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# Peer-mediated assisted partner notification services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

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## Abstract

### Introduction

Targeted, tailored interventions to test high-risk individuals for HIV and hepatitis C (HCV) are vital to achieving HIV control and HCV micro-elimination in Africa. Compared with the general population, people who inject drugs (PWID) are at increased risk of HIV and HCV and are less likely to be tested or successfully treated. Assisted partner notification services (APNS) increases HIV testing among partners of people living with HIV and improves case-finding and linkage to care. We describe a study in Kenya examining whether APNS can be adapted to find, test, and link to HIV and HCV care the sexual and injecting partners of HIV-positive PWID using a network of community-embedded peer educators (PEs).

### Methods and analysis

This prospective cohort study leverages a network of PEs to identify 1,000 HIV-positive PWID for enrollment as index participants. Each index completes a questionnaire and provides names and contact information of all sexual and injecting partners from the past 3 years. PEs then use a stepwise locator protocol to engage partners in the community and bring them to study sites for enrollment, questionnaire completion and rapid HIV and HCV testing. Outcomes include number and type of partners per index who are mentioned, enrolled, tested, diagnosed with HIV and HCV and linked to care.

### Ethics and dissemination

All potential index participants are screened for intimate partner violence (IPV) and those at high risk are not eligible to enroll. Those at medium risk are monitored for IPV following enrollment.

A community advisory board (CAB) meets biennially to engage in feedback and discussion between the community and the research team. A safety monitoring board (SMB) meets biennially to discuss study progress and review data, including IPV monitoring data. Dissemination plans include presentations at quarterly Ministry of Health (MoH) working group meetings, local and international conferences, and publications.

## Strengths and limitations of this study

- This cohort study investigates the use of assistant partner notification services (APNS) for HIV and hepatitis C (HCV) to find, test, and link to care the sexual and injection partners of people who inject drugs (PWID) in Kenya—a high risk, difficult to reach population.
- Community embedded peer educators who are former drug users trained to provide harm reduction services and are known and trusted within the PWID community conduct partner tracing, and typically serve as the first point of contact with potential partner participants.
- An iris scanning biometric identification system ensures that each index participant enrolled is a unique individual and confirms that individual partner participants who enroll more than once in relation to different index participants are the same individual.
- Phylogenetic analysis of HIV and HCV viral sequences combined with APNS provides additional information about transmission dynamics within the cohort, including risk of onward transmission for different clusters and geographic regions.

## Introduction

Of the UNAIDS 90-90-90 goals,[1] diagnosing 90% of those living with HIV remains the most elusive target worldwide,[2] and strategies to reach high-risk individuals who have never been tested for HIV is increasingly important.[3] Sharing needles and other drug paraphernalia is the most efficient mode of HIV transmission, and accounts for 13% of new infections globally.[4,5] In Kenya, prevalence of HIV among people who inject drugs (PWID) has been estimated at 15 – 50%[5–9]—significantly higher than the general population prevalence of 4.9%,[10] and up to 30% of PWID in Kenya have never tested for HIV.[11,12] Multiple studies have demonstrated low knowledge of HIV

status and low engagement in care among Kenya's PWID.[12,13] Retention in care and adherence to ART are also both lower among drug users as compared with non-drug users worldwide,[2] and sub-Saharan Africa (SSA) has the lowest rates of ART use among HIV-positive PWID anywhere in the world.[14]

In addition to HIV, PWID are at high risk for hepatitis C virus (HCV) globally and have the highest HCV prevalence of any group studied in Kenya, between 13-40%[15–17] compared with the general population prevalence of <1-4%.[18,19] However, multiple barriers exist at individual, provider and system levels resulting in low rates of testing, engagement in care, and completion of treatment courses for PWID.[20–22] Although less than 20% of PWID with chronic HCV worldwide have undergone antibody screening, the number who have completed PCR confirmatory testing is even lower.[23] Despite the introduction of highly effective direct acting antivirals (DAAs) into Kenya in 2016, only a small fraction of HCV-infected individuals have been treated, prompting attention to micro-elimination strategies.

Assisted partner notification services (APNS) for HIV is an evidence-based partner notification strategy in which providers elicit information about the sexual or injecting partners of an HIV-positive index client, and then contact, HIV test and link to care any partners found to be positive.[24] APNS has been shown to significantly and safely increase the uptake of HIV testing services (HTS), case finding, and linkage to care for partners of HIV-positive people.[24–26] APNS can also reduce barriers to disclosing HIV status[27] and is cost-effective.[28] APNS has been successfully implemented among HIV-positive patients from the general population in the USA,[29] Mozambique,[30] Malawi,[31,32] and Kenya,[26] and has recently been incorporated into the World Health Organization (WHO) guidelines for routine care for HIV-positive people worldwide.[33] While programs have introduced the practice of APNS in high-risk key populations (KPs) such as

female sex workers (FSW)[34] and men who have sex with men (MSM),[35,36] this intervention has not been well-studied among PWID, an extremely high risk group.[24,37] Similar to FSW and MSM, PWID engage in behavior that is criminalized[38] while experiencing high rates of marginalization and displacement,[39] making them difficult to study. These factors and others also contribute to significant barriers in the implementation of health programs targeting PWID.[40–42]

Phylogenetic analysis is a method of identifying the role of specific risk groups and risk factors for onward transmission of HIV and HCV using the genetic sequence of each virus.[43–45] Viral phylogenetics can provide additional information on patterns of transmission,[46–48] epidemic growth,[49,50] risk groups,[51–53] and risk factors associated with onward transmission.[45,54–56]

Here we describe a prospective cohort study that seeks to determine whether and how APNS can be implemented to find, test, and link to care the injection and sexual partners of HIV-positive PWID in Kenya. Simultaneously, our study will use phylogenetic analysis to study genetic sequences of HIV and HCV within our cohort to further understand transmission patterns and risk for onward transmission. All index and partner participants are tested for HCV in addition to HIV. In Kenya, the large majority of PWID do not have regular access to cellular telephones, which are the typical communication modality for APNS in other populations. As such, our APNS model relies on the utilization of community-embedded peer educators (PEs) to locate and communicate with members of this difficult to reach population. We hypothesize that we will be able to employ these customized APNS procedures to reach a large number of injection and sexual partners, and that we will see differences in HIV and HCV testing, HIV and HCV prevalence, and engagement in care between sexual and injection partners. Additionally, we hypothesize that we will identify unique transmission patterns and risks for onward transmission in phylogenetic analysis.

## Methods and analysis

### *Approach*

APNS is a practice through which healthcare providers facilitate the notification, testing and linkage to care for partners who have been exposed to HIV or other sexually transmitted infections by an individual known to be positive. Typically, APNS is conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone to alert them to their exposure and arrange testing. We have designed customized procedures to ensure and improve the safety and efficacy of APNS in the unique population of PWID in Kenya. Because PWID and their partners in Kenya rarely own cellular phones, we work with community-embedded peer educators (PEs) to find and engage with partners. Additionally, our protocol includes different APNS procedures among injection partners and for sexual partners, as these groups have different risk profiles and different relationships to index participants.

### *Study design*

Our study is a prospective cohort study with two groups: index and partner participants ("indexes" and "partners"). We use tailored APNS procedures to identify, find, test and link to care the sexual and injection partners of HIV-positive PWID. All participants who are either HIV-positive or HCV-infected then complete a 6-month follow-up visit to assess linkage to and engagement in care.

### *Study sites/setting*

Study procedures take place in eight main sites including public health centers, medically assisted therapy (MAT) centers, and needle and syringe programs (NSPs) in Nairobi, Kilifi, and Mombasa

Counties in Kenya (Figure 1). Each site is staffed by at least one clinical officer (mid-level clinician) who works with the study team to ensure that indexes are HIV-positive. In Nairobi County, the activities are centered at two NSP sites and one MAT center in the Mathare North area. The NSP sites, run by Support for Addiction Prevention and Treatment in Africa (SAPTA), offer routine HIV counseling and testing. Referrals are made to local clinics providing care for those who test positive for HIV or HCV. We also recruit indexes from a government-run methadone clinic in Nairobi in the Ngara area. The Ngara Health Center MAT clinic offers HIV testing, care and treatment in addition to daily methadone administration, psychosocial services and treatment for other health conditions. In Kilifi county, participant recruitment and enrollment takes place at three needle and syringe program centers and one government hospital. The Omari Project is located in Malindi town and offers HIV counseling, testing, care and treatment in addition to harm reduction services. Malindi Sub-County Hospital's MAT center is a recruitment site in Kilifi County within a mid-sized government hospital that offers a large range of medical and social services. Malindi Sub-County Hospital also has a large laboratory that houses the study's samples collected in both Kilifi and Mombasa Counties. The Muslim Education and Welfare Association (MEWA) NSP sites in Kilifi and Mtwapa towns offer HIV counseling and testing, in addition to HIV care and treatment and harm reduction services. In Mombasa county, participants are recruited from the ReachOut Center, an NSP site in Mombasa city that offers a full range of harm reduction services in addition to HIV counseling, testing, care and treatment. All recruitment sites offer HCV testing when kits are available through specific donor-driven projects.

*Population*

This study includes index participants and their sexual and injecting partners . All indexes are HIV-positive PWID. Partners are either sexual partners or injecting partners of indexes. As such, partners need not be PWID or HIV-positive but are defined by their relationships with indexes.

Indexes are largely recruited from organizations and clinics that provide services to PWID populations, although they may also come from outreach efforts or informal referrals from other participants. Partners are identified and recruited through peer-mediated APNS and may come from any geographic area or community.

*Study procedures*

1. Peer educator recruitment and training

PEs are recovering PWID with established relationships in the PWID communities that they serve. The majority are between the ages of 25 and 50, are enrolled in Kenya's methadone program and have stopped injecting drugs, byself-report. These men and women have been identified by the individual organizations at which they work as being key community members, and have undergone extensive training for their roles as PEs. Training is an intensive 5-day course with modules covering a broad spectrum of content including basics of drugs and drug-related harms, harm reduction efforts including NSP and MAT, abscess prevention and management, overdose prevention and management and behavior change communication. PEs have access to relatively hidden PWID community spaces, and provide health counseling, linkage to support organizations, information, and other services to this vulnerable population.

For this study, PEs who were actively carrying out basic duties were chosen by the leadership at each organization based on several factors including awareness and knowledge of HIV in the

community and access to unique target populations (for instance, women who inject drugs are more easily accessed by women PEs). Once identified, PEs underwent an intensive 1-day training to educate them on the practice and ethics of research, study procedures, and their role in the study. PEs participate in regular health education and harm reduction training and engage in quarterly sessions with study leadership wherein PEs present barriers and lessons learned to the study team so that study-related issues can be addressed.

2. Inclusion & exclusion criteria

Inclusion and exclusion criteria are different for indexes and partners (Table 1). Any interested individuals who are under the age of 18 are referred to the site clinicians for routine counseling and harm reduction services.

3. Index recruitment and enrollment

PEs work with clinicians at each site to identify potential indexes at NSP sites, MAT centers and other areas where PWID congregate. Clinicians are employed by the sites, and are trained as clinical officers (COs), or mid-level providers. For this study, HIV rapid testing is performed by COs and takes place as part of standard clinic procedures. All potential indexes are re-tested using HIV rapid tests (as per the national guidelines) to confirm HIV status prior to enrollment. If HIV-seropositive, either newly diagnosed or known to be positive, clinicians either discuss the study directly with potential participants or engage PEs to find individuals and bring them to the study office. Importantly, PEs are not told whether participants are being traced as an index or a partner, protecting the confidentiality of indexes' HIV status.

Study staff health advisors (HAs) are the individuals responsible for conducting study procedures including data collection, HIV and HCV testing, and the coordination of APNS efforts (Figure 2). All HAs were trained and experienced in HIV counseling and testing prior to working for the study, and many had previous experience working with PWID. All HAs underwent a week-long training course at the beginning of the study in which they learned the basics and purpose of research, research ethics, study procedures, unique ethical and logistical issues to consider when working with PWID, and other topics. All HAs also completed the Collaborative Institutional Training Initiative (CITI) course on Human Subjects Research and the Responsible Conduct of Research. HAs explain the benefits and rationale for providing APNS, discuss the importance of learning more about HIV and HCV, and describe the process of notifying partners without revealing the identity of the index. They ask participants to provide written informed consent and use an iris-scanning biometric device to record a unique identifier for each participant, thus enabling the study team to confirm that a person does not enroll into the program as an index more than once.

Indexes undergo a structured questionnaire administered by the HA using open data kit (ODK) software on tablet devices (ODK, 2017, Seattle, WA, USA). Questionnaires cover a variety of topics including demographics, sexual and injecting behaviors, drug use history, and HIV testing and engagement history. Participants are then asked to recall all of their sexual and injecting partners over the past three years, naming these partners one by one and assigning each partner a letter ("A," "B," etc). Indexes are asked to give as much locator information as possible for each partner, including names (which may be nicknames), phone numbers, and location of employment or residence. Locator information is written on a paper form for each partner. Indexes then

complete a short ODK questionnaire about each partner mentioned, which includes information about the relationship between the index and the partner.

Indexes then undergo rapid HCV antibody testing as part of routine study procedures. HAs conduct pre- and post- test counseling and ensure individuals who test positive are available for follow-up visits to discuss confirmatory HCV PCR testing and enrolling in a treatment program administered by the Ministry of Health. All indexes then undergo phlebotomy with a sample of 10mL of blood drawn for further testing (see section 6 below). Indexes receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

4. Peer-educator mediated assisted partner services and partner recruitment

For those partners who have phone numbers listed, HAs attempt phone communication first. However, the vast majority of partners mentioned by indexes do not have working cellular phones; therefore, with very few exceptions, PEs locate and conduct the study's first interaction with identified partners. PEs are given paper forms containing names and locator information for identified partners. They are never told which index referred the team to each partner, and that information is not listed on locator forms or any other accessible file. PEs then locate and approach potential participants in the community. Using a standardized script, PEs inform potential participants that they have been identified as an individual who might be eligible for a research study on HIV and HCV. They then accompany interested individuals to the nearest research office, where the study's HAs conduct informed consent.

5. Partner enrollment

After informed consent and biometric identification, partners complete a structured questionnaire similar to that of indexes, administered by HAs on a handheld device using ODK software. Following the questionnaire, all partners undergo rapid antibody testing for both HIV and HCV. Testing and counseling services are provided in accordance with national HIV testing and counseling guidelines. Any partner found to be positive for either HIV or HCV antibodies undergoes a 10mL blood draw. Those partners who test negative for both HIV and HCV are finished with study procedures at this time, and are counseled on risk reduction measures and linked to HIV and HCV prevention services before leaving the study site. All partners receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

HIV-positive partners are invited to undergo screening as an index once data collection procedures for their partner enrollment are complete. If they meet eligibility criteria as an index, they may enroll as an index. Study procedures are slightly amended for indexes that have previously enrolled as partners. After undergoing informed consent and completing a short questionnaire that only includes questions that were not a part of the partner enrollment questionnaire, they complete the identification and data collection on each of their sexual and injection partners, identical to partner identification procedures for indexes described above.

6. Laboratory Procedures

Blood samples from both index and partner enrollment visits are collected in EDTA vacutainer tubes. Blood is mixed with the anticoagulant by inversion and the anticoagulated blood is stored at room temperature at the sites for less than 4 hours. A motorcycle courier picks samples from each site daily and brings them to the University of Nairobi Pediatric Research Laboratory in

Nairobi or the Malindi Sub-County Hospital Laboratory for coast sites. At each laboratory, samples are first used to prepare two Whatman 903 Protein Saver dried blood spot (DBS) cards with 50ul of whole blood on each spot. Blood samples are then centrifuged and used to prepare 2 to 3 aliquots of 1ml of plasma in labeled serum vials. Plasma aliquots and air-dried DBS cards (with desiccant in sealed Ziploc bags) are then stored at -80° Celsius and shipped on dry ice to the University of KwaZulu-Natal laboratory. There, samples undergo HIV and HCV viral load testing and amplification for sequencing.

7. Participant follow-up

All index and partner participants who were positive for HIV or HCV complete a six-month follow-up visit. HAs identify which participants are due for follow-up visits on a weekly basis and give PEs as list of these names. PEs then trace participants and bring them back to clinics where data collection procedures are conducted.

Six-month visits are short, and involve only a brief questionnaire covering questions on testing for HIV or HCV (if not infected with both on enrollment), enrollment in care and treatment, engagement in care, and follow-up testing. The purpose of this visit is to assess whether engagement in care has changed following APNS procedures.

8. Intimate partner violence (IPV) monitoring

Given historical concerns that APS may increase one's risk of experiencing intimate partner violence, all potential participants undergo screening for IPV before enrollment. IPV is defined as any physical, sexual or psychological harm inflected on a person by a current or former sexual partner. After answering a standardized set of six questions about physical, emotional and sexual

IPV and the timing of any previous experience of IPV based on published screening tools reviewed by the Centers for Disease Control and Prevention,[57] potential participants are classified as low, medium or high risk for IPV. Individuals are classified as at high risk for IPV if they report IPV within the last month. Any potential index who is classified as high IPV risk is excluded from study participation and provided with IPV counseling and resources. Any potential partner who is classified as high IPV risk is allowed to enroll, but then receives special monitoring for IPV following enrollment.

Potential participants are classified as at moderate risk for IPV if they report 1) IPV during their lifetime either from a current or past partner; and/or 2) fear of IPV if they participate in the study. All index or partner participants classified as moderate IPV risk receive special monitoring for IPV following their enrollment in the study.

Potential participants are classified as at low risk for IPV if they report 1) no IPV during their lifetime ; and 2) no fear of IPV if they participate in the study. These individuals undergo standard study procedures which include completing the baseline IPV case report form and a follow-up IPV case report to capture reports of any interim IPV.

9. Confidentiality and safety

*Participants*: All study procedures take place in private rooms at each study facility. To ensure the safety and confidentiality of indexes, PEs who are tasked with finding partners are blinded to the identity of the linked index through the use of partner locator forms that do not contain identifying information about the index participant. Locator forms do contain a printed barcode label that are then used by study staff to link the partner with the index who referred the partner.

