

Section 5 Participant Follow-up

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Section 5 Participant Follow-up

This section provides information related to the timing and scheduling of participant follow-up visits and visit procedures. The procedures for follow-up visits are also described in detail in the study protocol (SSP Section 2) and visit checklists (SSP Section 6). Considerations related to retaining participants in follow-up are described in SSP Section 8. Additional instructions for clinical and laboratory follow-up procedures can be found in SSP Sections 10 and 11 of this manual, respectively. Requirements for adverse event reporting are described in SSP Section 12.

5.1 Length of Study Participation

As described in SSP Section 4, the total duration of the study will be approximately four and a half years. The initial safety and feasibility phase will take approximately 30 weeks at each site, with 26 weeks to enroll the targeted 50 participants plus four weeks to complete the last safety phase visit. The accrual period in the full study will be approximately 104 weeks following the safety and feasibility phase. Participants will be followed for a minimum of 104 weeks from enrollment and a maximum of 156 weeks, depending on when they are enrolled.

5.2 Intervention Visits

The following two types of intervention visits may be conducted:

- **Dispensing Visits:** Participants will come to the study site daily for induction and detoxification (up to 18 days in detoxification arm) or during induction and dose stabilization treatment (up to 21 days in substitution arm). Participants in the substitution arm will then present for dispensing three times a week while they are receiving BUP/NX up to Week 52. Efforts will be made to make these visits as quick and convenient as possible to minimize participant burden and maximize adherence.
- **Drug- and Risk-Reduction Counseling Visits:** All participants will be scheduled for weekly individual drug- and risk-reduction counseling for twelve weeks, followed thereafter by monthly counseling sessions every four weeks through week 52. Counseling visits will last about 45 minutes. At some counseling visits, additional routine assessments may be conducted as described in section 5.4.2 below.

Additional dispensing visit procedures and counseling visit procedures are specified in the counseling manual (SSP Appendix H), the BUP/NX treatment manual (SSP Appendix G), and in the visit checklists (SSP Section 6).

5.2.1 Intervention Visit Scheduling

To the extent possible, site staff will work with participants to determine the best day of the week and time for the routine schedule of intervention visits (e.g., every Monday at 9 am). Dispensing visits can be combined with counseling and follow-up visits to minimize participant burden. Whenever both counseling and dosing are scheduled the same day, counseling should precede the dosing visit.

5.2.2 Missed Intervention Visits

Staff should set clear and reasonable boundaries with participants of what is allowable for missed or late visits. Missed counseling visits may be made up in the same week (during the first 12 weeks) if the counselor's schedule permits; "extra" counseling sessions are not to be encouraged

and should occur only when scheduled and with a specific purpose. Participants who miss a dosing visit should make up that dose as soon as possible. For example, a participant who misses a regularly scheduled visit on Tuesday could come on Wednesday to receive half the regular dose, and then return again to their regular schedule for Thursday and Saturday. Each site should determine how often this will be allowed and under what circumstances, and present this information to participants at the beginning of treatment.

Documentation of attended and missed intervention visits will be maintained in counseling session attendance logs and dosing records.

The following guidelines should be followed when participants miss a series of dosing or counseling visits:

- Participants in either study arm who miss intervention visits for any length of time may resume weekly (during the first twelve weeks of study participation) or monthly counseling sessions.
- Participants in the substitution treatment arm may resume BUP/NX treatment if they miss visits for two weeks or less but within 46 weeks after the date of randomization. Resumption of BUP/NX is based on the judgment of the clinician but may need to repeat BUP/NX induction. If greater than two weeks have been missed, the PSRT must be consulted before resuming the participant's treatment and re-induction must occur. **No participant will receive BUP/NX beyond 52 weeks from the time of randomization.**

Table 5-1 summarizes the procedures to be followed when participants miss intervention visits.

