Section 5. Study Procedures

5.1 Visit Locations **1**
5.2 Eligibility Determination SOP **1**
5.3 Screening Visit **2**
5.3.1 Screening and Enrollment Timeframe 2
5.3.2 Screening Visit Procedures 2
5.3.3 Screening and Enrollment Log 3
5.3.4 Participants Found to be Ineligible (Screen Failures) 3
5.4 Enrollment Visit **4**
5.4.1 Enrollment Visit Procedures 4
5.5 Follow-up Visits **6**
5.5.1 Visit Windows 6
5.5.2 Visits Conducted Over Multiple Days: "Split Visits" 6
5.5.3 Missed Visits 7
5.5.4 Final Contact Considerations 7
5.5.5 Participants Who Become Infected with HIV 8
5.5.6 Participants Who Become Pregnant 8
5.5.7 Participants Who Permanently Discontinue Study Product for Other Reasons 8
5.5.8 Criteria for Early Termination of Study Participants 9
5.6 Behavioral Assessments **9**

This section provides information on requirements for study procedures in MTN-036/ IPM 047, including screening, enrollment and participant follow-up visits.

5.1 Visit Locations

Given the nature of study procedures required to be performed during MTN-036/ IPM 047, all study procedures for all visits are expected to be completed at the study clinic.

5.2 Eligibility Determination SOP

Each study site must establish an SOP that describes how study staff will fulfill the responsibility of participant eligibility determination.

The 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)

Should study staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should contact the MTN-036/IPM 047 Study Management Team (mtn036mgmt@mtnstopshiv.org) and the MTN-036/IPM 047 Safety Physicians (mtn036safetymd@mtnstopshiv.org).

All eligibility criteria are initially assessed at the screening visit (Visit 1), 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 Eligibility Checklist by designated staff. This checklist can be found on the MTN-036 webpage under Study Implementation Materials.

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 SSP Section 4 Informed Consent 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-036/ IPM 047. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3.

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 i.e. the Informed Consent Form (ICF) is signed, even if no other 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.

The term "screening attempt" is used to describe each time a participant is screened for the study (i.e., each time s/he provides written informed consent for participation in the study). Potential participants may undergo one additional screening attempt, per the discretion of the IoR or designee.

If all screening and enrollment procedures are not completed up to 45 days after obtaining written informed consent, the participant must repeat the entire screening process. When rescreening participants, all screening procedures need to be repeated, including the informed consent process. Note, however, a new PTID is not assigned to the participant in this case. Rather, the original PTID assigned at the first screening attempt is used for the repeat screening attempt, 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 Protocol Section 7.2 and reflected in the applicable visit checklist available on the MTN-036/IPM 047 Study Implementation Materials webpage. Listed below is a brief review of all required screening procedures.

After provision of 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 Data Collection.

Behavioral eligibility criteria, which are based on self-report, may be evaluated by administration of the Screening Behavioral Eligibility Worksheet, provided on the MTN-036/IPM 047 Study Implementation Materials webpage. This worksheet is designed to be interviewer-administered and serve as a source document thus 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 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 SSP Section 8 Clinical Considerations, required for all participants are as follows:

- Collection of medical history, menstrual history, use of concomitant medications and evaluation of prohibited medications/products
- Completion of a physical exam and pelvic exam to assess overall general health
- Provision of HIV pre/post-test and HIV/STI risk-reduction counseling, contraceptive counseling, and offer condoms.
- Receipt all available test results and treatment or referrals for UTI/RTI/STIs.
- Details regarding laboratory tests and sample collection at screening are provided in SSP Section 10 Laboratory Procedures. In summary, participants will receive testing for:
- HIV 1,
- STIs (GC/CT, Syphilis, Trichomonas, and candidiasis and/or BV, if indicated),
- pregnancy,
- serum chemistries (AST/ALT),
- CBC with platelets and differentials, and a
- Pap Test*
  **if indicated (if participant [over age 21] is unable to provide documentation of a satisfactory Pap test within 3 years prior to enrollment.*