Sexual partners are brought to independent facilities for enrollment rather than to centers that serve PWID, in order to further protect the identity of the index participant who referred them. The independent facilities are local healthcare clinics that serve the general population.

*Peer educators*: PEs have frequent interactions with police, and can be victims of harassment or violence, both by police and by PWID. To reduce the risk of law enforcement troubles, PEs carry identification showing that they are working on a study being conducted by the Ministry of Health. Local law enforcement officials have also attended ongoing sensitization trainings by the Ministry of Health and by organizations working with PWID.

10. Referrals to care

*HIV Counseling and Care:* Participants are provided with their HIV test results in the context of post-test counseling, and are then referred to available medical and psychosocial care and support facilities either within the research site or in close proximity to the research site or the participant's home. Additionally, HIV-positive individuals are offered individual or group support sessions as available within each site.

*HCV Counseling and Care:* Participants who test positive for HCV antibodies using rapid testing are provided with their HCV antibody test results in the context of pre- and post-test counseling. They are informed that they may have active HCV infection; however, further confirmatory testing must be done prior to establishing the diagnosis. Confirmatory polymerase chain reaction (PCR) testing is done in batches of samples at our partnering laboratory at the University of KwaZulu-Natal, South Africa, and participants with active infection are later contacted for results and counseling. Once notified, those with active infection are paired with a PE at their site to ensure

close contact is maintained. Study participants with active HCV infections will be eligible to receive free treatment with direct acting antivirals, which the Kenyan MoH has procured.

*Data management*

After each study visit, HAs review their work for omissions or errors and all data are uploaded into the study database. Electronic data are stored securely in an encrypted database on servers using Open Data Kit Aggregate, within Kenya's Ministry of Health (MoH). All errors or omissions identified at any step in the quality assurance/quality control process are revised by the staff member who originally completed the document. All additions and corrections are initialed and dated by the staff member who records the entry.

A link-log is separately encrypted to further ensure that data remains secure. Any data transferred to investigators or MoH are de-identified and encrypted during the process of transfer from the server. Each investigator maintains and stores secure, complete, accurate and current study records throughout the study. A database manager performs regular data cleaning and resolves any discrepancies that occur. Study sites also conduct quality control and quality assurance procedures.

*Outcome measures*

The primary outcomes of interest to assess the success of the APNS intervention are: a) number of partners tested for HIV and HCV through APNS, identified by each index participant over the course of the study period; b) number of partners newly testing positive for HIV and HCV, per index participant; c) number of known HIV or HCV cases identified through APNS who are not engaged in care; d) number of index and partner participants with HIV and/or HCV infection who are linked to care; e) number of index and partners with HIV and/or HCV infection who remain in

care and are receiving appropriate treatment at 6 months after testing positive. Secondary outcomes are linked to inclusion in phylogenetic clusters identified as high risk for onward transmission of HIV and HCV.

*Sample size and power analysis*

We are enrolling 1000 HIV-positive indexes and their sexual and injecting partners . Based on HCV data from MoH and our preliminary results, we estimate that 20% of PWID with HIV will be co-infected with HCV and that each index will identify on average two partners who will accept HIV and HCV testing, 20% of whom will be HIV-positive, and 20% of whom will be HCV-infected. Thus, with provision of APNS to 1,000 HIV-positive indexes and testing of 2,000 partners, we will identify an estimated 600 indexes and partners infected with HCV and 400 HIV-positive partners.

*Statistical methods and analysis*

To determine efficacy of the APNS intervention, we will use generalized estimating equations (GEE) models with a Poisson link to compare the two arms of the study using the following variables and offsets: 1) rate of HIV and HCV testing of partners: number of individuals tested for HIV or HCV, offset by the number of partners located with locator information provided by the index participant; 2) prevalence of HIV and HCV infection: number of individuals identified as HIV or HCV-positive, offset by the number of individuals who were HIV tested; and 3) rate of linkage to HIV and HCV care: individuals who test HIV or HCV-positive and link to care, offset by the total number of individuals who test HIV or HCV-positive.

Additionally, using both GEE and phylogenetic analysis, we will determine the following: 1) identifiable and individual risk factors linked to high rates of HIV and HCV transmission, 2) risk factors linked to both needle-sharing and sexual transmission, and 3) identification of transmission clusters among PWID for both HIV and HCV.

*Phylogenetic analysis*

HIV and HCV gene sequencing is attempted for all study participants who test positive for either virus. Sequencing will be performed at the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP) at the University of KwaZulu-Natal in Durban, South Africa. For HIV we will subsequently combine our data with additional, publicly available, HIV sequences from Kenya and perform phylogenetic and phylodynamic analyses to describe patterns and rates of viral transmission among key populations in Kenya and identify traits associated with relative infectiousness. For HCV we will use phylogenetic methods to characterize the modes and risk factors for onward transmission among PWID.

## Ethics and Dissemination

*General ethical considerations*

This study is registered at clinicaltrials.gov and has ethical approval from both the University of Washington Human Subjects Division and the Kenyatta National Hospital Ethics and Research Committee. It also has approval from Kenya's National Commission for Science, Technology and Innovation.

Risks to study participants are minimal, as neither obtaining blood nor HIV testing is likely to cause serious harm to the study participant. While IPV has the potential to cause harm, it has not

increased in other US or African studies when this intervention has been implemented.[24,58,59] Study staff are highly trained in counseling about risk behaviors, implications of testing HIV-positive, and protecting confidentiality to avoid potential social harms. In addition, staff have undergone extensive training on IPV counseling and ensure that resources have been identified in all sites so we can safely refer participants who report abuse or are concerned for their safety. To further monitor and protect against IPV, we collect IPV data on case report forms during interviews with participants as described above.

A safety monitoring board composed of researchers and policy makers in both Kenya and the US reviews study data twice per year. The board monitors enrollments, deaths, loss to follow up, adverse events, and IPV monitoring data and makes recommendations of whether to continue study procedures.

Ethical considerations surrounding the use of biometric identification systems among vulnerable key populations in Kenya have been discussed extensively.[60] Despite early opposition from the Key Populations Consortium and other organizations to the government's use of fingerprint-based biometric data collection, the organizations and individuals working with PWID communities continued to report no opposition to iris scanning for research purposes among PWID. In November 2019, Kenya passed the Data Protection Bill, rendering it legal to collect biometric data as long as the use of such data does not violate the subjects' rights.[61] The use of biometrics is now standard practice in many research and clinical settings, and has been found to be acceptable to participants.[62] Our participants have not reported any concerns, fears, or hesitations regarding the use of an iris scanning biometric identification system.

*Dissemination plan*

Results from the study are presented on an ongoing basis at Kenya's quarterly MoH harm reduction and key population technical working group meetings, and discussed at biannual community advisory board meetings. Our study team includes several officials from the MoH. Ongoing study analyses are also presented at national conferences annually, including Kenya's HIV clinicians' society meeting, the Infectious Disease Society of Kenya (IDSK) biennial conference, or the Annual University of Nairobi STD/HIV/SRH Collaborative Conference. Additionally, study results are presented in at least one international conference per year, including the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference, and the College on Problems of Drug Dependence (CPDD) annual conference. Finally, the study team reviews data on a weekly basis and any changes in data trends or other concerns are discussed directly with the organizations through which study procedures take place.

## Authors' contributions

CF and JH conceived of the study; AMW, BG, BC, MD, PM, JH and CF contributed to the study design and data collection structure; AMW, LM, DB, BSa, BC, JS, PC, HM, RB, PM, SM, EW, TDO, JH and CF contributed to data collection; AMW, LM, BG, DB, BSa, PC, HM, RB, SM, EW, TDO, NLB, JH and CF contributed to data analysis and dissemination; AMW, BG, JH and CF wrote the manuscript; all authors reviewed the manuscript for content.

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## Competing interests

All authors state that they have no competing interests.

## Patient and Public Involvement

Members of the community of PWID being researched were consulted in the development of research questions and design of the study. The study is supported by a Community Advisory Board (CAB) composed of members of the community, peer educators and employees of organizations that provide services to the population. The CAB meets with the study team regularly and helps inform dissemination plans.



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**Table 1. Inclusion and Exclusion Criteria**

| Group | Inclusion | Exclusion |
|---|---|---|
| ***Index*** | • 18 years of age or older<br>• Recent intravenous drug use as defined by injecting at least once in the past year<br>• HIV-positive | • Classified as at high risk for IPV (described below) |

| | | |
|---|---|---|
| | • Willing and able to provide locator information for sexual and/or injecting partners<br>• Willing and able to provide informed consent | |
| ***Partner*** | • 18 years of age or older<br>• identified by an index as either having injected with the index in the past 3 years or had sexual intercourse with the index in the past three years HIV-positive<br>• Willing and able to provide informed consent | None |

**Figure 1. Map of Study Sites**

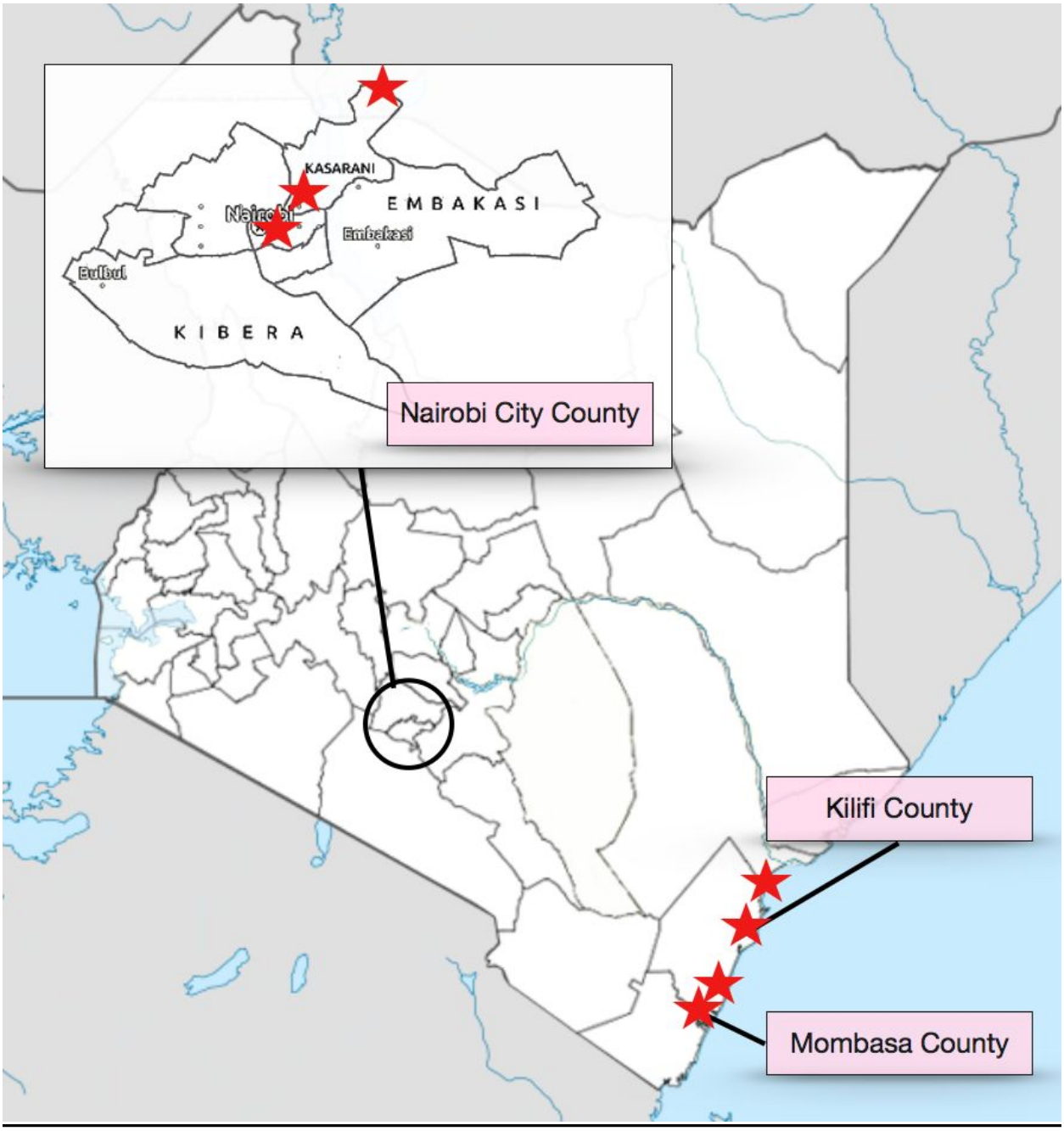
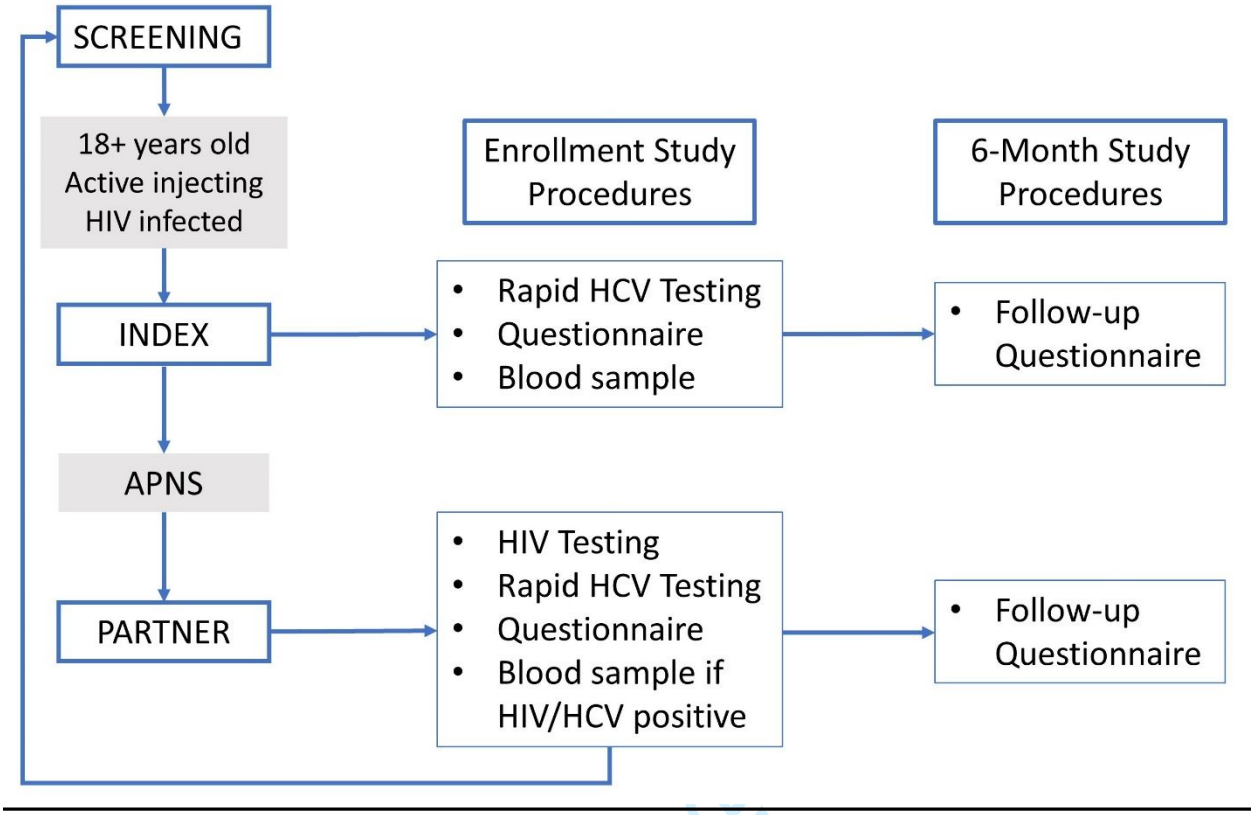


**Figure 2. Study Flow Diagram**



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# Peer-mediated assisted partner notification services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

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# Peer-mediated assisted partner notification services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

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## Abstract

### Introduction

Targeted, tailored interventions to test high-risk individuals for HIV and hepatitis C (HCV) are vital to achieving HIV control and HCV micro-elimination in Africa. Compared with the general population, people who inject drugs (PWID) are at increased risk of HIV and HCV and are less likely to be tested or successfully treated. Assisted partner notification services (APNS) increases HIV testing among partners of people living with HIV and improves case-finding and linkage to care. We describe a study in Kenya examining whether APNS can be adapted to find, test, and link to HIV and HCV care the sexual and injecting partners of HIV-positive PWID using a network of community-embedded peer educators (PEs). Our study also uses phylogenetic analysis to determine risk factors for onward transmission of both viruses.

### Methods and analysis

This prospective cohort study leverages a network of PEs to identify 1,000 HIV-positive PWID for enrollment as index participants. Each index completes a questionnaire and provides names and contact information of all sexual and injecting partners. PEs then use a stepwise locator protocol to engage partners in the community and bring them to study sites for enrollment, questionnaire completion and rapid HIV and HCV testing. Outcomes include number and type of partners per index who are mentioned, enrolled, tested, diagnosed with HIV and HCV and linked to care.

### Ethics and dissemination

Potential index participants are screened for intimate partner violence (IPV) and those at high risk are not eligible to enroll. Those at medium risk are monitored for IPV following enrollment. A community advisory board engages in feedback and discussion between the community and the research team. A safety monitoring board discusses study progress and reviews data, including IPV monitoring data. Dissemination plans include presentations at quarterly Ministry of Health working group meetings, local and international conferences, and publications.

**Strengths and limitations of this study**

- This cohort study investigates the use of assisted partner notification services (APNS) for HIV and hepatitis C (HCV) to find, test, and link to care the sexual and injection partners of people who inject drugs (PWID) in Kenya—a high risk, difficult to reach population. The study offers APNS to HIV-positive index participants; partner services were not offered to HIV-negative, HCV-positive clients to identify those exposed to HCV but not HIV.

- Community embedded peer educators formerly used drugs and have been trained to provide harm reduction services. They are known and trusted within the PWID community conduct partner tracing, and typically serve as the first point of contact with potential partner participants. While this approach has proved largely successful, there are limitations including logistical challenges and concerns for client confidentiality and safety of both the client and peer educator.