Table 5.1 Missed Intervention Visits

Guidance on Handling Missed Visits			
Arm	Phase	Situation	Response
Detoxification or Substitution	Induction	Misses 1-3 days starting during induction	<ul style="list-style-type: none"> ▪ Start with total dose given on last dosing day ▪ May give additional dose(s) to control withdrawal symptoms as described in induction protocol
Detoxification	Dose tapering phase	Misses 1-3 consecutive days of dosing	<ul style="list-style-type: none"> ▪ Give the same dose or a lower dose than that received on the last dosing day. ▪ Consider that the dose taper has to be complete by Day 18
Detoxification	Induction or tapering	Misses > 3 consecutive doses	<ul style="list-style-type: none"> ▪ Detoxification is complete ▪ Counseling and other visits continued
Substitution	Post-induction	Misses ≤ 3 consecutive days of dosing	<ul style="list-style-type: none"> ▪ Administer the regularly scheduled dose at next dosing visit
Substitution	Post-induction	Misses 4-14 days	<ul style="list-style-type: none"> ▪ May administer regular dose if risk of precipitated withdrawal felt to be low ▪ Assure that 8-10 hours have passed since last use of opioid drugs ▪ Consider abbreviated re-induction if longer time since last BUP/NX dose, subject used opioids during treatment gap, and subject on thrice weekly dosing
Substitution	Post-induction	Misses >14 days	<ul style="list-style-type: none"> ▪ Formal re-induction using induction protocol ▪ Consult PSRT prior to restart ▪ Re-induction should not be offered if subject is 46 weeks or more beyond randomization

5.3. Follow-up Visits

The following two types of follow-up visits may be conducted:

- **Scheduled visits** are those to be conducted after enrollment per the study protocol. Scheduled follow-up visits with HIV testing occur at 26, 52, 78, 104, 130, and 156 weeks. Scheduled follow-up visits also occur at weeks 12 and 40 for liver function monitoring (ALT & Bilirubin). Female participants randomized to the Substitution Arm are expected to return for a scheduled visit every four weeks while they are taking Suboxone for a urine pregnancy test. Participants enrolled during the safety and feasibility phase will also come to the site for scheduled visits every week for the first four weeks of their participation. Scheduled follow-up visits also have a specific target date for completion relative to the date of randomization (Day 0) and an allowable window. A scheduled visit is considered a ‘missed visit’ if it is not completed within the defined visit window. Section 5.3.1 below and Section 7.8 of this SSP Manual describe follow-up visit scheduling procedures.

- **Interim visits** are those that take place between scheduled visits and include study procedures in addition to the regularly scheduled study visits where data is captured on the DataFax CRFs. Interim visits may take place for a number of reasons, e.g., a participant may be sick, or additional testing may be required. A DataFax form is required for all interim visits at which data to be entered into the study database is collected; see Section 7.8.3 for instructions on assigning interim visit codes. All interim visits, including the purpose of the visit and the results of all evaluations including interim laboratory tests, must be recorded in study source documents and on the relevant DataFax Case Report Forms (CRFs), as described in SSP Section 7.

5.3.1 Target Follow-up Visit Dates

Day 0 will be assigned to the participant's randomization day. All follow-up visits will be scheduled relative to Day 0. The 26-week target date is 175 days from the day of randomization; the 52-week target date is 357 days after randomization, and so on until the participant reaches the last follow-up visit. If a participant is 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. Please note that visits and procedures should be scheduled for Week 24 or Week 26 but NOT both. Do not repeat procedures such as urine or blood collection at both Weeks 24 and 26.

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. Due to the potential complexities that may be encountered when scheduling and completing follow-up visits, it is recommended that sites use a participant visit tracking sheet or database, which the site should develop on their own.

Note: Any participant tracking database that is developed is to be used for tracking purposes only. It should not be used to record source data or to generate source documents. All information entered into the database should be based on other source documents contained in participants' study charts unless otherwise specified in the site's source document SOP.

5.3.2 Allowable Follow-up Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within an allowable window around the target date, though it is preferable to complete visits as close to the scheduled date as possible. The target visit day and corresponding windows are described in Section 7.8 of this SSP Manual.

Although the visit windows allow considerable flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at set intervals. Extreme deviation from the protocol specified time points should be avoided. Adherence to the target visit schedule will be closely monitored by the study team and the HPTN Study Monitoring Committee.

