Section 5. Study Procedures

Table of Contents

This section provides information on requirements for study procedures in MTN-017, including screening, enrollment and participant follow-up visits.

5.1 Visit Considerations

Because of the nature of study procedures required to be performed during the MTN-017 Screening, Enrollment/Initiate Period 1, and Follow Up visits (Initiate Period, Mid-Period, and Period End), all visits are expected to be completed at the study clinic only.

5.2 Eligibility Determination

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study. Each study site must establish a standard operating procedure that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
- During-visit eligibility assessment procedures

    - Post-screening visit eligibility assessment and confirmation procedures (i.e. review of laboratory results)
    - Final confirmation and sign-off procedures prior to enrollment/randomization
    - Documentation of each eligibility criteria (met or not met)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- QC/QA procedures (if not specified elsewhere)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-017 study management team, using the following email address: mtn017mgmt@mtnstopshiv.org.

All eligibility criteria are initially assessed at the Screening visit, and some are reconfirmed on the day of Enrollment/Initiate Period 1 visit. The Eligibility Checklist provides further operational guidance on the timing of assessment and source documentation for each eligibility criterion. This checklist can be found on the MTN-017 webpage under Study Implementation Materials.

A second screening attempt will be allowed only in the following cases:

- The participant did not complete all screening and enrollment visit procedures within 30 days of providing informed consent (see section 5.4.1 below)
- If a participant is identified at screening with non-anorectal GC/CT, in which case a second screening attempt should be scheduled two months after participant screens out (see protocol section 5.3)
- If a participant presents at screening or enrollment with symptoms suggestive of acute HIV seroconversion, per protocol (see protocol section 5.3) the participant is not eligible for study participation and should be deemed a screen fail. Participants who are deemed a screen fail due to concern of potential acute HIV seroconversion may be rescreened a maximum of one time, but no earlier than two months following the initial screening attempt;
    - ★ If, however, symptoms are clinically assessed to be related to an alternative diagnosis (for example, influenza) then the participant is not considered a screen fail, but the enrollment visit should be scheduled following the resolution of all symptoms.
    - ★ At sites with capacity to run viral load testing as part of the standard of care to confirm HIV negative status, a second screening attempt is not required and the participant may be enrolled within the same screening attempt once all symptoms have resolved, viral load is not detected and assuming no other interim contraindications are noted.
- Participants with exclusionary laboratory results may be rescreened a maximum of one time at the discretion of the IoR or designee after the condition is expected to be resolved, and treatment if applicable, is completed, in consultation with the PSRT;
- Participants that screen out due to IoR or designee's discretion may be rescreened a maximum of one time, in consultation with the PSRT.

Note: When rescreening participants, all screening procedures need to be repeated, including the informed consent process.

Prior to randomization, eligibility for study participation must be confirmed and documented on the enrollment visit column of the MTN-017 Eligibility Checklist.
In addition to the assessment of eligibility, the study informed consent should be reviewed with the participant to ensure that the participant clearly understands all information and is willing to participate in the study. Review of the informed consent must be documented in the participant's study files.

5.3 Visit Checklists

Sample visit checklists detailing protocol-specified procedures that must be completed during MTN-017 study visits are available for download on the MTN-017 webpage under Study Implementation Materials (http://www.mtnstopshiv.org/node/4524). The checklists also specify the data collection forms that must be completed at each visit. Sites are expected to conduct study procedures outlined in the visit checklist per their site SOPs.

The visit checklists are designed to guide site staff in proper study procedures as well as to serve as source documentation of procedures performed at study visits. Note, however, that checklists alone may not be sufficient for documenting all procedures. Chart notes may be required to supplement information documented during study visits.

