Section 5. Study Procedures

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5 Introduction

This section provides information on requirements for study procedures in MTN-043, including screening, enrollment, and follow-up visits for mothers and infants. All mother-infant pairs are expected to complete all visits together.

5.1 Visit Location

Given the nature of the study procedures required to be performed during the MTN-043 study, all visit procedures are expected to be completed at the study clinic whenever possible. If necessary, follow-up visits may be conducted off-site at the participant's home or location suitable to the participant with documented consent and when allowable per site-specific SOPs. See Section 5.5.6 for more information on the conduct of off-site study visits.

5.2 Eligibility Determination and SOP

It is the responsibility of each site Investigator of Record (IoR) and other designated staff to ensure that only participants (mothers and infants) who meet the study eligibility criteria are enrolled in the study. Each study site must establish a SOP that describes how site staff will fulfill the responsibility of determining participant eligibility for this study. It is recommended that this Participant Eligibility Determination SOP, at a minimum, contain the following elements:

- Eligibility determination procedures, including:
    - Eligibility assessment during the visit the Screening and Enrollment Visits
    - 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 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-043 Management Team (mtn043mgmt@mtnstopshiv.org).

5.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a mother and her infant are eligible to take part in MTN-043. The study eligibility criteria are listed in Protocol Sections 5.2 and 5.3; and required screening procedures are listed in Protocol Section 7.2.

In addition to the assessment of eligibility, informed consent should be reviewed to ensure that the mother clearly understands all information and is willing for her and her infant to participate in the study. To assist the mother in determining whether she wants to participant in the study, sites are to review/administer the MTN-042/MTN-043 Study Enrollment Decision Tool before the participant is asked to sign the Informed Consent Form (ICF). The tool is available on the MTN-043 study implementation materials website and instructions are detailed in SSP Section 4.7.1. Review of the informed consent(s) must be documented in the mother's study files. Sites are encouraged to use the Informed Consent Coversheet(s) for this purpose, though a chart note detailing all the essential elements of informed consent is also allowable. See SSP section 4 for details about mother and infant informed consent.

All protocol-specified screening procedures must take place no more than 35 days prior to the Enrollment Visit. This window begins the day written informed consent is obtained.

The term "screening attempt" is defined as "each time the participant provides written informed consent for participation in the study." If all screening and enrollment procedures are not completed within the allowable timeframe (i.e. 35 days) after obtaining written informed consent, one additional screening attempt will be allowed, per the discretion of the IoR or designee. The mother and infant must repeat the entire screening process, beginning with the informed consent process. A new PTID will not be assigned in this case. Rather, the original PTID assigned at the first screening attempt is used for any repeat screening attempts, as well as future study visits should the mother and infant successfully enroll in the study.

Per Protocol Section 7.2, multiple visits (as part of the same screening attempt) may be conducted if needed to complete all required screening procedures.

5.3.1 Screening Visit Procedures

Required screening procedures are reflected in the sample Visit Checklists available on the MTN-043 webpage. 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. Further details on PTID assignment, structure, and related information are included in SSP Section 12.

Administrative procedures include:

- Collection of locator and demographic information, including confirming age of infant for eligibility determination (must be between 6-12 weeks at time of enrollment)
- Obtain signed medical record release (if required per local laws/regulations) and pediatric care provider information
    - Mothers should be asked to bring any pediatric care records for the enrolling infant that she has to the screening visit. Postnatal care records for the mother should also be obtained, if available.
    - Sites should develop or adapt a site-specific medical release form or other documentation which allows for release of medical records (if required per local laws/regulations). See SSP section 7.17. If required, this documentation should be signed by the mother at the Screening visit (or during prescreening, per site SOPs) and study staff should attempt to obtain all available pediatric and postnatal care records prior to the enrollment visit.
    - Note that the behavioral screening eligibility worksheet also confirms the participants permission for access to her/her infant's medical records.
- If presumptively eligible, scheduling their enrollment visit
- Reimbursement provision

Behavioral eligibility criteria, based on self-report, should be evaluated using the Screening Behavioral Eligibility Worksheet provided on the MTN-043 webpage. It is suggested that staff administer this questionnaire early in the visit, so that more time-consuming clinical and laboratory evaluations can be avoided if the mother or infant are determined to be ineligible due to behavioral criteria. To maintain consistency across sites and participants, questions on this worksheet will be asked verbatim in the preferred language of the participant and participant responses should be recorded directly on the worksheet.

Clinical Screening Visit procedures, further described in detail in SSP Section 7, include:

- Collection of medical history and assessment of concomitant medications for mother and infant.
- Collection of pregnancy history and vaginal products and practices; and conduct of a physical and pelvic exam for mother.
- Review of available postpartum care and pediatric care records and conduct of a physical exam including weight collection for infant.
- Assessment of infant feeding to confirm exclusive breastfeeding of the infant.
- Assessment for STI/RTI/UTIs, cervicitis, genital signs/symptoms for mother, and overall general health for mother and infant.
- Provision of HIV pre/post-test and risk-reduction counseling and study approved condoms.
- Disclosure of all available test results to the participant, as well as treatment or referrals for UTI/RTI/STIs if indicated.

Per Protocol inclusion criteria #4 (Protocol Section 5.2), the mother is required be consistently using an effective contraceptive method by time of enrollment. The site may schedule enrollment after confirming the participant's contraceptive use or following provision of an acceptable method of contraception (IUD and other hormonal methods). While there is no required pre-enrollment timeframe for contraceptive use, women who enroll in MTN-043 are required to be "consistently using" an effective family planning method at the point of enrollment (e.g. using a method and planning to continue using). Potential participants who are not using a contraceptive method at their screening visit should be initiated on their preferred method of family planning prior to enrolling in the study.

Details regarding laboratory tests and sample collection at screening are provided in SSP Section 10. In summary, all mothers will:

- Receive testing for HIV, pregnancy, Hepatitis B surface antigen, STIs (Syphilis, Gonorrhea, Chlamydia and Trichomonas), CBC with platelets, AST/ALT and serum creatinine (along with calculated creatinine clearance).
    - The HIV testing algorithm for screening is included in Appendix III of the Protocol.
- If indicated, have a wet prep mount for candidiasis and/or BV, vaginal pH test, and urine dipstick urinalysis/ urine culture

If the mother and infant meet eligibility criteria at the end of the Screening Visit, they should be scheduled for their Enrollment Visit, making sure the enrollment visit takes place within the allowable 35-day time frame. Mothers should be provided with study informational materials, clinic contact information, and instructions to contact the clinic with any questions as needed prior to the scheduled Enrollment Visit. The participants should also be reminded to refrain from engaging in prohibited study practices beginning 24 hours prior to the enrollment visit. Breastfeeding support should be provided, as needed, to help the mother maintain exclusive breastfeeding of her infant.

Between screening and enrollment, appropriately delegated site staff should review lab results and other eligibility criteria. Note that per protocol, otherwise eligible participants with an exclusionary test (other than HBsAg or HIV) may be re-tested during the screening process. Repeat testing of exclusionary laboratory values at screening should only be conducted with specific clinical rationale for retesting. Chart notes should document decisions and rationale behind the retesting of abnormal, exclusionary results. If improvement to a non-exclusionary grade or resolution is documented within 35 days of providing informed consent for screening, the participant may be enrolled.

