

Section 4. Study Procedures

4.1	Visit Location	4-1
4.2	Eligibility Determination and SOP	4-1
4.3	Screening Visit	4-2
4.3.1	Screening Visit Procedures.....	4-3
4.3.2	Assignment of Participant ID Numbers	4-3
4.3.3	Screening and Enrollment Log.....	4-4
4.3.4	Participants Found to be Ineligible (Screen Failures)	4-4
4.4	Enrollment Visit	4-5
4.4.1	Enrollment Visit Procedures.....	4-5
4.5	Follow-up Visits	4-6
4.5.1	Target Visit Dates and Visit Windows	4-8
4.5.2	Visits Conducted Over Multiple Days: “Split Visits”	4-8
4.5.3	Missed Visits	4-8
4.5.4	Follow-up Visit Procedures	4-9
4.5.4.1	Day 35 Final Clinic Visit/Termination Considerations	4-10
4.5.5	Participants Who Become Infected with HIV.....	4-10
4.5.6	Participants Who Become Pregnant.....	4-11
4.5.7	Participants Who Permanently Discontinue Study Product for Other Reasons	4-11
4.5.8	Follow-up Procedures for Participants Who are on a Temporary Clinical Study Product Hold	4-11
4.5.9	Follow-up Procedures for Participants Who Decline Study Product Use	4-12
4.5.10	Replacing Participants	4-12
4.5.11	Criteria for Early Termination of Study Participants	4-13

This section provides information on requirements for study procedures in MTN-028, including screening, enrollment and participant follow-up visits.

4.1 Visit Location

Because of the nature of study procedures required to be performed during the MTN-028 study, all visit procedures are expected to be completed at the study clinic only.

4.2 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/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-028 Management Team (mtn028mgmt@mtnstopshiv.org) and the MTN-028 PSRT (mtn028psrt@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 randomization, eligibility for study participation must be confirmed and documented on the MTN-028 Eligibility Checklist by designated staff. This checklist can be found on the MTN-028 webpage under Study Implementation Materials.

A second screening attempt 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.

4.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a potential participant is eligible to take part in MTN-028. 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 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. In other words, the day the screening informed consent is signed is counted as "-45" and enrollment is counted as Day 0. For example, as shown below, a potential participant who provides written informed consent on 1 July 2015 could be enrolled on any day up to and including 15 August 2015.

July							August						
Su	M	Tu	W	Th	F	Sa	Su	M	Tu	W	Th	F	Sa
			1	2	3	4							1
5	6	7	8	9	10	11	2	3	4	5	6	7	8
12	13	14	15	16	17	18	9	10	11	12	13	14	15
19	20	21	22	23	24	25	16	17	18	19	20	21	22
26	27	28	29	30	31		23	24	25	26	27	28	29
							30	31					

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 up to 45 days of 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).

4.3.1 Screening Visit Procedures

Required screening procedures are specified in the MTN-028 protocol section 7.2 and reflected in the visit checklists available on the MTN-028 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 which are based on self-report will be evaluated by administration of the Screening Behavioral Eligibility worksheet provided on the MTN-028 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 8 of this manual, briefly:

- Clinical procedures include collection of medical/menstrual history, concomitant medications, physical exam, and pelvic exam.
- Participants will be evaluated for use of prohibited medications, STI/RTI/UTIs, genital signs/symptoms, and overall general health.
- Participants will also receive contraceptive counseling (as needed), and have discussion of pregnancy/breastfeeding history and future pregnancy intentions.
- Participants should receive all available test results and treatment or referrals for UTI/RTI/STIs if indicated.

The HIV testing algorithm for screening and testing considerations can be found in Section 9 of this manual. Participants will receive HIV pre- and post-test counseling as well as risk reduction counseling. Protocol and study product adherence expectations will be reviewed with participants. Counseling considerations are described in detail in SSP Section 10 of this manual.

Details regarding laboratory tests and sample collection at screening are provided in Section 9 of this manual. In summary:

- Participants receive testing for HIV, STIs (GC/CT, Trichomonas, and Syphilis), pregnancy, urine dipstick, HBsAg, Coagulation (INR), Anti-HCV, serum chemistries (creatinine, AST, ALT), and CBC with platelets and differentials.
- If indicated, participants may be tested for Bacterial Vaginosis, vaginal candidiasis, have vaginal pH measured, or have a Pap smear.

