

Section 5. Participant Follow-up

5.1 Overview of Section 5

This section provides an overview of requirements and procedures for participant follow-up in the study. Additional procedure-specific detail can be found in the visit checklists in Section 6 as well as in Sections 9 and 10.

5.2 Follow-up Periods

Study participant accrual will last 18 months and each couple will be followed until the last couple enrolled has completed 5 years of follow-up.

5.3 Follow-up Visits

Two types of follow-up visits may be conducted: protocol-required visits and interim visits.

- **Protocol-required visits** are those specified to be conducted during follow-up per the study protocol. The HPTN 052 protocol specifies that protocol-required follow-up visits include three (3) monthly visits for couples at the start of the study regardless of study treatment study arm. In addition, when an Index Case initiates ART, whether at the beginning of the study or sometime during the study, both members of the couple will have a two-week follow-up visit, followed by 3 monthly visits. All other scheduled visits will be on a quarterly basis for both members of the couple. All protocol-required follow-up visits are pre-assigned a visit code as described in Section 11.
- **Interim visits** are those that take place when the Index or Partner completes a protocol-required visit within the visit window, and then returns within the same visit window for another visit where data is collected.

For example, the couple's month 3 target visit date is October 15. The couple completes their month 3 visit on October 12, within the month 3 visit window. On October 20 the Partner returns to the clinic for treatment of new STI symptoms. Because all procedures were already completed for the month 3 visit and October 20 is still within the month 3 allowable visit window, this is an Interim Visit.

Site staff must assign visit codes to all interim visits as described in Section 11. If a participant or couple call or come into the clinic but no data are collected, the visit is not considered an interim visit and does not receive a visit code.

5.4 Follow-up Visit Scheduling

5.4.1 Target Visit Dates

All enrolled study participants will complete follow-up visits throughout their participation in the study. Monthly visits should be conducted every 30 days based on the date of enrollment and quarterly visits should be conducted every 90 days based on the date of enrollment. Couples should return for follow-up visits together. The one exception to this is the target date for the 2-week visit that will be conducted after ART is initiated. This visit should be calculated based on the date of the visit when ART is initiated.

5.4.2 Visit Windows

5.4.2.1 Target Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, visits may be completed within a 2-week target window, called the target window, around the target date (*i.e.*, ± 7 days from the target date). Care should be taken to calculate the target visit window based on the targeted 30-day (monthly) or 90-day (quarterly) visit, not the previous visit. The one exception to this is the visit that will be conducted 2 weeks after ART is initiated; the target window for this visit is ± 3 days. If neither the Index Case nor the Partner return to the clinic within the target visit window, the visit will be considered to be missed per the protocol and PPD monitoring; however, per the SCHARP database, a Couples Missed Visit CRF should only be completed if neither the Index Case nor the Partner have returned to the clinic within the allowable visit window (see Section 5.4.2.2). SCHARP will provide the Protocol Team with routine recruitment and retention reports that will include information about completed and missed visits for purposes of monitoring adherence to the monthly visit schedule.

If not all of the enrollment procedures can be completed at the initial visit, the sites may have the participant return to the clinic to complete these procedures within 7 days of enrollment. If at all possible, laboratory procedures and adherence counseling should take place before administering ART for the first time.

5.4.2.2 Allowable Visit Windows

An allowable visit window is a wider window to allow for situations where required visits cannot be done within the target window. See Section 11.5.2 for more information about allowable visit windows. The allowable visit window is used by SCHARP to help sites determine what visit code to assign to a visit conducted outside of the target visit window.

5.4.3 Visits Conducted Over Multiple Days

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 with both members of the couple.

In the event that all required procedures cannot be completed on a single day (for example because the participant must leave the study site before all required procedures are performed) or the couple cannot conduct the visit together, site staff should make every effort to complete the procedures within the target visit window. If necessary, procedures can be completed during the allowable visit window or at a future follow-up visit. See Section 11 for relevant visit coding instructions for this situation.

