

Section 6. Participant Follow-up

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

6.1 Study Follow-up Plan and Participant Retention Targets

The MTN-003 protocol specifies that each enrolled participant will be followed for a minimum of 14 months, through the study end date or for a maximum of approximately 38 months, whichever occurs first. Within her 14-38 months of follow-up, each participant is expected to complete a minimum of 12 months and a maximum of 36 months of study product use. After completing product use, each participant is expected to complete an additional two months of follow-up off study product.

To minimize bias and ensure the accuracy of study results, each site will target retention of at least 95 percent of enrolled study participants per year during the expected product use period. This target translates to the monthly visit targets shown in Figure 6-1. Further information on retention definitions and procedures for MTN-003 is provided in Section 8 of this manual.

Figure 6-1
Monthly Visit Retention Targets for MTN-003

Study Visit	Target % Retained		Study Visit	Target % Retained
Month 1	99.62		Month 20	92.33
Month 2	99.23		Month 21	91.95
Month 3	98.85		Month 22	91.56
Month 4	98.47		Month 23	91.18
Month 5	98.08		Month 24	90.79
Month 6	97.70		Month 25	90.41
Month 7	97.32		Month 26	90.03
Month 8	96.93		Month 27	89.64
Month 9	96.55		Month 28	89.26
Month 10	96.16		Month 29	88.88
Month 11	95.78		Month 30	88.49
Month 12	95.40		Month 31	88.11
Month 13	95.01		Month 32	87.73
Month 14	94.63		Month 33	87.34
Month 15	94.25		Month 34	86.96
Month 16	93.86		Month 35	86.58
Month 17	93.48		Month 36	86.19
Month 18	93.10			
Month 19	92.71			

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 MTN-003 protocol specifies monthly follow-up visits that are targeted to occur every 28 days following the participant's study enrollment date. All scheduled visits are pre-assigned a visit code for purposes of data management, per Section 14 of this manual.
- **Interim visits** are those visits that take place between scheduled visits. More specifically, a visit is considered an interim visit when a participant presents for additional procedures or assessments beyond the required procedures for a scheduled visit. There are a number of reasons why interim visits may take place (see protocol Section 7.7). Site staff may be required to assign visit codes to interim visits for purposes of data management, per Section 14 of this manual.

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

Follow-up visits are targeted to occur every 28 days following the participant's study enrollment date, which is the date upon which the participant is assigned an MTN-003 Clinic Randomization Envelope. Target dates for scheduled follow-up visits are always based on the participant's enrollment date and do not change if subsequent follow-up visits take place before or after the target date.

Figure 6-2 illustrates the first three target visit dates for a sample study participant enrolled on 15 January 2010. Figure 6-3 lists the target visit dates for this same sample participant for her first full calendar year of study participation; note that targeting follow-up visits to occur every 28 days results in 13 scheduled visits per calendar year.

The MTN Statistical and Data Management Center (SDMC) will provide each site with a visit scheduling tool that can be used to generate follow-up visit schedules for enrolled participants.

6.3.2 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-003 protocol specifies that scheduled visits may be completed within an approximate four-week window around the targeted date. For each scheduled follow-up visit, the visit window begins 14 days before the target date and ends 13 days after the target date (not including the target date). Figures 6-2 and 6-3 illustrate the visit windows for a sample study participant enrolled on 15 January 2010.

Figure 6-2
Follow-up Visit Target Dates and Visit Windows for a Sample Participant
Enrolled in MTN-003 on 15 January 2010

JANUARY 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
10	11	12	13	14	15 Enrollment Date	16
17	18	19	20	21	22	23
24	25	26	27	28	29 Month 1 Window Opens	30

FEBRUARY 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
31	1	2	3	4	5	6
7	8	9	10	11	12 Month 1 Target Date	13
14	15	16	17	18	19	20
21	22	23	24	25 Month 1 Window Closes	26 Month 2 Window Opens	27

MARCH 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
28	1	2	3	4	5	6
7	8	9	10	11	12 Month 2 Target Date	13
14	15	16	17	18	19	20
21	22	23	24	25 Month 2 Window Closes	26 Month 3 Window Opens	27

APRIL 2010						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
28	29	30	31	1	2	3
4	5	6	7	8	9 Month 3 Target Date	10
11	12	13	14	15	16	17
18	19	20	21	22 Month 3 Window Closes	23 Month 4 Window Opens	24

Figure 6-3
Follow-up Visit Target Dates and Visit Windows for a Sample Participant
Enrolled in MTN-003 on 15 January 2010

Follow-up Visit	Target Study Day	Target Visit Date	Visit Window	
			Window Opens	Window Closes
Month 1	28	12 FEB 2010	29 JAN 2010	25 FEB 2010
Month 2	56	12 MAR 2010	26 FEB 2010	25 MAR 2010
Month 3	84	9 APR 2010	26 MAR 2010	22 APR 2010
Month 4	112	7 MAY 2010	23 APR 2010	20 MAY 2010
Month 5	140	4 JUN 2010	21 MAY 2010	17 JUN 2010
Month 6	168	2 JUL 2010	18 JUN 2010	15 JUL 2010
Month 7	196	30 JUL 2010	16 JUL 2010	12 AUG 2010
Month 8	224	27 AUG 2010	13 AUG 2010	9 SEP 2010
Month 9	252	24 SEP 2010	10 SEP 2010	7 OCT 2010
Month 10	280	22 OCT 2010	8 OCT 2010	4 NOV 2010
Month 11	308	19 NOV 2010	5 NOV 2010	2 DEC 2010
Month 12	336	17 DEC 2010	3 DEC 2010	30 DEC 2010
Month 13	364	14 JAN 2011	31 DEC 2010	27 JAN 2011

Although the visit windows allow considerable flexibility in visit scheduling, the intent of the protocol-specified visit schedule is to conduct follow-up visits at 28-day intervals, and every effort should be made to do so. In the event that a follow-up visit cannot be scheduled on the target date, it is recommended to schedule it earlier rather than later in the visit window, to ensure that participants do not run out of study product. Extreme deviations from 28-day intervals should be avoided. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the 28-day interval visit schedule (see Section 17 of this manual for more information on the study reporting plan).

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 (e.g., 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 visit window. When this occurs, the visit is considered a split visit. As described in Section 14 of this manual, all case report forms completed for a split visit are assigned the same visit code (even though the dates recorded on the case report forms may be different).

Note: If a visit at which an ACASI interview is required is conducted as a split visit, the entire ACASI interview must be completed on one day. If an ACASI interview is begun, but not completed, on the first day of a split visit, the entire ACASI interview should be administered (starting from the beginning) on the second day of the split visit. If this occurs, you do not need to notify the SDMC; the fully completed ACASI questionnaire will be used for analysis purposes.

6.3.3.1 Study Product Considerations During Split Visits

When a visit is split, every effort should be made to conduct the minimum safety testing required (HIV rapid and pregnancy testing) so product can be re-supplied at the first part of the visit. The participant should also have unused product collected, and re-issued as needed. If all product-related procedures (returns, re-issues and re-supplies) are conducted during the first part of a split visit, no further product-related procedures or documentation are required at the second part of the visit. No unused product should be returned during the second part of the visit *unless* either of the following occur:

- 1) A product hold/discontinuation is warranted that requires retrieval of all unused study product, per protocol Section 6.6. Complete a new Unused Product Returns Slip – version 2, a new Product Returns CRF, a new Product Re-supply and Re-issues CRF (required any time the Product Returns CRF is completed and vice-versa), and a Product Hold/Discontinuation CRF, and assign them an interim visit code. (All other study procedures conducted to complete the split visit should be documented on CRFs and assigned the regularly scheduled visit code.)
- 2) The participant forgot to return some or all unused product at the first part of the split visit and is returning it at this time.

When a visit is split, product may not be re-supplied during the first part of the visit if the minimum safety testing cannot be completed, if product eligibility cannot be determined, and/or due to time constraints. If product is not re-supplied during the first part of a split visit, any unused study product that the participant brings to that visit should still be counted as a product return by the site pharmacist. It should be re-issued to her for her continued use until she returns to the site clinic, within the visit window, to complete the visit (taking into account product quality and expiry). It can only be re-issued to her upon completion of the Unused Product Returns Slip (Version 2) and a MTN-003 Study Product Request Slip (with the re-issue quantity ONLY indicated). If no unused product is returned at the first part of the visit, then she should be rescheduled for the second part of the visit as soon as possible in order to re-supply product. The Unused Product Returns Slip (version 2), Product Returns (PRT) CRF, and Product Re-supplies and Re-issues (PRD) CRF should still be completed per usual procedure during the first part of the visit.

If the participant fails to return to the clinic to complete the rest of the visit within the visit window, then no updates to the PRT or PRD CRFs should be made. The remaining required CRFs for the visit should be completed to reflect which study procedures were missed. If the participant is able to return to the clinic within the visit window to complete the split visit, a new Unused Product Returns Slip (version 2) and a new Study Product Request Slip should be completed. The site should then update the PRT and PRD CRFs to indicate what was returned, re-issued, and re-supplied at the second part of the visit (the later visit date) ONLY.

If HIV rapid and urine pregnancy testing were already done at the first part of the visit, and a participant returns for the second part of the split visit within seven days, then HIV rapid and pregnancy testing do NOT need to be repeated at the second part of the visit. Any other procedures conducted during the first part of the visit do not need to be repeated during the second part of the visit (as long as it is still within the same visit window), unless clinically indicated. Only the remaining tests required for the visit that were not done during the first part of the visit should be conducted at the second part of the visit (with the exception of HIV and pregnancy testing if more than seven days has passed). Study product may be re-supplied, as needed, at the second part of the visit, unless a product hold/discontinuation is warranted.

If HIV rapid and urine pregnancy testing were already done at the first part of the visit, but more than seven days have passed when the participant returns for the second part of her visit, HIV rapid and pregnancy testing should be repeated. In addition, any remaining tests required for the visit that were not done during the first part of the visit should be conducted at the second part of the visit. Any procedures (other than HIV rapid and pregnancy testing) that were already conducted during the first part of the visit do not need to be repeated during the second part of the visit (as long as it is still within the same visit window), unless clinically indicated. The Follow-up Visit CRF and Follow-up HIV Rapid Test Results CRF completed at the first part of the visit should be updated to reflect the repeat pregnancy and HIV rapid test results. The site must confirm that these repeat results are negative (and that there are no contraindications to study product use) in order to re-supply product to the participant.

Refer to Data Collection SSP Section 14 for more information on CRF completion for split visits.

6.3.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the visit window, the visit is considered “missed” and a Missed Visit case report form must be completed to document the missed visit (see Section 14 of this manual for more information on completion of this form). For participants who miss visits at which pelvic exams, dipstick urinalysis for protein and glucose, serum chemistries, complete blood counts, and/or plasma archive are specified to take place, these procedures must be conducted at the participants’ next visit. As a reminder, each time blood is collected for serum creatinine testing, participant weight must be measured, so that the creatinine clearance rate can be calculated.