See Section 2 of this manual for detailed information on source documentation requirements. Tips for completing visit checklists in accordance with these requirements are as follows:

- Enter the participant identification number (PTID) and visit date in the top section of each checklist. If checklists are multiple pages, enter the PTID and visit date on each page.
- For screening visits, mark the screening attempt number in step 3 of the checklist. Participants are allowed one screening attempt (see Section 5.2 above regarding when a second screening attempt is allowed).
- For follow-up visits, enter the visit code in the top section of each checklist.
- The “Required at visits” column indicates when the item is required during follow-up per-protocol. Complete staff initials next to procedures completed.
- Enter your initials only beside the procedures that you perform. Do not enter your initials beside procedures performed by other staff members. If other staff members are not available to initial checklist items themselves, enter, initial, and date a note on the checklist documenting who completed the procedure, e.g., “done by {name}” or “done by nurse.”
- If all procedures listed on a checklist are performed on the date entered in the top section of the form, the date need not be entered beside each item. If procedures listed on a checklist are performed on multiple dates, enter the date upon which each procedure is performed beside each item. Bracketing procedures which are consecutive and all done on the same date is also acceptable.
- If a procedure listed on the checklist is not performed, enter “ND” for “not done” beside the item and record the reason why on the checklist (if not self-explanatory); initial and date this entry.

5.3.1 Sequence of Procedures

The sequence of procedures presented on the visit checklists is a suggested ordering. In consultation with the MTN LOC (FHI 360), it is encouraged that site staff modify the example checklists to maximize the efficiency of site-specific study operations.

Sites may alter the sequence of procedures, with the following exceptions:

- Informed consent must be obtained before any study procedure is performed.
- On the day of enrollment/Initiate Period 1, random assignment must take place after final confirmation and verification of eligibility, completion of the CASI Baseline Questionnaire and collection of blood for plasma archive. It is recommended that for sites not doing finger stick HIV testing, blood for HIV serology and plasma archive be collected together, to limit venipuncture to a single blood draw. If a participant is subsequently found to be ineligible and is not randomized, the plasma archive sample should be destroyed.
- Rectal exam procedures must be performed in the sequence shown on the rectal exam checklist.
- During study follow-up, behavioral assessment forms and CASI questionnaires should be administered prior to the delivery of HIV and adherence counseling.

- It is recommended that procedures for determining eligibility for continued product use be conducted early in the visit to ensure that these procedures are conducted in the event that the participant needs to abruptly leave the clinic, or is short of time.

5.4 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-017. The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. Required screening procedures are listed in protocol Sections 7.1.

5.4.1 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place up to 30-days prior to enrollment/randomization, beginning on the day the potential participant provides written informed consent. In other words, the day the screening informed consent is signed is counted as "-30" and enrollment is counted as Day 0. For example, as shown below, a potential participant who provides written informed consent on 1 August 2012 could be enrolled on any day up to and including 31 August 2012.

August 2012

SUNDAY	MONDAY	TUESDAY	WEDNESDAY	THURSDAY	FRIDAY	SATURDAY
			1 Written consent (day -30)	2	3	4
5	6	7	8	9	10	11
12	13	14	15	16	17	18
19	20	21	22	23	24	25
26	27	28	29	30	31 Last day to enroll (Day 0)	

The screening process starts as soon as the participant signs the informed consent form, even if no other screening procedures were done on that day.

If all screening and enrollment procedures are not completed up to 30 days of obtaining written informed consent, the participant must repeat the entire screening process, beginning with the informed consent process. Note, however, that a new participant identification number (PTID) is not assigned to the participant in this case. The term "screening attempt" is used to describe each time a participant screens for the study (i.e., each time s/he provides written informed consent for participation in the study).