5.3.3 Missed Follow-up Visits

Efforts should be made to contact any participant who does not report for a protocol-required visit prior to the end of the allowable window period. For participants who do not complete scheduled follow-up visits within the allowable visit window (e.g. Weeks 12, 26, 40, etc.), the visit will be considered “missed,” and a Missed Visit CRF will be completed.

If a participant misses a follow-up visit and returns to the clinic after that visit but before the window of the next follow-up visit, sites should conduct all appropriate follow-up visit procedures at that interim visit. These procedures should be completed in addition to any procedures necessary to address the reason for the participant’s interim visit. For example, if a participant misses the Week 26 visit, but comes at Week 40 complaining of chest pain, all Week 26 visit procedures should be performed at this time. Additionally, appropriate assessments and referrals should be conducted to address the participant’s chest pain.

Note that the goal is to retain ALL enrolled participants throughout the entire follow-up period (at least 90% at Week 104).

5.3.4 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. In the event that all required procedures cannot be completed on a single day (for example because the clinician must leave the study clinic before all required procedures are performed), the remaining procedures should be completed as soon as possible but no later than seven days of beginning the visit procedures. See SSP Section 7 for relevant visit coding and data collection instructions.

5.4 Follow-up Visit Procedures

5.4.1 Assessments during Safety Phase

The first 50 participants enrolled at each site will undergo the following examinations and laboratory tests **each week** during the **first four weeks** of study participation:

- Interim medical history
- Symptom-directed physical exam
- Hematology (CBC and platelet count)
- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)
- Urine tests for drug use
- Assessment of social harms
- Counseling visits
- Acceptability assessment (**at Week 4 only**)

After the first four weeks, the follow-up schedule of procedures will be the same as for all participants as described in SSP Section 5.4.2 and 5.4.3 below.

5.4.2 Routine Assessments

Approximately every four weeks during for the first year of enrollment (with the exception of Weeks 24 and 26 when the test will be performed only at one of these visits), participants will be asked to provide the following:

- Urine testing for opiates and other drugs
- Urine for pregnancy testing for women in the substitution arm
- Locator information
- Information on adverse events, and concomitant medications

Women in the detoxification arm will have pregnancy tests at the fourth week and prior to and following the second detoxification at 26 weeks (if a second detoxification is deemed necessary).

At approximately Weeks 12 and 40 (as well as at the Week 26 and 52 follow-up visits) ALT and bilirubin testing will be performed for all participants during the first year of study participation. Whenever clinically indicated, hepatitis B or C testing may be done by the study clinician. The Hepatitis B vaccine series may be started at any time, if appropriate. These assessments should ideally be conducted while participants are at the site for counseling visits.

5.4.3 Week 26 and 52 Visits

The following procedures must be performed at each follow-up visit during the treatment phase of the study:

- Locator information update
- Symptom-directed physical exam and interim medical history
- Hematology (CBC, platelet count)
- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)
- Administer HBV vaccine if appropriate
- Urine testing for opiates
- Pregnancy urine test for women in substitution arm
- Risk assessment (sex and drug use)
- Rapid HIV testing with pre- and post-test counseling (with WB/IFA for positive or discordant rapid tests)
- Social harms assessment
- Intervention acceptability assessment

Note that if any assessment is performed during Week 24, they should not be repeated at Week 26. Therefore, it is recommended that all Week 26 procedures be performed at Week 24 to ease participant burden, and to ensure that the samples are collected. A Western Blot (WB) or Immunofluorescent Assay (IFA) will be conducted when the rapid HIV tests are positive or discordant. If the WB or IFA is positive, a second sample will be drawn on a different day for confirmatory testing.

Exceptions to procedures to be followed for participants who choose to terminate their participation prior to the end of the study, become HIV-infected, become pregnant, or stop taking study drug are included below in SSP Section 5.6.

