

HPTN 074

Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

A Study of the HIV Prevention Trials Network

Sponsored by:

Division of AIDS, US National Institute of Allergy and Infectious Diseases
US National Institute on Drug Abuse
US National Institutes of Health

Protocol Chair:

William Miller, MD, PhD, MPH

Protocol Co-Chair:

Irving Hoffman, PA, MPH

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARTAS	Antiretroviral Treatment and Access to Services
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CMC	Clinical Management Committee
DAERS	Division of AIDS Adverse Experience Reporting System
DAIDS PRO	Division of AIDS Protocol Registration Office
DAIDS	Division of AIDS
DAIDS-ES	Division of AIDS-Enterprise System
EAE	Expedited Adverse Event
EC	Ethics Committee
EQA	External Quality Assurance
EWG	Ethics Working Group
FDA	(United States) Food and Drug Administration
GCP	Good Clinical Practices
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HEART	Helping Enhance Adherence to Antiretroviral Therapy
HIV RNA	Human Immunodeficiency Virus Ribonucleic Acid
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IQA	Immunology Quality Assessment
IRB	Institutional Review Board
LC	(HPTN) Laboratory Center
LDMS	Laboratory Data Management System
LL	Local Laboratory
LOC	(HPTN) Leadership and Operations Center
MAPS	Managed Problem Solving
MoH	Ministry of Health
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIDA	(United States) National Institute on Drug Abuse
NIH	(United States) National Institutes of Health
PWID	People Who Inject Drugs

QA	Quality Assurance
QC	Quality Control
RCT	Randomized Controlled Trial
RE	Regulatory entity
ROC	Regulatory Operations Center
RSC	Regulatory Support Center, DAIDS
SAE	Serious Adverse Event
SBIRT	Screening, Brief Intervention, and Referral to Treatment
SDMC	(HPTN) Statistical and Data Management Center
SMART	Sharing Medical Adherence Responsibilities Together
SMC	Study Monitoring Committee
SOP	Standard Operating Procedures
SSP	Study Specific Procedures
STI	Sexually Transmitted Infection
SUSAR	Suspected Unexpected Serious Adverse Reaction
TB	Tuberculosis
UK NEQAS	United Kingdom National External Quality Assessment Service
VQA	Virology Quality Assurance
WHO	World Health Organization

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PROTOCOL TEAM ROSTER

Protocol Chair William C. Miller, MD, PhD, MPH Associate Professor University of North Carolina Chapel Hill School of Medicine, Department of Medicine Division of Infectious Diseases 2146 Bioinformatics Campus Box 7030 Chapel Hill, NC 27599 USA Phone: 919 966 9407 Email: bill_miller@unc.edu	Protocol Co-Chair Irving F. Hoffman, PA, MPH Associate Professor Director of International Operations University of North Carolina Chapel Hill School of Medicine, Department of Medicine Division of Infectious Diseases 2151 Bioinformatics Campus Box 7030 Chapel Hill, NC 27599 USA Phone: 919 966 6324 Email: hoffmani@med.unc.edu
Michael G. Hudgens, PhD Associate Professor, Department of Biostatistics Director, Center for AIDS Research (CFAR) University of North Carolina 3107-E McGavran-Greenberg Hall Chapel Hill, NC 27599 USA Phone: 919 966 7253 Email: mhudgens@bios.unc.edu	Carl Latkin, PhD Johns Hopkins University Bloomberg School of Public Health Department of Health Policy and Management 624 North Broadway Baltimore, MD 21205 USA Phone: 410 955 3972 Email: clatkin@jhsph.edu
Vivian Go, PhD University of North Carolina Chapel Hill Gillings School of Global Public Health Department of Health Behavior 361 Rosenau Hall Campus Box 7440 Chapel Hill, NC 27599-7440 USA Phone: 919 966 3908 Email: vgo@live.unc.edu	David Metzger, PhD University of Pennsylvania School of Medicine HIV Prevention Research Division Department of Psychiatry 3535 Market Street, Suite 4000 Philadelphia, PA 19104 USA Phone: 267 566 2483 Email: dsm@mail.med.upenn.edu

<p>Jeremy Sugarman, MD, MPH Johns Hopkins University, Berman Institute of Bioethics and Department of Medicine 1809 Ashland Ave Deering Hall, Room 203 Baltimore, MD USA Phone: 410 614 5634 Email: jsugarman@jhu.edu</p>	<p>David Burns, MD, MPH DAIDS Medical Officer Division of AIDS/NIAID/NIH 6700-B Rockledge Drive, Room 5249 MSC 7628 Bethesda, MD 20892 USA Phone: 301 435 8896 Email: burnsda@niaid.nih.gov</p>
<p>Steffanie Strathdee, PhD University of California San Diego School of Medicine Division of Global Public Health Institute of the Americas 10111 N. Torrey Pines Rd. La Jolla, CA 92093 USA Phone: 858 822 1952 Email: ssstrathdee@ucsd.edu</p>	<p>Susan Eshleman, MD, PhD Johns Hopkins University School of Medicine 720 Rutland Avenue Ross Bldg., Room 646 Baltimore, MD 21205 USA Phone: 410 614 4734 Email: seshlem@jhmi.edu</p>
<p>William Clarke, PhD, MBA, DABCC Johns Hopkins University School of Medicine 600 N. Wolfe Street Meyer B-125 Baltimore, MD 21287 USA Phone: 410 502 7692 Email: wclarke@jhmi.edu</p>	<p>Estelle M. Piwowar-Manning, BS, MT (ASCP), SI Johns Hopkins University Pathology Bldg., Room 313 600 North Wolfe Street Baltimore MD 21287 USA Phone: 410 614 6736 Email: epiwowa@jhmi.edu</p>
<p>Paul Richardson, M.Sc., FIBMS Senior QA/QC Coordinator Johns Hopkins University 600 North Wolfe Street Pathology 313 Baltimore, MD 21287 USA Phone: 410 502 0435 Email: pricha18@jhmi.edu</p>	<p>Deborah Donnell, PhD SDMC Biostatistician SCHARP-FHCRC 1100 Fairview Ave. North, LE-400 PO Box 19024 Seattle, WA 98109, USA Phone: 206 667 5661 Email: deborah@scharp.org</p>
<p>Lynda Emel, PhD Research Program Manager SCHARP-FHCRC 1100 Fairview Ave. North, E3-129 PO Box 19024 Seattle, WA 98109, USA Phone: 206 667 5803 Email: lemel@scharp.org</p>	<p>Laura McKinsty, MPH Project Manager SCHARP-FHCRC 1100 Fairview Ave. North, E3-129 PO Box 19024 Seattle, WA 98109, USA Phone: 206 667 7322 Email: lmckinst@scharp.org</p>

<p>Greg Lucas, MD, PhD Johns Hopkins University School of Medicine 1830 E. Monument Street, Room 421 Baltimore, MD 21287 USA Phone: 410 614 0560 Email: glucas@jhmi.edu</p>	<p>Nirupama Sista, PhD Associate Director FHI 360 359 Blackwell St. Suite 200 Durham, NC 27701, USA Phone: 919 544 7040, Ext. 11590 Email: nsista@fhi360.org</p>
<p>Scott Mitchell Rose, BS Sr. Clinical Research Manager FHI 360 359 Blackwell St. Suite 200 Durham, NC 27701, USA Phone: 919 405 1447 Email: srose@fhi360.org</p>	<p>Samsuridjal Djauzi, MD Faculty of Medicine University of Indonesia/Cipto Mangunkusumo Hospital Jalan Diponegoro No.71 Kenari Senen Jakarta Pusat, 10310 Phone: 62 818 853 856 Email: samsuridjal@yahoo.com</p>
<p>Erica Hamilton, MPH Clinical Research Manager FHI 360 359 Blackwell St. Suite 200 Durham NC 27701, USA Phone: 919 544 7040, Ext. 11295 Email: ehamilton@fhi360.org</p>	<p>Kathy Lancaster, MPH, PhD University of North Carolina Chapel Hill Department of Epidemiology Campus Box 7435 Chapel Hill, NC 27599-7435, USA Email: klanc@live.unc.edu</p>
<p>Jonathan Paul Lucas, MPH Community Programs Manager FHI 360 359 Blackwell St. Suite 200 Durham, NC 27701, USA Phone: 919 544 7040, Ext. 11458 Email: jlucas@fhi360.org</p>	<p>Tran Viet Ha, MD University of North Carolina Chapel Hill No. 6, Lane 76, Linh Lang Street Ba Dinh District, Hanoi, Vietnam Phone: 84 432 115 839 Email: tranvietha@jhsph.vn</p>
<p>Nguyen Van Vuong, MD Director, Pho yen Health District Center Ba Hang Town, Pho Yen District Thai Nguyen, Vietnam Phone: 84 987 984 887 Email: vuongttytpy@gmail.com</p>	<p>Sergii Dvoriak, MD, PhD Ukrainian Institute on Public Health Policy 4 Malopidvalna Str. Of. 6 Kyiv 01001 Ukraine Phone: 38 044 279 3586 Email: dvoryak@uiphp.org.ua</p>

Konstantin Dumchev, MD, MPH Ukrainian Institute on Public Health Policy 4 Malopidvalna Str. Of. 6 Kyiv 01001 Ukraine Phone: 38 044 279 3586 Email: k.dumchev@gmail.com	Zubairi Djoerban, MD Faculty of Medicine University of Indonesia/Cipto Mangunkusumo Hospital Jalan Diponegoro No.71 Kenari Senen Jakarta Pusat, 10310 Phone: 62 815 116 867 67 Email: zubairi_djoerban@yahoo.com
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U.S. National Institute on Drug Abuse
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PROTOCOL SIGNATURE PAGE

I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable U.S. Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

Name of Site Investigator of Record

Signature of Site Investigator of Record

Date

HPTN 074

Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

SCHEMA

- Purpose:** The purpose of this study is to determine the feasibility of a future trial that will assess whether an integrated intervention combining psychosocial counseling and supported referrals for antiretroviral therapy (ART) at any CD4 cell count and substance use treatment for HIV-infected people who inject drugs (PWID) will reduce HIV transmission to HIV-uninfected injection partners, as compared to routine care dictated by national guidelines for HIV-infected PWID.
- Design:** This is a multi-site, two-arm, randomized, vanguard study. Network units will consist of an HIV-infected index participant and his/her HIV-uninfected network injection partner(s). Network units will be randomized to the intervention or standard of care arms in a 1:3 ratio, stratified by site. To assess feasibility of the intervention, additional interviews will be conducted with study staff (systems navigators and counselors) and clinic-based stakeholders at each study site.
- Study Population:** The study population will consist of the following participant types:
- Index participants:***
HIV-infected PWID who have an HIV viral load $\geq 1,000$ copies/mL at Screening. This may include individuals who report that they are: (a) ART-naïve, (b) ART-exposed but currently off therapy, or (c) on ART.
- Network injection partners:***
HIV-uninfected injection partners of index participants (up to five active partners per index participant at a time).
- Study Size:** At least 500 network units, defined as one index participant and one network injection partner, will be recruited. The study will be performed at three study sites.
- Each site will enroll approximately 167 index participants and 250 network injection partners (up to five network injection partners per index participant). At least half of the index participants enrolled at each site are expected to report that they are ART-naïve at study enrollment. Provision is made for replacement of network injection partners (late-entry HIV-uninfected network injection partners) during the study.

Table 1. Estimated Sample Size						
	All Sites				Individual Sites	
	Total, All sites	Intervention	Standard Care		Total, Per Site	Standard Care
HIV-infected Index Participants	500	125	375		167	125
HIV-uninfected Network Injection Partners	~750	~188	~563		~250	~188
Late-entry HIV-uninfected Network Injection Partners (replacements)	~ 75	--	--		~ 25	--

Treatment Regimen: Index participants will be randomized to one of two study arms at a ratio of 1:3 (intervention: standard of care). Index participants in the intervention arm will receive (in addition to the standard harm reduction package) an integrated intervention that includes supported ART regardless of CD4 cell count and facilitated systems navigation and counseling for substance use treatment. The integrated intervention is designed to improve engagement and retention in HIV care and substance use treatment, and includes systems navigation, counseling to encourage engagement in care and adherence, and social support.

Index participants in the standard of care arm will receive referrals for the in-country standard of care for ART and substance use treatment and a standardized harm reduction package.

Network injection partners in both arms will receive a standardized harm reduction package with referral for substance use treatment, consistent with national guidelines.

Study Duration: Approximately 27 months at each site, with recruitment of index participants over 15 months and follow-up for a minimum of 12 months and a maximum of 24 months, regardless of study arm. All participants will end study participation when 27 months have passed since the first enrolled participant at the site. Network injection partners (including replacement partners) will be followed until the corresponding index participant reaches his/her Exit visit. After the originally scheduled Exit visit, Index participants will be offered the opportunity to re-enroll in the study for up to 12 additional months in order to further assess the durability of ART uptake and HIV viral suppression in the intervention. Should an effect of the intervention during the first phase of the study be realized during the additional 12 months of follow-up, participants in the standard of care arm will be offered all components of the intervention.

Primary Objectives:

- To assess the feasibility of a future randomized controlled trial by:
 - a) estimating the HIV incidence among network injection partners of index participants in the standard of care arm in three distinct global settings with epidemics driven predominantly by injection drug use;
 - b) evaluating enrollment and retention of HIV-infected PWID and their HIV-uninfected network injection partners over a period of 12-36 months for index participants and 12-24 months for partners.
 - c) assess the durability of ART uptake and viral suppression in the intervention arm
- To assess the feasibility, barriers, and uptake of an integrated intervention for prevention of HIV transmission among HIV-infected index participants.

Secondary Objectives:

- To estimate HIV incidence among network injection partners of index participants in the intervention arm.
- To explore the effect of the integrated intervention, as compared to standard of care, on engagement in HIV care, initiation of ART, retention on ART, ART adherence, and virologic suppression among ART-eligible index participants (index participants meeting national guidelines in the standard of care arm; all index participants in the intervention arm). If an effect is observed on ART uptake or HIV viral suppression in the intervention arm vs. standard of care arm, participants in the standard of care arm will be offered the intervention for the remainder of the study.
- To assess the uptake and retention on ART over the short term (additional 12 months of follow-up) in the standard of care arm.
- To explore the effect of the integrated intervention, as compared to standard of care, on the proportion of index participants and network injection partners engaged and retained in substance use treatment.
- To estimate the size and stability of the injection network of the index participants and how this affects recruitment and retention of network injection partners.
- To assess the social harms and benefits of research participation for PWID.
- If feasible and if funding is identified, to use phylogenetic methods to characterize transmission dynamics in the study cohort.
- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection; antiretroviral (ARV) drug use; substances of abuse; methadone and other treatments for substance abuse; cross-sectional HIV incidence estimation; characterization of HIV in infected participants, including phylogenetics and linkage; evaluation of the host response to HIV infection; and evaluation of laboratory assays related to study objectives.

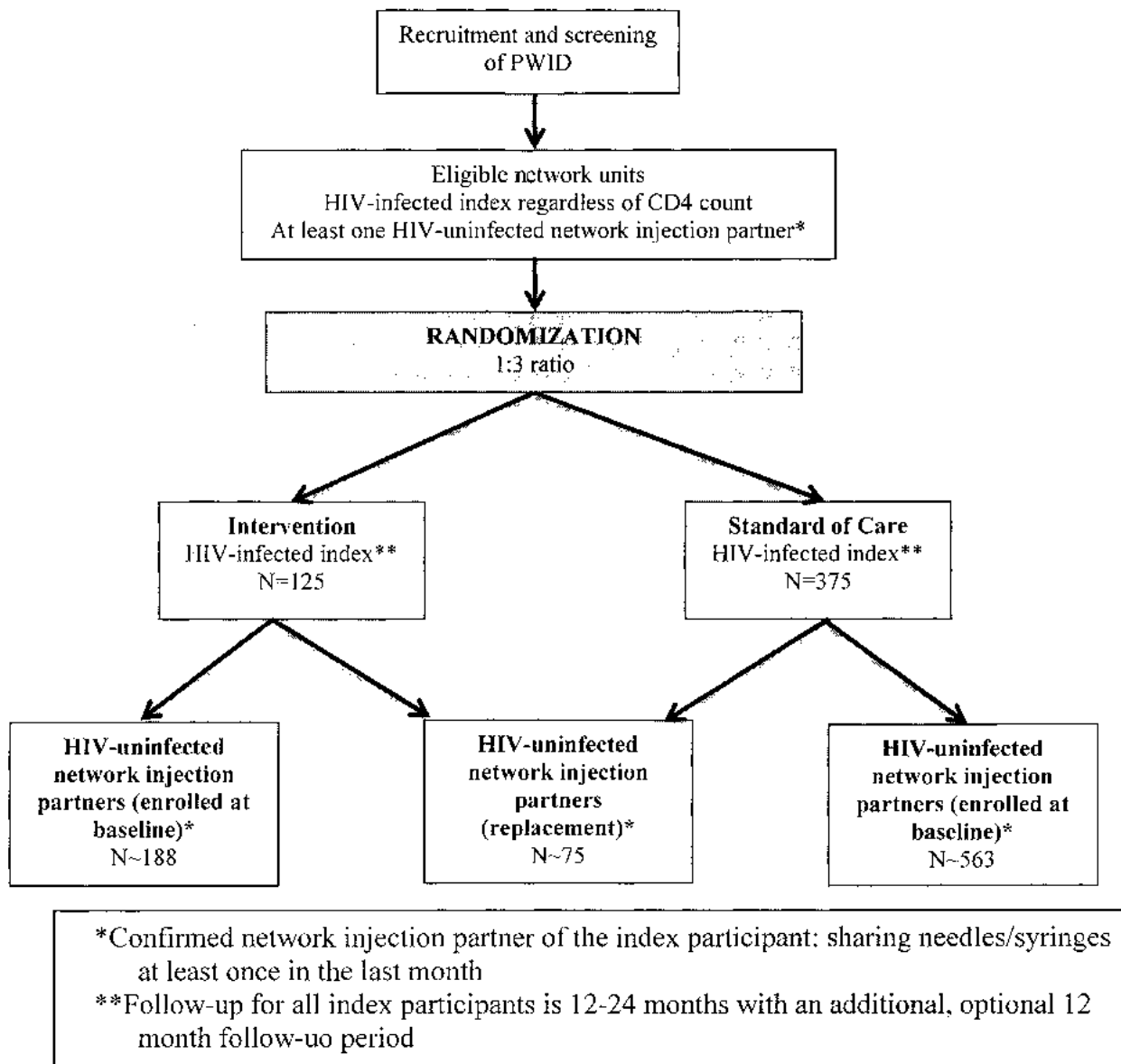
Study Sites:

- Research centers in Jakarta, Indonesia; Thai Nguyen, Vietnam; and Kiev, Ukraine.

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OVERVIEW OF STUDY DESIGN AND RANDOMIZATION SCHEME



1.0 INTRODUCTION

This protocol describes research to assess the feasibility of a future trial that will determine whether an integrated intervention with supported referral for ART at any CD4 cell count for HIV-infected people who inject drugs (PWID) will reduce HIV transmission to HIV-uninfected network injection partners, as compared to routine care dictated by national guidelines for care of HIV-infected PWID. The overall goal of this study is to ensure the feasibility of a future randomized trial by demonstrating sufficient HIV incidence among the standard of care arm and appropriate uptake of the integrated intervention.

1.1 Background

Injection drug use is the predominant risk behavior for HIV transmission in several parts of the world.[1, 2] Nearly 150 countries report injection drug use epidemics; 120 countries have a concurrent HIV epidemic. Injection drug use is a major factor underlying the HIV epidemics in Eastern Europe, the Commonwealth of Independent States, and many parts of Asia. The largest estimated populations of PWID are in Russia, China, and the United States (US). Notably, Ukraine, Vietnam and Indonesia have estimated HIV prevalence among PWID above 30%.[3] The persistently high incidence of HIV infection among PWID in many locations with concentrated epidemics necessitates aggressive efforts to prevent HIV transmission.[3]

HIV epidemics among PWID often result in rapid expansion of the epidemic. In the past decade, injection drug use has been responsible for a significant proportion of new HIV infections in Eastern Europe and East, Southeast, and Central Asia.[1, 2] Serial use and sharing of drug injection equipment, such as needles and syringes, create risks for acquiring and transmitting HIV, as well as viral hepatitis. Furthermore, preparing drugs for injection and collectively using shared drug solutions pose additional risks for HIV transmission.[4]

HPTN 052 clearly demonstrated the potential benefit of ART to prevent sexual HIV transmission within serodiscordant couples in stable relationships,[5] presumably by ART-induced reduction of HIV viral load in genital secretions.[6] HPTN 052 was the first randomized clinical trial to demonstrate that early initiation of ART in HIV-infected individuals reduces risk of sexual transmission of HIV to uninfected partners. This success provides a template for further HIV prevention efforts in other groups at high risk for HIV acquisition, including men who have sex with men and PWID.

The findings of HPTN 052, which excluded active PWID, have not been validated for prevention of parenteral transmission of HIV infection. In ecological and cohort studies, expanded ART to PWID appears to be effective. In Vancouver, expanded access to ART in an epidemic predominantly driven by injection drug use has led to reduced reporting of new HIV cases.[7, 8] However, these data are limited because (i) other interventions were previously introduced, confounding the association with ART, and (ii) new diagnoses were

used as a surrogate for HIV incidence. In a preliminary report of a cohort study in Baltimore, HIV incidence among PWID decreased with an increased frequency of ART use.[9] These studies support the concept of treatment as prevention in PWID, but clearly do not provide sufficient justification for widespread use of ART for prevention in this risk group.

Treatment of PWID, whether for prevention of HIV transmission to others or for the person's own benefit, presents unique challenges. HIV transmission in PWID takes place in the context of risk networks, typically with the involvement of multiple injection partners, varied injection practices, and sexual risk behaviors.[10, 11] ART should be offered to PWID in conjunction with prevention and substance use treatment activities to maximize the potential for ART success.[3] For example, ART effectiveness can be compromised in PWID due to poor adherence, potentially leading to treatment failure and transmission of resistant strains.[12] PWID may also exhibit behavioral risk compensation after initiating ART. Finally, the infectious dose is typically higher during parenteral transmission, as demonstrated by a higher transmission probability.[13] Prior to widespread implementation of treatment as prevention in PWID, the efficacy and potential harms, such as development of resistance secondary to poor ART adherence, must be assessed.

1.2 Rationale

HPTN 074 is a vanguard study designed to assess the feasibility of a proposed randomized clinical trial (RCT) assessing the effectiveness an integrated intervention to provide treatment as prevention to PWID. The intervention addresses the biological, behavioral, and social issues specific to this population. HPTN 074 also addresses the feasibility, barriers, and uptake of an integrated intervention to facilitate treatment as prevention. Designing this feasibility study and the future RCT presents several challenges unique to working with PWID.

Potential low incidence of HIV in PWID: PWID who are provided with risk reduction counseling and access to medication-assisted substance use treatment in HIV prevention trials have experienced very low HIV incidence. In particular, two HPTN trials, HPTN 037 and HPTN 058, were unable to address the impact of interventions on HIV incidence because the incidence in both intervention and control arms was low, less than 1 case/100 person-years in both studies.[14, 15] Thus, a critical question is whether any large RCT of HIV prevention in PWID can be conducted with HIV incidence as an outcome given the observed low incidence in previous studies.

