

Section 6. Participant Follow-up

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

6.1 Study Follow-up Plan and Participant Retention Targets

Each enrolled participant will be followed through twenty-one weeks post her enrollment date. The target accrual is expected to be completed within six months of study activation at each site. The protocol team will actively monitor and manage the study accrual process to ensure that the enrollment occurs within the specified timeframe.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of at least 95% for all enrolled study participants. Further information on MTN 001 retention definitions and procedures is provided in Section 8.

6.2 Types of Follow-up Visits

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

- **Scheduled visits** are those visits required per protocol. The protocol specifies that follow-up visits occur at: enrollment, 3-week, 6-week, 7-week, 10-week, 13-week, 14-week, 17-week, 20-week, and 21-week. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13.
- **Interim visits** are those visits that take place between scheduled visits. There are a number of reasons why interim visits may take place (see protocol Section 7.5). Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13.

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

6.3 Follow-up Visit Scheduling

6.3.1 Target Visit Dates

Enrolled participants will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, all follow-up visits are targeted to take place based on the participant's enrollment date. Each participant's enrollment date is defined as the date upon which she is assigned an MTN 001 Randomization Envelope or an MTN 001 Replacement Randomization Document (for replacement participants). For example, for a participant assigned a Randomization Envelope on 1 December, follow-up visits will be targeted to take place on 22 December, 12 January, 19 January, 9 February, 2 March, 9 March, 30 March, 20 April, and 27 April.

6.3.2 Allowable Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN 001 protocol allows for visits to be completed within a visit window. For each required study visit, there is an allowable visit window specifying on which study days (post-enrollment) the visit is "allowed" to be completed. The allowable visit windows are contiguous from visit to visit, and do not overlap. For example, a visit conducted on study day 38 is within the 6-Week visit allowable window (see figure 6-1).

Within each allowable visit window, there is a target visit window. The target visit window is the same for each visit, equal to +/- 3 days around the target visit date. For example, the target visit window for the 3-Week visit (target day 21) is day 18 to 24. Sites are encouraged to complete required study visits within the target window if at all possible. If it is not possible to complete the required visit within the target window, the visit may be completed within the allowable visit window. Visits completed outside of the target window but within the allowable visit window will be considered completed ("retained") visits, but they will be designated as being completed "early" or "late". For example, a 3-Week visit completed on day 25 will be listed as being completed "late" since it was completed outside of the target window. However, the participant is considered retained for the 3-Week visit since it was completed within the allowable window.

If the visit is not completed within the allowable visit window, the visit is considered "missed" and is documented using a Missed Visit case report form.

Note: During the "wash-out" periods (between the 6-Week and 7-week; 13-Week and 14-Week; and 20-Week and 21-Week visits), the allowable and target window dates are the same. For example, the 6-Week target and allowable windows both close on day 45. This is due to the short interval between these particular visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals, and every effort should be made to do so. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the weekly visit schedule (see Section 16).

Figure 6-1
MTN 001 Visit Windows

Visit	Visit Code	Window* Opens		Target Day	Window* Closes	
		Allowable	Target		Target	Allowable
Week 3	3.0	1	18	21	24	31
Week 6	4.0	32	39	42	45	45
Week 7	5.0	46	46	49	52	59
Week 10	6.0	60	67	70	73	80
Week 13	7.0	81	88	91	94	94
Week 14	8.0	95	95	98	101	108
Week 17	9.0	109	116	119	122	129
Week 20	10.0	130	137	140	143	143
Week 21	11.0	144	144	147	150	150

* All windows are listed in days

Figure 6-2
Example of Allowable Visit Windows for MTN 001

December-2008						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
	1 Enrollment Day	2 3W Allowable Window Opens	3	4	5	6
7	8	9	10	11	12	13
14	15	16	17	18	19 3W Target Window Opens	20
21	22 3W Target Day	23	24	25 3W Target Window Closes	26	27
28	29	30	31			
January-2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
				1 3W Allowable Window Closes	2 6W Allowable Window Opens	3
4	5	6	7	8	9 6W Target Window Opens	10
11	12 6W Target Day	13	14	15 6W Target and Allowable Window Closes	16 7W Allowable and Target Window Opens	17
18	19 7W Target Day	20	21	22 7W Target Window Closes	23	24
25	26	27	28	29 7W Allowable Window Closes	30 10W Allowable Window Opens	31
February-2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2	3	4	5	6 10W Target Window Opens	7
8	9 10W Target Day	10	11	12 10W Target Window Closes	13	14
15	16	17	18	19 10W Allowable Window Closes	20 13W Allowable Window Opens	21
22	23	24	25	26	27 13W Target Window Opens	28
March 2009						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
1	2 13W Target Day	3	4	5 13W Target and Allowable Window Closes	6 14W Allowable and Target Window Opens	7
8	9 14W Target Day	10	11	12 14W Target Window Closes	13	14
15	16	17	18	19 14W Allowable Window Closes	20	21
22	23	24	25	26	27	28
29	30	31				

3W = 3-Week Visit, 6W = 6-Week Visit, 7W = 7-Week Visit, 10W = 10-Week Visit, 13W = 13-Week Visit

6.3.3 Visits Conducted Over Multiple Days: “Split Visits”

All procedures specified by the protocol to be performed at a particular follow-up visit ideally will be completed at a single visit on a single day. In the event that all required procedures cannot be completed on a single day, (for example because the participant must leave the study site before all required procedures are performed), the remaining procedures may be completed on subsequent day(s) within the allowable visit window.

In the case of “end of study period” visits (6-Week, 13-Week, and 20-Week) when Pharmacokinetic (PK) procedures are conducted, every effort should be made to complete all PK procedures during this visit. These PK procedures may not be split over multiple days, meaning that all PK procedures must be completed on the same day. If a participant informs the staff that she will not be able to complete all required procedures during that visit and no PK procedures have been done, the participant can be rescheduled within the study window to complete the PK procedures. Since participants may not inform staff in a timely manner that they will not be able to complete procedures, they should be counseled about the importance of completing these procedures as scheduled. In addition, every effort should be made to schedule “end of study period” visits when the participant is not experiencing her menses. However, if the participant is on her menses, all PK procedures will be conducted, including collection of the Cervical Vaginal Lavage (CVL). There is not a need to reschedule a visit for PK procedures, including specimen collection, if a participant is on menses. As described in Section 13, all case report forms completed for a split visit are assigned the same visit code.

6.3.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable window, the visit will be considered “missed” and a Missed Visit case report form will be completed to document the missed visit (see Section 13). However, if a participant misses a “Study-Period Start” visit (7-Week and 14-Week), only the HIV counseling and testing procedures, and complete blood count testing, required at this missed visits must be conducted at the participants’ next visit. If the participant misses an “End of Study Period” visit (6-Week, 13-Week and 20-Week), only assessment of vaginal pH, and collection of vaginal fluid for wet mount required at the missed visit must be conducted at the participants’ next visit. For example, if a participant misses her 7-Week study visit and comes to the clinic when the window for the 10-Week visit has opened, you will conduct all the 10-Week required procedures, plus HIV counseling and testing, and complete blood count testing.