5.4.2 Assignment of Participant ID Numbers

The MTN SDMC will provide each study site with a listing of participant identification numbers (PTIDs) for use in MTN-017. As shown in Figure 5-1, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

Figure 5-1
Sample Site-Specific PTID List for MTN-017

	Participant ID	Participant Name	Date	Staff Initials
1	XXX-00001-Z			
2	XXX-00002-Z			
3	XXX-00003-Z			
4	XXX-00004-Z			
5	XXX-00005-Z			
6	XXX-00006-Z			
7	XXX-00007-Z			
8	XXX-00008-Z			
9	XXX-00009-Z			
10	XXX-00010-Z			

Further information regarding the structure of PTIDs for MTN-017 can be found in Section 11 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant, regardless of the number of screening attempts the participant undergoes. Study staff are responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID list such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

5.4.3 Screening and Enrollment Log

The DAIDS policy *on Requirements for Essential Documents at Clinical Research Sites Conducting DAIDS Funded and/or Sponsored Clinical Trials* requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one document. A sample screening and enrollment log suitable for use in MTN-017 is available on the MTN website (http://www.mtnstopshiv.org/node/4524). Study sites are encouraged to reference the eligibility codes on the MTN-017 Eligibility Checklist when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

5.4.4 Screening Visit Procedures

Required screening procedures are specified in the MTN-017 protocol section 7.2 and reflected in the visit checklists available on the MTN-017 webpage.

Clinical screening visit procedures are described in detail in Section 8 of this manual, briefly:

- Clinical procedures include collection of medical history, concomitant medications, physical exam, and rectal exam.
- Participants will be evaluated for use of prohibited medications, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- The HIV testing algorithm for screening and testing consideration can be found in Section 10. Participants will receive HIV pre- and post-test counseling as well as risk reduction counseling, including provision of condoms in conjunction with HIV testing during screening. Counseling considerations are described in detail in SSP Section 6 of this manual.
- Participants should receive all available test results and treatment or referrals for UTI/RTI/STIs.

Details regarding laboratory tests and sample collection at screening are provided in Section 10 of this manual. In summary:

- Participants receive testing for STIs, HBsAg, HBsAb, Hep C antibody, PT/INR (rectal subset only), serum chemistries, and CBC with platelets and differentials.

Per protocol Section 7.1, multiple screening visits (as part of the same screening attempt) may be conducted if needed, to complete all required procedures. In cases where the Screening visit is

conducted over multiple days, all procedures are considered part of the same screening visit/screening attempt.

5.4.5 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. If the participant is found to be ineligible at the beginning of the screening visit, sites may choose to continue with clinical and laboratory evaluations as a service to the participant, per their site SOPs. If a participant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure well-being of the participant. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to participants within a reasonable timeframe, regardless of eligibility determination. For all screened out participants, the following documentation should be in place:

- Completed Screening ICF
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist
- Completed Eligibility Criteria CRF, updated with screen failure reason(s) and faxed to SCHARP
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)
- All source documentation complete up until the time that ineligibility was determined
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)

In addition, the Screening and Enrollment Log should be updated with date of discontinuation of screening and reason for screen failure (list item number as appropriate from the Eligibility Checklist) and the Eligibility Criteria CRF should be completed and faxed.

5.5 Enrollment Visit

Participants will be considered enrolled in MTN-017 when they have been assigned a MTN-017 Randomization Envelope. Further information on methods and materials for random assignment is provided in section 5.6.1.1 below.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the MTN 017 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are provided in Section 9 of this manual. Additionally, the MTN-017 Management Team must be informed immediately.

5.5.1 Enrollment Visit Procedures

The Enrollment/Period 1 Initiation visit serves as the baseline visit for MTN-017. All procedures for this visit must be conducted on the same day, and cannot be split across multiple days. If it is determined, prior to study initiation, that a site is not able to conduct all Enrollment visit procedures on the same day, the MTN-017 Leadership should be immediately consulted. Further guidance will be provided in this instance by the MTN-017 leadership and Management team on a site-by-site basis.

