

Section 5. Study Procedures

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This section provides information on requirements for study procedures in MTN-026, including screening, enrollment and participant follow-up visits.

5.1 Visit Locations

Given the nature of study procedures required to be performed during MTN-026, all visit procedures are expected to occur at the study clinic or by phone (for the designated contact one week following Visit 16).

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 be enrolled in the study. Each study site must establish a standard operating procedure that describes how study staff will fulfill this responsibility. This SOP should contain, at a minimum, the following elements related to 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)

5.3 Screening Visit

The term “screening” refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-026. Required screening procedures are listed in protocol Sections 7.2

The study eligibility criteria are listed in protocol Sections 5.2 and 5.3. All eligibility criteria are initially assessed at the Screening visit. These same criteria, in addition to others, are confirmed on the day of Enrollment (Visit 2). 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-026 webpage under Study Implementation Materials.

5.3.1 Screening and Enrollment Timeframe

All protocol-specified screening and enrollment procedures must take place up to 45 days prior to enrollment/randomization, beginning on the day the potential participant provides written informed consent. The day the screening informed consent is signed is counted as “-45” and enrollment is counted as 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.

Per protocol Section 7.2, 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.

Potential participants may screen for MTN-026 up to two times (two attempts). 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).

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

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

- The participant did not complete all screening and enrollment visit procedures within 45 days of providing informed consent
- Participants that screen out due to IoR or designee’s discretion may be rescreened, in consultation with the PSRT.

If all screening and enrollment procedures are not completed within 45 days of obtaining written informed consent, the participant must repeat the entire screening process, beginning with the informed consent process. Note, however, a new participant identification number (PTID) is not assigned to the participant in this case. Rather, the original PTID assigned at the first screening attempt is used for any repeat screening attempts, as well as future study visits should the participant successfully enroll in the study.

5.3.2 Screening Visit Procedures

Required screening procedures are specified in the MTN-026 protocol section 7.2 and reflected in the applicable visit checklist available on the MTN-026 webpage. Listed below is a brief review of all required screening procedures which include a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests.

Administrative screening visit procedures include the provision of informed consent, generation of a PTID, and the conduct of a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Locator and demographic information will also be collected. Participants will be reimbursed for their time, and scheduled for their enrollment visit if presumptively eligible.

Behavioral eligibility criteria, which are based on self-report, may be evaluated by administration of the Screening Behavioral Eligibility worksheet, provided on the MTN-026 webpage under Study Implementation Materials. As this worksheet is designed to be interviewer-administered and serve as a source document, questions must be asked verbatim and participant responses should be recorded directly on the worksheet. It is suggested that staff administer this questionnaire early in the screening visit, so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is determined ineligible due to behavioral criteria (unless sites decide to administer clinical and laboratory evaluations regardless of eligibility as a service to the participant).

Clinical screening visit procedures, as described in detail in Section 7 of this manual, include:

- Collection of medical history, concomitant medications, physical exam, and genital exam.
- Evaluation of prohibited medications/products, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Female participants will also receive contraceptive counseling (as needed), and have discussion of pregnancy/breastfeeding and menstrual history and future pregnancy intentions.
- 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 9 of this manual. In summary, participants will receive:

- Testing for HIV, STIs (GC/CT, HSV, and Syphilis), pregnancy, HBsAg, Coagulation (INR), Anti-HCV, serum chemistries (creatinine, AST, ALT), and CBC with platelets and differentials.
- Participants will also be counseled about HIV and receive appropriate pre- and post-test counseling as well as risk reduction counseling.

Further information regarding the generation and structure of PTIDs for MTN-026 can be found in Section 12 of this manual.

5.3.3 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/or enrollment logs. Screening and/or enrollment logs may be maintained separately or combined into one document. A sample Screening and Enrollment Log suitable for use in MTN-026 is available on the MTN-026 webpage under Study Implementation Materials. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample log when recording the reason(s) for screening failure/discontinuation.

5.3.4 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the participant is determined to be ineligible. 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 ICF(s)
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist

- 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 including
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)

Should a participant be ineligible for enrollment, the Eligibility Criteria should be completed, including the applicable inclusion and/or exclusion criteria selected, and the screening file should be retained on site. In addition, the Screening and Enrollment Log should be updated with date of discontinuation of screening and reason for screen failure.

5.4 Enrollment Visit

A participant's final eligibility status should be determined after completion and final sign off on the Eligibility Checklist. The site IoR (or designee) and a second staff member, per site SOP, should sign and date the Eligibility Checklist to affirm/confirm eligibility. A participant may only be enrolled after the final assessment of eligibility is completed. A participant is considered enrolled in the study, only after s/he has been randomized. All baseline samples, assessments, and examinations must be collected/completed before a participant is randomized (the definition of enrollment). Further information on randomization is provided in Section 12 of this manual.

