

Section 6. Participant Follow-up

This section provides information on requirements and procedures for participant follow-up.

6.1 Study Follow-up Plan and Participant Retention Targets

Each enrolled participant will be followed through 24 weeks of the study. However, participants with chronic hepatitis B virus (CHBV) will be followed for an additional 12 weeks. The target accrual is expected to be completed within 10 months for Version 1.0 of the protocol 6 months for Version 2.0 of the protocol. The protocol team will actively monitor and manage the study accrual process to ensure that this ambitious enrollment plan occurs.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of at least 95% for all enrolled study participants. Further information on HPTN 059 retention definitions and procedures for is provided in Section 8.

6.2 Types of Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted:

- **Scheduled visits** are those visits required per protocol. The protocol specifies that follow-up visits occur on a monthly basis. Within the category of scheduled visits, the term “monthly visits” is used to refer to those visits scheduled to take place in follow-up at Weeks 4, 8, 12, 16, 20, 24. CHBV participants will have additional follow up at Weeks 28, 32, and 36. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13.3.3.
- **Interim visits** are those visits in which a participant undergoes additional clinical, laboratory, and/or pharmacy procedures outside of the required evaluations for a scheduled study visit. There are a number of reasons why interim visits may take place (see protocol Section 5.7).

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

6.3 Follow-up Visit Scheduling

6.3.1 Target Visit Dates

Enrolled participants will be scheduled to complete follow-up visits on a monthly basis throughout their participation in the study. For each participant, all follow-up visits are targeted to take place every four weeks from the participant’s enrollment date. Each participant’s enrollment date is defined as the date upon which she is assigned an HPTN 059 Clinic Randomization Envelope. For example, for a participant assigned a Clinic Randomization Envelope on 15 September 2005, follow-up visits will be targeted to take place on 13 October 2005 (four weeks from 15 September), 10 November 2005 (eight weeks from 15 September), 8 December 2005 (12 weeks from 15 September), 5 January 2006 (16 weeks from 15 September) etc.

6.3.2 Protocol-Specified Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, each follow-up study visit has a two-week window around the target date (i.e., ± 1 week from the target date).

The ± 1 week window is comprised of 7 days before the target date and 7 days after the target date (inclusive). Figure 6-1 illustrates protocol-specified visit windows for a participant enrolled in the study on 15 September 2005.

Figure 6-1
Allowable Visit Windows for HPTN 059

September 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1	2	3
4	5	6	7	8	9	10
11	12	13	14	15 Enrollment Date	16	17
18	19	20	21	22	23	24
25	26	27	28	29	30	

October 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	4	5	6 Wk 4 Window opens	7	8
9	10	11	12	13 Wk 4 Target Date	14	15
16	17	18	19	20 Wk 4 Window Closes	21	22
23	24	25	26	27	28	29
30	31					

Figure 6-1 continued
Allowable Visit Windows for HPTN 059

November 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1	2	3 Week 8 Window Opens	4	5
6	7	8	9	10 Week 8 Target Date	11	12
13	14	15	16	17 Week 8 Window Closes	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

Wk 4 = Week 4 Visit, Wk 8 = Week 8 Visit

Although the two-week visit windows allow considerable flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at four-week intervals, and every effort should be made to do so. Extreme deviation from four-week intervals must be avoided. However, in cases where a participant is unable and/or not available to complete a given scheduled study visit within the ± 1 week window, it is highly preferable to conduct the visit as an “early retained visit” (before the visit window opens) or as a “late retained visit” (after the visit window closes), rather than miss the visit entirely. “Early retained” and “late retained” visits should NOT be assigned interim visit codes; rather, they should be assigned the visit code of the visit being conducted (e.g. visit code 3.0 for a Week 4 Visit). Such visits should be conducted on a date as close as possible to the visit window. The HPTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the monthly visit schedule (see Section 15).

6.3.3 Incomplete Visits

All procedures specified by the protocol to be performed at a particular follow-up visit will 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 participant must leave the study site before all required procedures are performed), the study site staff is to make every effort to complete the remaining procedures as soon as possible.

6.3.4 Missed Visits

A regularly scheduled follow-up visit is considered “missed” when a participant does not complete any of the required visit evaluations [either as an “on-time retained” visit (within the visit window), an “early retained visit” (before the visit window opens) or a “late retained visit” (after the visit window has closed)], and the next visit window has opened. For example, a participant completed her Week 4 Visit and then did not return to the clinic until the day her Week 12 visit window opened. She did not complete the Week 8 Visit during the Week 8 visit window, and did not complete the visit as an “early retained visit.” The Week 12 visit window has already opened, so she cannot make up the Week 8 Visit as a “late retained visit.” Therefore, the Week 8 Visit is considered “missed.” A Missed Visit case report form will be completed to document the missed visit (see Section 13). Additionally, clinic staff will document the missed visit in the participants’ chart notes and forward a copy of the signed, dated, chart note to the Pharmacy.

6.3.5 Follow-up Visit Scheduling Scenarios

Presented in Section Appendix 6-1 are several follow-up visit scenarios that may occur during HPTN 059. These scenarios illustrate that the protocol-specified windows impact whether a completed visit will be considered an “on-time retained” visit or an “early or late retained” visit. The examples also illustrate the complexities that may be encountered when scheduling and completing study follow-up visits in a “real world” setting. Given these complexities, all sites are encouraged to use Participant Visit Tracking Sheets similar to the example in Section Appendix 6-2 for each enrolled participant. The India site will use the HPTN 059 Participant Tracking Database, which is pre-programmed to generate such sheets for enrolled study participants.

Note: The India site will use the Participant Tracking Database, which is 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. The US sites will not use the Participant Tracking database, but will develop site specific tracking tools.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 5 and protocol Appendix I. Highlighted for reference below are the primary differences in procedural requirements between CHBV participants and non-CHBV participants:

- CHBV participants will have HBV Viral load assessment and HBV serum archive at Enrollment and Week 12, 24.
- CHBV participants will have HBV Viral load assessment, HBV serum archive, and LFT at Week 28, 32, and 36 Visits.
- At the Week 24 Visit, only Non-CHBV participants will complete the study burden Assessment. [CHBV participants will complete the study burden assessment at the Week 36 Visit]

The HPTN 059 protocol specifies that interval medical/menstrual/genitourinary histories (with concomitant medication review) should be performed at all scheduled follow-up visits, and, when clinically indicated, at any interim follow-up visits.

- An interval medical/menstrual/genitourinary history is considered clinically indicated at interim visits if the participant presents complaining of symptoms since the last visit. An interval history also should be performed at interim visits to obtain updated information on previously reported adverse events, when applicable.