6.3.5 Follow-up Visit Scheduling Scenarios

Presented in Section Appendix 6-1 are several follow-up visit scenarios that may occur during MTN 001. These scenarios illustrate that the allowable visit windows impact whether a completed visit will be considered a scheduled visit or an interim visit. The examples also illustrate the complexities that may be encountered when scheduling and completing study follow-up visits in a “real world” setting. Given these complexities, SCHARP will provide each site a Microsoft Excel spreadsheet that will have the visit windows already programmed. When a participant is enrolled, the site will insert the Enrollment Date, and the spreadsheet will generate a participant visit calendar that will include the target dates and visit windows. It is strongly recommended that sites print this calendar and place it in the participant’s binder/file.

6.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in protocol Sections 7.1, 7.2 and 7.3. Highlighted for reference below are the primary procedural requirements:

- Perform physical exam at all scheduled visits, except 21-week when the exam is performed if indicated
- Perform pelvic exam at all scheduled visits, except 21-week when the exam is performed if indicated
- Urine pregnancy testing is conducted at every visit
- HIV test is conducted at screening, 7-week, 14-week, 21-week and if indicated at other visits
- Collect urine for Dipstick Urinalysis and SDA for Chlamydia and Gonorrhea at Screening Visit and as indicated at all other visits
- Blood draws are conducted at every visit
- Baseline behavioral questionnaire conducted at Enrollment and additional behavioral questionnaires conducted at the 3-week, 6-week, 10-week, 13-week, 17 week and 20-week visits
- Counseling for contraception, male condom, and HIV/STI risk reduction, conducted at all visits
- Protocol Adherence counseling conducted at all visits except 21-week; Product Use Adherence counseling conducted at Enrollment, 3-week, 7-week, 10-week, 14-week, and 17-week visits.
- In-depth qualitative interviews will be conducted with only a subset of study participants at 21-week visit
- The two types of visits that will include PK measures are the Mid-Study-Period and the End-of-Study-Period visits.
 - Mid-Study-Period: All participants will be asked to record the three doses of tenofovir taken prior to these visits with hour: minute accuracy. Participants will provide blood samples for tenofovir level.
 - End-of-Study-Period: All participants will be asked to record the three doses of tenofovir taken prior to these visits with hour: minute accuracy. Once at the site for their study visit, they will provide blood samples and then have an observed dose of study product(s). Post-dose blood and required vaginal samples will occur within 15 – 30 minutes of each other (either sample may be taken first). Participants at the Bronx-Lebanon Hospital Center CRS who opt to have rectal fluid samples taken, will have these samples taken after (within 15 minutes) the vaginal specimens are taken. The times of these samples must be recorded with hour: minute accuracy. The same sampling time point (within 15 minutes) in each study period should be used for all of a participant's End of Study Period Visits.
 - At the Non-US sites (non-intensive PK), participants will be assigned to a sampling window based on their sequence randomization assignment (See Section 7.8.2 of the protocol). At the US sites (intensive PK), participant randomization for PK procedures will be stratified within each of the sites, providing up to 18 women per time point (See Section 7.8.3 of the protocol). Figures 6-3 and 6-4 provides additional information on non-intensive and intensive PK procedures, respectively.

- Since PK procedures may not be split over multiple days, it is vital that participants are counseled of the importance of completing these visits on the scheduled date. Clinic staff should make all efforts to schedule these visits on a date that is the most convenient for the participant.
- To prevent dilution of the study product in the PK genital specimens and to minimize the impact on the levels of study product in the cervicovaginal tissue, participants will be asked to abstain from sexual activities, if possible, at least 24 hours prior to the End-of-Study-Period visit.

**Figure 6-3
Non-Intensive PK Sites**

	PRE-DOSE	POST-DOSE TIMING		
		1-3 HOURS	3-5 HOURS	5-7 HOURS
Blood: <ul style="list-style-type: none"> • Flow cytometry (at sites with capacity) 	Study Regimen Sequences A, B, C, D, E, and F			
Blood: <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Study Regimen Sequences A, B, C, D, E, and F	Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 		Study Regimen Sequences E and F	Study Regimen Sequences A and B	Study Regimen Sequences C and D

**Figure 6-4
Intensive PK Sites**

SPECIMEN	PRE-DOSE	POST-DOSE TIMING				
		1 HOUR	2 HOURS	4 HOURS	6 HOURS	8 HOURS
Blood draw <ul style="list-style-type: none"> • PBMC cell lysate (intracellular tenofovir diphosphate) (at sites with capacity) • Tenofovir 	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)	Groups M, N, O, and P)
Blood draw <ul style="list-style-type: none"> • Flow cytometry 	Groups M, N, O, and P)					
Cervical cytology brush <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	18 ppts (Group M)		18 ppts (Group N)	18 ppts (Group O)	18 ppts (Group P)	
CVL <ul style="list-style-type: none"> • Tenofovir • Proteomics and markers of inflammation 	Group M		Group N	Group O	Group P	
Vaginal biopsies <ul style="list-style-type: none"> • Cell lysates (intracellular tenofovir diphosphate) • Tenofovir 	Group M		Group N	Group O	Group P	
Rectal Fluid (Bronx-Lebanon Hospital Center CRS only)	Group M		Group N	Group O	Group P	

6.5 Follow-up Visit Locations

All visits must take place on-site.

6.6 Product Re-Supply During Follow-up

Study product(s) will be re-supplied only to enrolled participants, upon receipt of a written prescription from an authorized prescriber. Depending on the study period in which the participant is currently enrolled, she will receive either a bottle of 30 tenofovir tablets, or 28 pre-filled vaginal gel applicators (two cartons of 14 applicators), or 30 tenofovir tables and 28 pre-filled applicators at each regularly scheduled study visit, except the End of Study Period visits and the Termination visit.

At each follow-up visit, study staff will collect all unused study products to determine whether a participant remains eligible for continued study product use per protocol specifications. Protocol Section 9.4 lists conditions under which participants should be discontinued from study product use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring that these protocol specifications are followed for all participants.

At the start of each study period, an authorized prescriber will complete a prescription based on the participant randomization assignment. If the participant is in the dual period, the authorized prescriber will need to complete a prescription for both study products (vaginal gel and tablets).

Each site has the discretion to determine if study prescriptions will be used to dispense additional study product at the mid-study period visits (the Week 3, Week 10, and Week 17 Visits), in which case completion of the MTN-001 Study Product Hold/Resume/pK Supply/Resupply Slip only will be required or if dispensation of new study product at the mid-study period visits requires completion of a new MTN-001 prescription(s).

At the Mid-Study Period, the site will provide the Pharmacist with a new Prescription or a Study Product “Re-Supply” Slip, to have new study product supplies dispensed, according to site policies.

During follow-up visits, when a new prescription will be used at the mid study period visit, an authorized prescriber will complete a prescription in the same manner they are completed during enrollment.