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-026 Protocol Safety Review Team (PSRT) and the MTN-026 Management Team for guidance on subsequent action to be taken.

5.4.1 Enrollment Visit Procedures

The Enrollment/Visit 2 serves as the baseline visit for MTN-026. All procedures for this visit must be conducted on the same day, and cannot be split across multiple days. Further guidance will be provided on a site-by-site basis.

Per Protocol Section 7.3, for female participants, menses must not coincide with a participant's enrollment visit (Visit 2). This should be taken into consideration when scheduling the enrollment visit. If a participant is menstruating on the day of enrollment, her entire visit should be rescheduled for after the completion of menses, within the 45-day screening window, if possible.

Study enrollment procedures are specified in protocol section 7.3 and reflected in the visit checklist available on the MTN-026 webpage. The following procedures will be completed as part of eligibility confirmation prior to randomization on the day of enrollment.

Before randomization, the following procedures will be conducted:

- Review and update locator information
- Review informed consent and confirm participant remains interested in continued study participation
- Confirm behavioral eligibility criteria (through administration of the Enrollment Behavioral Eligibility worksheet provided on the MTN-026 study webpage under Study Implementation Materials.)
- Update medical history since screening visit. Evaluate use of prohibited medications, STI/UTIs, genital or reproductive track signs/symptoms, and overall general health.
- For female participants, provide contraceptive counseling (if indicated) and review/update menstrual history

- Collect urine to test for pregnancy (for females) and if clinically indicated, conduct a dipstick UA and/or urine culture for all participants.
- Collect blood for: HIV testing and plasma archive (Note: if site is not conducting finger stick HIV rapids, site should consider collecting plasma archive and HIV samples as part of a single blood draw to reduce participant burden). If indicated, also collect blood for serum chemistries, CBC with differential and platelets, and syphilis serology.
- In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling as well as risk reduction counseling.
- Conduct a physical exam
- Conduct a genital exam to confirm eligibility and collect baseline anorectal and pelvic samples
- Note: If participant is not eligible for enrollment, samples collected during this exam must be destroyed.
- 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, genital or reproductive tract infections.
- Complete the Baseline Behavior CASI 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

After randomization, the following procedures will be conducted:

- Provision of study product instructions and site contact information
- Reimbursement
- Schedule next visit

Please note, no product will be administered during the enrollment visit.

5.4.2 Pharmacokinetics, Pharmacodynamics, and Mucosal Safety Assignment

On the day of Enrollment, participants will be assigned to:

- Time assignment: At Dosing Visits 3 and 13, participants will be assigned to approximately 30-60 minutes or 120 minutes (2 hours) for blood and rectal sample collection. It is recommended that blood be collected first, followed by rectal sample collection.
 - Note: For participants assigned to the ~30-60-minute timepoint, sample collection may begin anytime within the designated time period. For participants assigned to the ~120 minute timepoint, there is an allowable +/- 15-minute window. Samples maybe collected as early as 105 minutes and as late as 135 minutes.
 - Sample collection should happen within 1 hour of blood collection. Per protocol, pelvic samples are not assigned to these times; however, it is recommended that while conducting the genital examination and collecting the rectal samples, that pelvic samples also be collected.
- Day assignment: Participants will be assigned to PK/PD sample collection at either 24, 48, or 72 hours after Dosing Visits 3 and 13. Efforts should be made to collect samples either at 24, 48, or 72 hours, based on assignment, following product administration.

Please note, assignment done at enrollment will be maintained throughout the study. Once a participant has received an assignment, that same assignment is maintained for the duration of his/her study participation.

For example, if a participant is assigned to have PK/PD samples collected 120 minutes after gel insertion at Visit 3 and 48 hours post product administration at Visit 5, samples will also be collected at 120 minutes (2 hours) after gel insertion at Visit 13, and at 48 hours post product administration at Visit 15. Ideally, on Visit 5 and 15, samples will be collected approximately 48 hours after the last product use (+/-2 hours). Further information on how the day and time assignments are generated is referenced in Section 12 of this manual.

Table 5-1 below shows the recommended sample collection windows when samples should be collected post dose administration.