Study enrollment procedures are specified in protocol section 7.2.1 and reflected in the visit checklists available on the MTN-017 webpage. The following procedures will be completed as part of eligibility confirmation prior to randomization on the day of enrollment. The IoR or designated staff will reconfirm and document the criteria indicated on the enrollment visit column of the Eligibility Checklist prior to proceeding with randomization/enrollment per site SOPs. Before randomization, the participant will undergo the following procedures:

- Confirm 30-day screening window has not been exceeded
- Update and confirm adequacy of locator information
- Confirm behavioral eligibility criteria through administration of the non-datafax Enrollment Behavioral Eligibility CRF
- Update medical history since screening visit. Evaluate use of prohibited medications, STI/UTIs, anorectal or reproductive track signs/symptoms, and overall general health.
- Perform HIV testing and plasma archive (Note for sites not conducting finger stick HIV rapids: to reduce participant burden, sites should consider collecting plasma archive and HIV samples as part of a single blood draw, prior to randomization)
- In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling as well as risk reduction counseling, including provision of condoms and lubricant.
- Conduct a physical exam and rectal exam
- All participants will provide rectal fluid sample for PD analysis.
- *****Those who agree to take part in the Rectal Biopsy/Fluid subset, will have:
    - rectal fluid and tissue collected via sponge for PD and mucosal immunology
    - rectal biopsy/fluid counseling
- Participants should be tested for GC/CT and HSV if indicated
- Participants should receive all available test results and treatment or referrals for STI/UTIs, anorectal or reproductive tract infections.
- Complete the following behavioral assessment: CASI Baseline Behavior Questionnaire
- Protocol adherence and study product adherence counseling. NOTE: this may also be conducted after randomization, but it could be helpful to provide the participant with more information about the study product prior to his/her final decision to enroll in the study

***** An exception will be made if conducted as part of a split Enrollment visit.

After randomization, participants will undergo the following procedures:

- Provision of study product instructions and site contact information
- Short message service (SMS) training.
- Observe first dose/simulation of first dose
- Reimbursement
- Schedule next visit

5.5.1.1 Random Assignment

At all study sites, participants will be randomly assigned to one of six study sequences (see Figure 5.2 below). Each participant will receive study product that includes:

- Once-daily rectally-administered Tenofovir (TFV) RG 1% gel
- Once daily Truvada (FTC/TDF) tablets
- RAI-dependent rectally-administered TFV RG 1% gel (BAT24) dosing.
    - BAT24 dosing refers to how participants will be instructed to insert the TFV RG 1% gel before and after sex. Participants will be instructed to insert one dose of TFV RG 1% gel up to 12 hours prior to RAI and one applicator of gel as soon as possible after RAI, but within 12 hours of intercourse. Participants will be instructed not to insert more than two doses within a 24-hour period.

Each sequence will consist of three eight-week periods of study product administration followed by a one-week washout period.

Figure 5.2 Study Regimen Assignment

Sequence	**Period 1** (8 weeks)	Washout (~1 week)	**Period 2** (8 weeks)	Washout (~1 week)	**Period 3** (8 weeks)	Washout (~1 week)
1	Oral (Daily FTC/TDF)		Rectal (Daily TFV RG 1% gel)		Rectal (RAI-associated TFV RG 1% gel)	
2	Rectal (RAI-associated TFV RG 1% gel)		Oral (Daily FTC/TDF)		Rectal (Daily TFV RG 1% gel)	
3	Rectal (Daily TFV RG 1% gel)		Rectal (RAI-associated TFV RG 1% gel)		Oral (Daily FTC/TDF)	
4	Rectal (Daily TFV RG 1% gel)		Oral (Daily FTC/TDF)		Rectal (RAI-associated TFV RG 1% gel)	
5	Oral (Daily FTC/TDF)		Rectal (RAI-associated TFV RG 1% gel)		Rectal (Daily TFV RG 1% gel)	
6	Rectal (RAI-associated TFV RG 1% gel)		Rectal (Daily TFV RG 1% gel)		Oral (Daily FTC/TDF)	

Participants will complete each of the study regimens in the order dictated by their randomization assignment.

