

## **Section 5. Follow-up and Retention**

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### **5.1. Overview of Section 5**

This section provides an overview of requirements and procedures for participant follow-up in the study.

### **5.2. Length of Study participation**

HPTN 074 will last approximately 39 months at each site, with recruitment of index participants over 15 months and follow-up in the main study for a minimum of 12 months and a maximum of 24 months, regardless of study arm. After termination of participants in the main study, index participants may choose to be re-enrolled in the 9-12 month study extension. In the main study, 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. Network injection partners will not be re-enrolled in the study extension.

### **5.3. Follow-up visits**

Three types of follow-up visits may be conducted: protocol-required visits, intervention-related (psychosocial or systems navigator) encounters and interim visits. Some key informants (Selected Study Navigators, Counselors or Key Clinic Personnel at the HIV Care and Substance Use Treatment Sites, and some index participants) will be selected for individual interviews which is covered in Appendix B (Qualitative Manual).

#### **5.3.1. Protocol required visits**

Protocol required visits are those specified to be conducted during follow-up per the study protocol. Index participants will have a visit at week 4 and then followed quarterly a minimum of 52 weeks, up to a maximum of 104 weeks (those enrolled early in the study will be followed longest). If possible, an Exit visit will be conducted for all index participants.

Re-enrollment into the study extension will be completed during the first of four visits (as possible) during the extension, following a quarterly schedule. There will be up to 4 visits total in the extension- Extension re-enrollment, Month 3, Month 6 and Exit after the Extension.

In the main study, 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 according to the index's schedule and will have all follow-up assessments performed, even if the index participant recruits a new, active network injection partner. All replacement (or late enrolling) partners will have a Week 4 visit

before assuming the visit schedule of the corresponding 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.

### **5.3.2. Intervention-Related Visits (Psychosocial or Systems Navigator encounters)**

As noted in Protocol 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 Protocol Sections 5.2 and 5.3. More information can be found in SSP Appendix A (Intervention Manual).

Indexes will have the opportunity for the same types of intervention visits (psychosocial or systems navigators encounters) in the study extension.

### **5.3.3. Interim Visits**

Interim visits, or unscheduled visits, occur when the participant visits the study site outside of the regular study visit schedule. See Section 9 Interim Visit Codes, Target Days and Visit Windows for more information. Visit codes are only assigned to an interim visit if data from that visit is collected for submission to SCHARP. In general, interim visits are only expected for reporting of Adverse Events (AE), adverse Social Impacts or additional HIV testing. Note, if an AE and/or adverse Social Impact is reported during a psychosocial or systems navigator encounter that occurs outside of a protocol required visit, documentation of that event will be treated as an Interim Visit. In other words, an intervention-related psychosocial counseling session would not be considered an Interim Visit unless an AE Log, Social Impact Assessment, or other CRF is completed, in which case an Interim Visit CRF should be completed as well.

### **5.3.4. Follow-up visit scheduling**

Each protocol- specified visit should be completed on or as close as possible to the target date. Sites are responsible for establishing follow-up procedures to ensure maximum adherence to the visit schedule. If an index or network partner participant is early or late for a scheduled visit, the next visit should be completed on or about the date originally scheduled – not adjusted relative to the actual completion date of the previous visit.

Detailed instructions regarding the timing of scheduled visits (i.e., target days and visit windows) are included in Section 9. An overview of all study visits and procedures is available in Appendices I, II, and IV of the protocol. Additional procedures for network partners with confirmed HIV infection after Enrollment are

included in Appendix III of the protocol.

#### **5.3.5. Site visit windows**

Acknowledging that it will not always be possible to complete follow-up visits on the precise target dates, visits must be completed within allowable visit windows (see Section 9 for Target Days and Visit Windows). If the visit is not completed within the allowable visit window, the visit will be considered to be missed per the protocol, and study retention report.

#### **5.3.6. Visits conducted over multiple days (split visits)**

All procedures required by the study protocol to be performed at a particular follow-up visit should be completed at a single visit on a single day. However, in the event that all required procedures cannot be completed on a single day (for example because the participant leaves the study clinic before all required procedures are performed), the remaining procedures should be completed as soon as possible but should be completed within the relevant visit window for that visit. Please see Section 9 for more information on split visits.