Table 5-1: Sampling Windows

Day Assignment	Sample collection window
Visit 4: 24 Hours After Application of Study Product Visit Code 4.0	(+/- 1 hour)
Visit 5: 48 Hours After Application of Study Product Visit Code 5.0	(+/- 2 hours)
Visit 6: 72 Hours After Application of Study Product Visit Code 6.0	(+/- 4 hours)
Visit 14: 24 Hours After Last Application of Study Product Visit code 14.0	(+/- 1 hour)
Visit 15: 48 Hours After Last Application of Study Product Visit code 15.0	(+/- 2 hours)
Visit 16: 72 Hours After Last Application of Study Product Visit code 16.0	(+/- 4 hours)

5.5 Follow-up Visits

Once a participant is enrolled in the study, follow-up visits will be divided into two categories: dose administration and sample collection. It is important to discuss the visit schedule with the participant to ensure that the participant can meet the study expectations.

5.5.1 Types of Follow-up Visits

Throughout the study follow-up period, two types of follow-up visits may be conducted (interim and scheduled visits):

- **Interim visits** are those visits that take place between scheduled visits. All interim contacts (e.g., phone calls and/or clinic visits) will be properly documented in study files and on applicable CRFs. Procedures required during an interim visit will depend on the reason for the visit. See SSP Section 12 for details on interim study visits and visit codes.
- **Scheduled visits** are those visits required per protocol. There is a total of 14 clinic follow-up visits, followed by the Follow-up contact/Termination.
 - Visit 3 (Dosing Visit): This visit is scheduled to occur approximately 7 days after Enrollment/Visit 2. Given subsequent visits (Visit 4-6) will take place ~24, 48, and 72 hours after this visit, attention should be given to what day Visit 3 is scheduled to ensure consecutive visits take place when adequate staff is available. Participants will provide samples at 0

minutes, and at approximately 30-60 minutes or 120 minutes (2 hours) after product use, per participant assignment.

- Visits 4-6 (Sampling Visits): Visits will be scheduled ~24, 48, and 72 hours after Visit 3. All participants will have blood collected at all these visits and will have rectal/pelvic samples collected based on their day assignment; when scheduling these visits, ensure adequate staff is available for the visits.

NOTE: Menses must not coincide with Study Visits 2-6; therefore, sites should take this into consideration when scheduling these visits.

- For example, if a participant is enrolled on 05 September 2017, clinic visits 3-6 will be as follows:

September 2017

Sun	Mon	Tue	Wed	Thu	Fri	Sat
					1	2
3	4	5 Enrollment Visit (Day 0)	6	7	8	9
10	11	12 Single Dose Administration (Visit 3)	13 Visit 4 (~24 hours)	14 Visit 5 (~48 hours)	15 Visit 6 (~72 hours)	16
17	18	19	20	21	22	23
24	25	26	27	28	29	30

NOTE: After Visit 6, participants will have a washout period. The washout period will be a minimum of 14 and a maximum of 28 days (see study Visit Windows below). The washout period should be timed to coincide with female participants' menses (i.e. avoiding female participants being on their menses during Study Visits 7-16.)

- Visits 7-13 (Dosing Visits): Participants will present to the clinic daily for directly-observed product administration. Samples will be collected only at visits 7 and 8. These visits take place on consecutive days, so arrangements need to be made at the clinic to ensure all required staff is available (e.g. clinical, pharmacy, lab), even on weekends.
- Visit 13 (Last Dosing Visit/Early Termination Visit): All participants will provide blood for PK at hour 0 and then at approximately 30-60 or 120 minutes after product use, per participant's timed assignment. If this visit is serving as the Early Termination visit, sample collection will be based on timing of last dose.

- ☞ Collect plasma and rectal/vaginal fluid samples if rectal gel was applied within the previous 7 days, prior to the visit.
- ☞ Tissue samples may be collected within three days of last product use. If product was not applied within the three days prior to the visit, tissue sample collection should not occur.
- Visits 14-16 (Sampling Visits): Visits will be scheduled ~24, 48, and 72 hours after Visit 13. Blood and rectal/pelvic samples will be collected, so when scheduling these visits, ensure adequate staff is available for the visits. All participants will have blood collected at all these visits; however, they will have rectal/pelvic samples collected per his/her assigned day.
- For example, if a participant has a 19-day washout period due to scheduling issues, and Visit 7 takes place on 4 October 2017, clinic visits 8-16 will be as follows:

October 2017

Sun	Mon	Tue	Wed	Thu	Fri	Sat
1	2	3	4 Visit 7 (Dosing Visit) *Labs Required	5 Visit 8 (Dosing Visit) *Labs Required	6 Visit 9 (Dosing Visit)	7 Visit 10 (Dosing Visit)
8 Visit 11 (Dosing Visit)	9 Visit 12 (Dosing Visit)	10 Visit 13 (Final Dose) *Labs Required	11 Visit 14 (Sampling Visit) *Labs Required	12 Visit 15 (Sampling Visit) *Labs Required	13 Visit 16 (Sampling Visit) *Labs Required	14
15	16	17	18	19	20 Visit 17 (Follow-up Contact)	21
22	23	24	25	26	27	28
29	30	31				

- Visit 17 (Follow-up Contact/Termination): This contact could be either a clinic visit or a telephone contact.
- NOTE: Further follow-up visit considerations are described in section 5.5.3 below.