- Record the Participant ID (PTID) assigned to the participant in the boxes provided.
- Mark the box for current study period based on participant’s randomization sequence: study period number (1, 2, or 3).
- Complete the prescription by providing an authorized prescribers’ printed name, signature and date in the provided area.
- Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow copy in the participant study notebook. Deliver the white original to the study pharmacy in the same manner that enrollment prescriptions are delivered to the pharmacy. Both the original and clinic copy of the prescription may be hole-punched.

Section 9 of this Study-Specific Procedures Manual contains detailed information on site clinic staff procedures for the dispensation of study product, as well as the return of used and unused study products.

6.6.1 MTN 001 Study Product Hold/Resume/pK Supply Slip

The MTN 001 Study Product Hold/Resume/pK Supply Slip (Study Product Slip, See Appendix 6-4) is a two-part no carbon required (NCR) document that is available in from the DAIDS Clinical Research Product Management Center (CRPMC). The PoR will order bulk supplies of the pads for use by clinic staff throughout the course of the study. The Study Product Slip will be used to inform the pharmacy if product needs to be held (permanently or temporarily), resumed, or in the case that a participant does not bring product to the clinic for PK procedures, this form will be used to order a single dose of product (one applicator, one tablet, or one applicator and one tablet).

At the Mid-Study Period, when a Study Product “Re-Supply” Slip will be used at the mid study period visit, an authorized clinic staff will complete a Study Product “Re-Supply” Slip based on the participant randomization assignment.

Complete the Study Product Request Slip as follows:

- Record the PTID and the number of the Randomization Envelope assigned to the participant (as recorded on her Randomization Document) in the boxes provided.
- Mark the box for HOLD, RESUME, or pK SUPPLY to indicate the action to be taken by the study pharmacy.
 - When designating HOLD, mark the box for either permanent or temporary hold and then choose which product will be held. A participant may be temporarily or permanently discontinued from one study product and be eligible to use the other product; however, if a participant is discontinued from either study product, she cannot use any product during the dual period.
 - When designating RESUME, mark which product will be dispensed. If the participant is in the dual period, mark both products. When resuming product, a new prescription for the appropriate study product (tablets, vaginal gel, or tablets and vaginal gel) will need to be completed and sent to the pharmacy along with the Study Product Slip. Study product will not be dispensed from the pharmacy unless/until another slip marked RESUME is subsequently completed and received in the pharmacy, along with the new prescription.
 - When designating pK SUPPLY, indicate which product will be dispensed. It is not necessary to complete a new prescription.
- The clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order product supplies for participants during follow-up. DAIDS does not require that an authorized prescriber sign and date the Study Product Slips; however site-specific pharmacy regulations may be more stringent than DAIDS requirements. All sites must comply with local requirements.

- Double-check the accuracy of all entries and then separate the two parts of the completed Study Product Slip. Retain the yellow copy in the participant study notebook. Deliver the white original to the study pharmacy in the same manner that original prescriptions are delivered to the pharmacy. Both the original and clinic copy of the slip may be hole-punched.

6.7 HIV Testing During Follow-Up

At all sites, follow-up HIV testing will be performed according to the algorithm in protocol Appendix II, which is re-printed in Figure 6-5. Section Appendix 6-6 presents several HIV testing scenarios that illustrate the testing procedures required by the algorithm. Further information on the procedural and documentation requirements of the algorithm is provided in the remainder of this section.

In Step One, an FDA-approved rapid HIV test (i.e., either the OraSure OraQuick test or the Uni-Gold Recombigen test) or an ELISA test, that has been validated at the study site is performed. If the rapid test or ELISA in Step One is negative, testing will stop after Step One. If the rapid test or ELISA is positive, testing will proceed to Step Two, in which the same sample that tested positive in Step One will be tested with the FDA-approved Genetic Systems Western blot (WB).

At some sites, a second rapid test may be performed in Step One. For example, HIV counseling and testing guidelines at some sites require that two rapid tests be performed whenever rapid testing is utilized. Sites required or otherwise wishing to perform a second test in Step One must specify their site-specific testing procedures in their local laboratory SOPs for MTN 001, and must obtain MTN Network Laboratory (NL) approval of these SOPs prior to study activation. Once approved, these SOPs must be followed consistently for all study participants. For sites that perform two tests in Step One, testing will proceed to Step Two if either of the two tests is positive/reactive.

If the WB in Step Two is negative, testing will stop after Step Two. If the WB is positive or indeterminate, a second FDA-approved Genetic Systems WB must be performed on a second sample collected from the participant. This sample is referred to as “sample 2” in the algorithm and will be used for plasma archive if HIV infection is confirmed. For participants with confirmed HIV infection, plasma archived at enrollment will be tested at the NL for evidence of HIV infection, as described in Section 12.

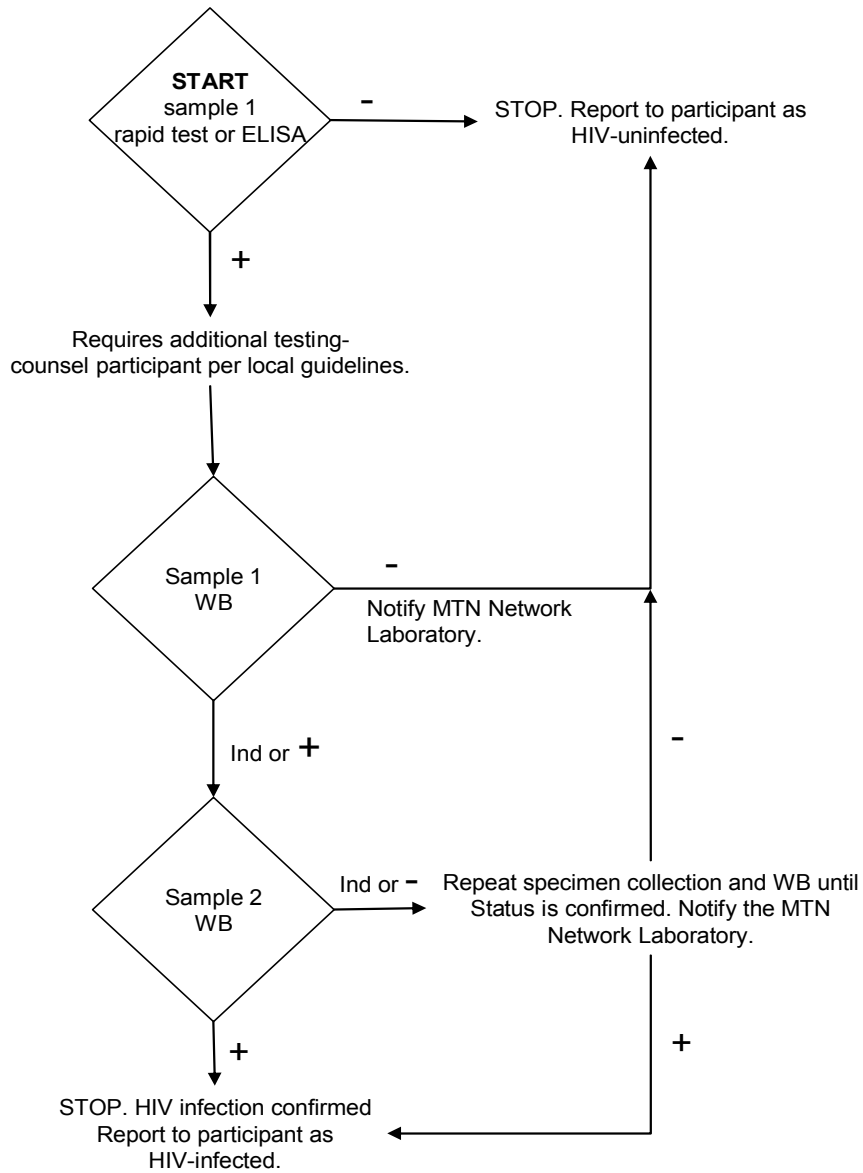
If the sample 2 WB is negative or indeterminate, additional WB testing must be performed on additional samples. In this case, inform the MTN NL via email of the sample 1 and sample 2 test results (copied to the MTN CORE and SDMC) and request NL input on next steps and timeframes for additional specimen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

