

Section 6. Participant Follow-up

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

NOTE: Effective with Version 2.0 of this section, prior references to the HIV Prevention Trials Network (HPTN) have been replaced where applicable with references to the Microbicide Trials Network (MTN).

6.1 Study Follow-up Plan and Participant Retention Targets

HPTN 035 will be conducted in uninterrupted two phases: the Phase II portion of the study and the Phase IIb portion of the study. Follow-up in the Phase II portion of the study consisted of the first three months of follow-up conducted among the 800 participants enrolled in the Phase II portion of the study. Follow-up in the Phase IIb portion of the study will consist of the Phase II follow-up as well as all subsequent follow-up among Phase II and Phase IIb participants.

The HPTN 035 protocol specifies that each enrolled participant will be followed for a minimum of 12 months and through the study end date or for a maximum of 30 months, whichever occurs first. As of the version date of this section, over 300 participants have completed 30 months of follow-up and have exited the study. In addition, the Protocol Team has now set a study end date and developed an operational plan for study close-out that identifies a targeted study exit visit date for each participant, as described in Section 6.12.

To minimize bias and ensure the accuracy of study results, each study site will target retention of at least 95 percent of enrolled study participants annually. This annual target translates to the monthly targets shown in Figure 6-1. Further information on retention definitions and procedures for HPTN 035 is provided in Section 8.

Figure 6-1
Monthly Retention Targets for HPTN 035

Month of Study	Target % Retained	Month of Study	Target % Retained
1	99.58	16	93.33
2	99.17	17	92.92
3	98.75	18	92.50
4	98.33	19	92.08
5	97.92	20	91.67
6	97.50	21	91.25
7	97.08	22	90.83
8	96.67	23	90.42
9	96.25	24	90.00
10	95.83	25	89.58
11	95.42	26	89.17
12	95.00	27	88.75
13	94.58	28	88.33
14	94.17	29	87.92
15	93.75	30	87.50

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 months 1, 2, 4, 5, 7, 8, 10, 11, 13, 14, 16, 17, 19, 20, 22, 23, 25, 26, 28, and 29. The term “quarterly visits” is used to refer to those visits scheduled to take place in follow-up months 3, 6, 9, 12, 15, 18, 21, 24, 27, and 30. 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 that take place between scheduled visits. There are a number of reasons why interim visits may take place (see protocol Section 5.5). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13.3.3.

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 on the same date as the participant’s study enrollment date (i.e., on the monthly “anniversary” of the enrollment date). Each participant’s enrollment date is defined as the date upon which she is assigned an HPTN 035 Clinic Randomization Envelope. For example, for a participant assigned a Clinic Randomization Envelope on September 15, follow-up visits will be targeted to take place on October 15, November 15, December 15, etc. For participants enrolled on the last day of a month with 31 days, follow-up visits will be targeted to take place on the last day of all subsequent months (e.g., February 28, April 30, June 30, September 30, November 30).

6.3.2 Allowable 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 four-week window around the target date (i.e., ± 2 weeks from the target date).

In all months except February, the ± 2 week window is comprised of 14 days before the target date and 14 days after the target date (inclusive). Because February is a 28-day month (except in leap years), the window for visits that take place in that month (except in leap years) is comprised of 14 days before the target date and 13 days after the target date (inclusive). Figure 6-2 illustrates the allowable visit windows for a participant enrolled in the study on 13 January 2005.

In the event that overlapping visit windows are identified in any months other than February, the overlapping day should be included in the window for the earlier visit.

**Figure 6-2
Allowable Visit Windows for HPTN 035**

JANUARY 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	4	5	6	7	8
9	10	11	12	13 Enrollment Date	14	15
16	17	18	19	20	21	22
23	24	25	26	27	28	29
30 M1 Window Opens	31					

FEBRUARY 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1	2	3	4	5
6	7	8	9	10	11	12
13 M1 Target Date	14	15	16	17	18	19
20	21	22	23	24	25	26 M1 Window Closes
27 M2 Window Opens	28					

MARCH 2005						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1	2	3	4	5
6	7	8	9	10	11	12
13 M2 Target Date	14	15	16	17	18	19
20	21	22	23	24	25	26
27 M2 Window Closes	28	29	30	31		

M1 = Month 1 Visit, M2 = Month 2 Visit

Although the four-week visit windows allow considerable flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at monthly intervals, and every effort should be made to do so. Extreme deviation from monthly intervals must be avoided. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the monthly visit schedule (see Section 15).

Please note that an exception to the standard visit window applies for Month 30 visits. See Section 6.12.3 for more information.

6.3.3 Visits Conducted Over Multiple Days: “Split Visits”

All procedures specified by the protocol to be performed at a particular follow-up visit ideally 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 remaining procedures may be completed on subsequent day(s) within the allowable visit window. As described in Section 13.3.3, all case report forms completed for a split visit are assigned the same visit code. See Section 6.12.4 for more information on split study exit visits.

6.3.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable window, the visit will be considered “missed” and a Missed Visit case report form will be completed to document the missed visit (see Section 13.6). However, for participants who miss quarterly visits, the pelvic exam and HIV counseling and testing procedures required at these visits must be conducted at the participants’ next visit. Accordingly, every effort should be made to conduct participants’ next visit at the study site, rather than at a community-based location. If this is not possible, an on-site visit in which the pelvic exam and HIV counseling and testing procedures are performed should be conducted as soon as possible.

Note: When quarterly visits are missed, only the pelvic exam and HIV counseling and testing required at quarterly visits are performed at the next monthly visit. Other quarterly procedures such as the Follow-up Behavior Assessment are not performed at the next monthly visit.

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 035. These scenarios illustrate that the allowable visit windows impact whether a completed visit will be considered a scheduled visit or an interim 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 HPTN 035 Participant Tracking Database is pre-programmed to generate such sheets for enrolled study participants.

Note: The Participant Tracking Database 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.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 5.4 and protocol Appendices II and III. Highlighted for reference below are the primary differences in procedural requirements for Phase II and Phase IIb participants:

- Pelvic exams were performed at follow-up Months 1 and 2 among Phase II participants only. Pelvic exams are performed at Month 3 and all subsequent quarterly visits for both Phase II and Phase IIb participants.
- Colposcopic exams were performed among a subset of Phase II study participants from selected sites at follow-up Months 1, 2, and 3 only. Colposcopic exams are not performed among Phase IIb participants.
- All of the safety laboratory tests listed in protocol Appendix IV were performed at follow-up Months 1, 2, and 3 among Phase II participants. None of these tests are performed at follow-up Months 1 and 2 among Phase IIb participants. At Month 3, only the hematology and coagulation tests are performed among Phase IIb participants. After Month 3, hematology and coagulation tests are performed annually (at Months 12 and 24) and at study exit for all participants.

The HPTN 035 protocol specifies that two follow-up visit procedures — interval medical/menstrual histories (with concomitant medication review) and pregnancy tests — should be performed at all scheduled follow-up visits and at interim follow-up visits when clinically indicated:

- An interval medical/menstrual 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 (AEs), when applicable.
- A pregnancy test is considered clinically indicated at interim visits if a test has not been performed within the last month, if the participant reports a missed menstrual period, and/or if there is any other reason to suspect pregnancy.

6.5 Follow-up Visit Locations

Quarterly follow-up visits must take place on-site. Monthly follow-up visits 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. If genital symptoms are reported during off-site visits, the participant will be instructed to report to the on-site clinic as soon as possible for a pelvic exam. For those sites planning to conduct off-site visits, site-specific standard operating procedures (SOPs) must detail how these visits will be conducted, including proper procedures for handling gel supplies and participant study records off-site. Further considerations that should be addressed in SOPs for off-site visits are as follows:

- What feedback and operational suggestions have been received from the Community Advisory Board or Group with regard to conducting off-site visits?
- Under what circumstances will off-site visits be conducted?

- Where will off-site visits be conducted?
- What protocol-specified procedures are allowed/not allowed to be conducted off-site by local regulations and/or health care practice guidelines?
- What staff members will conduct off-site visits? How will these staff members dress (uniform? lab coat? street clothes?) and how will they identify themselves so as to protect participant confidentiality and their own safety?
- Will any special training be completed before staff are authorized to conduct off-site visits?
- How will study staff and materials be transported to and from off-site visits? How will biological specimens and biowaste be handled?
- How will proper source documentation of off-site visits be ensured?
- How will routine participant identification procedures be modified for off-site visits?
- How will routine data management procedures be modified for off-site visits? Will participant study notebooks be transported to off-site visit locations (either in part or in their entirety)? How will this be logged/documentated? What procedures will be put in place to help ensure that documents are not lost, stolen, or mixed up across participants?
- For participants in the study gel groups, how will routine gel re-supply procedures be modified for off-site visits? Site-specific SOPs for gel re-supply during follow-up should specify procedures for all of the following (see also Section 9.4 of this manual):
 - Requesting gel supplies from the pharmacy prior to the off-site visit (how much to request, when the request will be made, how the request will be made)
 - Ensuring proper chain of custody of gel supplies from time of receipt from the pharmacy to time of delivery to the participant, including ensuring that gel supplies are delivered to the correct participant
 - Storing gel supplies at appropriate temperatures from time of receipt to time of delivery to the participant
 - Handling/returning gel supplies when the participant cannot be located
 - Handling/returning gel supplies when the participant refuses to receive the full quantity of gel dispensed for her
 - Handling participant requests for more gel than was dispensed for her
 - Documenting all of the above, and appropriately storing all documentation in the study clinic and pharmacy
- What procedures will be implemented to protect participant confidentiality during off-site visits?
- What procedures will be implemented to protect participant safety during off-site visits? How will issues requiring medical attention identified during off-site visits be handled? How will medical urgencies/emergencies be handled?
- What procedures will be implemented to protect the safety of study staff during off-site visits?

6.6 Gel Re-Supply During Follow-up

For participants assigned to one of the three study gel groups, procedures will be undertaken at follow-up visits to determine whether the participant remains eligible for continued gel use per protocol specifications. Protocol Section 4.6 lists conditions under which participants should be discontinued from 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.

For participants who are eligible to continue gel use, procedures will be undertaken at follow-up visits to determine the quantity of gel needed for use in all vaginal sex acts until participants' next scheduled visit, up to the protocol-specified cap of 60 applicators per 26-day period. This cap corresponds to the maximum frequency of gel use — twice per day — evaluated in previous studies of BufferGel and PRO 2000/5 Gel (P). Under exceptional circumstances, the IoR may approve dispensation of up to a three-month supply of gel for a participant. See Section 9.5 for more information on the circumstances under which up to a three-month supply may be dispensed and the documentation requirements associated with such dispensing.