5.3.2 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. These logs may be maintained separately or combined into one document. Also, in accordance with the MTN Manual of Operational Procedures (MOP) Section 13.1, participants' initials/names do not need to be recorded on screening and enrollment logs if it presents a potential threat to participant confidentiality. For the purposes of MTN-043, the template Screening and Enrollment log will not include initials/names, and a separate PTID Linkage Log will serve as a link between a participant's name and PTID. A single PTID Linkage Log will be maintained for mothers and infants. The PTID Linkage Log must be stored in a secure location. Further details on the PTID Linkage Log are included in SSP Section 11.

A sample Screening and Enrollment Log is available on the MTN-043 website. Study sites are encouraged to reference the eligibility codes listed on page 1 of the log when recording all reasons for screening failure/discontinuation for the mother and infant. Full completion instructions are within the log.

5.3.3 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the mother or infant are determined to be ineligible. If 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 mother or infant screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure the well-being of the mother and infant. Documentation of all referrals should be included in the participant chart. All lab results should be provided and explained to mothers within a reasonable timeframe, regardless of eligibility determination. It is anticipated that a number of participants will screen out due to a lack of exclusive breastfeeding. In these instances, sites should make sure to provide education, support, and counseling around infant feeding practices to ensure the health and safety of screened out infants. Sites are encouraged to identify appropriate referral agencies that may be able to assist with breastfeeding support, food security, and/or access to clean water, when needed.

For all screened-out participants, the following documentation should be in place:

- Completed informed consent form
- Reason(s) for ineligibility, with date of determination
- Completed Inclusion/Exclusion Criteria CRF
- Necessary referrals on file (as appropriate) and documentation that any clinically significant abnormalities (labs, etc.) were communicated to the participant (even if referral is not necessary)
- All source documentation completed up until the time that ineligibility was determined
- Chart notes complete up until the time ineligibility was determined
- Indication of what visit procedures were conducted (on Visit Checklists)
- Completed entry on the Screening and Enrollment Log (updated with date of discontinuation of screening and reason for screen failure)

Reasons for screen failures should be consistent between the Screening and Enrollment Log and the Inclusion/Exclusion Criteria CRF.

Due to the protocol defined eligibility criteria, documentation of ineligibility will differ depending on whether the mother or infant are eligible but the other is not.

- If the mother's eligibility is confirmed but the infant's is not: Mark "E1. At Screening or Enrollment, breastfeeding infant ineligible for enrollment in the study" on the Inclusion/Exclusion Criteria CRF and enter code 'M-E-1' on the mother's row of the Screening and Enrollment Log. Complete the reason for the infant ineligibility according to the infant eligibility criteria and infant codes on the CRF and log, respectively.
- If at enrollment, a mother who is eligible for the study reconsiders at the point immediately prior to randomization and decides not to enroll her and her infant: Mark "Eligible/Not Enrolled" on the mother and infant's Inclusion/Exclusion Criteria CRF and enter code N-1 on the mother and the infant's row of the Screening and Enrollment Log and specify the reason as "Mother declines enrollment."
- If the infant's eligibility is confirmed but the mother's is not: Mark "Eligible/Not Enrolled" on the Infant Inclusion/Exclusion Criteria CRF and enter code N-1 on the infant's row of the Screening and Enrollment Log, along with explanatory text like, "mother screened out." Complete the reason for the mother ineligibility according to the maternal eligibility criteria and codes on the CRF and log, respectively.

Similarly, if "Incomplete Screening" is marked on the Inclusion/Exclusion CRF for either the mother or infant, N-2 should be entered in the corresponding row on the Screening and Enrollment Log. This code should be used any time a mother or infant does not complete all procedures required for enrollment within the 35-day screening to enrollment window.

- Example: A mother and infant complete their screening visit but are lost to follow-up and do not return for enrollment visit within 35 days.

Regarding eligibility criteria categorization for HIV-related screen-outs:

- A mother with at least 1 positive HIV rapid test, no matter the outcome should be deemed ineligible per Exclusion Criteria 3 (E-3): At Screening or Enrollment, has a positive HIV test.
- A mother confirmed HIV-infected (i.e. has 2 positive rapids or discordant rapids with a positive confirmation) should be deemed ineligible per E-3 and Inclusion Criteria 8 (I-8): HIV-uninfected based on testing performed at Screening and Enrollment.

Screening HIV Rapid Test Results	Final HIV Diagnosis (confirmation)	Eligibility Criteria	
		I-8	E-3
Dual Negative	NA	No	No
Discordant	Infected	Yes	Yes
	Uninfected	No	Yes
Dual Positive	NA	Yes	Yes

Note that for protocol exclusion criteria that relate to prohibited practices within a certain number of days before enrollment, the day of enrollment date should be considered "Day 0". Some examples are provided below to aid in this interpretation:

- Use of vaginal medications or other vaginal products within 5 days prior to enrollment is exclusionary. If enrollment is scheduled 10 March, any vaginal practices/product use from 5-10th March is exclusionary.
- Participation in research involving drugs, vaccines or medical devices 30 days or less prior to enrollment is exclusionary. If enrollment is scheduled on 31 March, any participation in this type of study from 1-31st March is exclusionary.

5.4 Enrollment Visit

Enrollment procedures are specified in Protocol Section 7.3 and reflected in the sample Enrollment Visit Checklist available on the MTN-043 study website. A mother-infant pair is considered enrolled in the study when the mother is randomized via the MTN-043 Medidata Rave clinical database. Enrollment for the mother and infant must occur at the same visit and all baseline samples and examinations must be collected/completed for both the mother and infant participant before a mother is randomized and study product is administered. Further information on methods and materials for study arm assignment is provided in the SSP Section 11 Data Collection.

5.4.1 Mother Enrollment Visit Procedures

The Enrollment Visit serves as the baseline visit for all enrolled participants. An accurate assessment of baseline conditions must be documented, and eligibility must be confirmed, on the day of enrollment. All procedures for this visit must be conducted on the same day and cannot be split across multiple days.

The only exception to this will be for sites that are required to administer a separate ICF at the Enrollment visit per local IRB/EC regulations. For those sites, the IC for Enrollment may be performed on the first day of the split visit. All other protocol-specified visit procedures required at Enrollment must be completed at a single visit as close as possible to IC provision (i.e. the date in which the participant signed/dated/marked the Enrollment IC form). If the mother-infant pair cannot complete enrollment within their Screening to Enrollment window, they should be considered a screen fail. Per IoR discretion, the mother-infant pair may rescreen one additional time.

5.4.1.1 Procedures Completed PRIOR to Randomization

This section reviews, in brief, procedures occurring before randomization:

Mother:

- Confirm the informed consent form(s), as applicable, have been signed and dated and the mother remains willing and able for her and her infant to participate in the study.
- Confirm the 35-day screening window has not been exceeded.
- Update and reconfirm adequacy of locator information.
- Confirm behavioral eligibility criteria by administering the Enrollment Behavioral Eligibility Worksheet.
- Review and update the mothers medical/medications history, including of any newly available postpartum records, that was first collected at the Screening Visit. Assess for new vaginal practices.
- Administer the Edinburgh Postnatal Depression Scale CRF and calculate score; refer for counseling/support, if needed. (See SSP section 7.7 for more information)
- Collect urine for pregnancy testing.
- Assess for STI/RTI/UTIs or cervicitis signs/symptoms.
- Collect urine for urinalysis and/or culture, per site SOC, if indicated
- Collect blood for HIV testing, plasma archive, DBS for baseline TVF-DP and FTC-TP drug levels, and, if indicated, for syphilis serology.