Given the low incidence in HPTN 037 and HPTN 058, new network sites for HPTN 074 were identified (see Section 3.0). These sites were chosen based on demonstration of research capacity, HIV prevalence, and when available, HIV incidence. Given the previous experience with prevention trials among PWID, the first objective of HPTN 074 – to assess the incidence among HIV-uninfected PWID network injection partners – is critical. If incidence is low in HPTN 074, future randomized controlled prevention trials with PWID are unlikely to be successful and alternative designs will be necessary.

To ensure that an adequate estimate of the HIV incidence is obtained, the index participants will be allocated to the intervention and standard of care with an allocation ratio of 1:3 (intervention: standard of care). The larger number of participants randomized to the standard of care arm is intended to improve the precision of the HIV incidence estimate among the HIV-uninfected network injection partners under standard of care conditions. To evaluate the second primary objective, a smaller number of participants are randomized to the intervention arm to evaluate feasibility, barriers and uptake of the integrated intervention.

“Real-world” focus on HIV-infected PWID (Prevention for Positives): Fundamentally, HPTN 074 and the proposed future RCT, and their interventions, are focused on the HIV-infected PWID. In most settings, HIV-infected PWID will present alone for HIV testing or medical care (without an injection or sexual partner). The goal of this study is to develop and subsequently provide an integrated intervention that can be administered to HIV-infected PWID to interrupt future transmission events. The intervention is limited in scope to be feasible and sustainable, given the challenges in clinical settings.

This real-world focus on the HIV-infected PWID is evident in several design features of HPTN 074:

- 1) ART and substance use treatment are provided by existing health care facilities at each site and are not provided or directed by the study. This approach is critical to replicate the challenges faced by PWID in navigating the health care system, a common barrier to receipt of appropriate care.
- 2) Real-time in-country laboratory testing will be performed using locally-available test kits and methods; where necessary, testing will be repeated retrospectively at the HPTN LC using a single method to provide a consistent set of data for key analyses, and to evaluate the quality of locally-obtained test results.
- 3) The intervention is designed to be flexible to meet the needs of individual PWID. A principal focus is on facilitating entry into and retention in the HIV care and substance use treatment systems. At recruitment, PWID are likely to be at different stages of readiness for engagement in HIV care and substance use treatment. The PWID are also likely to face different types of problems with engagement and adherence. Thus, the flexibility of the intervention allows tailoring of the intensity of the intervention for different PWID. Identification of the key elements of the integrated intervention that will be feasible, effective, and scalable at the programmatic level is a critical goal of this study, and the future RCT.
- 4) The ultimate goal of this approach is to prevent transmission from HIV-infected PWID to their injection partners. Persons with higher viral loads are at increased risk for transmission. The eligibility criterion that index participants must have an HIV viral load $\geq 1,000$ copies/mL is designed to include persons with higher transmission potential. Recruitment of ART-naïve, HIV-infected participants is given emphasis to reflect the potential implementation of this approach with diagnosis and/or initial engagement in care.
- 5) HIV-uninfected network injection partners are enrolled specifically for the purpose of measuring transmission events (i.e., HIV incidence). The HIV-uninfected network

injection partners in both arms receive standard of care risk reduction counseling and referral for substance use treatment.

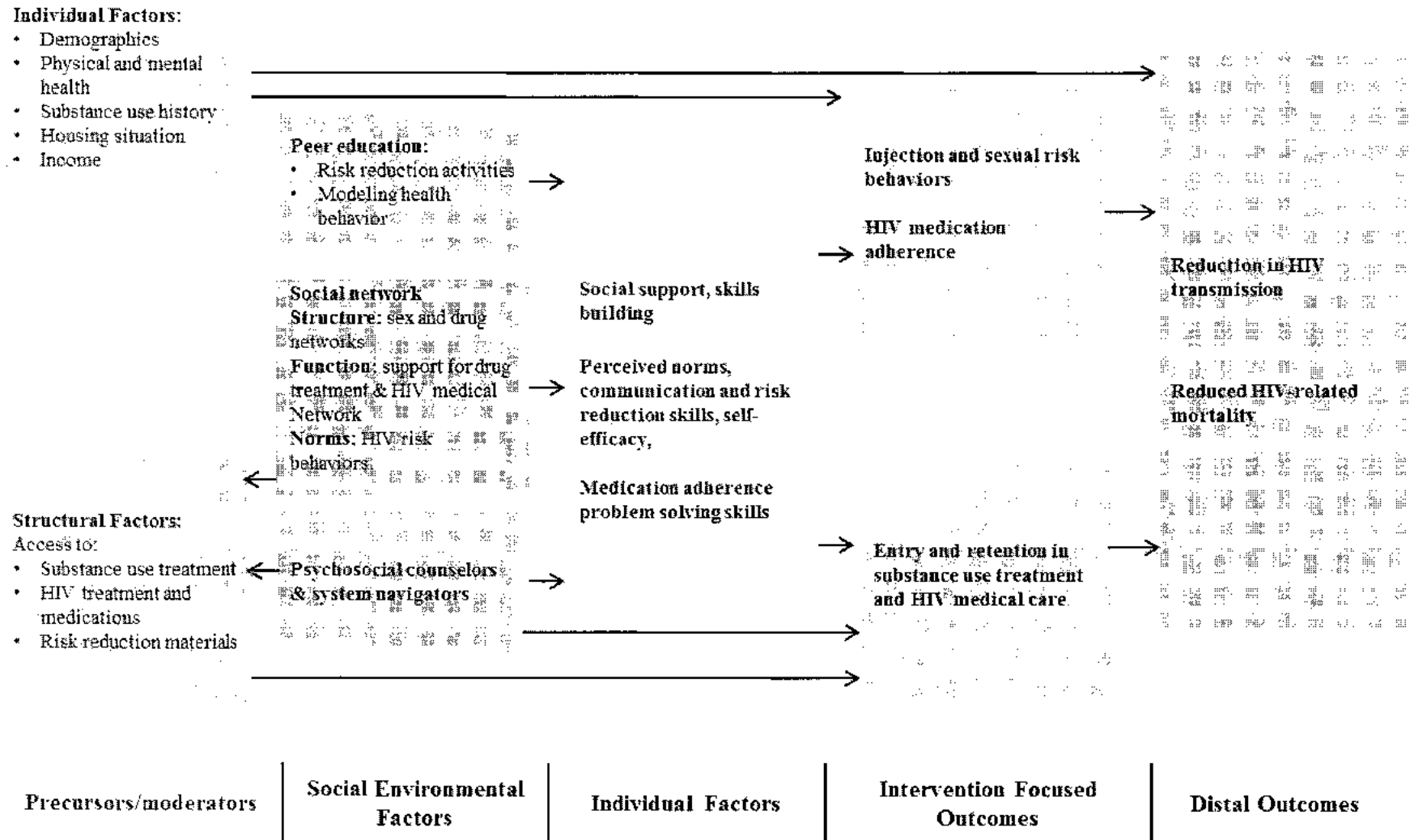
- 6) HIV-infected network injection partners are not enrolled. The study team considered enrolling all members of a network unit and providing the study interventions to all members of the component. However, in many settings, PWID are unlikely to be asked formally to recruit other network members to receive an intervention together, but instead, will face the challenges of engaging in care alone or with a support person.

Integrated intervention: The integrated intervention focuses on engaging HIV-infected PWID in HIV care and substance use treatment. The intervention is based on the following premises:

- 1) Achieving sustained virologic suppression will be an effective means to reduce HIV transmission from HIV-infected PWID to their injection partners;
- 2) PWID experience unique barriers to engaging and remaining in HIV care, preventing many PWID from receiving and remaining adherent to ART;
- 3) Overcoming these barriers requires a flexible intervention that addresses the specific needs of the PWID to engage in HIV care and substance use treatment, initiate and adhere to ART, and sustain these behaviors for the long-term.

The components of the integrated intervention are adapted from interventions that have been successful in facilitating engagement in health care. The components are intentionally limited in scope to ensure that implementation at scale would be feasible and sustainable. The theoretical basis for the non-biomedical intervention components are described in Section 1.4.

Figure 1: Conceptual Framework



1.3 Theoretical Basis for Intervention

This HIV prevention intervention integrates *systems navigation* to overcome structural barriers to engagement in care with *psychosocial counseling* to provide the support and skills necessary to initiate and sustain HIV care and substance use treatment.

The proposed integrated intervention is based on maintenance theory, social cognitive and diffusion of innovation meta-theories of behavior change, as well as theories of cognitive dissonance, role theory, social norms, and social identity that overlap and expand on those meta-theories.[16-21] According to maintenance theory, decisions regarding behavioral initiation are dependent on favorable expectations regarding future outcomes, whereas decisions regarding behavioral maintenance are predicted to depend on perceived satisfaction with received outcomes.[16] Social identity theory suggests that common experiences and knowledge frameworks are more likely in relationships in which individuals are invested and have mutual trust which facilitates interpersonal communication, knowledge transfer, and shared understanding.[19]

Our multidimensional framework (Figure 1) highlights the role of psychosocial, social networks, and structural processes on behavior change and maintenance. Recent recommendations for improving entry into care, retention, and ART adherence include “multidisciplinary education and counseling intervention approaches”, “one-on-one adherence support to patients through one or more adherence counseling approaches”, and “brief, strengths-based case management for individuals with a new HIV diagnosis”. The recommendations also include the potential use of paraprofessional patient navigators.[22]

The intervention in HPTN 074 integrates systems navigation and counseling to facilitate entry into HIV care and substance use treatment, initiation of ART, and sustain adherence to ART and substance use treatment. Systems navigation is relatively low intensity, short term case management, designed to be feasible and sustainable. The systems navigator approach is based on the literature of best evidence in case management, including the Antiretroviral Treatment and Access to Services (ARTAS) study and recent work in Russia.[23-27] System navigators identify barriers to treatment that reside outside the individual or are a function of an interaction between the individual and the health care system. For example, lack of familiarity with a health care organization and how to enroll in HIV medical care may be due to both system and individual factors. A systems navigator will help to identify these barriers as well as overcome the barriers. Case management services are now common in HIV medical care programs.[23] These approaches are based on findings that system and structural barriers to HIV care and substance use treatment are major impediments for entering and staying in medical care. As barriers to entry and retention in HIV care and substance use treatment are diverse and often context specific, a systems navigator approach provides sufficient flexibility to help people address the myriad of systems and structural barriers to health care.[23, 28, 29]

The systems navigation approach will be integrated with psychosocial counseling focusing on entry into HIV care and substance use treatment and adherence to ART. The counseling sessions to increase entry into HIV care and drug treatment will be based on brief

motivational interviewing techniques [30-37]; Screening, Brief Intervention, and Referral to Treatment (SBIRT) approaches; and Cognitive Behavioral Therapy (CBT) exercises for retention into drug treatment developed in HPTN 058. The HIV medication adherence intervention is based on the Managed Problem Solving (MAPS) intervention [38]. For index participants who choose to engage their medical care and adherence supporters in the counseling sessions, these optional dyad sessions will be based on the Sharing Medical Adherence Responsibilities Together (SMART) couples study, which included two dyad sessions [39], and Project Helping Enhance Adherence to Antiretroviral Therapy (HEART) [40]. Index participants in the intervention arm will be encouraged to recruit a support person to maintain engagement in care and adherence long-term. The positive role of social support on HIV medication adherence and substance use treatment outcomes is well documented.[41-43] The emotional social support promotes entry and retention into substance use treatment and HIV medical care as well as supports HIV medication adherence.[44] In HPTN 074, it is anticipated that supportive others can cue the behavior of taking medications, provide verbal reminders, reward timely and consistent taking of HIV medication as well as buffer stress which may lead to depression, as depression has been demonstrated to have a potentially negative effect on HIV medication adherence.[45, 46] In the field of substance use treatment, it is also well established that supportive behaviors by supporters that promote and reward non drug activities and encourage abstinence are linked to successful substance use treatment outcomes.[47]

A wide range of methods of psychosocial counseling have been found to be effective in substance use treatment programs. Generally, no one approach to psychosocial counseling has been clearly demonstrated to be superior to other approaches. It is likely that there are overlapping techniques in different psychosocial counseling programs. Many psychosocial counseling programs include techniques of goal setting, avoiding cue to use, reducing and coping with stress, developing activities that are alternatives to substance use, as well as increasing motivation for cessation of substance use. These techniques for behavior change have also been successfully applied to numerous behaviors including medication adherence.[48] In the proposed study the team will integrate motivational interviewing with brief intervention and cognitive behavioral counseling techniques.

2.0 STUDY OBJECTIVES AND DESIGN

2.1 Primary Objectives

The primary objectives of this study are:

- To assess the feasibility of a future randomized controlled trial by:
 - a) estimating the HIV incidence among network injection partners of index participants in the standard of care arm in three distinct global settings with epidemics driven predominantly by injection drug use;
 - b) evaluating enrollment and retention of HIV-infected PWID and their HIV-uninfected network injection partners over a period of 12-36 months for index participants and 12-24 months for partners.

c) assess the durability of ART uptake and viral suppression in the intervention arm

- To assess the feasibility, barriers, and uptake of an integrated intervention for prevention of HIV transmission among HIV-infected index participants.

2.2 Secondary Objectives

The secondary objectives of this study are to:

- To estimate HIV incidence among network injection partners of index participants in the intervention arm.
- To explore the effect of the integrated intervention, as compared to standard of care, on engagement in HIV care, initiation of ART, retention on ART, ART adherence, and virologic suppression among ART-eligible index participants (index participants meeting national guidelines in the standard of care arm; all index participants in the intervention arm).). If an effect is observed on ART uptake or HIV viral suppression in the intervention arm vs. standard of care arm, participants in the standard of care arm will be offered the intervention for the remainder of the study.
- To assess the uptake and retention on ART over the short term (additional 12 months of follow-up) in the standard of care arm.
- To explore the effect of the integrated intervention, as compared to standard of care, on the proportion of index participants and network injection partners engaged and retained in substance use treatment.
- To estimate the size and stability of the injection network of the index participants and how this affects recruitment and retention of network injection partners.
- To assess the social harms and benefits of research participation for PWID.
- If feasible and if funding is identified, to use phylogenetic methods to characterize transmission dynamics in the study cohort.
- To perform secondary laboratory assessments that may include evaluation of factors related to HIV infection; antiretroviral (ARV) drug use; substances of abuse; methadone and other treatments for substance abuse; cross-sectional HIV incidence estimation; characterization of HIV in infected participants, including phylogenetics and linkage; evaluation of the host response to HIV infection; and evaluation of laboratory assays related to study objectives.

2.3 Study Design

This vanguard study is designed to assess the feasibility of a future trial by estimating HIV incidence among HIV-uninfected network injection partners of HIV-infected PWID (index participants), and evaluating enrollment and retention of HIV-infected PWID and their HIV-uninfected network injection partners. The study is also designed to assess the feasibility, barriers and uptake of an integrated intervention to prevent HIV transmission

by HIV-infected PWID. The study will also collect data on the success of both standard of care and supported ART at any CD4 cell count in engagement in HIV care; ART treatment; adherence to ART; retention on ART; incidence of treatment failure; and engagement and retention in substance use treatment for both index participants and their HIV-uninfected network injection partners.

This is a multi-site, two-arm, randomized feasibility study. Network units of an HIV-infected participant (index) and his/her HIV-uninfected network injection partner(s) will be randomized to the intervention or standard of care arms in a 1:3 ratio.

Table 1. Estimated Sample Size							
	All Sites				Individual Sites		
	Total, All sites	Intervention	Standard Care		Total, Per Site	Intervention	Standard Care
HIV-infected Index Participants	500	125	375		167	42	125
HIV- uninfected Network Injection Partners	~750	~188	~563		~250	~62	~188
Late-entry HIV- uninfected Network Injection Partners (replacements)	~ 75	--	--		~ 25	--	--

The team has chosen an allocation ratio of 1:3 to improve precision of the estimate of HIV incidence in the standard of care arms. This information will inform sample size determination for a future RCT, while simultaneously assessing the feasibility and logistical challenges of implementing the intervention package for the larger trial.

3.0 STUDY SETTING AND POPULATION

This vanguard study will be conducted in three geographically-diverse sites. The sites will be determined based on several key parameters reflecting the status of the HIV epidemic in PWID at the site, site capabilities, and potential capacity to conduct a future, network-level RCT (e.g., laboratory, data, and clinical infrastructure; leadership; expertise). Specific criteria for site selection include: (1) proportion of HIV-infected population using injection drugs ($\geq 30\%$); (2) expected annual HIV incidence ($> 3\%$) or HIV prevalence ($\geq 25\%$) among PWID; (3) evidence of injection-sharing behavior among PWID; (4) access to ART, including agreement to provide ART for use during and after the study should a positive effect be observed (antiretroviral drugs will not be supplied by the study); (5) ability to enroll 167 HIV-infected PWID within 15 months; (6) access to evidence-based substance use treatment; and (7) previous or existing NIDA funded research.

Site selection was based on leadership, staffing, country import (e.g., for External Quality Assurance [EQA] samples) and export regulations (e.g., for study specimens), experience with network recruitment, and participant retention. Prior to initiation of the study, each study site will develop the necessary infrastructure to implement the study including personnel, clinical infrastructure (including the ART initiation and maintenance system), laboratory capacity, and data management capacity.

Three sites have been identified through the HPTN site selection process. These sites are research centers in Jakarta, Indonesia; Thai Nguyen, Vietnam; and Kiev, Ukraine.

The availability of substance use treatment for each proposed research center is outlined in Table 2 below as well as registration requirements for PWID.

Table 2. Availability of substance use treatment and registration requirements for the most suitable sites	
Ukraine	Detoxification with symptomatic treatment followed by: <ul style="list-style-type: none"> • Methadone - zero cost to those willing and registered as PWID • Buprenorphine - zero cost to those willing and registered as PWID however, extremely limited amounts of buprenorphine are available (very limited slots for treatment) • Registration is required for PWID
Indonesia	Detoxification when necessary with symptomatic treatment followed by: <ul style="list-style-type: none"> • Methadone - zero cost to those willing and registered as PWID • Buprenorphine, which is paid for by the patient • No registration is required for PWID
Vietnam	Detoxification with symptomatic treatment followed by: <ul style="list-style-type: none"> • Methadone - free to those willing and registered as PWID • Registration is required for PWID

Index participants will be HIV-infected PWID (men and women who report injecting drugs at least 12 times the past three months and six times in the past month and report sharing needles, syringes or drug solutions) who have an HIV viral load $\geq 1,000$ copies/mL at Screening. This may include individuals who report that they are: (a) ART-naïve, (b) ART-exposed but currently off therapy, or (c) on ART. The index participants may be recruited using a variety of methods, including referral from HIV-testing sites, community outreach, and personal referrals. Five hundred index participants (167 per site) will be enrolled. The goal for each site is to enroll at least half ART-naïve index participants. A screening ratio of more than 4:1 will likely be needed to consent and enroll 167 HIV-infected index participants at each site.

Each index participant will recruit one to five HIV-uninfected network injection partners using referral identification cards; at least one partner must be enrolled before the index and his/her partner(s) are randomized to the intervention or standard of care arm. The first network injection partner enrollment must occur within 60 days after the screening blood draw for the index participant. If the first injection network partner is not enrolled within 60 days after the index participant's screening blood draw, both the index participant and partner will be asked to return for another Screening visit. However, it will not be necessary to repeat HIV testing repeat for any participant whose HIV positive infection status was previously confirmed using two separate samples collected on different days.

Referred network injection partners who have one or more reactive/positive HIV test(s) at study entry (Screening and/or Enrollment) will not be eligible for enrollment as network injection partners. However, with appropriate consent, these individuals may screen as potential index participants if the initial referring index does not enroll.

At Screening, all partners will be asked to complete a brief behavioral risk and HIV care questionnaire and provide a blood sample for storage. If the partner has one or more reactive/positive HIV tests and is therefore ineligible to be a partner, and if the participant agreed to specimen storage, then the stored specimen will be saved for possible use in phylogenetic analyses. Ineligible partners who do not screen as potential index participants will be referred to local care centers for confirmation of HIV diagnosis (if the diagnosis is not established during the Screening and/or Enrollment visits), as well as HIV care (if HIV-infected) and substance use treatment; referrals to HIV care and substance use treatment will be made in the same manner as the standard of care group, as described in site-specific SOPs.

Index participants will be asked to identify members of their risk networks - individuals with whom they engage in HIV-risk related injection activities, interact with at least once a week, and have known for at least one month. The index participants will be asked to prioritize recruitment of the network injection partners with whom they have the most HIV-risk-related exposures, as assessed by sharing needles, syringes, or injection solution. Index cases will receive compensation (amount to be determined locally) for successful enrollment of network injection partners. The team will evaluate each partner referral to minimize the probability that a referral is being made for economic benefit only without actual injection exposure to the index case.

The network injection partner cohort will be dynamic to accommodate the duration of relationships within injection partnerships, recognizing that the partnerships of an index participant may change over time. Network injection partners will begin contributing person-time at the time of their enrollment. Person-time contribution will discontinue at the HIV test of a confirmed HIV seroconversion or at the HIV test following the reported discontinuation of the partnership. When a network injection partnership ends, the partner will continue to be followed, as it is likely that the injection relationship may continue at a later point in time. As the network injection partnership ends, person-time contribution will end at the HIV test visit following the reported end of the partnership. If the partnership is renewed, person-time contribution will start again at the visit following the reported renewal of the partnership. In these cases, the index participant will be asked to recruit a new partner to replace the ending partnership, if an alternative partner is available and willing to enroll. In addition, the index participant may recruit a *new* partner during the course of the study if the index participant develops a new relationship and has fewer than five partners enrolled in the study. If a new partner is enrolled, he/she will begin contributing person-time at the time of his/her enrollment and will discontinue contributing person-time at the visit following the reported end of the partnership. Follow-up of all partners will end when the corresponding index participant completes his/her last study visit.

3.1 Inclusion Criteria

Men and women who meet all of the following criteria are eligible for inclusion in this study as **index participants**:

- Age 18-60 years at the Screening visit (age verification procedures will be defined in the Study Specific Procedures [SSP] Manual)
- Able to provide informed consent
- Active injection drug user, defined as self-report of: a) injecting drugs at least 12 times in the past three months and at least 6 times in the past month; and b) a PWID in the opinion of site staff
- Reports sharing needles/syringes or drug solutions at least once in the last month
- HIV-infected based on a study-defined testing algorithm (defined in the SSP Manual)
- Viral load $\geq 1,000$ copies/mL at Screening
- CD4 > 50 cells/mm³ at Screening
- Willing and able to identify, recruit, and have enrolled at least one HIV-uninfected network injection partner who is eligible for study participation according to the criteria below
- Have no plans to move outside the study area for at least one year after study enrollment
- Willing to participate in intervention activities, including regular phone contact

Men and women who meet all of the following criteria are eligible for inclusion in this study as **HIV-uninfected network injection partner**:

- Age 18-60 years at the Screening visit (age verification procedures will be defined in the SSP Manual)
- Able to provide informed consent
- Active injection drug user, defined as: a) self-report of injecting drugs at least 12 times in the past three months and at least 6 times in the past month; and b) PWID in the opinion of site staff
- Confirmed injection partner, using referral identification cards, or other means of identification from the index participant
- HIV-uninfected based on the study-defined testing algorithm* (defined in the Study SSP Manual)
- Have no plans to move outside the study area for at least one year after study enrollment

*Individuals will not be eligible for enrollment as a partner if any of the HIV tests performed at Screening or Enrollment is reactive or positive, even if they are subsequently confirmed to be HIV-uninfected.