The HPTN 035 Gel Re-Supply Worksheet should be used during on-site follow-up visits to determine the number of cartons of gel to be ordered at follow-up visits, taking into account the participant's self-reported usual and expected sexual frequency, the number of applicators the participant has remaining from previous visits, and the 60 applicator cap. The worksheet is available in two different formats, one "long" and one "short" (see Section Appendix 6-3). Each site should select one format for use with all participants. Further information on completing these worksheets is provided in Section 6.6.1. For off-site follow-up visits, clinic staff will be required to estimate the number of gel cartons needed in advance of the visits, (typically without administering the Gel Re-Supply Worksheet); procedures for estimating the number of cartons needed for off-site visits should be specified in site SOPs for gel re-supply during follow-up.

The HPTN 035 Study Product 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 gel use for a participant or to resume gel use after a prior hold. Further information on completing this document is provided in Section 6.6.2. For off-site visits, Study Product Request Slips must be completed and provided to pharmacy staff in advance of the visits; procedures and timelines should be specified in site SOPs for gel re-supply during follow-up.

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

6.6.1 HPTN 035 Gel Re-Supply Worksheet

The HPTN 035 Gel Re-Supply Worksheet is an operational tool and source document designed to assist clinic staff in determining the quantity of gel to order for study participants during follow-up.

Both the long and short versions of the worksheet provide reminders for clinic staff regarding follow-up dispensing requirements and the 60-applicator cap. Both versions are formatted to assist staff in the mathematical calculations needed to determine the number of gel cartons to order for each participant. Follow all instructions and skip patterns printed on the worksheets. For item 3 on the long version of the worksheet, and item 4 on the short version, the mathematical result will be a negative number (less than zero) when participants already have enough gel in their possession to last until the next scheduled visit. In this case, record the result by recording a negative sign (-) to the left of the response boxes, and do not order more gel for the participant.

The main difference between the two versions of the worksheet is that the long version provides suggested scripting for obtaining participant estimates of the number of applicators remaining in her possession (from prior visits) and the number of times she expects to have vaginal intercourse in the next month. Sites that use this version of the worksheet should translate the suggested scripting into appropriate wording in local languages. Unlike the standardized interview forms used in HPTN 035, it is not necessary to administer the worksheet in a formal, word-for-word style. Rather, it is expected that clinic staff will become familiar with the suggested scripting as they gain experience in administering the worksheet, and that a more conversational rather than standardized interaction will take place. Staff are encouraged to share their experiences and tips for administering the worksheet to obtain accurate self-reported information from participants.

On both versions of the worksheet, the last item provides an opportunity for participants to identify loss or damage of their gel supplies. Space is provided to document any such incidents, and any follow-up action taken; notes may continue onto the back of the worksheet or on a separate note page (labeled with the PTID and date). Information and counseling on proper gel storage and use should be provided whenever needed to optimize the integrity of gel supplies and participant compliance with the protocol-specified gel use regimen.

***Note:** If any participant repeatedly reports loss of gel, or there is any other reason to suspect that she is sharing or selling 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 HPT 035 Protocol Safety Review Team (see Section 11). Document all action taken in signed and dated chart notes. For informational purposes, inform the MTN CORE Clinical Research Managers, SDMC Project Managers, and site Pharmacist of Record (PoR) of all cases of suspected gel sharing or selling. The PoR will inform the DAIDS Protocol Pharmacist.*

6.6.2 HPTN 035 Study Product Request Slip

The HPTN 035 Study Product Request Slip is a two-part no carbon required (NCR) document that is available in pads of 50 from the DAIDS Clinical Research Product Management Center. The PoR will order bulk supplies of the pads for use by clinic staff throughout the course of the study. Complete the Study Product 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 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 RESUPPLY, HOLD, or RESUME to indicate the action to be taken in the study pharmacy. When marking RESUPPLY or RESUME, record the number of cartons of study gel to be dispensed for the participant. When marking HOLD, the DAIDS Protocol Pharmacist recommends recording the reason for the product hold in the white space on the slip. If the hold represents a permanent discontinuation of product use, it is recommended that "permanent discontinuation" also be recorded on the slip.
 - When RESUPPLY is marked, gel will be dispensed for the participant in the quantity entered on the slip.
 - When HOLD is marked, gel will not be dispensed for the participant unless/until another slip marked RESUME is subsequently completed and received in the pharmacy.
 - When RESUME is marked, a previous hold will be ended and gel will be dispensed for the participant in the quantity entered on the slip.
- The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order gel supplies for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date the Product 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 Product Request Slip. Retain the yellow copy in the participant study notebook. Deliver the white original 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 according to the algorithm in protocol Appendix V, which is re-printed in Figure 6-3. 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 rapid HIV test (i.e., either the OraSure OraQuick test or the Uni-Gold Recombigen test) that has been validated at the study site is performed. If the rapid test in Step One is negative, testing will stop after Step One. If the rapid 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.

At some sites, a second rapid test may be performed in Step One. For example, HIV counseling and testing guidelines at some sites require that two rapid tests be performed whenever rapid testing is utilized. Sites required or otherwise wishing to perform a second test in Step One must specify their site-specific testing procedures in their local laboratory SOPs for HPTN 035, and must obtain HPTN Network Laboratory (NL) approval of these SOPs prior to study activation. Once approved, these SOPs must be followed consistently for all study participants. For sites that perform two tests in Step One, testing will proceed to Step Two if either of the two tests is positive/reactive.

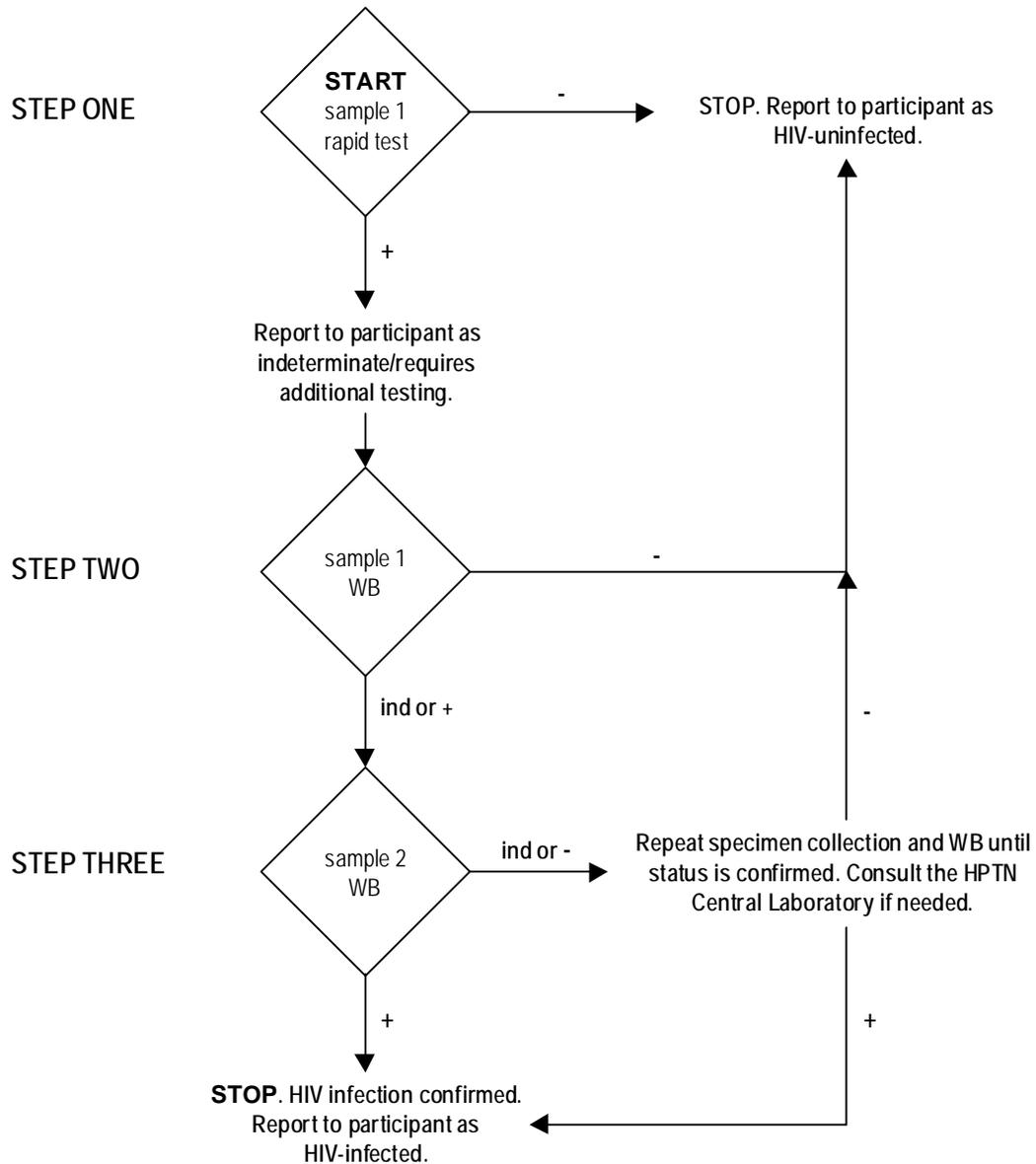
If the WB in Step Two is negative, testing will stop after Step Two. If the WB is positive or indeterminate, a second FDA-approved Genetic Systems WB must be performed on a second sample collected from the participant. This sample is referred to as “sample 2” in the algorithm and will be used for plasma archive if HIV infection is confirmed. For purposes of estimating the effectiveness of the gels tested in HPTN 035, only participants for whom infection is confirmed with two positive WB results on two different samples will be counted as having become HIV-infected. For participants with confirmed infection at their first HIV testing timepoint during follow-up, plasma archived at enrollment also will be tested for evidence of HIV infection, as described in Section 12.5.2.3.

If the sample 2 WB is negative or indeterminate, additional WB testing must be performed on additional samples. In this case, inform the HPTN NL via email of the sample 1 and sample 2 test results (copied to the MTN CORE and SDMC) and request NL 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 12.5.2.2. 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 within the timeframe of the tests and 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. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

Figure 6-3
Algorithm for HIV Antibody Testing During Follow-up in HPTN 035

NOTE: In order to correspond exactly with the HPTN 035 protocol, reference to the HPTN CL in this algorithm has not been modified; however, all HIV testing queries should be directed to the HPTN NL.



Notes:

WB=Western blot; + = positive; - = negative; ind = indeterminate.

If required by local HIV counseling and testing guidelines or regulations, and/or approved by the HPTN Central Laboratory, a second concurrent rapid test (at non-US sites) or enzyme immunoassay (at the US site) may be performed on sample 1 as part of Step One. In this case, testing will proceed to Step Two (sample 1 WB) if either of the two tests is positive/reactive.