- Note: For sites not conducting finger stick HIV rapids: to reduce participant burden, sites should consider collecting plasma archive and HIV samples as part of a single blood draw.

- In conjunction with HIV testing, participants will receive HIV pre- and post-test counseling, including offering condoms.
- Provide protocol counseling, using the MTN-043 Protocol Counseling Guide, available on the study website.
  - 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.
- Conduct a targeted physical exam to confirm the mother is in good general health.
- Conduct a pelvic exam and pelvic sample collection per Pelvic Exam Checklist
- Conduct the infant feeding assessment
- Disclose all participant's available test results and, if indicated, provide treatment or referrals for STI/RTI/UTIs/cervicitis.

Infant:

- Confirm age is within eligibility range for enrollment
- Review and update medical, medications, and pediatric care history that was first collected at the Screening Visit.
- Conduct a targeted physical exam, including Ages and Stages Assessment, to confirm the infant is in good general health.

Once the procedures above and final determination of participant eligibility have been completed by designated site staff with by documenting the status of each eligibility criterion on the Eligibility Checklist. The Eligibility Checklist should be completed 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. Staff responsible for confirming eligibility should be listed as sub-investigators on the FDA Form 1572. All staff members who are responsible for confirming or verifying eligibility on the Eligibility Checklist should be clearly delegated per the DoD Log, and sign off procedures specified in site SOPs. If the participant is found ineligible before the enrollment visit, the Eligibility Checklist does not need to be completed. 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.

5.4.1.2 Procedures Completed AFTER Randomization

Once the procedures above and final determination of both mother and infant participant eligibility have been completed by designated site staff, the mother may be randomized to a study product arm, at which point she and the infant will be considered officially enrolled in the study.

After randomization, the following procedures should also be completed for the mother (the infant has no further procedures at this visit):

- Confirmation of selection for IDI (sub-set of participants) and participant willingness to participate (See SSP section 14 for IDI selection details) Provide the applicable enrollment session Product Adherence Counseling (Oral Truvada or Ring) to discuss expectations and strategies for product adherence with the participants. Ideally, this session should be done while study product dispensation is occurring for purposes of visit efficiency.
- 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 mother may have.
- Once the clinic and participant know which study product the participant has been randomly assigned to, but before the participant has received the study product, complete the Baseline Behavioral Assessment. The COVID Behavioral Assessment can be conducted at the same time.
- All mothers will complete their first product use at the study clinic during their Enrollment Visit. Study staff should perform a digital exam to verify ring placement for Vaginal Ring (VR) users and

observe ingestion of the first study tablet for Truvada users and document on the applicable CRFs.

- The rationale for this is to help ensure participant understanding, comfort, and confidence with proper product use from the very beginning of study participation. Any questions or concerns that arise in the context of first product use can be addressed by study staff before the participant is required to use study product on her own. For further detailed guidance on first product use, refer to SSP section 9.4.2 and 9.4.4.
- After the mother completes the first product use, study staff should de-brief with the mother on the first product use experience. If the mother has any questions or issues, these should be documented so the information is easily available for reference at study follow-up visits.
- Schedule first follow-up visit and provide reimbursement.

5.4.1.3 Incomplete Enrollment Visits

As stated in 5.4.1, all enrollment visit procedures should be completed on the same day and these visits should not be split. Should an enrollment visit be incomplete, follow the guidance below:

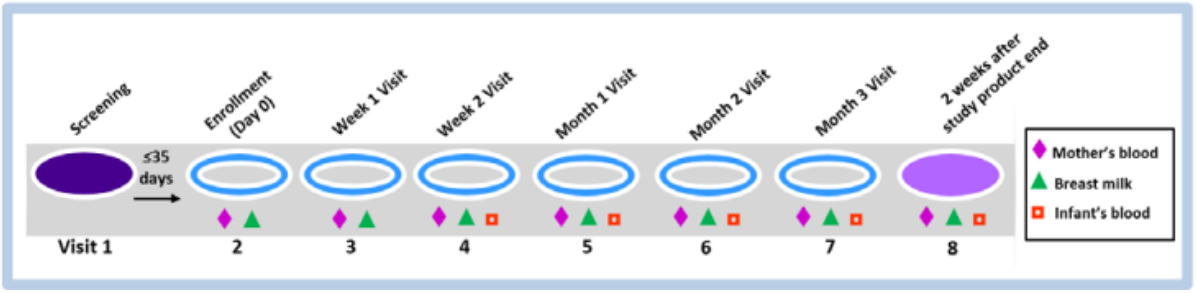
- If procedures are discontinued before the point of randomization, this participant is not considered enrolled and should be rescheduled for her enrollment visit within the allowable window, if possible and the participant is willing. All enrollment visit procedures should be redone on the day of rescheduled enrollment. Note this does not count a second screening attempt.
- If procedures are discontinued after the point of randomization, this participant is considered enrolled in the study. Notify the management team immediately, who will provide case-by-case guidance for completion of the enrollment visit procedures on a separate day as well as documentation. **This participant's enrollment date is the day she was randomized**, regardless of whether she must come back a separate day to complete the remaining visit procedures.

5.5 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. The protocol specifies six follow-up visits for the mother-infant pair to occur 1 and 2 weeks after Enrollment, and then once a month for three months post-enrollment, with product use ending at the third month (PUEV). Both mother and infant will return for a study exit visit approximately 2 weeks after the Month 3/PUEV. See figure 1 below for study visit schedule. Because the visit windows may allow for more than 30 days between monthly visits, site staff should be mindful of product resupply needs. This is especially important for participants continuing with the oral tablets to ensure they have no lapse in supply to cause missed doses.

Figure 1: Study Visit Schedule



Interim visits are those visits/contacts that take place, as needed, between scheduled visits. See SSP Section 11 for details on interim study visits and visit codes.

5.5.1 Follow-up Visit Procedures

Required follow-up visit procedures are listed in Protocol Section 7.4 and Appendix I and II. Several additional clarifications of the procedural specifications are provided in the remainder of this section. Further operational guidance on completing protocol-specific procedures during follow-up is incorporated into the Sample Visit Checklists available on the MTN-043 website.

As a general guide, clinic visit procedures may include:

Mothers

- Review/confirmation of locator information, visit scheduling and provision of reimbursement.
  - Reimbursement to follow site-specific SOP for visits including both mother and infant.
- HIV and urine testing (for urine dipstick and/or urine culture)*
- Provision of HIV pre- and post-test counseling and modified HIV/STI risk reduction counseling*
- Offering condoms
- Contraception counseling and, if needed, provision of contraception.* (See SSP section 9 for counseling requirements).
- Feeding assessment (and feeding inventory)
- Medical history review including recording/updating any adverse events (AEs) and concomitant medications, including vaginal products and practices.
- Provision of all available test results; provide/refer for treatment for UTI/RTI/STIs as needed.
- Administration of behavioral assessments*
- Provision of protocol counseling.
  - Note: In the instance that a participant reports not adhering to protocol requirements (i.e. she has had receptive intercourse within 24 hrs prior to the study visit), she should proceed with the visit but the deviation should be noted on sample collection documents and reported as a protocol deviation.
- Provision of product use and product adherence counseling
- Month 1-3 visits: Collection of used VR for storage and future testing, or unused oral Truvada for destruction.
- Month 1 and 2 visits: Provision of new supply of study product [new vaginal ring insertion with digital exam to check placement (as needed); or a new bottle of oral Truvada with first dose directly observed], as needed.
- For those selected/agreed for an IDI: Completion of IDI between Month 3 and study exit. (See SSP Section 14 for IDI implementation details).Performing a targeted physical exam, pelvic exam, and testing for UTI/RTI/STIs or other clinical condition, as required/indicated.*
- Collection and storage of blood, breast milk and pelvic samples for drug level testing/storage and safety and/or STI testing.
  - Note: no real-time drug level feedback will be provided in this study
- Assessment/review of social impact (spontaneously self-reported socials impacts by the mother at any visits should be appropriately documented and counseled)*
- PrEP counseling, at the Study Exit Visit (SEV).