#### **5.3.7. Missed Visits**

Efforts should be made to immediately contact any participant who does not report for a protocol-required visit. Trained outreach workers, or “tracers”, should be mobilized by each site to reach participants over the phone or on email or in person at their homes and/or other community locations. If all efforts to reach the participant have failed a Missed Visit (MV) CRF should be completed to document the missed visit. See Section 9 for more information on Missed Visits.

#### **5.3.8. Follow up visit procedures - Index**

A full list of visit procedures is included in Protocol Section 5 and Appendix I. Note the following points when completing protocol required procedures.

##### **5.3.8.1. Week 4 Visit**

- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews should be completed before brief, standardized injection and sexual transmission risk reduction counseling.
- As described in the Social/Sexual Network List, participants will be prompted to update any possible changes to their social networks at all subsequent visits.
- 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 partner in the study.

#### **5.3.8.2. Quarterly visits**

- Quarterly visits will occur at Weeks 13, 26, 39, 52, 65, 78, and 91. All participants will end study participation when 27 months have passed since the first enrolled participant at the site.
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews should be completed before brief, standardized injection and sexual transmission risk reduction counseling.
- As described in the Social/Sexual Network List, participants will be prompted to update any possible changes to their social networks at all subsequent visits.
- 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 partner in the study.

#### **5.3.8.3. Exit Visit**

- 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. All participants will end study participation when 27 months have passed since the first enrolled participant at the site.
- Exit visit assessments are similar to those completed during quarterly visits with the exception of specific exit sexual behavior, substance use, substance use treatment and ART experience interviews lasting approximately thirty minutes. As with behavioral assessments completed at other visits, they should be completed after any risk-reduction counseling.
- Site teams should work to ensure that ART will be continued as appropriate post-study through local authorities. \

#### **5.3.8.4 Study Extension Visits (for Indexes only)**

- Time allowing, each index participant re-enrolled into the study extension will be seen at up to four visits during a 9-12 month extension. Re-enrollment will take place during the first of these four visits.
- Therefore, 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). Number of visits will depend on when sites roll out the study extension.
- Quarterly visits in the study extension will include the same activities as the quarterly

visits in the main study (see Section 5.4.3.2 of the protocol for details).

- The following will take place at each (quarterly) study extension visit:
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews should be completed before brief, standardized injection and sexual transmission risk reduction counseling.
- As described in the Social/Sexual Network List, participants will be prompted to update any possible changes to their social networks.

Note that CD4 levels will only be determined at Months 3 and 9 following re-enrollment.

### **5.3.9. Follow up visit procedures – Network Partners**

A full list of visit procedures is included in Protocol Section 5 and Appendix II.

Provided below is an overview of the procedural requirement for all follow-up study visits for network partner participants and additional information. Note that index participants and network partners are likely to have visits on different days.

#### **5.3.9.1. Enrollment Visit**

- Written informed consent will be obtained from each study participant at prior to performing any enrollment procedures. See SSP Section 4 for more information on obtaining informed consent.
- HIV test results from both the Screening and Enrollment visit will be used to determine study eligibility for all participants and these visits must be on different days. See Lab section 8 for more information.
- Baseline risk assessments (Baseline sexual behavior, injection risk behaviors, substance use, substance use treatment and ART use and adherence interviews) should be completed prior to risk reduction counseling (HIV pre-test risk reduction and post-test counseling, brief standardized injection and sexual transmission risk reduction counseling session).
- Randomization of the index participant is dependent upon confirmation of eligibility of at least one network injection partner within 60 days of their Screening blood collection date. The effective point of enrollment is randomization.
- As described in the Social/Sexual Network List, network partner participants will participate in a Social Network Interview at enrollment focused on: (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 substance use treatment, and (3) frequency of injection and sexual risk behaviors with each identified injection network member (including both persons enrolled and not enrolled in the study).
- 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 enroll as another index participant's network injection partner (each network injection partner will be associated with a single index participant

throughout the study).

- 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 Protocol Section 5.

#### **5.3.9.2. Week 4**

- 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.
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews should be completed prior to brief, standardized injection and sexual transmission risk reduction counseling.
- As described in the Social/Sexual Network List, participants will be prompted to update any possible changes to their social networks at all subsequent visits.