6.8 Modified Follow-up Procedures for Participants Who Become Pregnant

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

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

- Pelvic exams will be conducted through 24 weeks of pregnancy, but then discontinued until after birth or other termination of the pregnancy, as evidenced by a negative pregnancy test performed by study staff.
- Swab specimens may be collected during pelvic exams through 24 weeks of pregnancy, however specimens should be collected with care and participants should be counseled that they may experience spotting for several hours following the exam. They also should be counseled to return to the clinic if bleeding is heavy or prolonged.
- 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).
- After 24 weeks of pregnancy, blood testing may be limited to HIV testing only.
- For participants assigned to one of the study gel groups, gel use will be discontinued until after birth or other pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff. A pelvic exam must be performed prior to reinstatement of gel use to confirm the absence of any findings that would contraindicate resumption of gel use, in the opinion of the site IoR or designee.
- For all participants who become pregnant, regardless of study treatment 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 (AE) Log case report forms (see Section 13.6) and/or DAIDS Expedited Adverse Event Forms, as described in Section 11 of this manual. Whenever possible, pregnancy outcomes should be ascertained based on medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, however, outcomes may be ascertained based on participant report.

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 gel use. Site pharmacy staff must be informed of the product hold/discontinuation in writing, 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.

6.9 Modified Follow-up Procedures for Participants Who Become Infected with 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 in Figure 6-3, and the participant's enrollment plasma specimen has been tested for evidence of HIV infection, if applicable, HIV testing will be discontinued.
- Counseling will be tailored to primary and secondary HIV/STD prevention for infected women.

Unless not permitted by site regulatory authorities or Institutional Review Boards/Ethics Committees (IRBs/ECs), participants who become infected with HIV who were assigned to one of the study gel groups will be offered the option to continue gel use through their originally scheduled study exit visit. At sites where continued gel use is not permitted by regulatory authorities or IRBs/ECs, gel use will be discontinued. In this case, site pharmacy staff must be informed of the product discontinuation in writing, product supplies previously dispensed to the participant must be retrieved as soon as possible after infection is confirmed, and a Product Hold/Discontinuation case report form (see Section 13.6) must be completed and transmitted to the SDMC.

6.10 Participant Transfers

During the course of the study, participants may leave the area in which they enrolled in the study and re-locate to another area where the study is taking place. To maximize participant retention, participants who re-locate from one study location to another should be encouraged to continue their study participation at their new location. To accomplish this, study staff at both the original site (called the “transferring” site) and the new site (called the “receiving” site) will complete the process of a participant transfer.

Upon identifying the need for a participant transfer to another site, the transferring site will notify the receiving site as well as the MTN CORE, MTN SDMC, HPTN NL, MTN NL, and DAIDS Pharmaceutical Affairs Branch (PAB). After the logistical details of the transfer have been discussed and agreed upon by the two sites, the following steps will be completed:

- The SDMC will notify the transferring site of all outstanding data QC notes for the transferring participant; the transferring site will resolve these QCs.
- The transferring site will explain the transfer arrangements to the participant and obtain her written permission to provide copies of her study records to the receiving site.
- The transferring site will deliver copies of all of the participant’s study records to the receiving site via courier or overnight mail service. Copies of participant-specific records maintained in the transferring site pharmacy must be delivered directly to the receiving site pharmacy, separate from the participant’s clinic records. Pharmacy records may not be delivered in the same shipping envelope or carton as the clinic records. The transferring site (clinic and pharmacy) will document all materials sent to the receiving site and inform the receiving site of the shipment date and expected arrival date. The receiving site (clinic and pharmacy) will confirm receipt of the shipment.
- The transferring site will complete and transmit a Participant Transfer case report form to the MTN SDMC (see Section 13.6). The SDMC will forward a copy of this form to the MTN CORE, HPTN NL, MTN NL, and DAIDS PAB for informational purposes.
- The receiving site will establish contact with the participant, obtain her written informed consent to continue in the study at the receiving site, and complete and transmit the Participant Receipt case report form to the SDMC (see Section 12.6).

- Upon receipt of the Participant Transfer and Participant Receipt forms, the SDMC will re-map the participant’s study ID number (PTID) to reflect the change in site follow-up responsibility. The participant’s original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged. For participants assigned to one of the study gels, an authorized prescriber at the receiving site will be required to prepare an original signed and dated note to pharmacy staff stating that the participant has provided written informed consent to take part in the study at the receiving site and that the prescriber authorizes the participant to continue gel use per the HPTN 035 protocol at the receiving site. Clinic staff will deliver the original signed and dated note to pharmacy staff and retain a photocopy of the note in the participant’s study chart. Upon receipt of the original signed and dated note, and a completed HPTN 035 Study Product Request Slip, pharmacy staff at the receiving site will dispense gel to the participant according to the random assignment documentation received from the transferring site pharmacy.
- The transferring site will retain responsibility for storage, and shipment to the HPTN NL if applicable, of all specimens collected from the participant prior to her transfer, unless otherwise instructed by the HPTN NL.

The above-listed procedures apply to a transfer from one HPTN 035 study site to another. For sites that are conducting HPTN 035 at more than one sub-site, under a single IoR and single set of responsible IRBs/ECs (i.e., MRC Clinics in Durban and Hlabisa, South Africa; Spilhaus and Seke South Clinics in Harare and Chitungwiza, Zimbabwe), the above-listed procedures also apply to permanent transfers from one sub-site to another. The above-listed procedures do not apply, however, to situations in which a participant enrolled at one sub-site clinic presents for one or more follow-up visits at another sub-site clinic that is part of the same site. In such situations, the guidance provided below should be followed. For ease of reference, the sub-site at which the participant enrolled is referred to as the “enrollment sub-site” and the other sub-site, at which the participant presents for follow-up, is referred to as the “non-enrollment sub-site.”

- Ideally the participant will inform study staff in advance of presenting to the non-enrollment sub-site for follow-up. In that case, clinic staff at both sub-sites will make arrangements to schedule the participant’s next follow-up visit at the non-enrollment sub-site and to transport her study notebook to the non-enrollment sub-site prior to the next follow-up visit. Clinic staff also will inform pharmacy staff at both sub-sites so they are aware of the situation and can plan accordingly (see more below).
- If the participant presents to the non-enrollment sub-site “unannounced,” clinic staff at the non-enrollment sub-site should ascertain the participant’s identity and PTID (if known), and the reason for the visit; clinic staff also should ascertain whether the participant is likely to complete more than one follow-up visit at the non-enrollment sub-site for any reason. Clinic staff at the non-enrollment sub-site should then confirm the details reported by the participant with clinic staff from the enrollment sub-site, inform pharmacy staff at both sub-sites, and make arrangements to transport the participant’s study notebook to the non-enrollment sub-site as quickly as possible. All communications between the two sub-sites, and transport of the study notebook, should be documented by clinic and pharmacy staff in writing.

- In the event that the participant presents to the non-enrollment sub-site complaining of an urgent medical problem or other urgent study-related concern, clinic staff at the non-enrollment sub-site should take immediate action to address the urgent problem or concern, and document all action taken, in accordance with the study protocol and relevant study site SOPs. Otherwise, clinic staff at the non-enrollment sub-site should explain to the participant that they first need to obtain her study records from the enrollment sub-site before conducting her next study follow-up visit. The participant should then be scheduled to return on the following day (or whenever her study notebook is expected to be available) to complete her next follow-up visit. Documentation completed for the initial contact with the participant as well as her follow-up visit should note the location of the contact/visit and the reason why the contact/visit took place at the non-enrollment sub-site.
- For participants assigned to one of the study gel groups, clinic staff at the non-enrollment sub-site may ascertain the number of gel applicators the participant currently has in her possession, and the number she expects to need for the following month, at the time of their initial contact with the participant. Clinic staff at either the enrollment site or the non-enrollment site may then use this information to complete an HPTN 035 Study Product Request Slip for delivery to the enrollment sub-site pharmacy (i.e., the Study Product Request Slip may be completed by clinic staff from either the enrollment sub-site or the non-enrollment sub-site, depending on the preferences of site clinic staff). Alternatively, clinic staff may routinely order a fixed amount of gel for the participant from the enrollment sub-site pharmacy, request the fixed amount on the HPTN 035 Study Product Request Slip, and then confirm the specific number of cartons to be provided to the participant her during her follow-up visit. For sites at which clinic staff from the non-enrollment sub-site will complete the Study Product Request Slip for unannounced visits at the non-enrollment sub-site, clinic staff at the non-enrollment sub-site must confirm the number of cartons to be provided to the participant with clinic staff from the enrollment sub-site prior to delivering the cartons to the participant, and document the communication/confirmation from clinic staff from the enrollment sub-site in a signed and dated chart note.

The completed Study Product Request Slip should be delivered to the enrollment sub-site pharmacy as quickly as possible, so the requested product supplies can be prepared and delivered to the non-enrollment sub-site pharmacy for subsequent dispensing to the participant when she returns to complete her follow-up visit at the non-enrollment sub-site. The Study Product Request slip may first be faxed to the pharmacy, however the signed original slip must be received in the pharmacy prior to release of the requested study products. Should the participant not require or accept the full quantity of product supplies prepared for her, this should be documented and the residual supplies should be returned to the enrollment sub-site pharmacy. If the participant plans to complete additional follow-up visits at the non-enrollment sub-site, the residual supplies may be retained in the non-enrollment sub-site pharmacy and dispensed to the participant at her subsequent visits.

6.11 Resumption of Study Participation After Voluntary Withdrawal

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. The protocol also allows, however, for participants who voluntarily withdraw from the study to reverse their decision and resume product use (if applicable) and protocol-specified follow-up visits and procedures through their originally scheduled study exit date. If such cases arise, study staff are advised to contact the MTN CORE and SDMC for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged.
- An interval (since the last visit) medical/menstrual history should be taken and a pregnancy test should be performed as soon as the participant resumes study participation. For participants assigned to a study gel, gel use will be resumed only among participants who are not currently pregnant or within 42 days of last pregnancy outcome.
- If at least three months have elapsed since the participant's last quarterly follow-up visit, a pelvic exam should be performed as soon as possible, and prior to re-instating gel use (if applicable). A pelvic exam and other clinically-indicated evaluations also should be performed if the participant reports current genital symptoms. Gel use will be reinstated (if applicable) only after any genital symptoms have resolved, any STDs/RTIs requiring treatment per World Health Organization guidelines have been treated, and any pelvic exam findings involving deep epithelial disruption have resolved.
- If at least three months have elapsed since the participant's last quarterly follow-up visit, HIV counseling and testing should be performed as soon as possible. At sites where gel use is not permitted by regulatory authorities or IRBs/ECs, gel use will only be re-instated (if applicable) for participants who are confirmed as HIV-uninfected per the algorithm in Figure 6-3.
- Clinic staff will communicate any re-instatement of gel use to the study pharmacy in writing, using the HPTN 035 Study Product Request Slip.