**Required or if indicated designation will vary across visits.*

Note: participants selected for an IDI will have the interview scheduled between their Month 3 Visit/PUEV and study exit as detailed in SSP section 14.

Infant:

- Medical history review and review of pediatric care records, recording/updating any adverse events (AEs) and concomitant medications
- Performing a targeted physical exam*

- Collection and storage of blood for DBS for TFV-DP and FTC-TP or plasma for DPV drug levels (depending on study arm)

**Required or if indicated designation will vary across visits.*

Detailed information on laboratory evaluations are described in SSP section 10.

Early termination visits will include a subset of procedures noted above; these are outlined in protocol section 7.4.4 Table 15 and 16 and are included in the Sample Early Termination Visit Checklist.

While sites should aim to perform procedures in the order indicated in the approved site study visit checklists, it is acknowledged that this might not always be possible, and that maximizing efficiencies should also be prioritized. If procedures are consistently listed out of order on the site study visit checklists, sites are encouraged to update their checklists and send to FHI 360 for review.

Since mother and infant visits are joint, sites should take care to ensure visits are as efficient and accommodating as possible for the comfort of mother and baby. Sites should consider creating an infant-friendly clinic setting and have adequate staff to handle the infant when the mother is occupied with study procedures such as clinical exams and sample collection. The mother of the infant is expected provide and receive relevant medical information about the infant. If the mother is no longer caring for the child due to the mother's death or another scenario that led to the separation of mother and infant, the legal caretaker/guardian for the infant can decide if they would like the infant to continue in the study. Note that per the DAIDS Enrolling Children Policy, sites must specify in SOPs, procedures in the event of the death of the parent, as well as definitions and procedures for guardianship identification.

5.5.2 Visits Conducted Over Multiple Days: Split Visits Procedures

All procedures specified by the protocol to be performed at a follow-up visit will ideally be completed at a single visit on a single day for both the mother and the infant. If both cannot represent, the study site may consider rescheduling the visit to a day when both participants can complete their visits together or, based on individual circumstances, the site may choose to proceed with study procedures for one member of the mother-infant pair and not the other. If not conducted on the same day, visits for mothers and infants should be scheduled as close together as possible. If the mother presents for her entire visit but cannot bring her baby for the infant visit until another day within the visit window (or vise versa) this is NOT considered a spilt visit since the mother and infant visits are discreet from one another in the database. In this situation, sites will need to clearly delineate the dates at which procedures were done on the visit checklist for each the mother and infant visit and explain in chart notes. Sites may choose to complete two separate checklists with 'ND' marked as relevant for procedures or use the same checklist across the two visits but clearly indicate the completion date for each mother and infant procedure.

If all required follow-up procedures for an individual participant 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 a separate day but within the visit window, if possible. When this happens, it is referred to as a "split visit."

Split visits are permitted for any type of follow-up visit in MTN-043.

If study visits must be split, note that:

- HIV pre- and post-test counseling and HIV testing should all occur on the same day.
- All drug level and PK specimens (blood, breast milk, and vaginal swabs for biomarkers) must be collected on the same day to avoid complicating interpretability of the data.
- Behavioral forms completion should occur on the same day.

If study product is to be dispensed during a split visit, all of the following procedures must be conducted prior to dispensation:

- AE assessment and reporting (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product).

- HIV testing, HIV pre- and post-test counseling (when required by visit type)
- If applicable, collection of used rings or unused study tablets.

5.5.3 Missed Visits

If no procedures of a scheduled visit are conducted within the visit window, a Missed Visit CRF is completed. In the event of a missed visit, an interim visit may be required to resupply rings/tablets and conduct associated safety assessments and counseling as needed (see minimum procedures required to dispense rings/tablets outlined in SSP Section 5.5.2 above). Additional information about a missed PUEV can be found in SSP Section 5.13.

5.5.4 Off-Site Visit Procedures

MTN-043 protocol Section 7 specifies that visit procedures may be conducted off-site with participant consent. **Note that it is generally expected that regularly scheduled study visits will be conducted at the study clinic, and off-site visit procedures should occur infrequently.** Off-site visit procedures are distinct from participant contacts made for the purposes of retention/tracing or to collect product in response to a product hold/discontinuation; these procedures are described separately in SSP Section 3.

This section describes requirements which must be met prior to implementation of off-site visits, as well as situations which may warrant an off-site visit and what visit procedures will be permitted. It is strongly suggested that sites include the option of off-site visits for a defined set of reasons and procedures based on site capacity thus ensuring advance preparation to respond to adherence and/or retention issues. Site-specific procedures for off-site visits should be described in site SOPs.

5.5.4.1 Off-Site Procedures Informed Consent

Off-site visit procedures (excluding site procedures for retention efforts and product collection due to product hold) may only be conducted if the mother has provided written consent for herself and her infant to be visited by study staff outside of the clinic. Sample text for off-site visit consent is included within the sample enrollment informed consent form. Should local IRB/ECs require a separate informed consent to conduct off-site visits; sites may develop the consent in conjunction with FHI 360.

During the administration of the informed consent for off-site visits, sites should discuss with participants any issues that may jeopardize participant confidentiality and/or safety, such as living situation (e.g., persons living with participant, availability of private space at participant's home or place of work). Also, in an effort to minimize the potential risk of social harm to participants and to study staff who will conduct off-site visits, discuss with participants whether they have disclosed participation in the study to family, neighbors, or others who may learn of these off-site visits. Where participation has not been disclosed, maximal effort should be made to ensure inadvertent unwanted disclosure does not occur as a consequence of the off-site visit.

Each time an off-site visit is warranted, clinic staff must verify consent for off-site visits. When communicating with participants ahead of off-site visits, when possible, the rationale and the procedures to be conducted for the visit should be clearly explained to her as well as the approximate time that will be needed to complete the required procedures. Every effort should be made to ensure that the time and location is convenient for the participant.

5.5.4.2 Reasons for Conducting Off-Site Visits

Site staff should use good clinical judgment and discretion when determining that an off-site visit is needed for a particular participant. Examples of situations which may warrant an off-site visit for MTN-043 include, but are not limited to:

- Participant does not have time or is unable to come to the clinic for the visit
- Follow-up on an adverse event/ serious adverse event

- Collect samples that were inadequately collected or inadvertently missed at scheduled visits or compromised in transit to or at laboratory
- Collect confirmatory HIV samples
- Provide/collect study product
- Follow-up on a participant who:
  - is unable to come to the clinic and may potentially fall outside of the visit window for the current visit
  - has voluntarily withdrawn from the study, but is willing to have a final HIV test/ be offered pregnancy test/ safety bloods drawn off-site.