For situations when couples cannot attend their visits together, which may occur due to work or childcare reasons, or when one member must leave before the visit is complete, the couple may not be able to participate in couples counseling with both members of the couples present. In these cases, it is important for the couple to consistently receive the messages of HIV education and risk reduction, which is the focus of this counseling, even if they cannot participate together. In this situation, couples counseling should be administered to each member separately, being sure to review each item of the couples counseling checklist with the individual members of the couple. It should be clearly stated in the source documentation that the counseling was done and that each item on the couples counseling checklist was reviewed - but that the counseling was conducted separately. If the counseling was done for the Index Case on one day and for the Partner on another day, the source documentation should clearly indicate that the couples counseling for each member took place on separate days. If both members received couples counseling within the allowable visit window, even if they are unable to attend the counseling together, the procedure will be considered complete for that visit.

5.4.4 Missed Visits

Efforts should be made to contact any participant who does not report for a protocol-required visit prior to the end of the target window period. A Couples Missed Visit CRF should be completed to document the missed visit at the end of the allowable window period; however, this should only occur if both members of the couple miss the visit. If either the Index Case or the Partner report for a protocol-required visit within the target visit window, the visit is not considered missed per the protocol; however, if either the Index or the Partner report with the allowable visit window, the visit will not be considered missed by SCHARP's accounting.

If a participant misses a monthly visit and returns to the clinic after that visit, but before the target window of the next visit, sites should conduct all preceding monthly visit procedures at that visit. These procedures should be completed in

addition to any procedures necessary to address the reason for the participant's visit. For example, if a participant misses the Month 2 visit, and comes in two weeks before the protocol-required Month 3 visit complaining of chest pain, all Month 2 visit procedures should be performed at this time. In addition, because the participant has come to the clinic complaining of chest pain, appropriate examinations and tests should be performed to diagnose and treat the symptom.

For participants who miss protocol-required quarterly or yearly visits, all procedures unique to that type of visit must be conducted at the participants' next visit (either monthly or interim visit). Refer to the Visit Checklists or the protocol to determine what procedures are unique to quarterly and yearly visits.

5.5 Follow-up Visit Procedures

Provided below is an overview of the procedural requirement for all follow-up visits.

5.5.1 All Follow-up Visits (Protocol-Required and Interim)

The following procedures must be performed at all follow-up visits, whether protocol-required or interim.

- Ongoing informed consent (Index and Partner)
- Review/update locator information (Index and Partner)
- Disease diagnosis and treatment if clinically indicated (Index and Partner)

5.5.2 ART Initiation Visit (for Delay Arm only)

For Index Case participants assigned to the delay arm, baseline data for hematology (CBC), blood chemistry, liver function tests, and viral load must be collected during the visit that ART is initiated. If this visit is a quarterly or yearly visit, these lab tests will be performed as part of the normal procedures; if not, they will be done in addition to the regular monthly procedures. Initiation of ART may begin at an interim visit, but only on a date when a monthly visit would occur in order to maintain the quarterly visit schedule.

Note that these procedures are performed at the enrollment visit for Index Case participants assigned to the immediate arm.

5.5.3 2-Weeks After ART Initiation Follow-up Visit

In addition to the procedures that must be performed at all follow-up visits, the following procedures must be performed at the 2-weeks after ART initiation follow-up visit:

- Couples counseling (Index and Partner)

- Adherence assessment (Index) and counseling (Index and Partner)
- Blood collection and testing (complete blood count [CBC], blood chemistry, liver function tests) (Index)
- Targeted medical history, concomitant medications assessment and physical exam (Index)
- Provide ART and/or primary HIV medication (Index)

5.5.4 Monthly Follow-up Visits

There will be three (3) monthly visits for couples at the start of the study regardless of study treatment arm. When an Index Case initiates ART, whether at the beginning of the study or sometime during the study, both members of the couples will have a two-week follow-up visit, followed by 3 monthly visits. All other scheduled visits will be on a quarterly basis for both members of the couple.

