

Section 5. Study Procedures

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This section provides information on requirements for study procedures in MTN-029/IPM 039, including screening, enrollment and participant follow-up visits.

5.1 Visit Location

Given the nature of study procedures required to be performed during the MTN-029/IPM 039 study, all visit procedures are expected to be completed at the study clinic only.

5.2 Eligibility Determination and 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 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
 - 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-029/IPM 039 Management Team

mtn029mgmt@mtnstopshiv.org) and the MTN-029/IPM 039 Safety Physicians
(mtn029safetymd@mtnstopshiv.org)

All eligibility criteria are initially assessed at the Screening visit, and some are reconfirmed on the day of Enrollment (Visit 2). Prior to enrollment, eligibility for study participation must be confirmed and documented on the MTN-029/IPM 039 Eligibility Checklist by designated staff. This checklist can be found on the MTN-029/IPM 039 webpage under Study Implementation Materials.

Additional screening attempts will be allowed, per the discretion of the IoR or designee.

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

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. See section 5 of this manual for additional information.

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-029/IPM 039. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3. Required screening procedures are listed in Protocol Sections 7.2.

All protocol-specified screening procedures must take place up to 56-days prior to enrollment, beginning on the day the potential participant provides written informed consent. The screening process starts as soon as the participant signs the informed consent form, even if no other screening procedures are conducted on that day.

If all screening and enrollment procedures are not completed within the allowable timeframe after 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 the participant provides written informed consent for participation in the study).

5.3.1 Screening Visit Procedures

Required screening procedures are specified in the MTN-029/IPM 039 Protocol Section 7.2 and reflected in the visit checklists available on the MTN-029/IPM 039 webpage. Briefly, after providing 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 collected during the screening visit. Participants will be reimbursed for their time, and scheduled for their enrollment visit if presumptively eligible.

Eligibility criteria that are based on self-report may be evaluated by administration of the Screening Behavioral Eligibility worksheet provided on the MTN-029/IPM 039 webpage under study implementation materials. 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). To maintain consistency across sites and participants, questions on this form will be asked verbatim.

Clinical screening visit procedures are described in detail in section 7 of this manual, briefly:

- Clinical procedures include collection of medical, concomitant medications, physical exam, breast exam (including a breastmilk sample for eligibility purposes) and pelvic exam.
- Participants will be evaluated for use of prohibited vaginal products and medications, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Participants will also receive contraceptive counseling and provision of contraception (as needed)
- Participants should receive all available test results and treatment or referrals for UTI/RTI/STIs if indicated.

The HIV testing algorithm for screening is included in Appendix II of the protocol. Details regarding laboratory tests and sample collection at screening are provided in Section 9 of this manual. In summary:

- All participants receive testing for HIV, pregnancy, STIs (GC/CT, Trichomonas), and AST/ALT.
- If indicated (see Protocol 7.2 for specific requirements), participants may also have a pap smear, wet prep and vaginal pH, urine dipstick/culture, and/or testing for Syphilis and Herpes.

Participants will receive HIV pre- and post-test counseling as well as counseling on breastmilk production and maintenance, if indicated. Counseling considerations are described in detail in Section 10 of this manual.

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. This is distinct from participants who rescreen for the study, in which case all screening procedures, including informed consent, must be repeated (with the exception of PTID assignment).

5.3.2 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-029/IPM 039. 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-029/IPM 039

	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-029/IPM 039 can be found in Section 11 of this manual. PTIDs will be assigned to all potential participants who provide

informed consent, 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.

5.3.3 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 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-029/IPM 039 is available on the MTN website under Study Implementation Tools. Study sites are encouraged to reference the eligibility codes listed at the bottom of the sample screening and enrollment log when recording the reason 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 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 ICF
- Reason(s) for ineligibility, with date of determination, as per the completed Eligibility Checklist
- Completed Eligibility Criteria CRF, updated with screen failure 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.

5.4 Enrollment Visit

A participant will be considered enrolled in MTN-029/IPM 039 after completion of the non-datafax Eligibility Checklist AND final sign-off of items 1a and 1b on the Eligibility Criteria CRF (ECI). The site PI (or designee) should provide his/her signature in item 1a on the ECI, and a second staff member designated to affirm eligibility, per site SOP, should sign item 1b. Note that all baseline sample collections, enrollment assessments, and examinations must be completed before a participant is considered enrolled and the study ring is inserted. The enrollment visit is considered Day 0 (Visit 2).