- An iris scanning biometric identification system ensures that each index participant enrolled is a unique individual and confirms that individual partner participants who enroll more than once in relation to different index participants are the same individual.

- Phylogenetic analysis of HIV and HCV viral sequences combined with APNS provides additional information about transmission dynamics within the cohort, including risk of onward transmission for different clusters and geographic regions.

## Introduction

Of the UNAIDS 90-90-90 goals,[1] diagnosing 90% of those living with HIV remains the most elusive target worldwide,[2] and strategies to reach individuals at high-risk for HIV who have never been tested is increasingly important.[3] Sharing needles and other drug paraphernalia is the most efficient mode of HIV transmission, and accounts for 13% of new infections globally.[4,5] In Kenya, prevalence of HIV among people who inject drugs (PWID) has been estimated at 15 – 50%[5–9]—significantly higher than the general population prevalence of 4.9%,[10] and up to 30% of PWID in Kenya have never tested for HIV.[11,12] Multiple studies have demonstrated low knowledge of HIV status and low engagement in care among Kenya's PWID.[12,13] Retention in care and adherence to ART are also both lower among PWID as compared with others worldwide.[2]

In addition to HIV, PWID are at high risk for hepatitis C virus (HCV) globally and have the highest HCV prevalence of any group studied in Kenya at 13-40%[9,14,15]. This is especially highwhen compared to the general population HCV prevalence in Kenya of <1-4%.[16,17] However, multiple barriers exist at individual, provider and system levels resulting in low rates of testing, engagement in care, and completion of treatment courses for PWID.[18–20] Although less than 20% of PWID with chronic HCV worldwide have undergone antibody screening, the number who have completed PCR confirmatory testing is even lower.[21] Despite the introduction of highly effective direct acting antivirals (DAAs) into Kenya in 2016, only a small fraction of individuals living with HCV have been treated, prompting attention to micro-elimination strategies.

Assisted partner notification services (APNS) for HIV is an evidence-based partner notification strategy in which providers elicit information about the sexual or injecting partners of an HIV-positive index client, and then contact, HIV test and link to care any partners found to be positive.[22]

APNS has been shown to significantly and safely increase the uptake of HIV testing services (HTS), case finding, and linkage to care for partners of HIV-positive people.[22–24] APNS can also reduce barriers to disclosing HIV status[25] and is cost-effective.[26] APNS has been successfully implemented among HIV-positive patients from the general population in the USA,[27] Mozambique,[28] Malawi,[29,30] and Kenya,[24] and has recently been incorporated into the World Health Organization (WHO) guidelines for routine care for HIV-positive people worldwide.[31] While programs have introduced the practice of APNS in high-risk key populations (KPs) such as female sex workers (FSW)[32] and men who have sex with men (MSM),[33,34] this intervention has not been well-studied among PWID,[35] an extremely high risk group.[22,36] Similar to FSW and MSM, PWID engage in behavior that is criminalized[37] while experiencing high rates of marginalization and displacement,[38] making them difficult to study. These factors and others also contribute to significant barriers in the implementation of health programs targeting PWID.[39–41]

Phylogenetic analysis is a method of identifying the role of specific risk groups and risk factors for onward transmission of HIV and HCV using the genetic sequence of each virus.[42–44] Viral phylogenetics can provide additional information on patterns of transmission,[45–47] epidemic growth,[48,49] risk groups,[50–52] and risk factors associated with onward transmission.[44,53–55]

Here we describe a prospective cohort study that seeks to determine whether and how APNS can be implemented to find, test, and link to care the injection and sexual partners of HIV-positive PWID in Kenya. Simultaneously, our study will use phylogenetic analysis to study genetic sequences of HIV and HCV within our cohort to further understand transmission patterns and risk for onward transmission. All index and partner participants are tested for HCV in addition to HIV. While many partner contact methods for conducting APNS have been used,[22] cellular telephones are the most common first-line communication modality for reaching partners in other

populations.[23,24,28,56] In Kenya, however, the large majority of PWID do not have regular access to cellular telephones. As such, our APNS model relies on the utilization of community-embedded peer educators (PEs) to locate and communicate with members of this difficult to reach population. We hypothesize that we will be able to employ these customized APNS procedures to reach a large number of injection and sexual partners, and that we will see differences in HIV and HCV testing, HIV and HCV prevalence, and engagement in care between sexual and injection partners. Additionally, we hypothesize that we will identify unique transmission patterns and risks for onward transmission in phylogenetic analysis.

## Methods and analysis

### *Approach*

APNS is a practice through which healthcare providers facilitate the notification, testing and linkage to care for partners who may have been exposed to HIV or other sexually transmitted infections by an individual known to be positive. Typically, APNS is conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone to alert them to their exposure and arrange testing. We have designed customized procedures to ensure and improve the safety and efficacy of APNS in the unique population of PWID in Kenya. Because PWID and their partners in Kenya rarely own cellular phones, we work with community-embedded peer educators (PEs) to find and engage with partners. Additionally, our protocol involves referrals to different facilities for injection partners and for sexual partners, as a precaution to ensure safety and confidentiality of index participants.

### *Study design*

Our study is a prospective cohort study with two groups: index and partner participants ("indexes" and "partners"). We use tailored APNS procedures to identify, find, test and link to care the sexual and injection partners of HIV-positive PWID. All participants who are diagnosed with either HIV or HCV- then complete a 6-month follow-up visit to assess linkage to and engagement in care.

*Study sites/setting*

Study procedures take place in eight main sites including public health centers, medically assisted therapy (MAT) centers, and needle and syringe programs (NSPs) in Nairobi, Kilifi, and Mombasa Counties in Kenya (Figure 1). Each site is staffed by at least one clinical officer (mid-level clinician) who works with the study team to ensure that indexes are HIV-positive. In Nairobi County, the activities are centered at two NSP sites and one MAT center in the Mathare North area. The NSP sites, run by Support for Addiction Prevention and Treatment in Africa (SAPTA), offer routine HIV testing services. Referrals are made to local clinics providing care for those who test positive for HIV or HCV. We also recruit indexes from a government-run methadone clinic in Nairobi in the Ngara area. The Ngara Health Center MAT clinic offers HIV testing, care and treatment in addition to daily methadone administration, psychosocial services and treatment for other health conditions. In Kilifi county, participant recruitment and enrollment takes place at three needle and syringe program centers and one government hospital. The Omari Project is located in Malindi town and offers HIV counseling, testing, care and treatment in addition to harm reduction services. Malindi Sub-County Hospital's MAT center is a recruitment site in Kilifi County within a mid-sized government hospital that offers a large range of medical and social services. Malindi Sub-County Hospital also has a large laboratory that houses the study's samples collected in both Kilifi and Mombasa Counties. The Muslim Education and Welfare Association (MEWA) NSP sites in Kilifi and Mtwapa towns offer HIV counseling and testing, in addition to HIV care and

treatment and harm reduction services. In Mombasa county, participants are recruited from the ReachOut Center, an NSP site in Mombasa city that offers a full range of harm reduction services in addition to HIV counseling, testing, care and treatment. All recruitment sites offer routine HCV testing when kits are available through specific donor-driven projects.

*Population*

This study includes index participants and their sexual and injecting partners . All indexes are HIV-positive PWID. Partners are either sexual partners or injecting partners of indexes. As such, partners need not be PWID or HIV-positive but are defined by their relationships with indexes.

Indexes are largely recruited from organizations and clinics that provide services to PWID populations, although they may also come from outreach efforts or informal referrals from other participants. Partners are identified and recruited through peer-mediated APNS and may come from any geographic area or community.

*Patient and Public Involvement*

Members of the community of PWID being researched were consulted in the development of research questions and design of the study. The study is supported by a Community Advisory Board (CAB) composed of members of the community, peer educators and employees of organizations that provide services to the population. The CAB meets with the study team regularly and helps inform dissemination plans.

*Study procedures*

1. Peer educator recruitment and training

PEs are recovering PWID with established relationships in the PWID communities that they serve. The majority are between the ages of 25 and 50, are enrolled in Kenya's methadone program and report having stopped injecting drugs.. These men and women have been identified by the individual organizations at which they work as being key community members, and have undergone extensive training for their roles as PEs. Training is an intensive 5-day course with modules covering a broad spectrum of content including basics of drugs and drug-related harms, harm reduction efforts including NSP and MAT, abscess prevention and management, overdose prevention and management and behavior change communication. PEs have access to relatively hidden PWID community spaces, and provide health counseling, linkage to support organizations, information, and other services to this vulnerable population.

For this study, PEs who were actively carrying out basic duties were chosen by the leadership at each organization based on several factors including awareness and knowledge of HIV in the community and access to unique target populations (for instance, women who inject drugs are more easily accessed by women PEs). Once identified, PEs underwent an intensive 1-day training to educate them on the practice and ethics of research, study procedures, and their role in the study. PEs participate in regular health education and harm reduction training and engage in quarterly sessions with study leadership where they present barriers and lessons learned to the study team so that study-related issues can be addressed.

2. Inclusion & exclusion criteria

Inclusion and exclusion criteria are different for indexes and partners (Table 1). Any interested individuals who are under the age of 18 are referred to the site clinicians for routine counseling and harm reduction services.

3. Index recruitment and enrollment

Enrollment began in March 2018. Clinicians at each site identify potential indexes using existing clinical data on known HIV-positive clients. Additionally, any client who tests positive for HIV during routine testing is invited to participate. Clinicians are employed by the sites, and are trained clinical officers (COs), or mid-level providers. For this study, HIV rapid testing is performed by COs and takes place as part of standard clinic procedures. All potential indexes are re-tested using HIV rapid tests (as per the national guidelines) to confirm HIV status prior to enrollment. If HIV-seropositive, either newly diagnosed or known to be positive, clinicians either discuss the study directly with potential participants or engage PEs to find individuals and bring them to the study office if they are not regular clients at the site. Importantly, PEs are not told whether participants are being traced as an index or a partner, protecting the confidentiality of indexes' HIV status.

Study staff health advisors (HAs) are the individuals responsible for conducting study procedures including data collection, HIV and HCV testing, and the coordination of APNS efforts (Figure 2). All HAs were trained and experienced in HIV testing services prior to working for the study, and many had previous experience working with PWID. All HAs underwent a week-long training course at the beginning of the study in which they learned the basics and purpose of research, research ethics, study procedures, unique ethical and logistical issues to consider when working with PWID, and other topics. All HAs also completed the Collaborative Institutional Training Initiative (CITI) course on Human Subjects Research and the Responsible Conduct of Research. HAs explain the benefits and rationale for providing APNS, discuss the importance of learning more about HIV and HCV, and describe the process of notifying partners without revealing the identity of the index. They ask participants to provide written informed consent for study participation, APNS, and future use of biological specimens and future contact for additional

studies, using an iris-scanning biometric device to record a unique identifier for each participant, thus enabling the study team to confirm that a person does not enroll into the program as an index more than once.

Indexes undergo a structured questionnaire administered by the HA using open data kit (ODK) software on tablet devices (ODK, 2017, Seattle, WA, USA). Questionnaires cover a variety of topics including demographics, sexual and injecting behaviors, drug use history, and HIV testing and engagement history. Participants are then asked to recall all of their sexual and injecting partners over the three years prior to enrollment, naming these partners one by one and assigning each partner a letter ("A," "B," etc). Indexes are asked to give as much locator information as possible for each partner, including names (which may be nicknames), phone numbers, and location of employment or residence. Locator information is written on a paper form for each partner. Indexes then complete a short ODK questionnaire about each partner mentioned, which includes information about the relationship between the index and the partner. Indexes who wish to notify partners themselves are given a 2-week window in which to do so, after which partners are contacted by study staff.

Indexes then undergo rapid HCV antibody testing as part of routine study procedures. HAs conduct pre- and post- test counseling and ensure individuals who test positive are available for follow-up visits to discuss confirmatory HCV PCR testing and enrolling in a treatment program administered by the Ministry of Health. All indexes then undergo phlebotomy with a sample of 10mL of blood drawn for further testing (see section 6 below). Indexes receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

4. Peer-educator mediated assisted partner services and partner recruitment

For those partners who have phone numbers listed, HAs attempt phone communication first. However, the vast majority of partners mentioned by indexes do not have working cellular phones; therefore, with few exceptions, PEs locate and conduct the study's first interaction in person with identified partners. PEs are given paper forms containing names and locator information for identified partners. They are never told which index referred the team to each partner, and that information is not listed on locator forms or any other accessible file. PEs then locate and approach potential participants in the community. Using a standardized script, PEs inform potential participants that they have been identified as an individual who might be eligible for a research study on HIV and HCV. PEs do not notify partners of their exposure during initial contact for several reasons: 1) to protect the HIV status of indexes, PEs are not told whether they are recruiting an index or a partner, and 2) PEs have not felt comfortable discussing HIV or HCV exposure with potential participants. Once PEs have notified potential participants of their possible eligibility, they then accompany interested individuals to the nearest research office, where the study's HAs conduct informed consent. Informed consent includes consent to future use of biological specimens and future contact for additional studies. In the rare event that a potential participant does not agree to come to the study office, an HA returns to the site with the PE and notifies the individual of the exposure.

5. Partner enrollment

After informed consent and biometric identification, partners complete a structured questionnaire similar to that of indexes, administered by HAs on a handheld device using ODK software. Following the questionnaire, all partners undergo rapid antibody testing for both HIV and HCV. HIV testingservices are provided in accordance with national HIV testing guidelines. Any partner found to be positive for either HIV or HCV antibodies undergoes a 20mL blood draw. Those

partners who test negative for both HIV and HCV are finished with study procedures at this time and are counseled on risk reduction measures and linked to HIV and HCV prevention services before leaving the study site. All partners receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

HIV-positive partners are invited to undergo screening as an index once data collection procedures for their partner enrollment are complete. If they meet eligibility criteria as an index, they may enroll as an index. Study procedures are slightly amended for indexes that have previously enrolled as partners. After undergoing informed consent and completing a short questionnaire that only includes questions that were not a part of the partner enrollment questionnaire, they complete the identification and data collection on each of their sexual and injection partners, identical to partner identification procedures for indexes described above.

6. Laboratory Procedures

Blood samples from both index and partner enrollment visits are collected in EDTA vacutainer tubes. Blood is mixed with the anticoagulant by inversion and the anticoagulated blood is stored at room temperature at the sites for less than 4 hours. A motorcycle courier picks samples from each site daily and brings them to the University of Nairobi Pediatric Research Laboratory in Nairobi or the Malindi Sub-County Hospital Laboratory for coast sites. At each laboratory, samples are first used to prepare two Whatman 903 Protein Saver dried blood spot (DBS) cards with 50ul of whole blood on each spot. Blood samples are then centrifuged and used to prepare 2 to 3 aliquots of 1ml of plasma in labeled serum vials. Plasma aliquots and air-dried DBS cards (with desiccant in sealed Ziploc bags) are then stored at -80° Celsius and shipped on dry ice to the

University of KwaZulu-Natal laboratory. There, samples undergo HIV and HCV viral load testing and amplification for sequencing.

7. Participant follow-up

All indexes and any partners who were positive for HIV or HCV complete a six-month follow-up visit. HAs identify which participants are due for follow-up visits on a weekly basis and give PEs as list of these names. PEs then trace participants and bring them back to clinics where data collection procedures are conducted. PEs make several attempts to find participants in the community before considering them lost to follow-up.

Six-month visits involve a brief questionnaire covering questions on testing for HIV or HCV (if not infected with both on enrollment), enrollment in care and treatment, engagement in care, and follow-up testing. The purpose of this visit is to assess whether engagement in care has changed following APNS procedures. We do not collect additional data from those lost to follow up.

8. Intimate partner violence (IPV) monitoring

Given historical concerns that APS may increase one's risk of experiencing intimate partner violence, all potential participants undergo screening for IPV before enrollment. IPV is defined as any physical, sexual or psychological harm inflected on a person by a current or former sexual partner. After answering a standardized set of six questions about physical, emotional and sexual IPV and the timing of any previous experience of IPV based on published screening tools reviewed by the Centers for Disease Control and Prevention,[57] potential participants are classified as low, medium or high risk for IPV. Individuals are classified as at high risk for IPV if they report IPV within the last month. Any potential index who is classified as high IPV risk is excluded from

study participation and provided with IPV counseling and resources. Any potential partner participant who is classified as high IPV risk is allowed to enroll, but then receives special monitoring for IPV following enrollment.

Potential participants are classified as at moderate risk for IPV if they report 1) IPV during their lifetime either from a current or past partner; and/or 2) fear of IPV if they participate in the study. All index or partner participants classified as moderate IPV risk receive special monitoring for IPV following their enrollment in the study.

Potential participants are classified as at low risk for IPV if they report 1) no IPV during their lifetime ; and 2) no fear of IPV if they participate in the study. These individuals undergo standard study procedures which include completing the baseline IPV case report form and a follow-up IPV case report to capture reports of any interim IPV.

9. Confidentiality and safety

*Participants*: All study procedures take place in private rooms at each study facility. To ensure the safety and confidentiality of indexes, PEs who are tasked with finding partners are blinded to the identity of the linked index through the use of partner locator forms that do not contain identifying information about the index participant. Locator forms do contain a printed barcode label that are then used by study staff to link the partner with the index who referred the partner.

Sexual partners are brought to independent facilities for enrollment rather than to centers that serve PWID, in order to further protect the identity of the index participant who referred them. The independent facilities are local healthcare clinics that serve the general population.

*Peer educators*: PEs have frequent interactions with police, and can be victims of harassment or violence, both by police and by PWID. To reduce the risk of law enforcement troubles, PEs carry identification showing that they are working on a study being conducted by the Ministry of Health. Local law enforcement officials have also attended ongoing sensitization trainings by the Ministry of Health and by organizations working with PWID.

10. Referrals to care

*HIV Counseling and Care:* Participants are provided with their HIV test results in the context of post-test counseling, and are then referred to available medical and psychosocial care and support facilities either within the research site or in close proximity to the research site or the participant's home. Additionally, HIV-positive individuals are offered individual or group support sessions as available within each site.