5.5.4.3 Permitted Locations, Visit Types, and Procedures

Off-site visits may occur at a participant's home or at other appropriate venues, provided that both participant and staff are comfortable with the venue and provided that safety and confidentiality can be maintained.

Any type of follow-up visit (i.e. scheduled or interim) may be conducted off-site; Screening and Enrollment Visits must occur on-site. Generally, the required visit procedures should remain largely the same as they would for an in-clinic visit. However, it is recognized that some procedures may need to be modified or omitted due to limited capacity to conduct them off-site. Site staff should document within participant records which visits were conducted off-site and what procedures were omitted or modified as a consequence (if any). As with any visit (in-clinic or off-site), participants have the right to decline/refuse completing any study procedures; site staff should clearly document refusals in the participant chart. Effort should be made to finish required visit procedures that are not conducted during an off-site visit as part of a split visit within the visit window.

The minimum procedures required to dispense study product from site pharmacy and deliver during at an off-site visit are the same as listed in Section 5.5 above for in-clinic visits.

NOTE: Per protocol, the IoR/designee may use his/her discretion to provide additional study product. This provision may occur in the clinic, or be delivered to the participant as an interim off-site visit. Should the IoR/designee approve of dispensing an additional vaginal ring or another bottle of 30 tablets, this should be adequately documented. In this situation, provided that safety tests (e.g. HIV testing) were conducted within the last 30 days, the only procedures that need to take place are AE assessment and recording (this can be based on participant-report), and adherence counseling/product use instructions, as needed. However, as with in-clinic visits, it is best to conduct as many of the scheduled visit procedures as feasible when off-site.

5.5.4.4 Off-Site Visit SOP Requirements

Sites are required to have approved SOPs for off-site visits in place prior to implementation of off-site visits. Considerations that should be addressed in the SOP for off-site visits are as follows:

- Feedback and operational suggestions received from the MTN-043 Community Working Group and Sites Community Advisory Board or Group as relevant with regard to conducting offsite visits.
- Procedures for contacting and scheduling participants for off-site visits.
- Procedures for verifying participants' consent prior to conducting off-site visits.
- Procedures to protect the safety of study staff, participants and any family members present during off-site visits, as well as confidentiality of participants.
- Identification of staff member roles and responsibilities for off-site visits:
  - In general, most off-site visits will require two staff members, including one who is able to provide clinical assistance in case of symptoms or AEs, perform phlebotomy, conduct and verify rapid tests results and assist with specimen processing
  - Ensure that at a minimum one of these staff members are conversant in the language of choice of the participant
  - Ensure that these staff members are thoroughly versed in confidentiality and pharmacy and lab chain of custody issues

- Procedures for management of symptoms/illness requiring medical attention. Specifically, procedures for management of positive pregnancy tests, positive or discordant HIV rapids, STI symptoms, contraceptive use and potential SAE/EAE, as well as provision of any necessary referrals should be described.
    - NOTE: If genital symptoms are reported during an off-site visit, the participant should be asked to report to the clinic as soon as possible for a pelvic exam.
- Generally, if any issues requiring further follow-up arise at an off-site visit, the participant should be referred (or brought) to the clinic as soon as possible for further evaluation. Depending on the severity of the issue, site staff may need to transport participant immediately from the off-site visit to the clinic or nearest healthcare facility.

- Description of how routine participant identification procedures will be modified for off-site visits.
- List of materials and supplies that will be needed for an off-site visit.

Lab considerations:

Sites may perform off-site visits to collect specimens for transport to an outsourced or site laboratory or to perform rapid HIV testing at the off-site location. Sites that wish to perform off site specimen collection or HIV testing will submit SOP(s)c to the Laboratory Center (LC) describing the process; LC approval will be noted in the comments on the Laboratory Activation Checklist or a separate memo if obtained after activation. It is recommended that the primary site SOP for off-site visits reference existing laboratory SOPs when possible, and these SOPs include components on off-site procedures (for example, performing HIV rapid tests off-site).

Considerations for collection of specimens for transport to an outsourced and on-site laboratory:

- Chain of custody, for specimens to be transported from off-site visits
- Safety considerations, including details on how biological specimens and bio-waste will be handled and procedures to prevent and respond to specimen accidents
- Adhering to allowable time intervals to get specimens to testing laboratories
- Specimen handling and transport methods
- All HIV rapid tests must have face-to-face post-test counseling conducted on the same day the test was conducted
- Equipment and supplies

Additional details regarding off site milk collection are provided in SSP Section 7.9.2.

Considerations for testing performed in an off-site location:

- Source documentation for test results
- Staffing: 2 staff members qualified in HIV rapid testing will be required to perform and review HIV testing results
- Safety considerations, including details on how biological specimens and bio-waste will be handled and procedures to prevent and respond to specimen accidents
- Equipment and supplies
- Appropriate area in off-site location to perform testing

NOTE: Staff should follow the same procedures specified in section 5.6 below in the event of a possible seroconversion (i.e., a reactive rapid HIV test) identified during an off-site visit. If possible and agreed upon by the participant, sites should offer immediate transport to clinic for directed post-test counseling, blood sample collection for seroconversion, and used study product collection for storage and future testing.

Source Document considerations:

- No *completed* CRFs or other source documents should leave the study clinic. It is recommended that paper CRFs be used in these instances and data-entered upon return to clinic. Blank CRFs and blank chart note pages should be taken off-site to allow visit documentation to occur in real time. Alternatively, if Wi-Fi connection can be obtained in the field, sites may use their discretion to take a tablet/computer off site and capture data directly into RAVE. All procedures should be outline in site SOPs for off-site visits.

- Staff notes (summarizing source documents in the binder) may be necessary to follow up on AEs/symptoms/con med use, etc. documented at the last visit. These may be *transcribed* from source documents in the participant binder or within Medidata Rave and brought off-site. Alternatively, if Wi-Fi connection can be obtained in the field, sites may use their discretion to take a tablet/computer off site to reference this information directly. The system for this should be outlined in the site off-site SOP.
- If a tablet/computer is not taken off-site, updates to log CRFs (e.g. AE logs, Con Meds log) or other site-specific trackers can be made upon return to the clinic based upon chart notes taken during the visit, but documentation of the off-site visit should never rely on memory. CRFs that are considered source documents must be completed during the visit. They should not be updated or completed after the visit based upon visit notes or memory.
- All documentation from the off-site visit should be filed in the participant binder and no documentation from the off-site visit should ever be destroyed (for instance, no notes should be jotted on scrap paper that is later thrown away at the clinic).
- Source Documentation and Data Management SOPs apply to off-site visit documentation and data collection/management just as they do for on-site visits.