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.

4.3.2 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-028. As shown in Figure 4-1, the listing will be formatted such that it may be used at each site as the log linking PTIDs to participant names.

**Figure 4-1
Sample Site-Specific PTID List for MTN-028**

	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-028 can be found in Section 11 of this manual. PTIDs will be assigned to all potential participants who provide informed consent for screening, 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.

4.3.3 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-028 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.

4.3.4 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 reason(s) and faxed to DF/Net
- 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 (list item number as appropriate from the Eligibility Checklist).

4.4 Enrollment Visit

A participant will be considered enrolled in MTN-028 when a designated staff member requests a randomization assignment via the FSTRF web-based randomization system once the site has confirmed that the participant has met all eligibility requirements. The enrollment visit is considered Day 0. Further information on methods and materials for random assignment is provided in section 6 of this manual.

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the Investigator of Record or designee should contact the MTN-028 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-028 Management Team and PSRT must be informed.

4.4.1 Enrollment Visit Procedures

The Enrollment/Visit 2 serves as the baseline visit for MTN-028. 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), and ideally with study visits 3-6 (Days 1, 2, 3, and 7). 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 1-7, the pelvic exam and sample collection should continue as long as the participant is comfortable (see also section 8.7 of this manual).

Study enrollment procedures are specified in Protocol Section 7.3 and reflected in the visit checklists available on the MTN-028 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 randomization/enrollment per site SOPs.

Before randomization, the participant will undergo the following procedures:

- Confirm 45-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 through administration of the Enrollment Behavioral Eligibility worksheet provided on the MTN-028 study webpage under Study Implementation Materials.
- Update medical/menstrual history since screening visit. Evaluate use of prohibited medications, STI/RTI/UTIs or reproductive tract signs/symptoms, conduct pregnancy testing, provide contraceptive counseling (if indicated) and evaluate overall general health. Document all pre-existing conditions.
- Collect blood for: Serum chemistries, CBC with differential and platelets, HIV testing and plasma archive (Note if site is not conducting finger stick HIV rapids: to reduce

participant burden, site should consider collecting plasma archive and HIV samples as part of a single blood draw, prior to randomization)

- In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling as well as risk reduction counseling.
- Conduct a physical exam and pelvic exam
- If indicated, participants should be tested for STIs (GC/CT, Trichomonas, syphilis), bacterial vaginitis, or candidiasis
- Participants should receive all available test results and if indicated treatment or referrals for STI/RTI/UTIs.
- Protocol adherence and study product adherence counseling. NOTE: this may also be conducted after randomization, but it could be helpful to provide the participant with more information about the study product prior to her final decision to enroll in the study

Once the procedures above and final determination of eligibility has been completed by designated staff, the participant should be randomized per the procedures in Section 6 of this manual. The MTN SDMC will generate and maintain the study randomization scheme and MTN Pharmacy will produce any associated printed materials. The act of Randomization (i.e. assignment to a study treatment arm) is considered the effective act of enrollment in the study.

After randomization, participants will undergo the following procedures:

- Provision of study product instructions and site contact information
- Self-collection of vaginal swab for PK (hour 0 sample, prior to ring insertion)
- Insertion of IVR
- Pelvic exam to check IVR placement
- PK: Blood and vaginal fluid (Post ring insertion at time points: 1, 2, 4, 6)
- Reimbursement
- Schedule next visit

Detailed instructions on IVR use including insertion/removal procedures and first product use, exam to check ring placement, as well as IVR adherence counseling is provided in Section 10 of this manual.

4.5 Follow-up Visits

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

Scheduled visits are those visits required per protocol. There are a total of 11 clinic follow-up visits, including the Final Clinic Visit

- Visits 3-8: (Days *1, *2, *3, *7, 14, 21)
 - *NOTE: Menses must not coincide with Study Visits 2 (Day 0) and ideally with Study Visits 3-6 (Days 1, 2, 3, 7), therefore participant's menstrual cycle must be considered when scheduling Visit 2- Enrollment Visit (Day 0).). In the event a participant has her menses during Enrollment Visit, the visit should be postponed until termination of menses. If participants have menses during visits 3-6, it should be document but all procedures should be done. As much as possible, menses should be avoid during these visits.
- Visit 9 (Day 28) Ring Removal Visit
- Visits 10-12 (Days 29, 30, 31)
- Visit 13 (Day 35) Final Clinic/Early Termination Visit