6.4 Follow-up Visit Locations

Because of the nature of study procedures that are required to be performed at MTN-003 follow-up visits, all scheduled visits are expected to be completed at the study clinic. However, some interim visits may take place at a participant’s home for the purpose of following up on a laboratory AE(s) or to deliver participant-specific study product dispensed by the pharmacy. In-home procedures will be limited to:

- Collection of blood and/or urine to follow up on a laboratory AE(s). Please note that no actual testing will be done during in-home visits. All samples will be transported to and processed at the study laboratory.
- Delivery of study product in cases when:
 - A participant was on a product hold due to an AE(s) and the AE(s) resolves in between study visits
 - The participant has left a clinic visit prior to receiving her study product.
Note: this applies only to cases where required safety procedures have been completed and there are no contraindications to study product use.

- Any other reason the IoR/designee deems it necessary to deliver study product to a participant's home. In such cases, PSRT approval is required prior to delivering participant-specific study product to the participant's home. When communicating with the PSRT, please include the rationale for dispensing at an in-home visit and any clinical or relevant participant history information. A copy of the final PSRT query must be filed in the participant's binder for documentation of approval. Also, include a note on the MTN-003 Study Product Request Slip documenting PSRT approval of the request and the date and time of the approval.

Sites interested in conducting in-home visits must complete certain requirements such as IRB approval and SOP development/update, prior to implementation of such visits. Sites should contact the MTN-003 management team (mtn003mgmt@mtnstopshiv.org) for the list of requirements. Completion of these requirements will be overseen by the management team. No sites should implement in-home visits without completing all requirements and receiving a notification from the MTN-003 management team to initiate implementation.

One of the requirements prior to the implementation of in-home visits is the development/update of SOPs to detail how in-home visits will be conducted, including proper procedures for handling participant-specific study product and biological samples. Further considerations that should be addressed in SOPs for in-home visits are as follows:

- Feedback and operational suggestions received from the Community Advisory Board or Group with regard to conducting in-home visits
- Procedures for obtaining participants' consent for these visits, including verbal or written consent (depending on local IRB requirements) and documentation of the consenting process

NOTE: During the administration of the informed consent for in-home visits, sites should discuss with participants any issues that may jeopardize participant confidentiality and/or safety, such as living situation (e.g., persons living with participant, availability of private space at participant's home). Also, in an effort to minimize the risk of social harm to participants and to study staff who will conduct home visits, discuss with participants whether they have disclosed participation in the study to family, neighbors, or others that may learn of these home visits.

- Procedures to identify binders of participants who provided consent for in-home visits
- Identification of staff member roles that will conduct in-home visits. Specification on how they will identify themselves so as to protect participant confidentiality and their own safety
- Completion of training before staff are authorized to conduct in-home visits
- Specification of specimen handling, including:
 - chain of custody, for specimens to be transported to and from in-home visits

- safety considerations, including details on how biological specimens and bio-waste will be handled and procedures to prevent and respond to specimen accidents
- allowable time intervals to get specimens to testing laboratories
- specimen transport methods
- Development of alternative source documentation to collect information during in-home visits. CRFs must not be taken outside the clinic site; therefore these forms should not be completed during in-home visits. The Source Document SOP should clearly describe source documentation requirements of in-home visits, and transcription of information onto CRFs at the site clinic.
- Description of how routine participant identification procedures will be modified for in-home visits.
- Specification of routine data management procedures that must be modified for in-home visits, including details on how the visit will be documented and what procedures will be put in place to help ensure that documents are not lost, stolen, or mixed up across participants.
- For participants receiving study product, specifications on product supply procedures for in-home visits. Site-specific SOPs for supply during in-home visits should specify procedures for all of the following (see also Section 9.6 of this manual):

NOTE: All pharmacy related SOPs should be reviewed and approved by Scharla Estep, DAIDS Protocol Pharmacist, and Cindy Jacobson, MTN Pharmacist prior to implementation.

- Requesting supplies (including participant-specific study product) from the pharmacy prior to the in-home visit (should include how this will be documented as an in-home visit on the MTN-003 Study Product Request Slip and the time line for notifying pharmacy prior to the in-home visit)
- Ensuring proper chain of custody of participant-specific study product from time of receipt from the pharmacy to time of delivery to the participant, including ensuring that participant-specific study product is delivered to the correct participant.
- Transporting participant-specific study product at appropriate temperatures from time of receipt to time of delivery to the participant
- Handling/returning participant-specific study product when the participant cannot be located (NOTE: To minimize the possibility that the participant cannot be located, study staff should not present to participant's home without prior discussion and agreement with the participant about the date and time of the visit.)
- Handling/returning participant-specific study product when the participant refuses to receive the full quantity of product dispensed to her. (NOTE: To minimize the possibility that the participant may refuse study product, when contacting the participant to schedule the visit, clearly explain to her the purpose of the visit and how much product will be dispensed).

- Handling/returning previously dispensed, unused participant-specific study product when the participant has unused study product at home. (NOTE: A mechanism should be in place to document whether the participant had unused product to return during the in-home visit, and whether the participant had unused product that she could not return as it was thrown away (e.g., empty bottles) and/or stored at another location (e.g., boyfriend or family member's house)).
- Documenting all of the above, and appropriately storing all documentation in either the study clinic and/or pharmacy.
- Procedures to protect participant confidentiality during in-home visits.
- Procedures to protect participant safety during in-home visits; including management of symptoms/illness requiring medical attention.
- Procedures to protect the safety of study staff, participants and any family members present during in-home visits.
- Procedures to contact the participant to schedule in-home visits. Each time an in-home visit is needed, clinic staff must contact the participant prior to the visit, verify consent for in-home visits, and agree on the best time to go to the participant's home to conduct the required procedures. When communicating with participants, the rationale and the procedures to be conducted for the visit should be clearly explained to her.

6.5 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Section 7.5 and Appendix I. The protocol specifies monthly, quarterly, semi-annual, and annual visit procedures, as well as procedures to be done when clinically indicated. As a general guide:

- Monthly visit procedures include interval medical and menstrual history; behavioral assessments; HIV counseling and testing; urine pregnancy testing; contraception counseling; provision of contraception (if needed); provision of study product, instructions, and adherence counseling; and provision of condoms.
- Quarterly visits include all monthly visit procedures plus additional behavioral assessments; physical exam; dipstick urinalysis; serum chemistries; and plasma archive.
- Semi-annual visits include all quarterly visit procedures plus pelvic exams and complete blood counts.
- Annual visits include all semi-annual procedures plus testing for sexually transmitted infections (STIs).

Several additional clarifications of the procedural specifications in protocol Section 7.5 are provided in the remainder of this section. Further operational guidance on completing protocol-specific procedures at follow-up visits is incorporated into the visit checklists included in Section 7 of this manual.

Protocol Section 7.5.1 specifies a number of different behavioral assessments to be performed at different time points throughout follow-up. These assessments will be performed via in-person interview and via audio computer-assisted self-interviewing (ACASI), as shown in Figure 6-4 below. At each protocol-specified time point, sexual behavior assessments should be administered before providing risk-reduction counseling and study product adherence assessments should be administered before providing study product adherence counseling. In addition, ideally, the site staff member providing risk-reduction counseling should differ from the site staff member who administers the sexual behavior assessment at a given participant visit. Similarly, the site staff member providing study product adherence counseling should differ from the site staff member who administers the study product adherence assessment at a given participant visit. These measures help to minimize bias and the likelihood of socially desirable reporting by the participant.

Figure 6-4
Interview Mode for MTN-003 Behavioral Assessments

Procedure	In-Person Interview	ACASI
Behavioral and study product adherence assessment		
- Sexual activity and condom use	✓	✓
- Adherence to study product use	✓	✓
- Partner reactions to study participation and product use		✓
Study product sharing assessment and last dose recall		
- Product sharing		✓
- Date and time of last product use	✓	
Intravaginal practices assessment		
-Menstrual practices	✓	
-Non-menstrual practices		✓
Social harms assessment	✓	
Perceived study product assessment	✓	

- ACASI interviews should ideally be completed uninterrupted in one sitting. If an ACASI interview is interrupted, for example if a participant needs to use the ladies room or attend to a child, the interview should be resumed as soon as possible after the interruption. If a visit at which an ACASI interview is required is conducted as a split visit, the entire ACASI interview must be completed on one day. If an ACASI interview is begun, but not completed, on the first day of a split visit, the entire ACASI interview should be administered (starting from the beginning) on the second day of the split visit. If a visit at which an ACASI interview is required is missed, the ACASI data will be considered missed (and the ACASI questionnaire should not be made up at the participant's next visit).
- Study product should be provided to each participant at each follow-up visit after all required safety assessments are completed (e.g., physical exam, pelvic exam, pregnancy and urine dipstick testing), and an authorized clinician confirms that the participant is eligible to continue product use. See Section 6.7 below for more information on study product re-supply and re-issue.

- Physical exams are performed at the Month 1 visit, at all quarterly visits, all semi-annual visits, all annual visits, at the Product Use End Visit (PUEV), and when clinically indicated. Required exam components are listed in protocol Section 7.10.
 - Participant weight should be measured at each exam; weight should also be measured at any visit in which blood is collected for serum creatinine testing, because weight is required to calculate the participant's creatinine clearance rate.
 - Participant height should be measured at all semi-annual visits, all annual visits, and at the PUEV.
- Serum chemistries — AST, ALT, creatinine, and phosphate — are performed at the Month 1 visit, at all quarterly visits, all semi-annual visits, all annual visits, at the PUEV, and when clinically indicated. Each participant's serum creatinine clearance rate should also be calculated each time her creatinine level is measured. If a Month 1 or quarterly visit is missed, serum chemistries should be performed at the participant's next visit.
- Dipstick urinalysis for nitrites and leukocyte esterase should be performed when clinically indicated based on:
 - Signs and symptoms of urinary tract infection
 - Dipstick urinalysis result of 1+ or higher for proteinuria
- Dipstick urinalysis for protein and glucose is performed at the Month 1 visit, at all quarterly visits, all semi-annual visits, all annual visits, at the PUEV, and when clinically indicated. If a Month 1 or quarterly visit is missed, dipstick urinalysis for protein and glucose should be performed at the participant's next visit.
- Dipstick urinalysis for protein and glucose as well as serum chemistries should also be performed to monitor renal function following resumption of product use after a product hold associated with management of any potential renal toxicity. Please refer to Section 9.5 of the protocol and the flow sheets in Section 10 of this manual for clinical management and the retesting schedule.

Thereafter, the frequency of testing should revert to the protocol-specified schedule. The Investigator of Record (IoR) or designee may consult with the Protocol Safety Review Team (PSRT) on any questions or concerns about the frequency of testing following resumption of product use.

- Plasma archive is performed at all quarterly visits, all semi-annual visits, all annual visits, at the PUEV, and at the Termination Visit. If a quarterly, semi-annual, or annual visit is missed, plasma archive should be performed at the participant's next visit. Study drug levels will be tested in these samples at the MTN Network Laboratory (NL).
- Complete blood counts are performed at all semi-annual visits, all annual visits, at the PUEV, and when clinically indicated. If a semi-annual or annual visit is missed, a complete blood count should be performed at the participant's next visit. Required complete blood count components are listed in protocol Section 7.11.
- Pelvic exams are performed, following the sequence of procedures shown on the checklist in Section 7 of this manual, at all semi-annual visits all annual visits, at the PUEV, and when clinically indicated. If a semi-annual or annual visit is missed, a pelvic exam should be performed at the participant's next visit. During all follow-up pelvic exams, *including unscheduled exams*:
 - Vaginal pH is assessed.
 - Vaginal fluid and endocervical swabs are collected.
 - Rapid testing trichomoniasis is performed annually, at PUEV and when clinically indicated.
 - Rapid testing for bacterial vaginosis is performed only when clinically indicated (i.e., if participant is symptomatic).
 - Wet prep and microscopy are only used to assess for candidiasis (KOH prep only) and are performed only when clinically indicated (i.e., when participant is symptomatic and vulvovaginal candidiasis is suspected).
- Hepatitis B surface antigen (HBsAg) testing is performed for all participants at the PUEV. For participants who are susceptible to Hepatitis B infection, but not vaccinated, HBsAg testing is also performed annually. For participants who are susceptible but not vaccinated, and are assigned to oral study product, HBsAg testing is also required six months after the PUEV.