Pharmacy considerations:

- Specifications on product supply procedures for off-site visits. *NOTE: All pharmacy procedures outlined in the MTN-043 off-site visit SOP should be reviewed and approved by an MTN pharmacist.*
- Requesting participant-specific study product from the pharmacy prior to the off-site visit (should include how this will be documented as an off-site visit on the MTN-043 Study Product Request Slip and the time line for notifying pharmacy prior to the off-site visit).
- Ensuring proper chain of custody of participant-specific study product from time of receipt from the pharmacy to time of delivery to the participant, including ensuring that participant-specific study product is delivered to the correct participant
- Transporting participant-specific study product at appropriate temperatures from time of receipt to time of delivery to the participant
- Handling/returning participant-specific study product when the participant cannot be located or refuses to receive the product dispensed for her
- Handling of used and unused study product, including procedures for collection and transportation back to clinic for disposal
- Documenting all of the above, and appropriately storing all documentation in either the study clinic and/or pharmacy (as per site SOP)

5.6 Procedures for Mothers Who Have a Positive Rapid HIV Test Result

In the event a mother has a positive rapid HIV test result(s), the following procedures must be done the same day of the reactive result is identified:

- Hold study product
- Plasma collection, CD4+ T cell count and HIV-1 RNA PCR
- CBC with platelets
- AST/ALT
- Blood creatinine and calculation of creatinine clearance
- Collection of blood for drug level and vaginal swab for biomarker specimens.
- Retrieve any study product in the participant's possession (within 24 hours of awareness).

Detailed guidance is specified on the MTN-043 HIV Confirmation and Seroconversion Guide. See SSP section 5.6.2 below for infants that require HIV-1 testing.

5.6.1 Participants with a Positive Rapid HIV Test Who Are Confirmed as HIV-Uninfected

For mothers who have a positive rapid HIV test result and are later confirmed HIV-uninfected per the algorithm in Protocol Appendix IV, product use and all protocol-specified visit procedures may be resumed if desired by the participant.

Once product is resumed, clinic staff should inform pharmacy staff of the resumption in writing, using a Study Product Request Slip signed by an authorized prescriber (or a prescription if the participant has not previously been accepting product).

Clinic staff should also update the Product Hold Log CRF to document eligibility to resume product use. If the participant declines study product use in this case and has had a prescription completed, a Study Product Request Slip marked 'Resume' should still be sent to the pharmacy. On this same slip, clinic staff will also mark 'decline,' to indicate that the participant is not accepting study product for use even though she is approved to resume product use.

Moving forward, sites must adhere to all guidance provided by the MTN LC for follow-up HIV testing plans for these participants (e.g. using alternate approved HIV rapid tests). In cases where an alternate HIV rapid kit is used, sites must have a system to alert testing personnel of this in advance. The HIV algorithm must be initiated whenever there is an HIV positive rapid test.

5.6.2 Procedures for Participants Who Become HIV-Infected

Mothers

The following procedures must be done for mothers whose HIV infection is confirmed per the algorithm in protocol Appendix III:

- **Permanently discontinue participant from study product.** Once the participant is identified as HIV-infected, complete a new Study Product Request Slip to notify the Pharmacy (mark 'permanent discontinuation'), update the status for the item "Was the participant instructed to resume study product use?" in the Product Hold Log CRF (the one originally completed for the reactive HIV rapid test result) to indicate the participant was permanently discontinued, complete a Product Discontinuation Log CRF, and update the participant's final HIV status in the HIV Confirmatory Results CRF to reflect the participant's HIV-infected status. Study staff should not wait to inform the participant of her HIV-infected status to complete these items.
- Inform participant of her confirmed HIV-infection status. Counsel and refer her to local care and treatment services per site SOPs.
- **Plasma collection, CD4+ T cell count and HIV-1 RNA PCR** will be performed at the clinic visit immediately following confirmation.
- **HIV-1 genotyping** may be performed on the stored plasma closest to the time of confirmed HIV-1 infection. It may be performed at additional/alternate time points as requested by site IoR or at the discretion of the MTN LC.

Infant:

Upon confirmation of maternal HIV infection, the following procedures are performed on the infant at the following timepoints:

- HIV-1 testing will be performed at the scheduled visit or an interim visit immediately following confirmation of the maternal HIV infection and will be done by HIV-1 RNA PCR, DNA PCR or other local standard of care testing. Contact the MTN Virology Core (mtnvirology@mtnstopshiv.org) immediately when performing infant HIV testing.
    - If negative, the infant will need to have additional PCR testing 4-6 weeks later. If infant testing continues to be negative at the 4-6 weeks test, it should be repeated again at 12 weeks after confirmation of the maternal infection.
    - If confirmed HIV infection per the algorithm in Appendix IV, the following procedures are performed on the infant if agreed to by the participant

- Repeat HIV-1 RNA PCR test and do HIV-1 genotyping. HIV-1 genotyping may be performed at additional/alternate time points as requested by site IOR or at the discretion of the Laboratory Center (LC).
- Facilitate rapid referral of the infant for appropriate further management including necessary blood tests (CD4+ T cell count, FBC), urgent ART initiation, and adherence counselling and follow up for the mother/guardian.

If a participant (mother or infant) misses the first visit following seroconversion, contact the MTN-043 Management Team for guidance on the missed laboratory procedures.

Infants whose mothers become infected with HIV while breastfeeding are at high risk for HIV acquisition. All women diagnosed with HIV during study participation will be counseled per national guidelines regarding immediate initiation of maternal ART with or without cessation of breastfeeding. The potential of infant prophylaxis will also be discussed if applicable. The women will be immediately referred for HIV treatment and long-term care as indicated above. Infant HIV testing and referral for care will also be performed as detailed above.

Participants (mother and/or infant) who acquire an HIV infection will continue in study follow-up with their original protocol-outlined schedule of visits until the point of study exit at Visit 8. Infants of mothers who seroconverted but they themselves did not seroconvert upon initial testing, will have an additional visit 4-6 weeks after maternal seroconversion is confirmed for the purposes of HIV testing. If confirmed infected at the 4-6 week visit, the infant will terminate from the study at this time, but if still testing negative, an additional visit 12 weeks post maternal seroconversion should be done for final testing. Sites should use the Seroconversion Scheduling Tool to determine target dates and visit windows for the infant 4-6 week and 12-week post-seroconversion visits. This may require the infant's study termination to be delayed if the testing repeat visits take place after the scheduled Visit 8/SEV. Termination from the study should be delayed until outcomes of all repeat testing have been determined. Should the infant become HIV infected during repeat testing that occurs after his/her Visit 8.0, exit the infant from the study after all needed referrals are provided and follow-up is completed.

For mothers who remain in follow-up, the following procedures will be discontinued during all regularly scheduled visits up to and including her SEV:

- HIV-1 testing, HIV pre- and post-test counseling.
    - Note: HIV/STI risk reduction counseling should continue and be modified to address primary and secondary infection prevention.
- Collection of blood for drug level and vaginal swab for biomarker specimens.
- Provision of study product, use instructions, product adherence and protocol counseling.
- Administration of Behavioral and product adherence assessments

Infants who also seroconvert and remain in follow-up will have collection of drug level specimens discontinued during scheduled visits.

The MTN-043/B-PROTECTED HIV Confirmation and Seroconverter Guide provides an overview of the HIV confirmation testing protocol, follow-up procedures for seroconverters who remain in the study, and study considerations for seroconverters. This guide is available on the MTN-043 study website and should be referenced upon an HIV rapid test result that is positive or indeterminate. Sites are encouraged to use a modified visit checklist for a participant who remains in follow-up to ensure only study procedures required for seroconverters are performed.

5.7 Modified Procedures for Participants Who Become Pregnant

Pregnancy testing will be performed for all participants at Screening, Enrollment, and Month 3/PUEV, and if indicated at all other visits. Testing will also be conducted, if indicated, at interim visits. Participants will be encouraged to report all signs or symptoms of pregnancy to study staff.