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 is available on the MTN-036/IPM 047 Study Implementation Materials webpage. 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. For all participants who screen fail, the following should be in place:

- Completed ICF(s)
- Reason(s) for ineligibility, with date of determination.
- 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 including
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on visit checklists)
- Completed the Eligibility Criteria CRF
- 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's final eligibility status should be determined after completion of the Eligibility Checklist. The Eligibility Checklist should be started on the day of enrollment and the site IoR (or designee) and a second staff member should sign and date the Eligibility Checklist to confirm eligibility status prior to being enrolled. 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. A participant is considered enrolled in the study only after s/he has been randomly assigned to a study arm.

Further information on methods and materials for study arm assignment is provided in the SSP Section 12 Data Collection.

5.4.1 Enrollment Visit Procedures

The enrollment visit (Visit 2) serves as the baseline visit for MTN-036/ IPM 047. 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, the participant's menstrual cycle should be considered when scheduling the enrollment visit such that no menses occurs during the first 7 days of product use (Visits 2-6). If a participant is menstruating on the day of enrollment, the entire visit should be rescheduled for after the completion of menses. If the participant is enrolled and subsequently starts menses during days 1-7, the pelvic exam and sample collection should continue as long as the participant is comfortable doing so, unless the participant is experiencing greater than mild bleeding, in which case the participant should be rescheduled if the exam can still occur in the visit window. See SSP 8.5.1 for further guidance on protocol procedures during menses.

Per MTN-036/IPM 047 inclusion criteria, a potential participant must agree to use an effective method of contraception at enrollment and throughout the duration of her study participation. During the informed consent process, staff should explain which methods are acceptable for study purposes and emphasize that if s/he cannot commit to using one of these methods during study follow-up, s/he should not enroll in the study.

Effective methods include:

- hormonal methods (except contraceptive ring)
- intrauterine device (IUD)
- sterilization (of participant or partner, as defined in site SOPs)
- having sex exclusively with individuals assigned female sex at birth
- abstinence from PVI for 90 days prior to Enrollment, and intending to remain abstinent from PVI for the duration of study participation

Some participants may wish to discontinue use of a contraceptive method during follow-up. In these cases, counselors should explore the participant's reasons for this and determine if other options would be acceptable to him/her. However, the possibility of resuming contraceptive use should be re-visited at each subsequent visit to determine whether the participant's circumstances may have changed. Contraception may be provided on site, however sites may opt to refer participants to non-study providers for contraception. All sites are strongly encouraged to obtain credible medical records as part of their verification procedures for participant-reported contraceptive use.

Study enrollment procedures are specified in Protocol Section 7.3 and reflected in the visit checklist available on the MTN-036/IPM 047 Study Implementation Materials webpage. On the day of enrollment, before a participant is randomized and can be considered enrolled in the study, site staff must complete the following enrollment visit procedures to confirm his/her study eligibility:

- Confirm 45-day screening window has not been exceeded

- 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)
- Update medical and menstrual history since screening visit. Evaluate use of prohibited medications, STI/UTIs, pelvic or reproductive track signs/symptoms, and overall general health.
- Collect urine to test for pregnancy and, if clinically indicated, conduct a dipstick UA and/or urine culture for all participants.
- Collect blood for: HIV testing, plasma archive, and if indicated, for CBC with differential and platelets.
- In conjunction with HIV testing, provide HIV pre- and post-test counseling as well as HIV/STI risk reduction counseling and offer condoms.
- Conduct a targeted physical exam to assess overall general health.
- Conduct a pelvic exam to confirm eligibility and collect baseline pelvic samples (CVL, vaginal gram stain, vaginal swabs for microbiota) and test for STIs, if indicated.
- Participants should receive all available test results and treatment or referrals for STI/UTIs, genital or reproductive tract infections.
- Complete the baseline behavioral assessment via CASI questionnaire. NOTE: questionnaire may be conducted either after randomization, depending on the site-specific clinic flow, but should occur prior to provision of the VR. See SSP Section 6 Behavioral Measures for more details.
- Provide protocol counseling for study adherence, VR use instructions, and contraception, and offer male condoms. 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. See SSP Section 11 Counseling Procedures for more details on counseling procedures.

