Final Letter of Amendment # 2 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 # 2: 28 September 2016

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.

Summary of Revisions and Rationale

1. Clarifications have been made regarding laboratory assessments, particularly those for urine testing. Only urine samples from a subset of participants will be tested and this will be done as supplies permit. Additional clarifications are made about contacting the HPTN LC in the case of a potential false-positive HIV test result and a minor editorial change to use the phrase "test result" instead of "test".
2. An additional 5 Index Participants per site (total additional 15) randomized to the Intervention Arm will take part in round 2 of the Qualitative Interviews, in order to assess any differences that may have occurred in ART treatment access since round 1 of the Qualitative Interviews.
3. Many publications require a clinicaltrials.gov registry for publication; therefore, the team is adding registration of HPTN 074 and participants will be updated on this fact.

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: Clarifications have been made regarding laboratory assessments, particularly those for urine testing. Only urine samples from a subset of participants will be tested and this will be done as supplies permit. Additional clarifications are made about contacting the HPTN LC in the case of a potential false-positive HIV test result and a minor editorial change to use the phrase "test result" instead of "test".

5.3.2 Laboratory Assessments for HIV-uninfected Network Injection Partners

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.

5.4.3.2 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 **as supplies permit** (Weeks 26, ~~and~~ 52 and Exit ~~only~~)

5.5.3.2 Quarterly visits for network injection partners

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)

5.6.1 HIV Confirmation Visit Following a Reactive or Positive HIV Result

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.

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:

Appendix I. Schedule of Procedures and Evaluations - Index

[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

[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** ~~test~~ after Enrollment. See Appendix III.

[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 ~~summary~~ **test** ~~test~~ **result** at any visit after Enrollment**

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

Revision 2: An additional 5 Index Participants per site (total additional 15) randomized to the Intervention Arm will take part in round 2 of the Qualitative Interviews, in order to assess any differences that may have occurred in ART treatment access since round 1 of the Qualitative Interviews.

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** ~~90~~ interviews across all sites).

Section 7.2.1 Primary Endpoints

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 =~~45~~ **60** across all sites) **will be based on a standard field guide that will be used at 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

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** ~~45~~ 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.

Revision 3: Many publications require a clinicaltrials.gov registry for publication; therefore, the team is adding registration of HPTN 074 and participants will be updated on this fact.

Appendices IV A through D

CONFIDENTIALITY:

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.