Participants in the detoxification arm will complete all of the assessments listed above and may be eligible for a second round of detoxification at Week 26 if they report that they are still injecting opiates. The detoxification regimen may be repeated if the participant meets the same criteria according to the Second Detoxification Eligibility Checklist. Women who receive a second detoxification will have another pregnancy test immediately prior to and approximately 4 weeks after the first dose of the detoxification. The following criteria will be used to determine eligibility for second detoxification:

- Meets Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for opioid dependence, as determined by study clinician
- Positive urine test for opioids
- Injected opioids at least twelve times in the last 28 days
- NOT currently or recently (within the past 12 weeks) received clinician-guided treatment for opioid dependence with methadone, LAAM, , naltrexone, or nalmefene, according to self-report
- NOT currently enrolled in another HIV prevention or drug use intervention study
- NO known clinically-diagnosed allergy to buprenorphine or naloxone, according to self-report
- DOES NOT meet the DSM-IV criteria for dependence on alcohol or benzodiazepines; or require immediate medical attention for dependence on or other substances (except tobacco) as judged by the study clinician
- NOT currently injecting substances other than opioids more than twice in the last 28 days, according to self report
- NOT Pregnant or lactating
- NO acute or chronic renal failure as judged by study clinician
- ALT NOT greater than three times the upper limit of normal value
- Hemoglobin NOT less than 8 g/dL for men, less than 7 g/dL for women
- Platelet count NOT less than 50,000/mm³
- Total bilirubin NOT greater than 2.5 times the upper limit of normal

5.4.4 78, 104, 130, and 156 Week Visits

These visits will include:

- Locator information update
- Risk assessment (RA-1 DataFax form)
- Urine testing for opiates and other drugs
- Rapid HIV testing with pre- and post-test counseling (with WB/IFA for positive rapid tests)
- Social harms assessment

A Western Blot (WB) or Immunofluorescent Assay (IFA) will be conducted when the rapid HIV tests are positive or discordant. If the WB or IFA is positive, a second sample will be drawn on a different day for confirmatory testing.

Exceptions to these procedures to be followed for participants who choose to terminate their participation prior to the end of the study, become HIV-infected, become pregnant, or stop taking study drug are included below in SSP Section 5.6.

5.5 Visit Locations/Outreach Visits

Study intervention and follow-up visits should take place at the study site unless prior approval has been granted by the OCSO representatives and the site's IRBs/ ECs. No visits may be conducted in prisons, jails, or detention centers. Participants who are incarcerated may rejoin the study after they are released and Suboxone administration should follow the missed doses schedule as indicated.

Outreach visits may be conducted throughout the study to remind participants of scheduled visits, to follow up on missed visits, and to request interim visits for additional lab testing or other assessments, as needed. Outreach visits are not considered to be study visits and should not involve conduct of any study assessments or counseling, or collection of information on adverse events. Participants should be told to report any illnesses or other problems to the study staff at the clinic. If necessary and locally acceptable, transportation to the clinic may be provided to ensure that a visit is completed. Information reported by participants during scheduled clinic visits or an interim visit is considered the source of study data rather than information reported during outreach visits. If an outreach worker learns of a participant's death or another condition that would preclude return to the study clinic, she/he should report this right away to the Investigator and his/her designee(s) at that site (e.g., Study Coordinator) for appropriate follow-up and documentation according to the DAIDS standard operating procedure (SOP) for Source Documentation (Appendix C).

Each site is responsible for developing a system for organizing and overseeing the outreach workers. For continuity, it is recommended that each participant be assigned to a single outreach worker who will follow him or her throughout the study. Outreach workers should carefully review the locator information provided by the study participant and should at all times respect the participant's wishes about when and where she/he may be contacted and in what manner. It is imperative that outreach visits be conducted with careful attention to maintaining a client's confidentiality. As noted in Section 3.2.3, each site's SOP for data management must specify procedures for handling participant study records if they are removed from the study site.

5.6 Modified Follow-up Procedures

Throughout the study, several circumstances may arise that affect the procedures to be conducted at scheduled follow-up visits. These include: early study drug discontinuation, pregnancy, HIV seroconversion, and early withdrawal/termination of study participation.

Note: All enrolled participants will remain in the study and complete all follow-up visits as scheduled, unless informed consent is withdrawn or invalidated, even if they seroconvert or study drug dosing is discontinued early.