6.12 Study Exit Considerations

The HPTN 035 protocol specifies that each enrolled participant will be followed for a minimum of 12 months and through the study end date or for a maximum of 30 months, whichever occurs first. As of the version date of this section, over 300 participants have completed 30 months of follow-up and have exited the study. In addition, the Protocol Team has set a study end date and developed an operational plan for study close-out that identifies a targeted study exit visit date for each participant. Figure 6-4 presents the study end date and operational plan.

Figure 6-4
HPTN 035 Study Close-Out Plan

For sites other than Hlabisa and Philadelphia, a participant should be seen for her study exit visit according to the following rules:

1. Study exit visits will begin June 1, 2008 for all women attending their Month 12 through Month 30 quarterly visits. The study exit visit should be the first quarterly visit with a target date on or after June 1, 2008 and that is at least 12 months after enrollment.
 - Note that eligibility for conducting a quarterly visit as a study exit visit is based upon the *target date* for the visit, not the date on which the visit is scheduled or conducted.
 - For example, suppose a participant's Month 24 visit has a target date of June 1, 2008. The Month 24 quarterly visit should be conducted as a study exit visit, and may be completed any time in the +/- 2-week visit window. That is, this study exit visit might occur up to two weeks prior to June 1, 2008.
 - In contrast, suppose a participant has a Month 24 quarterly visit target date of May 31, 2008. The Month 24 visit should be conducted as a regular quarterly visit and her Month 27 visit, with target date Aug 31, 2008, should be conducted as a study exit visit.
2. All participants must be followed until the Month 12 visit. Study exit visits will be conducted for Month 12 visits as long as the target date for the Month 12 visit is on or after June 1, 2008.
 - Note that August 31, 2008 is the last target date for a quarterly visit that will be conducted as a study exit date. The end of the 2-week window for such a visit is September 14, 2008.

This means that September 14, 2008, is the final day on which participants at sites other than Hlabisa and Philadelphia are expected to be seen for any visit in HPTN 035.

For the Hlabisa site, the target date for initiating study exit visits has been set as March 18, 2008. All other aspects of the plan described above will apply, including the requirement for all Hlabisa participants to complete at least 12 months of follow-up. The last date that participants are expected to be seen for visits in Hlabisa is July 1, 2008.

For the Philadelphia site, the target date for initiating study exit visits has been set for April 27, 2008. All other aspects of the plan described above apply, including the requirement for all Philadelphia participants to complete at least 12 months of follow-up. The last date that participants are expected to be seen for visits in Philadelphia is August 9, 2008.

Procedural requirements for conducting study exit visits are specified in protocol Section 5.4; further procedural guidance is incorporated in the Study Exit Visit checklists in Section 7 of this manual. Provided in the remainder of this section is additional information related to key aspects of study exit visits.

6.12.1 Certificate of Completion

All study sites are strongly encouraged to provide each participant who completes a scheduled study exit visit with a certificate of study completion. Sample certificates which may be tailored for use at each site are available in the Study Implementation Materials section of the HPTN 035 web page:

http://www.hptn.org/research_studies/hptn035.asp

As “written information to be provided to subjects,” certificates should be approved by site IRBs/ECs prior to use.

6.12.2 Participant Locator Information

As described in greater detail in Section 6.12.11, accurate participant locator information will be needed for post-study contact with study participants. As such, locator information should be actively reviewed and updated at all study exit visits and all participants should be counseled to contact the study site should their locator information change after study exit.

6.12.3 Study Exit Visit Windows and Visit Codes

As presented in Figure 6-4, all study exit visits are targeted to take place during a quarterly visit window. For participants who complete 30 months of follow-up, the study exit visit will take place at Month 30. For participants who complete fewer than 30 months of follow-up:

- At the Hlabisa site, the study exit visit will take place at the first quarterly visit targeted to take place on or after 18 March 2008.
- At the Philadelphia site, the study exit visit will take place at the first quarterly visit targeted to take place on or after 27 April 2008.
- At all other sites, the study exit visit will take place at the first quarterly visit targeted to take place on or after 1 June 2008.

The MTN SDMC has provided each site with a listing of the targeted quarterly study exit visit dates for each enrolled participant.

For participants who complete 30 months of follow-up, every effort should be made to complete study exit visits within the allowable Month 30 visit window. However, for these participants, exit visits are permitted to take place any time through the study end date (9 August 2008). Regardless of when the Month 30 visit is completed (assuming the Month 30 visit window has opened), the visit is assigned a visit code of 32.0. Because the Month 30 visit is allowed to take place after the ± 2 week visit window has elapsed, “Overdue Visit” reminders will appear on data QC reports for these visits through the study end date. These reminders are not considered when calculating each site’s data QC rate.

For participants who complete less than 30 months of follow-up, every effort should be made to complete study exit visits within the allowable window of the first quarterly visit targeted to take place on or after 1 June 2008 (18 March 2008 in Hlabisa, 27 April 2008 in Philadelphia). If the exit visit is not completed within the allowable window of the first quarterly visit targeted to take place on or after 1 June 2008 (18 March 2008 in Hlabisa, 27 April 2008 in Philadelphia), the quarterly visit should be considered missed and the exit visit should be conducted at the earliest possible opportunity thereafter. In such cases, the HIV counseling and testing and pelvic exam required at the missed quarterly visit should be completed at the exit visit.

The following examples illustrate study exit visit coding for participants who complete fewer than 30 months of follow-up; the target visit dates used in the examples are applicable to sites other than Hlabisa and Philadelphia, but the visit coding illustrated in the examples apply to all sites:

Example 1: A participant whose Month 18 visit is targeted to take place on 4 June 2008 presents to the study site two days after the target visit date and completes her exit visit that day. All case report forms completed at this visit are assigned the Month 18 visit code (20.0).

Example 2: A participant whose Month 18 visit is targeted to take place on 4 June 2008 presents to the study five days before the target visit date and completes her exit visit that day. All case report forms completed at this visit are assigned the Month 18 visit code (20.0).

Example 3: A participant whose Month 21 visit is targeted to take place on 4 June 2008 fails to present to the study site within the Month 21 visit window. On the day after the Month 21 visit window closes, a Missed Visit form is completed for the Month 21 visit. Then, after a successful tracing attempt, the participant returns to the study site five days after the Month 21 visit window closed. At this time, the Month 22 visit window has opened. The study exit visit should be completed at this time and all case report forms completed at the visit should be assigned the Month 22 visit code (24.0).

Example 4: A participant whose Month 21 visit is targeted to take place on 4 June 2008 fails to present to the study site within the Month 21 visit window. On the day after her Month 21 visit window closes, a Missed Visit form is completed for the Month 21 visit. The participant also cannot be located throughout the next month. As such, on the day after her Month 22 visit window closes, a Missed Visit form is completed for the Month 22 visit. Then, after a successful tracing attempt, the participant returns to the study site five days after the Month 22 visit window closed. At this time, the Month 23 visit window has opened. The study exit visit should be completed at this time and all case report forms completed at the visit should be assigned the Month 23 visit code (25.0).

Example 5: A participant whose Month 24 visit is targeted to take place on 4 June 2008 fails to present to the study site within the Month 24 visit window. On the day after her Month 24 visit window closes, a Missed Visit form is completed for the Month 24 visit. The participant returns to the study site on this same day. At this time, the Month 25 visit window has not yet opened. The study exit visit should be completed at this time and all case report forms completed at the visit should be assigned an interim visit code (26.1).

Please contact the MTN CORE and SDMC with any questions regarding study exit visit scheduling, procedures, visit codes, and case report form completion.

6.12.4 Split Study Exit Visits

Study exit visits may be conducted as split visits. In the event that all study exit visit procedures cannot be conducted on a single day, the remaining procedures may be conducted on subsequent days, through 14 September 2008. Every effort should be made to complete all required study exit procedures with all participants. However, if a participant does not return to complete the procedures not completed in the first part of a split exit visit, efforts to complete the remaining procedures may be discontinued after three active months of follow-up attempts (or on 14 September 2008, whichever comes first). Document all efforts to complete all required study exit procedures.

6.12.5 Final Study Contacts

Although the study exit visit is the last scheduled study visit, per protocol Section 5.5, a final contact is required after the exit visit to provide the participant with her final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants who are pregnant at study exit (see Section 6.8 above)
- Participants with positive or indeterminate HIV Western blot (WB) test results (see Section 6.12.5 below)
- Participants with certain types of AEs that are ongoing at study exit (see Section 6.12.8 below)

For each participant, a final contact should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. Study staff may complete final contacts at the study site or at community-based locations, depending on site capacities and site and participant preferences. It is recommended that final contact plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

6.12.6 HIV Counseling and Testing

HIV testing is performed at the study exit visit per the algorithm in Figure 6-3. For participants with one or more positive rapid test results, WB testing will be performed on the blood sample collected at the exit visit. If the WB is positive or indeterminate, additional specimen collection and testing will be required to clarify or confirm the participant's HIV status; therefore, additional visits will be required after the study exit visit. HIV pre- and post-test counseling provided at the study exit visit should emphasize that additional counseling and testing will be provided to the participant after her study exit visit if needed to clarify or confirm her HIV status.

6.12.7 Plasma Archive

All anticoagulated blood remaining in the lavender top (EDTA) tube after HIV testing is performed at the study exit visit should be processed within 24 hours of collection into at least four 0.5 mL aliquots of plasma (see Section 12.5.8 of this manual for more information). On a weekly basis, study clinic and laboratory staff should reconcile their records of archived plasma specimens to ensure that specimens are properly collected, aliquotted, and stored. Per site SOPs for plasma archive, study staff must notify the MTN CORE, MTN SDMC, and HPTN NL in the event that at least four 0.5 mL aliquots of plasma are not archived at each study exit visit.

6.12.8 Product Hold/Discontinuation

All participants assigned to gel are discontinued from gel use at their study exit visits. Therefore, for all participants assigned to gel, at the study exit visit, a Product Hold/Discontinuation case report form (PH-1) should be completed and all unused gel supplies should be collected from the participant and returned to the study pharmacy on the day of collection. In addition, clinic staff should add the participant's PTID to a cumulative listing of participants who have exited the study which should then be provided to pharmacy staff on a weekly basis.