In addition to the procedures that must be performed at all follow-up visits, the following procedures must be performed at all monthly follow-up visits:

- Couples counseling (Index and Partner)
- Adherence assessment (Index) and counseling (Index and Partner) (when on ART)
- Urine pregnancy test (women only) (Index)
- Blood collection and testing (CBC, blood chemistry, liver function tests) for the first two months after initiating ART (Index)
- Targeted medical history and physical exam (Index and Partner)
- Targeted concomitant medications assessment (Index)
- Blood plasma HIV-1 RNA for Arm 1, perform at first monthly visit. For Arm 2, perform on month following initiation of ART (Index).
- Provide ART and/or primary HIV medication (Index)

5.5.5 Quarterly Follow-up Visits

In addition to the procedures that must be performed at all monthly follow-up visits, the following procedures must be performed at all quarterly follow-up visits:

- Blood collection for testing (CD4+ cell count and HIV-1 RNA) and storage (plasma, serum, and PBMC) (Index)

- Sexual history assessment (Index and Partner)
- Blood collection for HIV testing and storage (plasma and PBMC) (Partner)
- HIV counseling and testing (including risk reduction) (Partner)
- Quality of Life assessment (Index)

5.5.6 Yearly Follow-up Visits

In addition to the procedures that must be performed at all monthly and quarterly follow-up visits, the following procedures must be performed at all yearly follow-up visits:

- Urine collection and testing for gonorrhea and chlamydia (for all men, only for women if FDA-approved urine assay is used at site) (Index and Partner)
- Semen collection for HIV RNA testing and storage (Index)
- Circumcision status (Index and Partner)
- Genital exam (Index and Partner) including swab if an ulcer is observed upon examination
- Pelvic exam including swab and testing for gonorrhea, chlamydia, TV, BV, and candida, as well as the collection of genital secretions for HIV RNA testing and storage (women only) (Index and Partner)
- Blood collection for syphilis serology (Index and Partner)
- Blood collection for storage (plasma, serum and PBMCs) (Index & Partner)

5.5.7 HIV-Negative Partner Seroconversion

If the HIV-negative Partner seroconverts during the study, the following procedures will be performed:

- Semen collection for HIV RNA testing and storage (male only) (Index and Partner)
- Targeted medical history and physical exam (Partner)
- Pelvic exam including the collection of genital secretions for HIV RNA testing and storage (women only) (Index and Partner)
- Genital exam including swab if an ulcer is observed upon examination (Partner)

- Blood collection for testing (HIV RNA and HIV genotyping) (Index and Partner) and storage (plasma, serum and PBMC [Partner] and plasma and PBMC [Index])
- Blood collection and testing (CBC, blood chemistry, liver function tests, CD4+ cell count) (Partner)

5.5.8 Confirmed Virologic Failure

If the Index Case experiences virologic failure during the study, the following procedures will be performed in the event that they have not already been performed at the scheduled visit:

- Adherence assessment (Index) and counseling (Index and Partner)
- Blood collection for testing (HIV RNA and HIV genotyping) and plasma storage (Index)
- Provide treatment as clinically indicated (Index and Partner)

5.5.9 Termination Visit

Termination visits may be conducted when a participant, either Index Case or Partner, will no longer continue in the study. The termination visit may be conducted at a regularly scheduled visit or at an interim visit.