*HCV Counseling and Care:* Participants who test positive for HCV antibodies using rapid testing are provided with their HCV antibody test results in the context of pre- and post-test counseling. They are informed that they may have active HCV infection; however, further confirmatory testing must be done prior to establishing the diagnosis. Confirmatory polymerase chain reaction (PCR) testing is done in batches of samples at our partnering laboratory at the University of KwaZulu-Natal, South Africa, and participants with active infection are later contacted for results and counseling. Turnaround time from enrollment to PCR result notification varies, but is typically between 1 and 4 months. Once notified, those with active infection are paired with a PE at their site to ensure close contact is maintained. Study participants with active HCV infections will be eligible to receive free treatment with direct acting antivirals, which the Kenyan MoH has procured.

*Data management*

After each study visit, HAs review their work for omissions or errors and all data are uploaded into the study database. Electronic data are stored securely in an encrypted database on servers using Open Data Kit Aggregate, within Kenya's Ministry of Health (MoH). All errors or omissions identified at any step in the quality assurance/quality control process are revised by the staff member who originally completed the document. All additions and corrections are initialed and dated by the staff member who records the entry.

A link-log is separately encrypted to further ensure that data remains secure. Any data transferred to investigators or MoH are de-identified and encrypted during the process of transfer from the server. Each investigator maintains and stores secure, complete, accurate and current study records throughout the study. A database manager performs regular data cleaning and resolves any discrepancies that occur. Study sites also conduct quality control and quality assurance procedures. All co-investigators have access to the final dataset and this is not limited by contractual agreements. Study data will be available upon request at the completion of the study.

*Outcome measures*

The primary outcomes of interest to assess the success of the APNS intervention are: a) number of sexual and injection partners tested for HIV and HCV through APNS, identified by each index participant over the course of the study period; b) number of sexual and injection partners newly testing positive for HIV and HCV, per index participant; c) number of known HIV or HCV cases identified through APNS who are not engaged in care; d) number of index and partner participants with HIV and/or HCV infection who are linked to care; e) number of index and partners with HIV and/or HCV infection who remain in care and are receiving appropriate treatment at 6 months after

testing positive. Secondary outcomes are linked to inclusion in phylogenetic clusters identified as high risk for onward transmission of HIV and HCV.

*Sample size*

We are enrolling 1000 HIV-positive indexes and their sexual and injecting partners. Based on HCV data from MoH and our preliminary results, we estimate that 20% of PWID with HIV will be co-infected with HCV and that each index will identify on average two partners who will accept HIV and HCV testing, 20% of whom will be HIV-positive, and 20% of whom will be HCV-infected. Thus, with provision of APNS to 1,000 HIV-positive indexes and testing of 2,000 partners, we will identify an estimated 600 indexes and partners infected with HCV and 400 HIV-positive partners. This study was designed to have high precision in estimating the prevalence of HIV and HCV infection among partners, providing valuable input for modeling the impact of APNS in the population. For an observed HIV or HCV prevalence of 10% among partners, precision is estimated at 1.9%; with an observed HIV or HCV prevalence of 30% among partners, precision is estimated at 2.9%. *Statistical methods and analysis*

To determine efficacy of the APNS intervention, we will use generalized estimating equations (GEE) models with a Poisson link using the following variables and offsets: 1) rate of HIV and HCV testing of partners: number of individuals tested for HIV or HCV, offset by the number of partners located with locator information provided by the index participant; 2) prevalence of HIV and HCV infection: number of individuals identified as HIV or HCV-positive, offset by the number of individuals who were HIV tested; and 3) rate of linkage to HIV and HCV care: individuals who test HIV or HCV-positive and link to care, offset by the total number of individuals who test HIV or HCV-positive.

Additionally, using both GEE and phylogenetic analysis, we will determine the following: 1) identifiable and individual risk factors linked to high rates of HIV and HCV transmission, 2) risk factors linked to both needle-sharing and sexual transmission, and 3) identification of transmission clusters among PWID for both HIV and HCV.

*Phylogenetic analysis*

HIV and HCV gene sequencing are attempted for all study participants who test positive for either virus. Sequencing will be performed at the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP) at the University of KwaZulu-Natal in Durban, South Africa. For HIV we will subsequently combine our data with additional, publicly available, HIV sequences from Kenya and perform phylogenetic and phylodynamic analyses to describe patterns and rates of viral transmission among key populations in Kenya and identify traits associated with relative infectiousness. For HCV we will use phylogenetic methods to characterize the modes and risk factors for onward transmission among PWID.

## Ethics and Dissemination

*General ethical considerations*

This study is registered at clinicaltrials.gov and has ethical approval from both the University of Washington Human Subjects Division and the Kenyatta National Hospital Ethics and Research Committee. It also has approval from Kenya's National Commission for Science, Technology and Innovation.

There are a number of potential risks to participants. Risks of conducting APNS include psychological distress, social or economic hardship, criminal penalties, and loss of privacy and/or

confidentiality. Study procedures, including confidentiality and counseling procedures, are specifically designed to minimize these risks to participants. While IPV has the potential to cause harm, it has not increased in other US or African studies when this intervention has been implemented in the general population.[22,58,59] We recognize that risks may be different when implementing APNS among key populations and study staff are highly trained in counseling about risk behaviors, implications of testing HIV-positive, and protecting confidentiality to avoid potential social harms. In addition, staff have undergone extensive training on IPV counseling and ensure that resources have been identified in all sites so we can safely refer participants who report abuse or are concerned for their safety. Participants reporting moderate IPV are monitored as described in Section 8; they are counseled and referred for services if IPV is reported at any of these follow-up visits.

A safety monitoring board composed of researchers and policy makers in both Kenya and the US reviews study safety data twice per year. The board monitors enrollments, deaths, loss to follow up, adverse events, including social harms, and IPV monitoring data and makes recommendations regarding study procedures.

Ethical considerations surrounding the use of biometric identification systems among key populations in Kenya have been discussed extensively.[60] Despite early opposition from the Key Populations Consortium and other organizations to the government's use of fingerprint-based biometric data collection, the organizations and individuals working with PWID communities continued to report no opposition to iris scanning for research purposes among PWID. In November 2019, Kenya passed the Data Protection Bill, rendering it legal to collect biometric data as long as the use of such data does not violate the subjects' rights.[61] The use of biometrics is now standard practice in many research and clinical settings, and has been found to be acceptable to

participants.[62] Our participants have not reported any concerns, fears, or hesitations regarding the use of an iris scanning biometric identification system.

*Dissemination plan*

Results from the study and changes to the study are presented on an ongoing basis at Kenya's quarterly MoH harm reduction and key population technical working group meetings, and discussed at biannual meetings by the Community Advisory Board that was established for this study. Our study team includes several collaborators from the MoH. Ongoing study analyses are also presented at national conferences annually, including Kenya's HIV clinicians' society meeting, the Infectious Disease Society of Kenya (IDSK) biennial conference, or the Annual University of Nairobi STD/HIV/SRH Collaborative Conference. Additionally, study results are presented in at least one international conference per year, including the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Conference, and the College on Problems of Drug Dependence (CPDD) annual conference. Finally, the study team reviews data on a weekly basis and any changes in data trends or other concerns are discussed directly with the organizations through which study procedures take place.

## Authors' contributions

CF and JH conceived of the study; AMW, BG, BC, MD, PM, BSi, JH and CF contributed to the study design and data collection structure; AMW, LM, DB, BSa, BC, JS, PC, HM, RB, PM, SM, EW, TDO, BSi, JH and CF contributed to data collection; AMW, LM, BG, DB, BSa, PC, HM, RB, SM, EW, TDO, NLB, JH and CF contributed to data analysis and dissemination; AMW, BG, JH and CF wrote the manuscript; all authors reviewed the manuscript for content.

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## Competing interests

All authors state that they have no competing interests.

Figure 1. Map of Study Sites

Figure 2. Study Flow Diagram

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**Table 1. Inclusion and Exclusion Criteria**

| Group | Inclusion | Exclusion |
|---|---|---|
| ***Index*** | • 18 years of age or older<br>• Recent intravenous drug use as defined by injecting at least once in the past year<br>• HIV-positive<br>• Willing and able to provide locator information for sexual and/or injecting partners<br>• Willing and able to provide informed consent | • Classified as at high risk for IPV (described below) |
| ***Partner*** | • 18 years of age or older<br>• identified by an index as either having injected with the index in the past 3 years or had sexual intercourse with the index in the past three years HIV-positive<br>• Willing and able to provide informed consent | None |

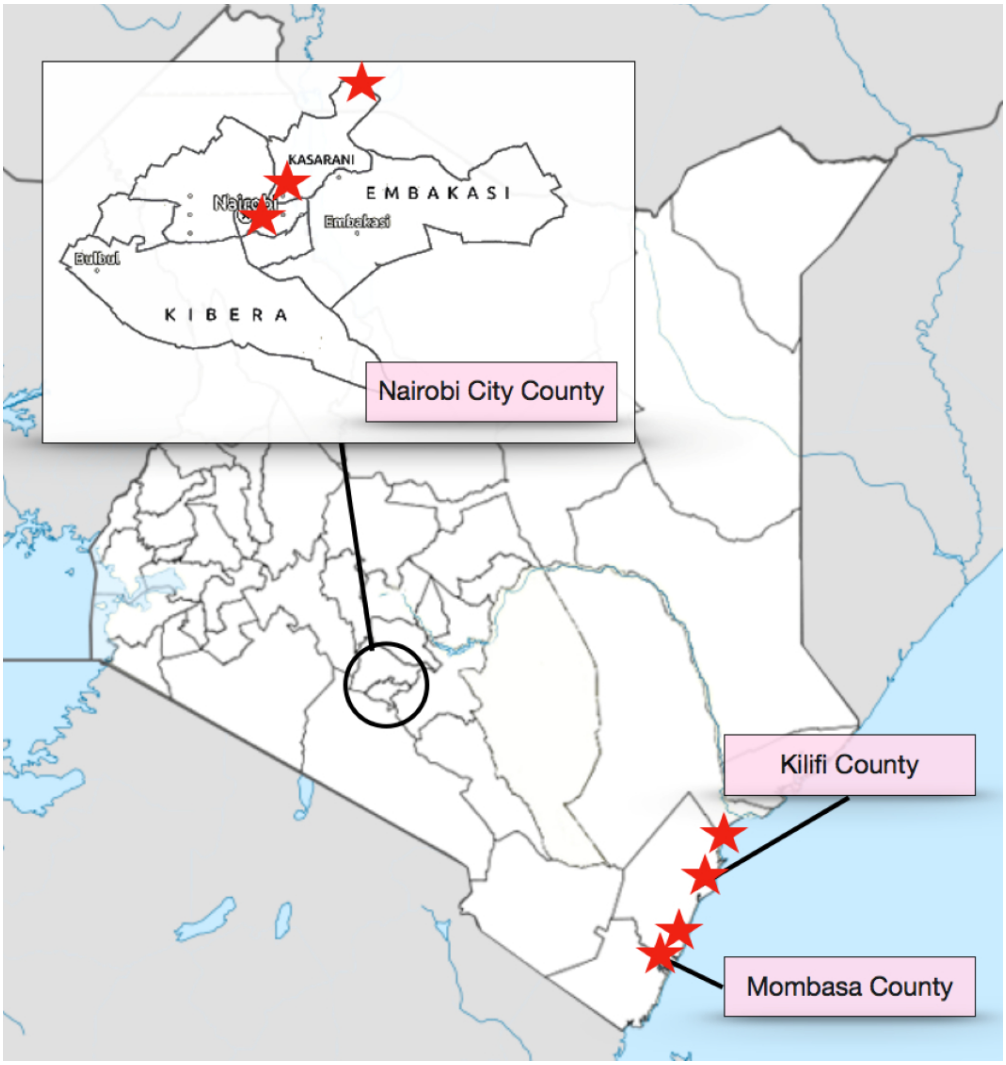


Figure 1. Map of Study Sites

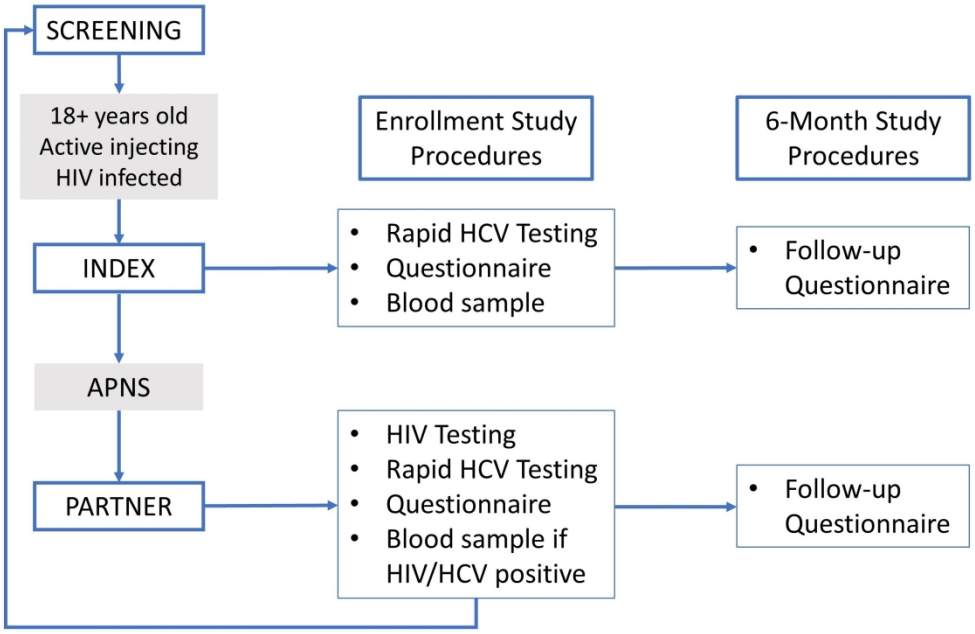


Figure 2. Study Flow Diagram

683x449mm (96 x 96 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 21 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Included |
| Protocol version | 3 | Date and version identifier | 1 |
| Funding | 4 | Sources and types of financial, material, and other support | 23 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 23 |
| | 5b | Name and contact information for the trial sponsor | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | N/A |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-7 |
| | 6b | Explanation for choice of comparators | N/A |
| Objectives | 7 | Specific objectives or hypotheses | 6-7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 8 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 8 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10-11 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11-14 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | N/A |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 17 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 18 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 15 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 19 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 11 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 15 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 18 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 19-20 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | N/A |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | N/A |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 21-22 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 21 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 22 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _12-13_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | __12-13_____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | __16-18_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ___23_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | ____18_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | ____17-18____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ____22-23____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | ____23_____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | ____N/A_____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | ____Attached__ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | __14-15, 20____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Peer-mediated HIV assisted partner services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

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# Peer-mediated HIV assisted partner services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

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V2.0 13/10/20

## Abstract

### Introduction

Targeted, tailored interventions to test high-risk individuals for HIV and hepatitis C (HCV) are vital to achieving HIV control and HCV micro-elimination in Africa. Compared with the general population, people who inject drugs (PWID) are at increased risk of HIV and HCV and are less likely to be tested or successfully treated. Assisted partner services (APS) increases HIV testing among partners of people living with HIV and improves case-finding and linkage to care. We describe a study in Kenya examining whether APS can be adapted to find, test, and link to HIV care the partners of HIV-positive PWID using a network of community-embedded peer educators (PEs). Our study also identifies HCV-positive partners and uses phylogenetic analysis to determine risk factors for onward transmission of both viruses.

### Methods

This prospective cohort study leverages a network of PEs to identify 1,000 HIV-positive PWID for enrollment as index participants. Each index completes a questionnaire and provides names and contact information of all sexual and injecting partners during the previous 3 years. PEs then use a stepwise locator protocol to engage partners in the community and bring them to study sites for enrollment, questionnaire completion and rapid HIV and HCV testing. Outcomes include number and type of partners per index who are mentioned, enrolled, tested, diagnosed with HIV and HCV and linked to care.

### Ethics and dissemination

Potential index participants are screened for intimate partner violence (IPV) and those at high risk are not eligible to enroll. Those at medium risk are monitored for IPV following enrollment. A community advisory board engages in feedback and discussion between the community and the research team. A safety monitoring board discusses study progress and reviews data, including IPV monitoring data. Dissemination plans include presentations at quarterly Ministry of Health meetings, local and international conferences, and publications.

## Strengths and limitations of this study

- This cohort study investigates the use of assisted partner services (APS) to find, test for HIV and hepatitis C (HCV) and link to care the sexual and injecting partners of HIV-positive people who inject drugs (PWID) in Kenya; however, APS is not offered to HIV-negative, HCV-positive clients to identify those exposed to HCV but not HIV.
- Community embedded peer educators trained to provide harm reduction services conduct partner tracing, but there are limitations including logistical challenges and concerns for client confidentiality and safety of both the client and peer educator.
- An iris scanning biometric identification system ensures that each index participant enrolled is a unique individual and confirms that individual partner participants who enroll more than once in relation to different index participants are the same individual.
- Phylogenetic analysis of HIV and HCV viral sequences combined with APS will provide additional information about transmission dynamics within the cohort, including risk of onward transmission for different clusters and geographic regions.