5.6.1 Early Study Drug Discontinuation

Decisions regarding discontinuation of study drug will be made in consultation with the PSRT. The study drug will be discontinued with appropriate dose tapering in participants who meet one or more of the following criteria:

- Intoxication with any drug at the time of the dispensing visit
- In need of temporary use of a medication that may interfere with BUP/NX (see Section 4.5)

- Serious adverse event (SAE) not related to withdrawal that is potentially related to the study drug
- Pregnancy
- Enrollment in another study that, in the judgment of the investigator, will interfere with full participation in or interpretation of HPTN 058
- Evidence of hypersensitivity to BUP/NX
- Participant's request
- Investigator's decision
- Continued dosing or dosing at the current level is contraindicated for any reason, as judged by the study clinician and/or PSRT (e.g. elevated ALT)
- Decisions regarding resumption of study drug following discontinuation will be made in consultation with the PSRT. If drug interruption occurs for two weeks or longer, induction may need to be repeated. Further details regarding discontinuing or adjusting study drug will be specified in the Treatment Manual (Appendix G).
- Participants who discontinue the study treatment (drug and/or counseling components) will remain in the study and continue all follow-up assessments as originally scheduled.

5.6.2 Pregnancy

Participants who become pregnant after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. In addition, for participants who become pregnant within nine months prior to their scheduled study exit visit, a post-study contact will be completed if needed to ascertain the participant's pregnancy outcome.

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for pregnant participants, with the following exceptions:

- If possible, the protocol-dictated blood draws should continue throughout pregnancy; however, the volume of any of these samples may be reduced at the discretion of the study physician based on the health of the woman and the stage of pregnancy. Priority should be given to blood draws for HIV testing.
- The monthly urine pregnancy test should be discontinued once 3 consecutive monthly pregnancy tests have yielded a positive result.
- BUP/NX use will be discontinued, with gradual tapering, until after birth or other pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff. The PSRT will be consulted before resuming drug. Women who give birth just prior to enrollment should be counseled not to breastfeed.

For all participants who become pregnant, regardless of study treatment group, a Pregnancy Report and History form must be completed to report the pregnancy. If not offered at the HPTN 058 site, the woman and her baby should be referred to other facilities for pregnancy and well-baby care. A Pregnancy Outcome form also must be completed to document the outcome of the pregnancy. If a woman withdraws from the study prior to completion of her pregnancy, every effort will be made to obtain this information. Certain pregnancy outcomes also must be reported on Adverse Experience Log case report forms (AE DataFax form) and/or DAIDS Expedited Adverse Event Forms (EAE), as described in SSP Section 12.

Pregnant women who were receiving study drug will be counseled about the risks and benefits of drug treatment during pregnancy and will be provided with referrals for alternative treatment options including methadone and buprenorphine alone when available.

All study sites are strongly encouraged to use a pregnancy management worksheet similar to the sample in Figure 5-1 to ensure proper documentation of the pregnancy and timely discontinuation and resumption (if applicable) of BUP/NX use. Resumption of BUP/NX in women who have pregnancy losses, either spontaneous or elective, will follow the same procedures as those outlined in Section 3.5.1 of the protocol.

Figure 5-1 Sample Pregnancy Management Worksheet for HPTN 058

PARTICIPANT ID:		
BACKGROUND INFORMATION		
First day of last menstrual period		
Date of positive pregnancy test		
Estimated full term pregnancy date		
PREGNANCY MANAGEMENT INFORMATION		Mark ✓ When Done
1	Pregnancy Report and History form completed and faxed to SCHARP	
2	Pharmacy informed of pregnancy <i>(NA if participant in detoxification arm)</i>	
3	“Product Hold/Discontinuation” indicated on the Weekly Dosing Log CRF and faxed to SCHARP <i>(NA if participant in detoxification arm)</i>	
4	Pregnancy outcome and outcome date ascertained, based on: <input type="checkbox"/> medical records or other written documentation from a licensed non-study health care practitioner <input type="checkbox"/> verbal report from a licensed non-study health care practitioner <input type="checkbox"/> participant self-report <input type="checkbox"/> negative pregnancy test performed by study staff <i>(medical records should be obtained whenever possible)</i>	
4a	Pregnancy Outcome form completed and faxed to SCHARP	
4b	If applicable, AE Log form completed and faxed to SCHARP	
4c	If applicable, EAE Report completed and faxed to DAIDS Safety Office	
<p>5. The participant is eligible to resume BUP/NX use as of the date of her first negative pregnancy test performed post-pregnancy by study staff after consultation with the PSRT. Record the date of the negative test here:</p> <div style="border: 1px solid black; width: 300px; height: 40px; margin: 10px auto;"></div> <p style="text-align: center;">Test performed by (initials and date): _____</p> <p style="text-align: center;">Test verified by (initials and date): _____</p> <p><i>Note: Contact the Protocol Safety Review Team with any questions related to resumption of Suboxone use.</i></p>		
6	Pharmacy informed of participant eligibility to resume Suboxone use	