For example, if a participant is enrolled on August 4, 2015, her clinic visits will be as follows:

August 2015						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
						1
2	3	4 Day 0	5 Day 1	6 Day 2	7 Day 3	8
9	10	11 Day 7	12	13	14	15
16	17	18 Day 14	19	20	21	22
23	24	25 Day 21	26	27	28	29
30	31					

September 2015						
Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		1 Day 28	2 Day 29	3 Day 30	4 Day 31	5
6	7 Labor Day	8 Day 35	9	10	11	12

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 need a replacement vaginal ring or 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 to appropriate medical care (see also Section 8).
- For interim STI counseling and testing in response to STI symptoms or interim HIV counseling and testing in response to presumed exposure to HIV or to provide participants with the results of confirmatory HIV 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.

4.5.1 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 1-28 follow-up visits (Visits 3-9) are targeted to take place based on the participant's enrollment date. Each participant's enrollment date is defined as the date upon which they were randomized to MTN-028. Follow-up visits for Days 29-35 (visits 10-13) are targeted to take place based on the date of a participant's actual Day 28 visit date. Sites can choose to enter the target date for the Day 28 visit when initially generating the visit schedule at Screening in order to generate visit dates for the full duration of follow-up (Visits 3-13/Days 1-35). In this case, the tool should be updated if the participant's actual Day 28/Visit 9.0 date differs from the target date, once known, so that accurate target dates for visits 10-13 are provided and scheduled accordingly.

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, the MTN-028 protocol allows for certain visits to be completed within a visit window, if possible. For Days 3, 7, 14, 21, 28, 31, and 35, there are visit windows specifying on which study days the visit can be completed. All other visits do not have visit windows as they are completed on consecutive calendar days. A complete listing of visit windows is available in Section 11 of this manual.

Sites are encouraged to complete required study visits on the target day if at all possible. If this is not possible, the visit may be completed within the visit window (for visits with a window). Visits completed within the visit window will be considered completed ("retained") visits.

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits at specific intervals, and every effort should be made to do so.

The MTN Statistical and Data Management Center (SDMC) will provide the site with a visit scheduling tool that can be used to follow-up visit schedules for enrolled participants. Every effort should be made to schedule participants within the allotted timeframes.

4.5.2 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 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 had a window. 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).

For study visits requiring collection of samples for PK, please ensure that these collections are done on the first day of the split visit to avoid complicating interpretability.

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 participant's file.

4.5.3 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 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).

For participants that miss Visit 9 (Day 28), meaning that the visit window has closed, participants should be contacted and counseled to remove the ring and return to the clinic as soon as possible. In addition to protocol-specified procedures for the applicable visit, the following procedures related to safety and product accountability should be completed the next time the participant presents to the site:

- Collection/Removal of IVR
- CBC with differential and platelets
- Chemistries (Creatinine, AST, ALT)
- Pregnancy Testing
- Urine Dipstick

Note that if a participant misses Visit 9.0/Day 28, the target date of the missed Visit 9.0/Day 28 visit should be entered into the visit calendar tool to generate the visit schedule for Visits 10.0-13.0. Should this occur, consult the management team for guidance on completing the remaining study visits and associated procedures.

Outside of what is outlined above for Visit 9 (Day 28), no other visit types or procedures will be made up for MTN-028 in the event a visit is missed.

4.5.4 Follow-up Visit Procedures

After participants enroll in the study, they are expected to complete 11 protocol-required clinic visits each. 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.
- Medical/menstrual history, physical and pelvic exams, AE assessment and documentation, assessment of concomitant medications, and provision of any available lab results, will be done at all study visits. Treatment and referrals for any diagnosed UTI/RTI/STIs will be provided if indicated.
- Blood and vaginal fluid will be collected for PK at all follow-up clinic visits at a single time point, except on Day 28.
- Participants will be reimbursed for their time at each visit, and scheduled for their next visit as applicable.
- Pregnancy test will be done at Days 14 and 28, and at any other time if clinically indicated.
- At Day 28, blood and vaginal fluid for PK will be collected at hours 0, 1, 2, 4, 6.
- Cervical tissue and Dipstick UA will be collected only at Day 28
- The IVR is collected and returned at the Day 28 visit.
- Gram stain is only done at Day 3, 28, and 35 (Final Clinic Visit/Termination Visit)
- Chemistries are only done at Day 28 and 35 (Final Clinic Visit/Termination Visit)
- CBC is only done at Day 28. At Day 35 (Final Clinic Visit/Termination Visit) is done only if clinically indicated
- HIV testing and counseling will be done at the Day 35/Final Clinic Visit/Termination Visit (and at any other time if clinically indicated).
- Vaginal fluid pH, rapid Trichomonas test, KOH wet mount for candidiasis, and saline wet mount for BV will be done only if indicated.