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-029/IPM 039 Protocol Safety Review Team (PSRT) for guidance on subsequent action to be taken. PSRT contact details are

provided in Section 8 of this manual. Additionally, the MTN-029/IPM 039 Management Team must be informed.

5.4.1 Enrollment Visit Procedures

The Enrollment/Visit 2 serves as the baseline visit for MTN-029/IPM 039 and is considered Day 0 of study participation. All procedures for this visit must be conducted on the same day, and cannot be split across multiple days. According to Protocol Section 7.3, menses must not coincide with a participant's enrollment visit (Visit 2), or with study visits 3-6. 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. If the participant is enrolled and subsequently starts her menses during days 1-16, the pelvic exam and sample collection should continue as long as the participant is comfortable, but the management team should be notified.

Study enrollment procedures are specified in Protocol Section 7.3 and reflected in the visit checklists available on the MTN-029/IPM 039 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 Eligibility Checklist prior to proceeding with enrollment per site SOPs.

Before the participant can be considered enrolled in the study, she must undergo the following procedures:

- Confirm 56-day screening window has not been exceeded
- Update and confirm adequacy of locator information
- Review informed consent and confirm participant is still interested in continued study participation
- Confirm behavioral eligibility criteria. Sites may use the Enrollment Behavioral Eligibility worksheet provided on the MTN-029/IPM 039 webpage under Study Implementation Materials, or other site method, as specified in site SOPs.
- Complete sexual practices assessment and vaginal practices assessment
- Review and update medical history, including childbearing and lactation history, since screening visit. Evaluate use of prohibited vaginal products and medications, STI/RTI/UTIs or reproductive tract signs/symptoms, conduct pregnancy testing, provide contraceptive counseling and contraception (if indicated), and evaluate overall general health. Document all pre-existing conditions.
- Provide protocol adherence counseling including vaginal ring use instructions and important information as well as counseling on the collection and storage of breast milk at home. NOTE: this may also be conducted after enrollment, but it could be helpful to provide the participant with more information about the study product and breast milk collection procedures prior to her final decision to enroll in the study
- Collect blood for: Blood DPV levels pre-insertion and plasma archive. HIV testing is also required if 30 days or more have passed between the screening and enrollment visits.
- In conjunction with HIV testing, if required, participants will receive HIV pre- and post-test counseling.
- Conduct a physical exam, breast exam, and pelvic exam. Collect vaginal biomarkers, quantitative vaginal culture, vaginal gram stain, and CVF DPV levels (pre-insertion). If indicated, urine dipstick/culture, GC/CT testing, syphilis serology, trichomonas testing, herpes culture, wet prep, and vaginal pH may also be performed. Pap smear interpretation should be done if the participant is over 21 and cannot provide documentation of a satisfactory pap smear within the 3 years prior to enrollment. However, if the pap smear result is not available at the timing of her enrollment visit, then her enrollment visit will need to be rescheduled.

- Collect breast milk for eligibility confirmation as well as anti-viral activity, pre-insertion DPV levels, and lipids. Note that the breast milk collected for eligibility confirmation may also be used for these other samples.
- Participants should receive all available test results and if indicated treatment or referrals for STI/RTI/UTIs.

Once the procedures above and final determination of eligibility has been completed by designated staff, the participant will be considered enrolled in the study.

After enrollment, an IoR or authorized clinician will prescribe study product, obtain product from the site pharmacy, and insert the study vaginal ring for the participant. Should the participant wish to practice insertion and removal, this should happen immediately prior to the final ring insertion, which must be done by the authorized clinician. The clinician will perform a digital exam to check for placement, after reviewing the product use instructions and answering any questions that the participant may have, as needed. Study staff will document the time of ring insertion on the Enrollment CRF.

Three hours AND six hours after ring insertion the following samples will be collected:

- Blood DPV levels
- CVF DPV levels
- Breast milk for anti-viral activity, DPV levels, and lipids

After all samples have been collected, but before the participant leaves the clinic, she will be provided with all the instructions and supplies needed for home breast milk collection. At home breast milk collection instructions are included in SSP Section 9.8. Supplies the participant should receive include the following:

- Freezer box containing 60 cryovials
- Transfer pipettes
- Cryovial labels
- Freezer packs and cooler for transport
- MTN-029 Participant Breast Milk Collection Log
- Breast pump and bottles for milk collection, if needed

The participant's next visit will be scheduled and she will be provided with her enrollment visit reimbursement.