Once the procedures above and final determination of participant eligibility have been completed by designated site staff, the participant may be randomized to a study arm, at which point s/he will be considered officially enrolled in the study. Participants will additionally be randomized at this time to be considered for an In-depth Interview (IDI). If a participant is invited for an IDI, clinic staff should confirm verbally the participant's willingness to participant in an IDI and be audio recorded. Document the IDI selection outcome on the Enrollment Visit Checklist and the Enrollment CRF. See SSP Section 12 Data Collection for more information on completing study arm and IDI randomization.

<u>After</u> enrollment, the following procedures should be completed:

- Prescribe study product (by the IoR or authorized clinician), obtain product from the site pharmacy, review the product use instructions and answer any questions that the participant may have.
- Have participant insert the study VR on his/her own at the study clinic, or the site clinician may insert it for him/her. After the VR is inserted, the clinician will perform a digital exam to check for placement. Study staff will document the date and time of ring insertion on the Ring Insertion and Removal CRF.
- <u>One, two, and four hours after ring insertion</u>, collect the following samples, per SSP section 10 Laboratory Considerations*
    - Blood DPV levels
    - CVF DPV levels

- Four hours after ring insertion, collect rectal fluid per SSP Section 10 Laboratory Considerations *
- Schedule follow-up visit for next day (Visit 3/Day 1) and provide reimbursement.
- Complete Enrollment CRF
- * Blood, CVF, CVL and rectal fluid samples should be collected in as close in proximity as possible (within 30 minutes) when collected at the same time point (e.g. at Hour 4)

5.5 Follow-up Visits

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. After each participant enrolls in the study, s/he is expected to complete nine protocol-required in-clinic visits including the Product Use End Visit (PUEV) (Visit 10), and the Final Contact (Visit 11). 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. Further operational guidance on completing protocol-specific procedures including procedure order during follow-up is incorporated into the Sample Visit Checklists and in SSP 2.3.4. 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.

Sites should take into consideration the days of the week when study visits will fall and plan the participant's visit schedule accordingly. Enrollment visits should occur on Monday or Tuesday to allow for the follow-up visits required on each of the first three days after VR insertion (Day 1, 2 and 3) to occur within the same work week (e.g. If a participant is enrolled on a Monday, s/he will come back for follow-up visits on Tuesday, Wednesday, and Thursday.)

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

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-036/ IPM 047 protocol allows for certain visits to be completed within a visit window, if possible. A complete listing of visit windows is available in the 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 scheduling tool is available on the MTN-036/IPM 047 website 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. As described in the SSP Section 12 Data Collection, all CRFs completed for a split visit are assigned the same visit code (even though the dates recorded on the CRFs may be different). Study visits may be split if necessary except for the Enrollment Visit, Visit 3/Day 1, and Visit 4/Day 2.

If study visits must be split, please ensure that:

- HIV pre- and post-test counseling and HIV testing should occur on the same day.
- Any CASI questionnaire and behavioral-related CRFs completion should occur on the same day.
- PK/PD and DVP specimens (blood, CVF, CVL, rectal fluid, as applicable) are collected on the same day to avoid complicating interpretability of the data.
- The Ring Insertion and Removal CRF, the Ring Adherence Summary and Ring Adherence CRFs are completed on the same day the above specimens are collected during a study follow-up visit to correlate VR use data with PK results.

Any procedures that are not conducted within the visit window will be considered missed. See section 5.5.3 below for guidance on which missed procedures should be made up at an interim visit

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 CRF completion guidelines for more information on completion of this form).

