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 35 months, whichever occurs first. Within her 14-35 months of follow-up, each participant is expected to complete a minimum of 12 months and a maximum of 33 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 annually. This annual target translates to the monthly 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 Retention Targets for MTN-003

Month of Study	Target % Retained	Month of Study	Target % Retained
1	99.58	19	92.08
2	99.17	20	91.67
3	98.75	21	91.25
4	98.33	22	90.83
5	97.92	23	90.42
6	97.50	24	90.00
7	97.08	25	89.58
8	96.67	26	89.17
9	96.25	27	88.75
10	95.83	28	88.33
11	95.42	29	87.92
12	95.00	30	87.50
13	94.58	31	87.08
14	94.17	32	86.67
15	93.75	33	86.25
16	93.33	34	85.83
17	92.92	35	85.42
18	92.50		

6.2 Types of Follow-up Visits

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

- Scheduled visits are those visits required per protocol. The 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 can not 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.

6.3.4 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 required to be performed at MTN-003 follow-up visits, all visits are expected to be completed at the study clinic.

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, 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 (i.e., per protocol Sections 9.5.3, 9.5.4, 9.5.6, 9.6, and/or 9.7). Specifically, dipstick urinalysis for protein and glucose, serum phosphate, serum creatinine, and calculated creatinine clearance rate should be performed:

    - Two weeks after product resumption
    - One month after product resumption
    - Two months after product resumption
    - Three months after product resumption

    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, 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 and when clinically indicated.
    - Rapid testing for bacterial vaginosis is performed only when clinically indicated.
    - Wet prep and microscopy are only used to assess for candidiasis (KOH prep only) and are performed only when clinically indicated (i.e., when 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.

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, 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 local testing stops. See Section 6.10 below for additional procedural requirements for participants with confirmed HIV infection.

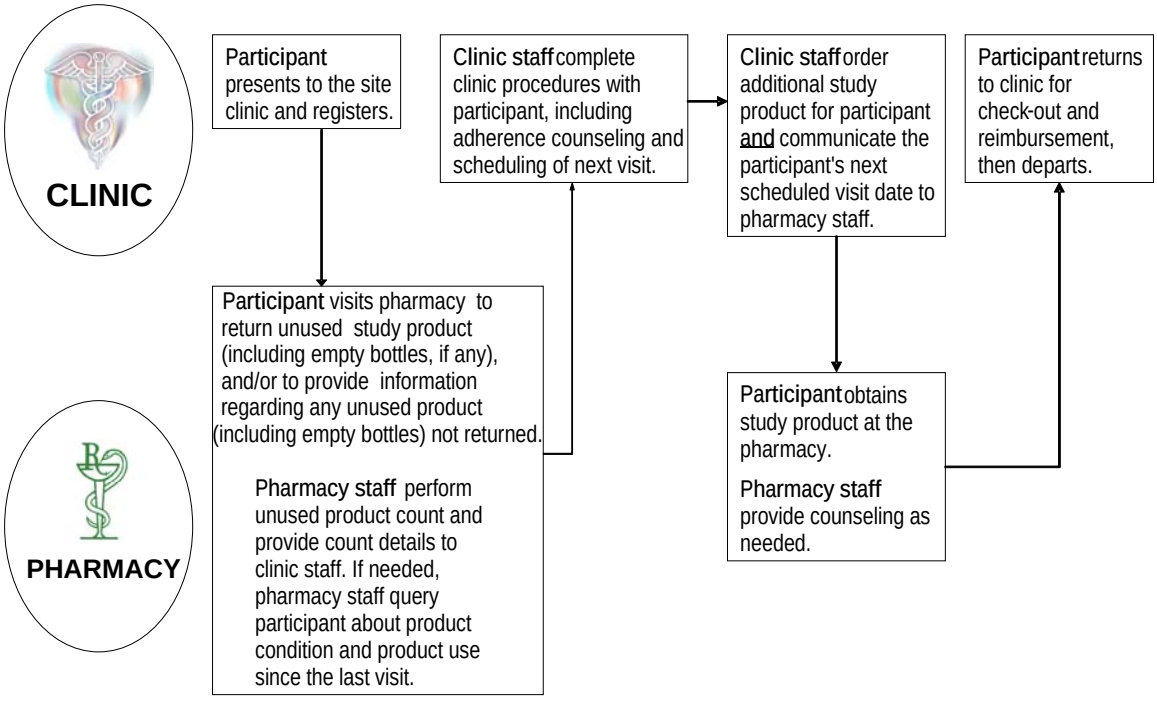
If the Sample 2 WB is negative or indeterminate, additional testing must be performed, possibly requiring additional sample collection. In this case, inform the MTN NL of all Sample 1 and Sample 2 test results (copying the study management team) and request NL input on next steps and timeframes for additional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

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 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.