5.5 Follow-up Visits

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

Scheduled visits are those visits required per protocol. There are a total of 4 clinic follow-up visits, including the Study Exit/Termination Visit

- Visit 3 (Day 1)
- Visit 4 (Day 7)
- Visit 5 (Day 14) Ring Removal Visit
- Visit 6 (Day 16) Study Exit/Termination Visit
 - NOTE: Menses must not coincide with any follow-up study visit, therefore a participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment Visit (Day 0).

For example, if a participant is enrolled on December 1, 2015, her clinic visits will be as follows:

December 2015

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 Day 0	2 Day 1	3	4	5
6	7	8 Day 7	9	10	11	12
13	14	15 Day 14	16	17 Day 16	18	19
20	21	22	23	24	25	26
27	28	29	30	31		

In addition to considering a participant's menses when scheduling her enrollment visit, sites will want to consider the days of the week when study visits will fall. If, for instance, your clinic is open Monday-Friday, you will only want to schedule enrollment visits on Mondays, Tuesdays, or Wednesdays.

Interim visits are those visits that take place between scheduled visits. More specifically, a visit is considered an interim visit when a participant presents for additional procedures or assessments beyond the required procedures for a scheduled visit. There are a number of reasons why interim visits may take place. Interim visits may be performed at any time during the study, for the following or other reasons:

- For product-related reasons, e.g., a participant may want to discuss problems with adherence to product use.
- In response to AEs. When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically and provide or refer the participant for appropriate medical care (see also Section 8).
- For interim STI counseling and testing in response to STI symptoms or to provide participants with lab test results

All interim contacts and visits will be documented in participants' study records and on applicable CRFs. Site staff may be required to assign visit codes to interim visits for purposes of data management as described in section 11 of this manual.

5.5.1 Target Visit Dates and Visit Windows

Enrolled participants will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, Day 1, 7, 14, and 16 follow-up visits (Visits 3-6) are targeted to take place based on the participant's enrollment date. *Sites must make every effort to conduct each visit on its target day.* When absolutely necessary, visits may be conducted within the short allowable visits windows that are specified in section 11 of this manual. Visits completed on the target date or within the allowable visit window will be considered completed ("retained") visits.

The MTN Statistical and Data Management Center (SDMC) will provide sites with a visit scheduling tool that can be used to generate 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 particular follow-up visit, ideally, will be completed at a single visit on a single day. In the event that all required follow-up 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 should be conducted within the visit window, if at all possible. 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). If study visits must be split, please ensure that all specimens collected for PK and PD analysis (blood, breast milk, and CVF) are done on the same day of the split visit to avoid complicating interpretability of the data.

Any procedures that are not conducted within the visit window will be considered missed and will not be made up.

5.5.3 Missed Visits

For participants who do not complete any part of a scheduled visit within the allowable visit window, the entire 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).

If a visit is missed, it cannot be made up outside the allowable visit window. Rather, sites must make every effort to retain the participant for her remaining scheduled study follow-up visits, and to conduct these visits on the target days.

For participants who are unable to complete Visit 5 on Day 14, site staff should contact the participants and counsel them to remove the ring on Day 14, rinse it, and place it in the storage bag provided by the site. The participant should be scheduled to return to the clinic as soon as possible to complete the visit within the visit window. If this is not possible and Visit 5 is missed, site staff should make every effort to obtain the used ring from the participant.

5.5.4 Follow-up Visit Procedures

Required follow-up visit procedures are listed in Protocol Sections 7.4 and Appendix I. As a general guide during follow up:

- Locator information must be obtained/reviewed at every visit.
- Review informed consent and confirm participant is still interested in continued study participation.
- Medical history and pelvic exams, AE assessment and documentation, assessment of concomitant medications, sexual practices assessment, and provision of any available lab results, will be done at all study visits. A breast exam is required at visit 6 (other visits if indicated) and a physical exam may be performed at any visit, if indicated. Treatment and referrals for any diagnosed UTI/RTI/STIs or mastitis will be provided, if indicated.
- Blood, CVF, and breast milk should be collected in as close proximity to one another as possible. Additionally, the following collection time points should be targeted:
 - Visit 3: 24 hours post-ring insertion
 - Visit 4: No time requirement