The termination visit should include as many procedures as possible from the yearly visit, unless a quarterly visit has been done within the previous 60 days prior to termination. If a quarterly visit has been done within 60 days prior to the termination visit, only these procedures of the yearly visit need to be done:

- Urine collection and testing for gonorrhea and chlamydia (for all men, only for women if FDA-approved urine assay is used at site) (Index and Partner)
- Circumcision status (Index and Partner)
- Genital exam (Index and Partner) including swab if an ulcer is observed upon examination
- Pelvic exam including swab and testing for gonorrhea, chlamydia, TV, BV, and candida, (women only) (Index and Partner)
- Blood collection for syphilis serology (Index and Partner)
- Blood collection for storage (plasma, serum and PBMC) (Index and Partner)

5.6 Follow-up Visit Locations

Off-site visits are allowed for the full HPTN 052 study; however, they cannot be conducted until the site has an SOP in place for such visits that has been approved by the HPTN 052 management team (052MGMT@HPTN.org), has included such visits in their current ICFs or created a stand-alone ICF to cover the process, and has received IRB approval for such a procedure.

All follow-up visits are to be conducted in the approved site facilities only, unless a site receives all required IRB/EC approvals for remote/off-site visits and thoroughly documents procedures for off-site visits in a site-specific SOP. The site-specific SOP for off-site visits should provide a detailed description of the following: 1) circumstances justifying the visits, 2) the resources necessary per visit and how this impacts the site, 3) determine which procedures/samples may be done/collected during a home visit and which can only be done at the clinic, 4) a chain of custody for samples and drug product as well as proper documentation, 5) procedures for study drug dispensation, 6) the availability of appropriately qualified and trained study staff, 7) participant confidentiality, 8) data management and accessibility of records, 9) participant availability and retention, and 10) additional test scheduling and time frames. With the appropriate approvals (if necessary) and documentation as described above, monthly follow-up visits may take place in a participant's home, or at other community-based locations, depending on site capacity, participant preference, staff and resource availability, and other logistical and confidentiality considerations.

Even if a visit is conducted off-site, the participant must return to the clinic for any procedures that can only be performed there (*e.g.*, pelvic exam, x-ray, *etc.*).

5.7 Follow-up Visit Scenarios

Presented below are several examples of follow-up visit schedules and study scenarios that may occur during HPTN 052. The examples illustrate that the allowable visit windows impact whether a completed visit will be considered a protocol-required visit or an interim visit. It may be helpful to refer to a calendar when attempting to calculate visit target dates. 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 similar to the example provided below.

5.7.1 **Suppose a couple is enrolled into the study on 01 April 2004 and they have been assigned to the study arm that receives ART upon enrollment. What are the target dates, the target visit windows, and the allowable visit windows for their visits through study month 6?**

Visit	Target Date	Target Window	Allowable Window
Two week	15 Apr 2004	12 – 18 Apr 2004	12-18 Apr 2004
Month 1	01 May 2004	24 Apr – 08 May 2004	24 Apr – 23 May 2004
Month 2	31 May 2004	24 May – 07 Jun 2004	24 May – 22 Jun 2004
Month 3	30 Jun 2004	23 Jun – 07 Jul 2004	23 Jun – 28 Aug 2004
Month 6	28 Sep 2004	21 Sep – 05 Oct 2004	21 Sep – 26 Nov 2004

*If the date falls on a weekend, visit should be scheduled on the following Monday.

Monthly target visit dates are set to occur every 30 days from the couple's study enrollment date and quarterly target visit dates are set to occur every 90 days from the couple's study enrollment date. For couples that receive ART at enrollment, they will have a 2-week follow-up visit, 3 monthly visits, then all other scheduled visits will be on a quarterly basis. Because not all months have 30 days, the target visit will not occur on the same date number (e.g., the 15th) or day (e.g., the 1st Monday) of every month. The target visit window is ± 3 days from the target date for the two week visit and ± 7 days from the target date for the monthly and quarterly visits. The week 2 allowable window is $-3/+3$ days from the target visit date; the monthly allowable window is $-7/+22$ days from the target visit date; and the quarterly and yearly target window is $-7/+59$ days from the target visit date.

5.7.2 Suppose the same couple that was enrolled on 01 April 2004 completes their Month 1 visit on 01 May 2004. What are the target visit dates, target visit windows and allowable visit windows for their visits in study months 2, 3, and 6?