Participants assigned to gel should be reminded to bring all unused gel supplies to their exit visits. For participants who do not bring all unused supplies to their exit visits, arrangements must be made to collect the remaining supplies as soon as possible. It is recommended that plans to collect remaining gel supplies be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9. If the applicators are not collected within five working days after the study exit visit, the HPTN 035 Protocol Safety Review Team (PSRT) must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold (i.e., study exit), actions taken to try to collect the unused applicators, and plans and timelines for further action to collect the applicators.

6.12.9 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed. For AEs that are ongoing at the exit visit, the status/outcome of the AE should be updated to "continuing at end of study participation" and the AE Log form should be re-faxed to SCHARP DataFax.

For any serious or expedited AEs (SAEs/EAEs) that are continuing at a participant's study exit visit, the IoR/designee must establish a clinically appropriate follow up plan for the AE (see Section 11.1 of this manual for more information on SAEs and EAEs). At a minimum, the AE must be re-assessed by study staff 30 days after the participant's study exit visit; additional evaluations also may take place at the discretion of the IoR/designee. The same approach must be taken for any AEs that are found to have increased in severity at the study exit visit. It is recommended that AE follow-up plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9. Note that re-assessment of the above-listed types of AEs is required regardless of the assessed relationship of the AE to study product and regardless of the severity grade of the AE at the study exit visit.

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The HPTN 035 PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis. In the event that efforts to re-assess AEs requiring follow-up after study exit are unsuccessful, site staff should contact the MTN CORE for further guidance, which will be provided in consultation with the PSRT. As a general guideline, for AEs that are considered not related to study product, the PSRT will likely recommend that efforts to re-assess the AE be discontinued after two months of active follow-up attempts. Document all efforts to complete all required re-assessments.

For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log case report forms based on the re-assessments.

6.12.10 Partner Status Assessment

Effective 1 April 2008, the Follow-up Partner Status case report form will be administered at all study exit visits. This interviewer-administered form is designed to collect information on whether study participants changed sexual partners during the study and, if so, to collect demographic and other information about their current partners.

6.12.11 Unblinding Assessment

As part of the Study Exit Acceptability Assessment, participants assigned to gel are asked to report which gel they think they were using during the study (see SAA-3, item 7). Similarly, the clinician who performs the last pelvic exam of each participant assigned to gel is asked to report which gel he/she thinks the participant was using during the study. The clinician's response to this question is recorded on the End of Study Inventory form (see ESI-1, item 4).

6.12.12 Referral to Non-Study Service Providers

After completing their study exit visits and final study contacts, participants will no longer have routine access to services provided through the study, such as reproductive health care and HIV counseling and testing. Participants should be counseled about this — ideally before and during their study exit visits — and provided information on where they can access such services after study exit. It is strongly recommended that all study sites develop a sample script which can be used when discussing this issue with exiting participants, as well as written referral sheets that can be given to participants at their study exit visits (after obtaining IRB/EC approval of the written information). A sample script which may be tailored for use at each site is provided in Section Appendix 6-10.

6.12.13 Post-Study Contacts

In addition to the contacts described in 6.12.5, all participants will be contacted post-study to be informed of the study results and, if applicable, their random assignments. It is currently expected that study results and unblinding information will be available within six months after the study end date.

To facilitate post-study contact with participants, locator information should be updated at the study exit visit, and participants should be counseled to contact the study site should their locator information change after study exit. In addition, participant preferences for methods to be used for contacting them when unblinding information and study results are available should be documented in participant study records. It is recommended that participant preferences be recorded on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. It is recommended that participant permission (or lack thereof) for future about other studies be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9. In addition, for ease of retrieving information on participant permissions, is it recommended that study staff maintain future study contact permission logs similar to the examples provided in Section Appendix 6-11.

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for HPTN 035

6.1	<p>Suppose Miss X enrolls in the study on September 15. What are the target and allowable dates for her visits in study months 1, 2, 3, 4, 5, and 6?</p> <table style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Target</u></th> <th style="text-align: center;"><u>Allowable</u></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Month 1</td> <td style="text-align: center;">October 15</td> <td style="text-align: center;">October 1-29</td> </tr> <tr> <td style="text-align: center;">Month 2</td> <td style="text-align: center;">November 15</td> <td style="text-align: center;">November 1-29</td> </tr> <tr> <td style="text-align: center;">Month 3</td> <td style="text-align: center;">December 15</td> <td style="text-align: center;">December 1-29</td> </tr> <tr> <td style="text-align: center;">Month 4</td> <td style="text-align: center;">January 15</td> <td style="text-align: center;">January 1-29</td> </tr> <tr> <td style="text-align: center;">Month 5</td> <td style="text-align: center;">February 15</td> <td style="text-align: center;">February 1-28</td> </tr> <tr> <td style="text-align: center;">Month 6</td> <td style="text-align: center;">March 15</td> <td style="text-align: center;">March 1-29</td> </tr> </tbody> </table> <p>Why? Target dates are set on the monthly anniversary of the participant's study enrollment date. The allowable visit window is ± 2 weeks from the target date. In all months except February, the ± 2 week window is comprised of 14 days before the target date and 14 days after the target date (inclusive). Because February is a 28-day month (except in leap years), the window for visits that take place in that month (except in leap years) is comprised of 14 days before the target date and 13 days after the target date (inclusive).</p>		<u>Target</u>	<u>Allowable</u>	Month 1	October 15	October 1-29	Month 2	November 15	November 1-29	Month 3	December 15	December 1-29	Month 4	January 15	January 1-29	Month 5	February 15	February 1-28	Month 6	March 15	March 1-29
	<u>Target</u>	<u>Allowable</u>																				
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Month 3	December 15	December 1-29																				
Month 4	January 15	January 1-29																				
Month 5	February 15	February 1-28																				
Month 6	March 15	March 1-29																				
6.2	<p>Suppose Miss X completes her Month 1 visit on October 20. What are the target and allowable dates for her visits in study months 2, 3, 4, 5, and 6?</p> <table style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th></th> <th style="text-align: center;"><u>Target</u></th> <th style="text-align: center;"><u>Allowable</u></th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">Month 2</td> <td style="text-align: center;">November 15</td> <td style="text-align: center;">November 1-29</td> </tr> <tr> <td style="text-align: center;">Month 3</td> <td style="text-align: center;">December 15</td> <td style="text-align: center;">December 1-29</td> </tr> <tr> <td style="text-align: center;">Month 4</td> <td style="text-align: center;">January 15</td> <td style="text-align: center;">January 1-29</td> </tr> <tr> <td style="text-align: center;">Month 5</td> <td style="text-align: center;">February 15</td> <td style="text-align: center;">February 1-28</td> </tr> <tr> <td style="text-align: center;">Month 6</td> <td style="text-align: center;">March 15</td> <td style="text-align: center;">March 1-29</td> </tr> </tbody> </table> <p>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.</p>		<u>Target</u>	<u>Allowable</u>	Month 2	November 15	November 1-29	Month 3	December 15	December 1-29	Month 4	January 15	January 1-29	Month 5	February 15	February 1-28	Month 6	March 15	March 1-29			
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Month 6	March 15	March 1-29																				
6.3	<p>Suppose Miss X does not complete her Month 2 visit on the target date of November 15, but presents to the study site on November 21. What do you do?</p> <ul style="list-style-type: none"> • Complete a Month 2 visit per protocol on November 21. <p>Why? November 21 is within the allowable Month 2 visit window.</p>																					
6.4	<p>Suppose Miss X does not complete her Month 2 visit between November 1 and November 29, but presents to the study site on December 2. What do you do?</p> <ul style="list-style-type: none"> • On November 30, consider the Month 2 visit missed. • On December 2, complete a Month 3 visit per protocol. <p>Why? The Month 2 visit window closed on November 29, but the Month 3 visit window opened on December 1.</p>																					

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for HPTN 035

6.5	<p>Suppose Miss X does not complete her Month 2 visit between November 1 and November 29, but presents to the study site on November 30. What do you do?</p> <ul style="list-style-type: none"> • On November 30, consider the Month 2 visit missed. • On November 30, complete an interim visit with interval medical/menstrual history and pregnancy test if clinically indicated. • Confirm and reinforce the scheduling of Miss X's Month 3 visit. <p>Why? The Month 2 visit window closed on November 29, but the Month 3 visit window has not opened on November 30. This is the reason why the November 30 visit is considered an interim visit. An interval medical/menstrual history and pregnancy test (and any appropriate clinical follow-up) must be completed at interim visits when clinically indicated. An interval medical/menstrual 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. A pregnancy test is considered clinically indicated if a test has not been performed within the last month, if the participant reports a missed menstrual period, and/or if there is any other reason to suspect pregnancy.</p>
6.6	<p>Suppose Miss X completes her Month 1 visit on October 15 and then presents to the study site complaining of genital pain and irritation on November 9. What do you do?</p> <ul style="list-style-type: none"> • On November 9, complete a Month 2 visit per protocol. • For Phase II participants, the Month 2 visit routinely includes a pelvic exam. Additionally complete any clinically indicated STD/RTI testing in response to the participant's symptoms and observed exam findings. • For Phase IIb participants, the Month 2 visit does not routinely include a pelvic exam. Additionally complete a pelvic exam and any clinically indicated STD/RTI testing in response to the participant's symptoms and observed exam findings. <p>Why? The Month 2 visit opened on November 1. A pelvic exam and clinically-indicated RTI/STD testing are required to evaluate the participant's symptoms.</p>
6.7	<p>Suppose Miss X does not complete her Month 3 visit between December 1 and December 29, but presents to the study site on January 12. What do you do?</p> <ul style="list-style-type: none"> • On December 30, consider the Month 3 visit missed. • On January 12, complete a Month 4 visit per protocol. • On January 12, additionally complete the pelvic exam and HIV counseling and testing procedures specified for the missed Month 3 visit. <p>Why? The Month 3 visit window closed on December 29 and the Month 4 visit window opened on January 1. When quarterly visits are missed, a pelvic exam (including pH assessment, homogenous discharge assessment, and wet mount) and HIV counseling and testing should be performed at the next study visit.</p>