- Protocol, adherence, and contraceptive counseling will be provided at any visit, if indicated

4.5.4.1 Day 35 Final Clinic Visit/Termination Considerations

Note: For participants who terminate early from the study, procedures outline in Section 7.4.4 of the protocol should be followed. Please note that if the vaginal ring has been out for more than three consecutive days, no PK procedures will be done.

Although the Day 35 Final Clinic Visit/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 8.6 of this manual)

For each participant, a final contact should be scheduled based on the participant's overall clinical picture at study exit, as well as the time required to obtain all final study test results. It is recommended that final contact plans be documented on chart notes or a site-specific tool (e.g. worksheet). All final contacts must be documented in participant study records, but no case report forms are completed for these contacts.

After completing their Day 35 Final Clinic Visit/Termination visits and final study contacts, participants will no longer have routine access to services provided through the study such as HIV counseling and testing or contraceptive provision. Participants should be counseled about this — ideally before and during their Day 35 Final Clinic Visit/Termination visits — and provided information on where they can access such services after study exit. It is recommended that all study sites develop a written referral sheets that can be given to participants at their Day 35 Final Clinic Visit/Termination visits.

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

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the participant and documented. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet or other site-specific documentation that can be easily accessed by study staff.

4.5.5 Participants Who Become Infected with HIV

Per protocol section 7.5.1, study product use must be held immediately for participants with a reactive rapid HIV test result (this includes participants with discordant rapid results from the same visit).

If a participant becomes infected with HIV-1 after the Enrollment Visit, 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. 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.

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

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

4.5.7 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), site investigators may, after consultation with the PSRT and MTN-028 Management Team, decide to discontinue study participation (see Protocol Section 7.5.3).

If a participant is permanently discontinued from product use due to an AE, they must continue to be followed until the resolution or stabilization of the AE is documented.

In the event study follow-up is continued, participants will have the protocol-specified weekly visits through Day 35, specifically those visits at Day 7, Day 14, Day 21, Day 28 and Day 35. Protocol-specified procedures will continue except the following:

- Pelvic exams*
- Collection of blood for safety assessments*
- Protocol counseling will be modified
- PK specimen collection

* (Unless required for AE follow-up)

The above procedures should be collected/conducted at either the scheduled or interim visit in which study product is discontinued and omitted thereafter, unless the participant was previously on a temporary hold.

NOTE: Participants that miss more than three consecutive visits or have the ring out for more than three consecutive days will be permanently discontinued from study product. If the participant undergoes early termination, guidance in Section 7.4.4 of the protocol and Section 4.5.4.1 of this manual should be followed.

4.5.8 Follow-up Procedures for Participants Who are on a Temporary Clinical Study Product Hold

All protocol-specified study visits and procedures will continue except the following (see Protocol Section 7.6):

- Pelvic exams*
- Provision of product use/protocol adherence counseling
- PK specimen collection for participant that are on product hold for more than three consecutive days

*Unless required for AE follow-up

The collection of samples for PK should be collected/conducted at either the scheduled or interim visit in which study product is temporarily held and omitted thereafter. Completion of these procedures will resume at the visit following resumption of study product use.

4.5.9 Follow-up Procedures for Participants Who Decline Study Product Use

In the event that a participant declines further use of study product during follow-up, the MTN-028 management team should be informed. See Section 7.6 of this manual for information on how to document participant-initiated declines on the study product request slip. Counseling should explore the reasons for the self-initiated decline, and work with the participant to develop a plan for product resumption. If in the opinion of the IoR/designee the participant is unlikely to resume study product use during study follow-up, early termination for noncompliance with required study procedures should be considered after consultation with the PSRT (see Section 4.5.10 below). As always, participants may withdraw consent and exit the study for any reason at any time. Note that all protocol-specified procedures should continue in the interim (unless the participant declines) until the participant is terminated or decides to withdraw from the study.