6.4.1 Procedures for Follow-Up Visits with PK

Participants will have PK testing at Week 4, 12 and 20 Visits. On the Week 20 visit, participants in the daily use group should insert the study gel approximately 2 to 6 hours before the visit. Study staff should remind participants to use the study gel on the morning of their visit, or if the visit is scheduled in the afternoon, to insert the study gel 2 to 6 hours before the visit. For example if the visit is scheduled at 2:00 pm, participants can be instructed to use the study gel at 12:00 pm (noon).

6.5 Follow-up Visit Locations

All visits must take place on-site. The final contact after the last regularly scheduled follow up visit may take place either on-site, in a participant's home, or at other community-based locations, depending on site capacities and site and participant preferences.

6.6 Study Gel Re-Supply During Follow-up

Steps will be taken at follow-up visits to determine whether a participant remains eligible for continued study gel use per protocol specifications. Protocol Section 6.2 and Protocol Appendix II lists conditions under which participants should be discontinued from study gel use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

If eligible, participants in the daily use group will receive a standard number of four cartons (40 tubes and applicators) at the Enrollment Visit, and four cartons at each regularly scheduled follow – up visit. Participants in the coitally dependent group will receive a standard number of eight cartons (80 tubes and applicators) at the Enrollment Visit, and up to a maximum of eight cartons (80 tubes and applicators) at each regularly scheduled follow-up visit, depending on the participant's reported sexual frequency and the date of her next scheduled study visit.

If a participant loses or misplaces study gel after leaving the site, she will be instructed to return to the site to have new study supplies dispensed.

Several possible study gel re-supply scenarios are presented for illustrative purposes in Section Appendix 6-5 in this SSP section.

6.6.1 HPTN 059 Study Gel Re-Supply Worksheet

The HPTN 059 Study Gel Re-Supply Worksheet is an operational tool and source document designed to assist clinic staff in documenting the quantity of unused study gel returned by the participant and calculating the quantity of study gel to be ordered (and dispensed by study

pharmacy staff) at a given study visit for participants in the coitally dependent group only. The HPTN 059 Study Gel Re-Supply Worksheet should be completed at each regularly scheduled follow-up visit through Week 24 for BOTH coitally dependent and daily use participants. Unused study gel returns will be documented on the HPTN 059 Study Gel Re-Supply Worksheet for participants in both study arms. For coitally dependent participants, the HPTN 059 Study Gel Re-Supply Worksheet will calculate the number of cartons of study gel to be ordered at follow-up visits, taking into account the participant's self-reported usual, expected sexual frequency, and when her next visit is scheduled. A similar calculation is not required for daily use participants, who should receive a standard number of four cartons of study gel at each regularly scheduled follow-up visit.

The Study Gel Re-Supply Worksheet also will serve as source documentation of unused study gel that is returned by a participant at a given visit. Specifically, participants will be instructed to return any unused study gel in their possession to the site clinic at their next study visit, when new study gel supplies will be dispensed unless study gel is held or permanently discontinued, or the next visit is the Week 24/Early Termination Visit.

***Note:** If any participant repeatedly reports loss of study gel, or there is any other reason to suspect that she is sharing or selling study gel, inform the IoR and/or other designated site supervisory staff so that appropriate follow-up action can be taken. Guidance in management of such cases also may be sought from the HPTN 059 Protocol Safety Review Team (see Section 11). Clinic staff will document all action taken in signed and dated chart notes. For informational purposes, inform the HPTN CORE Clinical Research Managers, SDMC Project Manager, and Study Pharmacist of Record (PoR) of all cases of suspected study gel sharing or selling. The PoR will inform the DAIDS Protocol Pharmacist.*

6.6.2 HPTN 059 Study Gel Request Slip

The HPTN 059 Study Gel Request Slip (see Section Appendix 6-4) should be used by clinic staff to communicate to pharmacy staff the number of cartons to be re-supplied to each participant at each visit. The slip also should be used to communicate clinic staff decisions to hold study gel use for a participant, to resume study gel use after a prior hold, or to permanently discontinue study gel use.

The HPTN 059 Study Gel Request Slip is a two-part no carbon required (NCR) document that is available in pads of 50 from the NIAID Clinical Research Product Management Center. Shipments of study gel to the sites will include bulk supplies of the pads for use by clinic staff throughout the course of the study. In the event that clinic staff require additional pads, they should contact the DAIDS Protocol Pharmacist for a resupply. Complete the Study Gel Request Slip as follows:

- Record the clinic name at the top of the slip. The name recorded must be identical to the clinic name listed on the site's randomization envelopes and prescriptions, unless an alternative clinic name or abbreviation is designated in the site SOP for study gel re-supply during follow-up.
- Record the PTID and the number of the Clinic Randomization Envelope assigned to the participant in the boxes provided.

- Mark the box for either “RE-SUPPLY,” “HOLD,” “PERMANENT DISCONTINUATION” or “RESUME” to indicate the action to be taken in the study pharmacy. When marking “RE-SUPPLY” or “RESUME,” record the number of cartons of study gel to be dispensed for the participant.
 - When “RE-SUPPLY” is marked, study gel will be dispensed for the participant in the quantity entered on the slip.
 - When “HOLD” is marked, study gel will not be dispensed for the participant unless/until another slip marked RESUME is subsequently completed and received in the pharmacy.
 - When “PERMANENT DISCONTINUATION” is marked, no study gel will be dispensed to the study participant starting from the point the Study Gel Request Slip is received in the pharmacy.
 - When “RESUME” is marked, a previous hold will end, and study gel will be dispensed for the participant in the quantity entered on the slip. A signed, dated photocopy of the chart note documenting the original purpose for HOLD should be attached to the Study Gel Request Slip marked “RESUME.”
- The clinic staff name, signature, and signature date must be completed on the same day as the participant’s visit by a clinic staff member authorized to order study gel supplies for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date the Study Gel Request Slips; however site-specific pharmacy regulations may be more stringent than DAIDS requirements. All sites must comply with local requirements.
- Double-check the accuracy of all entries and then separate the two parts of the completed Study Gel Request Slip. Retain the yellow copy (labeled “Clinic”) in the participant study notebook. Deliver the white original (labeled “Pharmacy”) to the study pharmacy in the same manner that original prescriptions are delivered to the pharmacy. Both the original and clinic copy of the slip may be hole-punched.

6.7 HIV Testing During Follow-Up

At all sites, follow-up HIV testing will be performed at the Screening Visit, Enrollment Visit, Week 24/Early Termination, and when indicated during the first 24 weeks of follow-up according to the algorithm provided in Section 12 of the SSP.

Section Appendix 6-6 presents several HIV testing scenarios that illustrate the testing procedures required by the algorithm. Further information on the procedural and documentation requirements of the algorithm is provided in the remainder of this section.

In Step One, an FDA approved enzyme immunoassay (EIA) HIV test will be performed.

If the test in Step One is negative, testing will stop after Step One. If the test is positive, testing will proceed to Step Two, in which the same sample that tested positive in Step One will be tested with the FDA-approved Genetic Systems Western blot (WB) test manufactured by Bio-Rad Laboratories.