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for HPTN 035

6.8	<p>Suppose Miss X does not complete her Month 3 visit between December 1 and December 29. Also suppose Miss X has agreed to complete her monthly study visits in her home, but she cannot be contacted or located in her home until January 12. What do you do?</p> <ul style="list-style-type: none"> • On December 30, consider the Month 3 visit missed. • On January 12, complete a Month 4 visit per protocol in the participant's home. Additionally perform HIV counseling and testing in the participant's home if possible. Additionally arrange for the participant to present to the study site as soon as possible to complete the pelvic exam required for the missed Month 3 visit. <p>Why? The Month 3 visit window closed on December 29 and the Month 4 visit window opened on January 1. When quarterly visits are missed, a pelvic exam (including pH assessment, homogenous discharge assessment, and wet mount) and HIV counseling and testing should be performed at the next study visit. In such cases, every effort should be made to complete the participants' next visit at the study site, so the pelvic exam and HIV counseling and testing procedures can be performed. However, when this is not possible — as in this example — the pelvic exam and HIV counseling and testing should be completed as soon as possible thereafter.</p>
6.9	<p>Continuing from Scenario 6.8, suppose Miss X completes her Month 4 Visit at her home on January 12, but does not present to the study site to complete her missed pelvic exam and HIV counseling and testing until February 14. What do you do?</p> <ul style="list-style-type: none"> • On February 14, complete a Month 5 visit per protocol. • Additionally complete the pelvic exam and HIV counseling and testing procedures required for the (missed) Month 3 visit. • Confirm and reinforce the scheduling of Miss X's Month 6 visit. <p>Why? The Month 5 visit window opened on February 1. Since this is the first time Miss X has presented to the study site since missing her Month 3 visit, the missed Month 3 pelvic exam (including pH assessment, homogenous discharge assessment, and wet mount) and HIV counseling and testing procedures should be performed at this visit.</p>
6.10	<p>Suppose Miss X presents to the study site for her Month 3 visit on December 16, and completes some but not all of the protocol-specified procedures for Month 3 visits. What do you do?</p> <ul style="list-style-type: none"> • Document all procedures performed on December 16 as usual. Use the scheduled Month 3 visit code (05.0) for all DataFax forms completed for this visit. 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 to complete the remaining Month 3 procedures. • When Miss X returns to the study site, provided the Month 3 visit has not elapsed, perform an interval medical/menstrual history and pregnancy test if clinically indicated, and all remaining Month 3 visit procedures. Use the scheduled Month 3 visit code (05.0) for all DataFax forms completed for this visit. • Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms. • Confirm and reinforce the scheduling of Miss X's Month 4 visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her Month 3 visit is considered a split visit. Split visits may be conducted over two or more days, provided the allowable visit window does not elapse. DataFax forms completed for all parts of a split visit are assigned the same scheduled visit code.</p>

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for HPTN 035

6.11	<p>Suppose Miss X completes her Month 3 Visit on December 28, tests positive on her rapid HIV test at this visit, and is scheduled to return in five days for her Western blot result. If Miss X returns on January 2 to receive her Western blot result, what do you do?</p> <ul style="list-style-type: none">• On January 2, conduct a Month 4 visit per protocol. Additionally provide Miss X's Western blot result and post-test counseling during the visit. <p>Why? January 2 is within the allowable visit window for Miss X's Month 4 visit.</p>
6.12	<p>Re-considering Scenario 6.11, suppose Miss X completes her Month 3 visit on December 19, tests positive on her rapid HIV test that day, and returns to the study site for her Western blot result on December 24. What do you do?</p> <ul style="list-style-type: none">• 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 history and pregnancy test if clinically indicated. Confirm and reinforce the scheduling of Miss X's next scheduled (Month 4) visit. <p>Why? Miss X already has completed her Month 3 visit, but on December 24 her Month 4 visit window has not yet opened. This is the reason why the December 24 visit is considered an interim visit. An interval medical/menstrual history and pregnancy (and appropriate clinical follow-up) are completed at interim visits when clinically indicated.</p>

***Note:** In both Scenarios 6.11 and 6.12, 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 the reason for not performing other protocol-specified procedures is documented in participants' study charts.*

Section Appendix 6-2
Sample Participant Visit Tracking Sheet for HPTN 035

Participant ID Number	
Participant Enrollment Date	

Instructions: The Participant Enrollment Date is defined as the date upon which an HPTN 035 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	Allowable Visit Window	Scheduled Visit Date	Actual Visit Date	Pelvic Exam Performed?	HIV Testing Performed?
Month 1						
Month 2						
Month 3						
Month 4						
Month 5						
Month 6						
Month 7						
Month 8						
Month 9						
Month 10						
Month 11						
Month 12						

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.

Section Appendix 6-3
HPTN 035 Gel Re-Supply Worksheet — Long Form — Page 1 of 2

HPTN 035 Gel Resupply Worksheet

Participant ID

--	--	--	--	--	--	--	--	--	--	--

Visit Date

dd		MMM		yy	

Clinic Staff: Applicators are dispensed in cartons of 10 only. At each visit, dispensing must take into account the participant's sexual frequency, supplies remaining from the prior visit(s), and the maximum number of 6 cartons allowed to be dispensed per 26-day period. Before administering this worksheet, complete item 2a based on worksheet item 2c from last visit and information from the participant's most recent behavior assessment form.

1. Now we are going to talk about how much study gel you may need between now and your next visit. Can you tell me how many unopened or full cartons of gel you have left now, and how many you have left that are partially used? *Probe here as needed to help the participant determine her best estimate of remaining supplies.*

1a. Number of unopened/full cartons: → **Clinic Staff:** Multiply by 10: applicators

1b. Number of partially used cartons: → How many individual applicators do you think you have left from these cartons? applicators

+

=

1c. **Clinic Staff:** Add items 1a and 1b to get the number of applicators remaining:..... applicators

2. We want to be sure you have enough applicators so that you can use one each time you have vaginal sex between now and your next visit.

2a. At your last visit you thought you usually had sex about: times per week

Thinking ahead to next month, do you think you will have sex about the same number of times per week, or might you have sex either more or less often than that?
Probe here as needed by asking about, for example, planned partner absences or returns from absences.

about the same → 2b. **Clinic Staff:** Multiply item 2a times 4: times per month

Go to item 3. ←

more or less often → 2c. How many times per week do you think you will have sex over the next month? times per week

x 4

=

→ 2d. **Clinic Staff:** Multiply item 2c times 4: times per month

2e. That would add up to about (item 2d) _____ times per month. Does that sound about right?..... yes no → **If no, go to 2c.**

3. **Clinic Staff:** Subtract item 1c from the estimated number of applicators needed for the next month (item 2b or 2d). Record result. **If "00", skip to item 5 and record "01".** applicators

If item 1c is greater than 2b or 2d, participant does not need any additional applicators at this visit. Do not complete a Study Product Request Slip. Go to item 7 on page 2.

Section Appendix 6-3
HPTN 035 Gel Re-Supply Worksheet — Short Form — Page 1 of 1

HPTN 035 Gel Resupply Worksheet

Participant ID

Site Number	Participant Number						Chk				

Visit Date

dd		MMM		yy	

Clinic Staff: Applicators are dispensed in cartons of 10 only. At each visit, dispensing must take into account the participant's sexual frequency, supplies remaining from the prior visit(s), and the maximum number of 6 cartons allowed to be dispensed per 26-day period.

- | | |
|--|---|
| <p>1. Previously reported (last visit) sexual frequency:
<i>Review with participant.</i></p> | <p>1a. Weekly <input type="text"/> <input type="text"/> times per week</p> <p>1b. Monthly <input type="text"/> <input type="text"/> times per month</p> |
| <p>2. Projected sexual frequency for next month:
<i>Probe here as needed by asking about planned partner absences, returns from absences, etc.</i></p> | <p>2a. Weekly <input type="text"/> <input type="text"/> times per week</p> <p>2b. Monthly <input type="text"/> <input type="text"/> times per month</p> |

3. Participant reports that she currently has the following:
- | | | | | | |
|---|---|---|-------------------------------|---|-------------|
| 3a. Number of unopened/full cartons: | <input type="text"/> <input type="text"/> | ➔ | Multiply by 10: | <input type="text"/> <input type="text"/> | applicators |
| 3b. Number of partially used cartons: | <input type="text"/> <input type="text"/> | ➔ | Number of unused applicators: | <input type="text"/> <input type="text"/> | applicators |
| | | | | + | |
| | | | | = | |
| 3c. Add items 3a and 3b to get the number of applicators remaining: | | | | <input type="text"/> <input type="text"/> | applicators |

If item 3c is greater than 2b, participant does not need any additional applicators at this visit. Do not complete a Study Product Request Slip. Go to item 7.

4. Subtract 3c from 2b to determine the number of additional applicators needed for the next month. **If "00", skip to item 6 and record "01"**..... applicators
5. Divide item 4 by 10: cartons
6. Round item 5 to the next highest whole number: cartons

Clinic Staff: The number in item 6 is the number of cartons to be ordered at this visit. **Before ordering/dispensing, review item 6 to ensure that no more than 60 applicators are dispensed per 26 day period.** Complete a Product 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 applicators were used other than as directed or that anything else happened to any of her applicators (e.g., they were lost or damaged) since the last visit?..... yes no ➔ **If no, go to counseling message after item 7a.**
- 7a. Describe what happened, number of applicators involved, and any follow-up discussion with the participant (continue on back if necessary):
- _____
- _____

Counseling Message: In order to properly test if the gel protects against HIV, it is important that you use your gel during every sex act, even when condom use is not possible.

Section Appendix 6-4
HPTN 035 Study Product Request Slip

HPTN 035 Study Product Request Slip

Clinic:		
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><i>Clinic Staff Instruction: Mark whether this is a product resupply, hold, or resume request. Record number of cartons to be dispensed (if applicable), and sign and date. Deliver top copy to pharmacy. File bottom copy in participant study notebook.</i></p>		
<p><input type="checkbox"/> RESUPPLY → Pharmacy: Dispense <input type="text"/> cartons of study gel (10 applicators/carton) to participant as directed in protocol.</p>		
<p><input type="checkbox"/> HOLD → Pharmacy: Do not dispense study gel to participant unless/until another Product Request Slip marked "Resume" is received.</p>		
<p><input type="checkbox"/> RESUME → Pharmacy: Dispense <input type="text"/> cartons of study gel (10 applicators/carton) to participant as directed in protocol.</p>		
<p>Clinic Staff Name (please print): _____</p>		
<p>Clinic Staff Signature: _____</p>		
<p>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"/></p> <p style="text-align: center;"><i>dd MMM yy</i></p>		

Pharmacy

Section Appendix 6-5
Gel Re-Supply Scenarios for HPTN 035

6.13 One day after receiving two cartons of study gel, a participant returns to the clinic to report that she left both 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 Product Request Slip for two more cartons of gel for the participant. To pre-empt questions about why the participant needs more gel so soon after her last visit, note that the participant lost the supplies she received on the previous day on the slip. Provide and document follow-up instructions and counseling to avoid further loss of gel supplies.

If the participant repeatedly reports loss of gel, or there is any other reason to suspect that she is sharing or selling her 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 MTN CORE Clinical Research Managers, SDMC Project Managers, and site Pharmacist of Record (PoR) of all cases of suspected gel sharing or selling; the PoR will inform the DAIDS Protocol Pharmacist.

