

Section 5. Study Procedures

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5. Introduction

This section provides information on requirements for study procedures in MTN-033, including screening, enrollment and participant follow-up visits.

5.1 Visit Locations

Given the nature of study procedures required to be performed during MTN-033, all visit procedures are expected to occur at the study clinic or by phone (for the designated contact one week following Visit 6).

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. The 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 criterion (met or not met)
 - Ethical and human subjects considerations
 - Staff responsibilities for 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-033. 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-033 webpage under Study Implementation Materials.

5.3.1 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. The day the screening informed consent is signed is counted as “-30” 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-033 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. 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.

If all screening and enrollment procedures are not completed within 30 days of obtaining written informed consent, the participant must repeat the entire screening process, beginning with the informed consent process.

5.3.2 Screening Visit Procedures

Required screening procedures are specified in the MTN-033 protocol section 7.2 and reflected in the applicable visit checklist available on the MTN-033 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, assessment of behavioral eligibility criteria and completion of 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-033 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 (Clinical Considerations) of this manual, include:

- Collection of medical history, concomitant medications and physical, genital and anorectal exams.
- Evaluation of prohibited medications/products, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Participants should receive all available test results and treatment or referrals for treatment for UTI/RTI/STIs.

Details regarding laboratory tests and sample collection at screening are provided in Section 9 (Laboratory Considerations) of this manual. In summary, participants will receive:

- Testing for HIV, STIs (GC/CT, HSV, and Syphilis), HBsAg, Coagulation (PT/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-033 can be found in Section 12 (Data Collection) 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-033 is available on the MTN-033 webpage under Study Implementation Materials. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample log when recording all 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 the 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)
- Completed Inclusion/Exclusion CRF
- 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 completed 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 Checklist 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 the date of discontinuation of the screening and reason for the 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 (Data Collection) of this manual.

If site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the MTN-033 Protocol Safety Review Team (PSRT) and the MTN-033 Management Team for guidance on subsequent action to be taken.

5.4.1 Enrollment Visit Procedures

Enrollment/Visit 2 serves as the baseline visit for MTN-033. 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.

Study enrollment procedures are specified in protocol section 7.3 and reflected in the visit checklist available on the MTN-033 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-033 study webpage under Study Implementation Materials.)
- Update medical history since screening visit.
- Evaluate use of prohibited medications, STI/UTIs, genital or reproductive tract signs/symptoms, and overall general health.
- If clinically indicated, conduct a dipstick UA and/or urine culture.
- Collect blood for: HIV testing and plasma archive. 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 and anorectal exam to confirm eligibility and collect baseline anorectal 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 product administration prior to his/her final decision to enroll in the study

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

- Time assignment: Participants will be assigned a time point in which they will provide rectal fluid and tissue samples at Dosing Visits 3 and 5. During these visits, participants will either provide samples 1 hour or 4 hours after study product is administered. This assignment will be maintained for each dosing visit.
- Gel Application Sequence: Participants will be asked to apply the study gel twice during their time in the study. During enrollment, participants will be told the order in which they will use the study product application methods at Dosing Visits 3 and 5. At these visits, participants will follow their assigned rectal gel application method study sequence and insert the study gel into the rectum using either an applicator or a coital simulation device (dildo).

Prior to the participant leaving the clinic, site staff should provide the participant with site contact information and reimbursement, and schedule the participant's next visit.

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

5.5 Follow-up Visits

Once a participant is enrolled in the study, the participant will have 5 more visits/contacts. 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 (scheduled and interim visits):

Scheduled visits are those visits required per protocol. There are 4 clinic follow-up visits, followed by the Follow-up contact/Termination.

- **Visits 3 and 5 (Dosing Visits):** Visit 3 is scheduled approximately 10 days after Visit 2/Enrollment. Visit 5 ideally should occur 14-28 days after Visit 4/Sampling Visit. Participants will be randomized to provide samples at either 1 hour or 4 hours after dose administration (see section 5.4.1 above). Please note, there is a +/- 15minute allowable window around each of these sampling timepoints.
- **Visit 4 (Sampling Visit):** Visit 4 should ideally occur ~24 hours after Dosing Visit 3. Participants will have rectal samples collected and, if indicated, blood collected. When scheduling this visit, ensure enough staff will be available to perform visit procedures. Please note, there is a +/- 4-hour allowable window around this visit.
 - **Visit 6 (Sampling Visit):** Visit 6 should ideally occur ~24 hours after Dosing Visit 5. All participants will have blood and rectal samples collected, so when scheduling this visit, ensure enough staff will be available to perform visit procedures. Please note, there is a +/- 4-hour allowable window around this visit.

NOTE: Between Visit 4 and Visit 5 participants will have a washout period. The washout period will be a minimum of 14 days and a maximum of 28 days (see study Visit Windows below).

- Visit 7 (Follow-up Contact/Termination): This contact could be either a clinic visit or a telephone contact.
- Early Termination Visit: If a participant must be terminated early, the procedures for Visit 6 are to be followed.

NOTE: Further follow-up visit considerations are described in section 5.5.3 below.

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 data forms. Procedures required during an interim visit will depend on the reason for the visit. See SSP Section 12 (Data Collection) for details on interim study visits and visit codes.

5.5.2 Follow-up Visit Scheduling

5.5.2.1 Target Visit Dates

Each participant's enrollment date is defined as the date upon which the MTN-033 staff member randomizes a participant via Medidata Rave. Staff should strive to have the participant complete a specified follow-up visit on the target date for that visit.

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-033 protocol allows for visits to be completed within a visit window. All visits have visit windows specifying which study days the visit can be completed on.

A complete listing of visit windows is available in Section 12 (Data Collection) of this manual.