If Visits 6-10 (Days 7, 14, 28, 56, and/or Day 91(PUEV)) are missed, sites must make every effort to make up the missed visit and required study procedures (as soon as possible) at an interim visit, and retain the participant for his/her remaining scheduled study follow-up visits. Sites should contact the MTN- 036/IPM 047 Study Management Team for additional guidance.

5.5.4 Final Contact Considerations

Visit 11/Final Contact should be scheduled as an in-clinic visit between 24 to 72 hours after the Visit 10/PUEV (except for participants who have terminated early from the study). Site staff should discuss with the participant what procedures will be conducted during this visit. It is also ideal to remind participants at the prior visit to ensure the participant is agreeable and understands what may be expected after study termination.

Additional contacts after a participant exits the study may be 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

For each participant, this additional 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 additional 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.

After completing their Visit 11/Final Contact, 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 11/Final Contact— 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 at this visit.

All participants will be contacted post-study to be informed of the study results. It is currently expected that study results will be available within approximately 6-9 months after the last participant study follow-up. Participants 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 7.5.1, study product use must be discontinued immediately for participants who test positive for HIV-1.

If a participant becomes infected with HIV-1 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 per site SOP.

Once HIV status is confirmed positive, 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).

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

The site should develop a plan with the participant to attain the pregnancy outcome. 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.

Pregnant participants will be referred to MTN-016, if the site is taking part in MTN-016. Written referrals to MTN-016 are not required; documentation of referral (verbal or otherwise) should be present in participant chart notes. All discussions related to potential participation in MTN-016 must be fully documented in participant study records.

For participants who decline enrollment in MTN-016, the study site will make effort to contact participants and collect infant outcomes at approximately one year after delivery for those pregnancies that result in live birth.

5.5.7 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 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 7.5.3).

5.5.8 Criteria for Early Termination of Study Participants

As outlined in Protocol Section 9.9 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 IPM, 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 PUEV/ Early Termination Visit should be completed.
- Record the reason(s) for the withdrawal in the participant's study records.
- Document, print and file in the participant chart any consultation with the PSRT regarding early terminations per IoR decision. 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.

5.6 Behavioral Assessments

The following types of behavioral assessments will be conducted in MTN-036/IPM 047:

- Baseline Behavioral Questionnaire CASI
- Follow-up Behavioral Questionnaire CASI
- Ring Adherence Summary and Ring Adherence CRFs
- In-Depth Interview (IDI) **Sub-set of 24 participants, assigned at enrollment.*

Information on the timing of the behavioral questionnaires administered via CRF and CASI is presented below in Table 5-1. See SSP Section 6 Behavioral Measures for more details.

Table 5-1

Timing of Behavioral Assessments, Product-related Information, and IDIs

Study Visit	Behavioral Measures
Visit 2 (Enrollment)	○ Baseline CASI (For Behavioral Assessment, and product preference/ acceptability information)
Visit 8 (Day 28)	○ Ring Adherence CRFs (For product use information) ○ Visit 8 Follow-Up CASI (For Behavioral Assessment, and product preference/ acceptability information)
Visit 9 (Day 56)	○ Ring Adherence CRFs (For product use information) ○ Visit 9 Follow-up CASI (For Behavioral Assessment)
Visit 10 (Day 91)/PUEV/ Early Termination	○ Ring Adherence CRFs (For product use information) ○ Exit CASI (For Behavioral Assessment, and product preference/ acceptability information) ○ IDI

Note: Participants who permanently discontinue study product use early are requested to complete all visit procedures scheduled to occur at the PUEV/Early Termination Visit, including the behavioral assessments listed above, at the visit when study product use is permanently discontinued. Behavioral assessment procedures will be discontinued for the remaining study visits that occur after permanent study product discontinuation if the participant continues with study follow-up. See Protocol Section 7.9 Behavioral Measures for further information.