Pharmacy Staff: Upon receipt of the new Product Request Slip, dispense gel per standard procedures.

6.14 Two participants routinely come to the clinic together for their monthly visits. At one of their visits they both receive two new cartons of 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: Verify the two participants' PTIDs and then return their cartons to them based on the PTIDs present on the cartons. Document the occurrence in a signed and dated chart note in each participant's chart. Forward a photocopy of each note to the pharmacy for informational purposes.

Pharmacy Staff: File the copies of the clinic staff notes in the participant-specific pharmacy files.

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, if the participants are able to read numbers, provide them with a card bearing their own PTID, which they can compare to the PTIDs on the cartons. If participants are not able to read, mark the boxes with a colored sticker or other symbol (e.g., blue for one participant, green for the other).

Section Appendix 6-5
Gel Re-Supply Scenarios for HPTN 035

6.15 Suppose only one of the participants in Scenario 6.14 returns to the clinic to report this problem. What do you do?

Clinic Staff: Verify the participant's PTID and examine the PTID on the outside of the cartons she has with her.

- If the cartons are labeled with the participant's PTID, no further action is required. Return the cartons to the participant to take home with her. Document the occurrence in a signed and dated chart note.
- If the cartons are not labeled with the participant's PTID, collect the cartons from her and prepare a Study Product Request Slip to order two new cartons for her. Document the occurrence in a signed and dated chart note. Attach a photocopy of the note to the new signed original Study Product Request Slip and deliver the note, the slip, and the other participant's gel to the pharmacy. Contact the other participant to arrange to collect and replace her gel supplies as well.

Pharmacy Staff: If a new Study Product Request Slip is received, dispense gel per standard procedures. If copies of any clinic staff notes are received, file these in participant-specific pharmacy files. If returned gel supplies are received, document the returns and store the applicators per the HPTN 035 Pharmacist Study Product Management Procedures Manual.

6.16 A participant returns to the clinic for a scheduled monthly visit and is re-supplied with 60 applicators (based on her self-reported sexual frequency). Three weeks later she returns to the clinic to request more applicators. What do you do?

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

- If the participant reports that she has used all of her applicators, counsel her that the study only allows for enough gel to be given for twice daily use, so the total number of applicators she can have between monthly visits is 60. Remind her that she can receive more applicators at her next scheduled visit (which should occur at least six days later, at which time she will be eligible to receive more applicators) and re-emphasize instructions to use condoms for all sex acts, whether or not gel is used. Document the participant request and action taken in signed and dated chart notes.
- If the participant reports that she has lost some of her gel supplies, discuss and probe as needed to confirm — to the extent possible — that the supplies have actually been lost. If so, additional 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 gel, or that she is sharing or selling her 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 MTN CORE Clinical Research Managers, SDMC Project Managers, and site Pharmacist of Record (PoR) of all cases of suspected gel sharing or selling; the PoR will inform the DAIDS Protocol Pharmacist.

Pharmacy Staff: If a new Study Product Request Slip is received, dispense gel per standard procedures. Otherwise no action is required.

Section Appendix 6-5
Gel Re-Supply Scenarios for HPTN 035

6.17 A participant returns to the clinic for a scheduled monthly visit and hands a damaged gel carton to the clinic staff member who greets her at the clinic reception area. The participant reports that she does not know what happened to the carton, but that the applicators inside the box also are damaged. What do you do?

Clinic Staff: Place the damaged carton in a paper bag. Do not attempt to examine the carton or the applicators inside the carton. When determining the quantity of new gel supplies to order for the participant at that visit, consider the damaged carton a “completely empty” carton with no applicators remaining to be used by the participant. Refer/escort the participant to pharmacy staff to further discuss her damaged gel supplies; at the same time, deliver the Study Product Request Slip for the visit and the damaged carton to the study pharmacy.

Pharmacy Staff: Answer any participant questions and provide and document follow-up instructions for the participant to avoid further damage of gel supplies. Dispense gel for the participant per the Study Product Request Slip. Document the participant report and receipt of the damaged carton/applicators. Inform clinic staff of the outcome/resolution of the participant’s report and provide written documentation for inclusion in the participant’s study chart (e.g., a photocopy of signed and dated pharmacy staff notes or a separate signed and dated note or memo to file). Be sure the documentation provided does not contain coded information related to the participant’s random assignment. Do not attempt to examine the damaged applicators, but store them in a designated ‘quarantine’ area for returned applicators. The DAIDS Protocol Pharmacist may provide instructions at a later date for destruction of returned applicators. Follow any such instructions.

Section Appendix 6-6
Follow-up HIV Testing Scenarios for HPTN 035

<p>6.18 Suppose Miss X's rapid HIV test is positive at Month 3. What do you do?</p> <ul style="list-style-type: none">• Record the rapid test result on the Follow-up Laboratory Results form for the Month 3 visit.• At the Month 3 visit, counsel Miss X that her initial HIV test indicates that she may be infected with HIV, but that an additional test (that requires N days to complete) is required to verify the result.• Deliver Miss X's blood sample to the local lab for WB testing. Note that this testing is performed on the same sample that tested positive on the rapid test (sample 1).• Schedule another visit to take place when Miss X's WB result will be available.
<p>6.19 Continuing from Scenario 6.18 suppose Miss X's WB is negative. What do you do?</p> <ul style="list-style-type: none">• Record the WB result on an 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. <p>If the return visit takes place before Miss X's Month 4 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Month 4) visit.</p> <p>OR</p> <p>If the return visit takes place after Miss X's Month 4 visit window has opened, additionally conduct the Month 4 visit per protocol (if possible).</p>
<p>6.20 Continuing from Scenario 6.18, suppose Miss X's WB is indeterminate. What do you do?</p> <ul style="list-style-type: none">• Record the WB result on an HIV Test Results form.• When Miss X returns for her test result:<ul style="list-style-type: none">– 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.– Collect blood (sample 2) and deliver it to the local lab for WB testing and plasma archive.– Schedule another visit to take place when Miss X's WB test result will be available. <p>If the return visit takes place before Miss X's Month 4 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Month 4) visit.</p> <p>OR</p> <p>If the return visit takes place after Miss X's Month 4 visit window has opened, additionally conduct the Month 4 visit per protocol (if possible).</p>

Section Appendix 6-6
Follow-up HIV Testing Scenarios for HPTN 035

6.21 Continuing from Scenario 6.18, suppose Miss X's WB is positive. What do you do?

- Record the WB result on an 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).
 - Collect blood (sample 2) and deliver it to the local lab for WB testing and plasma archive.
 - 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 Month 4 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Month 4) visit.

OR

If the return visit takes place after Miss X's Month 4 visit window has opened, additionally conduct the Month 4 visit per protocol (if possible).

6.22 Continuing from Scenario 6.20 or 6.21, 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.
- Inform the HPTN NL of Miss X's test results via email (copied to the MTN CORE and SDMC) and seek guidance on how best to clarify the participant's HIV status.
- When Miss X returns for her test result:
 - Counsel her that her HIV status remains unclear.
 - Collect blood (sample 3) for further testing per NL guidance.
 - 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 Month 4 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Month 4) visit.

OR

If the return visit takes place after Miss X's Month 4 visit window has opened, additionally conduct the Month 4 visit per protocol (if possible).

Section Appendix 6-6
Follow-up HIV Testing Scenarios for HPTN 035

6.23 Continuing from Scenario 6.20 or 6.21, 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.
- If Month 3 is the participant's first follow-up HIV testing timepoint, test her plasma archived at enrollment for evidence of HIV infection (see Section 12.5.2.3 of this manual).

If the return visit takes place before Miss X's Month 4 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Month 4) visit.

OR

If the return visit takes place after Miss X's Month 4 visit window has opened, conduct the Month 4 visit per protocol (if possible).

6.24 Suppose Miss X tests positive for HIV on her sample 1 rapid 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 having become HIV-infected. 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 035

6.25 Suppose Miss X is randomized to one of the HPTN 035 gel groups on 4 June 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>
Month 1	03 JUL 05	NEGATIVE
Month 2	01 AUG 05	POSITIVE
Month 3	02 SEP 05	NEGATIVE

Also suppose Miss X reports no action taken or symptoms experienced with regard to the pregnancy loss between Months 2 and 3. What actions are required at the Month 2 and Month 3 visits?

Month 2: In addition to all other routinely required procedures for Month 2 visits, 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 035 Study Product Request Slip marked "HOLD" to inform pharmacy staff of the product hold. Arrange to retrieve all remaining gel supplies from Miss X as soon as possible. Continue to use the Pregnancy Management Worksheet to guide and track further action.

Month 3: The negative pregnancy test at this visit is considered the outcome of the pregnancy identified at Month 2. In addition to all other routinely required procedures for Month 3 visits, complete and fax a Pregnancy Outcome form and an AE Log form to SCHARP (pregnancy outcome date = 2 SEP 05, AE term = spontaneous abortion). Indicate in the comments section of the Pregnancy Outcome form that the outcome date is based on a pregnancy test performed by study staff. Complete and submit an EAE form to the DAIDS Safety Office within three business days.

A pelvic exam is required per protocol at Month 3. When performing this exam, determine whether any findings that would contraindicate resumption of gel use are present:

- If no such findings are observed, given that the participant has a negative pregnancy test at this visit, instruct her to resume product use. Complete an HPTN 035 Study Product Request Slip marked "RESUME" to inform pharmacy staff of the re-instatement of gel use. Dispense gel to Miss X per standard procedures. Update and fax to SCHARP the Product Hold/Discontinuation form first completed at Month 2.
- If such findings are observed, defer resumption of product use until after the findings have resolved.

Section Appendix 6-7
Pregnancy Management Scenarios for HPTN 035

6.26 Suppose Miss X is randomized to one of the HPTN 035 gel groups on 10 August 2005 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>
Month 1	12 SEP 05	POSITIVE
Month 2	14 OCT 05	NEGATIVE
Month 3	MISSED	NOT AVAILABLE
Month 4	09 DEC 05	NEGATIVE
Month 5	13 JAN 06	NEGATIVE
Month 6	13 FEB 06	POSITIVE

Also suppose Miss X reports no action taken or symptoms experienced with regard to the pregnancy loss between Months 1 and 2. What actions are required at each visit?

Month 1: In addition to all other routinely required procedures for Month 1 visits, 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 035 Study Product Request Slip marked “HOLD” to inform pharmacy staff of the product hold. Arrange to retrieve all remaining gel supplies from Miss X as soon as possible. Continue to use the Pregnancy Management Worksheet to guide and track further action.

