

**Letter of Amendment # 1 to:**

**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, Version 1.0, 26 February 2014**

**DAIDS Document ID: 11917**

**Final Version of LoA # 1: 10 September 2015**

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**The following information impacts the HPTN 074 study and must be forwarded to all responsible Institutional Review Boards (IRBs) as soon as possible for their information and review. This Letter of Amendment must be approved by all responsible IRBs before implementation.**

**The following information impacts the sample informed consents. Your IRB will be responsible for determining the process of informing subjects of the contents of this letter of amendment (LoA).**

**Upon receiving final IRB and any other applicable Regulatory Entity (RE) approval(s) for this LoA, sites should implement the LoA immediately. Sites are still required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. An LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with this letter and any IRB correspondence should be retained in the site's regulatory files.**

**If the HPTN 074 protocol is amended in the future, this Letter of Amendment will be incorporated into the next version.**

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**Summary of Revisions and Rationale**

1. A DSMB will not be required for this study. The HPTN SMC will assume primary responsibility along with site staff and the Clinical Management Committee for monitoring of safety during the trial.
2. The SCHEMA and secondary objectives have been clarified regarding viral load requirements for study entry and consistency of labelling the intervention.
3. Background requirements for the site selection process have been clarified.
4. Requirements for eligibility have been updated to allow for more rapid identification and recruitment of the at-risk population. Included are provisions (in line with Clarification Memo 2) for partners who screen as HIV positive to continue screening as potential index participants if they wish and the original index does not enroll, and identification of substance treatment program failures, and a CD4 limit of at least 50 cells/mm<sup>3</sup> for study entry.
5. Dried urine storage is clarified to be collected on all participants at Weeks 26, 52 and Exit.
6. Semi-structured interviews have been expanded to include index participants randomized to the intervention arm.
7. Other minor revisions to match the Schedule of Evaluations with the Procedures Section and Informed Consents, and clarifications to Confidentiality as applicable and requested by the Ethics Working Group, etc.

## Implementation of the Protocol Modification

The modifications detailed below will be formally incorporated into the body of the protocol with the next full amendment. Deletions to the protocol text are indicated by ~~strikethrough~~; additions are indicated in **bold**.

Revision 1: A DSMB will not be required for this study. The HPTN SMC will assume primary responsibility along with site staff and the Clinical Management Committee for monitoring of safety during the trial.

### LIST OF ABBREVIATIONS AND ACRONYMS

DSMB ——— Data Safety and Monitoring Board

#### Section 6.2 Clinical Data Safety Review

HPTN SDMC ~~Clinical Affairs staff~~ will review incoming safety data on an ongoing basis.

#### Section 6.6 Social Impacts Reporting

In addition, the NIAID DSMB will routinely review these data:

#### Section 8.1 Ethical Review

In addition, all open DSMB reports will be provided to the IRBs/ECs.

Revision 2: The SCHEMA and secondary objectives have been clarified regarding viral load requirements for study entry and consistency of labelling the intervention.

### SCHEMA

#### Index participants:

HIV-infected PWID who have an HIV viral load  $\geq 1,000$  copies/mL at Screening.

#### 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 **referral 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.

#### SCHEMA, Section 2.2 Secondary Objectives and Section 7.1.2 Secondary Endpoints:

- **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.**

**Revision 3: Background requirements for the site selection process have been clarified.**

### *Section 3.0 STUDY SETTING AND POPULATION*

~~(7) the ability to link to an existing HPTN Clinical Trial Unit (CTU); and (78) previous or existing NIDA funded research.~~

**Revision 4: Requirements for eligibility have been updated to allow for more rapid identification and recruitment of the at-risk population. Included are provisions (in line with Clarification Memo 2) for partners who screen as HIV positive to continue screening as potential index participants if they wish and the original index does not enroll, and identification of substance treatment program failures, and a CD4 limit of at least 50 cells/mm<sup>3</sup> for study entry.**

### *Section 3.0 STUDY SETTING AND POPULATION*

Index participants will be HIV-infected PWID (men and women who report injecting drugs **at least twelve times twice per week for during** the past three months **and six times the past month** and report sharing needles, syringes or drug solutions) who have an HIV viral load  $\geq 1,000$  copies/mL at Screening.

A screening ratio of **more than about** 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 30** days after the ~~confirmation of HIV status screening blood draw for~~ the index participant. If the first injection network partner ~~presents to be screened more than is not enrolled within 60 30~~ days after ~~confirmation of the index participant's HIV status screening blood draw,~~ **both the index participant and partner will** may be asked to return for another Screening visit. **However, it will not be necessary to repeat HIV testing for any participant whose HIV positive infection status was previously confirmed using two separate samples collected on different days.** ~~prior to randomization and the initial partner may be asked to return for an Enrollment visit.~~

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 continue to be screened (or be re-screened at a later date) as potential Index participants provided that the 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. ~~These 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.