## Introduction

Diagnosing 90% of those living with HIV has been among the most difficult of the UNAIDS 90-90-90 goals to achieve worldwide,[1,2] and strategies to reach individuals at high-risk for HIV who have never been tested is increasingly important.[3] In Kenya, despite success in achieving or

approaching the 2nd and 3rd UNAIDS goals, only 79.4% of people testing for HIV know their status.[4] Sharing needles and other drug paraphernalia is the most efficient mode of HIV transmission, and accounts for 13% of new infections globally.[5,6] In Kenya, prevalence of HIV among people who inject drugs (PWID) has been estimated at 15 – 50%[6–10]—significantly higher than the general population prevalence of 4.9%,[11] and up to 30% of PWID in Kenya have never tested for HIV.[12,13] Multiple studies have demonstrated low knowledge of HIV status and low engagement in care among Kenya's PWID.[13,14] Retention in care and adherence to ART are also both lower among PWID as compared with others worldwide.[1]

In addition to HIV, PWID are at high risk for hepatitis C virus (HCV) globally and have the highest HCV prevalence of any group studied in Kenya at 13-40%[10,15,16]. This is especially high when compared to the general population HCV prevalence in Kenya of <1-4%.[17,18] However, multiple barriers exist at individual, provider and system levels resulting in low rates of testing, engagement in care, and completion of treatment courses for PWID.[19–21] Although less than 20% of PWID with chronic HCV worldwide have undergone antibody screening, the number who have completed PCR confirmatory testing is even lower.[22] Despite the introduction of highly effective direct acting antivirals (DAAs) into Kenya in 2016, only a small fraction of individuals living with HCV have been treated, prompting attention to micro-elimination strategies.[23,24]

Assisted partner notification services (APS) for HIV is an evidence-based partner notification strategy in which providers elicit information about the sexual or injecting partners of an HIV-positive index client, and then contact, HIV test and link to care any partners found to be positive.[25] APS has been shown to significantly and safely increase the uptake of HIV testing services (HTS), case finding, and linkage to care for partners of HIV-positive people.[25–27] APS can also reduce barriers to disclosing HIV status[28] and is cost-effective.[29] APS has been successfully implemented

among HIV-positive patients from the general population in the USA,[30] Mozambique,[31] Malawi,[32,33] and Kenya,[27] and has recently been incorporated into the World Health Organization (WHO) guidelines for routine care for HIV-positive people worldwide.[34] While programs have introduced the practice of APS in high-risk key populations (KPs) such as female sex workers (FSW)[35] and men who have sex with men (MSM),[36,37] this intervention has not been well-studied among PWID,[38] an extremely high risk group.[25,39] Similar to FSW and MSM, PWID engage in behavior that is criminalized in many parts of the world[40] while experiencing high rates of marginalization and displacement,[41] making them difficult to study. These factors and others also contribute to significant barriers in the implementation of health programs targeting PWID.[42–44]

Phylogenetic analysis is a method of identifying the role of specific risk groups and risk factors for onward transmission of HIV and HCV using the genetic sequence of each virus.[45–47] Viral phylogenetics can provide additional information on patterns of transmission,[48–50] epidemic growth,[51,52] risk groups,[53–55] and risk factors associated with onward transmission.[47,56–58]

Here we describe a prospective cohort study that seeks to determine whether and how APS can be implemented to find, test, and link to care the injection and sexual partners of HIV-positive PWID in Kenya. Simultaneously, our study will use phylogenetic analysis to study genetic sequences of HIV and HCV within our cohort to further understand transmission patterns and risk for onward transmission. All index and partner participants are tested for HCV in addition to HIV. While many partner contact methods for conducting APS have been used,[25] cellular telephones are the most common first-line communication modality for reaching partners in other populations.[26,27,31,59] In Kenya, however, the large majority of PWID do not have regular access to cellular telephones. As such, our APS model relies on the utilization of community-embedded peer educators (PEs) to locate and communicate with members of this difficult to reach population. We hypothesize that

we will be able to employ these customized APS procedures to reach a large number of injection and sexual partners, and that we will see differences between sexual and injection partners in uptake of HIV testing, HIV and HCV prevalence, and engagement in care. Additionally, we hypothesize that we will identify unique transmission patterns and risks for onward transmission in phylogenetic analysis, which may include behavioral, geographic, or other factors.

## Methods and analysis

### *Approach*

APS is a practice through which healthcare providers facilitate the notification, testing and linkage to care for partners who may have been exposed to HIV or other sexually transmitted infections by an individual known to be positive without revealing the identity of the person who may have exposed them. While there are many ways to provide partner services, APS in Kenya is often conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone or physically trace them to alert them to their exposure and provide testing. We have designed customized procedures to ensure and improve the safety and efficacy of APS in the unique population of PWID in Kenya. Because PWID and their partners in Kenya rarely own cellular phones, we work with community-embedded peer educators (PEs) to find and engage with partners. Additionally, our protocol involves referrals to different facilities for injection partners and for sexual partners, as a precaution to ensure safety and confidentiality of index participants who may theoretically be at risk of negative outcomes if partners become aware of their HIV-positive status.

### *Study design*

Our study is a prospective cohort study with two groups: index and partner participants ("indexes" and "partners"). We use tailored APS procedures to identify, find, test and link to care the sexual and injection partners of HIV-positive PWID. All index participants, as well as partner participants who are diagnosed with HIV or HCV, complete a 6-month follow-up visit to assess linkage to and engagement in care.

*Study sites/setting*

Study procedures take place in eight main sites including public health centers, medication-assisted treatment (MAT) centers, and needle and syringe programs (NSPs) in Nairobi, Kilifi, and Mombasa Counties in Kenya (Figure 1). Each site is staffed by at least one clinical officer (mid-level clinician) who works with researchers to ensure that only participants with documented HIV infection are enrolled as indexes, verifying HIV status through re-testing if documentation is not provided. In Nairobi County, the activities are centered at two NSP sites and one MAT center in the Mathare North area. The NSP sites, run by Support for Addiction Prevention and Treatment in Africa (SAPTA), offer routine HIV testing services. Referrals are made to local clinics providing care for those who test positive for HIV or HCV. We also recruit indexes from a government-run methadone clinic in Nairobi in the Ngara area. The Ngara Health Center MAT clinic offers HIV testing, care and treatment in addition to daily methadone administration, psychosocial services and treatment for other health conditions. In Kilifi county, participant recruitment and enrollment takes place at three needle and syringe program centers and one government hospital. The Omari Project is located in Malindi town and offers HIV counseling, testing, care and treatment in addition to harm reduction services. Malindi Sub-County Hospital's MAT center is a recruitment site in Kilifi County within a mid-sized government hospital that offers a large range of medical and social services. Malindi Sub-County Hospital also has a large laboratory that houses the

study's samples collected in both Kilifi and Mombasa Counties. The Muslim Education and Welfare Association (MEWA) NSP sites in Kilifi and Mtwapa towns offer HIV counseling and testing, in addition to HIV care and treatment and harm reduction services. In Mombasa county, participants are recruited from the ReachOut Center, an NSP site in Mombasa city that offers a full range of harm reduction services in addition to HIV counseling, testing, care and treatment. All recruitment sites offer routine HCV testing when kits are available through specific donor-driven projects.

*Population*

This study includes index participants and their sexual and/or drug-injecting partners . All indexes are HIV-positive PWID. Partners are either sexual partners or injecting partners of indexes.

Indexes are largely recruited from organizations and clinics that provide services to PWID populations, although they may also come from outreach efforts or informal referrals from other participants. Partners are identified and recruited through peer-mediated APS and may come from any geographic area or community.

*Patient and Public Involvement*

Members of the community of PWID being researched were consulted in the development of research questions and design of the study. The study is supported by a Community Advisory Board (CAB) composed of members of the community, peer educators and employees of organizations that provide services to the population. The CAB meets with the study team regularly and helps inform dissemination plans.

*Study procedures*

1. Peer educator recruitment and training

PEs are recovering PWID with established relationships in the PWID communities that they serve. The majority are between the ages of 25 and 50, are enrolled in Kenya's methadone program and report having stopped injecting drugs. These men and women have been identified by the individual organizations at which they work as being key community members, and have undergone extensive training for their roles as PEs. Training is an intensive 5-day course with modules covering a broad spectrum of content including basics of drugs and drug-related harms, harm reduction efforts including NSP and MAT, abscess prevention and management, overdose prevention and management and behavior change communication. PEs have access to relatively hidden PWID community spaces, and provide health counseling, linkage to support organizations, information, and other services to this vulnerable population.

For this study, PEs who were actively carrying out basic duties were chosen by the leadership at each organization based on several factors including awareness and knowledge of HIV in the community and access to unique target populations (for instance, women who inject drugs may be more easily accessed by women PEs). Once identified, PEs underwent an intensive 1-day training to educate them on the practice and ethics of research, study procedures, and their role in the study. PEs are supervised by clinic managers, who are all collaborators in the study. PEs participate in regular health education and harm reduction training and engage in quarterly sessions with study leadership where they present barriers and lessons learned to the study team so that study-related issues can be addressed.

2. Inclusion & exclusion criteria

Inclusion and exclusion criteria are different for indexes and partners (Table 1). Any interested individuals who are under the age of 18 are referred to the site clinicians for routine counseling and harm reduction services.

3. Index recruitment and enrollment

Enrollment began in March 2018. Clinicians at each site identify potential indexes using existing clinical data on known HIV-positive clients. Additionally, any client who tests positive for HIV during routine testing is invited to participate. Clinicians are employed by the sites, and are trained clinical officers (COs), or mid-level providers. For this study, HIV rapid testing is performed by non-study COs and takes place as part of standard clinic procedures. All potential indexes are re-tested using HIV rapid tests (as per the national guidelines) to confirm HIV status prior to enrollment. If HIVpositive, either newly diagnosed or known to be positive, clinicians approach potential indexes with one of two strategies. Either the clinicians discuss the study directly with potential participants or engage PEs to find individuals and bring them to the study office if they are not regular clients at the site. Importantly, PEs are not told whether participants are being traced as an index or a partner, protecting the confidentiality of indexes' HIV status.

Study staff health advisors (HAs) are the individuals responsible for conducting study procedures including notification of exposure, data collection, HIV and HCV testing, and the coordination of APS efforts (Figure 2). All HAs were trained and experienced in HIV testing services prior to working for the study, and many had previous experience working with PWID. All HAs underwent a week-long training course at the beginning of the study in which they learned the basics and purpose of research, research ethics, study procedures, unique ethical and logistical issues to consider when working with PWID, and other topics. All HAs also completed the Collaborative

Institutional Training Initiative (CITI) course on Human Subjects Research and the Responsible Conduct of Research. HAs explain the benefits and rationale for providing APS, discuss the importance of learning more about HIV and HCV, and describe the process of notifying partners without revealing the identity of the index. They ask participants to provide written informed consent for study participation, APS, and future use of biological specimens and future contact for additional studies, using an iris-scanning biometric device to record a unique identifier for each participant, thus enabling the study team to confirm that a person does not enroll into the program as an index more than once.

Indexes undergo a structured questionnaire administered by the HA using open data kit (ODK) software on tablet devices (ODK, 2017, Seattle, WA, USA). Questionnaires cover a variety of topics including demographics, sexual and injecting behaviors, drug use history, and HIV testing and history of engagement in HIV care. Participants are then asked to recall all of their sexual and injecting partners over the three years prior to enrollment, naming these partners one by one and assigning each partner a letter ("A," "B," etc). Sexual intercourse is defined as vaginal, oral, or anal sex and drug injecting partner is defined as a friend that you inject with frequently. Indexes are asked to give as much locator information as possible for each partner, including names (which may be nicknames), phone numbers, and location of employment or residence. Locator information is written on a paper form for each partner. Indexes then complete a short ODK questionnaire about each partner mentioned, which includes information about the relationship between the index and the partner. Indexes who wish to notify partners themselves are given a 2-week window in which to do so, after which partners are contacted by study staff. Partners notified by indexes through passive referral are told to present to the study site for enrollment in the study, and mode of referral is recorded for each partner in the study.

Indexes then undergo rapid HCV antibody testing as part of routine study procedures. HAs conduct pre- and post- test counseling and ensure individuals who test positive are available for follow-up visits to discuss confirmatory HCV PCR testing and enrolling in a treatment program administered by the Ministry of Health. All indexes then undergo phlebotomy with a sample of 10mL of blood drawn for further testing (see section 6 below). Indexes receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

4. Peer-educator mediated assisted partner services and partner recruitment

For those partners who have phone numbers listed, HAs attempt phone communication first. However, the vast majority of partners mentioned by indexes do not have working cellular phones; therefore, with few exceptions, PEs locate and conduct the study's first interaction in person with identified partners. PEs are given paper forms containing names and locator information for identified partners, and they verify that the names and locations provided on the locator form matches those of the person they have contacted. They are never told which index referred the team to each partner, and that information is not listed on locator forms or any other accessible file. PEs then locate and approach potential participants in the community and inform them that they have been identified as an individual who might need to be seen in a clinic due to a health concern. When approaching a partner, PEs alert partners that the PEs are working with a research study, and that the partner may have a health issue that should be addressed. The PEs then urge the partner to accompany them to a health facility for testing and possible enrollment in the study. Although PEs are trained using a standardized script, they are encouraged to allow the conversation to progress naturally, responding to questions and concerns that may arise and urging partners to come to the site for further information. PEs do not notify partners of their exposure during initial contact for several reasons: 1) to protect the HIV status of indexes, PEs are not told whether they

are recruiting an index or a partner, and 2) PEs have not felt comfortable discussing HIV or HCV exposure with potential participants. Once PEs have notified potential participants of their possible eligibility, they then accompany interested individuals to the nearest research office, where the study's HAs inform partners of their potential exposure to HIV and/or HCV, and conduct informed consent. Informed consent includes consent to future use of biological specimens and future contact for additional studies. In the rare event that a potential participant does not agree to come to the study office, an HA returns to the site with the PE and notifies the individual of the exposure, and in the rare event that a potential participant agrees to come to the study office but does not want to enroll in the study, the health advisor notifies the individual of the exposure and encourages the individual to undergo testing for HIV and HCV outside of study procedures.

5. Partner enrollment

After informed consent and biometric identification, partners complete a structured questionnaire similar to that of indexes, administered by HAs on a handheld device using ODK software. Following the questionnaire, all partners undergo rapid antibody testing for both HIV and HCV. HIV testingservices are provided in accordance with national HIV testing guidelines. Any partner found to be positive for either HIV or HCV antibodies undergoes a 20mL blood draw. Those partners who test negative for both HIV and HCV are finished with study procedures at this time and are counseled on risk reduction measures and provided information about HIV and HCV prevention services before leaving the study site. All partners receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

HIV-positive partners are invited to undergo screening as an index once data collection procedures for their partner enrollment are complete. If they meet eligibility criteria as an index, they may

enroll as an index. Study procedures are slightly amended for indexes that have previously enrolled as partners. After undergoing informed consent and completing a short questionnaire that only includes questions that were not a part of the partner enrollment questionnaire, they complete the identification and data collection on each of their sexual and injection partners, identical to partner identification procedures for indexes described above.

6. Laboratory Procedures

Blood samples from both index and partner enrollment visits are collected in EDTA vacutainer tubes. Blood is mixed with the anticoagulant by inversion and the anticoagulated blood is stored at room temperature at the sites for less than 4 hours. A motorcycle courier picks samples from each site daily and brings them to the University of Nairobi Pediatric Research Laboratory in Nairobi or the Malindi Sub-County Hospital Laboratory for coast sites. At each laboratory, samples are first used to prepare two Whatman 903 Protein Saver dried blood spot (DBS) cards with 50ul of whole blood on each spot. Blood samples are then centrifuged and used to prepare 2 to 3 aliquots of 1ml of plasma in labeled serum vials. Plasma aliquots and air-dried DBS cards (with desiccant in sealed Ziploc bags) are then stored at -80° Celsius and shipped on dry ice to the University of KwaZulu-Natal laboratory. There, samples undergo HIV and HCV viral load testing and amplification for sequencing.

7. Participant follow-up

All indexes and any partners who were positive for HIV or HCV complete a six-month follow-up visit. HAs identify which participants are due for follow-up visits on a weekly basis and give PEs as list of these names. PEs then trace participants and bring them back to clinics where data

collection procedures are conducted. PEs make several attempts to find participants in the community before considering them lost to follow-up.

Six-month visits involve a brief questionnaire covering questions on testing for HIV or HCV (if not infected with both on enrollment), enrollment in care and treatment, engagement in care, and follow-up testing. The purpose of this visit is to assess whether engagement in care has changed following APS procedures, for both indexes and partners. We do not collect additional data from those lost to follow up.

8. Intimate partner violence (IPV) monitoring

Given historical concerns that APS may increase one's risk of experiencing intimate partner violence, all potential participants undergo screening for IPV before enrollment. IPV is defined as any physical, sexual or psychological harm inflected on a person by a current or former sexual partner. After answering a standardized set of six questions about physical, emotional and sexual IPV and the timing of any previous experience of IPV based on published screening tools reviewed by the Centers for Disease Control and Prevention,[60] potential participants are classified as low, medium or high risk for IPV. Individuals are classified as at high risk for IPV if they report IPV within the last month. Any potential index who is classified as high IPV risk is excluded from study participation and provided with IPV counseling and resources. Any potential partner participant who is classified as high IPV risk is allowed to enroll, but then receives special monitoring for IPV following enrollment.

Potential participants are classified as at moderate risk for IPV if they report 1) IPV during their lifetime either from a current or past partner; and/or 2) fear of IPV if they participate in the study.

All index or partner participants classified as moderate IPV risk receive special monitoring for IPV following their enrollment in the study.

Potential participants are classified as at low risk for IPV if they report 1) no IPV during their lifetime ; and 2) no fear of IPV if they participate in the study. These individuals undergo standard study procedures which include completing the baseline IPV case report form and a follow-up IPV case report to capture reports of any interim IPV.

9. Confidentiality and safety

*Participants*: All study procedures take place in private rooms at each study facility. To ensure the safety and confidentiality of indexes, PEs who are tasked with finding partners are blinded to the identity of the linked index through the use of partner locator forms that do not contain identifying information about the index participant. Locator forms do contain a printed barcode label that are then used by study staff to link the partner with the index who referred the partner.

Sexual partners are brought to independent facilities for enrollment rather than to centers that serve PWID, in order to further protect the identity of the index participant who referred them. The independent facilities are local healthcare clinics that serve the general population.

*Peer educators*: PEs have frequent interactions with police, and can be victims of harassment or violence, both by police and by PWID. To reduce the risk of law enforcement troubles, PEs carry identification showing that they are working on a study being conducted by the Ministry of Health. Local law enforcement officials have also attended ongoing sensitization trainings by the Ministry of Health and by organizations working with PWID.

10. Referrals to care

*HIV Counseling and Care:* Participants are provided with their HIV test results in the context of post-test counseling, and are then referred to available medical and psychosocial care and support facilities either within the research site or in close proximity to the research site or the participant's home. Additionally, HIV-positive individuals are offered individual or group support sessions as available within each site.