Further instructions for performing HIV tests during follow-up are provided in Section 12. 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 timeframe of the tests and prior to disclosure of results to participants. For positive/reactive results, review, verification, and sign-off must be performed by a nurse, clinician, or physician. In addition to initialing or signing the testing logs to document review and verification of the results, the second staff member must also record the time at which the results were reviewed and verified.

Figure 6-5

Algorithm for HIV Antibody Testing During Follow-up in MTN 001

Algorithm for HIV antibody testing during follow-up



6.8 Modified Follow-up Procedures for Participants Who Become Pregnant

Participants who become pregnant after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. Participants who are pregnant at the termination visit will continue to be followed until the pregnancy outcome is ascertained (or, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained).

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:

- Administration of study products (site staff will make every effort to recover any unused study product within 5 days once the site becomes aware of the pregnancy)
- Product use and adherence counseling will be discontinued.
- All pharmacokinetic measures
- For all participants who become pregnant, regardless of study treatment group, a Pregnancy Report and History form must be completed to report the pregnancy. A Pregnancy Outcome form also must be completed to document the outcome of the pregnancy. Certain pregnancy outcomes also must be reported on Adverse Experience Log case report forms (see Section 13.6) and/or DAIDS Expedited Adverse Event Forms, as described in Section 11 of this manual. Whenever possible, pregnancy outcomes should be ascertained based on medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, however, outcomes may be ascertained based on participant report.

Several illustrative pregnancy management scenarios are provided in Section Appendix 6-7. All study sites are strongly encouraged to use a pregnancy management worksheet similar to the sample in Section Appendix 6-8 to ensure proper documentation of the pregnancy and timely discontinuation and resumption (if applicable) of product use. Site pharmacy staff must be informed of the product hold/discontinuation in writing, product supplies previously dispensed to pregnant participants must be retrieved as soon as possible and within 5 days after the pregnancy is identified, and a Product Hold/Discontinuation case report form (see Section 13) must be completed and transmitted to the SDMC.

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

Participants who become infected with HIV after enrollment/randomization will be maintained in follow-up according to their original study follow-up schedule. All participants who become infected with HIV will be counseled and referred to available sources of medical and psychosocial care and support, as well as to any available research studies for HIV-infected persons. For any participants who become HIV-infected and also become pregnant during follow-up, every effort will be made to facilitate access to interventions such as single-dose nevirapine to reduce the probability of HIV transmission to the participant's infant.

While in scheduled follow-up, all protocol-specified study procedures will continue to be conducted for participants who become infected with HIV, with the following exceptions:

- After HIV infection is confirmed per the algorithm in Figure 6-3, and the participant's enrollment plasma specimen has been tested for evidence of HIV infection, if applicable, HIV testing will be discontinued.
- Product use will be permanently discontinued (site staff will make every effort to recover any unused study product immediately after the site becomes aware of the participant's HIV status)
- Counseling will be tailored to primary and secondary HIV/STI prevention for infected women.
- Product use and adherence counseling will be discontinued.
- All pharmacokinetic measures

Participants, who become infected with HIV, may be offered participation in the MTN Seroconverter Study (MTN-015).

6.10 Participant Transfers

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

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

- The SDMC will notify the transferring site of all outstanding data QC notes for the transferring participant; the transferring site will resolve these QCs.
- The transferring site will explain the transfer arrangements to the participant and obtain her written permission to provide copies of her study records to the receiving site.
- The transferring site will deliver copies of all of the participant's study records to the receiving site via courier or overnight mail service. Copies of participant-specific records maintained in the transferring site pharmacy must be delivered directly to the receiving site pharmacy, separate from the participant's clinic records. Pharmacy records may not be delivered in the same shipping envelope or carton as the clinic records. The transferring site (clinic and pharmacy) will document all materials sent to the receiving site and inform the receiving site of the shipment date and expected arrival date. The receiving site (clinic and pharmacy) will confirm receipt of the shipment.
- The transferring site will complete and transmit a Participant Transfer case report form to the MTN SDMC (see Section 13). The SDMC will forward a copy of this form to the MTN CORE, MTN NL, and DAIDS PAB for informational purposes.
- The receiving site will establish contact with the participant, obtain her written informed consent to continue in the study at the receiving site, and complete and transmit the Participant Receipt case report form to the SDMC (see Section 13).
- Upon receipt of the Participant Transfer and Participant Receipt forms, the SDMC will re-map the participant's study ID number (PTID) to reflect the change in site follow-up responsibility. The participant's original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged. An authorized prescriber at the receiving site will be required to prepare an original signed and dated note to pharmacy staff stating that the participant has provided written informed consent to take part in the study at the receiving site and that the prescriber authorizes the participant to continue product use per the MTN 001 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 001 Study Product Prescription, pharmacy staff at the receiving site will dispense the product to the participant according to the random assignment documentation received from the transferring site pharmacy.
- If applicable, the transferring site will retain responsibility for storage and shipment of all specimens collected from the participant to the MTN NL, prior to her transfer, unless otherwise instructed by the MTN NL.

6.11 Resumption of Study Participation After Voluntary Withdrawal

As stated in protocol Section 9.8, regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time. The protocol also allows, however, for participants who voluntarily withdraw from the study to reverse their decision and re-join the study during their planned 21-week follow-up period, resume study procedures and follow-up at the investigator's decision. If such cases arise, study staff are advised to contact the MTN CORE and SDMC for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged. Her random assignment also will remain unchanged and she will continue product use per her random assignment.
- An interval (since the last visit) medical/menstrual history should be taken and a pregnancy test should be performed as soon as the participant resumes study participation. Product use will be resumed only among participants who are not currently pregnant or within 90 days of last pregnancy outcome.
- A pelvic exam should be performed as soon as possible, and prior to re-instating gel use. A pelvic exam and other clinically-indicated evaluations also should be performed if the participant reports current genital symptoms. Gel use will be reinstated (if applicable) only after any genital symptoms have resolved, any STIs/RTIs requiring treatment per World Health Organization guidelines have been treated, and any pelvic exam findings involving deep epithelial disruption have resolved.
- If the participant missed her last scheduled HIV counseling and testing, it should be performed as soon as possible. Product use will only be re-instated for participants who are confirmed as HIV-uninfected per the algorithm in Figure 6-3.
- Clinic staff will communicate any re-instatement of product use to the study pharmacy in writing, using the MTN 001 Study Product Prescription.