NOTE: As mentioned in Section 4.5.7 above, participants that have the ring out for more than three consecutive days will have permanent discontinuation of product use. Guidance for permanent product discontinuation applies.

4.5.10 Replacing Participants

Participants will be replaced if:

- If the participant is terminated early for any reason (e.g. pregnancy, HIV status, clinician discretion, permanent product discontinuation, participant voluntary withdraw)
- If the participant has had the ring out for more than 3 consecutive days, voluntarily or by site's decision.
- If the participant misses 3 (consecutive) visits

NOTE: Participants that have had the ring out for longer than three consecutive days will be permanently discontinued from product use and replaced. Participants may remain in the study if the ring has been out and re-inserted within three days (including the third day).

NOTE: If the ring is removed on Day 26 or if participant misses three consecutive visits after Day 26, it is not necessary to replace that participant.

The purpose of replacing participants is to compensate for the potential data loss due to loss of follow-up and/or on temporary hold or permanent product discontinuation. If a participant discontinues study participation or is placed on hold (and the ring has been out for longer than three consecutive days) and needs to be replaced contact the MTN-028 Management Team immediately (mtn028mgmt@mtncstopshiv.org). Please refer to Section 6 Web Randomization for more information on the process of replacing participants.

In the event that a replacement participant terminates early or is placed on product hold for longer than three consecutive days, the replacement participant will need to be replaced and the PTID for the original participant that is being replaced should be recorded on the Enrollment CRF. The MTN-028 Management Team should also be contacted immediately (mtn028mgmt@mtncstopshiv.org) and the steps described in Section 6 of this manual for replacing participants should be followed.

4.5.11 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 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 Merck & Co., 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 she is willing to complete one last visit, during which visit procedures for the Day 35/Final Clinic/Termination visit should be completed; with the addition that the IVR should be collected. Please note, PK procedures will not be conducted for participants that have the ring removed for three or more consecutive days.
- Record the reason(s) for the withdrawal in participants' study records.
- Consultation with the PSRT regarding early terminations per IoR decision should be printed and filed in the participant chart. PSRT consultation is not required for voluntary withdrawals.
- Update participant locator form, and document how the participant would like to receive any follow up test results (as needed), and be informed of study results.

Although the protocol allows for participants who voluntarily withdraw from the study to reverse their decision and re-join the study during their planned follow-up period, according to their original visit schedule, the investigator should weight the benefits of having the participant rejoin the study. As noted in Section 4.10.5 above, participants that have their rings removed for longer than three consecutive days, will have product permanently discontinued, thus they will not contribute to the safety and PK endpoints in the study. Resumption of study procedures and follow-up are subject to the investigator's discretion, pending PSRT consultation. If such cases arise, study staff are advised to contact the MTN-028 Management Team for additional guidance on how to manage various aspects of protocol implementation and data collection as the participant resumes participation in the study. In general, however, the following instructions and requirements should be adhered to:

- The participant's original PTID and follow-up visit schedule will remain unchanged.
- Prior to performing any study procedure, the participant must provide written informed consent to document that she voluntarily rejoined the study. For re-consenting procedures, refer to Sections 5 of this study manual.
- An interval (since the last visit) medical and medication history should be taken and HIV and safety laboratory testing should be done as soon as the participant resumes study participation. Product use will be resumed only among participants who are confirmed HIV-uninfected per the MTN-028 HIV testing algorithm, are not pregnant, and ring has not been out for longer than three consecutive days.
- A pelvic exam should be performed as soon as possible, and prior to re-instating IVR use. IVR use will be reinstated (if applicable) only after any genital symptoms have resolved, any STIs/RTIs requiring treatment per CDC guidelines have been treated.
- After the above procedures are performed, the IoR or designee should include the results and findings of these procedures, and any other relevant participant history information, in a PSRT query form, and should submit the form to request PSRT consultation on resumption of study participation.

- If vaginal ring has not been out for more than three consecutive days and if resumption of study product use is endorsed by the MTN SDMC and PSRT, site clinic staff will communicate this decision to site pharmacy staff in writing, using the MTN-028 Intravaginal Ring Request Slip. A copy of the final PSRT query form should be filed in the participant's study notebook.
- Site staff should thoroughly document, in the participant's chart notes, resumption of study follow-up and study product use.