3.2 Exclusion Criteria

Men or women who meet any of the following criteria will be excluded from this study as an **index participant**:

- Current participation in any HIV prevention study
- Previous or current participation in an HIV vaccine trial
- Appearance of psychological disturbance or cognitive impairment that would limit the ability to understand study procedures, as determined by the investigators
- Any other condition that, in the opinion of the investigators, would make participation in the study unsafe, or otherwise interfere with the study activities
- Prior screening as a potential network member of a enrolled index participant in this study (NOTE: Screened partners who fail screening because they have one or more reactive/positive HIV test(s) may screen as an Index participant only if the original referring Index participant does not enroll).
- Currently or previously a partner of an index participant

Men or women who meet any of the following criteria will be excluded from this study as **network injection partner**:

- Current participation in any HIV prevention study
- Previous or current participation in an HIV vaccine trial
- Any reactive or positive HIV test at Screening or Enrollment, even if the individual is confirmed to be HIV-uninfected
- Appearance of psychological disturbance or cognitive impairment or any other condition that in the opinion of the investigator would limit the ability to understand study procedures, would make participation in the study unsafe, or otherwise interfere with the study activities
- Previously named and enrolled as a partner of another index participant

3.3 Recruitment process for index participants

Approximately 167 index participants will be recruited at each study site (N=500 minimum across all sites). This may include individuals who report that they are: (a) ART-naïve, (b) ART-exposed but currently off therapy, or (c) on ART; it is expected about half of the index participants will be ART-naïve. Participants who fail screening may re-screen only once. HIV testing will not be necessary during a re-screening visit for

participants previously confirmed as HIV infected using two separate samples collected on different days.

Screening of index participants will take place for approximately 15 months. A variety of methods will be used for recruitment, including referral from HIV-testing sites, community outreach, identification of substance treatment program failures, and injection network referrals. Sites will be able to use their previously established systems for recruiting participants. Trained outreach workers will identify geographic areas, HIV testing sites, or other settings and organizations that are frequented by PWID. Outreach workers will disseminate information about the study, will provide oral and written descriptions of the studies to prospective participants, and will encourage index participants to participate in screening activities at a local study site. Potential Index participants will also be informed that they should pass the information on to other individuals if the study does not apply to them.

Outreach workers will be trained to not pre-select individuals who fit their description of “drug users”; instead, they will provide information to a range of individuals and encourage those individuals to pass information about the study to others in the community. Outreach workers will be selected from the community and must be knowledgeable about the community’s dynamics and trained on basic methods of rapid assessment procedures in order to target areas of high drug use. They will also be trained, as part of the study, in methods of approaching and communicating with potential participants, personal safety, and confidentiality.

Potential index participants who present at the study site will be offered HIV counseling and testing and receive a brief introduction to the study. Those who are interested in participating will be asked to provide informed consent for Screening. A sample of the consent forms can be found in Appendix IV. After providing informed consent for screening, volunteers will undergo an eligibility screening survey. If at any time during screening, they are found to be ineligible, screening will be discontinued; however, HIV counseling and testing will be offered to all persons who present for screening. Participants who meet initial study screening eligibility criteria will undergo pre- and post-test counseling. HIV-infected individuals who have an HIV viral load $\geq 1,000$ copies/mL and are otherwise eligible for enrollment will be asked to provide study consent. These individuals may report that they are: (a) ART-naïve, (b) ART-exposed but currently off therapy, or (c) on ART. Participants who are found to be eligible will be asked to provide informed consent for enrollment.

Index participants who are confirmed to be HIV-infected will not be randomized to a study arm until their first HIV-uninfected network injection partner is enrolled. The effective point of enrollment is randomization of the index participant. After confirmation of eligibility of their first HIV-uninfected network injection partner, the index participant will return to the study site for randomization and will initiate study activities, as appropriate. Study site staff members are responsible for developing and implementing local SOPs to help ensure index participants return for randomization. These procedures will be similar to the participant retention procedures (as described in Section 3.6).

The index participant will be informed that his/her HIV status will be disclosed to network injection partners who are referred for study screening. The index participant will be counseled at the time of consent to disclose his/her HIV status prior to referring the partner for the study. Brief counseling by study staff will be provided to support this disclosure. If the index participant prefers, he/she may opt to bring the partner to the study site for screening and undergo a joint disclosure session with the study staff. Care will be taken to prevent inadvertent HIV disclosure in individual networks. Finally, the index participant may opt not to have his/her HIV status directly disclosed to the injection partner. In this case, the network injection partner will be able to deduce the HIV status of the index through the screening consent process. The informed consent of the index will clearly address the need for disclosure and the options for disclosure.

3.4 Identification of network injection partners

After confirmation of HIV status, HIV-infected index participants will be asked to identify members of their injection network with whom they engage in HIV-risk related activities. Index participants will be asked to prioritize recruitment of the partners with whom they have the most HIV-related injection exposures; network injection partners must have injected with the index partner in the past month. Sexual partners will not be recruited unless he/she is an active injection partner. Up to five concurrent HIV-uninfected network injection partners per index participant, designated as network injection partners, may be enrolled in the study. If partners withdraw from the study, additional replacement partners may be added. Whether an enrolled partner continues to be an injection partner of the index may change over time, and will be recorded longitudinally throughout the study. Index participants will be provided with referral identification cards marked with their study identification number to facilitate the recruitment of their network members. There will be no identifying information on the cards to indicate participation in an HIV or substance use study. Eligible index participants will be asked to give the cards to injection drug use partners and will encourage the partner(s) to bring the cards to the local study site to serve as their identification for participation in screening. Index participants will receive compensation for successful enrollment of partners. Partners also will be compensated for their time and participation. The amount and form of compensation will vary by site. Each site/country will be encouraged to include fair and ethical compensation in their site specific Informed Consent Forms which will be reviewed and approved at the local level. Sites will review partner referrals for validity to ensure that partner referrals are not based solely for economic benefit. HIV disclosure by index participants to partners will be recommended and facilitated.

For HIV-uninfected injection partners to participate in the screening process, they must either present at a local study site with a card bearing their index participant's identification (ID) number, or match the description provided by the index during his or her screening survey according to site-specific procedures. Such partners will then be asked to provide study informed consent for enrollment. Individuals who provide study consent will complete social network interview, the baseline sexual and drug behavior

data collection, and will participate in HIV risk reduction counseling and testing. Injection partners who are confirmed to be HIV-infected at Screening will not be enrolled as network injection partners. Once an HIV-uninfected injection partner is enrolled in the study as a network injection partner, he/she will be unable to enroll as an index participant (i.e., if he/she acquires HIV infection during the study), or in as other index participant's network injection partner (each network injection partner will be associated with a single index participant throughout the study). The frequency with which HIV-uninfected partners are referred by more than one index participant will be documented and assessed as part of the network structure.

The network injection partner cohort will be dynamic, to accommodate the variable duration of relationships within risk networks. The partnerships of an index participant may change over time. If an index participant has fewer than five partners enrolled in the study, the index participant may recruit new HIV-uninfected partners at any time prior to the penultimate study visit (last routine study visit prior to the termination visit). If a network injection partnership ends, the index participant will be asked to recruit a new injection partner to replace the ending partnership, if an additional partner is available and willing. An index participant will be actively encouraged to recruit another HIV-uninfected partner to the study if he/she has zero or one active partners in the study. Although the number of replacement partners is not limited, the team expects each site may enroll approximately 25 replacement partners. Index participants who have no partners on follow up will not be terminated. New partners cannot be recruited after the index's penultimate or termination visits. Additionally, if an index participant terminates participation in the study after randomization, network injection partners will also terminate early. Partners will terminate follow-up at the next scheduled visit after their index participant's termination visit.

All partners will begin contributing person-time at the time of their enrollment and will discontinue contributing person-time at the HIV test following the reported discontinuation of the partnership or confirmed HIV seroconversion. However, in the case of reported discontinuation of the partnership the network injection partner will continue to be followed, as it is likely that the injection relationship may continue at a later point in time. If the partnership is renewed, person-time contribution will start again at the visit following the reported renewal of the partnership. Template tracking systems of index participants and network injection partners will be developed in collaboration with the sites and will be described in the SSP Manual and in site specific SOPs.

3.5 Co-Enrollment Guidelines

Participants should not be currently participating in any HIV prevention study and may not enroll in any HIV prevention trial during this study; these guidelines are needed to reduce participant burden with study visits, to facilitate high levels of retention, and to avoid confounding in the interpretation of the primary and secondary endpoint data. Also, participants may not enroll if they have been or are currently enrolled in an HIV vaccine trial, since vaccination could complicate interpretation of HIV test results.

3.6 Participant Retention

Once an index participant enrolls in this study, the study site will make every effort to retain him/her for 12-24 months (plus a potential additional 12 months for willing and re-consenting index participants) of follow-up to minimize possible bias associated with loss-to-follow-up. The sites will also make every effort to retain network injection partners through the exit interview of the index participant. Study site staff members are responsible for developing and implementing site-specific procedures and local SOPs to reach this goal. A basic philosophy of the retention strategy is that follow-up begins at recruitment and is a priority at every visit. Components of such procedures include:

- Thorough explanation of the study visit schedule and procedural requirements during the informed consent process, with re-emphasis at each study visit.
- Thorough explanation of the importance of both study arms (intervention and standard of care) to the overall success of the study.
- Collection of detailed locator information at the Screening visit, with active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other venues that participants frequent. This information will be used only for participant retention. No study procedures will be conducted at participants' homes.
- Use of appropriate and timely visit reminder mechanisms.
- Visit calendars, flyers or other handouts will be offered at enrollment to assist with retention.
- Immediate and multifaceted follow-up on missed visits, including outreach/locator efforts such as phone calls, text messages, or home contacts. (The timing and number of contacts will be outlined in site-specific procedures.)
- Mobilization of trained outreach workers or "tracers" to complete in-person contact with participants at their homes and/or other community locations.
- Regular review of follow-up procedures and current status by site leadership and staff.
- Regular communication with the study community at large to build trust and increase awareness about substance use treatment and HIV/AIDS.

3.7 Participant Withdrawal

Regardless of the participant retention methods just described, participants may voluntarily withdraw from the study for any reason at any time. The investigators also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, DAIDS Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and LOC Protocol Specialist. Participant non-adherence to the intervention is not a reason for participant withdrawal from the study.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site institutional review boards (IRBs) or ethics committees (ECs) terminate the study prior to its planned end date.

Participants will not be considered withdrawn unless the participant actively withdraws or dies, or the investigators withdraw the participant for the reasons given above.

Every reasonable effort will be made to complete a final evaluation (as described in Sections 5.4.3.3 and 5.5.3.3) of participants who terminate from the study early, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

4.0 STUDY INTERVENTION PACKAGE

All participants in both intervention and standard of care arms will receive a comprehensive set of integrated harm reduction services intended to reduce HIV incidence through effective behavioral, biological and social interventions. The basic package, provided to all participants (intervention, standard of care, index, network injection partner), is described below.

Table 3. Summary of intervention and standard packages of services by study arm				
	HIV-infected index		HIV-uninfected network injection partner	
	Control	Intervention	Control	Intervention
Harm reduction services				
Referral for treatment of substance use / addiction	X	X	X	X
Referral to needle and syringe exchange programs, if legal and available	X	X	X	X
Injection risk reduction counseling	X	X	X	X
Sexual risk reduction counseling including access to condoms	X	X	X	X
HIV counseling and testing	X	X	X	X
Referral for ART according to national guidelines	X	X		
Referral for diagnosis and treatment of sexually transmitted infections (STIs), hepatitis B and C virus (HBV, HCV), and tuberculosis (TB) as appropriate	X	X	X	X
Systems Navigator		X		
Psychosocial Counseling and Social Network support		X		X ^a
ART at any CD4 count		X		

*Psychosocial counseling and social network support for HIV uninfected partners of intervention arm index participants may be available at the request of the index participant.

4.1 Standard package of services (standard care arm)

All index participants will receive, as a minimum, the in-country standard of care, based on current national guidelines for PWID that are largely based on the WHO comprehensive package of care for PWID.[49, 50] This standard of care typically includes:

- Harm reduction services
 - Referral for treatment of substance use / addiction
 - Referral to needle and syringe exchange programs, if legal and available
 - Injection risk reduction counseling
 - Sexual risk reduction counseling including access to condoms
- HIV counseling and testing
- Referral for ART according to national guidelines
- Referral for diagnosis and treatment of sexually transmitted infections (STIs), hepatitis B and C virus (HBV, HCV), and tuberculosis (TB) as appropriate

All index participants in the standard of care arm will receive a standardized counseling session that will include referral to programs for needle and syringe exchange (where available), referral for medication assisted substance use treatment and/or detoxification (where available), risk reduction counseling for injection drug use, sexual risk reduction counseling, and referral for STI, hepatitis, and TB diagnosis and treatment. All participants eligible for ART according to the national guidelines will be referred to local centers for ART initiation.

Standard care network injection partners: Network injection partners in the standard of care arm will receive the applicable national guidelines, as described above, with exception of referral for ART. Based on site information, pre-exposure prophylaxis is not currently available and is not expected to become available in any of the sites under consideration.

4.2 Intervention package of services (intervention arm)

The integrated intervention draws upon multiple successful psychosocial and structural interventions with PWID. The focus of the intervention is the index participants.[51-53] The intervention includes the following components: a) **systems navigators** to facilitate engagement, retention, and adherence in substance use treatment and HIV care; b) **psychosocial counseling** using motivational interviewing, problem solving, skills building, and goal setting to facilitate substance use treatment and HIV care and medication adherence; optional sessions involving supporters will be offered; and c) **ART at any CD4 count**. The intervention is rooted in cognitive-behavioral theory, motivational interviewing, and diffusion of behavioral change.[16, 17] This intervention is designed to be flexible and appropriate across a range of cultures. The program will be adapted to individual contexts and cultures, while remaining comparable across sites and cultures.

Prior to study implementation, a limited number of in-depth interviews will be conducted in a subset of the study sites to explore barriers and facilitators for uptake of substance use treatment, HIV care, ART use, and adherence. Interviews will be conducted with PWID, support persons, and health care providers. These interviews will be used to refine the intervention manual and inform the final questionnaires.

Intervention arm network injection partners: Network injection partners in the intervention arm will receive the applicable national guidelines, as described above, with exception of referral for ART. Partners will not have access to the systems navigators or psychosocial counseling provided to index participants except at the request of the index participant as noted in Section 5.

4.2.1 Systems navigators

Each index participant in the intervention arm will be assigned a systems navigator who will work with the index participant to identify the primary obstacles to engaging in both substance use treatment and HIV care. A systems navigator is defined as a staff member who is knowledgeable about local HIV care and substance use treatment services and possesses the skills to facilitate initiation and retention in care. Systems navigators may also serve as counselors at the discretion of the sites. Systems navigators will emphasize entry into substance use treatment, HIV care, ART initiation, retention in care, and ART adherence. During contact with the index, the systems navigator will assess the progress of the index through each stage of engagement in HIV care and substance use treatment using a standardized checklist. Barriers to progress will be identified and the systems navigator and index will formulate specific plans to overcome those barriers. Such plans may include, for example, facilitation of appointments by the systems navigator, assistance recruiting support persons, or identification of the need for additional counseling sessions.

The systems navigator and index participant will have two initial sessions held in conjunction with psychosocial counseling sessions (section 4.2.2). Subsequently, contacts will be made in person, or with telephone calls or text messages to maintain regular contact with the index participants. Home contacts will be used as a last resort if repeated calls and text messages are unsuccessful. The systems navigator will communicate weekly for the first eight weeks, then monthly for the duration of the study. Additional contact may be made to remind participants of scheduled appointments. Contact frequency may be increased during any crisis period, such as resuming active drug use after initial discontinuation, withdrawal from HIV care, discontinuation of ART, or withdrawal from substance use treatment.

4.2.2 Psychosocial counseling

Index participants in the intervention arm will receive a minimum of two psychosocial counseling sessions. The counselor will use a standardized inventory to assess the participants' need for counseling on risk reduction, drug treatment entry and retention, HIV medical care, and medication adherence. Based on this assessment, additional optional individual sessions will be conducted. Common circumstances where additional sessions would be added would be supplemental adherence counseling, failure to engage in care, withdrawal from substance use treatment, or if the index participant has a specific request.

To enhance ART adherence and adherence to drugs used for substance use treatment, index participants in the intervention arm will be asked to identify adherence supporters, persons identified by the index participants within their broader social network to provide support for ART and substance use treatment adherence. The supporter may be any person close to the index participant, such as a parent, sibling, or friend, whom the index participant trusts to take an active role in encouraging adherence to ART. The psychosocial counselor and/or systems navigator will facilitate the identification of an appropriate person. The index participant and the supporter may participate in up to two optional counseling sessions together to practice adherence communication skills, enhance the HIV literacy of their supporters, and the development of a medication adherence plan. If the supporter is also a sexual or injection partner the counseling session will also address risk reduction. If an index participant is unable to identify a support person, he/she remains eligible to participate in all other components of the study intervention.

Prior to facilitating entry into substance use treatment and HIV care, the systems navigator and counselor will identify level of interest in substance use treatment. For participants who are ambivalent about entering substance use treatment, the counselors will use motivational interview techniques to enhance interest in enrolling in substance use treatment programs.[54] For those participants who are interested in substance use treatment, the counselor will identify barriers to substance use treatment entry and retention. This same approach will be used for individuals who are ambivalent about entering HIV care. Using motivational interviewing, problem solving, skills building, and goal setting, the counselors will work with the index participants to overcome barriers to enrollment and retention in substance use and HIV treatment, adherence, and risk reduction.[53, 55] Once the participants are prescribed ART, based on a problem solving and goal setting approach, the counselors will work with them on issues of medication adherence, including addressing side effects, developing a routine for taking medications, developing a plan to obtain medication refills, and for obtaining ART adherence social support from their network.

Participants will be offered the opportunity for two additional booster sessions approximately one month and three months after Enrollment. For individuals

who have low levels of adherence to ART or substance use treatment, additional counseling sessions will be available through self-referral or referral by the systems navigator.

4.2.3 Systems navigator and psychosocial counseling personnel

At the discretion of the study sites, systems navigators and psychosocial counselors may either be the same staff members or two distinct groups (navigators and counselors). The study is designed to be low cost and require minimal staff expertise so that it could be readily disseminated and translated into the community. The staff will have previous experience in harm reduction and working with PWID. The staff must also be familiar with the HIV and substance use treatment systems and will typically have two years of experience for those designated as counselors. Prior to study initiation, each counselor will receive training including role plays, conducting tasks such as addressing participants' interest in substance use treatment, identification of barriers, entry and retention in those programs. This training will address prioritization and suitability of programs for the individual participant, but also the priority of risk reduction for HIV, including needle/syringe exchange, oral versus injectable opiate replacement treatment besides all other common measures such as social stabilization, partner frequency reduction and condom counseling. Systems navigators and counselors will not be used for data collection such as behavioral risk assessments.

4.2.4 Initiation of ART

All index participants in the intervention arm will be referred for ART, regardless of CD4 cell count. The systems navigator will support the initial referral to and engagement in care. This support will be developed and targeted within each country. ART adherence will be a focal point of psychosocial counseling and social network support.

ART will be provided through the local authorities. As part of the site selection process, each potential site was required to obtain an official approval from local authorities stating specifically that ART would be provided to all willing study participants regardless of CD4 count. This would continue as appropriate post study. The participants will be provided with a letter describing participation in the study and stating approval from the appropriate regulatory agencies. Prior to study initiation, ART clinics will be alerted to the study procedures and the authenticity of these letters. The letters will be personalized and appropriately authorized to minimize the potential for forgery.

5.0 STUDY PROCEDURES

An overview of study visits and procedures is presented in Appendices I, II, and III. Additional information on visit-specific study procedures is presented below. Detailed

instructions to guide and standardize study procedures across sites are provided in the SSP Manual.

5.1 Study Intervention Package

As noted in Section 4.0, all participants will receive a comprehensive set of integrated harm reduction services aimed at reducing HIV risk behavior. Index participants in the intervention arm will also be offered systems navigation and psychosocial counseling, as described below. These may be scheduled in conjunction with or separate from the standard biological and behavioral assessment visits described in Sections 5.2 and 5.3. At the discretion of the study sites, systems navigators and psychosocial counselors may either be the same staff members or two distinct groups (navigators and counselors).

5.1.1 Systems Navigation

At enrollment, index participants in the intervention arm will meet with a systems navigator (see Section 4.2.1). The systems navigator will communicate with participants weekly for the first eight weeks, then monthly for the duration of the study. Contact frequency may be increased during any crisis period, such as resuming active drug use after initial discontinuation, withdrawal from HIV care, or withdrawal from substance use treatment. Contacts with study participants will be recorded on an encounter form.

5.1.2 Psychosocial Counseling

Sites will be expected to offer index participants in the intervention arm a minimum of two psychosocial counseling sessions (see Section 4.2.2) during their study participation. Optional additional individual sessions should be offered at the discretion of the counselor based on identified needs. Participants will be offered the opportunity for two additional booster sessions, approximately one month and three months after enrollment. For individuals who report low levels of adherence to ART or substance use treatment, additional counseling sessions will be available. Counselors can also offer a group session with the index participant and their identified support person, at the request of the index participant.

5.2 Behavioral measurements - index participants and network injection partners

5.2.1 Sexual behavior, substance use, substance use treatment and ART experience interviews (for Index Participant only)

At Enrollment, an interview will be conducted for all participants including: substance use history, HIV status, HIV testing history, previous substance use treatment, injection risk behaviors, sexual risk behaviors, and the impact of perceived stigma on engagement in substance use treatment. Additionally, for

index participants, the interview will include previous ART exposure, ART adherence, and perceived stigma on engagement in ART. This interview is anticipated to take about 30 minutes.

At Week 4 and each subsequent quarterly visit, as appropriate (based on timing of partner enrollment), shorter 20-minute interviews will be conducted with all participants to evaluate: (1) injection behaviors since the previous visit, (2) use of non-injectable drugs, including alcohol, (3) enrollment in substance use treatment and the use of methadone, buprenorphine, or naltrexone, (4) adherence to substance use treatment, and (5) injection partner turnover among all injection partners, as described below. Index participants on ART will also be asked about: (6) ART adherence, and (7) side effects of ART. Note that the index participant and network injection partner(s) may have visits on different days.

At study Exit, an approximately 30-minute interview will be conducted to address those items in the quarterly visit interviews, plus additional information regarding perceived stigma on engagement in HIV care (index only) and substance use treatment.

5.2.2 Social Network Interviews

At Enrollment, Week 4 and all quarterly visits, all participants will also be asked about: (1) current injection partners, including terminated and new relationships, and (2) social network measures, including turnover of all injection network members, network density, network support for adherence to ART (index only) and/or substance use treatment, and (3) frequency of injection and sexual risk behaviors with each identified injection network member (including persons enrolled and not enrolled in the study). At all subsequent visits, all participants will be prompted to update any possible changes to their social networks.