6.12 Study Exit Considerations

Procedural requirements for conducting study exit visits are specified in protocol Sections 7, Table 8 and 7.13; further procedural guidance is incorporated in the Study Termination Visit checklist in Section 7 of this manual. Provided in the remainder of this section is additional information related to key aspects of study exit visits.

6.12.1 Certificate of Completion

All study sites are strongly encouraged to provide each participant who completes a scheduled study exit visit with a certificate of study completion. Sample certificates which may be tailored for use at each site are available on the MTN 001 web page:

<http://www.mtnstopshiv.org/node/71>.

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

6.12.2 Participant Locator Information

As described in greater detail in Section 6.12.9, accurate participant locator information will be needed for post-study contact with study participants. As such, locator information should be actively reviewed and updated at all study exit visits and all participants should be counseled to contact the study site should their locator information change after study exit.

6.12.3 Final Study Contacts

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

- Participants who are pregnant at study exit (see Section 6.8 above)
- Participants with positive or indeterminate HIV Western blot (WB) test results (see Section 6.12.4 below)
- Participants with certain types of AEs that are ongoing at study exit (see Section 6.12.7 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, by telephone, or at community-based locations, depending on site capacities and site and participant preferences. It is recommended that final contact plans be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9.

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

6.12.4 HIV Counseling and Testing

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

6.12.5 Plasma Archive

All anticoagulated blood remaining in the lavender top (EDTA) tube after HIV testing is performed at the study exit visit should be processed within 24 hours of collection into at least four 0.5 mL aliquots of plasma (see Section 12 of this manual for more information).

6.12.6 Product Hold/Discontinuation

All participants are discontinued from product use at their study exit visits. Therefore, for all participants at the study exit visit, the End of Study Inventory (ESI) CRF and Termination (TM) CRF should be completed and all unused product supplies should be collected from the participant and returned to the study pharmacy on the day of collection. In addition, clinic staff should add the participant's PTID to a cumulative listing of participants who have exited the study which should then be provided to pharmacy staff on a weekly basis.

Participants should be reminded to bring all unused product supplies to their exit visits. For participants who do not bring all unused supplies to their exit visits, arrangements must be made to collect the remaining supplies as soon as possible. It is recommended that plans to collect remaining product supplies be documented on a study exit worksheet similar to the sample provided in Section Appendix 6-9. If the study product is not collected within five working days after the study exit visit, the MTN 001 Protocol Safety Review Team (PSRT) must be informed, using the PSRT Query Form. When informing the PSRT, please describe the reason for the product hold (i.e., study exit), actions taken to try to collect the unused product, and plans and timelines for further action to collect the product.

6.12.7 AE Management and Documentation

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

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

For those AEs requiring re-assessment, if the AE has not resolved or stabilized at the time of re-assessment, study staff will continue to re-assess the participant at least once per month while the study is ongoing. After the study has ended, all AEs requiring re-assessment will be re-assessed at least once within the 30-60 days after the study end date. The MTN 001 PSRT may advise study staff as to whether any additional follow-up may be indicated on a case by case basis.

For AEs that are re-assessed after study exit, information on the status of the AE at the time of re-assessment will be recorded in source documents only — no updates should be made to AE Log case report forms based on the re-assessments. All information related to the re-assessment of AEs should be documented in the participant's chart notes, including all efforts to contact the participant.

6.12.8 Referral to Non-Study Service Providers

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

6.12.9 Post-Study Contacts

It is expected that all participants will be re-contacted by study staff approximately three to nine months after study completion, when it is expected that study results will be available for dissemination to all participants.

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

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

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 001

6.1	Suppose Miss X enrolls in the study on 3 April. What are the target dates for her visits in study weeks 3, 6, 7, and 10?		
		<u>Target</u>	
	3-Week	24 April	
	6-Week	15 May	
	7-Week	22 May	
	10-Week	12 June	
	Why? Target dates are set based on the participant's study enrollment date (day 0) and occur at 3, 6, 7, 10, 13, 14, 17, 20, and 21 weeks after enrollment.		
6.2	Continuing from scenario 6.1, what are the allowable and target windows for this participant?		
		<u>Target Window</u>	<u>Allowable Window</u>
	3-Week	21-27 April	4 April – 4 May
	6-Week	12-18 May	5 May – 18 May
	7-Week	19-25 May	19 May – 1 June
	10-Week	9-15 June	2-22 June
	Why? The allowable visit windows are contiguous from visit to visit starting with the day after enrollment (day 1), and do not overlap. Within each allowable visit window, there is a target visit window. The target visit window is the same for each visit, equal to +/- 3 days around the target visit date.		
6.3	Suppose Miss X completes her 3-Week visit on 21 April. What are the target and allowable dates for her visits in study weeks 6, 7, and 10?		
		<u>Target</u>	<u>Allowable</u>
	6-Week	15 May	5 May – 18 May
	7-Week	22 May	19 May – 1 June
	10-Week	12 June	2-22 June
	Why? Target dates always remain linked to the enrollment date. Target dates do not shift when a previous visit does not take place on the target date.		
6.4	Suppose Miss X does not complete her 6-Week visit on the target date of 15 May, but presents to the study site on 17 May. What do you do?		
	<ul style="list-style-type: none"> • Complete a 6-Week visit per protocol on 17 May. 		
	Why? 17 May is within the allowable 6-Week visit window.		
6.5	Suppose Miss X does not complete her 6-Week visit between 5 May and 18 May, but presents to the study site on 19 May. What do you do?		
	<ul style="list-style-type: none"> • On 18 May, consider the 6-Week visit missed. • On 19 May, complete a 7-Week visit per protocol. 		
	Why? The 6-Week visit window closed on 18 May, but the 7-Week visit window opened on 19 May.		