The site is encouraged to complete required study visits within the visit 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 calendar tool (also available on the MTN-033 webpage under Study Implementation Materials) 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"

Ideally, all procedures specified by the protocol to be performed at a follow-up visit will be completed at a single visit on a single day. If 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 12 (Data Collection) of this manual, all forms completed for a split visit are assigned the same visit code (even though the dates recorded on the forms may be different).

For study visits requiring collection of PK, PD, and mucosal safety samples, please ensure 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 a single day. If at Visit 3 or 5 the CASI interview is begun but not completed, the entire CASI questionnaire must be re-administered (starting from the beginning) at the next visit, in addition to

other protocol-specified procedures for the applicable visit. If this occurs, the SDMC and the BRWG should be notified and a new CASI ID should be administered for the CASI; 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

A visit is considered "missed" if none of that visit's procedures are completed within the allowable visit window. If the visit is missed, a Missed Visit form must be completed to document the missed visit (see the CRF Completion Guidelines for more information on completion of this form).

If Visit 3 or 5 is missed, site staff should consult the Management Team for guidance on whether a replacement participant should be enrolled. A missed visit in this case is defined as a participant not completing the visit (e.g., participant does not present to the clinic for the visit within the allowable window, 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-033 Management Team. Site staff should complete the Participant Replacement Assessment form as soon as a participant meets a criterion for replacement and has approval of the Management Team.

If Visit 4 or 6 is missed, the participant should be requested to return to the clinic as soon as possible, if willing, to complete protocol-specified procedures that were missed (please contact SCHARP as to the coding of this visit):

- If Visit 4 is missed, participants should return to the clinic as soon as possible to make up the following procedures:
 - Review/update locator information, medical and medication history and assess for AEs
 - Provide protocol counseling
 - Collect blood for PK
 - Conduct rectal exam and collect required PK, PD and mucosal safety samples (rectal fluid, tissue and effluent)
- If Visit 6 is missed, participants should return to the clinic as soon as possible to make up the following procedures:
 - Review/update locator information, medical and medication history and assess for AEs
 - Provide protocol counseling and HIV pre/post and risk reduction counseling
 - Collect blood for PK, serum chemistries and HIV testing
 - Conduct rectal exam and collect required PK, PD and mucosal safety samples (rectal fluid, tissue and effluent)

Refer to section 5.5.4 below for additional guidance to be followed when disclosing available tests results to the participants. Study termination can occur up to 14 days after the last sampling visit

5.5.3 Follow-up Visit Procedures

Each participant enrolled in the study is expected to complete 4 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 will be provided at all visits.

- Medical 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 at all visits.
- HIV testing and counseling are required at visits 2 and 6.
- Chemistries are required only at visit 6 only.
- Targeted physical exam, CBC with differential and platelets, dipstick UA, urine culture, and NAAT for GC/CT are done only if clinically indicated.

Per protocol, on the day of dosing (Visits 3 and 5), blood will be collected at baseline (prior to gel application and at 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after gel application. Depending on randomization, rectal samples (fluid and tissue) will be collected at either 1 or 4 hour(s) after gel application. At sampling visits (Visits 4 and 6), blood and rectal samples (fluid and tissue) should be collected approximately 24 hours after gel application. Please reference Section 9 (Laboratory Considerations) for additional information related to genital specimen and blood collection considerations.

The table below shows the allowable windows for samples collected post dose administration.

Visit/Visit Type	Sample Schedule	Sample Collection Window
Visit 3 (Dosing Visit)	<ul style="list-style-type: none"> • Blood: baseline (0 hours/pre-dose) and 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after dose • Rectal samples: 1 or 4 hours after dose 	<p>-/+ 15 minutes</p> <p>+/- 30 minutes</p>
Visit 5 (Dosing Visit)	<ul style="list-style-type: none"> • Blood: baseline (0 hours/pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, and 4 hours after dose • Rectal samples: 1 or 4 hours after dose 	<p>-/+ 15 minutes</p> <p>+/- 30 minutes</p>

Note: Rectal swab for PK must be collected within one hour of the PK blood draw. Given the 1 and 4-hour rectal samples overlap with the 1 and 4-hour required blood samples, there is a -/+30-minute allowable window around the rectal samples.

5.5.4 Visit 7 Contact/Termination Considerations

The Visit 7 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 the results of labs collected at Visit 6, or if Visit 6 is missed, a clinic visit may be necessary or a call may suffice. 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 6 to ensure the participant is agreeable and understand what may be expected after study termination.

Additional contacts also are required for:

- 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 ((Adverse Event Reporting and Safety Monitoring) of this manual)

For each participant, a final contact, which may occur after Visit 7, 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), but no forms are submitted for these post-termination contacts.

After completing the Visit 7 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 condom provision. Participants should be counseled about this — ideally before and during their Visit 7 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 the Visit 7 Contact/Termination visit is planned as a phone call, this information should be provided to the participant prior to Termination. If the Visit 7 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. Participant preferences for methods to be used for contacting them when 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 9.3, study product use must be discontinued immediately for participants with a reactive 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, s/he 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 Permanently Discontinue Study Product for Other Reasons

For participants who permanently discontinue study product use for any other clinician initiated reason (other than HIV seroconversion) 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 7.5.2).

5.5.7 Criteria for Early Termination of Study Participants

As outlined in Protocol Section 9.5, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study, after consultation with the PSRT, to protect their safety and/or if they are unwilling or unable to comply with required study procedures. 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 the Visit 6 Sampling Visit/Early Termination Visit procedures should be completed.
 - Please note, PK, PD and mucosal safety sample collection will be done at the discretion of the MTN-033 Management Team (see section 5.5.1 above for additional guidance). If specimens are collected, this must occur within 72 hours of a previously received dose and if biopsies were not collected for Visit 4 or 6.
- 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 the 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.