Reduced Visit Procedures

To maximize participant retention while ensuring that participants' safety needs and the study's primary objectives are met, site staff should make every effort to assist participants to adhere to scheduled study visits. If participants are unable to complete an entire study visit or are able to spend only a limited amount of time in the clinic, staff should prioritize completing the following minimal required procedures:

- HIV counseling and testing
- Urine pregnancy testing
- Interval medical and menstrual history
 - *NOTE: If indicated based on medical/menstrual symptoms, please conduct physical and/or pelvic exam.*
- Review/update of Concomitant Medications
- Safety Labs: urinalysis, blood chemistries, hemogram, and differentials
 - *NOTE: If indicated, conduct STI testing*
- AE assessment and reporting
- Condom and risk reduction counseling
- Study product supply

- Product use instructions
- Adherence counseling
- Test results disclosure
- Review/update contact information
- Reimbursement
- Schedule next visit

Sites should discuss with the participant if she is willing to complete any additional visit procedures. For documentation purposes, the visit checklist should clearly document procedures that were not conducted and include a note explaining the reasons procedures were not done (e.g. “Participant refused,” “Participant declined due to time constraints.” Also, chart notes should indicate that a reduced visit was conducted and the rationale for the reduced visit. For participants completing reduced procedures, please complete and fax all CRFs, and write “not done” for skipped procedures and also include on the comment section of the CRF that the participant refused/declined the procedures.

Reduced visit procedures should be restricted to a limited number of participants, e.g. those who asked to terminate the study, missed 3 or more consecutive study visits, express that they are willing to continue in the study only if their time at the clinic is limited, or participants that cannot attend a full study visit due to work/school commitments. The IoR should determine if reduced procedures are appropriate for any given participant. IoR determination should also be documented in participants’ files.

**Collection of Peripheral Blood Mononuclear Cells (PBMCs) for PK analysis
[Under Protocol Version 2.0, Letter of Amendment (LoA) #01]**

NOTES: Collection of PBMCs for PK analysis will take place only at selected sites. Prior to implementation of this procedure, sites must obtain approval from NL. PBMC samples will be collected only on consenting participants.

Upon approval from NL, sites conducting collection of PBMC will:

- Determine which participants have provided informed consent for collection of PBMCs.
- For those participants who provide consent, collect blood for PBMC at the next quarterly visit following consent, every six months thereafter until the participant terminates from the study, and at the PUEV.

Example: Participant provided consent for PBMC collection on Month 4 study visit, PBMC collection should happen on:

Study Month 6
Study Month 12
Study Month 18
Study Month 24
Study Month 30
Study Month 36
Study PUEV

If a scheduled collection is missed, PBMC should be collected at the next completed visit (scheduled or interim), unless the next visit is less than 4 weeks away from the next scheduled PBMC collection, (in which case collection could occur at the latter visit).

Example: If a participant who consented to PBMC collection at Month 4 study visit misses her Month 6 visit, PBMC should be collected at her Month 7 visit. On the other hand, if a participant who consented to PBMC collection at her Month 4 visit misses her Month 6 visit and does not return to the site until her Month 11 visit, PBMC should not be collected at the Month 11 visit if the Month 11 visit is scheduled to be less than 4 weeks away from her scheduled Month 12 visit. Instead, it should be collected at the Month 12 visit.

- Participants who are temporarily held from study product use should not have PBMC collected if the hold is ongoing and was implemented 14 days or more prior to the visit when PBMC collection is expected. Once the site instructs the participant to resume product use, she will resume PBMC collection per her original collection schedule.
- Participants who are permanently discontinued from study product use should discontinue scheduled PBMC collection, if participant has been off product for 14 days or more. Specific guidance for seroconverters is provided in Section 6.10.
- At any visit where PBMC are to be collected and the collection is missed, AND a product hold/discontinuation is implemented at that visit, try and collect the PBMC within 7 days. If that is not possible, attempt to recollect within 14 days. If that is not possible, discontinue efforts to collect the sample.
- Note that the above bullet points refer to site-initiated product holds/discontinuations only, and do not apply to cases where participants have stopped product use on their own (participant non-adherence).

* In general, PBMC should be collected for anyone who provided consent and who has not been on a site-initiated product hold/discontinuation for the past 14 days.

Collection of Hair Samples for PK Analysis
[Under Protocol Version 2.0, Letter of Amendment (LoA) #02]

NOTES: Prior to implementation of this procedure, sites must obtain approval from NL. Hair samples will be collected only from consenting participants.

Upon receiving all required approvals (e.g., IRBs/ECs, regulatory, and NL approvals), sites conducting collection of hair will do the following:

- Administer the supplemental informed consent (IC) form to participants who meet the following requirements:
 - HIV negative, or HIV status not yet determined to be HIV positive per the protocol algorithm
 - Not permanently discontinued from product use 6 or more months ago (*applies to site-initiated permanent discontinuations only*)
- Start collecting hair samples from participants the same day IC is obtained (or as soon as possible thereafter), and then every other month prior to PUEV.
- Collect a final hair sample from participants during their PUEV, regardless of their hair collection schedule.

Example: A participant provided consent for hair collection during her Month 7 follow-up visit, and she is expected to have her PUEV at Month 18. Hair samples should be collected at the following visits:

- Study Month 7
 - Study Month 9
 - Study Month 11
 - Study Month 13
 - Study Month 15
 - Study Month 17
 - PUEV
- If a scheduled collection is missed, hair should be collected at the next visit (scheduled or interim), independently of when their next hair collection is scheduled.

Example: If a participant who consented to hair collection at her Month 7 study visit misses her Month 9 visit, hair should be collected at her Month 10 study visit (if this is the next time she presents at the clinic). When she returns for her Month 11 study visit, hair should be collected as scheduled.
 - If hair collection is missed during a PUEV, hair will **not** be collected at any subsequent visits (e.g., Interim or Termination).
 - Participants who are temporarily held or permanently discontinued from study product use should continue hair collection for PK analysis (unless product hold is due to potential HIV seroconversion; see below).

For participants with positive HIV results, the following procedures should be followed:

- Participants with only one positive HIV rapid test result at a given follow-up visit (discordant rapid results) will **not** have hair collected at the same visit unless the visit coincides with a scheduled hair collection.
- Participants with two positive HIV rapid test results during a follow-up visit will have hair collected during the same visit, unless a temporary delay is deemed by the IoR/designee to be in the best interest of the participant. If hair collection does not occur at the same visit, hair should be collected at the participant's next visit (scheduled or interim). Participants who are confirmed HIV positive per the protocol algorithm will no longer have hair collected at subsequent follow-up visits.

NOTE: Please see Section Appendix 6-6 for hair collection procedures.

6.6 HIV Testing During Follow-Up

Follow-up HIV testing will be performed according to the algorithm in protocol Appendix III. Further information on the procedural and documentation requirements of the algorithm is provided in the remainder of this section. Always contact the MTN NL in cases of unusual test results or problems with testing methods.

Per the algorithm in protocol Appendix III, first, an FDA-approved rapid HIV test that has been validated and approved for use at the site by the MTN NL is performed. If the rapid test is negative, the participant is considered HIV-uninfected and testing stops. If the rapid test is positive, an FDA-approved Genetic Systems Western blot (WB) test manufactured by Bio-Rad Laboratories is performed to confirm the participant's HIV status.

In the first testing step described above, sites may perform a second rapid test if required by local HIV testing policies or guidelines. The second rapid test used must be validated and approved by the MTN NL. At sites performing two rapid tests, a WB should be performed if either of the two rapid tests is positive. In the event that discordant rapid HIV test results are obtained, the MTN NL should be notified for informational purposes; while the NL may provide technical guidance to the site if needed, WB testing at the local lab should proceed immediately upon identification of at least one positive rapid test result.

Fingerstick blood collection may be used for rapid HIV testing during follow-up. However, use of fingerstick samples must be validated with the rapid test kit(s) planned to be used at the site. When fingerstick blood collection is used, for participants with positive rapid test results, venous blood collection will be required at the same visit for WB testing. This venous sample, collected on the same day as the positive rapid test, is considered part of "Sample 1" in the algorithm.

If the Sample 1 WB is negative or indeterminate, the site should consult the MTN Network lab and continue with the algorithm. An HIV viral load (RNA PCR) test is performed at the local lab using the same sample collected for the WB (Sample 1). If the viral load test is negative (i.e., below the limit of detection for the test), the participant is considered HIV-uninfected and testing stops.

If the Sample 1 WB is positive, or if the Sample 1 HIV viral load is positive, a second FDA-approved Genetic Systems WB must be performed on a second blood sample collected from the participant. This sample is referred to as "Sample 2" in the algorithm. In addition to being used for WB testing, Sample 2 includes blood that will be used for CD4+ cell count, HIV viral load, and plasma archive at the local laboratory. Approximately 25 mL of blood is required to perform all protocol-specified testing and processing of Sample 2 (site-specific volumes to be confirmed with the MTN NL).

If the Sample 2 WB is positive, HIV infection is considered confirmed and further local HIV testing stops. See Section 6.10 below for additional procedural requirements for participants with confirmed HIV infection.

If the Sample 2 WB is negative or indeterminate, additional testing must be performed, possibly requiring additional sample collection. In this case, inform the MTN NL of all Sample 1 and Sample 2 test results (copying the study management team) and request NL input on next steps and timeframes for additional specimen

collection and testing. Always contact the MTN NL as soon as possible after obtaining the participant's Sample 2 test results, so that adequate time is available for consultation before the participant returns to receive her Sample 2 results.

Guidelines for performing HIV tests during follow-up are provided in Section 13 of this manual. All tests must be documented on local laboratory log sheets or other laboratory source documents; such documents must capture the start and end/read times of each test. 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 specified timeframes for the tests and prior to disclosure of results to participants. 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.

**Updated HIV Testing Schedule for Sites Collecting PBMC
[Under Protocol Version 2.0, Letter of Amendment (LoA) #01]**

*NOTE: The guidance below refers only to those sites who are approved to collect specimens for PBMC under LoA #01 AND who are **not** utilizing fingerstick HIV rapid testing.*

- Following positive rapid HIV tests, sites will send that specimen to the lab for a Sample 1 Western Blot. On this same day:
 - Specimen collection for PBMC should be conducted per guidance in Sections 6.10 and 13 of this manual.
 - Sample 2* specimens, including Western Blot, CD4+ count, HIV RNA PCR, and plasma archive, should be collected at the time of specimen collection for PBMC.
 - If Sample 2 does not occur at this visit, sites should continue all efforts to collect the Sample 2 specimens as soon as possible.
 - When Sample 1 and Sample 2 are collected at the same visit, these must be collected from two completely separate venous draws.
 - Clinics should specify to processing laboratories that two Western Blots are being requested on the same participant on the same day.