Figure 5-1 Sample Pregnancy Management Worksheet for HPTN 058

PARTICIPANT ID:
Additional Comments (if any; initial and date all entries; continue on back if needed):

5.6.3 Participant Seroconversion

Participants who become infected with HIV after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. All HIV-infected participants will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. HIV post-test counseling will include information on primary and secondary HIV/STD prevention for infected individuals.

It is critical that the participant receive her/his test result and post-test counseling and that the participant's HIV infection status be confirmed with a WB or IFA test. If the first WB or IFA is indeterminate or positive, a second sample must be drawn on a different day to re-test. Among all participants targeted at a given time for tracing and other locator/retention efforts, participants with a positive WB test result should be given highest priority.

For any participants who become HIV-infected and also become pregnant during follow-up, every effort will be made to facilitate access to interventions such as single-dose nevirapine to reduce the probability of HIV transmission to the participant's infant.

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for participants who become infected with HIV, except that HIV testing will be discontinued for remaining follow-up visits after the HIV infection is confirmed per the follow-up algorithm in Appendix II-B of the protocol.

Participants who become infected with HIV who are taking BUP/NX will be able to continue study drug use as originally scheduled. Participants receiving HIV protease inhibitors should be monitored closely and may need to have their BUP/NX dose reduced.

5.6.4 Early Termination

Participants may choose to terminate their participation in the study at any time. The site Investigator also may withdraw participants from the study *only* to protect the safety and well-being of the participant and/or the study staff and *only after* consultation with the Protocol Chair, Medical Officer, Protocol Statistician, and CORE Protocol Specialist. Participation may also end if the sponsor, government or regulatory authorities, or site IRBs/ECs terminate the study early.

Should an individual's participation in the study be terminated for any reason before the scheduled study exit visit, the participant will be asked to complete a final evaluation prior to termination, if possible. Study staff will record the reason(s) for all withdrawals from the study in participants' study records. Participants who withdraw voluntarily will not be allowed to re-screen for the study; however, with permission, HIV status will be ascertained.

Participants who terminate their participation *on or before the 52 week follow-up visit* will have the following clinical and laboratory evaluations performed prior to termination, if possible:

- Symptom-directed physical exam, interim medical history
- Hematology (CBC, platelet count)
- Blood chemistry (creatinine)
- Liver function tests (ALT, bilirubin)
- Urine testing for drugs
- Risk assessment

- Rapid HIV testing with pre- and post-test counseling (with a WB or IFA on a second sample if positive or discordant results as according to the algorithm in Appendix II-B of the protocol).
- Social harms assessment
- Intervention acceptability assessment

Participants who terminate their participation at any time *after the 52 week visit* will have the following clinical and laboratory evaluations performed prior to termination, if possible:

- Risk assessment (sex and drug use)
- Urine testing for drugs
- Rapid HIV testing with pre- and post-test counseling (with a WB or IFA on a second sample if positive or discordant results as according to the algorithm in Appendix II-B of the protocol).
- Social harms assessment

Note: These assessments should be performed only if the participant is available and willing; it is imperative that the participant's wishes be respected with regard to elective termination from the study. The participant's agreement or lack thereof for these final assessments should be documented in the participant's study record. If the participant is not available for these assessments, this should be also documented.

Note: Early discontinuation of study drug dosing, pregnancy, or HIV infection is not a reason for withdrawal/termination from the study.