5.5.2 Follow-up Visit Scheduling

5.5.2.1 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-026 staff member randomizes a participant via Medidata Rave.

5.5.2.2 Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-026 protocol allows for certain visits to be completed within a visit window, if possible. Visits 3, 6, 7, 16, and 17 have visit windows specifying which study days the visit can be completed. All other visits do not have visit windows as they are completed on consecutive calendar days.

A complete listing of visit windows is available in Section 12 of this manual.

Sites are encouraged to complete required study visits on the target day, if possible. If this is not possible, the visit may be completed within the visit window (for visits with a window). Visits completed within the visit window will be considered completed ("retained") 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 Statistical and Data Management Center (SDMC) will provide the site with a visit scheduling tool that can be used to create follow-up visit schedules for enrolled participants. Every effort should be made to schedule participants within the allotted timeframes.

5.5.2.3 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, if that visit has a window. When this occurs, the visit is considered a split visit. As described in Section 12 of this manual, all case report forms (CRFs) completed for a split visit are assigned the same visit code (even though the dates recorded on the CRFs may be different).

For study visits requiring collection of PK, PD, and mucosal safety samples, please ensure that these procedures are done on the first day of the split visit to avoid complicating interpretability.

Additionally, if a CASI interview is required, 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.

If all required procedures cannot be completed on a single day and that visit does not have a window, the remaining procedures are considered missed. Documentation of the rationale for not completing the procedures should be included in the participant's chart.

5.5.2.4 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 CRF must be completed to document the missed visit (see the CRF Completion Guidelines for more information on completion of this form).

If a participant misses the following visits, in addition to protocol-specified procedures for the applicable visit, some procedures should be completed when the participant returns to the clinic:

- Visit 3: Behavioral assessment (IDI and CASI) and pregnancy testing
- Visit 7: HIV testing and counseling and pregnancy testing
- Visit 13: Collection of unused study product and pregnancy testing
- Visit 14: Behavioral assessment (IDI and CASI)
- Visit 16: HIV testing and counseling, plasma archive, and chemistries

5.5.3 Follow-up Visit Procedures

After each participant enrolls in the study, s/he is expected to complete 14 protocol-required in-clinic visits and one Follow-up Contact/Termination visit. Required follow-up visit procedures are listed in Protocol Sections 7.4-7.9 and Appendix I. As a general guide, during follow up, the following will occur:

- Locator information must be obtained/reviewed at every visit.
- Protocol counseling, including adherence and product use instructions counselling will be provided at all visits.
- Medical/menstrual history, AE assessment and documentation, assessment of concomitant medications, and provision of any available lab results, will be done at all follow-up study visits.
- Participants will be reimbursed for their time at each visit, and scheduled for their next visit as applicable.
- Condoms will be offered only at visit 6
- Pregnancy test is only required at visits 3, 7 and 13
- HIV testing and counseling are only required at visits 7 and 16
- Chemistries are required only at visit 16
- Targeted physical exam, CBC with differential and platelets, Dipstick UA, urine culture, and NAAT for GC/CT are done only if clinically indicated.

NOTE: Please reference Section 9 for information related to genital specimen and blood collection considerations.

5.5.4 Visit 17 Follow-up Contact/Termination Considerations

The Visit 17 Follow-up Contact/Termination visit could be scheduled as an in-clinic visit or as a phone call. Site staff should discuss with the participant what procedures will be conducted during this visit/contact. Depending on results from labs collected during Visit 16 or if Visit 16 is missed, plans may need to change. For example, staff and participant may have agreed to a phone call, but based on test results or if missed labs need to be made up, it may be necessary for the participant to present to the clinic to receive study results and counseling. It is important that staff discuss this with participants during the informed consent process as well as when the participant's follow up visit schedule is generated. It is also ideal to remind participants during Visit 16 to ensure the participant is agreeable and understand what may be expected after study termination.

