

Section 5. Study Procedures

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5. Introduction

This section provides information on requirements for study procedures in MTN-035, including screening, enrollment and participant follow-up visits.

5.1 Visit Locations

Given the nature of study procedures required for MTN-035, study procedures for all visits are expected to occur at the study clinic.

5.2 Eligibility Determination SOP

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 (SOP) that describes how study staff will fulfill this responsibility. The SOP should contain, at a minimum, the following elements related to eligibility determination procedures:

- During-visit eligibility assessment procedures
 - Post-screening visit eligibility assessment and confirmation procedures (e.g., 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 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-035. The study eligibility criteria are listed in protocol sections 5.2 and 5.3; and required screening procedures are listed in protocol section 7.2.

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 45-day window begins the day written informed consent is obtained (signed), even if no other procedures are done on that day. A Last Day to Enroll calculator is available within the Visit Calendar Tool on the MTN-035 webpage.

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/ attempt.

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). No more than two screening attempts are permitted at the discretion of the IoR or designee.

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. When rescreening participants, all screening procedures must be repeated. Note, however, that 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.

5.3.2 Screening Visit Procedures

Required screening procedures are specified in protocol section 7.2 and reflected in the applicable visit checklist available on the MTN-035 webpage.

After staff have ensured participant comprehension of the study and obtained written informed consent, participants will be assigned a PTID and undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. Locator and demographic information will also be obtained. Participants will be reimbursed for their time and scheduled for their enrollment visit, if found presumptively eligible.

Further details on PTID assignment, structure, and related information are included in SSP Section 12.

Behavioral eligibility criteria at screening, which are based on self-report, should be evaluated by administration of the Screening Behavioral Eligibility Worksheet, available on the MTN-035 Study Implementation Materials webpage. It is suggested that staff administer this questionnaire early in the visit so that more time-consuming clinical and laboratory evaluations can be avoided if the participant is deemed 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 SSP Section 7 (Clinical Considerations), required for all participants are as follows:

- Collection of medical history and use of concomitant medications (including evaluation of prohibited medications/products)
- Conduct of a physical exam to assess overall general health; a rectal exam to assess participants' baseline genital signs/symptoms and preliminary eligibility (a visual and digital exam and anoscopy must be performed)
 - If applicable, sites may perform genital and/or pelvic exams to assess abnormal findings and/or reported symptoms
- Provision of all available test results and treatment or referrals for UTI/RTI/STIs.

Additional details regarding laboratory tests and sample collection at screening are provided in Section 7 of this SSP Manual. In summary, all participants will receive testing for STIs (including HIV 1/2, GC/CT/Trichomonas (TV) and Syphilis). Sites with capacity (i.e., US sites) will also test participants for HSV, if indicated (i.e., if active lesions are present). Additional details regarding clinical evaluations are provided in Section 7 of this Manual. Participants will be counseled about HIV and will receive appropriate pre- and post-test counseling, as well as risk reduction counseling; they will also be offered condoms. Participants who can get pregnant will be tested for pregnancy and counseled on effective contraceptive use.

All participants will be counseled about the requirements of the study, including the need to refrain from using non-study rectally-administered medications or products during their participation in the study. Participants are permitted to use non-study personal lubricants and usual pre-RAI douches that do not contain nonoxynol-9 (N-9).

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. A sample Screening and Enrollment Log suitable for use in MTN-035 is available on the MTN-035 Study Implementation Materials webpage. This log must be maintained in hard copy. When recording reason(s) for screen failure/discontinuation, study sites should reference the eligibility codes listed at the bottom of the sample log screening failure.

5.3.4 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when a participant is determined to be ineligible. For all participants who screen fail, the following should be in place:

- Completed ICF(s)
- Reason(s) for ineligibility, with date of determination, documented in chart notes and on the Eligibility Criteria CRF
- 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 and documentation of all referrals should be included in the participant chart.
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were provided and explained to the participant within a reasonable timeframe (even if referral is not necessary), regardless of eligibility determination.
- All source documentation completed 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)
- Complete row on the Screening and Enrollment Log, updated with date of discontinuation of screening and reason for screen failure.