If the WB in Step Two is negative, testing will stop after Step Two. If the WB is positive or indeterminate, a second FDA-approved Genetic Systems WB must be performed on a second sample collected from the participant. This sample is referred to as “sample 2” in the algorithm and additional aliquots of plasma from this specimen will be archived for quality control/quality assurance testing by the Central Lab in the event that HIV infection is confirmed. For purposes of estimating the effectiveness of the study gels tested in HPTN 059, only participants for whom infection is confirmed with two positive WB results on two different samples will be counted as having become HIV-infected.

If the sample 2 WB is negative or indeterminate, additional WB testing must be performed on additional samples. In this case, inform the HPTN CL via email of the sample 1 and sample 2 test results (copied to the HPTN CORE and SDMC) and request CL input on next steps and timeframes for additional specimen collection and testing.

Further instructions for performing HIV tests during follow-up are provided in Section 12.5.2. All tests must be documented on local laboratory log sheets or other laboratory source documents. A second independent clinic or laboratory staff member trained in proper HIV testing and result recording procedures must review, verify, and sign-off on test results prior to disclosure of results to participants. For positive/reactive results, review, verification, and sign-off must be performed by a nurse, clinician, or physician.

6.8 Procedures for Participants Who Discontinue Product

As stated in protocol Section 3.6, regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time.

Protocol Section 5.9 specifies procedures for participants who discontinue study gel use. Participants who discontinue study gel because they seroconvert to HIV or become pregnant will be encouraged to remain in the study if they are willing, for safety evaluations according to the study follow up schedule with the exceptions described in the following sections. PK sampling and analysis will not be completed for these participants; and study gel cartons will not be dispensed.

6.8.1 Modified Follow-up Procedures for Participants Who Seroconvert to HIV

Participants who become infected with HIV after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. All participants who become infected with HIV 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. 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, with the following exceptions:

- After HIV infection is confirmed per the algorithm SSP Section 12, HIV testing will be discontinued.
- Counseling for HIV/STI risk reduction will be discontinued. Counseling will be modified to address primary and secondary HIV/STI prevention for infected women.
- Study gel use will be discontinued.
- PK Assessments will be discontinued.

Study pharmacy staff must be informed of the product discontinuation in writing using the Study Gel Request Slip. Clinic staff will attach to the Study Gel Request Slip a signed, dated chart note documenting the participant's seroconversion. Study gel supplies previously dispensed to the participant must be retrieved as soon as possible after pregnancy is confirmed, and a Product Hold/Discontinuation case report form (see Section 13.6) must be completed and transmitted to the SDMC.

6.8.2 Modified Follow-up Procedures for Participants Who Become Pregnant

Participants who test positive for pregnancy after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule until their study exit date or their pregnancy outcome is ascertained, whichever is longer. In addition, for participants who become pregnant 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, including routine pregnancy testing, will continue to be conducted for pregnant participants, with the following exceptions:

- Study gel use will be discontinued during pregnancy.
- Since ascending genital tract infection — although rare — could be facilitated by a bimanual exam during pregnancy, and since pelvic tenderness/discomfort observed during pregnancy may not be due to infection, the bimanual exam may be omitted during pregnancy (unless otherwise clinically indicated).

- PK assessments will be discontinued.

Study pharmacy staff must be informed of the product hold in writing using the Study Gel Request slip. Clinic staff will attach to the Study Gel Request Slip a signed, dated chart note documenting the participant's pregnancy. Study gel supplies previously dispensed to the participant must be retrieved as soon as possible after pregnancy is confirmed, and a Product Hold/Discontinuation case report form (see Section 13.6) must be completed and transmitted to the SDMC. Participants may resume study gel use after birth or pregnancy termination, as evidenced by a negative pregnancy test result and a normal pelvic exam performed by study staff. In the case that study gel use is resumed, clinic staff will communicate this to the study pharmacy in writing, using the HPTN 059 Study Gel Request Slip, complete items 4-4a on the Product Hold/Discontinuation form and fax the form to SCHARP. For participants who remain pregnant at study exit, the response to item 4 on the Product Hold/Discontinuation form should be marked "no (permanently discontinued).

Several illustrative pregnancy management scenarios are provided in Section Appendix 6-7. All study sites are strongly encouraged to use a pregnancy management worksheet similar to the sample in Section Appendix 6-8 to ensure proper documentation of the pregnancy and timely discontinuation and resumption (if applicable) of study gel use. Study pharmacy staff must be informed of the product hold or discontinuation in writing via the Study Gel Request Slip, study gel supplies previously dispensed to pregnant participants must be retrieved as soon as possible after the pregnancy is identified, and a Product Hold/Discontinuation case report form (see Section 13.6) must be completed and transmitted to the SDMC.

For all participants who become pregnant, regardless of study gel group, a Pregnancy Report and History form must be completed to report the pregnancy. A Pregnancy Outcome form also must be completed to document the outcome of the pregnancy. Certain pregnancy outcomes also must be reported on Adverse Experience Log case report forms (see Section 13.6) and/or DAIDS Expedited Adverse Event Forms, as described in Section 17.2 of this manual.

6.8.3 Modified Follow-up Procedures for Participants Who Become Infected with Hepatitis B

Participants who become infected with Hepatitis B after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule.

While in scheduled follow-up, all protocol specified study procedures will continue to be conducted for participants who become infected with Hepatitis B, and the infection will be managed in accordance with current clinical practice at each site. Hepatitis B symptoms will be managed in accordance with conventional clinical practice.

If the participant provides written informed consent as a CHBV participant, she may be followed according to protocol evaluations for CHBV participants. These include all protocol evaluations for non-CHBV participants, Hepatitis B viral load testing, storage of serum for possible future Hepatitis B resistance testing, and an additional 3 months of study follow-up (Week 28, Week 32, and Week 36 Visits) with liver function testing.

6.8.4 Participants Who Voluntarily Discontinue Study Gel Use or Miss One or More Follow Up Visits

Participants who return to the clinic following a missed visit or discontinuation of study gel may resume study gel usage at the discretion of the clinician. If the participant resumes study gel use, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged.
- An interval (since the last visit) medical/menstrual/genitourinary history should be taken and a pregnancy test should be performed as soon as the participant resumes study participation. Study gel use will be resumed only among participants who are not currently pregnant, and those participants who tested pregnant on-study but have since fulfilled the following 3 criteria: given birth or had a pregnancy termination, tested negative for pregnancy, and had a normal pelvic exam performed by study staff.

Clinic staff will communicate any re-supply of study gel for participants who have a missed visit or miss one or more follow up visits to the study pharmacy in writing, using the HPTN 059 Study Gel Request Slip.