The MTN SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-017 Randomization Envelopes
- MTN-017 Randomization Envelope Tracking Records
- MTN-017 Randomization Documents (contained inside the envelopes)
- MTN-017 Participant-Specific Pharmacy Dispensing Records

Once all eligibility assessments have been done and participants are found to be eligible, a randomization envelope will be assigned to each participant. Randomization Envelopes will be shipped from the MTN SDMC to each study clinic and will be stored in the clinic. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an envelope is assigned to a participant, it may not be re-assigned to any other participant. All envelopes are sealed with tamper-resistant security tape.

Envelope assignment to eligible participants will be documented in the MTN-017 Randomization Envelope Tracking Record that will accompany the envelope shipment to each site. The act of assigning a Randomization Envelope to a participant is considered the effective act of randomization and enrollment in the study.

The MTN 017 Randomization Envelopes will contain a two-part no carbon required (NCR) randomization document pre-printed with the site name, site location, Randomization Envelope number, and study regimen sequence. After recording the PTID and other details on the randomization document, clinic staff will separate the two parts of the form and deliver the white original form to the pharmacy. The pharmacy will use this form to verify against the prescription to ensure the correct product is being dispensed at a given visit, according to the participant's assigned sequence of study product regimens. The envelope and the yellow copy of the randomization document will be retained in the participant's study record.

5.5.1.2 Prescription Overview

The MTN-017 Study Prescription is a two-part no carbon required (NCR) document that is available from the MTN LOC Pharmacist. Prior to site activation, sites must order the blank MTN-017 Study Prescriptions along with the study product.
An authorized prescriber will complete a prescription based on the participant randomization information on the participant's MTN-017 randomization document (see Section 7 of this manual for information on completing study prescriptions). Once the prescription has been completed,

site clinic staff will separate the two parts of the form and deliver the white original form to the pharmacy. The white original form must be delivered to the pharmacy prior to study product dispensation for a given study regimen. The yellow copy of the prescription will be retained in the participant's study notebook.

5.5.1.3 Product Dispensation, Product Use Instructions, First Product Use, and Adherence Counseling

After random assignment has been completed, participants will be provided with detailed instructions for the use of their assigned product based on their sequence assignment, followed by adherence counseling. Participants also will complete their first product use or simulation of their first dose, at the clinic during their enrollment visits (see Section 7 of this manual for information on product dispensation). Further guidance related to product use instructions, first product use, and adherence counseling is provided in Section 6 of this manual.

5.6 Follow-up Visits

5.6.1 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-017 protocol specifies follow-up visits at three study periods. There are two types of scheduled visits:
  - Clinic Visits: Three visits at each study period (nine visits in total):
    - Study Product Use Initiate Visits: Enrollment (day 0), Week 9, Week 18
    - Mid-Product Use Visits: Week 4, Week 13, Week 22
    - Product Use End Visits: Week 8, Week 17, Week 26
  - Follow-up Phone calls: Two phone calls following the Initiate Period Visit (Period 1, 2, and 3), six phone calls in total, scheduled to occur:
    - 48-72 hours (2-3 business days) following the expected date of study product initiation for each period. For example, for participants that start product use on the day of enrollment, the phone call should take place 48-72 hours after enrollment.
      - Participants in the Rectal Biopsy/Fluid Subset who are randomized to gel use during the first period (i.e., sequences 2, 3, 4 and 6) will be instructed to abstain from product use for 72 hours after their biopsies. The expected date of study product initiation for them is 72 hours after enrollment. Therefore, for them, this follow-up phone call should take place 5-6 days after the enrollment visit (48-72 hours after expected product initiation in the given period).
      - Participants randomized to the RAI period, the phone call should take place 48-72 hours after period start.
    - Two weeks (14 business days) following the expected date of study product initiation for each period. Please note, this phone call takes place two weeks after the expected date of product initiation, not two weeks following the 48-72 phone call.
- **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 7.7).