*Sample 2 should only be collected on the same day as Sample 1 if a participant consented to PBMC collection. If a participant did not consent to PBMC collection, then the Sample 2 should be collected per the algorithm in protocol Appendix III.

6.7 Study Product Return, Re-Supply, and Re-Issue During Follow-up

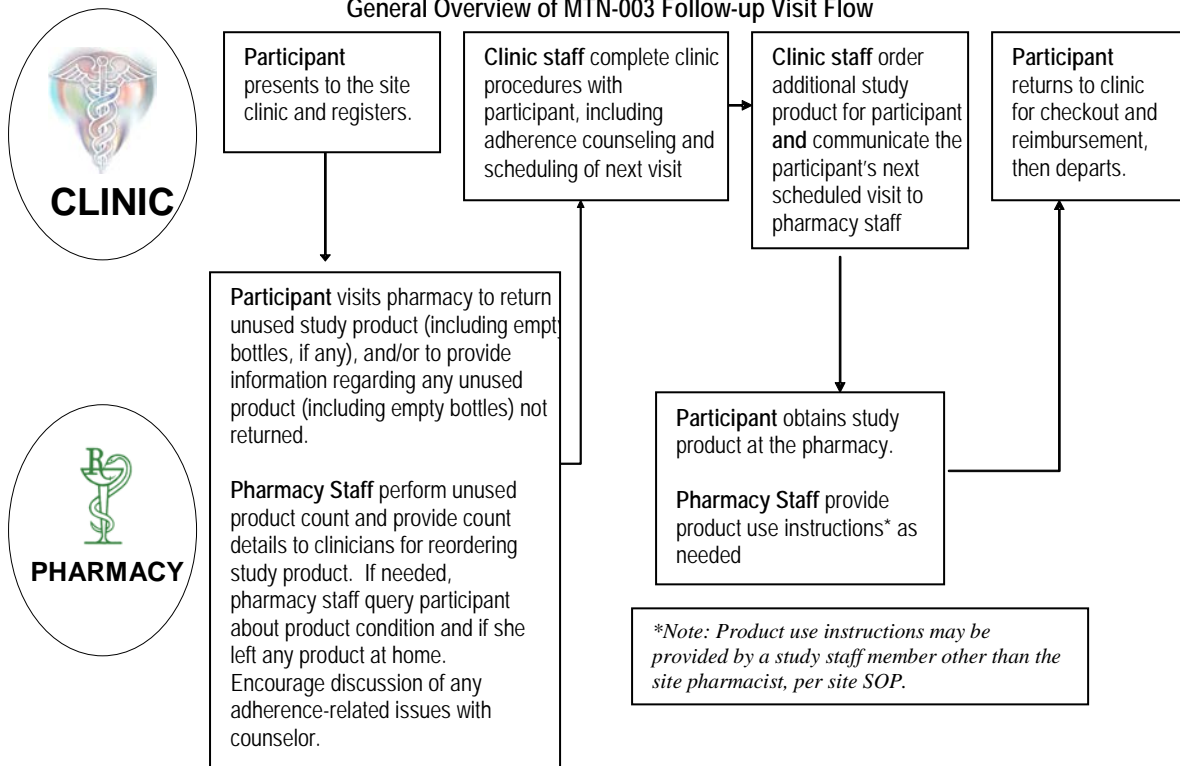
As an orientation to the study product return, re-supply, and re-issue information provided in this section, please refer to Figure 6-5 (below) which provides a general overview of the flow of MTN-003 follow-up visits. Please also refer to the operational definitions below Figure 6-5 for the terms “study product return,” “re-supply,” and “re-issue” for MTN-003.

Study product return refers to study participants bringing their unused study tablets, empty study bottles, and unused study applicators to follow-up visits for purposes of counting at the site pharmacy. Product returns are expected at each monthly study visit, at the PUEV, and at interim visits when product is re-supplied, held or permanently discontinued by site staff. Returned (unused) study tablets or study applicators may either be retained in the pharmacy or re-issued to the participant to whom it was originally dispensed. See Section 6.7.1 for more information on study product return.

Study product re-supply refers to dispensing new participant-specific study product. Study tablets will be re-supplied in quantities of 30 (each bottle contains 30 tablets). Study gel will most commonly be re-supplied in quantities of 30 as well. However, because gel is packaged in cartons containing 10 pre-filled applicators each, gel may be re-supplied in quantities of 10, 20, or 30 applicators. See Section 6.7.2 for more information on study product re-supply.

Study product re-issue refers to providing participants with their own unused participant-specific study product which they previously returned to the site pharmacy for purposes of counting. See Section 6.7.3 for more information on study product re-issue.

Figure 6-5
General Overview of MTN-003 Follow-up Visit Flow



6.7.1 Study Product Return

Participants will be instructed to bring all unused study product to all follow-up visits. At scheduled monthly visits, the PUEV, and interim where product is re-supplied, held, or permanently discontinued by site staff, participants will visit the site pharmacy. They will

- deliver any unused study product (including any empty bottles) to the site pharmacy, where pharmacy staff will inspect and count the product according to the *MTN-003 Pharmacist Study Product Management Procedures Manual*
- inform the site pharmacist of any unused study product, including empty bottles, that they were unable to bring with them to the clinic (e.g., left at home or thrown away)
- communicate to the site pharmacist whether a dose was used already that day.

The MTN-003 Unused Product Returns Slip – Version 2 (see Figure 6-6) is a two-part no carbon required (NCR) document. Bulk supplies of the slip are available from the DAIDS Clinical Research Product Management Center (CRPMC); the site Pharmacist of Record (PoR) will order supplies of the slip for use by pharmacy staff throughout the course of the study.

Pharmacy staff will determine and document on the MTN-003 Unused Product Returns Slip–Version 2:

- the quantity of product expected to be returned if the participant had been adherent to daily product use since her last regularly scheduled visit, or an interim visit in which product was re-supplied, re-issued, or returned, whichever is more recent (taking any site-initiated product holds/discontinuations into account).
Note: if a participant provides any reason why an extra dose may have been used, the pharmacist will note this in the comments section of the MTN-003 Unused Product Returns Slip-Version 2, but will not factor this information into their calculations.
- the quantity of product actually returned from the product re-supplied/re-issued at the last visit
- the quantity of unused product not returned, including empty bottles (e.g., unused product left at home or thrown away) from the last visit, based on participant self-report
Note: the quantity of bottles not returned must be determined by pharmacist calculation, such that the quantity of bottles not returned plus the quantity of bottles returned equals the quantity of bottles re-supplied/re-issued at the last visit. The quantity of tablets/applicators not returned is based on participant self-report; when added to the quantity actually returned, it should not exceed the total quantity of tablets/applicators re-supplied/re-issued at the last visit.
- the quantity of product available for re-issue (based on factors such as expiry dates and the observed physical condition of the returned product)

Questions beyond those required to accurately complete the Unused Product Returns Slip – version 2 (i.e., did you leave any product at home?) should be avoided. If a major discrepancy is noted in the product counts, the potential issue (e.g., product sharing, using expired product) should be discussed as a general topic in the context of product use instructions later in the visit (when product is re-supplied/re-issued) without reference to the participant’s product count. In order to maintain the accuracy of product counts as a measure of adherence (and to avoid potential bias), site staff should not ask participants any additional questions about her product counts in an attempt to explain any observed discrepancies between what was returned, what was expected to be returned, and participant self-reported product use. Each is an independent measure of adherence, and discrepancies are expected.

The site pharmacist should use the comments section of the slip to document any additional relevant information about the study product count. Additional guidance on completion of this slip and the Product Returns CRF is available via the Product Returns Training Presentation, which is available in the Study Implementation Materials section of the MTN-003 web page.

Note: Despite minimal questioning, the participant may spontaneously report information relating to adherence or clinical issues while returning product. The comments section of the slip may also be used to communicate any information for clinicians relating to participant’s clinical management, safety, or study participation, if these issues arise in conversations between the pharmacist and the participant. If sites choose to use this method of communication, they must ensure that site clinicians routinely review the comments section of the slip so that they are aware of any potential clinical concerns and can follow up appropriately. Alternatively, sites may communicate this type of information from pharmacy to clinic using site-specific methods designated in site SOPs (e.g., Note-to-File, Action Log, Communication Log). If adherence-related issues arise in pharmacist-participant conversations, participants should be encouraged to discuss these issues in the adherence counseling session with site clinic staff. At their discretion, pharmacists may document spontaneously reported adherence-related issues in the comments section of the slip, but they should also document that the participant was advised to discuss these issues with the counselor. As adherence counselors should not review the Unused Product Returns Slip prior to counseling, they are not responsible for follow-up on adherence-related issues documented in the comments section of this slip; rather, the participant will be the conduit of this information. If issues related to product use instructions (including potential product sharing and product storage) arise, the pharmacist (or designated site staff) should discuss with the participant only after completion of ACASI and administration of the behavioral CRF(s), as required. See Sections 12.4 and 12.5 for further guidance regarding adherence counseling and product use instructions during follow-up.

After completing the MTN-003 Unused Product Returns Slip-Version 2, pharmacy staff will separate the two parts of the slip and deliver the yellow copy to the clinic, where the information recorded on the slip will be used by clinic staff to guide ordering of study product to be re-supplied and re-issued to the participant.

Clinic staff will use the slip as source documentation to complete the Product Returns case report form (CRF). Comments from the slip will be transcribed onto the comments section of the CRF. Preferably, this transcription will be done by a staff member who does not provide the adherence counseling. If it must be the same staff member, they should transcribe this information only after the adherence counseling session is completed. The white original of the slip will be retained in the site pharmacy.

6.7.2 Study Product Re-Supply

At each follow-up visit, the IoR or designee will assess whether the participant remains eligible to continue study product use per protocol specifications. Protocol Section 9 lists conditions under which product use should be temporarily held or permanently discontinued; the IoR is responsible for ensuring that protocol specifications are followed.

For participants who are eligible to continue product use, authorized clinic staff will determine the quantity of study product needed for daily use until the next scheduled visit. In most circumstances, a 30-day supply will be ordered and re-supplied at each follow-up visit. However, under exceptional circumstances (e.g., when participants will not be able to attend a scheduled visit or when the minimum quantity of study product needed for daily use until the next scheduled visit is greater than the standard 30-day supply plus available re-issue), up to a 60-day re-supply plus re-issue may be ordered and dispensed. If a participant will miss two or more consecutive visits, such that she requires more than a 60-day re-supply of study product, approval from the DAIDS Medical Officer must be obtained prior to dispensing more than a 60-day re-supply. See Section 9 of this manual for further information on dispensing more than a 60-day re-supply.

The MTN-003 Study Product Request Slip (see Figures 6-7a and 6-7b) will be used by clinic staff to communicate the quantity of study product to be re-supplied to each participant at each follow-up visit. The slip also will be used to communicate the quantity of study product to be re-issued and to communicate clinic staff decisions to temporarily hold, permanently discontinue, or resume study product use.

Two different MTN-003 Study Product Request Slips are available: one for oral tablets (Figure 6-7a) and one for vaginal gel (Figure 6-7b). Care should be taken to use the correct slip for each participant, based on her randomization assignment. Each slip is a two-part NCR document. Bulk supplies of the slips are available from the DAIDS CRPMC; the site PoR will order supplies of slips for use by clinic staff throughout the course of the study.