When a participant has a missed visit, site Study pharmacy staff must be informed of the discontinuation in writing by forwarding a signed, dated chart note documenting the participant's missed visit. When the participant returns to the clinic, clinic staff will communicate any resumption-supply of study gel use to the study pharmacy in writing, using the HPTN 059 Study Gel Request Slip with an updated, signed and dated chart note documenting the participant's missed visit and the investigator's decision to resume the participant's study gel use with study gel.

6.8.5 Participants Who Discontinue Study Gel Use Permanently (as advised by study staff)

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

- Participants will not be provided with study gel.
- PK assessments will not be done.

Study pharmacy staff must be informed of the permanent product discontinuation of study gel in writing using the Study Gel Request Slip. Clinic staff will attach a copy of a signed, dated chart note documenting the participant's study gel discontinuation (the original will be kept with the participant's clinic study records). Gel supplies previously dispensed to the participant must be retrieved as soon as possible after pregnancy is confirmed, and a Product Hold/Discontinuation case report form (see Section 13.6) must be completed and transmitted to the SDMC.

6.8.6 Final Contact

The week 24 follow up visit for non-CHBV participants will include laboratory testing for HIV and other infections; and, the week 36 visit for CHBV participants will include laboratory test for hepatitis B surface antigen testing and liver function testing. As the results may not be available at these final visits for participants, a final contact (in person or by telephone [except for positive HIV test results]) may be required to provide the final study test results, post-test counseling, and treatment from these visits. For participants who become pregnant prior to the study end date, an additional contact may be required to ascertain the participant's pregnancy outcome. If genital symptoms are reported during the final contact, the participant will be instructed to report to the on-site clinic as soon as possible for non-study clinical follow-up, per local standard of care practice.

Study sites may complete these contacts at the study site or at community based locations, depending on site capacities and site and participant preferences. All final contacts must be documented in participant study records.

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for HPTN 059

6-1.1	Suppose Miss X enrolls in the study on September 22. What are the target and visit window dates for her visits at Weeks 4, 8, 12, 16, 20, and 24?		
	<u>Target</u>	<u>Allowable</u>	
	Week 4	October 20	October 13-20
	Week 8	November 17	November 10-24
	Week 12	December 15	December 08-22
	Week 16	January 12	January 05-19
	Week 20	February 09	February 02-16
	Week 24	March 09	March 02-16
	Why? Target dates are set every four weeks from the study enrollment date. The allowable visit window is ± 1 week from the target date.		
6-1.2	Suppose Miss X has her Week 4 visit on October 27. What are the target and visit window dates for her visits at Weeks 8, 12, 16, 20 and 24?		
	<u>Target</u>	<u>Allowable</u>	
	Week 8	November 17	November 10-24
	Week 12	December 15	December 08-22
	Week 16	January 12	January 05-19
	Week 20	February 09	February 02-16
	Week 24	March 09	March 02-16
	Why? Target dates always remain linked to the enrollment date. Target dates do not shift when a previous visit does not take place on the target date.		
6-1.3	Suppose Miss X does not have her Week 8 visit on the target date of November 17, but presents to the study site on November 21. What do you do?		
	<ul style="list-style-type: none"> • Conduct a Week 8 visit per protocol on November 21. 		
	Why? November 21 is within the Week 8 visit window.		

Section Appendix 6-1 continued
Follow-up Visit Scheduling Scenarios for HPTN 059

<p>6-1.4 Suppose Miss X does not have her Week 8 visit between November 10 and November 24, and does not present to the study site until December 16. What do you do?</p> <ul style="list-style-type: none">• On December 8 (the day the Week 12 visit window opens), consider the Week 8 visit missed, complete a Missed Visit form and fax to SCHARP.• On December 16, conduct a Week 12 visit per protocol.• If the participant reports an AE that requires clinical follow up prior to the next regularly scheduled visit (Week 16), schedule an interim visit. <p>Why? The Week 8 visit window closed on November 24, and the Week 12 visit window opened on December 8.</p>
<p>6-1.5 Suppose Miss X does not have her Week 8 visit between November 10 and November 24, and does not presents to the study site until November 30. What do you do?</p> <ul style="list-style-type: none">• The visit window for the next regularly scheduled visit (Week 12) has not yet opened, so the Week 8 Visit can still be made up as a “late retained visit” outside the visit window.• On November 30, conduct all Week 8 visit procedures and assign the Week 8 visit code (04.0) to all CRFs completed during this visit.• Confirm and reinforce the scheduling of Miss X’s Week 12 visit. <p>Why? The Week 8 visit window has not yet opened as of November 30th, so although the Week 8 visit window has passed, the Week 8 visit can still be made up as a “late retained visit.” All Week 8 visit procedures should be conducted in the same manner as if the visit were being conducted within the Week 8 visit window, and the Week 8 visit code should be assigned to all CRFs completed at this time.</p>
<p>6-1.6 Suppose Miss X completes her Week 4 visit on October 22 and then presents to the study site complaining of genital pain and irritation on November 17. What do you do?</p> <ul style="list-style-type: none">• On November 17, complete a Week 8 Visit per protocol.• In addition to routine Week 8 visit procedures, complete a pelvic exam and any clinically indicated STI testing in response to the participant’s symptoms and observed exam findings. <p>Why? The Week 8 visit window opened on November 10, so a Week 8 Visit should be conducted if and when the participant presents to the site at this time. A pelvic exam and clinically-indicated STI testing also are required to evaluate the participant’s symptoms.</p>

Section Appendix 6-1 continued
Follow-up Visit Scheduling Scenarios for HPTN 059

6-1.7 Suppose Miss X presents to the study site for her Week 12 visit on December 16, and completes some but not all of the protocol-specified procedures for Week 12 visit. What do you do?

- Document all procedures performed on December 16 as usual. Use the scheduled Week 12 visit code for all CRFs completed on this day. Explain in chart notes why all protocol-specified procedures were not completed.
- Schedule Miss X to return to the study site as soon as possible, and preferably within the Week 12 visit window, to complete the remaining Week 12 Visit procedures.
- When Miss X returns to the study site, perform all remaining Week 12 Visit procedures. Use the same Week 12 Visit code for all CRFs completed for this visit, regardless of whether the remaining Week 12 visit procedures are conducted within the Week 12 visit window, or after the window has closed.
- Take care to document the actual date that each procedure was performed in visit chart notes, on visit checklists, on CRFs, and on all other relevant documents and forms.
- Confirm and reinforce the scheduling of Miss X's Week 16 Visit.

Why? Since Miss X could not complete all protocol-specified procedures in a single visit, all efforts must be made to conduct the remaining protocol-specified study evaluations at a later date and as soon as possible.

6-1.8 Suppose Miss X requests an HIV test at her Week 12 Visit on December 22, tests EIA positive on her HIV test for this visit, and is scheduled to return in ten days for her Western blot result. If Miss X returns on January 16 to receive her Western blot result, what do you do?