5.2.3 Social Impact Assessments

At all study visits after Screening, participants will be asked to report any social harms or benefits experienced due to study participation. Both harms and benefits will be recorded using a short standardized assessment tool based on previous experience with PWID participation in research.

5.2.4 Assessment of barriers and facilitators to ART (Index only) and substance use treatment

At Enrollment, Week 4 and all quarterly visits (including the Exit visit), the barriers and facilitators to the receipt of ART for HIV-infected participants and substance use treatment for all participants will be assessed. This brief assessment will address likely barriers and facilitators derived from previous research and will include an open ended “and other, specify” option for the participant to report any barrier not included in the given responses.

5.3 Laboratory Assessments

5.3.1 Laboratory Assessments for HIV-infected Index Participants

HIV testing will be performed using testing algorithms described in the SSP Manual. These testing algorithms may vary across sites. The HPTN LC will perform extended QA testing for HIV diagnosis using a single testing algorithm. Index participants will only be enrolled if HIV infection is confirmed on site according to the SSP Manual. In all cases, confirmation of HIV infection will be based on results obtained from samples collected at both the Screening and Enrollment visits; these visits must be performed on different dates.

HIV viral load testing will be performed in real time at study sites for all index participants at Screening (after an initial reactive or positive HIV test result is obtained). Viral load testing will be performed retrospectively at the HPTN LC for quality assurance and to obtain additional data for the assessment of adherence to ART.

CD4 cell count testing will be performed for all index participants at Screening (after an initial reactive or positive HIV test result is obtained). CD4 cell count testing will also be performed at Weeks 26, 52, 78, 104, 130 and 156.

Plasma samples will be stored for other assessments at the HPTN LC, as described in Section 9 and Appendix I. This will include retrospective ARV drug testing at the HPTN LC; these data will be analyzed as part of the ART adherence assessment. Results of this testing will not be reported to study sites or participants.

Urine testing for substances of abuse will be performed in real-time at all study visits except the Screening visit, using locally-available test kits. Plasma and urine samples, including dried urine samples, will be stored for retrospective testing for substances of abuse and medications used for substance use treatment. This testing will be performed at the HPTN LC. Results of this testing will not be reported to study sites or participants.

5.3.2 Laboratory Assessments for HIV-uninfected Network Injection Partners

Injection partners of enrolled index participants will be tested for HIV infection at the Screening visit and at the Enrollment visit according to the SSP Manual; if this testing indicates that the individual is HIV uninfected, the individual will be considered for enrollment in the study as a network injection partner. Injection partners who have one or more reactive/positive HIV test(s) at the Screening or Enrollment visits will not be eligible for enrollment as network injection partners, even if they are confirmed to be uninfected.

Enrolled network injection partners will be tested for HIV infection at each study visit using testing algorithms described in the SSP Manual. Note that these algorithms may vary from site to site. The HPTN LC will perform extended QA testing for HIV diagnosis using a single HIV testing algorithm. In all cases, confirmation of HIV seroconversion will be based on results obtained from samples collected on two different dates.

Plasma samples will be stored for testing at the HPTN LC, as described in Section 9 and Appendix II.

Urine testing for substances of abuse will be performed in real-time at all study visits except the Screening visit, using locally-available test kits. Plasma and urine samples, including dried urine samples from a subset of participants, will be stored for retrospective testing for substances of abuse and medications used for substance use treatment. This testing will be performed retrospectively at the HPTN LC. A subset of dried urine samples will be tested. Results of this testing will not be reported to study sites or participants.

5.3.3 Additional Laboratory Assessments for Network Injection Partners Who Acquire HIV During the Study

Some network injection partners may become HIV infected during the study period. These network injection partners will continue to be followed according to their existing schedule of visits, including the collection of behavioral data. Site-specific HIV testing algorithms, including tests required to confirm HIV acquisition, are described in the SSP Manual. All possible HIV seroconversion events will be confirmed retrospectively at the HPTN LC (see Section 9.3.1). HIV testing will not be performed on site at subsequent visits after HIV infection is confirmed (see SSP Manual). CD4 cell count testing will be performed at the HIV confirmatory visit (see Appendix III) and at Weeks 26, 52, 78, and 104 (if HIV infection is confirmed prior to those visits).

5.3.4 Laboratory Assessments for Ineligible HIV-infected Network Injection Partners

Network injection partners who have one or more positive/reactive HIV test results at Screening or Enrollment will not be enrolled as Partners. These individuals will be referred for further HIV confirmatory testing according to national guidelines. These individuals may continue screening as a potential index participant (provided that the original index does not enroll). For these individuals, if they agree, plasma obtained during the initial “Partner” screening process will be stored for possible phylogenetic analysis.

5.4 Visit Procedures for Index Participants

5.4.1 Screening Visit for Index Participants

It is the responsibility of the local site to determine the best approach to screening which will be documented in a site specific standard operating procedure (SOP). For each participant, independent written informed consent for Screening will be obtained before Screening procedures are initiated. For each index participant, Enrollment must occur on a separate date within 60 days of the date of blood collection at the Screening visit. See Section 3.3 for important screening information. Note that all Screening procedures (including completion of the HIV testing algorithm for the Screening visit) must be completed before a participant is enrolled. HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility. In addition to testing for HIV infection at the Screening visit using local testing guidelines, at least one HIV test (e.g. HIV rapid test) must be positive/reactive at the Enrollment visit for the index participant to be considered eligible for the study.

Administrative, Behavioral and Regulatory Procedures

- Informed consent
- Demographic information
- Locator information
- HIV pre-test, risk reduction, and post-test counseling
- Brief assessment of injection risk behavior, substance use, substance use treatment, and ART use for eligibility
- Referral to needle and syringe exchange programs (if legal and available)
- Referral to substance use treatment
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate) Brief, standardized injection and sexual transmission risk reduction counseling

Clinical Procedures

- Blood collection

Laboratory Procedures – Local Laboratory

- HIV testing (see SSP Manual)*
- CD4 cell count (if an HIV test is reactive or positive)
- HIV viral load (if an HIV test is reactive or positive)
- Plasma storage

*HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility (two different blood draws collected on different days are required for confirmation of HIV infection). If this is a re-screening visit for a participant who has not previously been confirmed to be HIV-infected based on

testing performed using specimens collected on two separate dates (index or partner screening), HIV testing will be required at re-screening.

5.4.2 Enrollment Visit for Index Participants

The effective point of enrollment is randomization.

Administrative, Behavioral and Regulatory Procedures

- Informed Consent
- Update locator information
- Randomization
- Baseline sexual behavior, injection risk behaviors, substance use, substance use treatment and ART use and adherence interviews
- Assessment of barriers and facilitators to HIV care and substance use treatment, mediators and moderators of key outcomes.
- Social network interview
- Social impact assessment
- HIV pre-test, risk reduction, and post-test counseling
- Referral for ART (If clinically indicated according to national guidelines and/or participant is randomized to the intervention group)
- Brief, standardized injection and sexual transmission risk reduction counseling
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical Procedures

- Blood collection
- Urine collection

Laboratory Procedures – Local Laboratory

- HIV testing (see SSP Manual)*
- Urine testing for substances of abuse will be performed in real-time at study sites using locally-available methods
- Plasma storage
- Urine storage
- Dried urine storage

*HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility.

5.4.3 Follow-up visits for Index Participants

Index participants will have a visit at week 4 and followed quarterly a minimum of 52 weeks, up to a maximum of 156 weeks. If possible, an Exit visit will be conducted for all index participants.

Index participants will only be considered terminated from the study if the participant actively withdraws or dies during the course of the study. Incarcerated participants will be able to resume study participation on release from incarceration.

5.4.3.1 Week 4 visits for Index Participants

Administrative, Behavioral and Regulatory Procedures

- Update locator information
- Assessment of barriers and facilitators to HIV care and substance use treatment, mediators and moderators of key outcomes.
- Social network interview
- Social impact assessment
- Brief, standardized injection and sexual transmission risk reduction counseling
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as needed)
- Referral for ART (If clinically indicated according to national guidelines and/or participant is randomized to the intervention group)

Clinical Procedures

- Blood collection
- Urine collection
- Adverse Event Assessment

Laboratory Procedures

- Urine testing for substances of abuse
- Plasma storage
- Urine storage

5.4.3.2 Quarterly Visits for Index Participants

*Quarterly visits will occur at Weeks 13, 26, 39, 52, 65, 78, 91, and 104. Note that Weeks 52, 65, 78, 91, 104, 117, 130, 143 or 156 may be an Exit visit for some participants, depending on the timing of the participant's enrollment relative to the enrollment period at the site. For Exit visit procedures, refer to Section 5.4.3.3.

Administrative, Behavioral and Regulatory Procedures

- Update locator information
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews

- Referral for ART (If clinically indicated according to national guidelines and/or participant is randomized to the intervention group)
- Assessment of barriers and facilitators to HIV care and substance use treatment, mediators and moderators of key outcomes.
- Social network interview
- Social impact assessment
- Brief, standardized injection and sexual transmission risk reduction counseling
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as needed)

Clinical Procedures

- Blood collection
- Urine collection
- Adverse Event Assessment

Laboratory Procedures – Local Laboratory

- Urine testing for substances of abuse
- CD4 cell count (Weeks 26, 52, 78, 104, 130 and 156 only)
- Plasma storage
- Urine storage
- Dried urine storage as supplies permit (Weeks 26, 52 and Exit)

5.4.3.3 Exit Visit for Index Participants

* Weeks 52, 65, 78, 91, 104, 117, 130, 143 or 156 may be an Exit visit for some participants, depending on the timing of the participant's enrollment relative to the enrollment period at the site.

Administrative, Behavioral and Regulatory Procedures

- Update locator information
- Exit sexual behavior, substance use, substance use treatment and ART experience interviews
- Social network interview
- Social impact assessment
- Brief, standardized injection and sexual transmission risk reduction counseling
- Assessment of barriers and facilitators to HIV care and substance use treatment, mediators and moderators of key outcomes.
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical and Laboratory Procedures are the same as those performed at quarterly visits.

5.5 Visit Procedures for Network Injection Partners

5.5.1 Screening visit for Network Injection Partners

It is the responsibility of the local site to determine the best approach to Screening. For each participant, independent written informed consent for Screening will be obtained before Screening procedures are initiated. For each network partner participant, Enrollment must occur on a separate date within 60 days of the blood collection for the Index Screening visit. See Section 3.3 for important screening information. Note that all Screening procedures (including completion of the HIV testing algorithm for the Screening visit) must be completed before a participant is enrolled. HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility.

Administrative, Behavioral and Regulatory Procedures

- Informed consent
- Demographic information
- Locator information
- HIV pre-test, risk reduction, and post-test counseling
- Brief assessment of injection risk behavior, substance use, and substance use treatment for eligibility
- Confirmation via local procedures of relationship to an index participant (network association)
- Referral to needle and syringe exchange programs (if legal and available)
- Referral to substance use treatment
- Brief, standardized injection and sexual transmission risk reduction counseling
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical Procedures

- Blood collection

Laboratory Procedures

- HIV testing (see SSP Manual)*
- Plasma storage

*HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility.

5.5.2 Enrollment visit for Network Injection Partners

The effective point of enrollment is randomization.

Administrative, Behavioral and Regulatory Procedures

- Informed Consent
- Update locator information
- HIV pre-test, risk reduction, and post-test counseling
- Baseline sexual behavior, injection risk behaviors, substance use and substance use treatment interviews
- Assessment of barriers and facilitators to substance use treatment, mediators and moderators of key outcomes
- Social network interview
- Social impact assessment
- Brief, standardized injection and sexual transmission risk reduction counseling
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical Procedures

- Blood collection
- Urine collection

Laboratory Procedures

- HIV testing (see SSP Manual)*
- Urine testing for substances of abuse
- Plasma storage
- Urine storage
- Dried urine storage

*HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility.

5.5.3 Follow-up visits for Network Injection Partners

Network injection partners (including replacement partners) will be followed until the index participant's Exit visit. If a network injection partner ends his/her relationship with the index participant, this network injection partner will continue to be followed and will have all follow-up assessments performed, even if the index participant recruits a new, active network injection partner.

Network injection partners will only be considered terminated from the study if the participant actively withdraws or dies during the course of the study. Incarcerated participants will be able to resume study participation on release from incarceration.

All replacement (or late enrolling) partners will have a Week 4 visit before assuming the visit schedule of the corresponding Index.

5.5.3.1 Week 4 Visit for Network Injection Partners

Administrative, Behavioral and Regulatory Procedures

- Update locator information
- HIV pre-test, risk reduction, and post-test counseling
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews
- Assessment of barriers and facilitators to substance use treatment, mediators and moderators of key outcomes
- Social network interview
- Social impact assessment
- Brief, standardized injection and sexual transmission risk reduction counseling
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical Procedures

- Blood collection
- Urine collection
- Adverse Event Assessment

Laboratory Procedures

- HIV testing (see SSP Manual)*
- Urine testing for substances of abuse (may be performed in the clinic or the local laboratory)
- Plasma storage
- Urine storage

5.5.3.2 Quarterly visits for network injection partners

Quarterly visits will occur at Weeks 13, 26, 39, 52, 65, 78, 91, and 104. Note that Weeks 52, 65, 78, 91, or 104 may be an Exit visit for some participants, depending on the timing of the participant's enrollment relative to the enrollment period at the site. For Exit visit procedures, refer to Section 5.5.3.3.

Administrative, Behavioral and Regulatory Procedures

- Update locator information
- Follow up sexual behavior, substance use and substance use treatment interviews
- Assessment of barriers and facilitators to substance use treatment, mediators and moderators of key outcomes
- Social network interview
- Social impact assessment

- HIV pre-test, risk reduction, and post-test counseling
- Brief, standardized injection risk reduction counseling
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical Procedures

- Blood collection
- Urine collection
- Adverse Event assessment

Laboratory Procedures

- HIV testing (see SSP Manual)
- Urine testing for substances of abuse (may be performed in the clinic or the local laboratory)
- Plasma storage
- Urine storage
- Dried urine storage as supplies permit (Weeks 26,52 and Exit only)

5.5.3.3 Exit visit for Network Injection Partners

Weeks 52, 65, 78, 91 or 104 may be an Exit visit for some participants, depending on the timing of the participant's enrollment relative to the enrollment period at the site.

Administrative, Behavioral and Regulatory Procedures

- Update locator information
- Exit sexual behavior, substance use, and substance use treatment experience interviews
- Social network interview
- Social impact assessment
- HIV pre-test, risk reduction, and post-test counseling
- Brief, standardized injection and sexual transmission risk reduction counseling
- Assessment of barriers and facilitators to substance use treatment, mediators and moderators of key outcomes
- Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)

Clinical and Laboratory Procedures are the same as those performed at Quarterly Visits

5.6 Additional procedures for network injection partners who have a reactive or positive HIV test at any visit after Enrollment (See Appendix III).

5.6.1 HIV Confirmation Visit Following a Reactive or Positive HIV Result

This visit should occur within 14 days of the first reactive/positive HIV test) and must occur on a different date than the date at which the first reactive/positive HIV test result was obtained. Referrals will be made for standard of care treatment as indicated. Referrals for expanded access to ART will not be provided to network injection partners who become HIV infected while on follow up.

Clinical Procedures

- Blood collection

Laboratory Procedures – Local Laboratory

- HIV testing (see SSP Manual) *
- CD4 cell count
- Additional plasma storage

*Sites may contact the HPTN LC to see if these procedures may be waived for individuals who have a single assay result that is near the assay cutoff and likely to be a false-positive result based on other HIV test results obtained at the regularly scheduled study visit.

5.6.2 Weeks 26, 52, 78 and 104 (if HIV infection has been confirmed)

If HIV infection was confirmed at a prior visit, a CD4 cell count should be obtained (in addition to other study procedures and tests) at these visits. HIV pre-test, post-test and risk reduction counseling as well as HIV testing will not be completed at these visits.

5.7 Data collection procedures for systems navigators and psychosocial counselors

5.7.1 Systems Navigators

Systems navigators' contacts with index participants will be recorded with a standard encounter form. The encounter form will address the duration and content of the interaction with the participant, including the relationship to HIV care or substance use treatment, barriers addressed, and outcome.

Systems navigators will also maintain a log book of contacts with health care settings or agencies. The log book will document the purpose of the contact, outcome/plan, and participants served by the interaction.

At the conclusion of follow-up, semi-structured interviews will be conducted with the systems navigators to address feasibility of and barriers to the intervention following the procedures outlined in Section 5.8.

5.7.2 Psychosocial Counselors

Psychosocial counselors will record encounters with participants on a standard encounter form. The form will identify the type of encounter (individual or group), topics addressed, barriers identified, duration of encounter, and planned actions.

At the conclusion of follow-up, the counselors will complete individual semi-structured interviews addressing feasibility of and barriers to the intervention following the procedures outlined in Section 5.8.

5.8 Data Collection Procedures for Semi-Structured Interviews

To assess the feasibility of the intervention, individual semi-structured interviews will be conducted with 4-10 stakeholders (minimum=12, maximum=30 across all sites) at each study site during the initial stages of enrollment and the final stages of follow-up (minimum = 24, maximum =60 interviews across all sites). The stakeholders will include navigators and counselors at the research sites as well as key clinic personnel at the HIV care and substance use treatment sites. The clinic (non-study) personnel will include HIV care and substance use treatment providers and supervisors.

Sites will also have the option to conduct individual semi-structured interviews with a subset of index participants randomized to the intervention arm. For each site that opts to conduct these interviews, a total of 4-15 intervention index participants (maximum=45 intervention index participants across all sites) will be conducted during the initial stages of enrollment and a total of 4-20 intervention index participants (maximum=60 intervention index participants across all sites) during the final stages of follow-up (maximum=105 interviews across all sites).

Participation of stakeholders and index participants will be entirely voluntary. If a stakeholder/participant chooses not to participate, he/she will experience no penalty or loss of benefits. Furthermore for stakeholders, procedures will be undertaken to ensure that supervisors are not informed of a stakeholders decision regarding participation. If an index participant chooses not to participate, this decision will not affect his/her participation in the trial. Specific measures to handle and ensure protection of stakeholders and index participant refusal and participation will be outlined in a Qualitative Methods Handbook (included in the SSP). The informed consent process and interviews will be conducted in a location that assures adequate privacy and confidentiality, such as a non-study related office.

No personal identifiers will be retained on the collected data to assure privacy and confidentiality for stakeholders and index participants. Reports and publications will be carefully redacted to ensure that identities cannot be discerned.

Semi-structured interviews will be conducted using a standard guide that includes site-specific probes and a combination of client- and provider-centered queries. The interviews will explore the heterogeneity of treatment services available for clients. This will include objective measures such as hours of clinic operations, differences in rules for termination of substance use treatment, and any costs to participants. Additionally, the interviews will elicit what the clinic personnel believe are the common barriers and/or facilitators for them as providers – as well as their clients – to the intervention outcomes of:

- the uptake of HIV testing
- initiation of HIV care and substance use treatment
- medication adherence

The interviews will also explore the sustainability, strengths and weaknesses of the intervention in addressing the barriers and/or enhancing the facilitators. An example of a client-centered query is stakeholders' perception of why participants may not be able or willing to initiate HIV or substance use care. An example of a provider-centered query is staffing at methadone maintenance therapy and ART sites and scalability of the intervention. Interviews will last approximately one hour. All interviews will be audio-taped, transcribed and translated by qualified personnel. All participant identifiers will be removed from transcripts. Coding will be approached with a two-phase analytic method (fully detailed in Section 7.2.1.3.) including topical and interpretive analyses.

6.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

6.1 Safety Monitoring

Close cooperation between the Protocol Chair(s), study site Investigator(s), NIAID Medical/Program Officer, LOC Protocol Coordinator, SDMC Biostatistician, HPTN LC, and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner.

A sub-group of the Protocol Team, including the Protocol Chair and Co-Chair, DAIDS Medical Officer, one or more site clinicians, and the SDMC Clinical Affairs Safety Associate will serve as the Clinical Management Committee (CMC). The CMC is a resource for site clinicians in the management of individual participants which will meet if there is a particular participant situation that merits discussion.

The study site Investigators are responsible for continuous close monitoring of reportable AEs (refer to Section 6.3.3) that occur among study participants from enrollment until the participant exits the study, and for alerting the CMC if unexpected concerns arise.

6.2 Clinical Data Safety Review

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the CMC if unexpected concerns arise. The Study Monitoring Committee (SMC) will conduct periodic detailed reviews of reports of safety data (e.g., SAEs, Social Harms). Additional reviews may be conducted at each of these levels as dictated by the occurrence of certain events.

Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer for review.

If at any time a decision is made to discontinue the study, DAIDS will notify the site Investigators of Record who will in turn notify the responsible IRBs/ECs/ Ministries of Health (MoH) expeditiously.

6.3 Adverse Events

6.3.1 Non-Serious Adverse Events

Non-serious adverse events will be collected and recorded in the source documentation with referrals as necessary, but not reported in the database as part of this research protocol for all study participants.

6.3.2 Serious Adverse Events

Serious AEs (SAEs) are defined per International Conference on Harmonisation (ICH) guidance, as specified in Version 2.0 of the Manual for Expedited Adverse Events to DAIDS, dated January 2010 (Section 2.1) and will be collected and reported on Case Report Forms (CRFs) for all study participants. However, only Suspected Unexpected Serious Adverse Reactions (SUSAR) will be collected and reported in an expedited manner to the DAIDS Adverse Event Reporting System (DAERS) (http://rsc.tech-res.com/docs/default-source/safety/manual_for_expedited_reporting_aes_to_daids_v2.pdf?sfvrsn=10).

The reporting period for all participants is from the time of enrollment through when a participant exits the study. Any SAEs that come to the attention of the Investigator after a participant has exited the study but before the database has been locked will also be reported in the same manner as when the participant was on study.

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent defined as the participant's current or last known ART and/or opiate substitution therapy. The relationship of all SAEs to study product will be assessed as specified in Version 2.0, January 2010 (or most

current version) of the DAIDS Expedited Adverse Event (EAE) Reporting Manual.

6.3.3 AE Reporting to DAIDS

For all SUSARs as defined above, DAERS, an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Site queries may also be sent with the DAERS application itself.

For questions about EAE reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

6.3.4 Grading severity of adverse events

The severity of all AEs will be graded according to the current Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Version 1.0, dated December 2004 (with Clarification dated August 2009), or most current version, which is available on the RSC website at <http://rsc.tech-res.com/safetyandpharmacovigilance/>.

6.3.5 Toxicity Management

Toxicity associated with ART or substitution therapy will be managed by the host country medical authorities, given that ART will be administered under their authority. Toxicity associated with medication-assisted substance use treatment will also be managed by host country medical authorities. The CMC exists as an additional resource to site clinicians should questions arise.

6.4 Concomitant Medications

Concomitant medications are permitted at the discretion of the local medical authorities.

6.5 Regulatory Requirements

Information on hospitalizations and deaths occurring among all study participants will be recorded on case report forms and included in reports to applicable government and regulatory authorities. The site IoR/designee will submit this information in accordance with local regulatory agencies' or other local authorities' requirements. The site IoR/designee also will submit any other relevant safety information to the IRB/Ethics Committee (EC) in accordance with IRB/EC requirements.