Instructions for completion of the Study Product Request Slips are printed on the slips themselves. Additional guidance for clinic staff is as follows:

- Record the participant's study ID number (PTID) and the number of the Clinic Randomization Envelope assigned to the participant in the boxes provided at the top of the slip. Record the date the form is completed along with the date of the participant's next scheduled visit in the boxes provided at the bottom of the slip.
- Mark the box for RE-SUPPLY, HOLD, PERMANENTLY DISCONTINUE, RESUME and/or RE-ISSUE to indicate the appropriate action to be taken in the site pharmacy.
- When marking RE-SUPPLY or RESUME, record the number of bottles (of tablets) or cartons (of gel) to be newly dispensed for the participant. Also mark RE-ISSUE, if applicable, and record the number of tablets or applicators to be re-issued to the participant (see Section 6.7.3 below for more information on re-issuing study product).

- Only mark the HOLD or PERMANENTLY DISCONTINUE box for site-initiated hold/discontinuations. Record the reason for the hold or discontinuation on the line provided.
- **If a participant decides on her own to stop product use** and refuses to be re-supplied/re-issued study product, **do not mark the “Hold” box**; instead, record on the adjacent “Reason” line that the participant refuses additional study product.
- The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up. When marking RESUME, this clinic staff member must be an authorized prescriber. In all other circumstances, DAIDS does not require the slips to be signed by an authorized prescriber; 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 slip. Retain the yellow copy in the participant study notebook and deliver the white original to the pharmacy.
- If corrections are needed, the corrections must be made on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete the original prescription.

Figure 6-7a
 MTN-003 Study Product Request Slip – Oral Tablets

MTN-003 Study Product Request Slip – ORAL TABLETS

Participant ID

- -

Clinic Randomization Envelope #

Clinic Staff Instructions: Mark RE-SUPPLY, HOLD, PERMANENTLY DISCONTINUE, or RESUME. If re-supply, mark RE-ISSUE if applicable. If re-supply or resume, record the number of bottles to be dispensed. If re-issue, record the number of tablets to be re-issued. If hold or permanently discontinue, record the reason. Sign and date at the bottom. Deliver white original to pharmacy. File yellow copy in participant study notebook.

RE-SUPPLY (mark all products that apply)

- TDF 300mg or placebo tablets. Dispense bottles (30 tablets/bottle) to participant as directed in protocol.
- FTC/TDF 200mg/300mg or placebo tablets. Dispense bottles (30 tablets/bottle) to participant as directed in protocol.

HOLD Reason: _____

Pharmacy Staff Instructions: Do not dispense any further study tablets unless/until another MTN-003 Study Product Request Slip – ORAL TABLETS marked "RESUME" is received.

PERMANENTLY DISCONTINUE Reason: _____

Pharmacy Staff Instructions: Do not dispense any further study tablets.

RESUME (Mark all products that apply)

- TDF 300mg or placebo tablets. Dispense bottles (30 tablets/bottle) to participant as directed in protocol.
- FTC/TDF 200mg/300mg or placebo tablets. Dispense bottles (30 tablets/bottle) to participant as directed in protocol.

Comments: _____

Clinic Staff Instructions: For product resumptions, this slip must be signed by an authorized prescriber.

RE-ISSUE (mark all products that apply)

- TDF 300mg or placebo tablets. Re-issue tablets to participant.
- FTC/TDF 200mg/300mg or placebo tablets. Re-issue tablets to participant.

Comments: _____

Clinic Staff Name (please print): _____

Clinic Staff Signature: _____

Date completed: - - Participant's next visit date: - -

dd *MMM* *yy* *dd* *MMM* *yy*

Figure 6-7b
 MTN-003 Study Product Request Slip — Vaginal Gel

MTN-003 Study Product Request Slip – VAGINAL GEL

Participant ID

- -

Clinic Randomization Envelope #

Clinic Staff Instructions: Mark RE-SUPPLY, HOLD, PERMANENTLY DISCONTINUE, or RESUME. If re-supply, mark RE-ISSUE if applicable. If re-supply or resume, record the number of cartons to be dispensed. If re-issue, record the number of applicators to be re-issued. If hold or permanently discontinue, record the reason. Sign and date at the bottom. Deliver white original to pharmacy. File yellow copy in participant study notebook.

RE-SUPPLY

Dispense cartons of study gel (10 applicators/carton) to participant as directed in protocol.

HOLD Reason: _____

Pharmacy Staff Instructions: Do not dispense any further study gel unless/until another MTN-003 Study Product Request Slip – VAGINAL GEL marked "RESUME" is received.

PERMANENTLY DISCONTINUE Reason: _____

Pharmacy Staff Instructions: Do not dispense any further study gel.

RESUME

Dispense cartons of study gel (10 applicators/carton) to participant as directed in protocol.

Comments: _____

Clinic Staff Instructions: For product resumptions, this slip must be signed by an authorized prescriber.

RE-ISSUE

Re-issue applicators of study gel to participant.

Comments: _____

Clinic Staff Name (please print): _____

Clinic Staff Signature: _____

Date completed: - - Participant's next visit date: - -

dd MMM yy dd MMM yy

6.7.3 Study Product Re-Issue

For participants who are eligible to continue study product use, authorized clinic staff will determine the quantity of product needed for daily use until the next scheduled visit. Newly dispensed study product will be re-supplied as described in Section 6.7.2. In addition, returned unused product may be re-issued to the participant at follow-up visits as needed.

When determining the quantity of product to re-issue at each follow-up visit, authorized clinic staff should consider the number of days between the current visit and the next scheduled visit, the quantity of product to be re-supplied, and the quantity of product available for re-issue as determined by the site pharmacist (per the MTN-003 Unused Product Returns slip).

Ideal Quantity: In general, to maximize study product adherence, unless specific concerns are identified by the IoR or designee, clinic staff should aim to provide participants with the quantity of study product required for daily use through the next scheduled visit date, plus seven days, or the quantity of product required for daily use through the next target visit date, plus seven days, whichever is greater.

Minimum Quantity: At a minimum, participants must be provided with enough study product for daily use until their next scheduled study visit. As mentioned in Section 6.7.2, approval from the DAIDS Medical Officer must be obtained prior to dispensing more than a 60-day re-supply.

For example, consider a participant assigned to oral study product who completes a follow-up visit on 1 September 2010. At this visit, she returns two (2) of each type of study tablet (Tenofovir/placebo and Truvada/placebo), all of which is documented by the PoR as available for re-issue. The target date for this participant's next visit is 27 September 2010, which is 26 days from today's visit. The scheduled date for this participant's next visit is 25 September 2010, which is 24 days from today's visit. The ideal quantity of study product to provide to this participant at today's visit is 33 of each tablet (i.e., the larger of 24 and 26, plus 7). The minimum quantity of study product to provide to this participant is 24 of each type of tablet (as there are 24 days until her next scheduled study visit). Given that the participant has 2 of each type of tablet available for re-issue, she cannot be provided the ideal quantity of 33 of each tablet, but she can be provided with 32 of each tablet by re-supplying 30 and re-issuing 2 of each tablet.

As another example, consider a participant assigned to vaginal study product who completes a follow-up visit on 1 September 2010. At this visit, she returns eight (8) applicators, all of which are documented by the PoR as available for re-issue. The target date for this participant's next visit is 26 September 2010, which is 25 days from today's visit. The scheduled date for this participant's next visit is 28 September 2010, which is 27 days from today's visit. The ideal quantity of study product to provide to this participant at today's visit is 34 applicators (i.e., the larger of 25 and 27, plus 7). The minimum quantity of study product to provide to this participant is 27 applicators (as there are 27 days until her next scheduled study visit). Given that the participant has 8 applicators available for re-issue, she could be provided with the ideal quantity of 34 applicators by re-supplying 30 applicators and re-issuing 4 applicators.

Finally, consider a participant assigned to oral study product who completes a follow-up visit on 1 September 2010. At this visit, she returns no study product. The target date for this participant's next visit is 29 September 2010, which is 28 days from today's visit. The scheduled date for this participant's next study visit is 8 October 2010, which is 37 days from today's visit. The ideal quantity of study product to provide to this participant at today's visit is 44 of each tablet (i.e., the larger of 28 and 37, plus 7). The minimum quantity of study product to provide to this participant is 37 of each type of tablet (as there are 37 days until her next scheduled study visit). Given that the participant has no product available for re-issue and a 30-day supply will not provide enough product to make it to her next scheduled visit, the IoR should consider allowing a 60-day supply to be dispensed. Alternatively, clinic staff could try and reschedule the participant earlier in her visit window.

All sites should use the Product Ordering Tool to help determine **both the minimum and the ideal quantity** of study product to provide. This tool is available in the Study Implementation Materials section of the MTN-003 webpage. Sites need to print the completed Product Ordering Tool, initial and date it, and place it in the participant's file. Also, a copy should be sent to the pharmacy along with the Study Product Request Slip.

The MTN-003 Study Product Request Slip (see Figures 6-7a and 6-7b) will be used by clinic staff to communicate the quantity of study product to be re-issued to each participant at each visit. Instructions for proper completion of the Study Product Request Slips are printed on the slips themselves and additional guidance is provided in Section 6.7.2.

6.8 Modified Follow-up Procedures for Participants Who Become Pregnant

Refer to protocol Sections 7.6.3 and 9.12.

Participants who become pregnant will remain in follow-up according to their original study follow-up schedule. In addition, participants who become pregnant within nine months prior to their scheduled study Termination Visit will complete a post-study contact if needed to ascertain their pregnancy outcome.

All participants who become pregnant will be actively referred to antenatal care. Participants who become both pregnant and infected with HIV will also be referred to prevention of mother-to-child transmission (PMTCT) services and will be offered expedited resistance testing at the MTN NL to provide information that may be useful for identifying optimal PMTCT regimens. HIV testing of participants' infants will be offered through the study if such testing is not otherwise available. All referrals and offers of additional testing available through the study will be documented in participants' MTN-003 study records.

All pregnant participants also will be referred to MTN-016. They may be informed about MTN-016 upon first identification of their pregnancy, but should not be actively referred for screening and enrollment in MTN-016 until after the pregnancy confirmation requirements of MTN-016 are met. All discussions related to potential participation in MTN-016 must be fully documented in participant study records.

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:

- Contraceptives (other than condoms) will not be provided during pregnancy. Contraceptive counseling need not be routinely provided during pregnancy, unless requested by the participant, until such time that counseling is indicated to prepare for resumption of contraceptive use post-pregnancy.
- Pelvic exams will be conducted through 24 weeks of pregnancy, 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 vaginal spotting for several hours following the exam. They also should be counseled to return to the clinic to report any heavy or prolonged genital bleeding.
- 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, if limited blood collection is clinically indicated in the opinion of the IoR or designee.

- Study product use must be held immediately upon identification of a positive pregnancy test result. The period of product hold will continue until after birth or other pregnancy outcome, as evidenced by a negative pregnancy test performed by study staff, provided the participant is not breastfeeding. Clinic staff should inform pharmacy staff of the product hold in writing, using the Study Product Request Slip, and should complete and fax a Product Hold/Discontinuation Log form to the MTN SDMC. If the participant still has any unused study product in her possession when her pregnancy is identified, all product should be retrieved within five working days. If all product cannot be retrieved within five working days, the PSRT must be informed. For participants assigned to study gel, a pelvic exam must be performed prior to resumption of gel use to confirm the absence of any findings that would contraindicate gel use, in the opinion of the IoR or designee.