Month 2: The negative pregnancy at this visit is considered the outcome of the pregnancy identified at Month 1. In addition to all other routinely required procedures for Month 2 visits, complete and fax a Pregnancy Outcome form and an AE Log form to SCHARP (pregnancy outcome date = 14 OCT 05, AE term = spontaneous abortion). Indicate in the comments section of the Pregnancy Outcome form that the outcome date is based on a pregnancy test performed by study staff. Complete and submit an EAE form to the DAIDS Safety Office within three business days.

A pelvic exam is required per protocol at Month 2 study visits for Phase II study participants, but not for Phase IIb study participants. For Phase II participants, perform the protocol-specified pelvic exam. For Phase IIb participants perform a “clinically indicated” pelvic exam. When performing this exam, determine whether any findings that would contraindicate resumption of gel use are present:

- If no such findings are observed, given that the participant has a negative pregnancy test at this visit, instruct her to resume product use. Complete an HPTN 035 Study Product Request Slip marked “RESUME” to inform pharmacy staff of the re-instatement of gel use. Dispense gel to Miss X per standard procedures. Update and fax to SCHARP the Product Hold/Discontinuation form first completed at Month 1.
- If such findings are observed, defer resumption of product use until after the findings have resolved.

Months 4 and 5: Complete monthly visits per protocol.

Month 6: In addition to all other routinely required procedures for Month 6 visits, initiate a second Pregnancy Management Worksheet. Complete and fax a new Pregnancy Report and History form and a new Product Hold/Discontinuation form to SCHARP. Complete an HPTN 035 Study Product Request Slip marked “HOLD” to inform pharmacy staff of the product hold. Arrange to retrieve all remaining 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 Month 2.)

Section Appendix 6-7
Pregnancy Management Scenarios for HPTN 035

6.27 Suppose Miss X is randomized to one of the HPTN 035 gel groups on 11 July 2005 and has the following sequence of study visits and pregnancy tests:

<u>Study Visit</u>	<u>Visit Date</u>	<u>Pregnancy Test Result</u>
Month 1	13 AUG 05	POSITIVE
Month 2	12 SEP 05	POSITIVE
Month 3	10 OCT 05	POSITIVE
Month 4	13 NOV 05	POSITIVE
Month 5	15 DEC 05	POSITIVE
Month 6	13 JAN 06	POSITIVE
Month 7	10 FEB 06	POSITIVE
Month 8	10 MAR 06	POSITIVE
Month 9	15 APR 06	POSITIVE
Month 10	21 MAY 06	NEGATIVE

Also suppose Miss X reports at her Month 10 visit that she delivered a baby on 6 May 2006 in the district hospital. What actions are required at each visit?

Month 1: In addition to all other routinely required procedures for Month 1 visits, 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 035 Study Product Request Slip marked “HOLD” to inform pharmacy staff of the product hold. Arrange to retrieve all remaining gel supplies from Miss X as soon as possible. Continue to use the Pregnancy Management Worksheet to guide and track further action.

Months 2-9: Complete monthly visits per protocol (with modifications listed in Section 6.8 of this manual).

Month 10: Complete Month 10 visit per protocol. In addition, obtain as much information as possible from the participant about the birth of her infant, obtain permission for release of her medical records from the district hospital and obtain hospital records to document Miss X’s pregnancy outcome if possible. Complete and fax a Pregnancy Outcome form to SCHARP. If medical records or other written documentation from a licensed health care practitioner are obtained to document the pregnancy outcome, record the pregnancy outcome date based on the written records. Otherwise, record the outcome date based on participant report. Indicate in the comments section of the form whether the outcome date is based on medical records or participant report.

A pelvic exam is not routinely required at the Month 10 visit; however, a pelvic exam must be performed before instructing the participant to resume product use. Perform a “clinically indicated” pelvic exam and determine whether any findings that would contraindicate resumption of gel use are present:

- If no such findings are observed, given that the participant has a negative pregnancy test at this visit, instruct her to resume product use. Complete an HPTN 035 Study Product Request Slip marked “RESUME” to inform pharmacy staff of the re-instatement of gel use. Dispense gel to Miss X per standard procedures. Update and fax to SCHARP the Product Hold/Discontinuation form first completed at Month 1.
- If such findings are observed, defer resumption of product use until after the findings have resolved.

Section Appendix 6-7
Pregnancy Management Scenarios for HPTN 035

6.28 Supposed Miss X is randomized to one of the HPTN 035 gel groups on 13 June 2005 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>
Month 1	15 JUL 06	NEGATIVE
Month 2	14 AUG 06	POSITIVE
Month 3	13 SEP 06	POSITIVE
Month 4	17 OCT 06	NEGATIVE

Also suppose that Miss X reports at her Month 3 visit that she had an elective abortion on 5 September 2005. What actions are required at the Month 2 and Month 3 visits? What actions are required after Month 3?

Month 2: In addition to all other routinely required procedures for Month 2 visits, 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 035 Study Product Request Slip marked “HOLD” to inform pharmacy staff of the product hold. Arrange to retrieve all remaining gel supplies from Miss X as soon as possible. Continue to use the Pregnancy Management Worksheet to guide and track further action.

Month 3: Although Miss X reports a pregnancy outcome at this visit, no documentation of her elective abortion is available, and her pregnancy test at this visit is positive. Therefore Miss X cannot resume product use at this time. Complete the Month 3 visit per protocol. In addition, obtain permission for release of Miss X’s medical records from the clinic or hospital where the elective abortion was performed. Obtain medical records if possible.

Month 4: Complete Month 4 visit per protocol. In addition to all other routinely required procedures, complete and fax a Pregnancy Outcome form to SCHARP. If medical records or other written documentation from a licensed health care practitioner are obtained to document the pregnancy outcome, record the pregnancy outcome date based on the written records. Otherwise, record the outcome date based on participant report. Indicate in the comments section of the form whether the outcome date is based on medical records or participant report.

A pelvic exam is not routinely required at the Month 4 visit; however, a pelvic exam must be performed before instructing the participant to resume product use. Perform a “clinically indicated” pelvic exam and determine whether any findings that would contraindicate resumption of gel use are present:

- If no such findings are observed, given that the participant has a negative pregnancy test at this visit, instruct her to resume product use. Complete an HPTN 035 Study Product Request Slip marked “RESUME” to inform pharmacy staff of the re-instatement of gel use. Dispense gel to Miss X per standard procedures. Update and fax to SCHARP the Product Hold/Discontinuation form first completed at Month 2.
- If such findings are observed, defer resumption of product use until after the findings have resolved.

Section Appendix 6-8
Sample Pregnancy Management Worksheet for HPTN 035

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 <i>(NA if participant in condom only group)</i>		
3	Product supplies retrieved from participant and returned to pharmacy <i>(NA if participant in condom only group)</i>		
4	Product Hold/Discontinuation form completed (items 1-3) and faxed to SCHARP <i>(NA if participant in condom only group)</i>		
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"/> participant self-report <input type="checkbox"/> negative pregnancy test performed by study staff <input type="checkbox"/> other (specify in comments) <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 <i>(NA if participant in condom only group)</i>		
<i>For participants in a gel group, continue with items 7-9. For participants in the condom only group, items 7-9 are not applicable. Stop here.</i>			

Section Appendix 6-8
Sample Pregnancy Management Worksheet for HPTN 035

PARTICIPANT ID:

7. The participant is eligible to resume gel use as of the date of her first negative pregnancy test performed post-pregnancy by study staff, provided a pelvic exam is performed before resumption of gel use, and the exam identifies no findings that would contraindicate resumption of gel use. Based on pregnancy tests and pelvic exams performed by study staff, enter the date when the participant is eligible to resume product use here:

Date determined by (initials and date): _____

Date verified by (initials and date): _____

Note: Contact the HPTN 035 Protocol Safety Review Team with any questions related to resumption of gel use.

8	Pharmacy informed of participant eligibility to resume 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):

**Section Appendix 6-9
Sample Study Exit Worksheet**

PTID:	Exit Visit Date:
Plan for providing participant with final study test results	
Method by which participant wishes to be contacted when unblinding information and study results are available	
<p>Does participant have study gel remaining in her possession?</p> <input type="checkbox"/> NA (condom only participant) <input type="checkbox"/> No, per participant report, all gel supplies have been used/collected/returned <input type="checkbox"/> Yes ⇒ describe plan for gel collection (continue on back if needed)	
<input type="checkbox"/> Completed _____	
<p>Is participant currently pregnant?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for ascertaining pregnancy outcome (continue on back if needed)	
IoR approval: _____ <input type="checkbox"/> Completed: _____	
<p>Does participant have any ongoing SAEs/EAEs or any AEs found to have increased in severity at this visit?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for AE follow-up (continue on back if needed)	
IoR approval: _____ <input type="checkbox"/> Completed: _____	
<p>Is participant willing to be contacted about future studies for which she may be eligible?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes	
Staff Signature and Date:	

Section Appendix 6-10 Sample Script for Study Exit Visits

Before we finish your visit today, I would like to take some time to sincerely thank you for taking part in this study. By taking part, you have made an important contribution to the fight against HIV/AIDS. In recognition of this contribution, I would like to present you with this certificate of completion which you can take with you today.

I also would like to review a few more details with you:

- *If applicable, reinforce plans to collect remaining gel supplies.*
- Your appointment to receive your final exam and test results is scheduled for [date]. This appointment will take place [here at the clinic / other specify]. If you need to change this appointment for any reason, please contact us to let us know.
- Although your scheduled study visits have now been completed, the study is planned to be ongoing for another [X] months. After that, we expect it will take about 3-6 months to determine the results of the study. At that time, we will also learn which participants received which gel in the study. In order for us to share the results of the study with you [*include for gel participants only*: and tell you which gel you received], we need to be able to keep in touch with you. Therefore we ask you to please inform us if you move to a new home, change your phone number, or have any other new details that would help us keep in touch with you. [Give contact card.]
- As you know, [project name] is involved in many different types of research studies. We would like to be able to contact you in the future about other studies that you may be eligible for. Are you willing to give us your permission to do that? [Record response on study exit worksheet; if permission is granted, explain that information recorded on the participant's locator form would be used for this purpose and enter participant on future contact permission log.]
- *If applicable, reinforce plans to determine pregnancy outcome.*
- *If applicable, reinforce plans for AE follow-up.*
- Lastly, we would like to give you some information on places where you can go for different types of services now that you will not be coming here for regular study visits [give referral sheet]:
 - For HIV counseling and testing
 - For family planning and other reproductive health care
 - For other types of health care
 - Other
- *If applicable, replace above bullet with a discussion of plans for ongoing participation in MTN 015.*
- Please feel free to contact us if you have any questions about the study that we have not answered today, or if you encounter any problems related to your participation in the study. Once again, we sincerely thank you for your contributions to the study and we look forward to sharing the results with you when they become available.