5.4 Enrollment Visit

A participant is considered enrolled in the study only after s/he has been randomly assigned to a product regimen sequence. A participant's final eligibility status is confirmed on the day of enrollment, which must occur within 45 days of providing written informed consent. Final eligibility status is documented by completing and signing off on all items on the Eligibility Checklist on the day of enrollment. The site IoR (or designee) and a second staff member must sign and date the Eligibility Checklist to confirm eligibility status prior to proceeding with randomization. If the participant is found ineligible before the enrollment visit, the Eligibility Checklist does not need to be started. If a participant is found to be ineligible at the enrollment visit and the checklist has been partially completed, there is no need to continue filling out the checklist past the point when ineligibility is determined.

Further information on methods and materials for sampling assignment is provided in SSP Section 12 (Data Collection).

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

5.4.1. Enrollment Visit Procedures

The Enrollment Visit serves as the baseline visit for MTN-035. For this reason, all procedures for this visit must be conducted on the same day and cannot be split across multiple days.

Study enrollment procedures are specified in protocol section 7.3 and reflected in the applicable visit checklist available on the MTN-035 webpage. The following should be completed as part of eligibility confirmation prior to randomization on the day of enrollment:

- Review of informed consent and confirmation that participant remains interested in continuing with study participation
- Review and update of locator information
- Assignment of CASI ID for behavioral surveys and SMS set up, at sites with SMS capacity (further details on CASI ID assignment, structure, and related information are included in SSP Section 11)
- Completion of the Baseline Behavioral Assessment via CASI. Note, this may be done after randomization, for purposes of visit flow, as long as the participant completes the CASI prior to being informed of their first study product assignment.
- Re-assessment of behavioral eligibility criteria (through administration of the Enrollment Behavioral Eligibility worksheet, available on the MTN-035 webpage)
- Collection of blood to test for HIV and for plasma for archive.
- In conjunction with HIV testing, provision of HIV pre- and post-test counseling as well as HIV/STI risk reduction counseling and offering of condoms.
- Review and update of medical and concomitant medications history since Screening Visit, including evaluation of use of prohibited medications.
- Conduct of a rectal exam (a visual and digital exam and anoscopy are required) to assess baseline anorectal signs/symptoms to confirm eligibility.
 - If indicated, testing for STIs and conduct of a genital and/or pelvic exam to assess abnormal findings and/or reported symptoms.
- For participants who can get pregnant, review of contraceptive counseling requirements and collection of urine for pregnancy testing.
- If clinically indicated, collection of a dipstick UA and/or urine culture for all participants.

- Conduct of a targeted physical exam to assess general health.
- Provision of all available test results and treatment or referrals for STI/UTIs.

Once the procedures above and final determination of participant eligibility have been completed by designated site staff, the participant may be randomized to a product regimen sequence. See SSP Section 12 (Data Collection) for information on completing the randomization process.

After randomization, the following procedures should be conducted:

- Disclosure and explanation of the participant's product regimen sequence assignment
- Review of protocol requirements with regards to prohibited medications and practices and instructions on how to set up and respond to weekly SMS contacts (at sites with SMS capacity)
- Provision of study product and review of product use instructions.
 - Participants will be asked to use one dose of their assigned study product at the clinic under the supervision of study staff. This will be done to ensure the participant can tolerate using the product and will be able to use it as instructed during the study.

Note: review of product use instructions can be done prior to randomization, as 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. See SSP Section 10 (Counseling Procedures) for more details on counseling procedures.
- Provision of site contact information, condoms and lubricant as indicated, and any other study instructions.
- Provision of reimbursement.
- Update to participant's study visit calendar and provision to the participant of a copy of his/her expected follow up visit schedule.