Note: All participants who give birth will be counseled to breastfeed their infants in accordance with current World Health Organization and/or local guidelines.

- While participants are on study product hold due to pregnancy, they will not receive product use instructions or adherence counseling. In addition, administration of their behavioral questionnaires — both interviewer-administered and ACASI — will be tailored, per guidance in the behavioral CRF form instructions and ACASI Manual (SSP Section 16), to reflect their non-use of product.

For all participants who become pregnant during study follow up, a Pregnancy Report and History case report form (CRF) must be completed to report each new pregnancy. A Pregnancy Outcome CRF must be completed to document the outcome of each new pregnancy that occurs during study follow-up, even if the outcome occurs after the participant has terminated from the study. If a new pregnancy results in multiple outcomes (e.g., twins), a new Pregnancy Outcome CRF should be completed for each outcome of the pregnancy. Under protocol Version 1.0, certain pregnancy outcomes also must be reported as adverse events and expedited adverse events (see protocol Section 8 and 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.

All study sites are strongly encouraged to use a pregnancy management worksheet similar to the sample in Section Appendix 6-1 to ensure proper management and documentation of pregnancies and timely discontinuation and resumption (if applicable) of study product use. The sample worksheet is available as a separate electronic file in the Study Implementation Materials section of the MTN-003 web page.

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

Refer to protocol Sections 7.6.2 and 9.11.

Study product use must be held for participants who develop signs or symptoms of clinical hepatitis during study follow-up. Participants with such signs or symptoms should be tested for hepatitis, including serology for HBsAg, and any other testing consistent with local standard of care. Site pharmacy staff should be informed of the product hold in writing, using the Study Product Request Slip, and a Product Hold/Discontinuation Log form should be completed and faxed to the MTN SDMC.

If the participant has any unused study product in her possession at the time when product use is held, the IoR or designee should determine whether collection of the remaining product is required per protocol Section 6.6. Specifically, if the period of product hold is expected to extend for seven days or more, based on the expected turnaround time for receipt of Hepatitis B serology results at the site clinic, all product should be retrieved within seven working days. If all product cannot be retrieved within seven working days, the PSRT must be informed.

Study product use must be permanently discontinued for participants with confirmed acute or chronic active Hepatitis B infection. Participants with confirmed infection will be clinically managed or referred for clinical management according to local standard of care. In addition, participants with confirmed infection who are assigned to oral study product must undergo AST and ALT testing one, two, and three months following discontinuation of product use. The IoR or designee may consult with the PSRT on any questions or concerns related to discontinuation of product use or other aspects of clinical management of participants with Hepatitis B.

Clinic staff should inform pharmacy staff of the permanent discontinuation of study product in writing, using the Study Product Request Slip, and should complete and fax a Product Hold/Discontinuation Log form to the MTN SDMC. If the participant has any unused study product in her possession at the time when product use is permanently discontinued, all product should be retrieved within five working days. If all product cannot be retrieved within five working days, the PSRT must be informed.

Following permanent discontinuation of study product use, participants will not receive product use instructions or adherence counseling. In addition, administration of their behavioral/adherence questionnaires — both interviewer-administered CRFs and ACASI — will be tailored, per guidance in the Data Collection Section (SSP Section 14.5-“When to Skip Product Adherence Questions”) and ACASI Manual (SSP Section 16, Appendix F).

6.10 Modified Follow-up Procedures for Participants Who Become Infected with HIV

Refer to protocol Sections 7.6.1 and 9.10.

Study product use must be held immediately for participants with at least one positive rapid HIV test result (this includes participants with discordant rapid results from the same visit). Clinic staff should inform pharmacy staff of the product hold in writing, using a Study Product Request Slip, and should complete and fax a Product Hold/Discontinuation Log form (with item 2 marked “HIV positive result”) to the MTN SDMC. If the participant has any unused study product in her possession at the time when product use is held, all product should be retrieved within 24 hours. If all product cannot be retrieved within 24 hours, the PSRT must be informed.

- For participants in who are later confirmed HIV-**un**infected per the algorithm in protocol Appendix III, product use should be resumed (unless another contraindication to study product use is present). Clinic staff should inform pharmacy staff of the resumption in writing, using a study Product Request Slip signed by an authorized prescriber. Clinic staff should also update the Product Hold/Discontinuation Log form to document resumption of product use, then re-fax the form to the MTN SDMC. If the IoR or designee is concerned that product use should not be resumed, he/she should immediately consult with the PSRT.

- For participants in whom HIV infection is confirmed per the algorithm in protocol Appendix III, product use must be permanently discontinued. Clinic staff should inform pharmacy staff of the permanent discontinuation in writing, using the Study Product Request Slip. Clinic staff should also update the Product Hold/Discontinuation Log form to document the permanent discontinuation and date of permanent discontinuation (i.e., the date site staff informed the participant that her HIV infection was confirmed), then re-fax the form to the MTN SDMC. The PSRT does not need to be notified

Participants with confirmed HIV infection will be offered the option to continue follow-up in MTN-003 per their original study follow-up schedule until their original study exit date. They also will be referred to MTN-015. Participants may be informed about MTN-015 when they are informed of their Sample 1 WB or viral load results that indicate HIV infection, but they should not be actively referred for screening and enrollment in MTN-015 until HIV infection is fully confirmed per the algorithm in protocol Appendix III. All discussions with participants related to ongoing participation in MTN-003, and potential participation in MTN-015, must be fully documented in participant study records.

All participants with confirmed HIV infection will be counseled and actively referred to available sources of medical and psychosocial care and support, per site SOPs. Site staff will actively follow-up on all referrals at each subsequent follow-up visit to determine if the participant actually sought the care to which she was referred, the outcome of the referral, and whether additional referrals are needed. All referrals, outcomes, and follow-up plans and actions must be fully documented in participant study records.

For participants that have completed all required testing per the HIV testing algorithm (protocol appendix III) and have been determined to be HIV-infected per testing at the local lab, all protocol-specified study procedures will continue, with the following exceptions:

- HIV serology and PBMC (at participating sites) will not be performed.
- Product use instructions and adherence counseling will not be provided.
- Administration of behavioral/adherence CRFs will be tailored, per guidance in the Data Collection Section (SSP Section 14.5-“When to Skip Product Adherence Questions”)
- ACASI surveys will no longer be administered.
- HIV/STI counseling will be tailored to primary (STI) and secondary (HIV) prevention for infected women.
- Last dose recall at Quarterly visits is not done.
- Vaginal fluid swabs (for dried smear for Gram stain assessment at MTN NL) are not collected.
- Following a final test eight weeks after initiation of product hold, the following tests will no longer be completed:
 - Complete blood count with differential and platelets
 - Phosphate, creatinine, AST and ALT
 - Dipstick urinalysis for protein and glucose
- Plasma archive at Quarterly visits and PUEV.

Note: The final test eight weeks after product hold is intended to be conducted during the participant’s scheduled VOICE study visit that occurs approximately two months after initiation of product hold. If the participant does not present to the site for this visit, she should be called and scheduled to come to the clinic as soon as possible

(within two calendar weeks) to collect these safety confirmatory labs. If these procedures cannot be collected within two weeks following the 8-weeks post-seroconversion timeframe, sites should document their efforts to bring the participant back to the clinic within this timeframe and efforts to collect these samples can be stopped. These labs should be collected eight weeks post-seroconversion, even if they were collected the previous month during a quarterly visit. For example, if the participant has her first rapid positive result for HIV at her Month 5 study visit (i.e., her date of seroconversion), her confirmatory labs should be collected eight weeks after product hold at her Month 7 study visit. Sites should consult the PSRT with any questions or concerns regarding these procedures.

As described below, HBsAb testing may be clinically indicated for HIV-infected participants.

For participants who choose to continue follow-up in MTN-003, but decline or defer enrollment in MTN-015, the following additional procedures will be completed as part of MTN-003:

- CD4+ T cell count
- HIV-1 RNA PCR
- Plasma archive

Each of the above procedures will be performed approximately 1, 3, and 6 months following the participant's date of seroconversion, and every six months thereafter for the duration of the participant's study follow-up, with the date of seroconversion defined as the specimen collection date for Sample 1 in the algorithm in protocol Appendix III. Sites are expected to collect the participant's 1-month post-seroconversion specimens, within the -14 days/+13 days window (ideally, on the target date) of the next regularly scheduled study visit following the date of seroconversion. For example, if a participant seroconverts at Month 6 (meaning, she is confirmed HIV-infected per the protocol algorithm, and Sample 1 was collected as part of Month 6 visit procedures), then her 1-month post-seroconversion specimen collection should occur within the window of the Month 7 Visit. For the 1-month post-seroconversion specimens only, the target date for specimen collection is dependent on the regularly scheduled visit windows, and not the date of seroconversion. If a participant's HIV status is not confirmed, per the protocol algorithm, until after the 1-month post-seroconversion window has passed, then the 1-month post-seroconversion specimen collection may be omitted (per protocol Section 7.6.1).

The target dates and visit windows for subsequent post-seroconversion specimen collections (3-months, 6-months, and every 6 months thereafter post-seroconversion) match the MTN-015 visit window schedule, allowing for greater flexibility and consistency with the MTN-015 protocol. See Figure 6-8 below for details on target dates and visit windows for post-seroconversion specimen collections. Ideally, sites will conduct post-seroconversion specimen collections within the context of regularly scheduled MTN-003 visits; however if sites prefer to utilize the larger MTN-015 visit windows, they should reference the on-line MTN-015 SSP Manual (<http://www.mtnstopshiv.org/node/467>) and utilize the MTN-015 visit window calculator (<http://www.mtnstopshiv.org/node/468>).

If a participant enrolls in MTN-015, all of her subsequent post-seroconversion specimen collections will occur in the context of regular MTN-015 study procedures. These post-seroconversion specimen collections will be discontinued in VOICE.

Figure 6-8
Visit Windows for HIV Post-Seroconversion Specimen Collections in VOICE

Specimen Collections	Window Opens	Target Date	Window Closes
1 month post-seroconversion	-14 days from target date of next regularly scheduled visit after first rapid HIV test	Target date of next regularly scheduled visit after first rapid HIV test	+13 days from target date of next regularly scheduled visit after first rapid HIV test
3 months post-seroconversion	61 days following first rapid HIV test	90 days following first rapid HIV test	136 days following first rapid HIV test
6 months post-seroconversion	137 days following first rapid HIV test	182 days following first rapid HIV test	273 days following first rapid HIV test
12 months post-seroconversion	274 days following first rapid HIV test	365 days following first rapid HIV test	456 days following first rapid HIV test
18 months post-seroconversion	457 days following first rapid HIV test	548 days following first rapid HIV test	639 days following first rapid HIV test
24 months post-seroconversion	640 days following first rapid HIV test	730 days following first rapid HIV test	821 days following first rapid HIV test
30 months post-seroconversion	822 days following first rapid HIV test	913 days following first rapid HIV test	1,004 days following first rapid HIV test
36 months post-seroconversion	1,005 days following first rapid HIV test	1,095 days following first rapid HIV test	1,186 days following first rapid HIV test

Approximately 20 mL of blood will be required at each time point (site-specific volumes to be confirmed with the MTN NL). Study sites will be responsible for calculating the above-listed time points for each participant, in addition to the participant's MTN-003 target visit dates, and collecting the required specimens when applicable. Archived plasma will be shipped to the MTN NL on a schedule to be determined by the NL and utilized for HIV confirmatory testing, HIV resistance testing and testing for tenofovir and emtricitabine levels. Archived plasma also may be used for long-term storage and possible future research testing if the participant has consented to this.