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 001

6.6	<p>Suppose Miss X completes all her 7-Week visit procedures on 24 May, but presents to the study site on 26 May to report genital bleeding. What do you do?</p> <ul style="list-style-type: none"> • On 26 May, complete interim visit required procedures, including a pregnancy test. • Perform pelvic exam to assess Miss X symptoms and manage accordantly. • Complete necessary documentation such as chart notes and AE log form. • Confirm and reinforce the scheduling of Miss X’s 10-Week visit. <p>Why? The 7-Week visit procedures were completed, and the window for the 10-Week visit does not open until 2 June. Appendix I of the protocol lists the procedures that are required at each interim visit.</p>
6.7	<p>Continuing from scenario 6.6, suppose Miss X comes to the study site for follow-up on the genital bleeding on 3 June. What do you do?</p> <ul style="list-style-type: none"> • On 3 June, complete a 10-Week visit per protocol. <p>Why? The 10-Week visit opened on 2 June. A pelvic is a required procedure at the 10-Week study visit. Clinician should assess whether or not the genital bleeding has resolved and update documentation as appropriate.</p>
6.8	<p>Suppose Miss X does not complete her 6-Week visit between 5 May and 18 May, but presents to the study site on 19 May. What do you do?</p> <ul style="list-style-type: none"> • On 18 May, consider the 6-Week visit missed. • On 19 May, complete a 7-Week visit per protocol. • Additionally during the pelvic exam, collect swab for wet mount and assess vaginal pH specified for the missed 6-Week visit. <p>Why? The 6-Week visit window closed on 18 May and the 7-Week visit window opened on 19 May. When End-of-Study-Period visits are missed, during the pelvic exam at the next visit, you need to assess vaginal pH and collect vaginal fluid for wet mount.</p>
6.9	<p>Suppose Miss X presents to the study site for her 7-Week visit on 20 May, and completes some but not all of the protocol-specified procedures for 7-Week visits. What do you do?</p> <ul style="list-style-type: none"> • Document all procedures performed on 20 May as usual. Explain in chart notes why all protocol-specified procedures were not completed. • Schedule Miss X to return to the study site as soon as possible to complete the remaining 7-Week procedures. • When Miss X returns to the study site, provided the 7-Week visit window has not elapsed, perform an interval medical/menstrual history and pregnancy test, and all remaining 7-Week visit procedures. • Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms. • Confirm and reinforce the scheduling of Miss X’s 10-Week visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her 7-Week visit is considered a split visit. Split visits may be conducted over two or more days, provided the allowable visit window does not elapse. DataFax forms completed for all parts of a split visit are assigned the same scheduled visit code.</p>

Section Appendix 6-1
Follow-up Visit Scheduling Scenarios for MTN 001

<p>6.10</p>	<p>Suppose Miss X presents to the study site for her 13-Week visit on 28 June, and has to leave the site before completing some but not all of the protocol-specified PK procedures for 13-Week visits. What do you do?</p> <ul style="list-style-type: none"> • Document all procedures performed on 28 June as usual. Explain in chart notes why all protocol-specified procedures were not completed, and all efforts to complete these procedures during this visit, including participant counseling. • Schedule Miss X to return to the study site as soon as possible (taking into consideration the visit window) to complete the remaining 13-Week procedures. • When Miss X returns to the study site, provided the 13-Week visit window has not elapsed, perform an interval medical/menstrual history and pregnancy test, and all remaining 13-Week visit procedures, <u>except</u> PK procedures. • Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms. • Confirm and reinforce the scheduling of Miss X’s 14-Week visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her 13-Week visit is considered a split visit. PK procedures cannot be completed at a later visit because some of the procedures had already started and PK procedures cannot be split.</p>
<p>6.11</p>	<p>Re-considering scenario 6.10, suppose Miss X presents to the study site for her 13-Week visit on 28 June, and during registration informs the staff that she can only stay for a few hours and cannot complete all the procedures for 13-Week visit. What do you do?</p> <ul style="list-style-type: none"> • Document all procedures performed on 28 June as usual. Explain in chart notes why all protocol-specified procedures were not completed. • If PK procedures cannot be completed all in one visit, do not start any PK procedures and complete these at the next visit. <ul style="list-style-type: none"> ○ For Non-US sites, if the participant is assigned to the 1-3 hours post-dose timing, it may be possible that there will be sufficient time to complete these procedures. Before any PK procedures are initiated, please ensure that it can be completed within this visit. • Schedule Miss X to return to the study site as soon as possible to complete the remaining 13-Week procedures, including PK procedures. Discuss with the participant the importance of completing these procedures and schedule the visit on a day that the participant will be available to complete all required procedures. • When Miss X returns to the study site, provided the 13-Week visit window has not elapsed, perform an interval medical/menstrual history and pregnancy test, and all remaining 13-Week visit procedures, including PK procedures. • Take care to document the actual date of all procedures performed in visit chart notes, on visit checklists, and all other documents and forms. • Confirm and reinforce the scheduling of Miss X’s 14-Week visit. <p>Why? Since Miss X could not complete all protocol-specified procedures in a single visit, her 13-Week visit is considered a split visit. PK procedures can be done since procedures were not started on 28 June; therefore these were not split.</p>

Section Appendix 6-2
Sample Participant Visit Tracking Sheet for MTN 001

Participant ID Number	
Participant Enrollment Date	

***Instructions:** The Participant Enrollment Date is defined as the date upon which an MTN 001 Randomization Envelope or an MTN 001 Replacement Randomization Document (for replacement participants) is assigned to the participant. Once the enrollment/randomization date is determined, enter target visit dates and allowable visit windows below. File this sheet with the participant's study chart and update it with scheduled and actual visit information at each visit.*

Follow-up Timepoint	Target Visit Date	Allowable Visit Window	Scheduled Visit Date	Actual Visit Date	Physical / Pelvic Exam Performed?	HIV Testing Performed?
Enrollment						
3-Week						
6-Week						
7-Week						
10-Week						
13-Week						
14-Week						
17-Week						
20-Week						
21-Week						

***Note:** This tracking sheet is not a source document. Information on this sheet is based on other source documents contained in the participant study chart.*

Section Appendix 6-3
MTN 001 Study Product Prescriptions

**MTN 001
ORAL TDF 300 MG TABLETS
PRESCRIPTION**

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Site Number:	
Site Location:			

Participant ID: -

Study Period: (check one) Sequence: ____

- Study Period 1
- Study Period 2
- Study Period 3

Tenofovir Disoproxil Fumarate 300 mg tablets

30

Directions: 1 tablet by mouth once each day before the longest period of rest (usually at night).

Refill/Repeat ____

Note to Pharmacist: May dispense 1 additional Tenofovir Disoproxil Fumarate 300 mg tablet if needed on day of pK visit without a new prescription.

Authorized Prescriber Name or ID (please print): _____

Authorized Prescriber Signature: _____

Date: - -
dd MMM yy

Clinic Staff Instruction: Deliver top copy to pharmacy. File bottom copy in participant study notebook.

**MTN 001
VAGINAL TENOFOVIR 1% GEL
PRESCRIPTION**

Instructions: All entries must be made in blue or black ink. Press firmly when completing this form. Corrections may be made by drawing a line through incorrect entries, recording correct information, and initialing and dating the correction.

Site Name:		Site Number:	
Site Location:			

Participant ID:

Study Period: (*check one*) **Sequence:** _____

- Study Period 1
- Study Period 2
- Study Period 3

Tenofovir 1% Gel (14 pre-filled applicators per carton)

2 cartons

Directions: Insert entire contents of one applicator vaginally once each day before the longest period of rest (usually at night).

Refill/Repeat _____

Note to Pharmacist: May dispense 1 additional applicator containing tenofovir 1% gel if needed on day of pK visit without a new prescription.