- On January 16, conduct a Week 16 visit per protocol. Additionally provide Miss X's Western blot result and post-test counseling during the visit. If the WB result is indeterminate or positive, collect a second sample for HIV confirmatory testing and schedule an interim visit to provide the participant with the second sample Western blot result. Additionally, aliquot plasma from this second sample and send to CL for archiving for QA/QC measures. Record the EIA test result on the STI Laboratory Results form and the WB result on the HIV Test Results form. Both forms should be assigned the Week 16 visit code.

Why? January 16 is within the visit window for Miss X's Week 16 Visit, so all Week 16 visit procedures should be conducted at this time.

Section Appendix 6-1 continued
Follow-up Visit Scheduling Scenarios for HPTN 059

6-1.9 Re-considering Scenario 6-1.8, suppose Miss X completes her Week 12 Visit on December 19, tests positive on her HIV test that day, and returns to the study site for her Western blot result on December 24. What do you do?

- On December 24 complete an interim visit and provide Miss X with her Western blot result and post-test counseling. Additionally perform an interval medical/menstrual/genitourinary history, if clinically indicated, and a pregnancy test. If the WB result is indeterminate or positive, collect a second sample for HIV confirmatory testing. Additionally, aliquot plasma from this second sample and send to CL for archiving for QA/QC measures. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 16) visit. If available, the WB result from this second sample should be provided to the participant, along with post-test counseling, at the next (Week 16) visit. Record the EIA test result on the STI Laboratory Results form. Record the WB test results on the HIV Test Results form. Both forms should be assigned the appropriate interim visit code

Why? Miss X already has completed her Week 12 Visit, but on December 24 her Week 16 visit window has not yet opened. This is the reason why the December 24 visit is considered an interim visit. An interval medical/menstrual/genitourinary history review and appropriate clinical follow-up are completed at interim visits when clinically indicated. Pregnancy testing is required at all interim visits.

***Note:** In both Scenarios 6-1.8 and 6-1.9, delivery of appropriate post-test counseling related to the participant's Western blot result is of highest priority. Depending upon the test result, and the participant's reaction to it, it may or may not be possible to perform any other protocol-specified procedures during post-test visits. This is expected and acceptable, provided that site staff offers to conduct all protocol-specified procedures for the visit, and that the reason for not performing other protocol-specified procedures is documented in participants' study charts as participant refusal.*

Section Appendix 6-2
Sample Participant Visit Tracking Sheet for HPTN 059

Participant ID Number	
Participant Enrollment Date	

Instructions: *The Participant Enrollment Date is defined as the date upon which an HPTN 059 Clinic Randomization Envelope is assigned to the participant. Once the enrollment/randomization date is determined, enter target visit dates and allowable visit windows below. File this sheet with the participant's study chart and update it with scheduled and actual visit information at each visit.*

Follow-up Timepoint	Target Visit Date	Visit Window	Scheduled Visit Date	Actual Visit Date	Pelvic Exam Performed?	HIV Testing Performed?	Safety Labs Performed?
Week 4							
Week 8							
Week 12							
Week 16							
Week 20							
Week 24							
Week 28							
Week 32							
Week 36							

Note: *This tracking sheet is not a source document. Information on this sheet is based on other source documents contained in the participant study chart. Areas shaded in gray, indicate visits for CHBV participants.*

**Section Appendix 6-3
HPTN 059 Study Gel Re-Supply Worksheet - Page 1 of 2**

HPTN 059 Study Gel Re-supply Worksheet

Participant ID

Site Number			Participant Number						Chk		

Visit Date

dd		MMM		yy	

Clinic Staff: Study gel is dispensed as 10 tubes/applicators per carton. Complete items 1–2 before the interview.

1. Participant was dispensed cartons at her last study visit.
2. Participant is in the: Coitally dependent arm
 Daily use arm

3. At this visit, the participant returned the following:

3a. Number of unopened/full cartons:	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	→	Multiply by 10:	<input style="width: 20px; height: 20px;" type="text"/>	+	<input style="width: 20px; height: 20px;" type="text"/>	tubes	
3b. Number of partially used cartons:	<input style="width: 20px; height: 20px;" type="text"/>	<input style="width: 20px; height: 20px;" type="text"/>	→	Number of unused tubes:	<input style="width: 20px; height: 20px;" type="text"/>	=	<input style="width: 20px; height: 20px;" type="text"/>	tubes	
3c. Add items 3a and 3b to get the number of unused tubes returned:							<input style="width: 20px; height: 20px;" type="text"/>	tubes

Items 4–6 are for coitally dependent participants only. For daily use participants, go to statement above item 7.

- | | | | | |
|--|-------------------|---|---|-----------------|
| 4. Previously reported (last visit) sexual frequency:
<i>Review with participant.</i> | 4a. Weekly | <input style="width: 20px; height: 20px;" type="text"/> | <input style="width: 20px; height: 20px;" type="text"/> | times per week |
| | 4b. Monthly | <input style="width: 20px; height: 20px;" type="text"/> | <input style="width: 20px; height: 20px;" type="text"/> | times per month |
| 5. Projected sexual frequency for next month:
<i>Probe here as needed by asking about planned partner absences, returns from absences, etc.</i> | 5a. Weekly | <input style="width: 20px; height: 20px;" type="text"/> | <input style="width: 20px; height: 20px;" type="text"/> | times per week |
| | 5b. Monthly | <input style="width: 20px; height: 20px;" type="text"/> | <input style="width: 20px; height: 20px;" type="text"/> | times per month |
| 6. Divide item 5b by 10 and round to the next highest whole number: | | <input style="width: 20px; height: 20px;" type="text"/> | <input style="width: 20px; height: 20px;" type="text"/> | cartons |

Clinic Staff: For coitally dependent participants, the number in item 6 (up to a maximum of 8 cartons) is the number of cartons to be ordered at this visit. For daily use participants, 4 cartons should be ordered at each scheduled study visit. Complete a Study Gel Request Slip based on this number and inform the participant of the number of cartons to be dispensed to her today.