The same target dates, target visit windows and allowable visit windows listed in the table in Section 5.7.1 apply here. Because target dates *always* remain linked to the enrollment date, target dates are *not* shifted when a previous visit does not take place on the target date.

5.7.3 Suppose the same couple that was enrolled on 01 April 2004 misses their Month 2 visit scheduled to take place on 01 June 2004, but they do return to the clinic on 07 June 2004. What do you do?

07 June 2004 is within the target Month 2 visit window. A missed visit form should not be completed, and the site should conduct all Month 2 study procedures, as specified in the protocol, on 07 June 2004.

5.7.4 Suppose the same couple does not complete their Month 2 visit between 24 May – 07 June 2004, but they do return to the clinic on 18 June 2004. What do you do?

Noting that the Month 2 visit window closed on 07 June 2004, but the allowable visit window is still open, proceed with the following steps:

- On 18 June 2004, complete all forms required for the Month 2 visit using the Month 2 Visit Code.

- Document in the source documentation that the visit took place outside of the protocol visit window (the target visit window).
- Confirm and reinforce the scheduling of the couple's Month 3 visit, which should still take place between 23 June and 07 July 2004.

5.7.5 Suppose the same couple does not complete their Month 2 visit between 24 May – 07 June 2004, but they do return to the clinic on 24 June 2004. What do you do?

The Month 2 allowable visit window closed on 22 June 2004, but the Month 3 visit window opened on 23 June 2004. The Month 2 visit is considered a missed visit, and none of the study procedures associated with this visit are performed to make up for the missed visit. Specifically, the site should perform the following study procedures:

- On 22 June 2004, complete a Couples Missed Visit Form for the Month 2 visit.
- On 24 June 2004, complete a Month 3 (Quarterly) visit per protocol.
- Confirm and reinforce the scheduling of the participant's Month 6 visit, which should occur between 21 September and 05 October 2004.

5.7.6 Suppose the same couple completes their Month 1 visit on 01 May 2004 and then the HIV-negative Partner presents to the study site complaining of a genital pain and irritation on 25 May 2004. What do you do?

The Month 2 visit window opened on 24 May 2004. Although not routinely scheduled at Month 2, a genital exam is required to evaluate the participant's genital symptoms. The site should proceed with the following steps:

- Complete a Month 2 visit per protocol.
- Complete a genital exam and collect swab(s) of genital ulcer(s) (if present). The swab(s) should be frozen, stored, and shipped to the HPTN Network Laboratory when the local laboratory has accumulated 15 specimens (see SSP Section 10).
- Treat symptomatic STD(s) syndromically.
- Remind the participant that s/he must return to the clinic with his/her Partner to complete the Month 2 visit before 07 June 2004. When the couple returns to the site, Month 2 visit procedures do not have to be repeated for the Partner; however, there should be clinical follow-up for the STD (or other diagnosis). If the Partner cannot return with the Index Case, ask that the Index Case come alone to complete the Month 2 visit.

- Confirm the scheduling of the couple's Month 3 visit, which should occur between the 23 June and 07 July 2004.

5.7.7 Suppose the same couple does not complete their Month 3 visit between 23 June and 07 July 2004, but presents to the study site on 10 July 2004. What do you do?

The Month 3 target visit window closes on 07 July 2004 but the Month 3 allowable visit window is still open. The site should perform all quarterly visit procedures at this study visit. The site should proceed with the following steps:

- If the Index Case is currently taking ART, attempt to find some manner by which the site can provide study drug to the Index Case and ensure that s/he does not run out of study drug prior to their visit.
- On 10 July 2004, complete the visit following the quarterly visit procedures specified for the Month 3 visit.
- Document in the source documentation that the visit took place outside of the protocol visit window (the target visit window).
- Confirm and reinforce the scheduling of the couple's next quarterly visit, which should take place between 21 September and 05 October 2004.