Additional contacts also are required for:

- Participants who are pregnant during the study to obtain pregnancy outcome(s)
- Participants with positive or indeterminate HIV rapid or confirmatory test results
- Participants with certain types of AEs that are ongoing at study exit (See detailed guidance in Section 8 of this manual)

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. It is

recommended that final contact plans be documented on chart notes or a site-specific tool (e.g. worksheet). All final contacts must be documented in participant study records, but no CRFs are completed for these post-termination contacts (with the exception of the Pregnancy Outcome (Summary and Log) CRFs to collect pregnancy outcome data for pregnancies that are ongoing at the time of study termination).

After completing their Visit 17 Follow-up Contact/Termination visit and final study contacts, participants will no longer have routine access to services provided through the study such as HIV counseling and testing or contraceptive provision. Participants should be counseled about this — ideally before and during their Visit 17 Follow-up Contact/Termination visit — and provided information on where they can access such services after study exit. It is recommended that all study sites develop written referral sheets that can be given to participants; if Visit 17 Follow-up Contact/Termination visit is planned as a phone call, this information should be provided to the participant prior to Termination. If Visit 17 Follow-up Contact/Termination visit is planned as an in-clinic visit, this information could be provided to participants at that time.

All participants will be contacted post-study to be informed of the study results and their random assignments. It is currently expected that study results and any additional unblinding information will be available within approximately 6-9 months after last participant study follow-up. Participant preferences for methods to be used for contacting them when unblinding information and study results are available should be documented in participant study records.

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 or other site-specific documentation that can be easily accessed by study staff.

5.5.5 Participants Who Become Infected with HIV

Per protocol section 7.10.1, study product use must be discontinued immediately for participants with a reactive rapid HIV test result (this includes participants with discordant rapid results from the same visit).

If a participant becomes infected with HIV-1 after the Enrollment Visit, participant will be referred to local care and treatment services and may return to the research clinic for additional counseling and other support services, as needed per site SOP. Once HIV status is confirmed, study follow-up visits will be discontinued and the participant will be considered terminated from the study. Participants who seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing), as clinically indicated per site SOP.

5.5.6 Participants Who Become Pregnant

If a participant becomes pregnant, follow-up visits and procedures will be discontinued and the participant will be considered terminated from the study (see Protocol Section 7.10.2). The participant will be referred to local health care services and may return to the research clinic for additional counseling, as needed per site SOP.

Site should develop a plan with participant to attain pregnancy outcome(s) for pregnancies that are ongoing at the time of study exit. One contact to obtain this information is sufficient. For example, participant could call or e-mail the site to inform the site of the outcome.

5.5.7 Participants Who Permanently Discontinue Study Product for Other Reasons

Given the short duration of study participation, there will be no temporary product holds. For participants who permanently discontinue study product use for any other clinician initiated reason (other than HIV seroconversion or pregnancy) or participant initiated (participant decides

to withdraw from the study or stop using study product), will be considered terminated from the study (see Protocol Section 7.10.3).

5.5.8 Criteria for Early Termination of Study Participants

As outlined in Protocol Section 9.6, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, after consultation with the PSRT. Participants also may be withdrawn if NIAID, MTN, government or regulatory authorities, including the FDA and Office for Human Research Protections (OHRP), or site IRBs/ECs terminate the study prior to its planned end date.

If the participant is terminating early from the study for any reason, staff should complete the following:

- Ask participant if s/he is willing to complete one last visit, during which visit procedures for the Visit 13: Last Study Product Administration Visit/Early Termination Visit should be completed.
 - Please note, PK, PD, sample collection will be done at the discretion of the MTN-026 Management Team (see section 5.5.1 for additional guidance).
- Record the reason(s) for the withdrawal in participants' study records.
- Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.
- Update participant locator form, and document how the participant would like to receive any follow up test results (as needed), and be informed of study results.

Once a participant withdraws from the study, s/he will not be able to rejoin the study at a later time.

5.5.9 Replacing Participants

The following criteria has been established for replacement participants. Participants will be replaced if any of the following criteria is met:

- Single Observed Dose (Visit 3) is missed
- 7 Day Observed Product Administration (Visits 7-13) are missed
 - Note: to be replaced, the participant must miss all the 7 observed daily doses. If the participant attends at least one of these visits, the participant does not need to be replaced.

NOTE: A missed visit in this case is defined as participant not completing the visit (e.g. participant does not present to the clinic for the visit, participant has been discontinued from study product use and has been withdrawn from the study).

The purpose of replacing participants is to compensate for the potential data loss. Replacement decisions will be made on a case by case basis by study leadership and the MTN-026 Management Team. Site staff should complete the Participant Replacement Assessment CRF as soon as a participant meets a criterion for replacement.