Authorized Prescriber Name or ID (*please print*): _____

Authorized Prescriber Signature: _____

Date:
 dd *MMM* *yy*

Clinic Staff Instruction: Deliver top copy to pharmacy. File bottom copy in participant study notebook.
--

Section Appendix 6-4
Study Product Request Slip

MTN 001 STUDY PRODUCT HOLD/RESUME/pK SUPPLY/RE-SUPPLY SLIP

Participant ID:

- -

Randomization Envelope #

Clinic Staff Instruction: Mark whether this is a product hold, resume or permanent discontinuation request. Sign and date. Deliver top copy to pharmacy. File bottom copy in participant study notebook.

<input type="checkbox"/> HOLD (<i>Mark all products that apply</i>)	<input type="checkbox"/> TEMPORARY	<input type="checkbox"/> PERMANENT
<input type="checkbox"/> Tenofovir 1% gel (vaginal)		
<input type="checkbox"/> TDF tablets (oral)		
<p>Pharmacy: For temporary holds, do not dispense study product marked above unless/until another Product Request Slip marked "RESUME" is received in addition to a new prescription. For permanent holds, do not dispense any further study product marked above.</p>		
<hr/>		
<input type="checkbox"/> RESUME (<i>Mark all products that apply</i>)		
<input type="checkbox"/> Tenofovir 1% gel (vaginal)		
<input type="checkbox"/> TDF tablets (oral)		
<p>Clinic: A new prescription must be completed for the appropriate study product and sent with this slip to pharmacy.</p>		
<hr/>		
<input type="checkbox"/> pK SUPPLY (<i>Mark all products that apply</i>)		
<input type="checkbox"/> Tenofovir 1% gel (vaginal) – Dispense one applicator		
<input type="checkbox"/> TDF tablets (oral) – Dispense one tablet		
<hr/>		
<input type="checkbox"/> RE-SUPPLY (<i>Mark all products that apply</i>)		
<input type="checkbox"/> Tenofovir 1% gel (<i>14 pre-filled applicators per carton</i>) Dispense 2 cartons		
<input type="checkbox"/> Tenofovir Disoproxil Fumarate 300 mg Dispense 30 tablets		
<hr/>		
Clinic Staff Name (<i>please print</i>): _____		
Clinic Staff Signature: _____		
Date: <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/>		
<p style="text-align: center;"><i>dd MMM yy</i></p>		

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.12 **One day after receiving two cartons of study gel, a participant returns to the clinic to report that she left both cartons on the bus that she took home from the clinic. What do you do?**

Clinic Staff: Document the participant report and complete a vaginal tenofovir gel prescription for the participant. Send an official communication, per site SOP, to the pharmacy stating that the participant lost the supplies she received on the previous day and additional gel needs to be supply. Provide and document follow-up instructions and counseling to avoid further loss of gel supplies.

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

Pharmacy Staff: Upon receipt of the new prescription, dispense gel per standard procedures and file the communication from the clinic explaining why additional product was dispensed.

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.13 Suppose Miss X is randomized on 2 September 2008 and has the following sequence of follow-up visits and pregnancy tests:

<u>Study Visit</u>	<u>Visit Date</u>	<u>Pregnancy Test Result</u>
Week 3	23 September 08	POSITIVE
Week 6	14 October 08	NEGATIVE

Also suppose Miss X reports no action taken or symptoms experienced with regard to the pregnancy loss between Weeks 3 and 6. What actions are required at the Week 3 and 6 visits?

Week 3: In addition to all other routinely required procedures for Week 3 visits, initiate a Pregnancy Management Worksheet. Complete and fax a Pregnancy Report and History form and a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked “HOLD” and “PERMANENT” for both products to inform pharmacy staff of the product hold and that no further product will be dispensed for this participant. Arrange to retrieve all remaining product supplies from Miss X as soon as possible and within 5 days. Continue to use the Pregnancy Management Worksheet to guide and track further action.

All protocol-specified study procedures will continue except:

- Product dispensation
- Product use counseling
- PK assessment

Week 6: The negative pregnancy test at this visit is considered the outcome of the pregnancy identified at Week 3. In addition to all other routinely required procedures for Week 6 visits, complete and fax a Pregnancy Outcome form and an AE Log form to SCHARP (pregnancy outcome date = 14 October 08, AE term = spontaneous abortion). Indicate in the comments section of the Pregnancy Outcome form that the outcome date is based on a pregnancy test performed by study staff. Complete and submit an EAE form to the DAIDS Safety Office within three business days.

- NOTE: Participants who become pregnant during the course of the study will discontinue permanently all study product(s).

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.14 Suppose Miss X is randomized in the study on 12 June 2008. During screening and enrollment, she reports that she is not breastfeeding; however, on her 3-Week study visit on 9 July she is seen breastfeeding her baby while seated in the waiting room. What you do?

- Counsel the participant about the unknown effects of tenofovir on breast milk and thoroughly document the incident and participant counseling on the chart notes.
- Complete and fax a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked “HOLD” and “PERMANENT” and choose both products to be permanently discontinued, to inform pharmacy staff of the product hold and that no further products will be dispensed for this participant. Arrange to retrieve all remaining product supplies from Miss X as soon as possible and within 5 days.

All protocol-specified study procedures will continue except:

- Product dispensation
- Product use counseling
- PK assessment

6.14 Suppose Miss X is randomized to sequence C (Oral + Vaginal, Oral, Vaginal) on 3 April 2008. At 10-Week study visit, her liver function test shows an elevation in ALT of Grade 3. What you do?

- Carefully assess if the elevation could be due to other reasons such as alcohol, hepatitis, or non-study medications.
- Conduct an HBsAg test and assess for signs or symptoms of clinical hepatic to determine if participant may be infected with hepatitis. If participant tests positive for Hepatitis B, all product should be permanently discontinued.
- Complete and fax a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked “HOLD” and “PERMANENT” to inform pharmacy staff of the product hold and that no further oral product will be dispensed for this participant. Arrange to retrieve all remaining product supplies from Miss X as soon as possible and within 5 days.
- Re-check ALT levels as soon as possible (at most within one week) and continue weekly testing until levels are Grade 1 or below. If ALT levels are Grade 1 or below prior to her 13 Week visit, product could be restarted with close follow-up and in consultation with the PSRT. If levels have not returned to Grade 1 or below within three weeks, oral product must be permanently discontinued.

Section Appendix 6-5
Product Use Management Scenarios for MTN 001

6.15 Continuing from scenario 6.14, suppose Miss X comes for follow-up testing on 8 July and her ALT level are Grade 0. What you do?

- On 8 July, the window for 14-Week study visit has opened; conduct 14-Week visit procedures.
- If participant has no other conditions that would contraindicate dispensing of study product, complete a vaginal tenofovir gel prescription and dispense two cartons of study gel, per participant's randomization sequence
- Confirm and reinforce the scheduling of Miss X's 17-Week visit.