7. Did the participant report that tubes and/or applicators were used other than as directed or that anything else happened to any of her tubes and/or applicators (e.g., they were lost or damaged) since the last visit? yes no → *If no, end of form.*

7a. Describe what happened, number of tubes/applicators involved, and any follow-up discussion with the participant (continue on back if necessary):

HPTN 059 Study Gel Re-supply Worksheet

Q:\protocols\HPTN059\Product&randomization\Gel_resupply\ge_resupply_14Feb06.fm

**Section Appendix 6-4
HPTN 059 Study Gel Request Slip**

HPTN 059 Study Gel Request Slip

Clinic Name:			
Participant ID			Clinic Randomization Envelope #
<input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/>			<input type="text"/> <input type="text"/> <input type="text"/>
<p>Clinic Staff Instruction: Mark whether this is a study gel re-supply, hold, resume, or permanent discontinuation request. Record the number of study gel cartons to be dispensed (if applicable), and sign and date. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant study notebook.</p>			
<input type="checkbox"/> RE-SUPPLY	→	Pharmacy: Dispense	<input type="text"/> cartons of study gel (10 tubes/applicators per carton).
<input type="checkbox"/> HOLD	→	Pharmacy: Do not dispense study gel to participant unless another HPTN 059 Study Gel Request Slip marked "Resume" is received.	
<input type="checkbox"/> RESUME	→	Pharmacy: Dispense	<input type="text"/> cartons of study gel (10 tubes/applicators per carton) as authorized by the Investigator of Record and/or designated clinic staff.
<input type="checkbox"/> PERMANENT DISCONTINUATION	→	Pharmacy: Do not dispense any further study gel to participant.	
Clinic Staff Name (please print): _____			
Clinic Staff Signature: _____			
Date:	<input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/>	<input type="text"/> <input type="text"/>
	<i>dd</i>	<i>MMM</i>	<i>yy</i>

Pharmacy

Section Appendix 6-5
Study Gel Re-Supply Scenarios for HPTN 059

6-5.1 One day after receiving new cartons of study gel, a participant returns to the clinic to report that she left all the cartons on the bus that she took home from the clinic. What do you do?

Clinic Staff: Document the participant report and prepare a Study Gel Request Slip for more cartons of study gel for the participant. Document the occurrence in a signed and dated chart note in the participant's chart. Attach a photocopy of the chart note to the Study Gel Request Slip. Provide and document follow-up instructions and counseling to avoid further loss of study gel supplies.

If the participant repeatedly reports loss of study gel, or there is any other reason to suspect that she is sharing or selling her study gel, inform the Investigator of Record and/or other designated site supervisory staff so that appropriate follow-up action can be taken. Document the situation and action taken in signed and dated chart notes. For informational purposes, inform the HPTN CORE Clinical Research Managers, SDMC Project Manager, and Study Pharmacist of Record (PoR) of all cases of suspected study gel sharing or selling; the PoR will inform the DAIDS Protocol Pharmacist.

Pharmacy Staff: Upon receipt of the new HPTN 059 Study Gel Request Slip, dispense study gel per pharmacy SOPs. File the copies of the clinic staff notes in the participant's specific pharmacy files.

6-5.2 Two participants routinely come to the clinic together for their monthly visits. At one of their visits they both receive new cartons of study gel. After their visits, the participants take the same bus home. The bus is crowded and when they arrive at their bus stop, they cannot tell which cartons belong to whom. They return to the clinic two days later to report what has happened. What do you do?

Clinic Staff: Document the participant's report and prepare a Study Gel Request Slip for each participant requesting more cartons of study gel to be dispensed. Document the occurrence in a signed and dated chart note in each participant's chart. Attach a photocopy of each chart note to the respective participant's Study Gel Request Slip. Provide and document follow-up instructions and counseling to avoid further loss of study gel supplies. Contact the DAIDS Protocol Pharmacist, SCHARP Protocol Manager, and FHI Clinical Research Manager.

Pharmacy Staff: Upon receipt of the new HPTN 059 Study Gel Request Slip, dispense study gel per pharmacy SOPs. File the copies of the clinic staff notes in the participant-specific pharmacy files.

Note: Information relating to participant's blinded product assignment (tenofovir gel or placebo) is strictly confidential. With the exception of designated study pharmacy staff, clinic staff MUST remain blinded to a participant's random product assignment; in the case above, clinic staff must remain blinded as to whether or not the two participants were randomly assigned to the same or different treatment arms (tenofovir gel or placebo)

To prevent this problem in the future, pharmacy staff may mark the cartons of study participants who often travel together to help the participants differentiate their supplies. For example, mark the boxes with a colored sticker or other symbol (e.g., blue for one participant, green for the other). The pharmacy staff should document in the participant's pharmacy records if and when cartons are marked for purposes of differentiation, so that they can later distinguish between different participants' cartons should such an occasion arise.

Section Appendix 6-5 continued
Study Gel Re-Supply Scenarios for HPTN 059

6-5.3 Following from the scenario in 6-5.2, if two participants are traveling home together and confuse their study gel cartons so that they are not sure which study gel cartons belong to whom, but only one of the participants return to the clinic to report this problem. What do you do?

Clinic Staff: Present the cartons to the Study Pharmacist and ask him or her to verify whether or not either carton belongs to the participant by looking up the Participant-Specific Pharmacy Dispensing Record. Document the occurrence in a signed and dated chart note.

- If one or all of the cartons do not belong to the participant, collect the carton(s) that do not belong to her and prepare a Study Gel Request Slip to order new cartons for her. Document the occurrence in a signed and dated chart note and attach a copy of the participant's chart note to the Study Gel Request Slip. Forward a copy of the Study Gel Request Slip (with signed, dated chart note) to the pharmacy. Contact the other participant to arrange to collect and replace her study gel supplies as well.

Pharmacy Staff: If a new Study Gel Request Slip is received, dispense study gel per Pharmacy SOPs. If copies of any clinic staff notes are received, file these in participant-specific pharmacy files. If returned study gel supplies are received, document the returns and store the tubes. .

6-5.4 A coitally dependent participant returns to the clinic for a follow-up scheduled visit and is re-supplied with the maximum allowable number of cartons to be dispensed based on her self-reported sexual frequency. Three weeks later she returns to the clinic to request more tubes/applicators. What do you do?

Clinic Staff: Ask the participant whether she has used all of the tubes/applicators that were given to her at her previous visit.

- If the participant reports that she has used all of her tubes/applicators, counsel her that the study only allows for enough study gel to be given for twice daily use, so the maximum total number of cartons she can receive at one time (to last until her next regularly scheduled monthly visit) is eight. Remind her that she can receive more tubes/applicators at her next scheduled visit (which will occur about one week later) and re-emphasize instructions to use condoms for all sex acts. Document the participant request and action taken in a signed and dated chart note.
- If the participant reports that she has lost some of her study gel supplies, discuss and probe as needed to confirm — to the extent possible — that the supplies have actually been lost. If so, additional gel supplies needed to last until the next scheduled visit may be ordered and dispensed.

If there is any reason to suspect that the participant has actually used all of her study gel or that she is sharing or selling her study gel, inform the Investigator of Record and/or other designated site supervisory staff so that appropriate follow-up action can be taken. Document the participant request and action taken in signed and dated chart notes. For informational purposes, inform the HPTN Clinical Research Managers, SDMC Project Manager, and Study Pharmacist of Record (PoR) of all cases of suspected study gel sharing

or selling; the PoR will inform the DAIDS Protocol Pharmacist.

Pharmacy Staff: If additional gel supplies are ordered using a new Study Gel Request Slip (with a signed, dated chart note), dispense study gel per Pharmacy SOPs.

Section Appendix 6-6 Follow-up HIV Testing Scenarios for HPTN 059

6-6.1 Suppose Miss X's requests an HIV test at the Week 12 Visit and tests EIA positive. What do you do?