5.7.8 Suppose the same couple misses their Month 3 visit because the HIV-positive Index Case has broken his/her leg. The couple has every intention of remaining in the study, but the Index Case cannot come into the clinic for a few more weeks. The couple is willing to complete their Month 3 visit at their home on 05 August 2004 or return to the clinic on 15 August 2004. What do you do?

Proceed with the following:

- Determine whether or not off site visits are permissible at your site (see SSP Section 5.6).
- If off-site visits are permitted, complete visit Month 3 off-site following the appropriate site SOPs.
- If off-site visits are not permitted, ask that the HIV-negative Partner return to the clinic for the Month 3 visit within the target window. The Index Case should come back to the clinic on 15 August 2004 to complete the Month 3 visit, however, the Index Case can complete the Month 3 visit any time up until 28 August 2004. Document the circumstances of the visit in the Index Case's chart.

- Attempt to find some manner by which the site can provide study drug to the participant and ensure that s/he does not run out of study drug.
- Confirm and reinforce the scheduling of the couple's next quarterly visit which should take place between 21 September and 5 October 2004.

5.7.9 Suppose the same couple completes their Month 3 visit and the HIV test results for the HIV-negative Partner are positive. What do you do?

According to the HPTN 052 protocol, the HIV-negative Partner must return to the clinic for post-HIV test counseling and a second blood draw for a confirmatory HIV test (Western Blot [WB] or immunofluorescent assay [IFA]). This second blood sample must be divided into two specimens so that a second WB or IFA can be run to confirm a positive or indeterminate result. The return visit for the blood draw and for the test results should be documented as interim visits. If the Partner is a confirmed seroconversion, the following steps must be taken:

- The Partner will be terminated from the study and should be informed of their rights in terms of primary HIV care and access to ART from the clinic.
- The Partner should undergo all of the assessments required for a seroconversion as well as those normally required for a termination visit.
- The Index Case should undergo all of the assessments required for a seroconversion visit.
- To the extent possible, the Index Case will remain in the study and continue to return for all protocol-required visits.

5.7.10 Suppose the Index terminates at follow-up, does the Partner remain active?

If the Index and the Partner are still a couple, the Partner may remain in the study. However, if the couple separates, the Partner should be terminated.

5.7.11 Suppose the Index and Partner come in for protocol-required quarterly visit on different days (the Index is outside the target visit window, the Partner is not). What do you do?

Complete the Partner quarterly visit as usual. Complete the Couples Status form, indicating the Index was not present.

- Complete the quarterly visit procedures for the Index using the Visit Code for the quarterly visit as the visit is still within the allowable visit window. Document in the source documentation that the visit took place outside of the protocol visit window (the target visit window).

5.7.12 Suppose an Index reports to the clinic for his/her quarterly visit with a new Partner, not previously enrolled in the study. What do you do?

Confirm with the Index that the relationship with the previous Partner has ended. If possible, confirm this information with the previous Partner and inform them they are no longer eligible to participate in the study. Try to conduct a termination visit for the original Partner.

Begin screening process for new Partner to determine eligibility.

- If the Partner is eligible, complete Partner enrollment and quarterly visit procedures.
- If the Partner is not eligible, stop screening procedures and document the reason for ineligibility in the screening log.
- If Partner test results are indeterminate, perform a Western Blot using the same blood sample.
- Schedule the next appointment for receipt of results within 14 days. Encourage the couple to attend the next visit together.

Complete the Index quarterly visit.

5.7.13 Suppose a couple is enrolled in the study, and at one of the follow-up visits, the Index Case, who is a man, explains that he has two wives, but did not report that upon screening. What do you do?

Nothing. As long as this couple met the entrance criteria, they were legitimately enrolled and should continue in the study. The second wife should not be enrolled in the study.

5.7.14 Suppose a couple report for a follow-up visit and report independently that they have determined it would be safer to abstain from sex altogether. What do you do?

Nothing. This information will be captured as part of the sexual history assessment, but does not precipitate termination of either member of the couple.