#### **5.3.9.3. Quarterly visits**

- Quarterly visits will occur at Weeks 13, 26, 39, 52, 65, 78, and 91. All participants will end study participation when 27 months have passed since the first enrolled participant at the site.
- Follow up sexual behavior, substance use, substance use treatment and ART experience interviews should be completed prior to brief, standardized injection and sexual transmission risk reduction counseling.
- As described in the Social/Sexual Network List, participants will be prompted to update any possible changes to their social networks at all subsequent visits.

#### **5.3.9.4. Exit Visit**

- 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. All participants will end study participation when 27 months have passed since the first enrolled participant at the site.

#### **5.3.10. Modified Follow-up Visit Procedures for participants with a positive or reactive HIV result**

- HIV confirmation visit following a reactive or positive HIV result 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 (regardless of index randomization assignment).

- 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 follow up visits.
- Follow up visits after confirmation will include Weeks 26, 52, 78 and 104 as appropriate based on the participant's enrollment date.
- HIV pre-test, post-test and risk reduction counseling as well as HIV testing will not be completed at follow up visits after confirmation of HIV infection.

#### **5.4. Participant Withdrawal and termination**

- 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 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.
- When an index participant is withdrawn from the study, any partners will also be brought in for study termination.

#### **5.5. Qualitative component**

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.

Semi-structured interviews with systems navigators, counselors, and stakeholders will be based on a standard field guide that will be used at all sites (overall minimum of 12; maximum of 30).

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 and maximum total interviews=90 interviews across all sites).

All interviews will be conducted during the initial stages of enrollment and the final

stages of follow-up and will be audiotaped, transcribed and translated into English at each study site by qualified personnel. See Qualitative Manual (Appendix B) for more information.

## **5.6. Retention Definition**

The term “retention” refers in general to the completion of expected study follow-up visits and procedures as specified in the study protocol. For HPTN 074, retention will be measured for all participants at weeks 13, 26, 39, 52, 65, 78, 91 and 104.

Participants who do not complete a particular scheduled study visit within the allowable window (See SSP Section 9 for definitions), but then complete the next scheduled study visit, will not be considered retained for the missed visit. However, they will be considered retained for the next scheduled visit. Thus retention rates can fluctuate over time and across visits.

Throughout the study, SCHARP will generate retention reports that present visit completion rates for all study visits. SCHARP will generate a final overall end-of-study retention rate for each site after the study is completed. For recent 074 retention rates, please visit SCHARP’s Atlas website at: [https://atlas.scharp.org/cpas/files/HPTN/074/hptn\\_074\\_retention\\_report.pdf](https://atlas.scharp.org/cpas/files/HPTN/074/hptn_074_retention_report.pdf).

Once an index participant enrolls in this study, the study site will make every effort to retain him/her for 12-24 months 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.

### **5.7. Retention Plan**

The site staff is responsible for establishing a participant retention plan for the study, and for updating the plan and retention efforts undertaken to meet the study retention goal of no more than 10% lost to follow-up per year (excluding incarceration and death).

Because elements of the retention plan will affect study participants, it is recommended that the site seek input from both the IRB/Ethics Committee and CAB before implementing the plan. However, EC approval is not required for the retention plan.

At screening, a particular emphasis should be placed on the eligibility requirement that participants must be willing to meet the study requirements, and do not plan to re-locate out of the study area for the duration of the study. In addition, a thorough explanation of the study visit schedule and procedural requirements should take place during the informed consent process and be re-emphasized at each study visit.

### **5.8. Retention Target**

The overall sample size of HIV-infected index participants is 500 persons. Given the allocation ratio of 1 intervention to 3 control or standard of care, 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. Ideally, each study site should strive for 100% retention at all visits. However, recognizing that this ideal may not always be attainable, per the protocol, each study site should strive for no more than 10% annual loss to follow-up. Participants who die or are incarcerated are not considered lost to follow-up, as noted in section 5.7 above.

### **5.9. Retention Strategies**

Some general strategies for maximizing participant retention are presented below:

- Dedicate adequate staff time and effort to retention efforts.
- Work with community members to identify the most applicable contact and retention strategies for the local study population, including the type and amount of participant incentives.
- Keep participants and community members up-to-date on study progress to foster a sense of partnership and ownership of the study (through the use of participant newsletters, for example).
- Inform local service providers (i.e. ART and SU clinics) who interact with the local study population about the study, so that they also can express their support for the study.
- Emphasize the value of the participant's involvement in the study during the study

informed consent process and subsequently at follow-up visits.