5.6.2 Follow-up Visit Scheduling

5.6.2.1 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 the MTN-017 Randomization Envelope is assigned.

5.6.2.2 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-017 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.

Within each allowable visit window, there is a target visit window. The target visit window is the same for each visit, equal to +/- 2 days around the target visit date. For example, the target visit window for the Visit 3.0, Mid-period 1 visit (target day 28) is day 26 to day 30. Sites are encouraged to complete required study visits on the target day. If it is not possible to complete the required visit on the target day, sites should aim to complete the visit, ideally, within the target window. If it is not possible to complete the required visit within the target visit 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 Mid-period 1 visit completed on day 39 will be listed on the SCHARP retention report as being completed "retained - late" since it was completed outside of the target window, but 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.

Figure 5.3
MTN-017 Visit Windows

Visit #	Visit	Visit Code	Allowable Window Opens	Target Window Opens	Target Day	Target Window Closes	Allowable Window Closes
1	Screening	1.0	N/A	N/A	N/A	N/A	N/A
2	Enrollment/ Initiate Period 1	2.0	Day after Screening	N/A	0	N/A	30 days after Screening informed consent date
3	Mid-period 1 (Week 4)	3.0	14	26	28	30	41
4	End Period 1 (Week 8)	4.0	42	54	56	58	60
5	Initiate Period 2 (Week 9)	5.0	61	61	63	65	76
6	Mid-period 2 (Week 13)	6.0	77	89	91	93	104
7	End Period 2 (Week 17)	7.0	105	117	119	121	123
8	Initiate Period 3 (Week 18)	8.0	124	124	126	128	139
9	Mid-period 3 (Week 22)	9.0	140	152	154	156	167
10	End Period 3 (Week 26)	10.0	168	180	182	184	195

5.6.2.3 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 allowable visit window. When this occurs, the visit is considered a split visit. As described in Section 11 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).

For study visits requiring collection of samples for PK/PD, please ensure that these collections are done on the first day of the split visit. **Bangkok CRS only**: PK, PD and mucosal immunology samples (blood, fluid and tissue) must be collected on the second day of the split visit.

Note: If a visit, at which a CASI interview is required, is conducted as a split visit, the entire CASI interview must be completed on one day. If a CASI interview is begun, but not completed, on the first day of a split visit, the entire CASI questionnaire must 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 CASI questionnaire will be used for analysis purposes.

5.6.2.4 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable visit window, the visit is considered "missed" and a Missed Visit case report form must be completed to document the missed visit (see Section 11 of this manual for more information on completion of this form).

For participants that miss a Period End Visit (Visit 4, 7, and 10), the following missed procedures will be performed the next time the participant presents to the site:

- Collection of unused study product
- HIV testing and counseling
- Creatinine testing
- Plasma for storage
- Data Convergence Interview
- PK Data Convergence Interview (if PK results available)
- CASI
- IDI (if Visit 4 is missed)
- NAAT for CG/CT (only if clinically indicated)

5.6.3 Follow-up Visit Procedures

After participants enroll in the study, they are expected to complete eight protocol-required clinic visits each. Required follow-up visit procedures are listed in protocol Sections 7.2.1 – 7.5 and Appendix I. The protocol specifies Initiate Period, Mid-Period, and Period End clinic visits, as well as Follow-up Phone Calls and procedures to be done when clinically indicated. As a general guide:

- Locator information must be obtained/reviewed at every visit, starting at the Screening visit.
- HIV testing and counseling will be done at all visits with the exception of the Initiate Period visits (unless clinically indicated).
- Urine will be collected only at the screening and Period End 3 Visit/Final Clinic Visit, unless clinically indicated.
- Medical history, rectal exams, AE assessment and documentation, and assessment of concomitant medications will be done at all study visits.
- Male condoms will be provided at all study visits.
- Follow-up CASI will be done only at End Period visits. If a participant misses a visit when CASI is required, administer the missed CASI questionnaire the next time the participant presents to the clinic.
- Data Convergence Interviews will be conducted at the Mid-Period and End Period Visits. PK Data Convergence Interviews will be conducted at the next scheduled visit following

PK sample collection, or when results are available. Information on the process for conducting these interviews is found in Section 6 of this manual and Section 7.10 of the protocol.