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



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.

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 comment 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)

The site pharmacist should use the comments section of the slip to document any additional relevant information. 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.

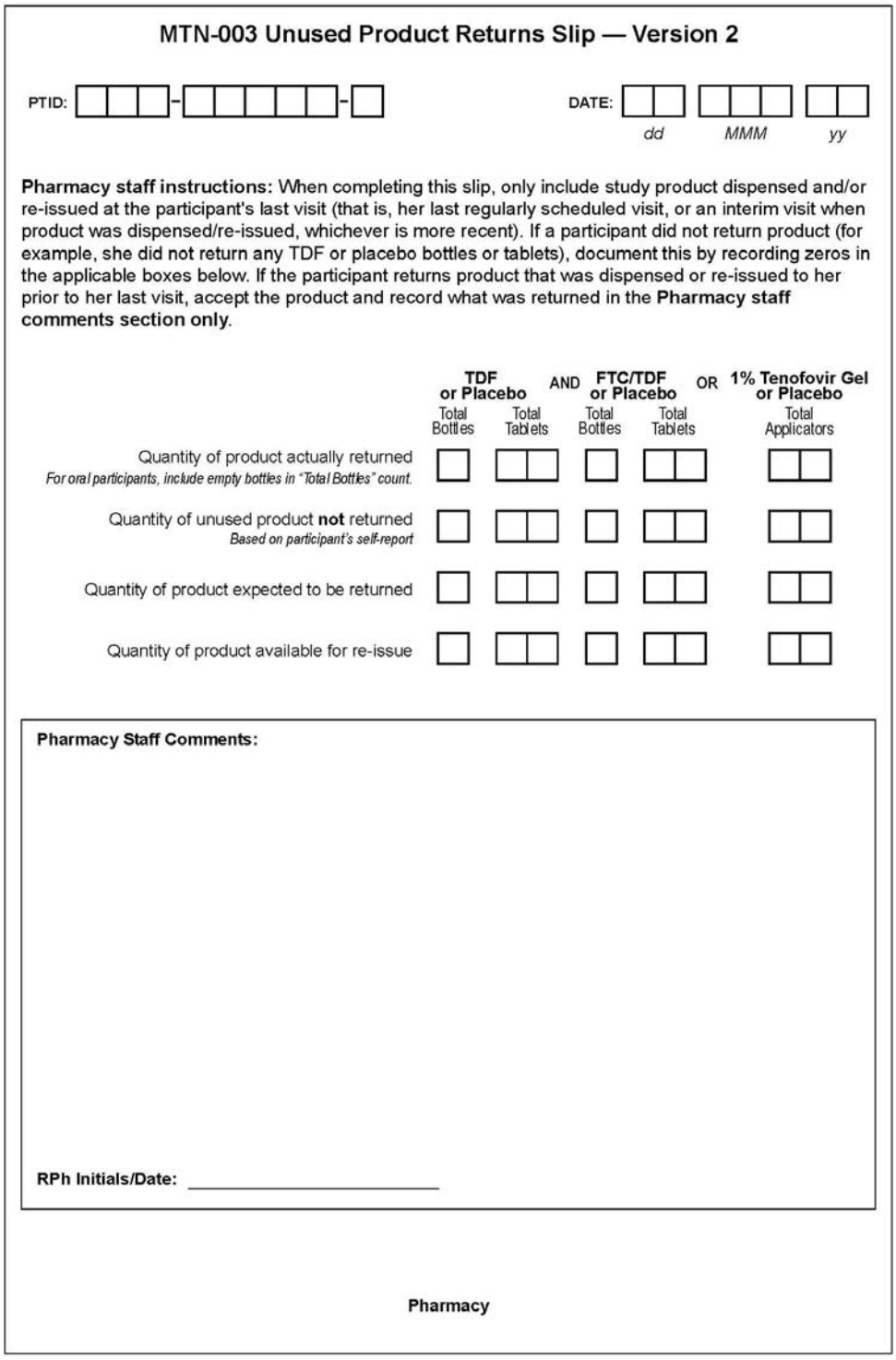
After completing the MTN-003 Unused Product Returns Slip-Version 2, pharmacy staff will separate the two parts of the slip and deliver the yellow copy to the clinic, where the information recorded on the slip will be used by clinic staff to guide:

- Study product adherence counseling that will be provided to the participant
- 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.

The white original of the slip will be retained in the site pharmacy.

Figure 6-6
MTN-003 Unused Product Returns Slip-Version 2



MTN-003 Unused Product Returns Slip — Version 2

PTID: ☐☐☐-☐☐☐☐☐-☐ DATE: ☐☐ (dd) ☐☐☐ (MMM) ☐☐ (yy)

Pharmacy staff instructions: When completing this slip, only include study product dispensed and/or re-issued at the participant's last visit (that is, her last regularly scheduled visit, or an interim visit when product was dispensed/re-issued, whichever is more recent). If a participant did not return product (for example, she did not return any TDF or placebo bottles or tablets), document this by recording zeros in the applicable boxes below. If the participant returns product that was dispensed or re-issued to her prior to her last visit, accept the product and record what was returned in the **Pharmacy staff comments section only**.