*HCV Counseling and Care:* Participants who test positive for HCV antibodies using rapid testing are provided with their HCV antibody test results in the context of pre- and post-test counseling. They are informed that they may have active HCV infection; however, further confirmatory testing must be done prior to establishing the diagnosis. Confirmatory polymerase chain reaction (PCR) testing is done in batches of samples at our partnering laboratory at the University of KwaZulu-Natal, South Africa, and participants with active infection are later contacted for results and counseling. Turnaround time from enrollment to PCR result notification varies, but is typically between 1 and 4 months. Once notified of their PCR results, those with active infection are paired with a PE at their site to ensure close contact is maintained. Study participants with active HCV infections will be eligible to receive free treatment with direct acting antivirals, which the Kenyan MoH has procured.

*Data management*

After each study visit, HAs review their work for omissions or errors and all data are uploaded into the study database. Electronic data are stored securely in an encrypted database on servers using Open Data Kit Aggregate, within Kenya's Ministry of Health (MoH). All errors or omissions identified at any step in the quality assurance/quality control process are revised by the staff

member who originally completed the document. All additions and corrections are initialed and dated by the staff member who records the entry.

A link-log is separately encrypted to further ensure that data remains secure. Any data transferred to investigators or MoH are de-identified and encrypted during the process of transfer from the server. Each investigator maintains and stores secure, complete, accurate and current study records throughout the study. A database manager performs regular data cleaning and resolves any discrepancies that occur. Study sites also conduct quality control and quality assurance procedures. All co-investigators have access to the final dataset and this is not limited by contractual agreements. Study data will be available upon request at the completion of the study.

*Outcome measures*

The primary outcomes of interest to assess the success of the APS intervention are: a) number of sexual and injection partners tested for HIV and HCV through APS, identified by each index participant over the course of the study period; b) number of sexual and injection partners newly testing positive for HIV and HCV, per index participant; c) number of known HIV or HCV cases identified through APS who are not engaged in care; d) number of index and partner participants with HIV and/or HCV infection who are linked to care; e) number of index and partners with HIV and/or HCV infection who remain in care and are receiving appropriate treatment at 6 months after testing positive. Secondary outcomes are linked to inclusion in phylogenetic clusters identified as high risk for onward transmission of HIV and HCV.

*Sample size*

We are enrolling 1000 HIV-positive indexes and their sexual and injecting partners. Based on HCV data from MoH and our preliminary results, we estimate that 20% of PWID with HIV will be co-infected with HCV and that each index will identify on average two partners who will accept HIV and HCV testing, 20% of whom will be HIV-positive, and 20% of whom will be HCV-infected. Thus, with provision of APS to 1,000 HIV-positive indexes and testing of 2,000 partners, we will identify an estimated 600 indexes and partners infected with HCV and 400 HIV-positive partners. This study was designed to have high precision in estimating the prevalence of HIV and HCV infection among partners, providing valuable input for modeling the impact of APS in the population. For an observed HIV or HCV prevalence of 10% among partners, precision is estimated at 1.9%; with an observed HIV or HCV prevalence of 30% among partners, precision is estimated at 2.9%. *Statistical methods and analysis*

To determine efficacy of the APS intervention, we will use generalized estimating equations (GEE) models with a Poisson link using the following variables and offsets: 1) rate of HIV and HCV testing of partners: number of individuals tested for HIV or HCV, offset by the number of partners located with locator information provided by the index participant; 2) prevalence of HIV and HCV infection: number of individuals identified as HIV or HCV-positive, offset by the number of individuals who were HIV tested; and 3) rate of linkage to HIV and HCV care: individuals who test HIV or HCV-positive and link to care, offset by the total number of individuals who test HIV or HCV-positive.

Additionally, using both GEE and phylogenetic analysis, we will determine the following: 1) identifiable and individual risk factors linked to high rates of HIV and HCV transmission, 2) risk factors linked to both needle-sharing and sexual transmission, and 3) identification of transmission clusters among PWID for both HIV and HCV.

*Phylogenetic analysis*

HIV and HCV gene sequencing are attempted for all study participants who test positive for either virus. Sequencing will be performed at the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP) at the University of KwaZulu-Natal in Durban, South Africa. For HIV we will subsequently combine our data with additional, publicly available, HIV sequences from Kenya and perform phylogenetic and phylodynamic analyses to describe patterns and rates of viral transmission among key populations in Kenya and identify traits associated with relative infectiousness. For HCV we will use phylogenetic methods to characterize the modes and risk factors for onward transmission among PWID.

## Ethics and Dissemination

*General ethical considerations*

This study is registered at clinicaltrials.gov (NCT03447210) and has ethical approval from both the University of Washington Human Subjects Division and the Kenyatta National Hospital Ethics and Research Committee. It also has approval from Kenya's National Commission for Science, Technology and Innovation.

There are a number of potential risks to participants. Risks of conducting APS include psychological distress, social or economic hardship, criminal penalties, and loss of privacy and/or confidentiality. Study procedures, including confidentiality and counseling procedures, are specifically designed to minimize these risks to participants. While IPV has the potential to cause harm, it has not increased in other US or African studies when this intervention has been implemented in the general population.[25,61,62] We recognize that risks may be different when

implementing APS among key populations and study staff are highly trained in counseling about risk behaviors, implications of testing HIV-positive, and protecting confidentiality to avoid potential social harms. In addition, staff have undergone extensive training on IPV counseling and ensure that resources have been identified in all sites so we can safely refer participants who report abuse or are concerned for their safety. Participants reporting moderate IPV are monitored as described in Section 8; they are counseled and referred for services if IPV is reported at any of these follow-up visits.

A safety monitoring board composed of researchers and policy makers in both Kenya and the US reviews study safety data twice per year. The board monitors enrollments, deaths, loss to follow up, adverse events, including social harms, and IPV monitoring data and makes recommendations regarding study procedures.

Ethical considerations surrounding the use of biometric identification systems among key populations in Kenya have been discussed extensively.[63] Despite early opposition from the Key Populations Consortium and other organizations to the government's use of fingerprint-based biometric data collection, the organizations and individuals working with PWID communities continued to report no opposition to iris scanning for research purposes among PWID. In November 2019, Kenya passed the Data Protection Bill, rendering it legal to collect biometric data as long as the use of such data does not violate the subjects' rights.[64] The use of biometrics is now standard practice in many research and clinical settings, and has been found to be acceptable to participants.[65] Our participants have not reported any concerns, fears, or hesitations regarding the use of an iris scanning biometric identification system.

*Dissemination plan*

Results from the study and changes to the study are presented on an ongoing basis at Kenya's quarterly MoH harm reduction and key population technical working group meetings, and discussed at biannual meetings by the Community Advisory Board that was established for this study. Our study team includes several collaborators from the MoH. Ongoing study analyses are also presented at national conferences annually. Additionally, study results are presented in at least one international conference per year. Finally, the study team reviews data on a weekly basis and any changes in data trends or other concerns are discussed directly with the organizations through which study procedures take place.

## Authors' contributions

CF and JH conceived of the study; AMW, BG, BC, MD, PM, BSi, JH and CF contributed to the study design and data collection structure; AMW, LM, DB, BSa, BC, JS, PC, HM, RB, PM, SM, EW, TDO, BSi, JH and CF contributed to data collection; AMW, LM, BG, DB, BSa, PC, HM, RB, SM, EW, TDO, NLB, JH and CF contributed to data analysis and dissemination; AMW, BG, JH and CF wrote the manuscript; all authors reviewed the manuscript for content.

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## Competing interests

All authors state that they have no competing interests.

Figure 1. Map of Study Sites

Figure 2. Study Flow Diagram

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**Table 1. Inclusion and Exclusion Criteria**

| Group | Inclusion | Exclusion |
|---|---|---|
| ***Index*** | • 18 years of age or older<br>• Recent intravenous drug use as defined by injecting at least once in the past year<br>• HIV-positive<br>• Willing and able to provide locator information for sexual and/or injecting partners<br>• Willing and able to provide informed consent | • Classified as at high risk for IPV (described below) |
| ***Partner*** | • 18 years of age or older<br>• identified by an index as either having injected with the index in the past 3 years or had sexual intercourse with the index in the past three years<br>• Willing and able to provide informed consent | None |

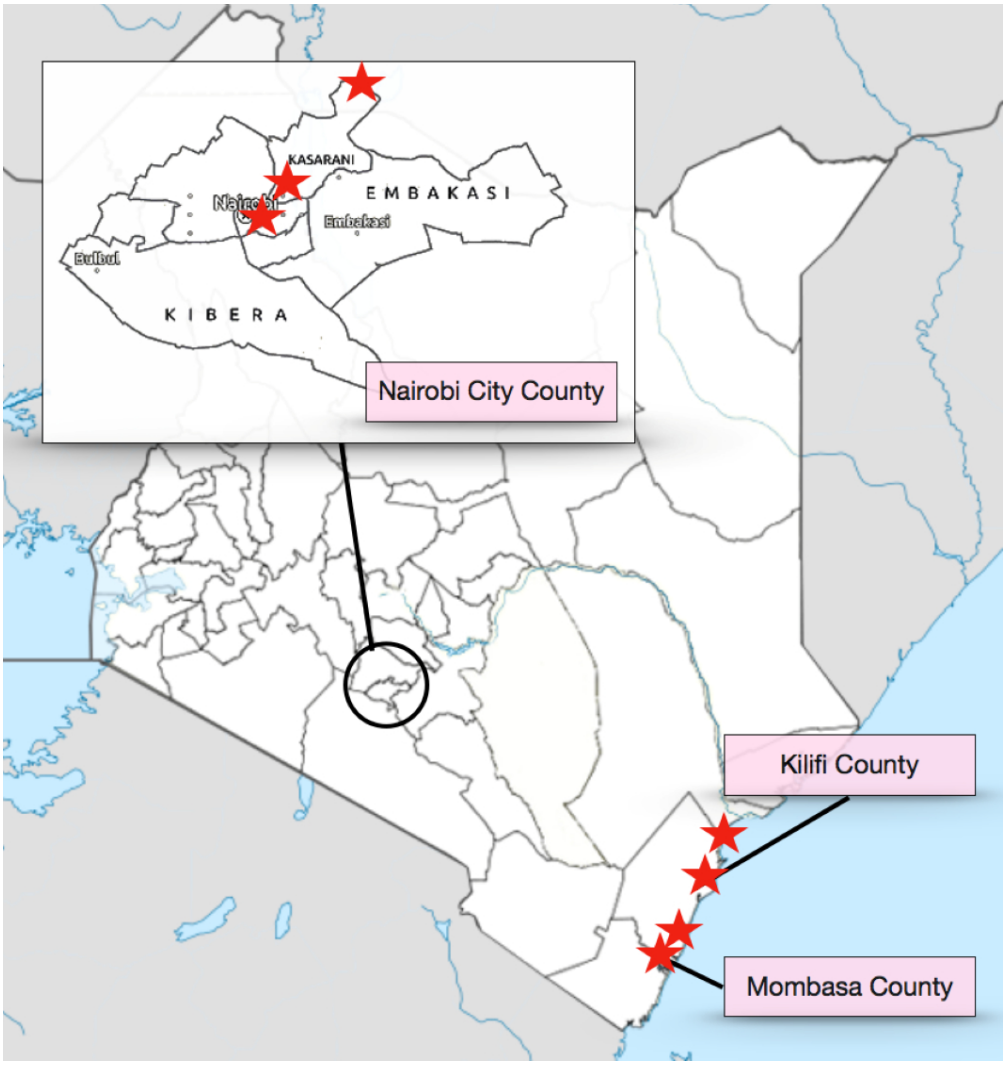


Figure 1. Map of Study Sites

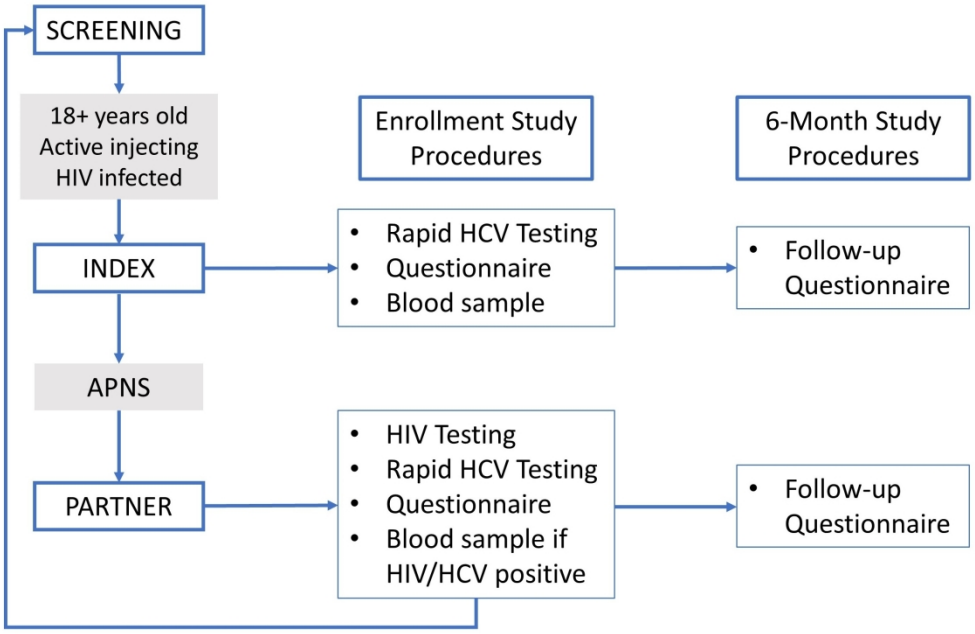


Figure 2. Study Flow Diagram

683x449mm (96 x 96 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 21 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Included |
| Protocol version | 3 | Date and version identifier | 1 |
| Funding | 4 | Sources and types of financial, material, and other support | 23 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 23 |
| | 5b | Name and contact information for the trial sponsor | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | N/A |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-7 |
| | 6b | Explanation for choice of comparators | N/A |
| Objectives | 7 | Specific objectives or hypotheses | 6-7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 8 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 8 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10-11 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11-14 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | N/A |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 17 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 18 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 15 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 19 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 11 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 15 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 18 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 19-20 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | N/A |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | N/A |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 21-22 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 21 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 22 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _12-13_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | __12-13_____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | __16-18_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ___23_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | ____18_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | ____17-18____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ____22-23____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | ____23_____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | ____N/A_____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | ____Attached__ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | __14-15, 20____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

# Peer-mediated HIV assisted partner services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

| | |
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# Peer-mediated HIV assisted partner services to identify and link to care HIV-positive and HCV-positive people who inject drugs: a cohort study protocol

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V2.0 13/10/20

## Abstract

### Introduction

Targeted, tailored interventions to test high-risk individuals for HIV and hepatitis C (HCV) are vital to achieving HIV control and HCV micro-elimination in Africa. Compared with the general population, people who inject drugs (PWID) are at increased risk of HIV and HCV and are less likely to be tested or successfully treated. Assisted partner services (APS) increases HIV testing among partners of people living with HIV and improves case-finding and linkage to care. We describe a study in Kenya examining whether APS can be adapted to find, test, and link to HIV care the partners of HIV-positive PWID using a network of community-embedded peer educators (PEs). Our study also identifies HCV-positive partners and uses phylogenetic analysis to determine risk factors for onward transmission of both viruses.

### Methods

This prospective cohort study leverages a network of PEs to identify 1,000 HIV-positive PWID for enrollment as index participants. Each index completes a questionnaire and provides names and contact information of all sexual and injecting partners during the previous 3 years. PEs then use a stepwise locator protocol to engage partners in the community and bring them to study sites for enrollment, questionnaire completion and rapid HIV and HCV testing. Outcomes include number and type of partners per index who are mentioned, enrolled, tested, diagnosed with HIV and HCV and linked to care.

### Ethics and dissemination

Potential index participants are screened for intimate partner violence (IPV) and those at high risk are not eligible to enroll. Those at medium risk are monitored for IPV following enrollment. A community advisory board engages in feedback and discussion between the community and the research team. A safety monitoring board discusses study progress and reviews data, including IPV monitoring data. Dissemination plans include presentations at quarterly Ministry of Health meetings, local and international conferences, and publications.

## Strengths and limitations of this study

- This cohort study investigates the use of assisted partner services (APS) to find, test for HIV and hepatitis C (HCV) and link to care the sexual and injecting partners of HIV-positive people who inject drugs (PWID) in Kenya; however, APS is not offered to HIV-negative, HCV-positive clients to identify those exposed to HCV but not HIV.
- Community embedded peer educators trained to provide harm reduction services conduct partner tracing, but there are limitations including logistical challenges and concerns for client confidentiality and safety of both the client and peer educator.
- An iris scanning biometric identification system ensures that each index participant enrolled is a unique individual and confirms that individual partner participants who enroll more than once in relation to different index participants are the same individual.
- Phylogenetic analysis of HIV and HCV viral sequences combined with APS will provide additional information about transmission dynamics within the cohort, including risk of onward transmission for different clusters and geographic regions.