- Visit 5: At ring removal
- Visit 6: 48 hours post-ring removal
- Vaginal Gram stain and vaginal swab for biomarkers are collected at visits 3-6 and a quantitative vaginal culture should be collected at visits 5 and 6.
- Retrieval of breast milk samples collected at home as well as the participant breast milk collection logs, and participant ring use logs occurs at visits 4 and 5 (a new log is given and returned at each visit). Breast milk expression supplies should be provided at enrollment, but may be replenished during follow-up, if needed.
- Pregnancy testing will be done at visit 6.
- The VR is collected and returned at visit 5.
- HIV testing and counseling will be done at any time if clinically indicated, as will vaginal fluid pH, urine dipstick/culture, wet prep, herpes culture, rapid Trichomonas test, GC/CT, and syphilis serology.
- Protocol adherence counseling is required at visits 3 and 4 and may be provided at visit 5, if indicated. A digit exam to check ring placement may be done at visits 3 and 4, if needed.
- Contraceptive counseling and contraception can be provided at any visit, if indicated.
- Participants will be reimbursed for their time at each visit, and scheduled for their next visit as applicable.

5.5.4.1 Day 16 Study Exit/Termination Considerations

Although the Day 16 Study Exit/Termination visit is the last scheduled study visit, a final contact is required after this visit to provide the participants with their final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Participants who are pregnant during the study to obtain pregnancy outcome
- 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 in chart notes or a site-specific tool (e.g., worksheet). All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

Participants may be contacted post-study to be informed of the study results, if requested by the participant. 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 who 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

If a participant becomes infected with HIV-1 after enrolling into the study, she 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. Per Protocol Section 7.6.1, once a participant seroconverts, study follow-up visits will be discontinued and the participant will be

considered terminated from the study. Participants who seroconvert should be instructed to remove the vaginal ring as soon as possible and return it to the study clinic (permanent study product discontinuation). They may also 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 7.6.2). Participants should remove the vaginal ring as soon as possible and return it to the study clinic (permanent study product discontinuation). Pregnant participants will be referred to local health care services and may return to the research clinic for additional counseling, as needed, per site SOP.

Sites should develop a plan with participants to attain pregnancy outcomes. One contact to obtain this information is sufficient. For example, the participant could call or e-mail the site to inform the site of the outcome.

5.5.7 Participant Who State an Intention to Reinitiate Feeding Infants with Their Own Breast Milk after Study Product Exposure

In order to enroll in MTN-029/IPM 039, participants must have weaned their child(ren). Should a participant wish to reinitiate breastfeeding after study product exposure, she will be permanently discontinued from study product and terminated from the study. She should remove the vaginal ring as soon as possible and return it to the study clinic. In consultation with the management team, participants should be counseled on resumption of infant feeding and discarding of expressed milk, if applicable.

5.5.8 Participants Who Permanently Discontinue Study Product for Other Reasons

There are no protocol-specified temporary product holds in MTN-029/IPM 039. Any participant who needs to discontinue use of the vaginal ring for any reason must be permanently discontinued from further ring use. Participants who permanently discontinue study product use for any reason, whether clinician-initiated or self-initiated, will be terminated from the study. However, the visit 6 Study Exit/Termination Visit should be completed prior to termination, if the participant is willing. If a participant is permanently discontinued from vaginal ring use due to an AE, site staff must continue to follow her for clinical management purposes until resolution or stabilization of the AE is documented.

5.5.9 Criteria for Early Termination of Study Participants

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 the study is terminated 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 she is willing to complete one last visit, during which visit procedures for the Visit 6 Study Exit/Termination visit should be completed; with the addition that the VR should be collected.
- Record the reason(s) for the termination in participants' study records.
- Print and file consultation with the PSRT regarding early terminations per IoR discretion. Note: 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.

5.5.10 Criteria for Replacing Study Participants

Protocol section 10.10 allows for the replacement of participants who are non-adherent to the study product or visit schedule. Replacement decisions will be made on a case by case basis by study leadership and the management team. To ensure that these decisions are made in a timely fashion, the management team should be notified as soon as possible if a participant reports product non-use for 24 hours or more. Notification should include the timing and duration of vaginal ring non-use. See SSP Section 2 for protocol deviation reporting requirements for product non-use. Other decisions regarding replacement (e.g., for study visit non-compliance) will be made by study leadership and the management team considering the totality of the data provided by a given participant.