Section Appendix 6-6
Follow-up HIV Testing Scenarios for MTN 001

6.13 Suppose Miss X's rapid HIV test is positive at Week 7. What do you do?

- Record the rapid test result on the Follow-up Laboratory Results form for the Week 7 visit.
- At the Week 7 visit, counsel Miss X that her initial HIV test indicates that she may be infected with HIV, but that an additional test (that requires N days to complete) is required to verify the result.
- Deliver Miss X's blood sample to the local lab for WB testing. Note that this testing is performed on the same sample that tested positive on the rapid test (sample 1).
- Schedule another visit to take place when Miss X's WB result will be available.
- Complete and fax a Product Hold/Discontinuation form to SCHARP. Complete an MTN 001 Study Product Hold/Resume/PK Supply Slip marked "HOLD" and "PERMANENT" to inform pharmacy staff of the product hold and that no further product will be dispensed for this participant.
- Arrange to retrieve all remaining product supplies from Miss X immediately.

6.14 Continuing from Scenario 6.18 suppose Miss X's WB is negative. What do you do?

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

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

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

- Record the WB result on an HIV Test Results form.
- When Miss X returns for her test result:
 - Counsel her that her tests continue to indicate that she may be infected with HIV, but the second test did not confirm her status for sure, so you must collect another blood sample for additional testing (that requires N days to complete) to confirm whether she is infected or not.
 - Collect blood (sample 2) and deliver it to the local lab for WB testing and plasma archive.
 - Schedule another visit to take place when Miss X's WB test result will be available.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

Section Appendix 6-6
Follow-up HIV Testing Scenarios for MTN 001

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

- Record the WB result on an HIV Test Results form.
- When Miss X returns for her test result:
 - Counsel her that her tests indicate that she is infected with HIV, and although you are confident that her test result is correct, you need to collect another blood sample for an additional test to be absolutely sure about the results (e.g., to rule out specimen mix-up or other errors).
 - Collect blood (sample 2) and deliver it to the local lab for WB testing and plasma archive.
 - Provide counseling and referral services for psychosocial and medical needs
 - Schedule another visit to take place when Miss X's WB test result will be available.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

6.17 Continuing from Scenario 6.20 or 6.21, suppose Miss X's sample 2 WB is either negative or indeterminate. What do you do?

- Record the WB result on the HIV Test Results form on which Miss X's sample 1 WB result has been recorded.
- Inform the MTN NL of Miss X's test results via email (copied to the MTN CORE and SDMC) and seek guidance on how best to clarify the participant's HIV status.
- When Miss X returns for her test result:
 - Counsel her that her HIV status remains unclear.
 - Collect blood (sample 3) for further testing per NL guidance.
 - Schedule another visit to take place when Miss X's test results will be available.

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Week 10 visit window has opened, additionally conduct the Week 10 visit per protocol (if possible).

Section Appendix 6-6
Follow-up HIV Testing Scenarios for MTN 001

6.18 Continuing from Scenario 6.20 or 6.21, suppose Miss X's sample 2 WB is positive. What do you do?

- Record the WB result on the HIV Test Results form on which Miss X's sample 1 WB result has been recorded.
- When Miss X returns for her test result, counsel her that the test confirmed that she is infected with HIV.
- Provide counseling and referral services for psychosocial and medical needs
- Since Week 7 is the participant's first follow-up HIV testing timepoint, test her plasma archived at enrollment for evidence of HIV infection (see Section 12 of this manual).

If the return visit takes place before Miss X's Week 10 visit window has opened, consider the visit an interim visit. Confirm and reinforce the scheduling of Miss X's next scheduled (Week 10) visit.

OR

If the return visit takes place after Miss X's Month 4 visit window has opened, conduct the Week 10 visit per protocol (if possible).

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

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

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

Section Appendix 6-8
Sample Pregnancy Management Worksheet for MTN 001

PARTICIPANT ID:			
BACKGROUND INFORMATION			
First day of last menstrual period			
Date of positive pregnancy test			
Estimated week 24 and full term pregnancy dates		Week 24:	Full Term:
PREGNANCY MANAGEMENT INFORMATION		Mark ✓ When Done	Initials/Date/Comments
1	Pregnancy Report and History form completed and faxed to SCHARP		
2	Pharmacy informed of pregnancy		
3	Product supplies retrieved from participant and returned to pharmacy		
4	Product Hold/Discontinuation form completed (items 1-3) and faxed to SCHARP		
5	Pregnancy outcome and outcome date ascertained, based on: <input type="checkbox"/> medical records or other written documentation from a licensed non-study health care practitioner <input type="checkbox"/> participant self-report <input type="checkbox"/> negative pregnancy test performed by study staff <input type="checkbox"/> other (specify in comments) <i>(medical records should be obtained whenever possible)</i>		
6a	Pregnancy Outcome form completed and faxed to SCHARP		
6b	If applicable, AE Log form completed and faxed to SCHARP		
6c	If applicable, EAE Report completed and faxed to DAIDS Safety Office		

**Section Appendix 6-9
MTN 001 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 study results are available	
<p>Does participant have study product remaining in her possession?</p> <input type="checkbox"/> No, per participant report, all product supplies have been used/collected/returned <input type="checkbox"/> Yes ⇒ describe plan for product collection (continue on back if needed)	
<input type="checkbox"/> Completed _____	
<p>Is participant currently pregnant?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for ascertaining pregnancy outcome (continue on back if needed)	
IoR approval: _____ <input type="checkbox"/> Completed: _____	
<p>Does participant have any ongoing SAEs/EAEs or any AEs found to have increased in severity at this visit?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes ⇒ describe plan for AE follow-up (continue on back if needed)	
IoR approval: _____ <input type="checkbox"/> Completed: _____	
<p>Is participant willing to be contacted about future studies for which she may be eligible?</p> <input type="checkbox"/> No <input type="checkbox"/> Yes	
Staff Signature and Date:	

Section Appendix 6-10 Sample Script for Study Exit Visits

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

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

- *If applicable, reinforce plans to collect remaining product supplies.*
- Your appointment to receive your final exam and test results is scheduled for [date]. This appointment will take place [here at the clinic / other specify]. If you need to change this appointment for any reason, please contact us to let us know.
- Although your scheduled study visits have now been completed, the study is planned to be ongoing for another [X] months. After that, we expect it will take about 9 months to have the results of the study available to share with all study participants. In order for us to share this information with you, we need to be able to keep in touch with you. Therefore we ask you to please inform us if you move to a new home, change your phone number, or have any other new details that would help us keep in touch with you. [Give contact card.]
- As you know, [project name] is involved in many different types of research studies. We would like to be able to contact you in the future about other studies that you may be eligible for. Are you willing to give us your permission to do that? [Record response on study exit worksheet; if permission is granted, explain that information recorded on the participant's locator form would be used for this purpose and enter participant on future contact permission log.]
- *If applicable, reinforce plans to determine pregnancy outcome.*
- *If applicable, reinforce plans for AE follow-up.*
- Lastly, we would like to give you some information on places where you can go for different types of services now that you will not be coming here for regular study visits [give referral sheet]:
 - For HIV counseling and testing
 - For family planning and other reproductive health care
 - For other types of health care
 - Other
- *If applicable, replace above bullet with a discussion of plans for ongoing participation in MTN 015.*
- Please feel free to contact us if you have any questions about the study that we have not answered today, or if you encounter any problems related to your participation in the study. Once again, we sincerely thank you for your contributions to the study and we look forward to sharing the results with you when they become available.