6.6 Social Impacts Reporting

Social Impacts will be monitored closely throughout the study. At each follow-up visit, a series of structured questions will be used to probe for interpersonal, legal, housing and healthcare problems that have occurred as a result of study participation. All subjects will also be reminded of the importance of reporting problems to study staff between regularly scheduled visits and instructed on how to contact study staff should problems occur during intervals between visits. Additionally, Social Impacts reported by anyone other than study participants, e.g., family or staff members, will also be monitored and documented in site source records and monitored by study staff. When these events are serious, including incarceration, physical abuse, suicidal behavior, or homicidal behavior, they will be reported on case report forms. Whenever problems are identified, additional data regarding the severity and resolution will be described and recorded on a case report form and will include a description of actions taken by the participant, the site staff, and others to resolve or respond to the problem. The nature and frequency of these social impact reports will be monitored by the SMC as they occur.

Given the status of illegal drug use, the associated social stigma and perceptions of drug users held by many members of the communities in which the study will be conducted, social harms could occur purely as a result of participation in a study targeting drug users. These could include discriminatory treatment and violence associated with possible disclosure of participants' drug or sex-related behaviors or of their HIV serostatus.

Prior to site activation, a review of local and national policies and practice affecting injection drug users will be conducted. The purpose of this review will be to verify that laws, policies and enforcement strategies do not place participants in the research at significantly elevated risk of arrest, incarceration, physical harm, unwanted disclosure of drug use, or loss of access to health care relative to injection drug users not participating in the research.

The assessment will consist of two components. The first component will review and analyze the laws relevant to injection drug use by examining laws concerning drug control, drug use, access to health care and privacy of medical information in each study country. This review will identify and collate constitutions and any treaties that have the force of law, statutes passed by the national, regional or local legislature, administrative regulations with the force of law and relevant court decisions interpreting these laws or regulations. This review of the legal and social risks will roughly follow the recently released Legal Assessment Tool (LAT), which is endorsed by the American Bar Association and the United States Agency for International Development (American Bar Association). Details on the use of the LAT are available in the LAT methodology manual.[56] This review will be conducted with the close involvement of independent legal experts in each study country.

The second component will assess how these laws are put into practice and what possible influence they have on the risks and benefits of PWID participation in the study. Qualitative data regarding the effects of law on PWID will be gathered, along with data

on stigma, social risk, and social attitudes as they apply to PWID. These data will be collected via interviews with key informants in the legal and public health fields as well as current and former injection drug users. Data will be collected via standardized interview forms by independent researchers at each site.

The review will provide a narrative summary and analysis of the law and its likely effects on study participants. As these laws, policies and practice strategies can be expected to change over time, site staff will continue to monitor relevant laws and policies for the duration of HPTN 074.

To the extent possible, activities involving participants will be conducted in venues that mask the criteria for study participation. It is impossible and unwise to think that the primary purpose of the study can be kept secret (i.e., a prevention study for PWID) from the community, including the police. An appropriate working relationship with the local law enforcement agency at each site, which recognizes the urgent need to prevent HIV in this population, will be established. Such relationships are believed to assist outreach staff whose presence in the community is understood and respected. Site staff will not disclose the names of participants to anyone other than members of the field research staff and have strict policies regarding the situations in which discussions of participants can take place, such as staff meetings on topics of recruitment and follow-up. All interview and laboratory data are securely stored in a confidential manner.

6.7 Clinical Management of Pregnancy

Participants who identify as pregnant, either index participants or network injection partners, will remain in the study. For HIV-infected pregnant women, ART will be managed according to national guidelines for prevention of mother-to-child transmission of HIV and treatment of the mother's HIV infection.

7.0 STATISTICAL CONSIDERATIONS

7.1 Review of Study Design

This is a multisite, two-arm, randomized vanguard study. Network units consisting of an HIV-infected index participant and his/her HIV-uninfected network injection partner(s) will be randomized to the intervention or standard of care arms in a 1:3 ratio, stratified by site.

7.1.1 Primary Endpoints

Consistent with the primary study objective to assess the feasibility of a future randomized controlled trial by:

- a) estimating the HIV incidence among network injection partners of index participants in the standard of care arm in three distinct global settings with epidemics driven predominantly by injection drug use;
- b) evaluating enrollment and retention of HIV-infected PWID and their HIV-uninfected network injection partners over a period of 12-24

months plus an additional 12 months for those index participants willing to continue and re-consent.

The following endpoints will be assessed:

HIV incidence

- 1) Overall and by site HIV seroconversion rates of network injection partners in the standard of care arm

Enrollment and retention

- 1) Calendar time to enroll and allocate to study arm 500 eligible HIV-infected PWID overall and 167 eligible HIV-infected PWID by study site
- 2) Number of eligible HIV-uninfected network injection partners overall and at each site
- 3) Proportion of index participants retained at each visit overall and at each site
- 4) Proportion of network injection partners, enrolled at index participant's allocation to study arm, retained at each visit overall and at each site
- 5) Mean (SE) person years at risk accumulated per index participant overall and at each site

Consistent with the primary study objective to assess the feasibility, barriers, and uptake of an integrated intervention for prevention of HIV transmission among HIV-infected index participants, the following endpoints will be assessed overall and by site among participants in the intervention group only:

Uptake measures

Intervention component: Systems navigators

- 1) Overall: Proportion of index participants using systems navigators at least once.
- 2) Overall: Mean (standard error) number of contacts (text, email, telephone call, home visit, other) with index participants made with systems navigators (mean contacts per index participant)
- 3) Use of navigators for ART: Mean (SE) number of contacts with HIV care sites made by systems navigators per index initiating ART.
- 4) Use of navigators for uptake of substance use treatment: Mean (SE) number of contacts with medication-assisted substance use treatment centers made by systems navigators per index initiating substance use treatment.

Intervention component: Psychosocial counseling

- 1) Proportion of index participants completing two counseling sessions within four weeks of enrollment

Intervention component: Social network support

- 1) Proportion of index participants with an identified social support person within 13 and 52 weeks of enrollment
- 2) Proportion of index participants completing a joint counseling session with an identified HIV medical care social support person within 13 and 52 weeks of enrollment

Intervention component: Substance use treatment

- 1) Proportion of index participants self-reporting substance use treatment by 4 and 13 weeks
- 2) Proportion of index participants with detectable methadone or buprenorphine at selected study visits

Intervention component: Supported ART (all intervention index participants ART-eligible)

- 1) Proportion of index participants self-reporting initiating ART by 4 and 13 weeks
- 2) Proportion of index participants on ART with detectable antiretroviral drugs at selected study visits
- 3) Proportion of index participants who achieve virologic suppression by 26 and 52 weeks

Feasibility and Barriers

Analyses for feasibility of and barriers to the intervention will be exploratory. Feasibility of the intervention will be assessed through individual semi-structured interviews with the systems navigators, counselors, additional stakeholders, and a subset of index participants randomized to the intervention arm . Barriers will be assessed through the barrier questionnaire with the participants, systems navigators' and counselors' data forms/log books, and interviews with additional stakeholders.

7.1.2 Secondary Endpoints

Consistent with the following secondary study objectives, the following endpoint(s) will be assessed:

- To estimate HIV incidence among network injection partners of index participants in the intervention arm.
 - 1) Overall HIV seroconversion rates of network injection partners in the intervention arm
- To explore the effect of the integrated intervention, as compared to standard of care, on engagement in HIV care, initiation of ART, retention on ART, ART adherence, and virologic suppression among ART-eligible index

participants (index participants meeting national guidelines in the standard of care arm; all index participants in the intervention arm).

- 1) Number of HIV medical visits reported at 26 weeks and 52 weeks by index participants (self-report)
 - 2) Proportion of baseline ART-eligible index participants self-reporting ART initiation by 4 and 13 weeks
 - 3) Proportion of baseline ART-eligible index participants self-reporting current use of ART at 26 and 52 weeks
 - 4) Proportion of index participants on ART self-reporting high adherence to ART at 26 and 52 weeks
 - 5) Proportion of ART-eligible index participants with virologic suppression, at 26 and 52 weeks
 - 6) Proportion of index participants on ART for at least 3 months with virologic suppression at 26 and 52 weeks
- To explore the effect of the integrated intervention, as compared to standard of care, on the proportion of index participants and network injection partners engaged and retained in substance use treatment.
 - 1) Proportion of index participants and network injection partners initiating substance use treatment within 4 and 13 weeks
 - 2) Proportion of index participants and network injection partners in substance use treatment at 26 and 52 weeks
 - 3) Proportion of index participants and network injection partners in methadone treatment at 26 weeks
 - To estimate the size and stability of injection networks of the index participants and how this affects recruitment and retention of network injection partners.
 - 1) Number of reported network injection partners (size of injection network) at Enrollment, 13, 26, 39 and 52 weeks
 - 2) Number of new network injection partners reported over 13, 26, 39, and 52 weeks
 - 3) Number of new network injection partners reported and recruited into the study over 26 and 52 weeks
 - 4) Number of “discontinued” network injection partners over 26 and 52 weeks
 - 5) Number of referred network injection partners who were HIV-infected at Screening or Enrollment
 - To assess the social harms and benefits of research participation for PWID.
 - 6) Benefits will be assessed in exploratory analyses to address improvement of physical health, mental health, quality of life, relationships, financial, or employment. Additional benefits to be explored include reduced drug use, reduced cravings, reduce HIV stigma, and gained knowledge.
 - 7) Harms will be assessed in exploratory analyses.

- If feasible and if funding is identified, to use phylogenetic methods to characterize transmission dynamics in the study cohort.
 - 1) Overall and by site HIV seroconversion rates of network injection partners in the standard of care arm, including phylogenetically confirmed transmission events only
 - 2) Overall HIV and by site seroconversion rates of network injection partners in the intervention arm, including phylogenetically confirmed transmission events only
 - 3) Proportion of all HIV seroconversions among network injection partners in both the standard of care and intervention arm that are phylogenetically confirmed.
- Evaluation of factors related to HIV infection, antiretroviral (ARV) drug use; substances of abuse; methadone and other treatments for substance abuse; cross-sectional HIV incidence estimation; characterization of HIV in infected participants, including phylogenetics and linkage; evaluation of the host response to HIV infection; and evaluation of laboratory assays related to study objectives.

7.2 Accrual, Follow-up, and Sample Size

7.2.1 Primary endpoints

HIV incidence

The sample size represents a balance between obtaining an estimate of HIV incidence among network injection partners in the standard of care group and the need to assess feasibility of the intervention components.

The overall sample size of HIV-infected index participants is 500 persons. Given the allocation ratio of 1:3, 375 index participants will be randomized to the standard of care arm. Assuming recruitment of 1.5 network injection partners per index, the standard of care group will include approximately 563 network injection partners for estimation of HIV incidence. The team also assumes 10% annual loss to follow-up. PWID who die or are incarcerated are not considered lost to follow-up.

Table 4. Exact Poisson Confidence Intervals for Annual Standard of Care Arm Incidence Rates								
Standard of Care Arm incidence	1.5 partners/index; 90% annual retention				1.5 partners/index; 80% annual retention ¹			
	Overall (N indexes= 375)		Three sites (N indexes = 125)		Overall (N indexes = 375)		Three sites (N indexes = 125)	
	N partners = 563, Person Years = 715		N partners = 188, Person Years = 238		N partners = 563, Person Years = 594		N partners = 188, Person Years = 198	
	N events	95% CI	N events	95% CI	N events	95% CI	N events	95% CI
2%	14	1.07-3.29	5	0.68-4.90	12	0.79-3.26	4	0.00-4.54
3%	21	1.82-4.49	7	1.18-6.06	18	1.58-4.48	6	0.20-5.86
5%	36	3.53-6.97	12	2.61-8.81	30	3.24-6.86	10	1.71-8.39
8%	57	6.04-10.33	19	4.81-12.47	48	5.86-10.30	16	4.11-12.05
10%	71	7.76-10.33	24	6.46-15.00	59	7.50-12.36	20	5.78-14.42

¹ The same number of person years (and therefore the same confidence intervals) would apply with 1.25 partners per index and 90% annual retention.

The estimates provide reasonable precision for estimating the sample size in a future study.

Note: These are estimated under the assumption of independence. While outcomes of HIV-infected partners of the same index will be correlated, because HIV incidence is expected to be a rare event and the networks are small, the impact of this correlation on the confidence limits is likely to be small.

Intervention uptake

The most critical endpoints for intervention uptake (defined in 7.1.1) are substance use treatment, support ART initiation and viral load suppression among the index participants assigned to the intervention arm. The targeted proportion achieving each of these is 75-95% of participants in the intervention arm. Table 5 gives the 95% confidence intervals for proportions observed.

Table 5. Intervention Uptake		
	Intervention N Indexes = 125	
N Observed	Proportion	95% confidence bounds
94	75.2%	(66.7, 82.5)
100	80.0%	(71.9, 86.6)
106	84.8%	(77.1, 90.6)
112	89.6%	(82.9, 94.4)
119	95.2%	(89.9, 98.2)

Table 6: Effect sizes for the HPTN074 intervention with 90% power.

Standard of Care Arm incidence	Total (N indexes = 500)	Control (N indexes= 375)	Intervention (N indexes = 125)	Minimum alternative HR for which trial has 90% power.
	N partners = 750, PYears = 953	N partners = 563, PYears = 715	N partners = 167 PYears = 238	
	Total number of events	Expected number of events under alternative HR	Expected number of events under alternative HR	
2%	14	14	0	0.135
3%	22	21	1	0.203
5%	39	36	3	0.306
8%	64	57	7	0.392
10%	81	71	10	0.435

Intervention feasibility and barriers

Analyses of feasibility and barriers will have both exploratory quantitative and qualitative components. The exploratory quantitative components will involve descriptions of the frequencies of identified barriers, assessed over time during follow-up. Planned stratifications include gender and study site. Separate analyses will be conducted for index participants and network partners.

Qualitative analyses: Semi-structured interviews with systems navigators, counselors, stakeholders (minimum = 12, maximum = 30 across all sites), and a sub-set of index participants randomized to the intervention arm (maximum = 60 across all sites) will be based on a standard field guide that will be used at all sites. All interviews will be audiotaped, transcribed and translated into English at each study site by qualified personnel. All participant identifiers will be removed from transcripts. Transcripts will be analyzed in two phases: topical and interpretive.

In the first phase, topical analyses will identify content categories a priori and will cull data into units that reflect core content categories for summary. A codebook consisting of main topics of interest (e.g., utilization of systems navigators and counselors, uptake of ART, pill-taking patterns, uptake of substance use treatment, and provider burden) will be developed by a centralized team. A standardized workshop will train local staff in the codebook, the application of codes and the use of Atlas ti.[57] Interviews will be indexed by pre-determined topics through the application of topical codes by trained teams of 2-3 site-level coders.[58] Specifically, coders will review transcript content for references to barriers and facilitators of both the intervention (engagement in counseling and utilization of systems navigators) and uptake of HIV and drug treatment services from both patient and provider perspectives. Each identified barrier and facilitator will be further coded for content that is motivational, behavioral skills related, or informational. To maintain coding quality, each coder will complete a

certification exercise prior to initiating the work, qualitative supervisors will regularly review coded transcripts and senior data analysts will spot check coded transcripts from each site. The team anticipates that these data will provide nuanced information about the feasibility of and barriers to the various components of the intervention as well as HIV and drug treatment services. Data that are topically coded will be used to generate code reports for each of the feasibility endpoints across sites at the central level. Based on these code reports, detailed summary reports will note insights, key themes and patterns that emerge from the data.

The second phase of analyses is interpretative and will occur at the central level. The team will use an iterative, inductive process of reviewing content and identifying themes within, across and outside of topical codes that characterize, qualify or define the phenomenon of interest.[59] This phase of analyses will begin with an iterative review of site-specific topical code reports by senior data analysts familiar with the phenomenon of interest to ensure an adequate level of sensitivity in the development of coding schemes. In addition to descriptions of the phenomenon identified through topical coding, the team will explore the context in which it occurs, specific conditions in which it occurs, activities done in response to the phenomenon and outcomes of the activities. This process will produce a set of general categories that describe the characteristics and patterns both within and across sites and topical codes. Given the interview objectives, the team anticipates that a priori phenomena would include utilization of systems navigators and counselors, uptake of ART, pill-taking patterns, uptake of substance use treatment, and provider burden. However, additional phenomena that may emerge from the interview data will also be included. Codes will then be consolidated into a final coding system that can be compared across sites. Through this process, critical aspects of intervention delivery as well as uptake of services along the HIV treatment cascade will be defined both a priori and through the identification of emerging phenomena that may not have been anticipated.

7.2.2 Secondary endpoints

The secondary endpoints primarily compare proportions of observed events across study arms. Proportions will be compared between study arms using odds ratios. Table 6 provides an indication of the differences the team has reasonable power to detect, both overall and at each site in indexes and network partners, assuming comparisons at specific time points. For comparisons with repeated observations at multiple study visits, the team would have considerably more power.

Table 6. Power for detecting Odds Ratios for comparison between arms				
Odds Ratio	Overall		Three sites	
	N (Intervention: SOC)		N (Intervention: SOC)	
	N Indexes = 500 (125:375) N Partners = 750 (188:563)		N Indexes = 167 (42:125) N Partners = 250 (62:188)	
	Indexes	Partners	Indexes	Partners
1.50	48.9%	65.8%	20.0%	27.7%
1.75	74.9%	89.7%	33.0%	46.1%
2.00	89.4%	97.6%	45.8%	62.2%
2.25	95.8%	99.5%	56.9%	74.3%
2.50	98.4%	99.9%	66.0%	82.8%
3.00	99.7%	100.0%	78.5%	92.0%

7.3 Random Assignment / Study Arm Assignment

HIV-infected index participants and their HIV-uninfected network injection partners will be randomized in a 1:3 ratio to the intervention and standard of care arms. The randomization will be stratified by site.

7.4 Data Analysis

7.4.1 Primary Analyses

HIV incidence

The primary outcome of the study is the HIV incidence in the standard of care arm overall and by site. HIV incidence will be assessed using two approaches reflecting different assumptions about infections within a network:

- Treating all of the network injection partners of an index as representative of time exposed to the index participant (i.e., allowing for dependence between index participants' risk of infection). Poisson regression with GEE methods will be used fitting only an intercept term, for the overall rate (site as a covariate for site specific rates), with study time in an offset term using index as the cluster, and robust standard errors will be used.
- Assessing the rate of infection amongst all network injection partners enrolled in the study. Confidence intervals will be based on the Poisson distribution (assuming independent observations).

Feasibility of and uptake of Integrated Intervention

Descriptive statistics will be used to assess feasibility characteristics. The following methods will be used: for categorical variables, the number and percent

in each category; for continuous variables, the mean, median, standard deviation, quartiles and range (minimum, maximum); for time-to-event outcomes, estimate and confidence limits will be based on Kaplan-Meier curves.

7.4.2 Secondary Analyses

Statistical analyses for secondary objectives will be conducted as follows: Comparisons of proportions between arms will use odds ratios, stratified by site, adjusted for clustering by network.

Comparison of time to event data between arms (e.g., time to initiating ART) will use a log rank test stratified by site. Distributions of time to event data will be estimated using the Kaplan-Meier method. Interval censored and discrete time methods for time-to-event data will be used where appropriate, and analyses will account for clustering by network.

Appropriate descriptive statistics will be used to summarize required study elements overall and by site (e.g., mean, standard error, median and interquartile ranges). Analyses will be adjusted for clustering by network as appropriate.

8.0 HUMAN SUBJECTS CONSIDERATIONS

8.1 Ethical Review

This protocol and the template informed consent forms contained in Appendix IV — and any subsequent modifications — will be reviewed and approved by the HPTN Scientific Review Committee (SRC) and DAIDS Prevention Science Review Committee (PSRC) with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study sites.

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigators will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. Study sites will submit documentation of continuing review to the DAIDS Protocol Registration Office, in accordance with the current DAIDS Protocol Registration Policy and Procedure Manual.

8.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing a study informed consent form for local use, based on the templates in Appendix IV, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. The study site also is responsible for translating the template form into local languages, and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their informed consent forms. Non-literate participants will be asked to document their informed consent by marking their informed consent forms (e.g., with an X, thumbprint, or other mark) in the presence of a literate third party witness. (Further details regarding DAIDS requirements for documenting the informed consent process with both literate and non-literate participants are provided in the DAIDS Standard Operating Procedure for Source Documentation.) Participant literacy will be determined according to local site SOPs. Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with a copy of their informed consent forms if they are willing to receive them.

8.3 Risks

By participating in the study, participants run the risk of social harm as described in Section 6.6. This could include discriminatory treatment and violence associated with possible disclosure of participants' drug or sex-related behaviors or of their HIV status. Participants also may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become anxious while waiting for their HIV test results. Trained counselors will be available to help participants deal with these feelings. Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities."

Prisoners will not be recruited or enrolled in HPTN 074. Study-related visits will not be conducted in prisons or jails with study participants. Incarcerated participants will be eligible to resume study participation upon release.

8.4 Benefits

Participants in this study will be offered free HIV testing and counseling for HIV risk reduction. HIV-infected individuals eligible for enrollment as an index participant will

be offered assistance in navigating disclosure of their status to people with whom they share drugs whom they believe to be HIV uninfected.

As noted in Section 4.1, all participants will receive the in-country standard of care (including referral for harm reduction services, ART and treatment for noted infections) based on current national guidelines package of services for PWID. Index participants in the intervention arm will receive referral for expanded access to ART and a package of interventions designed to improve engagement and retention in care.

Participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the development of a safe and effective intervention that helps prevent HIV infection by reducing high-risk behaviors where treatment options are very limited.

8.5 Incentives

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

8.6 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored securely in areas with access limited to study staff. To maintain participant confidentiality, a coded number will identify all study specific laboratory specimens, reports, study data collection, process, and administrative forms. Study-specific laboratory specimens, case report forms or documents that are transferred or transmitted off-site for processing will be identified only by a coded number to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate area with limited access. The use of participant identifiers on study records will comply with the DAIDS SOPs for Source Documentation and Essential Documents.

Individual semi-structured interviews will be transcribed by qualified personnel and all identifiable information will be removed from the transcripts. All reports and publications will be carefully redacted to ensure that discernment of individual stakeholders is not possible.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by NIDA, NIAID and/or its contractors; representatives of the HPTN LOC, SDMC, and/or LC; other government and regulatory authorities; and/or local IRBs/ECs.

8.7 Communicable Disease Reporting Requirements

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

8.8 Study Discontinuation

The study may be discontinued at any time by the sponsor (US NIH), the HPTN, Office of Human Research Protection (OHRP), and/or local government or regulatory authorities, and/or site IRBs/ECs.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

9.1 Local Laboratory (LL) Specimens

As described in Section 5, specimens will be collected for the following tests and procedures at study sites (LL); note: this includes testing performed in the clinic:

- HIV testing
- CD4 cell count testing
- HIV viral load testing
- Urine test for substances of abuse
- Plasma storage
- Urine storage
- Dried urine storage

Each study site will adhere to standards of good clinical laboratory practice, and local SOPs for specimen management, including proper collection, processing, labeling, transport, and storage of specimens to the LL. Specimen collection, testing, and storage at the local laboratory will be documented using the Laboratory Data Management System (LDMS) as described in the SSP Manual.