### *Section 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- ~~45~~ **60** years at the Screening visit (age verification procedures will be defined in the Study Specific Procedures [SSP] Manual)
- Active injection drug user, defined as self-report of: a) injecting drugs approximately at least 12 times in the past three months and at least 6 times in the past month ~~one or more times per week for the past three months~~; and b) **a PWID in the opinion of site staff** ~~ability to identify the anatomical location of the most recent injection site, as determined by study staff~~
- **CD4 > 50 cells/mm<sup>3</sup> at Screening**

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- ~~45~~ **60** years at the Screening visit (age verification procedures will be defined in the SSP Manual)
- Active injection drug user, defined as self-report of: a) injecting drugs approximately at least 12 times in the past three months and at least 6 times in the past month ~~one or more times per week for the past three months~~; and b) **a PWID in the opinion of site staff** ~~ability to identify the anatomical location of the most recent injection site, as determined by study staff~~
- Confirmed injection partner, using referral identification cards, **or other means of identification from the** ~~of~~ index participant ~~within the past 1 month~~

\*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.

### *Section 3.2 Exclusion Criteria*

- Prior screening as a potential network member of an **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**).

### *Section 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.

### *Section 3.4 Identification of Network Injection Partners*

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.**

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 ~~in terms of name, age, gender, frequency of contact with the index, and duration of relationship with the index.~~ HIV-uninfected injection **according to site-specific procedures**. Such partners will then be asked to provide study informed consent for enrollment.

#### *Section 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 ~~to care~~ 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-use ~~in~~ phylogenetic analysis.

#### *Section 5.4.1 Screening Visit for Index Participants*

For each index participant, Enrollment must occur on a separate date within ~~30~~ **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.**

**\*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.**

#### *Section 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 ~~30~~ **60** days of the blood collection ~~at the~~ **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. ~~At least one HIV test (e.g. HIV rapid test) must be negative/non-reactive at the Enrollment for the network partner to be considered eligible for the study.~~

**Revision 5: Dried urine storage is clarified to be collected on all participants at Weeks 26, 52 and Exit.**

#### *Section 5.4.3.2 Quarterly Visits for Index Participants*

##### Laboratory Procedures – Local Laboratory

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

**Revision 6: Semi-structured interviews have been expanded to include index participants randomized to the intervention arm.**

#### *Section 5.8 Data Collection Procedures for Stakeholders 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 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 the final stages of follow-up (maximum=90 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.

#### *Section 7.1.1 Primary Endpoints*

## *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, ~~and~~ additional stakeholders, **and a subset of index participants randomized to the intervention arm.**

### *Section 7.2 Accrual, Follow-up, and Sample Size*

*Qualitative analyses:* Semi-structured interviews with systems navigators, counselors, ~~and~~ stakeholders **(minimum =12; maximum =30 across all sites), and a sub-set of index participants randomized to the intervention arm (maximum =45 across all sites)**

### *Appendix IV-D. 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*

#### *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, ~~or~~ 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.

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 again when they have completed all visits. This means up to 12-30 **navigators, counselors, and persons directly involved with antiretroviral or substance use dispensation and up to 45 HIV positive study participants randomized to the intervention arm** from all three study centers combined.

Revision 7: Other minor revisions to match the Schedule of Evaluations with the Procedures Section and Informed Consents, and clarifications to Confidentiality as applicable and requested by the Ethics Working Group, etc.
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#### *Section 5.5.3 Follow-up Visits for Network Injection Partners*

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

#### *SAMPLE INFORMED CONSENTS*

##### *Appendix IV-A. Sample Screening Consent*

*If you have HIV:*

- 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.

*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.

*SIGNATURE PAGE: SAMPLE SCREENING CONSENT*

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 used for future testing related to HIV infection, **and how HIV spreads in the community**.

*Appendix IV-B: Sample Enrollment Consent for Index*

*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. ~~The stored blood samples will also be used to learn more about how HIV is spread throughout the community.~~

*Appendices IV-B and C: Sample Enrollment Consent Index and Partner*

\_\_\_\_\_ 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 ~~drug use~~ **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 drug use HIV infection.

*Appendices IV-A, B and C: Consent Confidentiality Sections*

**CONFIDENTIALITY:**

~~Efforts will be made to keep your screening records and test results confidential to the extent permitted by law. However, we cannot guarantee absolute confidentiality. You will be identified by a code, and personal information from your records will not be released without your written permission except to health care providers when needed. Any publication of this study will not use your name or identify you personally. However, your records may be reviewed by the sponsor of the study (United States 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].~~

**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.**

*Appendices I and II: Schedule of Evaluations*

	Screening	Enrollment	Week4	Quarterly Visits	Exit

<sup>3</sup> Dried urine will be stored at Enrollment and Weeks 26 and 52/ Exit.