- All participants will provide the following specimens for PK and PD analysis:
    - Blood will be collected at the Mid-Period (Plasma only) and End Period (PBMC and Plasma) visits.
    - Rectal fluid will be collected via sponge for PK and PD at all follow-up clinic visits.
- Participants in the Rectal Biopsy/Fluid Subset will provide specimens for PK, PD and Mucosal Immunology analysis at End Period Visits.
- All participants will be instructed to call-in to the clinic to report any new or worsening AEs within 7 days following the Final Clinic Visit 10 (Week 26). The study termination date is defined as the 7th day after the End Period 3/Final Clinic Visit (Visit Code 10.0). Therefore, a participant should not be terminated prior to the 7th day unless consent is withdrawn and the participant terminates early from the study. For MTN-017, the AE reporting period begins at the time of randomization and ends 7 days after the End Period 3/Final Clinic Visit.

5.6.3.1 Interim Visits

Interim visits may be done at any time during the study. All interim contacts (e.g., phone calls and/or clinic visits) will be properly documented in study files and on applicable CRFs (see Section 11 of this manual for further information on CRF completion). Procedures required during an interim visit will depend on the reason for the visit. For example, if a participant presents to the site to report an AE, all clinically-related procedures to assess the AE and required documentation would be the required procedures for that interim visit. In contrast, if a participant presents to the site to obtain further instructions/clarification on product use, no clinical procedures or CRF completion are required; rather, product use instructions and related documentation are required. Refer to section 7.7 of the protocol for the list of procedures that may be indicated at an interim visit.

5.6.4 Modified Visit Procedures for Participants Who Discontinue Product Use

Section 7.6 of the protocol provides information on the procedures for participants who discontinue study product. Participants that discontinue study product will be encouraged to remain in the study, if they are willing, until their scheduled end-date.

5.6.4.1 Participants Who Discontinue Product Use Either Voluntarily or per Investigator Discretion

All protocol-specified study procedures will continue except:

- Provision of study product
- Provision of product use/protocol adherence counseling
- Rectal exams, unless required for AE follow-up

If product is held or permanently discontinued early at a visit where PK, PD, mucosal immunology and behavioral assessments are required (per protocol Appendix I), sites must perform these procedures at that visit, then discontinue them at subsequent visits. For example, if product is discontinued at Study Visit 7 (Period End Visit), the site will collect samples for PK and PD, administer the CASI questionnaire, and conduct the Data Convergence interview (if applicable) at that visit. These procedures will be discontinued for the remaining study visits that occur during the hold, or after the permanent discontinuation.

- If PK,PD, and/or mucosal immunology specimen collection and associated procedures are required, per protocol Appendix I, but cannot be performed at the visit in which study product use is temporarily held or permanently discontinued, these required specimens may be collected up to 2 weeks following the hold/permanent discontinuation of product.
- Participants who have study product use temporarily held or permanently discontinued at a regularly scheduled visit should administer the CASI questionnaire and conduct the PK

and/or Data Convergence Interview(s) and In-Depth Interview (if applicable) as required per protocol Appendix I. These procedures will be discontinued for the duration of the product hold or after the permanent discontinuation.

Note: PK Data Convergence Interviews should only be omitted if no PK result is available because blood (plasma samples) were not collected due to the hold/discontinuation. If this occurs, the PK Data Convergence Interview CRF should be completed as required per the CRF completion schedule. However, site staff should mark on the form that no interview was performed because of the hold/discontinuation.