	TDF or Placebo		AND	**FTC/TDF or Placebo**		OR	**1% Tenofovir Gel or Placebo**
	Total Bottles	Total Tablets		Total Bottles	Total Tablets		Total Applicators
Quantity of product actually returned *For oral participants, include empty bottles in "Total Bottles" count.*	☐	☐☐		☐	☐☐		☐☐
Quantity of unused product **not** returned *Based on participant's self-report*	☐	☐☐		☐	☐☐		☐☐
Quantity of product expected to be returned	☐	☐☐		☐	☐☐		☐☐
Quantity of product available for re-issue	☐	☐☐		☐	☐☐		☐☐

Pharmacy Staff Comments:

RPh Initials/Date: _____

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 supply may be ordered and re-supplied. If a participant will miss two or more consecutive visits, such that she requires more than a 60-day supply of study product, approval from the DAIDS Medical Officer must be obtained prior to dispensing more than a 60-day supply. See Section 9 of this manual for further information on dispensing more than a 60-day 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: ☐☐–☐☐☐–☐☐ (*dd*–*MMM*–*yy*) Participant's next visit date: ☐☐–☐☐☐–☐☐ (*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: ☐☐ (*dd*) – ☐☐☐ (*MMM*) – ☐☐ (*yy*) Participant's next visit date: ☐☐ (*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. 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 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 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 study product.

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 positive rapid HIV test results. 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 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 whom HIV infection is not confirmed 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, then re-fax the form to the MTN SDMC.

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 who choose to continue follow-up in MTN-003, all protocol-specified study procedures will continue, with the following exceptions:

- HIV serology will not be performed.
- Product use instructions and adherence counseling will not be provided.
- Administration of 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 non-use of study product.
- HIV/STI counseling will be tailored to primary (STI) and secondary (HIV) prevention for infected women.

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 at 1, 3, and 6 months following the participant's date of seroconversion, and every six months thereafter, with the date of seroconversion defined as the specimen collection date for Sample 1 in the algorithm in protocol Appendix III. 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.

The MTN-003 protocol specifies that HBsAb testing be performed for seroconverters six months after completion of the Hepatitis B vaccine series; however, some clinical management guidelines, including the guidelines of the US Centers for Disease Control and Prevention, recommend testing 1-2 months after completion of the vaccine series. Until such time that this aspect of the MTN-003 protocol can be updated, study sites are advised to:

- Perform HBsAb testing 1-2 months after completion of the vaccine series;
- Inform the PSRT of the test results; and
- Seek PSRT guidance on whether additional HBsAb testing is clinically indicated at the six-month time point.

If the PSRT advises that additional HBsAb testing is not clinically indicated, no further testing is required. The PSRT also may be consulted on when repeat courses of the Hepatitis B vaccine series are warranted. In general, participants whose HBsAb levels are lower than 10 mIU/mL should receive another three-dose course of vaccinations.

Note: The above guidance related to HBsAb testing assumes that HIV seroconversion is identified either before completion of the Hepatitis B vaccine series or within 1-2 months after completion of the vaccine series. If this is not the case, i.e., if HIV seroconversion is identified more than two months after completion of the Hepatitis B vaccine series, HBsAb testing is still clinically indicated to assess the participant's immune response to the vaccine series.

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.

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 missing. 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 sections 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.

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 *(NA if no product left to retrieve)*		
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: ❒ Medical records or other written documentation from licensed practitioner *(obtain whenever possible)* ❒ Participant self-report ❒ Negative pregnancy test performed by study staff ❒ Other *(specify in comments)*		
9	Pregnancy Outcome form completed and faxed		
10	AE Log form completed and faxed *(NA if pregnancy outcome not a reportable AE)*		
11	EAE Report completed and submitted *(NA if pregnancy outcome not an EAE)*		
12	Contraception counseling provided		
13	Participant counseled to breastfeed per current WHO guidelines *(NA if ppt did not give birth)*		
14	Confirmed complete cessation of breastfeeding *(NA if ppt did not give birth)*		
15	Pelvic exam done confirming absence of contraindications to gel use *(NA if ppt assigned to oral tablets)*		
16	If applicable, product use RESUMED: participant instructed to use product		
17	Study Product Request Slip marked RESUME completed and delivered to pharmacy *(NA if product use not resumed)*		
18	Product Hold/Discontinuation Log form updated (item 4) and faxed		

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.

Final Version 1.0, 7 August 2009