In addition to the above, Hepatitis B surface antibody (HBsAb) testing should be performed for seroconverters who receive, or have previously received, the Hepatitis B vaccine series. The purpose of this testing is to assess the participant's immune response to the vaccine and determine whether repeating the vaccine series may be needed to elicit an adequate immune response. For this purpose, quantitative testing is required, which differs from the qualitative testing performed as part of the study screening process.

- Perform HBsAb testing 1-2 months after completion of the vaccine series; if seroconversion occurs more than 2 months after completing the vaccine series, perform HBsAb once seroconversion is confirmed;
- Participants whose HBsAb levels are lower than 10 mIU/mL should receive another three-dose course of vaccinations. HBsAb testing should be repeated once more 1-2 months after the completion of this second vaccination series. If the HBsAb levels remain lower than 10 mIU/mL, a third vaccination course is not indicated. Rather, the participant will be assumed to be susceptible to Hepatitis B.
- Participants whose HBsAb levels are ≥ 10 mIU/mL do not require revaccination
- If additional guidance is needed regarding repeat vaccination, contact the PSRT

**Collection of Peripheral Blood Mononuclear Cells (PBMCs) for PK analysis for
Participants Who Become Infected with HIV
[Under Protocol Version 2.0, Letter of Amendment (LoA) #01]**

NOTES: Collection of PBMCs for PK analysis will take place only at selected sites. Prior to implementation of this procedure, sites must obtain approval from the NL. PBMC samples will be collected only on consenting participants.

Upon approval from NL, sites conducting collection of PBMC will:

- Determine which participants have provided informed consent for collection of PBMCs.
- Participants will have PBMC collected at the same visit as their first dual positive HIV rapid tests.
- If PBMC collection does not occur at the same visit as the dual positive rapid tests, sites should schedule the participant to return to the clinic for PBMC collection, ideally, within 1 calendar week but with an allowable window of 2 calendar weeks.
- If PBMC collection does not occur within this timeframe, sites will omit PBMC collection for this participant but continue all attempts to complete the HIV testing algorithm and collect additional seroconverter specimens as required per protocol.
- For sites not utilizing fingerstick rapid HIV testing: Sample 1, Sample 2 and PBMC should be collected at the same visit as the dual positive rapid tests.
 - When Sample 1 and Sample 2 are collected at the same visit, these must be collected from two completely separate venous draws.
 - Clinics should specify to processing laboratories that two Western Blots are being requested on the same participant on the same day.
- For sites utilizing fingerstick rapid HIV testing: Sample 1 and PBMC should be collected at the same visit as the dual positive rapid tests. Sample 2 collection should occur as soon as possible.

Note: Participants who are permanently discontinued from study product use due to HIV seroconversion should discontinue further PBMC collections once PBMC are collected at the visit with dual positive rapid test results.

6.11 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-003 study management team and the DAIDS Protocol Pharmacist. After the logistical details of the transfer have been discussed and agreed upon by the two sites, the following steps will be completed:

- The MTN 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 certified 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 fax a Participant Transfer case report form to the MTN SDMC (see Section 14 of this manual).
- The receiving site will establish contact with the participant, obtain her written informed consent to continue in the study at the receiving site (using the receiving site’s informed consent form), and complete and fax the Participant Receipt case report form to the MTN SDMC (see Section 14 of this manual).
- Upon receipt of the Participant Transfer and Participant Receipt forms, the MTN SDMC will re-map the participant’s 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.

- An authorized prescriber at the receiving site will be required to prepare an original signed and dated note to pharmacy staff at the receiving site 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 study product use per the MTN-003 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 MTN-003 Study Product Request Slip, pharmacy staff at the receiving site will dispense study product 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 MTN NL, if applicable, of all specimens collected from the participant prior to her transfer, unless otherwise instructed by the MTN NL.

6.12 Early Terminations Prior to the Expected PUEV

A participant may choose to withdraw consent from the study and terminate early during her expected study product use period (that is, prior to when she was expected to permanently discontinue product use). In these cases, site staff should ask the participant if she would be willing to complete one final study visit, which would count as her Product Use End Visit (PUEV). If she is willing, site staff should conduct all required Product Use End Visit procedures at this final visit and complete all required CRFs for the Product Use End Visit, as listed in SSP Table 14-3. In addition, site staff should complete the Study Exit Visit CRF, Termination CRF, and the End of Study Inventory CRF. If the participant is not willing to complete one final study visit, site staff should complete the following CRFs: Perceived Product Assessment, Product Use End Visit, Study Exit Visit, Termination, and End of Study Inventory. No other CRFs should be completed. When completing the Termination form, mark item 2c "participant refused further participation, specify" as the reason for termination. This reason applies, regardless of whether the participant is able to complete a final study visit (PUEV). It also applies to cases where a participant is terminating early due to her male partner/husband's disapproval of her study participation.

Regardless of whether or not the participant agrees to complete the early PUEV, the Study Exit/Termination Visit (expected 8 weeks after the PUEV) and all associated procedures will not be done and will be considered missed.

Site staff should ask the participant for permission to contact her in 1-3 months to see if her situation may have changed and she would like to consider rejoining the study. Consent to contact the participant in the future should be clearly documented in the chart.

6.12.1 Early Terminations After the PUEV

A participant may complete her PUEV and then either decide to terminate early from the study, or become lost to follow-up. In both cases, the Study Exit/Termination Visit will be missed. Site staff should complete the following CRFs: Study Exit Visit, Termination, and End of Study Inventory. No other CRFs should be completed for the missing Study Exit Visit/Termination Visit.

6.13 Resumption of Study Participation After Voluntary Withdrawal

As noted in Protocol Section 9.14, regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study at any time. The protocol also allows, however, for participants who voluntarily withdraw from the study to reverse their decision and resume product use and follow-up through their originally scheduled study exit date, pending consultation with the MTN SDMC and PSRT. If such cases arise, study staff should contact the MTN-003 study management team 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 apply:

- Prior to performing any study procedure, the participant must provide written informed consent to document that she voluntarily rejoined the study. For re-consenting procedures, refer to Section 5.3.1 of this study manual.
- 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, pregnancy and HIV testing should be performed, and a pelvic exam should be performed. Among participants not previously vaccinated against Hepatitis B, rescreening for both Hepatitis B surface antigen (HBsAg) and Hepatitis B surface antibodies (HBsAb) should be performed. Other procedures also should be performed if required per the guidance in Section 6.3.4 of this manual.
- Study product use may be resumed only among participants who are HIV-uninfected, HBsAg negative, not currently pregnant or breastfeeding, and who do not have any other contraindications to product use per protocol Section 9.
- After the above procedures are performed, the IoR or designee should include the results and findings of these procedures, and any other relevant participant history information, in a PSRT query form, and should submit the form to request PSRT consultation on resumption of product use.
- If resumption of study product use is endorsed by the MTN SDMC and PSRT, site clinic staff will communicate this decision to site pharmacy staff in writing, using the Study Product Request Slip. A copy of the final PSRT query form should be filed in the participant's study notebook.
- Site staff should thoroughly document, in the participant's chart notes, her resumption of study follow-up and study product use.

6.14 Study Exit Considerations

The VOICE protocol specifies that each enrolled participant is expected to have a minimum of 12 and a maximum of 36 months of study product use. Each participant will have an additional approximate 8 weeks of follow-up off study product to identify potential delayed seroconversions due to masked infections that are not detected during the product use period. As of the version date of this section, the Protocol Team has set a study end date of August 13, 2012. This means that no VOICE study visits will occur after this date. Operational plans for study close-out are presented in the remainder of this section. Figure 6-9 presents an overview of the study close-out plan.

Figure 6-9
Study Close-Out Plan for Oral Truvada/Placebo Participants
To Be Implemented Starting 1 February 2012



Note: For participants with Month 15 Target Visit Dates on or prior to 31 May 2012, no PUEV will take place before Month 15.

This closeout plan applies to only participants assigned to the oral Truvada and oral placebo groups. Participants assigned to oral tenofovir or to the gel groups have separate study exit guidelines based on the September 2011 and November 2011 DSMB reviews, respectively.

Beginning Wednesday, 1 February 2012, conduct product use end visits (PUEVs) and Study Exit/Termination visits (SEVs) according to the following guidelines:

1. For participants whose Month 15 visit target date falls on or before 31 May 2012: schedule and conduct a PUEV at the participant's Month 15 visit, or at her next regularly scheduled quarterly, semi-annual, or annual visit, (that is, Month 18, 21, 24, 27, 30, 33, or 36), whichever is next. For this group of participants, PUEVs should not occur before the Month 15 study visit. For example, if a participant presents to the clinic for her Month 12 visit on 1 February 2012 and her Month 15 target date is 25 April 2012, schedule and complete her PUEV at Month 15. If a participant presents to the clinic for her Month 15 visit on 1 February 2012, conduct a PUEV at that time. If a participant already completed her Month 15 visit prior to 1 February 2012, conduct her PUEV at her next quarterly, semiannual, or annual visit, whichever is next (after 1 February 2012).

SCHARP can provide a listing of the PTIDs that meet these criteria to each site as needed.

2. For participants whose **Month 15** visit target date is **on or after 1 June 2012**, schedule and conduct the PUEV at the participant's scheduled Month 13 visit. This affects those participants enrolled on or after April 8, 2011.

SCHARP can provide a listing of the PTIDs that meet these criteria to each site as needed.

3. Based on the date of the last participant enrolled (= 7 June 2011), the last possible date to complete any remaining VOICE study visits (PUEV or SEV) is 13 August 2012.
 - a. In order to be able to complete the SEV 8 weeks after the PUEV, the last optimal date to complete a PUEV is 18 June 2012. PUEVs completed after 18 June 2012 will have SEVs completed less than 8 weeks after the PUEV. This is acceptable, but not ideal. Every effort should be made to conduct all PUEVs by 18 June 2012.
4. Any participants who have not completed the SEV by 13 August 2012 should be terminated from the study. The reason for termination documented on the Termination CRF should be something other than "scheduled study exit".
 - a. If the participant did not complete the PUEV and the SEV, complete the following CRFs to document that both visits were missed: Perceived Product Assessment, Product Use End Visit, Study Exit Visit, Termination, and End of Study Inventory. No other CRFs should be completed including the Missed Visit CRF.
 - b. If the participant completed the PUEV but not the SEV, complete the following CRFs to document the missed SEV: Study Exit Visit, Termination, and End of Study Inventory. No other CRFs should be completed including the Missed Visit CRF. On the Study Exit Visit CRF, mark item 1 "no", since the participant was not able to complete her SEV 8 weeks after the PUEV.

6.14.1 PUEV Visit Windows and Visit Codes

The visit code, target date, and visit windows for the PUEV will vary based on the visit window in which the PUEV is conducted. See SSP Section 14 and the "Guidance on VOICE PUEV" document for additional information on PUEV visit codes and visit windows.

