and society is documented evidence that a couples-based ART adherence intervention can be used to improve ART adherence among HIV-positive individuals. This can help patients better manage their health and minimize the disruptions and negative health consequences caused by non-adherence to ART.

6.7. Compensation
Compensations will be based on those routinely offered at the study site for this type of research. Participants in 2-hour focus groups will receive approximately $30 USD for their time and effort. Participants completing each assessment visit will receive approximately $15-20 USD to compensate for time and biosampling. Intervention participants will receive $10-15 USD for each intervention session. Participants will also receive a bonus incentive (approximately $35) for returning their EMD device, and an additional small incentive ($1 USD) for each weekly survey they complete.

6.8. Participant Privacy and Confidentiality. All participant-related data, including biospecimens, assessment data, EMD output, mobile app survey data, and participant files will be kept strictly confidential. All data and records will be labeled only with PIDs, and no participant names will be attached to study data. The participant "key" linking study identification numbers with participant names will be kept by the project manager in locked file cabinets at GHRCCA offices. Only the project manager/PI will have access to this “key” and file cabinets. Personal information including participant’s name, address and phone number will be stored separately from research data. Electronic data files will be password protected and stored on the study server, which requires authentication to access. All paper research data will be kept in locked file cabinets and will be available only to research staff directly involved in this project and institutional personnel for the purpose of routine audits. All study staff are trained on procedures to protect participant confidentiality and will take all required courses and certification tests. Participants will be told that all data are confidential within the limits of the law.

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