- When a positive EIA HIV test is obtained, confirm with a WB test (note that this testing is being performed on the same sample that tested positive on the test (Sample 1). Record the positive EIA test result on the STI Laboratory Results form for the Week 12 Visit.
- An interim visit already should have been scheduled at the Week 12 Visit in order to provide the participant with her HIV test results.
- If the first WB is positive, at the interim visit counsel Miss X that her initial HIV tests indicate that she may be infected with HIV, but that an additional blood sample for an additional test (that requires N days to complete) is required to verify the result. Provide appropriate post-test counseling per site SOPs. Conduct pregnancy testing (required for all study interim visits). Complete an interval medical/menstrual/genitourinary history review and appropriate clinical follow-up if clinically indicated. If available at the time of the Week 16 Visit, inform the participant of her second sample WB result and provide appropriate post-test counseling per site SOPs. If the second sample WB result is not available at the time of the Week 16 Visit, schedule an interim visit (to occur as soon as possible after the anticipated receipt date of the WB result) to provide the participant with her second sample WB result and appropriate post-test counseling.
- If the first WB is indeterminate, at the interim visit counsel Miss X that her initial HIV test indicated that she may be infected with HIV and an additional blood sample and test (that require N days to complete) is required to verify the result. Provide appropriate post-test counseling per site SOPs. Conduct pregnancy testing (required for all study interim visits). Complete an interval medical/menstrual/genitourinary history review and appropriate clinical follow-up if clinically indicated. If available at the time of the Week 16 Visit, inform the participant of her second sample WB result and provide appropriate post-test counseling per site SOPs. If the second sample WB result is not available at the time of the Week 16 Visit, schedule an interim visit (to occur as soon as possible after the anticipated receipt date of the WB result) to provide the participant with her second sample WB result and appropriate post-test counseling.
- If the first WB is negative, at the interim visit inform the participant that she is HIV-uninfected and provide the appropriate post-test counseling per site SOPs. Conduct pregnancy testing (required for all study interim visits). Complete an interval medical/menstrual/genitourinary history review and appropriate clinical follow-up if clinically indicated.

HIV Test Results form should be used to document all HIV WB test results, and should be assigned the Week 12 visit code.

Section Appendix 6-6 continued
Follow-up HIV Testing Scenarios for HPTN 059

6-6.2 Continuing from Scenario 6-6.1 above, suppose Miss X's WB is negative. What do you do?

- Record the WB result on the HIV Test Results form.
- When Miss X returns for her test result, counsel her that her test indicates that she is not infected with HIV.

If the return visit takes place before Miss X's Week 16 visit window has opened, consider the visit an interim visit. Conduct pregnancy testing (required for all interim visits), and perform an interval medical/menstrual/genitourinary history and any other clinical follow-up, if clinically indicated. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 16) visit.

OR

If the return visit takes place after Miss X's Week 16 visit window has opened, additionally conduct the Week 16 Visit per protocol (if participant is willing).

6-6.3 Continuing from Scenario 6-6.1, suppose Miss X's WB is indeterminate. What do you do?

- Record the WB result on the HIV Test Results form.
- When Miss X returns for her test result:
 - Counsel her that her tests continue to indicate that she may be infected with HIV, but the second test did not confirm her status for sure, so you must collect another blood sample for additional testing (that requires N days to complete) to confirm whether she is infected or not.
 - Aliquot plasma from second sample and send to CL for archiving for QA/QC measures.
 - Schedule another visit to take place when Miss X's WB test result will be available.
 - If the return visit takes place before Miss X's Week 16 visit window has opened, consider the visit an interim visit. Conduct pregnancy testing (required for all interim visits), and perform an interval medical/menstrual/genitourinary history and any other clinical follow-up, if clinically indicated. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 16) visit).

OR

If the return visit takes place after Miss X's Week 16 visit window has opened, additionally conduct the Week 16 Visit per protocol (if participant is willing).

Section Appendix 6-6 continued
Follow-up HIV Testing Scenarios for HPTN 059

6-6.4 Continuing from Scenario 6-6.1, suppose Miss X's WB is positive. What do you do?

- Record the WB result on the HIV Test Results form.
- When Miss X returns for her test result:
 - Counsel her that her tests indicate that she is infected with HIV, and although you are confident that her test result is correct, you need to collect another blood sample for an additional test to be absolutely sure about the results (e.g., to rule out specimen mix-up or other errors).
 - Aliquot plasma from second sample and send to CL for archiving for QA/QC measures.
 - Schedule another visit to take place when Miss X's WB test result will be available.
 - If the return visit takes place before Miss X's Week 16 visit window has opened, consider the visit an interim visit. Conduct pregnancy testing (required for all interim visits), and perform an interval medical/menstrual/genitourinary history and any other clinical follow-up, if clinically indicated. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 16) visit.

OR

If the return visit takes place after Miss X's Week 16 visit window has opened, additionally conduct the Week 16 Visit per protocol (if participant is willing).

6-6.5 Continuing from Scenario 6-6.3 or 6-6.4, suppose Miss X's sample 2 WB is either negative or indeterminate. What do you do?

- Record the WB result on the HIV Test Results form on which Miss X's sample 1 WB result has been recorded.
- If sample 2 is negative or indeterminate, additional WB testing must be performed on additional samples. In this case, inform the HPTN CL via email of the sample 1 and sample 2 test results (copied to the HPTN CORE and SDMC) and request CL input on next steps and timeframes for additional specimen collection and testing.
- When Miss X returns for her test result:
 - Counsel her that her HIV status remains unclear.
 - Collect blood (sample 3) for further testing per CL guidance.
 - Collect blood (sample 3) and deliver it to the local lab for WB testing and plasma archive.
 - Schedule another visit to take place when Miss X's test results will be available.
 - If the return visit takes place before Miss X's Week 16 visit window has opened, consider the visit an interim visit. Conduct pregnancy testing (required for all interim visits), and perform an interval medical/menstrual/genitourinary history and any other clinical follow-up, if clinically indicated. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 16) visit.

OR

If the return visit takes place after Miss X's Week 16 visit window has opened, additionally conduct the Week 16 visit per protocol (if participant is willing).

Section Appendix 6-6 continued
Follow-up HIV Testing Scenarios for HPTN 059

6-6.6 Continuing from Scenario 6.18 or 6.19, suppose Miss X's sample 2 WB is positive. What do you do?

- Record the WB result on the HIV Test Results form on which Miss X's sample 1 WB result has been recorded.
- When Miss X returns for her test result, counsel her that the test confirmed that she is infected with HIV.
- Ask her to return any unused study gel supplies as soon as possible, and explain to her that she will be permanently discontinued from study gel use.
- Refer Miss X for follow-up care and counseling for HIV as appropriate. Explain to her that you would like to continue to follow her up in the study through her scheduled study exit visit, if she is willing

If the return visit takes place before Miss X's Week 16 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 16) visit.