5.5 Follow-up Visit Considerations

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

- **Scheduled visits** are those visits required per protocol. Each participant will complete a total of six clinic follow-up visits (Visits 3 through 8), which include Product Switch and Product Use End Visits, as well as a Final/Early Termination visit.
- **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. 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. See SSP Section 12 (Data Collection) for more details on recording interim visits.

5.5.1 Visit Windows

It may not always be possible to complete follow-up visits on the targeted dates. The MTN-035 protocol allows for certain visits to be completed within a visit window, if possible. A complete listing of visit windows is available in SSP Section 12 (Data Collection).

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. A Visit Calendar Tool is available on the MTN-035 webpage that can be used to create follow-up visit schedules for enrolled participants.

5.5.2 Visits Conducted Over Multiple Days: "Split Visits"

All procedures specified by the protocol to be performed at a follow-up visit, ideally, 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, if that visit has a window. When this occurs, the visit is considered a split visit. Please refer to SSP Section 12 (Data Collection) for split visit procedures visit code assignment.

Any procedures that are not conducted within the visit window will be considered missed. Guidance on which missed procedures should be made up at an interim visit are described below.

If an interview is required (CASI or brief in-depth interview [IDI]), the entire interview must be completed on one day. If an interview is begun but not completed on the first day of a split visit, the entire CASI questionnaire and/or IDI must be administered/conducted (starting from the beginning) on the second day of the split visit. If this occurs, you do not need to notify SCHARP and the behavioral team; the fully completed CASI questionnaire will be used for analysis purposes. The transcripts records from the fully completed IDI will be used for analysis.

Documentation of the rationale for not completing the procedures should be included in the participant's chart.

5.5.3 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 MTN-035 CRF Completion Guidelines for more information on completion of this form).

To avoid missed visits, participants should be scheduled early enough in the visit window to allow for rescheduling within the window, if needed.

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

- If Visit 3, 5 or 7 is missed, participants may make up missed CASI questionnaires and brief IDIs at their next scheduled visit (Visits 4, 6 or 8). Alternatively, they may be asked to return to the clinic for an interim visit as soon as possible to complete the brief IDI and applicable CASI questionnaire.
- If Visit 4 or 6 is missed, participants should be asked to return to the clinic for an interim visit as soon as possible to: obtain study product and study product use instructions and administer the first dose in-clinic.
- If Visit 7 is missed, participants should be asked to return to the clinic for an interim visit as soon as possible to: provide urine, anorectal, pharyngeal and, if applicable, pelvic samples

for STI testing (NAAT for GC/CT and/or TV); HIV testing and counseling; pregnancy testing, if applicable; and syphilis serology testing.

- If Visit 8 is missed, participants should be brought back to complete all required Visit 8 procedures that were missed, including the conjoint analysis and the IDI (those among the subset only) and the pregnancy test, for individuals who can get pregnant.

5.6 Follow-up Visit Procedures

- Required follow-up visit procedures are listed in protocol section 7.4. Several additional clarifications of the procedural specifications are provided in the remainder of this section. While sites should aim to perform procedures in the order indicated in the site-approved study visit checklists, it is acknowledged that this might not always be possible. Further operational guidance on completing protocol-specific procedures including procedure order during follow-up is incorporated into the visit checklist templates.

As a general guide, during follow up, the following should occur:

- Locator information will be obtained/reviewed at every visit.
- Protocol counseling will be provided at all visits, with the exception of the final visit.
- Medical, medication histories interim review, AE assessment and documentation, assessment of concomitant medications and provision of any available lab results will be done at all visits.
- Rectal examination is conducted at every Product Use End Visit (PUEV) (Visits 3, 5 and 7); pelvic and male genital exams are done only as indicated.
- Behavioral assessments via CASI are completed at every PUEV (Visits 3, 5 and 7) and the Final/Visit 8 (conjoint analysis)
- A brief IDI will be completed at every PUEV (Visits 3, 5 and 7); an IDI will also be conducted among a subset of participants at the Final Visit (Visit 8).
- Participants will be reimbursed for their time at each visit and scheduled for their next visit, as applicable.
- There will be a 1-week washout period following each PUEV.
- Condoms and lubricant will be offered at every visit, and study provided lubricant as indicated (provided with inserts and suppositories and per local guidelines)
- For individuals who can get pregnant, a pregnancy test is required at the Final Visit (Visit 8).
- HIV testing and counseling, NAAT for GC/CT (pharyngeal, urine, anorectal, and if applicable, pelvic) is required at Visit 7.
- Unused study product retrieval at every PUEV.
- Provision of study product and lubricant, if applicable, review of study product use instructions and in-clinic observation/use of first dose is required at Product Switch Visits (Visits 4 and 6).
- Weekly SMS behavioral surveys regarding product use (product use Periods 1, 2 and 3; between Visits 2-3, 4-5, and 6-7), if applicable. In the absence of SMS communications, data on product use will be collected during participants' PUEV IDIs.

5.7 Final Visit/Early Termination Considerations

Staff should discuss with the participant what procedures will be conducted during the Final Visit and ensure the participant is agreeable and understands what may be expected after study termination.

After completing the final contact/termination visit, participants will no longer have routine access to services provided through the study, such as HIV counseling and testing and medical exams. Participants should be counseled about this — ideally before and during their final 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.

Additional contacts after study exit may be required for:

- Participants who are pregnant during the study to obtain pregnancy outcome
- Participants with certain types of AEs that are ongoing at study exit

For each participant, these additional contact(s) 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 follow-up contact plans be documented on chart notes or a site-specific tool (e.g. worksheet). All additional contacts must be documented in participant study records, but no CRFs are completed for these contacts.

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.

5.7.1 Participants Who Become Infected with HIV

Per protocol section 7.5.1 and 9.6, study product use must be temporarily held upon the first positive/reactive HIV test. Study product must be permanently discontinued immediately for participants who are confirmed to be HIV-1/2 positive.

If a participant becomes infected with HIV-1/2 after the Enrollment Visit, the participant will be referred to local care and treatment services and may return to the clinic for additional counseling and other support services, as needed and 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 are taking oral PrEP for HIV prevention while on study and seroconvert after randomization may be offered additional laboratory testing (such as HIV RNA and HIV drug resistance testing).

5.7.2 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 7.5.2). The participant will be referred to local health care services and may return to the clinic for additional counseling, as needed and per site SOP.

5.7.3 Participants Who Permanently Discontinue Study Product for Other Reasons

When participants permanently discontinue study product use for any clinician-initiated reason other than HIV seroconversion or pregnancy, sites must consult the PSRT for guidance regarding continued study participation and progression to other study products.

Participants who permanently discontinue study product use for any self-initiated reason during the first or second product use period will be allowed to continue in the study, if willing.

Participants who permanently discontinue study product use for any self-initiated reason during the third product use period will be considered terminated from the study. If willing, an Early Termination Visit will be conducted.

5.7.4 Criteria for Early Termination of Study Participants

As outlined in Protocol section 9.8, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee may also 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 the 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 ask whether the participant is willing to complete one last visit, during which visit procedures for an early termination visit should be completed. Staff should record the reason(s) for the withdrawal in participant study records. If needed, sites may consult the PSRT regarding early terminations per IoR decision. Documentation of this consultation should be printed and filed in the participant chart (note, PSRT consultation is not required for voluntary withdrawals).

5.8 Replacing Participants

Participant replacements are permitted per protocol section 10.4. 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-035 Management Team. See SSP section 12 (Data Collection) for further information on replacement participants. If a site believes a participant may need to be replaced, the site should email the Management Team and provide the following information: PTID, date of enrollment, current follow-up status (i.e., where the participant currently is in their visit schedule), reason for replacement request, whether product use occurred as intended during Product Use periods, and date of next scheduled enrollment.