Sample Participant Visit Tracking Sheet for HPTN 052

Participant ID Number	
Participant Enrollment Date	

***Instructions:** For HPTN 052, the Participant Enrollment Date is defined as the date upon which the participant, as part of a couple, is randomized to an arm of the study and assigned a PTID. Once the enrollment date is determined, enter all Target Visit Dates, Target Visit Windows, and Allowable Visit Windows for the next year. For Arm 1, the date for the 2-week visit can be calculated at enrollment. For Arm 2, once ART is initiated, the 2-week and 3 monthly follow-up visits can be scheduled. A new tracking sheet will need to be prepared for each year that the participant remains in the study.*

For Arm 1 participants and Arm 2 Participants who have not begun ART

Follow-up Timepoint	Target Visit Date	Target Visit Window	Allowable Visit Window	Scheduled Visit Date	Actual Visit Date
Week Two					
Month 1					
Month 2					
Month 3 (Quarterly)					
Month 6 (Quarterly)					
Month 9 (Quarterly)					
Month 12 (Yearly)					

For ARM 2 Participants who have begun ART

Follow-up Timepoint	Target Visit Date	Target Visit Window	Allowable Visit Window	Scheduled Visit Date	Actual Visit Date
Art Initiation visit					
2-week visit					
Month 1 follow-up					
Month 2 follow-up					
Month 3 follow-up					

5.8 Modified Follow-up Procedures

5.8.1 Pregnancy Testing and Sterility Documentation

Because the risk of ART-exposure to the fetus can be significant, all female participants must be tested for pregnancy as indicated on the schedule of evaluations except for those who have undergone sterilization or are post-menopausal. For women not on ART or on ART regimens that do not include efavirenz, acceptable document for the lack of reproductive potential includes a woman's self-reported history of surgical sterilization, menopause, or male Partner's azoospermia. Any statement of self-reported sterility or that of her Partner's must be entered in the source documents. For women on ART regimens that include efavirenz, acceptable documentation includes oral communication from a clinician or clinician's staff, a physician report/letter, a discharge summary, or an FSH measurement elevated into the menopausal range.

5.8.2 Pregnancy

Women in the study **MUST** be on HAART starting at the beginning of the second trimester, regardless of arm. Therefore:

- Pregnant women screening for the study who are in the first trimester of pregnancy should defer enrollment until the start of the second trimester of pregnancy.
- Pregnant women screening for the study who are at any point beyond the first trimester of pregnancy must be placed on ART appropriate for use during pregnancy immediately upon enrollment, even if randomized to the delay arm.
- If a participant becomes pregnant during the study, she should return for her normal protocol-required visits and undergo follow-up procedures with the following modifications:

Index Case:

- The woman must sign the Pregnancy ICF. If she is unwilling to do so, she cannot continue in the study and must be terminated.
- Women who are randomized to the immediate ART arm who become pregnant at any time after enrollment, must be placed on a regimen appropriate for use during pregnancy once the pregnancy is confirmed. If desired, the study staff can consult with the HPTN 052 CMC.
- Women who are randomized to the delay arm who become pregnant at any time after enrollment must begin ART at the beginning of the second trimester.

- 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.
- The monthly urine pregnancy test should be discontinued once 3 consecutive monthly or 2 consecutive quarterly pregnancy tests have yielded a positive result.
- If not offered at the HPTN 052 site, the woman and her baby should be referred to other facilities for pregnancy and well-baby care.

Partner:

- 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. Reduction of protocol-required volumes in these cases should be documented in the participant's chart.

NOTE: Sites **must** register pregnancies that occur on study to The Antiretroviral Pregnancy Registry by fax at +44-1628-789-666 (for non-US sites) or 1-800-800-1052 from within the US. More information is available at: www.apregistry.com. If pregnancies exist that are not included in the registry, sites must add those pregnancies to the registry retrospectively.