If a patient dies prior to study termination, this should be noted in the source document and on the Termination (TM-1) DataFax form and every effort should be made to collect a death certificate which identifies the date and cause of death. In the event that a death certificate is not available, note this in the source document and on the CRF.

5.6.5 Participant Transfers

Transfer of participants in HPTN 058 from one research center to another (e.g., from Guangxi to Xinjiang) is anticipated to be very rare. However, if a participant notifies the original enrollment site that she/he is moving to another location where the study is being conducted, she/he should be encouraged to continue participation in the new locale. To accomplish this, study staff of both the originating and receiving sites will need to complete a formal participant transfer process. In such cases, the study coordinator or investigator must contact the CORE Protocol Specialist, the SDMC Project Manager and the DAIDS Protocol Pharmacist at PAB for complete transfer instructions *before* any study related activities are conducted at the receiving site.

Note: A participant who is enrolled and/or initially followed at one clinic and is then followed at another clinic within the same general site/geographical vicinity (e.g., from Department of Family Medicine to Fa Mai Clinic) is not considered a participant transfer.

As noted above, detailed instructions for handling transfers in HPTN 058 will be provided by the CORE PS, SDMC Project Manager (PM) and DAIDS Protocol Pharmacist, should the need arise. However, general instructions are provided in the HPTN Manual of Operations (MOP).

5.6.6 Resumption of Study Participation after Withdrawal

As described above, participants may voluntarily withdraw from the study for any reason at any time. The protocol also allows, however, for participants who voluntarily withdraw from the study to reverse their decision and resume study drug use under certain circumstances (for readministration of study drug and counseling see SSP section 5.2.2 above) and protocol-specified follow-up visits and procedures through their originally scheduled study exit date. If such cases arise, study staff are advised to contact the HPTN CORE and SDMC for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID, follow-up visit schedule, and random assignment will remain unchanged.
- For participants assigned to the substitution arm, BUP/NX use may be resumed after an assessment of continued eligibility for dosing and in consultation with the PSRT.
- Clinic staff will communicate any re-instatement of BUP/NX use to the study pharmacy.

5.7 Follow-up Visit Scenarios

Presented below are several examples of follow-up visit schedules and study scenarios that may occur during HPTN 058.

Scenario 1: Suppose a participant is randomized on July 3. The participant's target date for the Week 26 visit is January 1, but she comes to the clinic 3 weeks after the target date for the Week 26 visit. What do you do?

Complete the Week 26 visit procedures. Three weeks is still within the allowable target date.

Scenario 2: Continuing from above, because the participant was late for the Week 26 visit, when is Week 52 visit scheduled?

It is the same date as originally scheduled. Target dates are calculated from the **date of randomization** and do not vary in relation to the actual date of visit completion.

Scenario 3: You contact a participant to remind him of the Week 52 visit and he tells you he is now employed, no longer using drugs, and does not have the time to come for the visit. What do you do?

First of all, congratulate him for his life changes! Next, tell him how important it is to get data from everyone who enrolled in the study throughout the length of the study even if they are no longer using drugs. Ask him if he would be willing to come for one more visit. Find an agreeable time that does not interfere with his work schedule. If the participant still refuses to come in, tell him he is always free to change his mind and return to the clinic.

Scenario 4: A participant has come in for the Week 52 visit. The rapid HIV test is positive. What do you do?

- Record the rapid EIA result on the HIV Test Results Form for the Week 52 visit.
- Counsel the participant that his initial HIV test indicates that he may be infected with HIV, but that an additional test (that requires x days to complete) is required to verify the result. Provide referrals for other resources if needed.
- Deliver the participant's blood sample to the local lab for WB or IFA testing. Note that this testing is performed on the same sample (Sample 1).
- Complete the visit assessments for Week 52.
- Schedule the participant to obtain her/his WB or IFA test results when available.

If WB result is positive or indeterminate?

- When participant returns to clinic, explain that a *second sample* is needed. Provide appropriate counseling. (Follow algorithm in Appendix II-B of the protocol.)
- Schedule appointment to obtain results when available.
- Participant will continue with all future follow-up visits as originally scheduled; however if seroconversion is confirmed, no further HIV testing will be done at these future visits.