## Introduction

Diagnosing 90% of those living with HIV has been among the most difficult of the UNAIDS 90-90-90 goals to achieve worldwide,[1,2] and strategies to reach individuals at high-risk for HIV who have never been tested is increasingly important.[3] In Kenya, despite success in achieving or

approaching the 2nd and 3rd UNAIDS goals, only 79.4% of people testing for HIV know their status.[4] Sharing needles and other drug paraphernalia is the most efficient mode of HIV transmission, and accounts for 13% of new infections globally.[5,6] In Kenya, prevalence of HIV among people who inject drugs (PWID) has been estimated at 15 – 50%[6–10]—significantly higher than the general population prevalence of 4.9%,[11] and up to 30% of PWID in Kenya have never tested for HIV.[12,13] Multiple studies have demonstrated low knowledge of HIV status and low engagement in care among Kenya's PWID.[13,14] Retention in care and adherence to ART are also both lower among PWID as compared with others worldwide.[1]

In addition to HIV, PWID are at high risk for hepatitis C virus (HCV) globally and have the highest HCV prevalence of any group studied in Kenya at 13-40%[10,15,16]. This is especially high when compared to the general population HCV prevalence in Kenya of <1-4%.[17,18] However, multiple barriers exist at individual, provider and system levels resulting in low rates of testing, engagement in care, and completion of treatment courses for PWID.[19–21] Although less than 20% of PWID with chronic HCV worldwide have undergone antibody screening, the number who have completed PCR confirmatory testing is even lower.[22] Despite the introduction of highly effective direct acting antivirals (DAAs) into Kenya in 2016, only a small fraction of individuals living with HCV have been treated, prompting attention to micro-elimination strategies.[23,24]

Assisted partner notification services (APS) for HIV is an evidence-based partner notification strategy in which providers elicit information about the sexual or injecting partners of an HIV-positive index client, and then contact, HIV test and link to care any partners found to be positive.[25] APS has been shown to significantly and safely increase the uptake of HIV testing services (HTS), case finding, and linkage to care for partners of HIV-positive people.[25–27] APS can also reduce barriers to disclosing HIV status[28] and is cost-effective.[29] APS has been successfully implemented

among HIV-positive patients from the general population in the USA,[30] Mozambique,[31] Malawi,[32,33] and Kenya,[27] and has recently been incorporated into the World Health Organization (WHO) guidelines for routine care for HIV-positive people worldwide.[34] While programs have introduced the practice of APS in high-risk key populations (KPs) such as female sex workers (FSW)[35] and men who have sex with men (MSM),[36,37] this intervention has not been well-studied among PWID,[38] an extremely high risk group.[25,39] Similar to FSW and MSM, PWID engage in behavior that is criminalized in many parts of the world[40] while experiencing high rates of marginalization and displacement,[41] making them difficult to study. These factors and others also contribute to significant barriers in the implementation of health programs targeting PWID.[42–44]

Phylogenetic analysis is a method of identifying the role of specific risk groups and risk factors for onward transmission of HIV and HCV using the genetic sequence of each virus.[45–47] Viral phylogenetics can provide additional information on patterns of transmission,[48–50] epidemic growth,[51,52] risk groups,[53–55] and risk factors associated with onward transmission.[47,56–58]

Here we describe a prospective cohort study that seeks to determine whether and how APS can be implemented to find, test, and link to care the injection and sexual partners of HIV-positive PWID in Kenya. Simultaneously, our study will use phylogenetic analysis to study genetic sequences of HIV and HCV within our cohort to further understand transmission patterns and risk for onward transmission. All index and partner participants are tested for HCV in addition to HIV. While many partner contact methods for conducting APS have been used,[25] cellular telephones are the most common first-line communication modality for reaching partners in other populations.[26,27,31,59] In Kenya, however, the large majority of PWID do not have regular access to cellular telephones. As such, our APS model relies on the utilization of community-embedded peer educators (PEs) to locate and communicate with members of this difficult to reach population. We hypothesize that

we will be able to employ these customized APS procedures to reach a large number of injection and sexual partners, and that we will see differences between sexual and injection partners in uptake of HIV testing, HIV and HCV prevalence, and engagement in care. Additionally, we hypothesize that we will identify unique transmission patterns and risks for onward transmission in phylogenetic analysis, which may include behavioral, geographic, or other factors.

## Methods and analysis

### *Approach*

APS is a practice through which healthcare providers facilitate the notification, testing and linkage to care for partners who may have been exposed to HIV or other sexually transmitted infections by an individual known to be positive without revealing the identity of the person who may have exposed them. While there are many ways to provide partner services, APS in Kenya is often conducted by healthcare providers who elicit information about partners from an "index" patient and then call the partners over the telephone or physically trace them to alert them to their exposure and provide testing. We have designed customized procedures to ensure and improve the safety and efficacy of APS in the unique population of PWID in Kenya. Because PWID and their partners in Kenya rarely own cellular phones, we work with community-embedded peer educators (PEs) to find and engage with partners. Additionally, our protocol involves referrals to different facilities for injection partners and for sexual partners, as a precaution to ensure safety and confidentiality of index participants who may theoretically be at risk of negative outcomes if partners become aware of their HIV-positive status.

### *Study design*

Our study is a prospective cohort study with two groups: index and partner participants ("indexes" and "partners"). We use tailored APS procedures to identify, find, test and link to care the sexual and injection partners of HIV-positive PWID. All index participants, as well as partner participants who are diagnosed with HIV or HCV, complete a 6-month follow-up visit to assess linkage to and engagement in care.

*Study sites/setting*

Study procedures take place in eight main sites including public health centers, medication-assisted treatment (MAT) centers, and needle and syringe programs (NSPs) in Nairobi, Kilifi, and Mombasa Counties in Kenya (Figure 1). Each site is staffed by at least one clinical officer (mid-level clinician) who works with researchers to ensure that only participants with documented HIV infection are enrolled as indexes, verifying HIV status through re-testing if documentation is not provided. In Nairobi County, the activities are centered at two NSP sites and one MAT center in the Mathare North area. The NSP sites, run by Support for Addiction Prevention and Treatment in Africa (SAPTA), offer routine HIV testing services. Referrals are made to local clinics providing care for those who test positive for HIV or HCV. We also recruit indexes from a government-run methadone clinic in Nairobi in the Ngara area. The Ngara Health Center MAT clinic offers HIV testing, care and treatment in addition to daily methadone administration, psychosocial services and treatment for other health conditions. In Kilifi county, participant recruitment and enrollment takes place at three needle and syringe program centers and one government hospital. The Omari Project is located in Malindi town and offers HIV counseling, testing, care and treatment in addition to harm reduction services. Malindi Sub-County Hospital's MAT center is a recruitment site in Kilifi County within a mid-sized government hospital that offers a large range of medical and social services. Malindi Sub-County Hospital also has a large laboratory that houses the

study's samples collected in both Kilifi and Mombasa Counties. The Muslim Education and Welfare Association (MEWA) NSP sites in Kilifi and Mtwapa towns offer HIV counseling and testing, in addition to HIV care and treatment and harm reduction services. In Mombasa county, participants are recruited from the ReachOut Center, an NSP site in Mombasa city that offers a full range of harm reduction services in addition to HIV counseling, testing, care and treatment. All recruitment sites offer routine HCV testing when kits are available through specific donor-driven projects.

*Population*

This study includes index participants and their sexual and/or drug-injecting partners . All indexes are HIV-positive PWID. Partners are either sexual partners or injecting partners of indexes.

Indexes are largely recruited from organizations and clinics that provide services to PWID populations, although they may also come from outreach efforts or informal referrals from other participants. Partners are identified and recruited through peer-mediated APS and may come from any geographic area or community.

*Patient and Public Involvement*

Members of the community of PWID being researched were consulted in the development of research questions and design of the study. The study is supported by a Community Advisory Board (CAB) composed of members of the community, peer educators and employees of organizations that provide services to the population. The CAB meets with the study team regularly and helps inform dissemination plans.

*Study procedures*

1. Peer educator recruitment and training

PEs are recovering PWID with established relationships in the PWID communities that they serve. The majority are between the ages of 25 and 50, are enrolled in Kenya's methadone program and report having stopped injecting drugs. These men and women have been identified by the individual organizations at which they work as being key community members, and have undergone extensive training for their roles as PEs. Training is an intensive 5-day course with modules covering a broad spectrum of content including basics of drugs and drug-related harms, harm reduction efforts including NSP and MAT, abscess prevention and management, overdose prevention and management and behavior change communication. PEs have access to relatively hidden PWID community spaces, and provide health counseling, linkage to support organizations, information, and other services to this vulnerable population.

For this study, PEs who were actively carrying out basic duties were chosen by the leadership at each organization based on several factors including awareness and knowledge of HIV in the community and access to unique target populations (for instance, women who inject drugs may be more easily accessed by women PEs). Once identified, PEs underwent an intensive 1-day training to educate them on the practice and ethics of research, study procedures, and their role in the study. PEs are supervised by clinic managers, who are all collaborators in the study. PEs participate in regular health education and harm reduction training and engage in quarterly sessions with study leadership where they present barriers and lessons learned to the study team so that study-related issues can be addressed.

2. Inclusion & exclusion criteria

Inclusion and exclusion criteria are different for indexes and partners (Table 1). Any interested individuals who are under the age of 18 are referred to the site clinicians for routine counseling and harm reduction services.

3. Index recruitment and enrollment

Enrollment began in March 2018. Clinicians at each site identify potential indexes using existing clinical data on known HIV-positive clients. Additionally, any client who tests positive for HIV during routine testing is invited to participate. Clinicians are employed by the sites, and are trained clinical officers (COs), or mid-level providers. For this study, HIV rapid testing is performed by non-study COs and takes place as part of standard clinic procedures. All potential indexes are re-tested using HIV rapid tests (as per the national guidelines) to confirm HIV status prior to enrollment. If HIVpositive, either newly diagnosed or known to be positive, clinicians approach potential indexes with one of two strategies. Either the clinicians discuss the study directly with potential participants or engage PEs to find individuals and bring them to the study office if they are not regular clients at the site. Importantly, PEs are not told whether participants are being traced as an index or a partner, protecting the confidentiality of indexes' HIV status.

Study staff health advisors (HAs) are the individuals responsible for conducting study procedures including notification of exposure, data collection, HIV and HCV testing, and the coordination of APS efforts (Figure 2). All HAs were trained and experienced in HIV testing services prior to working for the study, and many had previous experience working with PWID. All HAs underwent a week-long training course at the beginning of the study in which they learned the basics and purpose of research, research ethics, study procedures, unique ethical and logistical issues to consider when working with PWID, and other topics. All HAs also completed the Collaborative

Institutional Training Initiative (CITI) course on Human Subjects Research and the Responsible Conduct of Research. HAs explain the benefits and rationale for providing APS, discuss the importance of learning more about HIV and HCV, and describe the process of notifying partners without revealing the identity of the index. They ask participants to provide written informed consent for study participation, APS, and future use of biological specimens and future contact for additional studies, using an iris-scanning biometric device to record a unique identifier for each participant, thus enabling the study team to confirm that a person does not enroll into the program as an index more than once.

Indexes undergo a structured questionnaire administered by the HA using open data kit (ODK) software on tablet devices (ODK, 2017, Seattle, WA, USA). Questionnaires cover a variety of topics including demographics, sexual and injecting behaviors, drug use history, and HIV testing and history of engagement in HIV care. Participants are then asked to recall all of their sexual and injecting partners over the three years prior to enrollment, naming these partners one by one and assigning each partner a letter ("A," "B," etc). Sexual intercourse is defined as vaginal, oral, or anal sex and drug injecting partner is defined as a friend that you inject with frequently. Indexes are asked to give as much locator information as possible for each partner, including names (which may be nicknames), phone numbers, and location of employment or residence. Locator information is written on a paper form for each partner. Indexes then complete a short ODK questionnaire about each partner mentioned, which includes information about the relationship between the index and the partner. Indexes who wish to notify partners themselves are given a 2-week window in which to do so, after which partners are contacted by study staff. Partners notified by indexes through passive referral are told to present to the study site for enrollment in the study, and mode of referral is recorded for each partner in the study.

Indexes then undergo rapid HCV antibody testing as part of routine study procedures. HAs conduct pre- and post- test counseling and ensure individuals who test positive are available for follow-up visits to discuss confirmatory HCV PCR testing and enrolling in a treatment program administered by the Ministry of Health. All indexes then undergo phlebotomy with a sample of 10mL of blood drawn for further testing (see section 6 below). Indexes receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

4. Peer-educator mediated assisted partner services and partner recruitment

For those partners who have phone numbers listed, HAs attempt phone communication first. However, the vast majority of partners mentioned by indexes do not have working cellular phones; therefore, with few exceptions, PEs locate and conduct the study's first interaction in person with identified partners. PEs are given paper forms containing names and locator information for identified partners, and they verify that the names and locations provided on the locator form matches those of the person they have contacted. They are never told which index referred the team to each partner, and that information is not listed on locator forms or any other accessible file. PEs then locate and approach potential participants in the community and inform them that they have been identified as an individual who might need to be seen in a clinic due to a health concern. When approaching a partner, PEs alert partners that the PEs are working with a research study, and that the partner may have a health issue that should be addressed. The PEs then urge the partner to accompany them to a health facility for testing and possible enrollment in the study. Although PEs are trained using a standardized script (Appendix A), they are encouraged to allow the conversation to progress naturally, responding to questions and concerns that may arise and urging partners to come to the site for further information. PEs do not notify partners of their exposure during initial contact for several reasons: 1) to protect the HIV status of indexes, PEs are

not told whether they are recruiting an index or a partner, and 2) PEs have not felt comfortable discussing HIV or HCV exposure with potential participants. Once PEs have notified potential participants of their possible eligibility, they then accompany interested individuals to the nearest research office, where the study's HAs inform partners of their potential exposure to HIV and/or HCV (Appendix B), and conduct informed consent. Informed consent includes consent to future use of biological specimens and future contact for additional studies. In the rare event that a potential participant does not agree to come to the study office, an HA returns to the site with the PE and notifies the individual of the exposure, and in the rare event that a potential participant agrees to come to the study office but does not want to enroll in the study, the health advisor notifies the individual of the exposure and encourages the individual to undergo testing for HIV and HCV outside of study procedures.

5. Partner enrollment

After informed consent and biometric identification, partners complete a structured questionnaire similar to that of indexes, administered by HAs on a handheld device using ODK software. Following the questionnaire, all partners undergo rapid antibody testing for both HIV and HCV. HIV testingservices are provided in accordance with national HIV testing guidelines. Any partner found to be positive for either HIV or HCV antibodies undergoes a 20mL blood draw. Those partners who test negative for both HIV and HCV are finished with study procedures at this time and are counseled on risk reduction measures and provided information about HIV and HCV prevention services before leaving the study site. All partners receive 400 Kenya Shillings (KES, equivalent to about $4) as compensation for travel and time spent in the study procedures.

HIV-positive partners are invited to undergo screening as an index once data collection procedures for their partner enrollment are complete. If they meet eligibility criteria as an index, they may enroll as an index. Study procedures are slightly amended for indexes that have previously enrolled as partners. After undergoing informed consent and completing a short questionnaire that only includes questions that were not a part of the partner enrollment questionnaire, they complete the identification and data collection on each of their sexual and injection partners, identical to partner identification procedures for indexes described above.

6. Laboratory Procedures

Blood samples from both index and partner enrollment visits are collected in EDTA vacutainer tubes. Blood is mixed with the anticoagulant by inversion and the anticoagulated blood is stored at room temperature at the sites for less than 4 hours. A motorcycle courier picks samples from each site daily and brings them to the University of Nairobi Pediatric Research Laboratory in Nairobi or the Malindi Sub-County Hospital Laboratory for coast sites. At each laboratory, samples are first used to prepare two Whatman 903 Protein Saver dried blood spot (DBS) cards with 50ul of whole blood on each spot. Blood samples are then centrifuged and used to prepare 2 to 3 aliquots of 1ml of plasma in labeled serum vials. Plasma aliquots and air-dried DBS cards (with desiccant in sealed Ziploc bags) are then stored at -80° Celsius and shipped on dry ice to the University of KwaZulu-Natal laboratory. There, samples undergo HIV and HCV viral load testing and amplification for sequencing.

7. Participant follow-up

All indexes and any partners who were positive for HIV or HCV complete a six-month follow-up visit. HAs identify which participants are due for follow-up visits on a weekly basis and give PEs

as list of these names. PEs then trace participants and bring them back to clinics where data collection procedures are conducted. PEs make several attempts to find participants in the community before considering them lost to follow-up.

Six-month visits involve a brief questionnaire covering questions on testing for HIV or HCV (if not infected with both on enrollment), enrollment in care and treatment, engagement in care, and follow-up testing. The purpose of this visit is to assess whether engagement in care has changed following APS procedures, for both indexes and partners. We do not collect additional data from those lost to follow up.

8. Intimate partner violence (IPV) monitoring

Given historical concerns that APS may increase one's risk of experiencing intimate partner violence, all potential participants undergo screening for IPV before enrollment. IPV is defined as any physical, sexual or psychological harm inflected on a person by a current or former sexual partner. After answering a standardized set of six questions about physical, emotional and sexual IPV and the timing of any previous experience of IPV based on published screening tools reviewed by the Centers for Disease Control and Prevention,[60] potential participants are classified as low, medium or high risk for IPV. Individuals are classified as at high risk for IPV if they report IPV within the last month. Any potential index who is classified as high IPV risk is excluded from study participation and provided with IPV counseling and resources. Any potential partner participant who is classified as high IPV risk is allowed to enroll, but then receives special monitoring for IPV following enrollment.

Potential participants are classified as at moderate risk for IPV if they report 1) IPV during their lifetime either from a current or past partner; and/or 2) fear of IPV if they participate in the study.

All index or partner participants classified as moderate IPV risk receive special monitoring for IPV following their enrollment in the study.

Potential participants are classified as at low risk for IPV if they report 1) no IPV during their lifetime ; and 2) no fear of IPV if they participate in the study. These individuals undergo standard study procedures which include completing the baseline IPV case report form and a follow-up IPV case report to capture reports of any interim IPV.

9. Confidentiality and safety

*Participants*: All study procedures take place in private rooms at each study facility. To ensure the safety and confidentiality of indexes, PEs who are tasked with finding partners are blinded to the identity of the linked index through the use of partner locator forms that do not contain identifying information about the index participant. Locator forms do contain a printed barcode label that are then used by study staff to link the partner with the index who referred the partner.

Sexual partners are brought to independent facilities for enrollment rather than to centers that serve PWID, in order to further protect the identity of the index participant who referred them. The independent facilities are local healthcare clinics that serve the general population.

*Peer educators*: PEs have frequent interactions with police, and can be victims of harassment or violence, both by police and by PWID. To reduce the risk of law enforcement troubles, PEs carry identification showing that they are working on a study being conducted by the Ministry of Health. Local law enforcement officials have also attended ongoing sensitization trainings by the Ministry of Health and by organizations working with PWID.

10. Referrals to care

*HIV Counseling and Care:* Participants are provided with their HIV test results in the context of post-test counseling, and are then referred to available medical and psychosocial care and support facilities either within the research site or in close proximity to the research site or the participant's home. Additionally, HIV-positive individuals are offered individual or group support sessions as available within each site.