- Implement a tracking system to easily identify when participants' scheduled visits are due. Establish routine mechanisms to remind both study staff and participants of upcoming scheduled visits.
- Always schedule the participants' next contact and/ or visit before he/she completes the prior contact or visit. Give the participant an appointment card with the scheduled contact or visit date and time noted.
- Prepare a calendar of scheduled visits for each enrolled participant, based on the couple's enrollment date (or offer a planner/calendar as an incentive and note all study appointments). Note the dates of all scheduled visits in the participant's file for easy reference.
- For participants who demonstrate a pattern of late or missed appointments, schedule follow-up visits for the beginning of the allowable visit window (see Section 9 for details) to allow maximum time for re contact and re-scheduling if needed.
- Pay close attention to the allowable visit window and prioritize retention efforts for participants nearing the end of the window, particularly for quarterly visits at which primary study endpoints are ascertained. Organize daily caseloads and work assignments based on these priorities.
- Follow-up on missed appointments with an attempt to re-contact/re-schedule within 24 hours (preferably on the same day). Continue these efforts per the local retention plan until contact is made.
- Keep locator information up-to-date and maintain thorough documentation of all efforts to contact the participant. Keep all this information in an organized manner, so that different staff members can easily review the information and contribute to re-contact efforts when necessary.
- Make use of all information collected on the participant's locator form. Even if a locator source is not useful/successful on one occasion, try it again later.
- Make use of all available contact methods (e.g. phone, mail, home visits, street outreach, newspapers, e-mail/internet). Also make use of other available locator information sources, such as phone and post office directories and other public registries.
- Send outreach workers to other local service organizations utilized by the study population.
- Attempt contact with the participant at different times during the day and the week, including evenings and weekends.
- Assist participants in making transportation arrangements if necessary. This may be done with vouchers, site-owned vehicles, or instructions about other modes of transportation.
- If a participant reports that s/he wishes to discontinue participation in the study, ask if s/he would be willing/interested to have a final assessment. If the participant refuses this level of involvement, explain that s/he is always welcome to come back if she wishes and the window for the Exit Visit has not closed.

## 5.10. Obtaining and Updating Locator Information

Successful retention begins with collection of exhaustive locator information from each study participant. All study participants will be asked to provide locator information at their Screening Visit, and to update this information at each subsequent visit. Each study site is encouraged to develop an exhaustive locator form to maximize contact effectiveness and participant retention. Potential locator items include:

- Participant's name, alias, and/or nickname; government-issued identification number; home address; home phone number; mobile phone number; pager number; work address; work phone number; fax number; e-mail address; daytime and night-time hangouts.
- Walking/driving/public transport directions and/or pictorial map to the participant's home, workplace, etc.
- Name, address, telephone number, and/or other contact information for stable community contacts (i.e., participant family members and friends) who typically know the whereabouts of the participant.
- Name, address, telephone number, and/or other contact information for the participant's health care provider, school or training program, social service case worker, counselor, rehabilitation provider, participant's child's health care provider, etc.
- Name, address, telephone number, and/or other contact information for support groups, shelters, food pantries, etc., frequented by the participant.

During the informed consent process and when collecting locator information, study participants must be informed that their locator sources will be contacted if study staff are unable to locate the participant directly. Study staff will negotiate with the participant how they will identify themselves when locator sources are contacted.

Study staff should view every participant contact as an opportunity to update the participant's locator information. When updating locator information, site staff should actively review each item on the locator form to determine whether the information is still current (i.e., rather than simply asking "Has any of your information changed since your last visit?"). In addition, site staff should probe for additional information that the participant was not able or willing to provide at previous visits.

Additional elements such as the ones described below may be added to the site's specific retention plan:

- Study retention goals
- Methods for tracking actual retention versus retention goals
- Planned retention methods, including what locator efforts are taken within 24 hours, 1-3 days, and 1-3 weeks after a missed appointment
- Methods for timely evaluation of the utility of retention methods
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements
- QC/QA procedures related to the above (if not specified elsewhere)
- Attached copies of locator forms, tracking reports, worksheets, etc.

For each participant, clinic staff will obtain confidential contact information. In the event

that a participant or couple misses a scheduled appointment, clinic staff will try to establish communication with the participant(s) through all possible means (e.g., telephone, e-mail, mail contact, and home or workplace visits). At each visit, site staff should emphasize to study participants the importance of attending all scheduled follow-up visits.