The IoR/designee also will refer the participant to antenatal care available, however sites will not be responsible for paying for pregnancy-related care.

Participants who become both pregnant and infected with HIV will also be referred to prevention of mother-to-child transmission (PMTCT) services and will be offered expedited resistance testing at the MTN LC to provide information that may be useful for identifying optimal PMTCT regimens. Site staff should notify the PSRT promptly. HIV testing of participants' infants will be offered through the study if such testing is not otherwise available. All referrals and offers of additional testing available through the study will be documented in participants' study records.

Upon confirmation of a positive pregnancy test, the following study procedures are required (regardless if scheduled to occur):

- HIV -1 testing, HIV pre- and post-test counseling
- Creatinine (per LoA #1)
- CBC with platelets
- AST/ALT
- Collection of blood for drug level and vaginal swab for biomarker specimens.
- Behavioral and product adherence assessments
- Retrieve any study product in the participant's possession (within 24 hours of awareness).

Participants who become pregnant during the study will have study product discontinued and will be terminated from the study along with their infants (Note: If the participant has also tested positive for HIV, she should not terminate from the study, but instead continue in study follow-up until the point of study exit at Visit 8). At the point of study termination, site staff should ensure that locator information is current and the participant is counseled to contact the clinic in the event that locator information needs to be updated prior to pregnancy outcome. The study site will make effort to continue to follow the mother until the pregnancy outcome is ascertained unless, in consultation with the PSRT, it is determined that the pregnancy outcome cannot be ascertained. Whenever possible, pregnancy outcomes should be collected from medical records or other written documentation from a licensed health care practitioner and should be documented on a **Pregnancy Outcome CRF**. Note that unlike other CRFs, this form can be completed after termination from MTN-043. When medical records cannot be obtained, outcomes may be based on participant report. Sites will also follow-up with participants to collect infant outcomes at approximately one year after delivery for those pregnancies that result in live birth. Information on infant outcomes one year after delivery should be documented in chart notes and on the **One Year Infant Assessment CRF**. Outcomes meeting EAE reporting criteria should be appropriately documented as well.

For participants who become pregnant, a **Pregnancy Report CRF** must be completed to report the pregnancy.

If a participant is pregnant, site staff should complete a Study Product Request Slip to notify the Pharmacy (mark 'permanent discontinuation') and complete a Product Discontinuation Log CRF. If the participant is willing, complete an Early Termination Visit. Finally, site staff should complete a Pregnancy Case Worksheet for participants who become pregnant during study participation. This worksheet is available on the MTN-043 study website.

Each site should have an SOP that includes information on the clinical management of pregnancies in MTN-043. At a minimum, this SOP should include information about:

- Counseling for pregnant participants on what is known about product exposure during pregnancy, why study product will be discontinued, and that the participant and her infant will be terminated from the MTN-043 study. This counseling may include messages such as:
    - Researchers are currently studying the effects of Dapivirine and Truvada when used as PrEP in pregnant women. Although none of the data that currently exists about these medications suggests they would be harmful to pregnant women or their babies, there is still a lot more to learn. Because many questions remain unanswered, women who become pregnant in B-PROTECTED will discontinue study product use. You and your baby will also exit the study.

    - Even though you will formally exit the study, the study staff are still here to support you. We will make sure you know how and where to access care in the community and with your permission will continue to periodically follow-up with you throughout the remainder of your pregnancy and up until your infant is one year old.
- Referrals for antenatal care and, if needed, PMTCT services.
- Tracking and documentation of pregnancy outcomes and infant health up to one year old.

5.8 Modified Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product Use

For this study, product use management may involve temporarily holding or permanently discontinuing either the VR or study tablet use for individual mothers, to protect their safety and well-being while in the study. Participants who either temporarily or permanently discontinue from one product use will not routinely be withdrawn from the study. Participants that discontinue study product will be encouraged to remain in the study, if they are willing, until their scheduled end-date. Every effort will be made to complete all protocol-specified follow-up visits, according to their original schedule. Infants of mothers who are permanently discontinued from study product use will also continue follow-up until their originally scheduled study exit date. Additional guidance regarding procedures to be completed in the event of a temporary or permanent discontinuation are noted below. For conditions requiring temporary or permanent product discontinuations, see Protocol Section 9.

5.8.1 Temporary Hold

If study product use is temporarily held, all other protocol-specified study procedures will continue except the for provision of study VR or tablet, product use instructions, and protocol adherence counseling. Drug level and biomarker specimens must be collected at the visit in which the study product is temporarily held, regardless of whether or not they were scheduled, and then discontinued at subsequent visits. The aforementioned procedures are to be resumed at follow-up visits once study product use has been resumed.

5.8.2 Permanent Discontinuation

Participants who permanently discontinue study product use due to an AE must continue to be followed until resolution or stabilization of the AE is documented.

Upon documentation of the product discontinuation, the following procedures must be performed regardless of whether or not they are scheduled to be completed:

- CBC with platelets
- AST/ALT
- Blood creatinine and calculation of creatinine clearance
- Collection of drug level and biomarker specimens
- Behavioral and product acceptability assessments

For those participants who permanently discontinue study product use for reasons other than seroconversion or loss of pregnancy and who remain in MTN-043 follow-up, protocol-specified procedures for MTN-043 will continue except the following:

- Provision of study VR or study tablets, provision of product use instructions, and retrieval and collection of study VR or study tablets
- Collection of drug level and biomarker specimens
- Behavioral and product acceptability assessments
- Provision of product adherence counseling

5.9 Participants who Discontinue Breastfeeding

Mothers who discontinue breastfeeding (e.g., due to decision to wean) will continue to receive study product and will continue with all regularly scheduled visits for the duration of their originally scheduled participation. Breast milk samples will continue to be collected for as long as a mother is able to produce breast milk, even if the infant is no longer receiving it. Should the mother no longer be producing sufficient breast milk to provide the 8 ml needed for study laboratory assessments, the procedure should be marked as not completed and the reason for the not stored specimen documented in the Specimen Storage CRF and LDMS tracking sheets. Document discontinuation of breastfeeding on the Feeding Assessment CRFs along with any reported foods being given to the infant.

Infants of mothers who report complete discontinuation of breastfeeding will discontinue drug detection procedures and remain in follow-up for the duration of their originally scheduled participations.

5.10 Voluntary Withdrawal/Early Termination

Mothers may voluntarily withdraw themselves and their infants from the study (withdraw consent) and terminate their study participation for any reason at any time. In these cases, site staff should ask the mother if she and her infant would be willing to complete one final study visit, which would count as their early termination visit. If the participant is willing, early termination procedures will be done per Protocol Section 7.4.4 Table 15 and 16. At the minimum for the mother, staff should:

- Perform a final HIV test.
- Complete the Study Termination CRF, mark “Withdrawal of Consent By Participant” and specify the reason the participant has refused further study participation.
- Record the reason(s) for the withdrawal in participants’ study records.
- Update participant locator form.
- Ensure all referrals are provided to participant as needed
- Collect any dispensed VRs or unused oral Truvada if applicable

A sample Early Termination Visit Checklist for the mother and infant is available on the MTN-043 website. Additionally, at these visits, the Study Termination CRF should be completed, and the reason for withdrawal/termination should be recorded in the source documents.