9.2 HPTN Laboratory Center (LC) Specimens

As described in Section 5, plasma, urine, and a subset of dried urine specimens will be stored for testing at the HPTN LC. At the discretion of the LC, some testing may be performed at another institution or at a commercial laboratory, designated by the HPTN LC. Results from testing performed at the HPTN LC (or a HPTN LC-designated laboratory) will not be returned to study sites or study participants (with the possible exception of HIV diagnostic testing, if test results for HIV infection status differ from those obtained at study sites). This testing may include:

- Extended QA for HIV diagnostic testing, including confirmation HIV acquisition
- Viral load testing

- Testing for substances of abuse
- Testing for antiretroviral drugs
- Testing for methadone and other medications used to treat substance use
- Testing related to cross-sectional assessment of HIV incidence
- Phylogenetic and linkage analysis (if feasible)
- Stored samples may also be used to characterize HIV viruses (e.g., for HIV subtyping, resistance testing, viral diversity analysis) and the host response to viral infection.

9.3 Quality Control and Quality Assurance Procedures

The study sites will participate in locally-approved External Quality Assurance (EQA) programs. The HPTN LC staff will conduct periodic visits to each site to assess the implementation of on-site Quality Control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents.

The LC will inform site staff of the samples selected for QA testing, and site staff will ship the selected specimens to the LC. LC staff will follow-up directly with site staff to resolve any problems identified through this process.

9.3.1 QC for HIV diagnostic testing

Before performing HIV diagnostic testing, all sites must have validated the testing algorithm, and the validation must be reviewed by the HPTN LC. Local laboratories (or clinics) will perform testing for HIV diagnosis at Screening, Enrollment, and other scheduled visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual. These algorithms are expected to vary from site to site based on national guidelines and other factors. Laboratories are encouraged to participate in an EQA program for HIV testing that is approved by the HPTN LC. In addition, the HPTN LC will perform extended QA testing. Samples will be shipped to the HPTN for QA of HIV testing, approximately once every three months.

If a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, additional testing may be performed using an HIV RNA test. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples collected on different days.

9.3.2 QC for HIV viral load

Quantitative HIV RNA (viral load) testing will be performed at local laboratories at the Screening visit for potential index participants who have a reactive or positive HIV test result. Local laboratories must participate in the DAIDS

Virology QA (VQA) program, with EQA results that are deemed satisfactory by the HPTN LC.

9.3.3 QC for CD4 cell count determination

Local laboratories must be enrolled in the United Kingdom National External Quality Assessment Service (UK NEQAS) program through the DAIDS Immunology Quality Assessment (IQA) program, with EQA results that are deemed satisfactory by the HPTN LC.

9.4 Specimen Storage and Possible Future Research Testing

Study sites will store all plasma, urine, and dried urine specimens collected in this study at least through the end of the study and until all HPTN LC assessments have been completed. In addition, study participants will be asked to provide written informed consent for their plasma, urine, and dried urine specimens to be stored after the end of the study for possible future testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed after all QA and protocol-related testing has been performed.

9.5 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, blood products and body fluids, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention. All infectious specimens will be transported in accordance with United States regulations (42 CFR 72).

10.0 ADMINISTRATIVE PROCEDURES

10.1 Protocol Registration

Prior to implementation of this protocol, and any subsequent full version amendments, each site must have the protocol and the protocol consent form(s) approved, as appropriate, by their local institutional review board (IRB)/ethics committee (EC) and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS Protocol Registration Office (DAIDS PRO) at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received.

Site-specific informed consent forms (ICFs) will be reviewed and approved by the DAIDS PRO and sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. Site-specific ICF(s) will not be reviewed and approved by the DAIDS PRO and sites will receive an Amendment Registration Notification from the DAIDS PRO that approves the site specific ICFs and indicates successful completion of the amendment protocol registration process. A copy of the final amendment Registration Notification issued by the DAIDS PRO should be retained in the site's regulatory files.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

10.2 Study Activation

Pending successful protocol registration and submission of all required documents, LOC staff will “activate” the site to begin study operations. Study implementation may not be initiated until a study activation notice is provided to the site.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual.

10.3 Study Coordination

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual — which will contain reference copies of the DAIDS SOPs for Source Documentation and Essential Documents, as well as the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, Version 2.0, dated January 2010 and the DAIDS Toxicity Tables — will outline procedures for conducting study visits, data and forms processing, AE assessment, management and other study operations.

Study case report forms and other study instruments will be developed by the study team and HPTN SDMC. Data will be transferred to the HPTN SDMC, processed, and cleaned. Quality Control reports and data queries will be generated on a routine basis and distributed to the study sites for verification and resolution.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, retention, and EAE incidence will be monitored

closely by the team as well as the HPTN SMC. The Protocol Chair, DAIDS Medical Officer, Protocol Biostatistician, and LOC Protocol Specialist will address issues related to study eligibility and EAE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

10.4 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- Verify compliance with human subjects and other research regulations and guidelines;
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices; and
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, SDMC, LC, NIAID, NIDA, and US and in-country government and regulatory authorities. A site visit log will be maintained at the study site to document all visits.

10.5 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and NIAID Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the DAIDS RSC prior to implementing the amendment.

10.6 Investigator's Records

The study site investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. The investigator will retain all study records for at least three years after submission of the CTU's final Financial Status Report to DAIDS, which is due within 90 days after the end of the CTU's cooperative agreement with DAIDS, unless otherwise specified by DAIDS or the HPTN LOC. Study records include administrative documentation — including protocol registration documents and all reports and correspondence relating to the study — as well as documentation related to each participant screened for and/or enrolled in the study — including informed consent forms, locator forms, case report forms, notations of all contacts with the participant, and all other source documents.

10.7 Use of Information and Publications

Publication of the results of this study will be governed by the HPTN Manual of Operations and policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, and DAIDS for review prior to submission.

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Appendix I. Schedule of Procedures and Evaluations - Index

	Screening	Enrollment	Week 4	Quarterly Visits ¹	Exit ¹
Administrative, Behavioral and Regulatory Procedures					
Informed consent	X	X			
Demographic information	X				
Locator information	X	X	X	X	X
Randomization		X			
HIV pre-test, risk reduction, and post-test counseling	X	X			
Referral for ART ²		X	X	X	
Brief assessment of injection risk behavior, substance use, substance use treatment, and ART use for eligibility	X				
Baseline/Exit assessment sexual behavior, substance use, substance use treatment and ART experience interviews		X			X
Follow up sexual behavior, substance use, substance use treatment and ART experience interviews			X	X	
Assessment of barriers and facilitators to HIV care and substance use treatment, mediators and moderators of key outcomes.		X	X	X	X
Social network interview		X	X	X	X
Social impact assessment		X	X	X	X
Referral to needle and syringe exchange programs (if legal and available)	X				
Referral to substance use treatment	X				
Brief, standardized injection and sexual transmission risk reduction counseling	X	X	X	X	X
Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)	X	X	X	X	X
Clinical Procedures					
Blood collection	X	X	X	X	X
Urine collection		X	X	X	X
AE Assessment			X	X	X
Laboratory Procedures					
HIV testing (see SSP Manual)	X	X			
CD4 cell count ³	X ³			X ³	X ³
HIV viral load ⁴	X ⁴				
Urine testing for substances of abuse ⁵		X	X	X	X
Plasma storage ⁶	X	X	X	X	X
Urine storage ⁶		X	X	X	X
Dried urine storage ^{6,7}		X		X ⁷	X ⁷

¹ Weeks 52, 65, 78, 91 or 104 may be an Exit visit for participants. Follow-up is for 52-104 weeks. Follow alternative procedures as indicated if it is an Exit visit.

² If clinically indicated (according to national guidelines) and/or participant is randomized to the intervention group.

³ CD4 cell count testing will be performed at Screening if any HIV test is reactive or positive; after Enrollment, CD4 cell count will only be performed at Weeks 26, 52, 78, and 104.

⁴ Viral load testing will be performed in real-time at study sites at Screening if any HIV test is reactive or positive.

⁵ Urine testing for substances of abuse will be in real-time study sites using locally-available methods; this testing can be performed in the clinic or laboratory.

⁶ Plasma, urine, and dried urine samples will be stored for Quality Assurance testing and other assessments at the IPTN LC (see Section 9.2).

⁷ Dried urine will be stored at Enrollment and as supplies permit at Weeks 26 and 52/ Exit.

Appendix II. Schedule of Procedures and Evaluations – Network injection partners

	Screening	Enrollment	Week 4	Quarterly Visits ¹	Exit ¹
Administrative, Behavioral and Regulatory Procedures					
Informed consent	X	X			
Demographic information	X				
Locator information	X	X	X	X	X
HIV pre-test, risk reduction, and post-test counseling ²	X	X	X	X	X
Brief assessment of injection risk behavior, substance use, and substance use treatment for eligibility	X				
Baseline/Exit sexual behavior, substance use, and substance use treatment interviews		X			X
Follow up sexual behavior, substance use, and substance use treatment interviews			X	X	
Assessment of barriers and facilitators to substance use treatment, mediators and moderators of key outcomes		X	X	X	X
Social network interview		X	X	X	X
Social impact assessment		X	X	X	X
Confirmation via local procedures of relationship to index participant (network association)	X				
Referral to needle and syringe exchange programs (if legal and available)	X				
Referral to substance use treatment	X				
Brief, standardized injection and sexual transmission risk reduction counseling	X	X	X	X	X
Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)	X	X	X	X	X
Clinical Procedures					
Blood collection	X	X	X	X	X
Urine collection		X	X	X	X
AE Assessment			X	X	X
Laboratory Procedures					
HIV testing (see SSP manual) ³	X	X	X	X	X
Urine testing for substances of abuse ³		X	X	X	X
Plasma storage ⁴	X	X	X	X	X
Urine storage ⁴		X	X	X	X
Dried urine storage ^{4,5}		X		X ⁵	X ⁵

Note: Network injection partners (including replacement partners) will be followed until the index participant's Exit visit. Network injection partners who are replaced will continue to be followed and will have all follow-up assessments performed.

¹ Weeks 52, 65, 78, 91 or, 104 may be an Exit visit for participants. Follow-up is for 52-104 weeks. Follow alternative procedures as indicated if it is an Exit visit.

² HIV testing (and associated counseling) is not required if HIV infection was confirmed at a previous visit. Additional testing is required at a subsequent visit (HIV confirmatory visit) if a participant has a positive or reactive HIV test result after Enrollment. See Appendix III.

³ Urine testing for substances of abuse will be performed in real-time at study sites using locally-available methods.

⁴ Plasma, urine, and dried urine will be stored for Quality Assurance testing and other assessments at the HPTN LC (see Section 9.2).

⁵ Dried urine will be stored at Enrollment and as supplies permit at Weeks 26 and 52/ Exit.

Appendix III. Additional procedures for network injection partners who have a reactive or positive HIV test result at any visit after Enrollment*

*Network injection partners will continue to be followed in the study after confirmation of HIV infection; all other assessments for network injection partners will be conducted during subsequent follow-up visits, with the exception of HIV counseling and testing.

This additional HIV confirmation visit should occur within 14 days of the first reactive/positive HIV test result and must occur on a different date than the date at which the first reactive/positive HIV test result was obtained.

	HIV confirmation visit following a reactive or positive HIV result	Weeks 26, 52, 78 and 104 (if HIV infection has been confirmed)
Clinical Procedures		
Blood collection	X	
Laboratory Evaluations		
HIV testing (see SSP Manual)	X	
CD4 count	X	X
Sample Storage		
Additional plasma storage ¹	X	

¹Plasma will be stored for Quality Assurance testing and other assessments at the HPTN LC (see Section 9.2).

Appendix IV- Schedule of Procedures and Evaluations – Index participants during the 12 month extension period beyond original Exit

	Re-Enrollment/ Quarterly Visits ¹	Exit ¹
Administrative, Behavioral and Regulatory Procedures		
Informed consent	X ¹	
Demographic information		
Locator information	X	X
Referral for ART ²	X	
Baseline/Exit assessment sexual behavior, substance use, substance use treatment and ART experience interviews		X
Follow up sexual behavior, substance use, substance use treatment and ART experience interviews	X	
Assessment of barriers and facilitators to HIV care and substance use treatment, mediators and moderators of key outcomes	X	X
Social network interview	X	X
Social impact assessment	X	X
Referral to needle and syringe exchange programs (if legal and available)	X	X
Referral to substance use treatment	X	X
Brief, standardized injection and sexual transmission risk reduction counseling	X	X
Referral for diagnosis and treatment of STIs, HBV, HCV and TB (as appropriate)	X	X
Clinical Procedures		
Blood collection (20ml whole blood for 10 ml plasma)	X	X
Urine collection	X	X
AE Assessment	X	X
Laboratory Procedures		
HIV testing (see SSP Manual)	X ¹	
CD4 cell count ³	X ³	X ³
HIV viral load ⁴		
Urine testing for substances of abuse ⁵	X	X
Plasma storage ⁶	X	X
Urine storage ⁶	X	X

¹ The first Quarterly visit after the Index participants' initial Exit visit will be a Re-Enrollment/Quarterly visit (up to 4 additional visits per participant). HIV testing per the site's normal algorithm must be performed to ensure that the correct participant is re-enrolled. Any Quarterly visit may be an Exit visit for participants. Follow-up is for up to 52 additional weeks. Follow alternative procedures as indicated if it is an Exit visit. Participants will have a re-enrollment visit, two quarterly visits and one exit visit (up to 4 visits total in the extension- Extension re-enrollment, Month 3, Month 6 and Exit after the Extension).

² If clinically indicated (according to national guidelines) and/or participant is randomized to the intervention group.

³ CD4 cell count testing will be performed 6 months and 12 months (Exit) after re-Enrollment.

⁴ Viral load testing will be performed at the HPTN LC.

⁵ Urine testing for substances of abuse will be in real-time study sites using locally-available methods; this testing can be performed in the clinic or laboratory.

⁶ Plasma and urine samples will be stored for Quality Assurance testing and other assessments at the HPTN LC (see Section 9.2).

SAMPLE INFORMED CONSENTS

Appendix IV A. Sample Screening Consent

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

DAIDS Document ID: 11917

Study Implementers: HIV Prevention Trials Network (HPTN) and the U.S. National Institutes of Health (NIH), Bethesda, MD, USA.

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID) and US National Institute on Drug Abuse (NIDA), Bethesda, MD, USA.

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION

You are being asked to take part in a research study that will help us design a new and better way to prevent the spread of HIV (human immunodeficiency virus, the virus that causes AIDS) among people who inject drugs. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator]. Before you decide whether or not to take part in the screening tests for this research study, you need to know the purpose of the screening tests, the possible risks and benefits of being screened, and what will be expected of you during the tests. This consent form provides that information. The study staff will discuss the information with you. They will answer any questions you may have. After the screening tests have been fully explained to you, you can decide whether or not you want to participate. If you understand the tests and agree to participate, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in the screening tests is entirely voluntary.
- You may decide not to take part or to withdraw from the screening tests at any time without losing the benefits of your standard health care.
- You are only being asked to take part in the screening tests at this time. Even if you agree to have the screening tests, you do not have to join or may not be eligible to join the research study.

Study Purpose

We are doing this study to help us develop a new and better way to prevent the spread of HIV from HIV-infected people who inject drugs to HIV uninfected people with whom they share needles/syringes or drug solutions.

- First, this study will help estimate the number of people who inject drugs who get new HIV infections in the countries where the sites are located.
- Second, this study will help researchers learn more about who, among HIV infected / HIV uninfected people who inject drugs, would be willing to take part in future studies related to HIV prevention. Researchers will also learn about whether or not taking part in this trial helps participants in their everyday lives.
- Third, in the intervention arm, the team will be comparing certain special support services with services which are usually available in your area and how these special support services might help people who inject drugs continue to take their HIV and/or substance use treatment.
- Fourth, we will be looking at the group of people who inject drugs with HIV infected drug users to see how big this group is and how often people join or leave the group.

All of these things will help us design a future study that will determine whether treating HIV-infected injection drug users with anti-HIV drugs and providing other support services including treatment for substance use where available will prevent them from passing the HIV virus to their injection drug partners. During the study, everyone with HIV will be referred for health care, which may include medications to treat HIV infection, substance use, or other conditions.

(Insert language as applicable) We will not provide treatment for HIV infection or substance use treatment or any medications at [INSERT NAME OF CLINIC/SITE]; instead we will send you to [REFERRAL LOCATION] if we recommend that you begin treatment.

Purpose of the screening tests:

- The purpose of the screening tests is to find out if you are eligible for the research study described above. Some people may not be asked to join the research study because of information found during the screening tests.
- The screening tests for the study include interview questions and at least one blood test for HIV.
- You may also have another blood test during these visits. If you agree to be screened for the study you may have up to two visits over the course of several weeks, and each visit will last about [one to two hours].
- You will be told the results of all of your screening tests as soon as they are available.
- After the screening tests, you will find out whether you are eligible for the research study. If you are eligible, the study staff will fully explain the research study to you and answer any questions you have. After the research study has been fully explained to you and if you decide to participate, you will be asked to sign another consent form.

Screening Visit

The first study visit is called the screening visit where we will test your blood for HIV. The screening visit will take about one to two hours. During this visit we will:

- Ask you questions about your age and other personal information to see if you are eligible to participate.

- Ask your name and contact information so that we can keep in touch with you during the study.
- We will draw [XX] mL of blood (about [XX] amount). This blood will be tested for HIV. We will talk to you about things you do which might put you at risk for HIV and talk to you about the results of this test. Some of the blood will be stored to check that test results from the study are correct and to perform other tests related to HIV prevention.
- We will refer you to a place where you can talk to someone about your substance use and how to reduce your risk of getting HIV or giving HIV to someone else if you are infected. [SITE TO ADJUST: You can also exchange your used needles for clean ones.]
- We will tell you the results of any tests we do at the study site during the study and refer you to [XX] clinic for treatment. If you have any concerns about any other infections (including tuberculosis, hepatitis, etc.) we will refer you to the appropriate place, which will examine you to see if you have any other infections and will offer you treatment.

As stated above, this is a study of HIV-infected people who inject drugs and HIV-uninfected people with whom they share needles/syringes or drug solutions. The results of your HIV tests will help us figure out if you can be in this study.

If you have HIV:

If your blood test shows that you do have HIV, we will continue with the following activities:

- We will draw additional blood (no more than XX mL, which is about XX teaspoons [change to local equivalent, if appropriate]). This blood will be tested to see what affect HIV has had on your body's ability to fight off infections and how much virus is in your blood. We will also study the virus to understand more about HIV transmission.
- In order to participate in the study, we will ask you to identify at least one person with whom you regularly share needles/syringes or drug solutions who you believe does not have HIV and who is willing and eligible to participate.
- We will also give you referral cards and ask you to give these to people with whom you have used drugs in the past month. We will screen these people and see if they are also able and willing to enroll in this study. We recommend that you tell them that you are HIV positive so that they can protect their own health. We can work with you to tell your injection partner about your HIV infection if you would like our help. Even if you are not eligible for this study, we may want to use your store blood and urine for future testing related to HIV infection and how HIV spreads in the community. If you agree to this use of your samples, we will ask you to initial the end of this form.

If you do not have HIV:

- If your blood test shows that you do not have HIV, you might still be eligible to participate in the study.
- We may ask you other questions related to your injection drug use, and whether or not you are willing to talk to people who you may share drugs with and ask them to come to this clinic to be tested for HIV. In order for you to be eligible, you must also have someone who you regularly share needles/syringes or drug solutions, who enrolls in our study.
- If we find that you are eligible, we may need to test you again to see that you still do not

have HIV.

RISKS and/or DISCOMFORTS:

If you participate in this screening, there are a few risks or discomforts you should know about.

- You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.
- You may become embarrassed, worried, or anxious when discussing your sexual or drug use practices, talking about HIV, or discussing or waiting for your test results. Learning that you have HIV may make you worried or anxious. It is also possible that participation in this screening process may cause disagreements between you and the people you share drugs with if you tell them that you are HIV positive and ask them if they want to be part of this study. A trained counselor will help you deal with any feelings or questions you may have.
- We will make every effort to protect your privacy and confidentiality. Your visits here will take place in private. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. Because of this, others may treat you unfairly or discriminate against you. For example, you could have problems getting or keeping a job. You could also have problems being accepted by your family or community. *(Sites to insert local registration requirements for antiretrovirals and substance use and the inherent risks)*

POTENTIAL BENEFITS:

- You may get no direct benefit from the screening tests. However, you will receive counseling about HIV and information on your HIV status.
- You and your partner will receive information about how to prevent the spread of HIV and you will get free condoms. *[SITE TO ADJUST: We will also refer you to a place where you can exchange dirty syringes for clean ones.]*
- If you have HIV, but not eligible for the study, you will be told where you can receive health care, counseling, substance use treatment and other services, as well as information about other research studies.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE SCREENING TESTS WITHOUT YOUR CONSENT:

You may be removed from the screening process without your consent for the following reasons:

- The study is stopped or cancelled.
- Undergoing the screening tests would be harmful to you.
- You are not able to attend the screening visits or complete the screening tests.
- You are not willing to refer at least one person you share drugs with for study screening.
- At least one person who you share drugs with is not willing or able to attend screening visits or complete the screening tests.
- You are not willing to find out your HIV test result.

COSTS AND COMPENSATION:

There is no cost to you for the screening tests. At the end of each visit, you will be given [insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, successful enrollment of network partners, etc.]

CONTACT INFORMATION

You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

CONFIDENTIALITY:

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Unless required by law or unless you give your written permission, study records that identify you will not be released to other parties or entities. However, your study records may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (US National Institutes of Health [NIH]), the [insert name of site] Institutional Review Board (IRB), study staff, study monitors, and (insert applicable local authorities). (If applicable: It is also possible that a court or other government agency could order that study records identifying you be released to others.) Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most the web site will include a summary of the results. You can search this web site at any time.

YOUR SAMPLES:

As part of screening for this study we will collect samples of your blood. There may be some leftover blood samples after all of the study-related testing has been completed. We would like to use these samples for future research related to HIV infection to develop new HIV tests, HIV vaccines and treatments and to learn more about HIV transmission and HIV prevention. If you agree to this use of your samples, we will ask you to initial the end of this form.

If you do not agree to have your leftover samples stored you can still be in this study. If you agree to store your samples but change your mind later, you can contact study staff. We will then destroy your leftover samples. If you agree, your leftover samples will be stored indefinitely [insert local guidelines]. Any future use of your samples that is not described here needs to be reviewed and approved by the NIH and local authorities. If these studies involve laboratories other than the study site laboratories and the HPTN Laboratory Center, we will need

approval from your local authorities to store or transfer them elsewhere. Your leftover samples will not be sold or used for commercial reasons.

RESEARCH-RELATED INJURY:

[Site-specific: insert institutional policy] It is unlikely that you will be injured as a result of having the screening tests. If you are injured, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS or QUESTIONS:

For questions about this study or a research-related injury, contact:

[insert name of the investigator or other study staff]

[insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

[insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]

[insert telephone number and physical address of above]

SIGNATURE PAGE: SAMPLE SCREENING CONSENT

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

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

Participant's Name (print) Participant's Signature or Thumbprint and Date

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

Study Staff Conducting Study Staff Signature and Date
Consent Discussion (print)

Please carefully read the statements below (or have them read to you) and think about your choice. No matter what you decide it will not affect whether you can be in the research study, or your routine health care.

_____ I agree to have samples of my blood used for future testing related to HIV infection and how HIV spreads in the community.