- For participants who have study product use held or permanently discontinued at an interim visit, site staff should administer the CASI questionnaire and conduct the Data Convergence interview and In-Depth Interview (if applicable) at the participants' next scheduled visit in which these assessments are required (per Protocol Appendix I). These procedures will be discontinued for the duration of the hold or after the permanent discontinuation. Additionally, site staff should consult the MTN-017 Management Team (mtn017mgmt@mtnstopshiv.org) immediately for further guidance regarding PK/PD specimen collection.

- In the case of temporary product holds, completion of the discontinued procedures will resume, per the protocol-specified schedule (Appendix I), if and when the participant resumes study product use.

- If the participant has any unused study product in his/her possession at the time when product use is held, the retrieval of unused study product will depend on the expected duration of the hold. Per protocol section 6.4.7, if the product hold has an expected duration of at least 7 days, unused product should be retrieved from the participant within 7 working days. If the expected duration of the hold is less than 7 days, it is not necessary to retrieve unused study product from the participant.

- If a participant permanently discontinues study product use, site staff should attempt to retrieve any unused study product in his/her possession within 7 working days.

5.6.4.2 Participants Who Become Infected with HIV

Study product use must be held immediately for participants with at least one positive rapid HIV test result (this includes participants with discordant rapid results from the same visit), or positive EIA result, or indeterminate result. Clinic staff should inform the pharmacist of the product hold in writing, using a Study Product Request Slip, and should complete and fax a Clinical Product Hold/Discontinuation Log form to the MTN SDMC.

In addition to the discontinued procedures stated above in section 5.6.4.1, participants who seroconvert during study follow-up will discontinue the following study procedures:

- HIV-1 Serology
- HIV pre-and post-test counseling (HIV/STI risk reduction counseling will be modified to address primary and secondary prevention)

Participants who seroconvert during follow-up will undergo the following additional procedures:

- CD4 testing
- HIV RNA testing
- HIV drug-resistance testing
- Consent to notify the participant's medical care provider of the participant's involvement in MTN-017
- Referral to available resources in the area for HIV testing, treatment, and support

5.6.5 Voluntary Withdraw of Study Participation

A participant may choose to withdraw consent from the study and terminate their study participation at any time. In these cases, site staff should ask the participant if *s/he* would be willing to complete one final study visit, which would count as his/her termination visit. If participant is willing, site staff should conduct all required termination procedures at this final visit. Early termination procedures will be done per Section 7.5 of the protocol (Period 3 End Visit) and will be documented via completion of all required CRFs for this visit, as listed in SSP manual Table 11-3. In addition, site staff should complete the 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: Termination, and End of Study Inventory. No other CRFs should be completed, unless sites are instructed otherwise by SCHARP.

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

5.6.5.1 Resumption of Study Participation After Voluntary Withdrawal

The protocol allows for participants who voluntarily withdraw from the study to reverse their decision and re-join the study during their planned follow-up period, according to their original visit schedule. The resumption of study procedures and follow-up are subject to the investigator's discretion, pending PSRT consultation. If such cases arise, study staff are advised to contact the MTN-017 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 should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged. Participant's random assignment also will remain unchanged and s/he will continue product use per his/her random assignment.
- Prior to performing any study procedure, the participant must provide written informed consent to document that s/he voluntarily rejoined the study. For re-consenting procedures, refer to Sections 4 of this study manual.
- An interval (since the last visit) medical and medication history should be taken and HIV and safety laboratory testing should be done as soon as the participant resumes study participation. Product use will be resumed only among participants who are confirmed HIV-uninfected per the MTN-017 HIV testing algorithm, and HBsAg negative.
- A rectal exam (visual and digital only) should be performed as soon as possible, and prior to re-instating gel use. A rectal exam and other clinically-indicated evaluations also should be performed if the participant reports current anorectal 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.
- 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 MTN-017 Study Prescription. 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, resumption of study follow-up and study product use.