5.8.3 Termination of HIV-Negative Partner Due to Seroconversion

If an HIV-negative Partner seroconverts (*i.e.*, becomes HIV-1 positive) during the course of the study, the Partner will be terminated, but the Index Case should continue to return to the clinic for protocol-required visits and procedures (including ART) for the ascertainment of secondary endpoints. The couple is no longer required to return together and couples counseling is no longer required for the protocol. However, if in the best interest of or requested by the couple, the site is encouraged to continue to provide this service.

Note that if an HIV-negative Partner becomes HIV-2 positive, they will remain in the study as before, as this is not a study endpoint.

5.9 Couple Transfers

During the course of the study, couples may permanently leave the area where they enrolled. If they move to the vicinity of another HPTN 052 study site, they should be encouraged to transfer to that study site and continue study participation. To accomplish this, study staff at both sites will complete the process if a couple transfers. If there is no way that the couple can return to the clinic where they enrolled and they are not close to another HPTN 052 clinic to transfer, they will be terminated from the study.

Upon identifying the need for a couple transfer to another site, the transferring site is responsible for notifying the HPTN CORE, SCHARP, the HPTN Network Lab, and the site to which the couple wishes to transfer (the “receiving site”). After the logistical details of the transfer have been agreed upon, the following steps will be completed:

- SCHARP will notify the transferring site of all outstanding data QC notes for both members of the transferring couple; the transferring site will resolve these QCs.
- The transferring site will explain the transfer arrangements to the couple and obtain written permission for the release of information from both members of the couple authorizing transfer of their study records to the receiving site.
- The transferring site will ship **copies** of all of the couple’s study records to the receiving site via courier or overnight mail service. The transferring site will track the shipment and the receiving site will confirm receipt of the shipment with the HPTN CORE, SCHARP, and the transferring site. The receiving site will verify receipt of said materials with the transferring site. At this point in time, follow-up of the couple becomes the receiving site’s responsibility.
- The transferring site will complete and fax a Participant Transfer form for each member of the couple to SCHARP DataFax .
- The transferring site will forward a copy of both Participant Transfer forms to the HPTN Network Lab representative for informational purposes. The transferring site will retain archived samples for the couple unless otherwise instructed by the Network Lab.
- No study drug should be shipped between study sites, as none of the drugs are participant-specific.
- The receiving site will establish contact with the couple, obtain a copy of the original enrollment and screening consent (and any others), along with their informed consent to continue in the study (have both members of the couple sign an enrollment consent at the receiving site), and complete and fax a Participant Receipt form for each member of the couple to SCHARP DataFax.

- Upon receipt of the Participant Transfer and Participant Receipt forms, SCHARP will re-map the participant’s ID number in the study database to reflect the change in study site follow-up responsibility. This will ensure that future questions and/or QCs will be sent to the appropriate site. The participant’s original ID number and follow-up visit schedule will remain unchanged.

5.10 Protocol-Required and Interim Visits at Sites Other Than Where Participants or Couples Enrolled

During the course of the study, it may happen that a participant or couple is temporarily (for a few days, or a week or more) in another location where there is an HPTN 052 clinic other than the one in which they originally enrolled (their “home clinic”). If the participant or couple is in this temporary location during a protocol-required visit or when they require medical attention, these protocol-required or interim visits may be conducted at the alternative clinic (“temporary clinic”) if both sites have a SOP in place to cover this situation. In addition, the local EC/IRB must have agreed to the procedures outlined in the site-specific SOP, which must cover the following areas:

- Whether or not informed consent will need to be re-administered at the temporary clinic.
- A method to transfer study information from the temporary to the home clinic.
- A standard method of communication between the two sites prior to the initiation of any procedure, for clinical information, final decision-making about primary and ART-related care, and determination of the duration of time during which care and visits will be conducted at the temporary clinic.

If a participant or couple completes a substantial number of visits at a temporary site, consideration of a transfer should be made.