_____ I do not agree to have samples of my blood stored and used for future testing related to HIV infection and how HIV spreads in the community.

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

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

Witness' Name (print)

Witness's Signature and Date

Appendix IV-B. Sample Enrollment Consent for Index

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

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DAIDS Document ID: 11917

Study Implementers: HIV Prevention Trials Network (HPTN) and the U.S. National Institutes of Health (NIH), Bethesda, MD, USA.

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID) and US National Institute on Drug Abuse (NIDA), Bethesda, MD, USA.

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION

You are being asked to take part in a research study that will help us design a new and better way to prevent the spread of HIV (human immunodeficiency virus, the virus that causes AIDS) among people who inject drugs by referring people who inject drugs for substance use treatment where available and referring HIV-infected drug users for treatment with anti-HIV drugs. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

This study includes groups of people who inject drugs in which one person is infected with HIV and the other people are not. The person who is infected with HIV will tell the clinic about people with whom they share drugs who are not infected with HIV. About 500 people who are HIV infected will take part in this study including 167 at this site. About 750 people who are not HIV infected but share drugs with someone who is HIV infected will also take part in the study including about 250 at this site. The people in this study will come from sites in Asia and Eastern Europe. Each person will be in this study for two years at the most. You will be asked to be in the study for [SITE TO ADJUST FOR EARLY ENROLLEES].

Before you decide whether to take part in this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you and they will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand this study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.
- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your standard health care.

PURPOSE OF THE STUDY:

We are doing this study to help us develop a new and better way to prevent the spread of HIV from HIV infected people who inject drugs to HIV uninfected people with whom they share needles/syringes or drug solutions. What we learn will help us design a future study that will determine whether treating HIV infected injection drug users with anti-HIV drugs and providing other support services including treatment for substance use where available will prevent them from passing the HIV virus to their injection drug partners. During the study, everyone with HIV will be referred for health care, which may include medications to treat HIV infection, substance use, or other conditions. We will not provide treatment for HIV infection or substance use or any medications at [INSERT NAME OF CLINIC/SITE]; instead we will send you to [REFERRAL LOCATION] if we recommend that you begin treatment. [SITE TO ADJUST] You may also be offered medication that will help you stop using drugs. You do not need to accept this treatment in order to be part of this study.

At [REFERRAL LOCATION], some people will also be referred for anti-HIV drugs to treat their HIV infection, and will be asked to start taking these drugs as soon as they join the study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count *[or whatever term is commonly used locally]* is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, if you have HIV we will recommend that you start anti-HIV drugs *before your* T-cell count gets so low that would make you very sick. If you decide to take part in the study, you and the people you use drugs with who enroll in this study will be placed in 1 of 2 groups (called the “Intervention” and “Control” groups). Both groups are very important to this study, and, and you cannot choose which group you are in. Your group will be chosen “by lot” (like drawing straws or flipping a coin) *[or other equivalent local term]*. Your injection partners who you encourage to enroll in this study will be in the same group as you.

You have a greater chance of being placed in the “Control” group, meaning that you will receive the usual clinical and counseling services available and will start taking anti-HIV drugs later in the study after your T-cell count is lower or you become sick, but you cannot choose your group.

The “Intervention” group will receive more intensive services such as meeting with someone who you can talk to about your drug use and how to access drug and HIV treatment here at the clinic. Participants in the intervention group will also be referred to start taking anti-HIV drugs as soon as they join the study. People in both groups will have generally the same study visits, but people in the intervention group will have more visits, some of a different kind, than the other group.

PROCEDURES:

If you agree to join this study, you will be asked to come back to the site on a regular basis. We will tell you the results of any tests we do during the study at the study site which may impact your health. A few of your samples will be sent out of the country for testing because it is not possible to do these tests at our site. *[Sites should modify as needed]*

Enrollment visit

During your first study visit, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff. This visit may last up to [XX] hours. This visit may be broken up into two visits. During this visit, we will also:

- Ask you to update the contact information you gave at screening.
- Ask you questions about your use of anti-HIV drugs, substance use, access to health care, sexual practices, people with whom you share drugs or related equipment, and other things about your personal life.
- We will ask you for the names of the people with which you regularly share needles/syringes or drug solutions.
- We will assign you to a study group. Your group will be determined “by lot”, as we said above.
- We will draw [XX] mL of blood (about [XX] amount). This blood will be tested for HIV. We will talk to you about ways to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs.
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for drugs, medications used to treat HIV infection and substance use, and other HIV-related tests. The stored blood samples may also be used to learn more about how HIV is spread throughout the community.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will tell you the results of any tests we do during the study at the study site and will refer you to [XXX] clinic for treatment for anything we may find if needed.
- If you are assigned to the study group which starts taking anti-HIV drugs early or if the virus has started making you sick, we will refer you to [XXX] to begin receiving anti-HIV drugs. You will have the opportunity to meet with a counselor to talk about problems you may have getting drug and HIV treatments and work with you to overcome these problems. They may also help you with ways to be sure that you take your HIV medications. For a couple of sessions you can also bring in a family member or friend so that they can assist you with your HIV health care.
- We will refer you to a place where you can talk to someone about your substance use and how to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs. [SITE TO ADJUST: You can also exchange your used needles for clean ones.]

One month visit

One month after the enrollment visit, we will ask you to come in for a visit which will last about XX hours. During this visit we will:

- Ask you to confirm or update your contact information.

- We will talk to you about ways to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs.
- We will ask you for the names of the people with which you regularly share needles/syringes or drug solutions.
- We will ask you questions about your use of anti-HIV drugs, substance use, sexual partners, people with whom you share drugs and other things about your personal life.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will ask you whether there have been any changes to your health since your last visit.
- Ask you if you have had any problems accessing health care like treatment for your HIV or substance use.
- We will draw [XX] mL of blood (about [XX] amount).
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for drugs, medications used to treat HIV infection and substance use, and other HIV-related tests. The stored blood samples may also be used to learn more about how HIV is spread throughout the community.
- We will tell you the results of any tests we do during the study at the study site and will refer you to [XXX] clinic for treatment if needed.
- We will store blood and urine samples for other future research, if you allow us to do so.
- We will refer you to a place where you can talk to someone about your substance use and how to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs. [SITE TO ADJUST: You can also exchange your used needles for clean ones.]

Every 3 months and your last visit

After your enrollment visit, we will ask you to come back for a visit one month later and then every 3 months for [SITE TO ADJUST ACCORDING TO ENROLLMENT DATE:XX] for another visit. Each of these visits will last about XX hours. During these visits we will:

- Ask you to confirm or update your contact information again.
- We will talk to you about ways to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will ask you whether there have been any changes to your health since your last visit.
- Ask you if you have had any problems accessing health care like treatment for your HIV or substance use.
- We will ask you questions about your use of anti-HIV drugs, substance use, sexual partners, people with whom you share drugs and other things about your personal life.
- We will draw [XX] mL of blood (about [XX] amount). At Weeks 26, 52, 78 and 104 (depending on how long you are in the study) we will test your T-cell count and amount of virus in your to measure the amount of damage that HIV has done to your body.
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for drugs, medications used to treat HIV infection and substance use, and

other HIV-related tests. The stored blood samples may also be used to learn more about how HIV is spread throughout the community.

- We will tell you the results of any tests we do during the study at the study site and will refer you to [XXX] clinic for treatment if needed.
- We will store some blood and urine samples for other future research, if you allow us to do so.
- We will refer you to a place where you can talk to someone about your substance use and how to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs. [SITE TO ADJUST: You can also exchange your used needles for clean ones.]

Risks Associated with Early versus Delayed Treatment with Anti-HIV Drugs:

During this study, you may receive anti-HIV drugs as soon as you start the study, or later, if your body weakens or you become sick. There are risks associated with both ways the anti-HIV drugs are given in the study. Your doctor at [site to complete] will talk to you about the risks of any anti-HIV medications that you are given.

If you get the drugs immediately, when you are feeling healthy, the drugs may make you feel sick. By taking the drugs right away and staying on them, you may experience side effects that last a long time. These side effects can be very serious. Also, when you take anti-HIV drugs there is a risk that the drugs will stop working to fight the virus. The longer you take the drugs, the greater the chance is that the drugs may stop working. If this happens, your HIV infection may develop into AIDS.

In some studies, people have found that taking anti-HIV drugs sooner may help your body stay strong. If you receive the drugs only when you become sick, you may be too sick for the drugs to help your body in fighting the infection. The damage done to your immune system by the virus may be permanent, even when you are treated with the anti-HIV drugs. By waiting to take the anti-HIV drugs, you may be more likely to spread HIV to anyone you have sex with.

Pregnancy and Breastfeeding:

If you are a woman and you become pregnant, you should tell your doctor right away. You are welcome to continue study participation if you become pregnant. If you are not already in care for your HIV infection, we will help you find a place where you can be treated while you are pregnant. Taking anti-HIV medications while you are pregnant may help you protect your baby from becoming infected with HIV.

Other Risks:

- You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.
- You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect your partner against HIV, or discussing or waiting for your test results during the study.
- Knowing that you have HIV or other infections passed through sex may make you worried or anxious. A trained counselor will help you deal with any feeling or questions you have.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are here for this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. It is also possible that others may find out that you have been screened for this study and assume that you are a person who injects drugs. If people think you are infected with HIV or a person who injects drugs, this could cause you problems finding or keeping a job. Others may treat you unfairly, including your family and community. *(Sites to insert local registration requirements for antiretrovirals and substance use and the inherent risks.)*

Telling other people you are HIV-positive can pose risks to you including violence. In addition, this information may change the relationships you have with other people, which may be difficult for you in how you feel and when you're with other people. Further, it is possible that those you tell, will tell others that you are HIV-positive.

POTENTIAL BENEFITS:

There may be no direct benefit to you from this study. However, you will be sent to [XX] to receive the anti-HIV drugs either at the beginning of the study, or when your T-cell count has fallen or you become very sick. Although we will not provide the anti-HIV drugs here, we will work to make sure that you can receive them at [XXX.] The anti-HIV drugs are not a cure for HIV infection or AIDS, but we know that they can make people infected with HIV feel better, not get as sick, and live longer. We will tell you the results of any tests done at the study site during the study or other information related to your health that is obtained during the study at the study site. You will be able to talk to counselors about your health and feelings. We will refer you to [XXX] where someone will talk to you about ways to reduce your drug use and slow the spread of HIV. You will also receive free condoms throughout the entire course of the study. In addition, knowledge gained from this study may help others infected with HIV in the future. Although participation in this study may also prevent you from spreading the HIV virus to others, no guarantee can be made, you should not share drugs, needles or works with anyone.

ACCESS TO CARE AFTER THE STUDY ENDS:

After this study ends, you will have on-going access to care for substance use and treat your HIV infection.

NEW FINDINGS:

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.

- We are not able to enroll at least one HIV negative person with whom you regularly share needles/syringes or drug solutions.

ALTERNATIVES TO PARTICIPATION:

If you choose not to take part in this study, it will have no effect on your access to regular services at this site. There may be other studies at this site in which you may be eligible to participate. Even if you choose to participate in this study, it is not known whether taking anti-HIV drugs can prevent you from giving HIV to others.

COSTS AND COMPENSATION:

There will be no cost to you for study-related visits or other procedures. There will *(or will not: Sites to insert appropriate cost language)* be a cost to you at XX or XX for which you may be sent for anti-HIV drugs or treatment for your substance use. At the end of each visit to this site, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc.]*

CONTACT INFORMATION

You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study. We will also ask you to give us contact information at the last study visit so we can contact you and share with you the results of this study.

CONFIDENTIALITY:

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Unless required by law or unless you give your written permission, study records that identify you will not be released to other parties or entities. However, your study records may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (US National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB), study staff, study monitors, and *(insert applicable local authorities)*. *(If applicable: It is also possible that a court or other government agency could order that study records identifying you be released to others.)* Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most the web site will include a summary of the results. You can search this web site at any time.

During the study, some of your samples (blood and urine) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy.

YOUR SAMPLES:

We will store blood and urine samples for testing related to this study. These samples will be used for study-related testing. This may include tests for drugs, medications used to treat HIV infection and substance use, tests of how HIV spreads in the community, and other tests related to the HIV virus and your body's response to HIV infection. There may be some left over samples of blood and urine samples after all of the study-related testing has been completed. We would like to use these samples for future research studies. If you agree to this use of your samples, we will ask you to **initial** the end of this form.

If you do not agree to have your left over samples stored you can still be in this study. If you agree to store your samples but change your mind later, you can contact the study staff listed on this form. We will then destroy your samples. If you agree, your left over samples will be stored indefinitely [insert local guidelines]. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we will need approval from your local authorities to store or transfer them elsewhere. Your left over samples will not be sold or used for commercial reasons.

RESEARCH-RELATED INJURY:

The study staff will ask you questions about your health at every study visit. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions]. [Sites to specify institutional policy:] If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS or QUESTIONS:

For questions about this study or a research-related injury, contact:

- [site insert name of the investigator or other study staff]
- [site insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

- [site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [site insert telephone number and physical address of above]

SIGNATURE PAGE: SAMPLE ENROLLMENT CONSENT FOR INDEX

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

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

Please carefully read the statements below (or have them read to you) and think about your choice. No matter what you decide it will not affect whether you can be in the research study, or your routine health care.

_____ I agree to have samples of my blood used for future testing related to HIV infection.

_____ I agree to have samples of my urine used for future testing related to HIV infection.

_____ I do not agree to have samples of my blood stored and used for future testing related to HIV infection.

_____ I do not agree to have samples of my urine stored and used for future testing related to HIV infection.

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

Participant's Name (print) Participant's Signature or Thumbprint and Date

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

Study Staff Conducting Study Staff Signature and Date
Consent Discussion (print)

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the

purpose, procedures, risks and benefits of the study and has voluntarily accepted to participate in this study.

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

Witness' Name (print)

Witness's Signature and Date

Appendix IV-C. Sample Enrollment Consent for Network Injection Partners

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

DAIDS Document ID: 11917

Study Implementers: HIV Prevention Trials Network (HPTN) and the U.S. National Institutes of Health (NIH), Bethesda, MD, USA.

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID) and US National Institute on Drug Abuse (NIDA), Bethesda, MD, USA.

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

INTRODUCTION

You are being asked to take part in a research study that will help us design a new and better way to prevent the spread of HIV (human immunodeficiency virus, the virus that causes AIDS) among people who inject drugs by referring people who inject drugs for substance use treatment where available and referring HIV-infected drug users for treatment with anti-HIV drugs. The person in charge of the study at this site is [insert name of principal investigator].

This study includes groups of people who inject drugs in which one person is infected with HIV and the other people are not. You are being asked to be in this study because someone who you inject drugs with has HIV and told you about the study. About 500 people who are HIV infected will take part in this study including 167 at this site. About 750 people who are not HIV infected but share drugs with someone who are HIV infected will also take part in the study including about 250 at this site. The people in this study will come from Asia and Eastern Europe. Each person will be in this study for two years at the most. You will asked to be in the study for [SITE TO ADJUST FOR EARLY ENROLLEES].

Before you decide whether to take part in this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you and they will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to participate. Once you understand this study, and if you agree to take part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.
- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your standard health care.

PURPOSE OF THE STUDY:

We are doing this study to help us develop a new and better way to prevent the spread of HIV from HIV infected people who inject drugs to HIV uninfected people with whom they share needles/syringes or drug solutions. What we learn will help us design a future study that will determine whether treating HIV infected injection drug users with anti-HIV drugs and providing other support services including treatment for substance use where available will prevent them from passing the HIV virus to their injection drug partners. During the study, everyone with HIV will be referred for health care, which may include medications to treat HIV infection, substance use, or other conditions. We will not provide treatment for HIV infection or substance use or any medications at [INSERT NAME OF CLINIC/SITE]; instead we will send you to [REFERRAL LOCATION] if we recommend that someone begins treatment. [SITE TO ADJUST] You may also be offered medication that will help you stop using drugs. You do not need to accept this treatment in order to be part of this study.

If you decide to take part in the study, your injection partner, who encouraged you to enroll in this study by giving you the referral card, will be placed in 1 of 2 groups (called the “Intervention” and “Control” groups). This group will be chosen “by lot” (like drawing straws or flipping a coin) *[or other equivalent local term]*.

You have a greater chance of being placed in the “Control” group, meaning that you will receive the usual clinical and counseling services available and your injection partner will start taking anti-HIV drugs later in the study. The “Intervention” group will receive more intensive services and your injection partner will be referred to start taking drugs as soon as they join the study. Both groups are very important to this study. You cannot choose which group you are in. You have a greater chance of being placed in the “Control” group, meaning that you will receive the usual clinical and counseling services available, but you cannot choose your group. You will be in the same group as your injection partner (the one who encouraged you to enroll in this study by giving you the referral card). Both groups are very important to this study. People in both groups will have generally the same study visits, but people in the intervention group will have more visits, some of a different kind, than the other group.

PROCEDURES:

If you agree to join this study, you will be asked to come back to the site on a regular basis. We will tell you the results of any tests we do during the study at the study site which may impact your health. A few of your samples will be sent out of the country for testing because it is not possible to do tests at our site. *[Sites should modify as needed]*

Enrollment visit

During your first study visit, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff. This visit may last up to XX hours. This visit may be broken up into two visits. During this visit, we will also:

- Ask you to update the contact information you gave at screening.
- Ask you questions about your substance use, access to health care, sexual practices, people with whom you share drugs or related equipment, and other things about your personal life.
- We will ask you for the names of the people with which you regularly share needles/syringes or drug solutions.
- We will draw [XX] mL of blood (about [XX] amount). We will talk to you about things you do which might put you at risk for HIV, test this blood for HIV and talk to you about the results of this test.
- We will talk to you about ways to reduce the chances that you may become infected with HIV.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will ask you if you have had any problems accessing health care like treatment for your substance use.
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for substances of abuse and medications used to treat substance use.
- We will tell you the results of any tests we do at the study site and will refer you to [XXX] clinic for treatment if needed.
- We will take samples of blood and urine that we will store for other future research, if you allow us to do so.
- We will assign you to a study group. Your group will be determined “by lot”, as we said above.

One month visit

One month after the enrollment visit, we will ask you to come in for a visit which will last about XX hours. During this visit we will:

- Ask you to confirm or update your contact information.
- We will talk to you about ways to reduce the chances that you may become infected with HIV.
- Ask you questions about your substance use, access to health care, sexual practices, people with whom you share drugs or related equipment, and other things about your personal life.
- We will ask you for the names of the people with which you regularly share needles/syringes or drug solutions.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will ask you whether there have been any changes to your health since your last visit.
- We will ask you if you have had any problems accessing health care like treatment for your substance use.
- We will draw [XX] mL of blood (about [XX] amount). We will talk to you about things you do which might put you at risk for HIV, test this blood for HIV and talk to you about the results of this test.
- We will also ask you for a urine sample for drug testing.

- We will store blood and urine samples for other testing related to this study. This may include tests for substance of abuse and medications used to treat substance use. If you become infected during the study, these samples may also be used to test for medications used to treat HIV infection and for other HIV-related testing.
- We will also store blood and urine samples for other future research, if you allow us to do so.
- We will tell you the results of any tests we do at the site during the study and refer you to [XX] clinic for treatment if needed.

Every 3 months and your last visit

After your enrollment visit, we will ask you to come back for a visit one month later and then every 3 months for one year (SITE TO ADJUST FOR EARLY ENROLLEES) for another visit. Depending on when you join the study, some participants may be asked to come for one year and others will be asked to come for up to two years. Each of these visits will last about XX hours. During these visits we will:

- Ask you to confirm or update your contact information again.
- We will draw [XX] mL of blood (about [XX] amount). We will talk to you about things you do which might put you at risk for HIV, test this blood for HIV and talk to you about the results of this test.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will ask you whether there have been any changes to your health since your last visit.
- We will ask you if you have had any problems accessing health care like treatment for your substance use.
- Ask you questions about your substance use, access to health care, sexual practices, people with whom you share drugs or related equipment, and other things about your personal life.
- We will ask you for the names of the people with which you regularly share needles/syringes or drug solutions.
- This blood will be tested for HIV.
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for substance of abuse and medications used to treat substance use. If you become infected during the study, these samples may also be used to test for medications used to treat HIV infection and other HIV-related tests.
- We will also store blood and urine samples for other future research, if you allow us to do so.
- We will tell you the results of any tests we do at the site during the study and refer you to [XXX] clinic for treatment if needed.

If you test positive for HIV

If you have a test result at any study visit that indicates you may have been infected with HIV, we will arrange to confirm the test result. If the confirmatory tests show that you do have HIV infection, we will perform tests to see how well your body can fight off infections and measure the amount of virus in your blood. If we confirm that you are infected with HIV later in the study we will ask you to continue to come to the study clinic as scheduled. [Insert any

additional local testing that may be performed]. [Insert any local reporting requirements.] We will also refer you for HIV treatment and care. If you become infected during the study, stored blood and urine samples may also be used to test for medications used to treat HIV infection and other HIV-related tests as noted above. The stored blood samples may also be used to learn more about how HIV is spread throughout the community.

Risks:

- You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.
- You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect yourself against HIV, or discussing or waiting for your test results during the study.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are here for this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. It is also possible that others may find out that you have been screened for this study and assume that you are a person who injects drugs. If people think you are infected with HIV or a person who injects drugs, this could cause you problems finding or keeping a job. Others may treat you unfairly, including your family and community. *(Sites to insert local registration requirements for antiretrovirals and substance use and the inherent risks)*

Even if the person you share drugs with is getting treatment for their HIV, you should not share drugs, needles or works with your partner or anyone else in order to protect yourself from getting HIV. If your partner is just starting treatment or does not take it when they are supposed to, they may have a high level of HIV in their body (called “viral load”) which will make it easier to pass HIV to you. Also, we do not know for sure at this time if being treated for HIV will make it less likely that they will pass the virus to you if you are sharing drugs, needles or works.

POTENTIAL BENEFITS:

We will tell you the results of any tests or other information related to your health during the study at the study site. You will be able to talk to counselors about your health and feelings. We will refer you to [XXX] where someone will talk to you about ways to reduce your drug use and slow the spread of HIV. You will also receive free condoms throughout the entire course of the study. In addition, knowledge gained from this study may help others infected with or at risk of infection with HIV in the future.

NEW FINDINGS:

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.

- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- The person who referred you to this study, who you regularly share needles/syringes or drug solutions leaves the study.

ALTERNATIVES TO PARTICIPATION:

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

COSTS AND COMPENSATION:

There will be no cost to you for study-related visits or other procedures. There will *(or will not: Sites to insert appropriate cost language)* be a cost to you at [XX] or [XX] for which you may be sent for treatment for your substance use. At the end of each visit to this site, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc.]*

CONTACT INFORMATION

You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study.

CONFIDENTIALITY:

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Unless required by law or unless you give your written permission, study records that identify you will not be released to other parties or entities. However, your study records may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (US National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB), study staff, study monitors, and *(insert applicable local authorities)*. *(If applicable: It is also possible that a court or other government agency could order that study records identifying you be released to others.)* Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most the web site will include a summary of the results. You can search this web site at any time.

During the study, some of your samples (blood and urine) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy.