OR

If the return visit takes place after Miss X's Week 16 visit window has opened, conduct the Week 16 Visit per protocol (if participant is willing).

6-6.7 Suppose Miss X tests positive for HIV on her sample 1 test and WB, but does not return to the study site to receive her WB result. What do you do?

- Make every effort to locate Miss X, provide her result and post-test counseling, and obtain a second blood sample for confirmatory WB testing.

Why? From a human subjects and HIV prevention perspective, it is critical that Miss X receive her test result and post-test counseling. From a study perspective, it is critical that Miss X's HIV infection status be confirmed with a second WB, since only participants with two positive WB results will be counted in study analyses as confirmed cases of HIV-infection per the protocol testing algorithm. As such, among all participants targeted at a given time for tracing and other locator/retention efforts, participants with a positive WB result should be given highest priority.

Section Appendix 6-7
Pregnancy Management Scenarios for HPTN 059

6-7.1 Suppose Miss X is randomized to one of the HPTN 059 groups on 4 October 2005 and has the following sequence of follow-up visits and pregnancy tests:

<u>Study Visit</u>	<u>Visit Date</u>	<u>Pregnancy Test Result</u>
Week 4	03 NOV 05	NEGATIVE
Week 8	01 DEC 05	POSITIVE
Week 12	02 JAN 06	NEGATIVE

What actions are required at the Week 8 and Week 12 visits? What actions are required after Week 12?

Week 8: In addition to all other routinely required procedures, initiate a Pregnancy Management Worksheet. Complete and fax a Pregnancy Report and History form and a Product Hold/Discontinuation form to SCHARP. Complete an HPTN 059 Study Gel Request Slip marked "HOLD" to inform pharmacy staff of the product hold. Arrange to retrieve all remaining study gel supplies from Miss X as soon as possible. Continue to use the Pregnancy Management Worksheet to guide and track further action.

Week 12: The negative pregnancy test at this visit is considered the outcome of the pregnancy identified at Week 8. In addition to all other routinely required procedures, complete and fax a Pregnancy Outcome form and an AE Log form (AE term = spontaneous abortion) to SCHARP. Complete and submit an EAE form to the DAIDS Safety Office within three business days. Conduct a pelvic exam test, and if normal and no other contraindications complete an HPTN 059 Study Gel Request Slip and mark "RESUME" to inform pharmacy staff to resume dispensation of study product. Dispense study gel to Miss X per Pharmacy SOPs. Update and fax to SCHARP the Product Hold/Discontinuation form first completed at Week 8.

Section Appendix 6-7 continued
Pregnancy Management Scenarios for HPTN 059

6-7.2 Suppose Miss X is randomized on 10 January 2006 and has the following sequence of follow-up study visits and pregnancy tests:

<u>Study Visit</u>	<u>Visit Date</u>	<u>Pregnancy Test Result</u>
Week 4	12 FEB 06	POSITIVE
Week 8	14 MAR 06	NEGATIVE
Week 12	MISSED	NOT AVAILABLE
Week 16	09 APR 06	NEGATIVE
Week 20	13 MAY 06	NEGATIVE
Week 24	13 JUN 06	POSITIVE

What actions are required at each visit?

Week 4: In addition to all other routinely required procedures, initiate a Pregnancy Management Worksheet. Complete and fax a Pregnancy Report and History form and a Product Hold/Discontinuation form to SCHARP. Complete an HPTN 059 Study Gel Request Slip marked "HOLD" to inform pharmacy staff of the product hold. Arrange to retrieve all remaining study gel supplies from Miss X as soon as possible. Continue to use the Pregnancy Management Worksheet to guide and track further action.

Week 8: The negative pregnancy at this visit is considered the outcome of the pregnancy identified at Week 4. In addition to all other routinely required procedures, complete and fax a Pregnancy Outcome form and an AE Log form (AE term = spontaneous abortion) to SCHARP. Complete and submit an EAE form to the DAIDS Safety Office within three business days. Conduct a pelvic exam test, and if normal and no other contraindications complete an HPTN 059 Study Gel Request Slip and mark "RESUME" to inform pharmacy staff to resume dispensation of study product. Dispense study gel to Miss X per Pharmacy SOPs. Update and fax to SCHARP the Product Hold/Discontinuation form first completed at Week 4.

Week 16: Complete all Week 16 visit procedures per protocol.

Week 20: Complete al Week 20 visit procedures per protocol.

Week 24: In addition to all other routinely required procedures, initiate a second Pregnancy Management Worksheet. Complete and fax a Pregnancy Report and History form and a Product Hold/Discontinuation form to SCHARP. Because this is the final visit where study gel is dispensed, you do NOT need to complete an HPTN 059 Study Gel Request Slip marked “HOLD” to inform pharmacy staff of the product hold, and you do not need to complete a Product Hold/Discontinuation form. Arrange to retrieve all remaining study gel supplies from Miss X as soon as possible. Continue to use the second Pregnancy Management Worksheet to guide and track further action. (Note: A new Pregnancy Outcome form must be completed for this second pregnancy; do not update the Pregnancy Outcome form completed at Week 4). If the participant is a non-CHBV participant, you should inform her that you may be in contact her after the study has ended to find out the pregnancy outcome. This post-study pregnancy outcome should be recorded on a new Pregnancy Outcome form and faxed to SCHARP.

**Section Appendix 6-8
Sample Pregnancy Management Worksheet for HPTN 059**

PARTICIPANT ID:			
BACKGROUND INFORMATION			
First day of last menstrual period			
Date of positive pregnancy test			
Estimated week 24 and full term pregnancy dates	Week 24:	Full Term:	
PREGNANCY MANAGEMENT INFORMATION	Mark ✓ When Done	Initials/Date/Comments	
1 Pregnancy Report and History form completed and faxed to SCHARP			
2 Pharmacy informed of pregnancy			
3 Product supplies retrieved from participant and returned to pharmacy			
4 Product Hold/Discontinuation form completed (items 1-3) and faxed to SCHARP			
5 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>			
6a Pregnancy Outcome form completed and faxed to SCHARP			
6b If applicable, AE Log form completed and faxed to SCHARP			
6c If applicable, EAE Report completed and faxed to DAIDS Safety Office			

**Section Appendix 6-8 continued
Sample Pregnancy Management Worksheet for HPTN 059**

7. Determine Date Participant Eligible to Resume Study gel Use

If pregnancy outcome and outcome date ascertained based on medical records or written health care practitioner report, enter outcome date:

Otherwise enter the date of the first negative pregnancy test performed by study staff after the positive pregnancy test noted on page 1:

Note: Contact the HPTN 059 Protocol Safety Review Team with any questions related to resumption of study gel use.

8	Pharmacy informed of participant eligibility to resume study gel use		
9	Product Hold/Discontinuation form updated (item 4) and faxed to SCHARP		

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