*HCV Counseling and Care:* Participants who test positive for HCV antibodies using rapid testing are provided with their HCV antibody test results in the context of pre- and post-test counseling. They are informed that they may have active HCV infection; however, further confirmatory testing must be done prior to establishing the diagnosis. Confirmatory polymerase chain reaction (PCR) testing is done in batches of samples at our partnering laboratory at the University of KwaZulu-Natal, South Africa, and participants with active infection are later contacted for results and counseling. Turnaround time from enrollment to PCR result notification varies, but is typically between 1 and 4 months. Once notified of their PCR results, those with active infection are paired with a PE at their site to ensure close contact is maintained. Study participants with active HCV infections will be eligible to receive free treatment with direct acting antivirals, which the Kenyan MoH has procured.

*Data management*

After each study visit, HAs review their work for omissions or errors and all data are uploaded into the study database. Electronic data are stored securely in an encrypted database on servers using Open Data Kit Aggregate, within Kenya's Ministry of Health (MoH). All errors or omissions identified at any step in the quality assurance/quality control process are revised by the staff

member who originally completed the document. All additions and corrections are initialed and dated by the staff member who records the entry.

A link-log is separately encrypted to further ensure that data remains secure. Any data transferred to investigators or MoH are de-identified and encrypted during the process of transfer from the server. Each investigator maintains and stores secure, complete, accurate and current study records throughout the study. A database manager performs regular data cleaning and resolves any discrepancies that occur. Study sites also conduct quality control and quality assurance procedures. All co-investigators have access to the final dataset and this is not limited by contractual agreements. Study data will be available upon request at the completion of the study.

*Outcome measures*

The primary outcomes of interest to assess the success of the APS intervention are: a) number of sexual and injection partners tested for HIV and HCV through APS, identified by each index participant over the course of the study period; b) number of sexual and injection partners newly testing positive for HIV and HCV, per index participant; c) number of known HIV or HCV cases identified through APS who are not engaged in care; d) number of index and partner participants with HIV and/or HCV infection who are linked to care; e) number of index and partners with HIV and/or HCV infection who remain in care and are receiving appropriate treatment at 6 months after testing positive. Secondary outcomes are linked to inclusion in phylogenetic clusters identified as high risk for onward transmission of HIV and HCV.

*Sample size*

We are enrolling 1000 HIV-positive indexes and their sexual and injecting partners. Based on HCV data from MoH and our preliminary results, we estimate that 20% of PWID with HIV will be co-infected with HCV and that each index will identify on average two partners who will accept HIV and HCV testing, 20% of whom will be HIV-positive, and 20% of whom will be HCV-infected. Thus, with provision of APS to 1,000 HIV-positive indexes and testing of 2,000 partners, we will identify an estimated 600 indexes and partners infected with HCV and 400 HIV-positive partners. This study was designed to have high precision in estimating the prevalence of HIV and HCV infection among partners, providing valuable input for modeling the impact of APS in the population. For an observed HIV or HCV prevalence of 10% among partners, precision is estimated at 1.9%; with an observed HIV or HCV prevalence of 30% among partners, precision is estimated at 2.9%. *Statistical methods and analysis*

To determine efficacy of the APS intervention, we will use generalized estimating equations (GEE) models with a Poisson link using the following variables and offsets: 1) rate of HIV and HCV testing of partners: number of individuals tested for HIV or HCV, offset by the number of partners located with locator information provided by the index participant; 2) prevalence of HIV and HCV infection: number of individuals identified as HIV or HCV-positive, offset by the number of individuals who were HIV tested; and 3) rate of linkage to HIV and HCV care: individuals who test HIV or HCV-positive and link to care, offset by the total number of individuals who test HIV or HCV-positive.

Additionally, using both GEE and phylogenetic analysis, we will determine the following: 1) identifiable and individual risk factors linked to high rates of HIV and HCV transmission, 2) risk factors linked to both needle-sharing and sexual transmission, and 3) identification of transmission clusters among PWID for both HIV and HCV.

*Phylogenetic analysis*

HIV and HCV gene sequencing are attempted for all study participants who test positive for either virus. Sequencing will be performed at the KwaZulu-Natal Research Innovation and Sequencing Platform (KRISP) at the University of KwaZulu-Natal in Durban, South Africa. For HIV we will subsequently combine our data with additional, publicly available, HIV sequences from Kenya and perform phylogenetic and phylodynamic analyses to describe patterns and rates of viral transmission among key populations in Kenya and identify traits associated with relative infectiousness. For HCV we will use phylogenetic methods to characterize the modes and risk factors for onward transmission among PWID.

## Ethics and Dissemination

*General ethical considerations*

This study is registered at clinicaltrials.gov (NCT03447210) and has ethical approval from both the University of Washington Human Subjects Division and the Kenyatta National Hospital Ethics and Research Committee. It also has approval from Kenya's National Commission for Science, Technology and Innovation.

There are a number of potential risks to participants. Risks of conducting APS include psychological distress, social or economic hardship, criminal penalties, and loss of privacy and/or confidentiality. Study procedures, including confidentiality and counseling procedures, are specifically designed to minimize these risks to participants. While IPV has the potential to cause harm, it has not increased in other US or African studies when this intervention has been implemented in the general population.[25,61,62] We recognize that risks may be different when

implementing APS among key populations and study staff are highly trained in counseling about risk behaviors, implications of testing HIV-positive, and protecting confidentiality to avoid potential social harms. In addition, staff have undergone extensive training on IPV counseling and ensure that resources have been identified in all sites so we can safely refer participants who report abuse or are concerned for their safety. Participants reporting moderate IPV are monitored as described in Section 8; they are counseled and referred for services if IPV is reported at any of these follow-up visits.

A safety monitoring board composed of researchers and policy makers in both Kenya and the US reviews study safety data twice per year. The board monitors enrollments, deaths, loss to follow up, adverse events, including social harms, and IPV monitoring data and makes recommendations regarding study procedures.

Ethical considerations surrounding the use of biometric identification systems among key populations in Kenya have been discussed extensively.[63] Despite early opposition from the Key Populations Consortium and other organizations to the government's use of fingerprint-based biometric data collection, the organizations and individuals working with PWID communities continued to report no opposition to iris scanning for research purposes among PWID. In November 2019, Kenya passed the Data Protection Bill, rendering it legal to collect biometric data as long as the use of such data does not violate the subjects' rights.[64] The use of biometrics is now standard practice in many research and clinical settings, and has been found to be acceptable to participants.[65] Our participants have not reported any concerns, fears, or hesitations regarding the use of an iris scanning biometric identification system.

*Dissemination plan*

Results from the study and changes to the study are presented on an ongoing basis at Kenya's quarterly MoH harm reduction and key population technical working group meetings, and discussed at biannual meetings by the Community Advisory Board that was established for this study. Our study team includes several collaborators from the MoH. Ongoing study analyses are also presented at national conferences annually. Additionally, study results are presented in at least one international conference per year. Finally, the study team reviews data on a weekly basis and any changes in data trends or other concerns are discussed directly with the organizations through which study procedures take place.

## Authors' contributions

CF and JH conceived of the study; AMW, BG, BC, MD, PM, BSi, JH and CF contributed to the study design and data collection structure; AMW, LM, DB, BSa, BC, JS, PC, HM, RB, PM, SM, EW, TDO, BSi, JH and CF contributed to data collection; AMW, LM, BG, DB, BSa, PC, HM, RB, SM, EW, TDO, NLB, JH and CF contributed to data analysis and dissemination; AMW, BG, JH and CF wrote the manuscript; all authors reviewed the manuscript for content.

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## Competing interests

All authors state that they have no competing interests.

Figure 1. Map of Study Sites

Figure 2. Study Flow Diagram

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**Table 1. Inclusion and Exclusion Criteria**

| Group | Inclusion | Exclusion |
|---|---|---|
| ***Index*** | • 18 years of age or older<br>• Recent intravenous drug use as defined by injecting at least once in the past year<br>• HIV-positive<br>• Willing and able to provide locator information for sexual and/or injecting partners<br>• Willing and able to provide informed consent | • Classified as at high risk for IPV (described below) |
| ***Partner*** | • 18 years of age or older<br>• identified by an index as either having injected with the index in the past 3 years or had sexual intercourse with the index in the past three years<br>• Willing and able to provide informed consent | None |

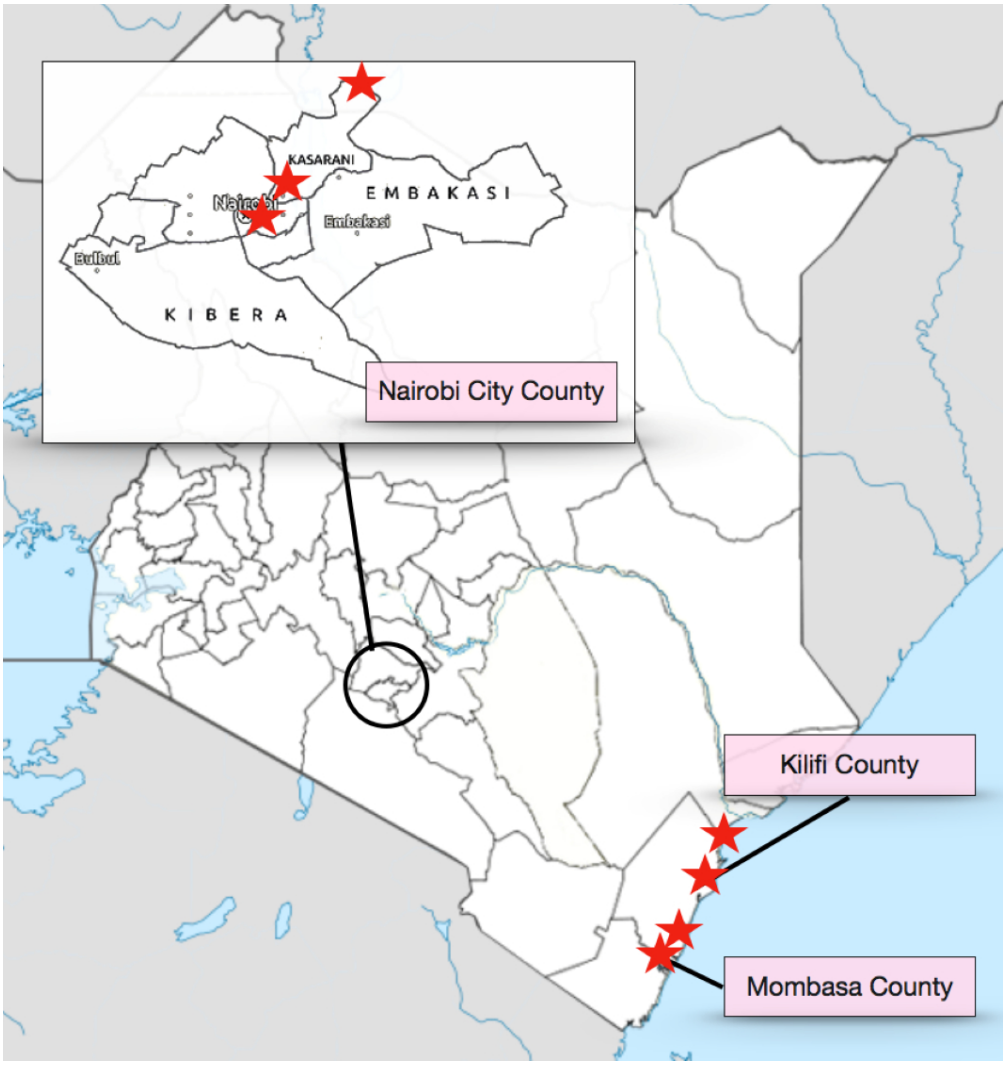


Figure 1. Map of Study Sites

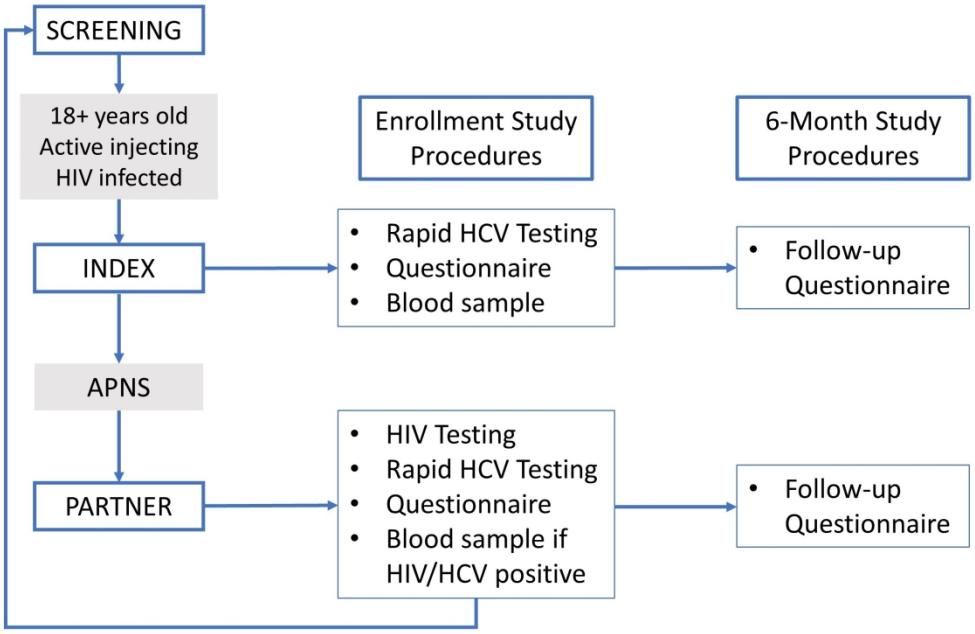


Figure 2. Study Flow Diagram

683x449mm (96 x 96 DPI)

## APPENDIX A: PEER EDUCATOR INTRODUCTION SCRIPT

Hello, I am _____, a Peer Educator from _____. Am I speaking with Ms/Mr._____? I want to be sure I have the right person in front of me. I work at the clinic and have come to talk with you about a health matter that concerns you. This is confidential information for you. Is this a good time to talk? This will not take long and I assure you that our discussion will be confidential.

The information I have concerns your health but it does not mean that something is wrong with your health. We have reason to believe that you may have a health problem, and that you may also be eligible for a research study. You will have to come to the clinic to get more information about both your health issue and the research study. If you agree, you can come to the clinic with me now and I will bring you to the clinician.

Do you have any questions about what I have said so far?

If you do not want to come to the clinic, I will return to find you again tomorrow with someone from the clinic who can talk to you about the health issue.

Have you made a decision about whether you'd like to come with me?

If yes, I will take you to [name of closest clinic] center for further discussions with the clinician at the clinic. If no, we will come back and find you again at a later date to discuss this issue with you further.

Thank you.

## APPENDIX B: HEALTH ADVISOR INTRODUCTION SCRIPT

Hello, I am _____, a Health Advisor from the Kenya Ministry of Health. Am I speaking with Ms/Mr._____? I want to be sure I have the right person in front of me. I work at the clinic and have come to talk with you about a health matter that concerns you. This is confidential information for you. Is this a good time to talk? This will not take long and I assure you that our discussion will be confidential.

The information I have concerns your health but it does not mean that something is wrong with your health.

I wish to inform you that you may have been exposed to HIV infection. I do not know who gave me information on your exposure to HIV infection.

This does not mean you are infected. It just means that you have been exposed to HIV and will need to test yourself soon to see what your HIV status is.

This HIV test will help you to know your status early and if you are not infected, you can plan to avoid future infections. If you are infected, you will receive advice on how to live positively.

You can do your test anywhere you choose, but it is advisable that you do it as soon as possible.

Do you have any questions about what I have said so far?

If you choose to do your HIV test now, I will do it for you free of charge, but before doing it, I will give you more information on voluntary counseling and testing for HIV.

If you want to do it later, I will give you more information on health facilities where you can go and do your test.

I will be in touch with you for any assistance which you made need. Would you like to have my telephone number? Would you like me to call you?

I have this information for you and would like you to read it carefully and discuss it with me. If it is ok with you, please sign it. I will keep it confidential. You do not have to sign it if you do not want to.

Have you made a decision to do the test? When and where will you like to do it?

Would you like for us to test you?

If yes, would you like to come to the [name of closest clinic] center for testing or where would you want us to offer the test for you? If at home or work, please arrange for a private place where we can offer the service. If no, we would still encourage you to seek services at [name of nearest clinic].

Thank you.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

| Section/item | Item No | Description | Addressed on page number |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | 21 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | Included |
| Protocol version | 3 | Date and version identifier | 1 |
| Funding | 4 | Sources and types of financial, material, and other support | 23 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | 1, 23 |
| | 5b | Name and contact information for the trial sponsor | |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | N/A |
| | 5d | Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) | N/A |

| | | | |
|---|---|---|---|
| **Introduction** | | | |
| Background and rationale | 6a | Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention | 5-7 |
| | 6b | Explanation for choice of comparators | N/A |
| Objectives | 7 | Specific objectives or hypotheses | 6-7 |
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | 8 |
| **Methods: Participants, interventions, and outcomes** | | | |
| Study setting | 9 | Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained | 8 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | 10-11 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | 11-14 |
| | 11b | Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) | N/A |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | N/A |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | 17 |
| Outcomes | 12 | Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended | 18 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | 15 |

| | | | |
|---|---|---|---|
| Sample size | 14 | Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations | 19 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | 11 |
| **Methods: Assignment of interventions (for controlled trials)** | | | |
| Allocation: | | | |
| Sequence generation | 16a | Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions | N/A |
| Allocation concealment mechanism | 16b | Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned | N/A |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | N/A |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | N/A |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | N/A |
| **Methods: Data collection, management, and analysis** | | | |
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | 12 |
| | 18b | Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols | 15 |

| | | | |
|---|---|---|---|
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | 18 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | 19-20 |
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | N/A |
| | 20c | Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) | N/A |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | N/A |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | N/A |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | 21-22 |
| Auditing | 23 | Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor | N/A |
| **Ethics and dissemination** | | | |
| Research ethics approval | 24 | Plans for seeking research ethics committee/institutional review board (REC/IRB) approval | 21 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | 22 |

| | | | |
|---|---|---|---|
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | _12-13_____ |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | __12-13_____ |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | __16-18_____ |
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | ___23_____ |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | ____18_____ |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | ____17-18____ |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | ____22-23____ |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | ____23_____ |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | ____N/A_____ |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | ____Attached__ |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | __14-15, 20____ |

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.