YOUR SAMPLES:

We will store blood and urine samples for testing related to this study. These samples will be used for study-related testing. This may include tests for drugs, medications used to treat HIV infection and substance use, and if you become infected with HIV, other tests related to the HIV virus and your body's response to HIV infection. There may be some left over samples of blood and urine samples after all of the study-related testing has been completed. We would like to use these samples for future research studies. If you agree to this use of your samples, we will ask you to initial the end of this form. The stored blood samples will also be used to learn more about how HIV is spread throughout the community.

If you do not agree to have your left over samples stored you can still be in this study. If you agree to store your samples but change your mind later, you can contact study staff. We will then destroy your samples. If you agree, your left over samples will be stored indefinitely [insert local guidelines]. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we will need approval from your local authorities to store or transfer them elsewhere. Your left over samples will not be sold or used for commercial reasons.

RESEARCH-RELATED INJURY:

The study staff will ask you questions about your health at every study visits. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, [insert site-specific instructions].[Sites to specify institutional policy:] If you are injured as a result of being in this study, the [institution] will give you immediate necessary treatment for your injuries. You [will/will not] have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS or QUESTIONS:

For questions about this study or a research-related injury, contact:

- [site insert name of the investigator or other study staff]
- [site insert telephone number and physical address of above]

For questions about your rights as a research subject, contact:

- [site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]
- [site insert telephone number and physical address of above]

**SIGNATURE PAGE: SAMPLE ENROLLMENT CONSENT FOR NETWORK
INJECTION PARTNERS**

**HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard
study for a network-based randomized HIV prevention trial comparing an integrated
intervention including supported antiretroviral therapy to the standard of care**

Final Version 2.0, 26 July 2017

Please carefully read the statements below (or have them read to you) and think about your choice. No matter what you decide it will not affect whether you can be in the research study, or your routine health care.

_____ I agree to have samples of my blood used for future testing related to HIV infection.

_____ I agree to have samples of my urine used for future testing related to HIV infection.

_____ I do not agree to have samples of my blood stored and used for future testing related to HIV infection.

_____ I do not agree to have samples of my urine stored and used for future testing related to HIV infection.

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

Participant's Name (print)

Participant's Signature or Thumbprint and Date

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

Study Staff Conducting
Consent Discussion (print)

Study Staff Signature and Date

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

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

Witness' Name (print)

Witness's Signature and Date

Appendix IV-D. Sample Key Informant Interview Informed Consent for Selected Study Index Participants, Navigators, Counselors or Key Clinic Personnel at the HIV Care and Substance Use Treatment Sites

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

DAIDS Document ID: 11917

Study Implementers: HIV Prevention Trials Network (HPTN) and the U.S. National Institutes of Health (NIH), Bethesda, MD, USA.

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID) and US National Institute on Drug Abuse (NIDA), Bethesda, MD, USA.

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

Introduction

You have been invited to participate in a research study which includes an interview to discuss your role as either: 1) provider or supervisor of providers to participants for antiretrovirals or substance use therapy, 2) as a navigator or counselor for participants, or 3) an Index participant assigned to the intervention arm in HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care. This “Key Informant Interview” is an individual discussion about a specific set of topics. The purpose of this interview is to help us learn more about:

Common barriers and facilitators for providers and for clinic participants for feasibility and barriers to the intervention provided during this study. This includes those services participants were referred for outside of this clinic including:

- Uptake of HIV testing
- Initiation of HIV care
- Initiation of substance use treatment
- Medication adherence

Approximately 4-10 navigators and counselors at the *[insert name]* clinic as well as persons directly involved in antiretroviral or substance use dispensation during HPTN 074 and up to 15 HIV positive study participants randomized to the intervention arm at each of the three study centers and referral locations will participate in individual Key Informant Interviews near the time when all participants at each of the sites are just beginning the study and up to 20 HIV

positive study participants randomized to the intervention arm at each of the three study centers when they have completed all visits. This means a total of about 12-30 navigators, counselors, and persons directly involved with antiretroviral or substance use dispensation and up to 60 HIV positive study participants randomized to the intervention arm from all three study centers combined. The information from these interviews will help us better understand what we learn from the rest of the study. We hope the information we learn will help us reduce the number of people who inject drugs who become infected with HIV in the future, as well as how best to support HIV-infected people who inject drugs seeking treatment for HIV and substance use. The information gathered from these interviews will be combined with the rest of the information that is collected during this research study.

Procedures

[Sites to adjust as needed] The interview will be led by an individual that is not directly a member of our research team here at [insert clinic] but is affiliated with our overall research organization. The individual will not be someone who has a supervisory role for your position. As stated previously, you will be asked to identify common barriers and facilitators for participants to:

- Uptake of HIV testing
- Initiation of HIV care
- Initiation of substance use treatment
- Medication adherence

Your participation in this interview is voluntary. You are not required to participate in this interview in order to remain employed at [insert site]. Although we hope that you will be comfortable answering all of the questions openly and honestly, please keep in mind that you may refuse to answer any of the questions, or stop your participation completely, at any time. Your decision about whether or not to participate in this study is confidential and we will not tell other people whether or not you participated.

[To be modified to reflect site practices]: The interview will take place in a location that the study team has determined will provide you with privacy and confidentiality. The study team will talk with you about this so you know where to go for the interview.

Each interview should take about one hour. There will be no cost to you for participation. You will receive [insert local amount] for your time and effort.

What Are the Potential Benefits?

You may not receive any other direct benefit from being in this study; however, the information gathered during this study may help to provide better access to antiretrovirals and substance use therapies for people who inject drugs.

What Are the Possible Risks or Discomforts?

As noted, to minimize discomfort and to protect your privacy, the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. The greatest

risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

What are the alternatives to participating in this study?

[Sites to amend as applicable] If you choose not to take part in this study, it will have no effect on your current employment. We will not tell your employer about whether or not you decide to participate in the interview.

How Will Your Privacy Be Protected?

The study team will try to protect the privacy of your study records and test results, to the extent permitted by law, but cannot guarantee that your study records and test results will never be released to others. As part of the study team's efforts to protect your study records from disclosure, you will be identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Unless required by law or unless you give your written permission, study records that identify you will not be released to other parties or entities. However, your study records may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (US National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB), study staff, study monitors, and *(insert applicable local authorities)*. *(If applicable: It is also possible that a court or other government agency could order that study records identifying you be released to others.)* Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most the web site will include a summary of the results. You can search this web site at any time.

PROBLEMS or QUESTIONS:

For questions about this study or a research-related injury, contact:

- *[site insert name of the investigator or other study staff]*
- *[site insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[site insert telephone number and physical address of above]*

SIGNATURE PAGE: Sample Key Informant Interview Informed Consent for Selected Study Participants, Navigators, Counselors or Key Clinic Personnel at the HIV Care and Substance Use Treatment Sites

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

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

Please carefully read the statements below (or have them read to you) and think about your choice. No matter what you decide it will not affect whether you can be in the research study, or your routine health care. If you have read this informed consent, or have had it read and explained to you, and understand the information, and you voluntarily agree to enroll into this study, please sign your name or make your mark below.

Participant's Name (print) Participant's Signature or Thumbprint and Date

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

Study Staff Conducting Study Staff Signature and Date
Consent Discussion (print)

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

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

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

Appendix IV-E. Sample Re-Enrollment Consent for Index Extension (up to 12 additional months)

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

DAIDS Document ID: 11917

Study Implementers: HIV Prevention Trials Network (HPTN) and the U.S. National Institutes of Health (NIH), Bethesda, MD, USA.

Study Sponsors: NIH, Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID) and US National Institute on Drug Abuse (NIDA), Bethesda, MD, USA.

PRINCIPAL INVESTIGATOR: [Insert Name]
PHONE: [Insert Number]

INTRODUCTION

You are being asked to take part in a research study that will help us design a new and better way to prevent the spread of HIV (human immunodeficiency virus, the virus that causes AIDS) among people who inject drugs by referring people who inject drugs for substance use treatment where available and referring HIV-infected drug users for treatment with anti-HIV drugs. This study is sponsored by the United States National Institutes of Health. The person in charge of the study at this site is [insert name of principal investigator].

The main study included groups of people who inject drugs in which one person is infected with HIV and the other people are not. As you are aware, you recently completed participation in that main study which is referred to as HPTN 074. We are asking that you participate in an extension to that study, adding up to 12 additional months of follow-up. Up to 500 people who are HIV infected will take part in this extension including about 200 at this site. The people in this study will come from sites in Asia and Eastern Europe. Each person will be in this study for up to 12 months at the most.

Before you decide whether to take part in the 12 month extension to this research study, you need to know the purpose, the possible risks and benefits to you, and what will be expected of you during the study. This consent form provides that information. The study staff will discuss the information with you and they will answer any questions you may have. After the study has been fully explained to you, you can decide whether or not you want to continue to participate in this 12 month extension to HPTN 074. Once you understand this study, and if you agree to take

part, you will be asked to sign this consent form or make your mark in front of someone. You will be offered a copy of this form to keep.

Please note that:

- Your participation in this study is entirely voluntary.
- You may decide not to take part or to withdraw from this study at any time without losing the benefits of your standard health care.
- You will be in the same “arm” of the study that you were previously in. In other words, if you were in the intervention arm, you will remain in that arm. If you were in the standard of care arm, you will remain in that arm. Should you have any questions, please feel free to ask the study staff for clarification.

PURPOSE OF THE STUDY:

We are doing this study to help us develop a new and better way to prevent the spread of HIV from HIV infected people who inject drugs to HIV uninfected people with whom they share needles/syringes or drug solutions and to look at the pattern of how people will continue to take ART and compare that to their HIV viral suppression over a longer period of time in order to see if the study intervention can be successful in helping people over a longer period of time. What we learn will help us design a future study that will determine whether treating HIV infected injection drug users with anti-HIV drugs and providing other support services including treatment for substance use where available and during the original portion of the study prevented them from passing the HIV virus to their injection drug partners. During the study, everyone with HIV will be referred for health care, which may include medications to treat HIV infection, substance use, or other conditions. We will not provide treatment for HIV infection or substance use or any medications at [INSERT NAME OF CLINIC/SITE]; instead we will send you to [REFERRAL LOCATION] if we recommend that you begin treatment. [SITE TO ADJUST] You may also be offered medication that will help you stop using drugs. You do not need to accept this treatment in order to be part of this study.

At [REFERRAL LOCATION], some people will also be referred for anti-HIV drugs to treat their HIV infection, and will be asked to start taking these drugs as soon as they join the study. You will continue with the same treatment arm you were assigned during the main study. Others may start to take the anti-HIV drugs later in the study, after their T-cell count *[or whatever term is commonly used locally]* is lower or if they become sick. The T-cell count is a blood test that we use to measure the amount of damage that HIV has done to your body. Regardless of which group you are in, if you have HIV we will recommend that you start anti-HIV drugs *before your* T-cell count gets so low that would make you very sick. If you decide to continue in the study, you and the people you use drugs with who enroll in this study will continue in the same group that you were in for the main HPTN 074 study (called the “Intervention” and “Control” groups). Both groups are very important to this study, and you cannot choose which group you are in. Your group will be chosen “by lot” (like drawing straws or flipping a coin) *[or other equivalent*

local term]. If you have any questions about what group you are in, please ask the research staff at this site.

PROCEDURES:

If you agree to join this study, you will be asked to come back to the site on a regular basis. We will tell you the results of any tests we do during the study at the study site which may impact your health. A few of your samples will be sent out of the country for testing because it is not possible to do these tests at our site. *[Sites should modify as needed]*

Re-Enrollment visit

During your first study visit for this extension, the study will be explained to you. You will have time to ask questions and discuss any concerns you may have with the study staff. This visit may last up to [XX] hours. This visit may be broken up into two visits. During this visit, we will also:

- Ask you questions about your use of anti-HIV drugs, substance use, access to health care, sexual practices, people with whom you share drugs or related equipment, and other things about your personal life.
- We will draw [20] mL of blood (about [4 teaspoons] amount). This blood will be tested for HIV. We will talk to you about ways to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs.
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for drugs, medications used to treat HIV infection and substance use, and other HIV-related tests. The stored blood samples may also be used to learn more about how HIV is spread throughout the community.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will tell you the results of any tests we do during the study at the study site and will refer you to [XXX] clinic for treatment for anything we may find if needed.
- We will refer you to [XXX] to begin receiving anti-HIV drugs. If you are in the “Intervention” group, you will have the opportunity to meet with a counselor to talk about problems you may have getting drug and HIV treatments and work with you to overcome these problems. They may also help you with ways to be sure that you take your HIV medications. For a couple of sessions you can also bring in a family member or friend so that they can assist you with your HIV health care.
- We will refer you to a place where you can talk to someone about your substance use and how to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs. [SITE TO ADJUST: You can also exchange your used needles for clean ones.]

Every 3 months and your last visit (4 visits total including this re-Enrollment visit)

After your re-enrollment visit, we will ask you to come back for a visit every 3 months for another visit. Each of these visits will last about XX hours. During these visits we will:

- Ask you to confirm or update your contact information again.
- We will talk to you about ways to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs.
- We will ask you if you have had any good or bad things happen to you because you are taking part in this study.
- We will ask you whether there have been any changes to your health since your last visit.
- Ask you if you have had any problems accessing health care like treatment for your HIV or substance use.
- We will ask you questions about your use of anti-HIV drugs, substance use, sexual partners, people with whom you share drugs and other things about your personal life.
- We will draw [20] mL of blood (about [4 teaspoons] amount).
- We will also ask you for a urine sample for drug testing.
- We will store blood and urine samples for other testing related to this study. This may include tests for drugs, medications used to treat HIV infection and substance use, and other HIV-related tests. The stored blood samples may also be used to learn more about how HIV is spread throughout the community.
- We will tell you the results of any tests we do during the study at the study site and will refer you to [XXX] clinic for treatment if needed.
- We will store some blood and urine samples for other future research, if you allow us to do so.
- We will refer you to a place where you can talk to someone about your substance use and how to reduce the chances that you may pass HIV on to the people with whom you have sex or share drugs. [SITE TO ADJUST: You can also exchange your used needles for clean ones.]

Risks Associated with Early versus Delayed Treatment with Anti-HIV Drugs:

During this study, you may receive anti-HIV drugs as soon as you start the study, already be on anti-HIV drugs, or receive anti-HIV drugs later, if your body weakens or you become sick. There are risks associated with all ways the anti-HIV drugs are given in the study. Your doctor at [site to complete] will talk to you about the risks of any anti-HIV medications that you are given.

If you get the drugs immediately, when you are feeling healthy, the drugs may make you feel sick. By taking the drugs right away and staying on them, you may experience side effects that last a long time. These side effects can be very serious. Also, when you take anti-HIV drugs there is a risk that the drugs will stop working to fight the virus. The longer you take the drugs, the greater the chance is that the drugs may stop working. If this happens, your HIV infection may develop into AIDS.

In some studies, people have found that taking anti-HIV drugs sooner may help your body stay strong. If you receive the drugs only when you become sick, you may be too sick for the drugs to help your body in fighting the infection. The damage done to your immune system by the virus may be permanent, even when you are treated with the anti-HIV drugs. By waiting to take the anti-HIV drugs, you may be more likely to spread HIV to anyone you have sex with.

Pregnancy and Breastfeeding:

If you are a woman and you become pregnant, you should tell your doctor right away. You are welcome to continue study participation if you become pregnant. If you are not already in care for your HIV infection, we will help you find a place where you can be treated while you are pregnant. Taking anti-HIV medications while you are pregnant may help you protect your baby from becoming infected with HIV.

Other Risks:

- You may feel discomfort, dizzy, or even faint when your blood is drawn. Redness, pain, swelling, bruising, or an infection may occur where the needle goes into your arm.
- You may become embarrassed, worried, or anxious when discussing your sexual practices, ways to protect your partner against HIV, or discussing or waiting for your test results during the study.
- Knowing that you have HIV or other infections passed through sex may make you worried or anxious. A trained counselor will help you deal with any feeling or questions you have.

We will make every effort to protect your privacy and confidentiality while you are in this study. However, it is possible that you could have problems if people learn that you are here for this study. People may think that you are infected with HIV or at risk of HIV because of sexual behavior or drug use. It is also possible that others may find out that you have been screened for this study and assume that you are a person who injects drugs. If people think you are infected with HIV or a person who injects drugs, this could cause you problems finding or keeping a job. Others may treat you unfairly, including your family and community. *(Sites to insert local registration requirements for antiretrovirals and substance use and the inherent risks.)*

POTENTIAL BENEFITS:

There may be no direct benefit to you from this study. However, you will be referred to receive anti-HIV drugs. Although we will not provide the anti-HIV drugs here, we will work to make sure that you can receive them at [XXX.] The anti-HIV drugs are not a cure for HIV infection or AIDS, but we know that they can make people infected with HIV feel better, not get as sick, and live longer. We will tell you the results of any tests done at the study site during the study or other information related to your health that is obtained during the study at the study site. You will be able to talk to counselors about your health and feelings. We will refer you to [XXX] where someone will talk to you about ways to reduce your drug use and slow the spread of HIV. You will also receive free condoms throughout the entire course of the study. In addition, knowledge gained from this study may help others infected with HIV in the future. Although participation in this study may also prevent you from spreading the HIV virus to others, no guarantee can be made, you should not share drugs, needles or works with anyone.

ACCESS TO CARE AFTER THE STUDY ENDS:

After this study ends, you will have on-going access to care for substance use and treat your HIV infection.

NEW FINDINGS:

You will be told of any new information learned during the course of the study that might cause you to change your mind about staying in the study. At the end of the study, you will be told when study results may be available and how to learn about them.

If the researchers find that the Intervention arm is beneficial to helping people get into HIV care, and helps lower their HIV virus, those in the standard of care arm will be offered the opportunity for all services provided in the intervention arm, including help from a “systems navigator” in order to assist with getting drugs to treat HIV infection and decrease substance use. The study researchers estimate that this information may be available as early as the first part of 2018. Please refer to the research staff should you have any questions.

REASONS WHY YOU MAY BE WITHDRAWN FROM THE STUDY WITHOUT YOUR CONSENT:

You may be removed from the study without your consent for the following reasons:

- The study is stopped or cancelled.
- Staying in the study would be harmful to you.
- You are not able to attend study visits or complete the study procedures.
- We are not able to enroll at least one HIV negative person with whom you regularly share needles/syringes or drug solutions.

ALTERNATIVES TO PARTICIPATION:

If you choose not to take part in this study, it will have no effect on your access to regular services at this site. There may be other studies at this site in which you may be eligible to participate. Even if you choose to participate in this study, it is not known whether taking anti-HIV drugs can prevent you from giving HIV to others.

COSTS AND COMPENSATION:

There will be no cost to you for study-related visits or other procedures. There will *(or will not: Sites to insert appropriate cost language)* be a cost to you at XX or XX for which you may be sent for anti-HIV drugs or treatment for your substance use. At the end of each visit to this site, you will be given *[insert amount of money or incentive package to compensate participant for food, travel expenses, lost work time, etc.]*

CONTACT INFORMATION

You will be asked to provide your address and phone number(s). The staff will ask you for names of people who will always know how to find you and places where you can be found. It is possible that the staff may visit you at your house or contact one of the people on your contact list if you are not able to attend your visits or if the staff have important information for you. If we talk to people on this list, we will not tell them why we are trying to reach you. If you are not willing to give us this information, you should not agree to be in this study. We will also ask you to give us contact information at the last study visit so we can contact you and share with you the results of this study.

CONFIDENTIALITY:

The study team will try to protect the privacy of your study records and test results to the extent permitted by law, but in some cases, local law can require this information to be released. As part of the study team’s efforts to protect your study records from disclosure, you will be

identified in the study records by a code, and the study team leadership will keep the link between the code and your identity separate from your study records. Unless required by law or unless you give your written permission, study records that identify you will not be released to other parties or entities. However, your study records may be reviewed by various government agencies that have a legal right to do so, such as the sponsor of the study (US National Institutes of Health [NIH]), the *[insert name of site]* Institutional Review Board (IRB)/ Ethics Committee (EC), study staff, study monitors, and *(insert applicable local authorities)*. *(If applicable: It is also possible that a court or other government agency could order that study records identifying you be released to others.)* Any publication or presentation of the results of findings of this study will not use your name and will not include any information that will identify you.

A description of this study will be available on www.ClinicalTrials.gov. This web site will not include information that can identify you. At most the web site will include a summary of the results. You can search this web site at any time.

During the study, some of your samples (blood and urine) may be stored for tests done later. These samples will be stored in containers that do not have your name on them but rather a code to protect your privacy.

YOUR SAMPLES:

We will store blood and urine samples for testing related to this study. These samples will be used for study-related testing. This may include tests for drugs, medications used to treat HIV infection and substance use, tests of how HIV spreads in the community, and other tests related to the HIV virus and your body's response to HIV infection. There may be some left over samples of blood and urine samples after all of the study-related testing has been completed. We would like to use these samples for future research studies. If you agree to this use of your samples, we will ask you to initial the end of this form.

If you do not agree to have your left over samples stored you can still be in this study. If you agree to store your samples but change your mind later, you can contact the study staff listed on this form. We will then destroy your samples. If you agree, your left over samples will be stored indefinitely *[insert local guidelines]*. Any future use or the ability to store your samples longer needs to be reviewed and approved by the NIH and local authorities. If these studies involve other laboratories, we will need approval from your local authorities to store or transfer them elsewhere. Your left over samples will not be sold or used for commercial reasons.

RESEARCH-RELATED INJURY:

The study staff will ask you questions about your health at every study visit. If you have any health problems between visits, please contact the study staff. If you have a medical emergency that requires immediate care, *[insert site-specific instructions]*. *[Sites to specify institutional policy:]* If you are injured as a result of being in this study, the *[institution]* will give you immediate necessary treatment for your injuries. You *[will/will not]* have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program for monetary compensation or other forms of compensation for such injuries either through this institution or the NIH. You do not give up any legal rights by signing this consent form.

PROBLEMS or QUESTIONS:

For questions about this study or a research-related injury, contact:

- *[site insert name of the investigator or other study staff]*
- *[site insert telephone number and physical address of above]*

For questions about your rights as a research subject, contact:

- *[site insert name or title of person on the Institutional Review Board (IRB) or other organization appropriate for the site]*
- *[site insert telephone number and physical address of above]*

SIGNATURE PAGE: SAMPLE RE-ENROLLMENT CONSENT FOR INDEX

HPTN 074: Integrated treatment and prevention for people who inject drugs: A vanguard study for a network-based randomized HIV prevention trial comparing an integrated intervention including supported antiretroviral therapy to the standard of care

Final Version 2.0, 26 July 2017

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

Please carefully read the statements below (or have them read to you) and think about your choice. No matter what you decide it will not affect whether you can be in the research study, or your routine health care.

_____ I agree to have samples of my blood used for future testing related to HIV infection.

_____ I agree to have samples of my urine used for future testing related to HIV infection.

_____ I do not agree to have samples of my blood stored and used for future testing related to HIV infection.

_____ I do not agree to have samples of my urine stored and used for future testing related to HIV infection.

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

Participant's Name (print) Participant's Signature or Thumbprint and Date

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

Study Staff Conducting Study Staff Signature and Date
Consent Discussion (print)

For witnesses for illiterate volunteers: I attest that the information contained in this written consent form has been read and explained to the participant. He/she appears to understand the

purpose, procedures, risks and benefits of the study and has voluntarily accepted to participate in this study.

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

Witness' Name (print)

Witness's Signature and Date