The IoR may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures, in consultation with the PSRT. It is recommended that site IoRs use their discretion with regards to terminating participants who relocate and can no longer come to the clinic, and are unlikely to resume study visits after counseling efforts and discussions with appropriate study staff. If a participant is known to have relocated but has not contacted the site to explicitly withdraw consent, the participant can be terminated early in absentia with the primary reason for completion/discontinuation indicated as “lost to follow-up’ on the Study Termination CRF.

All discussions, counseling, and decisions about early termination should be adequately documented in the participant’s 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.

Site teams are encouraged to review their Retention SOPs to make sure any site-specific procedures are in line with this guidance (e.g. that site teams may consider early termination as one option for participants who permanently relocate).

5.11 Resumption of Study Participation After Voluntary Withdrawal

- 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, per their original visit schedule. The resumption of study procedures and follow-up are subject to the IoR's discretion, pending PSRT consultation. Note the mother must be willing for both her and her infant to re-join the study. If such cases arise, study staff are advised to contact the MTN-043 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. Participant's random assignment also will remain unchanged and she will continue product use per her random assignment.
- Prior to performing any study procedure, the participant must re-consent to document that she and her infant voluntarily rejoined the study. Site staff should thoroughly document in the participant's chart notes her resumption of study follow-up, and if applicable, study product use and all communication with the study management team and PSRT.
- 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.
- Clinically-indicated evaluations should be performed if the participant reports symptoms.
- 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 product use. A copy of the final PSRT query form should be filed in the participant's study notebook.
- If resumption of study product use is approved by the PSRT, site clinic staff will communicate this decision to site pharmacy staff in writing. Resupply should be indicated on the Study Product Request Slip with a comment clearly stating that the participant has decided to rejoin the study and is clinically eligible to receive study product. If a participant has never previously accepted either study product but wants to initiate use, a prescription should be completed for this initial dispensation.

5.12 Participant Death

In the event of an infant death during study follow-up, the mother participant may remain in the study and continue follow-up on her regular visit schedule, if desired. Breast milk sample collection can also continue, if the mother is comfortable and for as long as breast milk production continues. Additional counseling and appropriate mental health referrals should be provided to the mother to help support her through the loss of her infant.

In the event of a maternal death during the study, the new legal guardian of the infant may choose to withdraw the infant from the study or may prefer to leave the infant enrolled for continued safety monitoring and care provided by the study staff. If the infant will remain in the study, a new informed consent for continued study participation should be obtained. , it would be fine for her to do so. As stated above, if the mother dies, I have a harder time justifying keeping the infant in the study since they are no longer exposed to product.

Additional details regarding SAE/EAE reporting requirements when a participant death occurs can be found in Section 8.16.

5.13 Product Use End Visit and Study Exit Visit

Both mother and infant will exit the study at the SEV/Visit 8, to occur 2 weeks following the PUEV. A mother or infant should not be terminated prior to the window opening of their scheduled SEV unless consent is withdrawn and/or the participant is terminated early from the study. As a reminder, the AE reporting period begins at the time of randomization and ends SEV visits are completed. Should a participant miss their SEV visit, the AE reporting period ends when their SEV visit window closes.

During the PUEV, site staff should discuss with the mother what procedures will be conducted during the SEV. If the PUEV is missed, it may be necessary for the participant to present to the clinic for specific safety testing, return study product, etc., or it may be necessary to incorporate some of the PUEV procedures into the participant's SEV. Site teams should contact the MTN-043 management team for guidance in the event that a PUEV is missed.

At the SEV, staff should complete the MTN-043/B-PROTECTED Study Exit Worksheet. Sites should also develop a Permission to Contact Log to record whether to contact the mother (or legal guardian of the infant, if changed from the mother) with study results or about future studies for which the participant may be eligible. Samples of the Study Exit Worksheet and Permission to Contact Log are available on the MTN-043 website.

5.13.1 Participant Locator Information

Accurate participant locator information will be needed for post-study contact with mothers and infants. As such, locator information should be actively reviewed and updated at all study exit visits and all mothers should be counseled to contact the study site should their locator information change after their study exit. Sites should outline their process for tracking locator information for both the infant and mother in site SOPs. See SSP section 3 (Accrual and Retention) for more information.

5.13.2 HIV Counseling and Testing at the PUEV and SEV

HIV testing will be performed at the PUEV for mothers. HIV pre- and post-test counseling provided at this visit should emphasize that additional counseling and testing will be provided to the mother after her study exit visit if needed to clarify or confirm her HIV status.

For participants who test HIV positive or have ambiguous HIV testing results (i.e., positive or discordant rapid tests and negative or indeterminate Geenius) at the PUEV or Study Exit Visit, study termination should be postponed until the algorithm is completed and all necessary samples are collected.

At the SEV, routine HIV counseling and testing is not required, but site staff should incorporate a PrEP counseling session into the visit at some point, per protocol. The content of this counseling should be driven by site-specific SOPs, but may include an assessment of participant interest in accessing PrEP post-study, provision of information on the local availability of PrEP, and referrals to PrEP providers, if appropriate.

5.13.3 AE Management and Documentation

All AE Log forms completed for each participant should be reviewed at the study exit visit and updated as needed.

5.13.4 Final Study Contact

Although the study exit visit is the last scheduled study visit for mother and infant, a final contact may be needed after the SEV to provide the mother with her or her infant's final study test results, post-test counseling, and treatment, if needed. Additional contacts also are required for:

- Infants of mothers who are HIV infected (must complete a visit 12-weeks post maternal seroconversion confirmation)
- Participants with certain types of AEs that are ongoing at study exit (see SSP Section 8)
- Mothers found pregnant during study follow-up (to be follow-up to ascertain pregnancy outcome and collect infant outcome data approximately one year after delivery)

For each mother and infant, 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. Study staff may complete final contacts at the study site, by telephone, or at community-based locations, depending on site capacities and site and mother's preferences. All final contacts must be documented in the participants (Mother/Infant) study records, but no CRFs are completed for these contacts.

5.13.5 Referral to Non-Study Service Providers

After completing their study exit visit and final study contact, participants will no longer have routine access to services provided through the study, such as reproductive health care and HIV counseling and testing for the mother, and HIV testing and developmental assessments for the infant. Mothers should be counseled about this —before and during their study exit visit — and provided information on where they can access such services after study exit, including current country policies and local access to PrEP. Study visits do not replace postpartum care that the mother and post-natal care that the infant should start receiving after the mother delivers. It is strongly recommended that all study sites develop a sample script which can be used when discussing this issue mothers as well as written referral sheets that can be given to mothers at their and their infant's study exit visits (after obtaining IRB/EC approval of the written information).

5.13.6 Post-Study Contact

It is expected that all mothers will be re-contacted by study staff when study results are available for dissemination.

To facilitate post-study contact with mothers, locator information should be updated at the SEV, and mothers should be counseled to contact the study site should their locator information change after study exit. In addition, mother's preferences for methods to be used for contacting them when study results are available should be documented in participant study records. It is recommended that participant preferences be recorded on a study exit worksheet.

Lastly, for participants whom study staff may wish to contact regarding participation in future studies, permission for such contact should be sought from the mother and documented. In addition, for ease of retrieving information on participant permissions, it is recommended that study staff maintain future study contact permission logs. It is recommended that participant permission (or lack thereof) for future studies be documented on a study exit worksheet similar to the sample reference above.