If a participant misses her scheduled PUEV, complete the PUEV the next time the participant reports to the clinic. Assign the PUEV the regular visit code (not interim) associated with the visit window in which the PUEV is done.

6.14.2 Study Exit Visit (SEV) Windows and Visit Codes

For each participant(excluding confirmed seroconverters), the SEV should be completed approximately 8 weeks (56 days) after completion of the PUEV.

Every effort should be made to complete Study Exit/Termination visits on the target date or, if not possible, soon after the target date. The allowable Study Exit/Termination visit window is 14 days prior to the target date through the study end date (13 August 2012). Regardless of when the Study Exit/Termination visit is completed, the visit is assigned a visit code of 89.0. For complete details on visit scheduling, target dates, and visit windows, see SSP Section 14.

Please contact the MTN-003 Management Team with any questions regarding study exit visit scheduling, procedures, visit codes, and case report form completion.

6.14.3 Split PUEV and Study Exit/Termination Visits

The PUEV can be conducted as a split visit over multiple days (e.g., if a participant is on menses and would like to delay the pelvic exam until after menses). **HIV testing (for non-seroconverters) must occur during the first part of the visit, if the PUEV is split.** Study procedures completed during the first part of the PUEV should not be completed during the second part of the visit, as long as the second part of the visit falls within the same visit window. Interviewer-administered CRFs and ACASI questionnaires must be completed on the same day. As with other split visits, assign the same PUEV visit code to all procedures/CRFs completed as part of the PUEV.

If the PUEV is split, ideally all PUEV visit procedures will take place within the PUEV visit window. However, if absolutely necessary, PUEV procedures may be completed outside of the visit window – until the SEV window opens. Please note that this is an exception made exclusively for the PUEV only, given its importance to the data analysis. Alert SCHARP if this occurs, so SCHARP can exclude any visit window QCs as needed.

Study Exit/Termination visits may also 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 the study end date (13 August 2012). Every effort should be made to complete all required study exit procedures with all participants who do not terminate early. 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 the study end date, whichever comes first. Document all efforts to complete all required study exit procedures.

6.14.4 Product Discontinuation

All participants are discontinued from product use at their PUEV visits, if not already discontinued prior to this date for safety reasons. Therefore, all unused product supplies should be collected from the participant and returned to the study pharmacy on the day of the PUEV. If participants do not return unused product at the PUEV, study staff must arrange to retrieve the product within 2 business days. Note: Per LoA #02, study staff must arrange to retrieve the product within 7 business days. If the study product is not retrieved within the required days, the MTN-003 PSRT must be informed. When informing the PSRT, please describe the reason for the product discontinuation (i.e., study exit), actions taken to try to collect the unused study product, and plans and timelines for further action to collect the study product.

6.14.5 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 MTN-003 web page:

<http://www.mtnstopshiv.org/node/737>

As with all written documentation provided to participants, certificates must be approved by site IRBs/ECs prior to use, in accordance with GCP guidelines.

6.14.6 Participant Locator Information

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. Post-study contacts are discussed in more detail in Section 6.14.12.

6.14.7 Final Study Contacts

Although the Study Exit/Termination visit is the last scheduled study visit, a final contact is required after this 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, indeterminate, or discordant HIV rapid or Western Blot test results (see Section 6.14.8 below)
- Participants with certain types of AEs that are ongoing at study exit (see Section 6.14.10 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, at community-based locations, or at the participant home if given permission, 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 6-2.

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

6.14.8 HIV Counseling and Testing

HIV testing is performed at the Study Exit/Termination visit per the algorithm in Protocol Appendix III. 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.

6.14.9 Plasma Archive

Approximately 10mL of (EDTA) anticoagulated whole blood should be collected for plasma archive at the Study Exit/Termination visit (see Section 13.6.7 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. Study staff must notify the MTN NL in the event that at least 4 mL of plasma are not archived at each Study Exit/Termination visit.

6.14.10 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the Study Exit/Termination visit and updated as needed. For reportable AEs that are ongoing at the Study Exit/Termination 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. AE Log forms should not be updated with new information based on changes that occur after the Study Exit/Termination Visit. Rather, this information should be recorded in the participant’s chart notes only.

For any AEs that have increased in severity at the Study Exit/Termination visit, or serious/expedited AEs (SAEs/EAEs) that are continuing at a participant’s Study Exit/Termination visit, the IoR/designee must establish a clinically appropriate follow-up plan for the AE (see Section 11 of this manual for more information on AEs/SAEs/ EAEs). At a minimum, the AE must be re-assessed by study staff within 30 days after the participant’s Study Exit/Termination visit; additional evaluations also may take place at the discretion of the IoR/designee. In addition, the PSRT is requesting that any new or ongoing Grade 3 or Grade 4 AEs (regardless of relationship to study product) present at the study exit/termination visit should be included in this group and reassessed within 30 days after the participant’s Study Exit/Termination visit.

For those AEs requiring re-assessment, the site should send an informational query regarding the case to the PSRT at the time of re-assessment (or if re-assessment is unable to be performed in a timely fashion). If the AE has not resolved or stabilized at the time of reassessment, 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 (those that have not resolved or stabilized) will be re-assessed at least once within 30-60 days after the study end date. The MTN-003 PSRT also may advise on whether any additional follow-up is indicated on a case by case basis. Document all efforts to complete all required re-assessments in the participant’s chart notes.

For AEs that are continuing at the study exit/termination visit but do not meet the criteria above, it is left to the discretion of the IoR or designee as to whether the AE needs to be followed. The PSRT is always available for consultation.

Note: after a participant’s Study Exit/Termination visit, all pregnancies must continue to be followed until an outcome is ascertained. Once the site receives the outcome information, this should be submitted on a Pregnancy Outcome CRF to DataFax.

For AEs that are re-assessed after the termination visit, information on the status of the AE at the time of re-assessment will be recorded in source documents and may be communicated to the PSRT, if applicable; however, no updates should be made to any case report forms based on the re-assessments. Please note, with the exception of the Pregnancy Outcome form, no CRFs should be submitted to SCHARP after the termination visit.

6.14.11 Referral to Non-Study Service Providers

After completing their Study Exit/Termination 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/Termination 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/Termination 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 6-3.

6.14.12 Post-Study Contacts

All participants will be contacted post-study to be informed of the study results and their random assignments (if not done already, per guidance based on previous DSMB reviews). It is currently expected that study results and any additional unblinding information will be available within one year after the study end date.

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 6-2.

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 studies be documented on a study exit worksheet. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs similar to the examples provided in Section Appendices 6-4 and 6-5.

Section Appendix 6-1 Sample Pregnancy Management Worksheet

PTID			
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		Initial and Date When Done	Comments
1	Product use HELD: participant instructed to stop using product		
2	Study Product Request Slip marked HOLD completed and delivered to pharmacy		
3	Product retrieved from participant <i>(NA if no product left to retrieve)</i>		
4	Pregnancy Report and History form completed and faxed		
5	Product Hold/Discontinuation Log form (items 1-3) completed and faxed		
6	Participant referred to antenatal care		
7	Participant referred to MTN-016		
8	Pregnancy outcome determined, based on: <input type="checkbox"/> Medical records or other written documentation from licensed practitioner <i>(obtain whenever possible)</i> <input type="checkbox"/> Participant self-report <input type="checkbox"/> Negative pregnancy test performed by study staff <input type="checkbox"/> Other <i>(specify in comments)</i>		
9	Pregnancy Outcome form completed and faxed		
10	AE Log form completed and faxed <i>(NA if pregnancy outcome not a reportable AE)</i>		
11	EAE Report completed and submitted <i>(NA if pregnancy outcome not an EAE)</i>		
12	Contraception counseling provided		
13	Participant counseled to breastfeed per current WHO guidelines <i>(NA if ppt did not give birth)</i>		
14	Confirmed complete cessation of breastfeeding <i>(NA if ppt did not give birth)</i>		
15	Pelvic exam done confirming absence of contraindications to gel use <i>(NA if ppt assigned to oral tablets)</i>		
16	If applicable, product use RESUMED: participant instructed to use product		
17	Study Product Request Slip marked RESUME completed and delivered to pharmacy <i>(NA if product use not resumed)</i>		
18	Product Hold/Discontinuation Log form updated (item 4) and faxed		
<p>Operational Guidance for Product Resumption: Refer to protocol Sections 7.6.3 and 9.12 and SSP Section 6.8. Participants may resume product use as of the date of their first negative pregnancy test performed by study staff, provided they are not breastfeeding. Additionally for participants assigned to gel, a pelvic exam must be performed prior to resumption to confirm the absence of any findings that would contraindicate resumption. All participants who give birth must be counseled to breastfeed per current WHO guidelines. In general, it is expected that product hold will continue for at least six months of breastfeeding; however, in many setting the recommended duration of breastfeeding will be longer than six months and product hold should continue for as long as the participant is breastfeeding. Consult the PSRT with any questions on resumption of product use.</p>			

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**Section Appendix 6-2
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 the participant have positive, indeterminate, or discordant rapid HIV tests?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for follow-up HIV counseling and testing:	
IoR approval: _____ <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	
Other? Include any other relevant information related to this participant.	
Staff Signature and Date:	

Section Appendix 6-3 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:

- 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 6-12 months to determine the results of the study. At that time, we will also learn which participants received which study product in the study. In order for us to share the results of the study with you and tell you which gel or tablet 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.*
- *If applicable, reinforce plans for follow-up HIV counseling and testing.*
- 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 and/or MTN-016.*
- 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.

Section Appendix 6-6
MTN-003 Hair Collection Instructions

Materials required:

- ✓ Hair scissors
- ✓ Piece of tin/aluminum foil
- ✓ PTID labels (2)
- ✓ Re-closable plastic bag
- ✓ Alcohol swabs
- ✓ Desiccant pellets
- ✓ Hand Sanitizer
- ✓ Hair Sample Collection CRF



Step 1: Clean the scissors blades with an alcohol swab and allow blades to completely dry



Step 2: Lift up the top layer of hair from the occipital region of the scalp. A hair clip (or an assistant's fingers) can be used to keep this top layer out of the way. Isolate a small thatch of hair (~100 fibers of hair) from underneath this top layer

Step 3: Cut the small hair sample as close to the scalp as possible



Step 4: Keep your fingers on the part of the hair that was FURTHEST (distal end) away from the scalp and put the hair sample down on an unfolded piece of tin foil



Step 5: Put a PTID label over the end of the hair sample that was FURTHEST (distal end) away from the scalp. Try as MUCH as possible to tape the hair down to distinguish the proximal (closer to scalp) from the distal end (furthest from scalp).



Step 6: Refold the foil over to completely enclose the hair and place a second PTID label on the folded piece of foil



Step 7: Place the folded piece of foil inside the plastic (e.g. Ziplock®) bag (each bag will have a desiccant pellet) and seal the bag; record the time on the Hair Sample Collection CRF.



Storage: Hair samples should be securely stored at room temperature and in a dark place at each site prior to batch shipment (without biohazardous restrictions) to the UCSF hair laboratory.

NOTE: Very short hair may be collected in an envelope and then transferred to the foil.



NOTE: If hair is braided, sample from tufts of hair between the braids.



CURLY HAIR

