Section 5. Study Procedures

5 Introduction 5-1
5.1 Visit Location 5-2
5.2 Eligibility Determination and SOP 5-2
5.3 Screening Visit 5-2
5.3.1 Screening Visit Procedures (All cohorts) 5-3
5.3.2 Screening and Enrollment Log 5-4
5.3.3 Participants Found to be Ineligible (Screen Failures) 5-5
5.4 Enrollment Visit (All Cohorts) 5-6
5.4.1 Mother Enrollment Visit Procedures 5-6
5.4.1.1 Procedures Completed PRIOR to Randomization 5-6
5.4.1.2 Procedures Completed AFTER Randomization 5-7
5.4.1.3 Incomplete Enrollment Visits 5-8
5.5 Follow-up Visits (Cohort 3) 5-8
Figure 1: Study Visit Schedule – Cohort 3 5-9
5.5.1 Phone Contact Visits 5-10
5.5.2 Infant Enrollment 5-10
5.5.3 Follow-up Visit Procedures 5-11
5.5.4 Visits Conducted Over Multiple Days: Split Visits Procedures 5-13
5.5.5 Missed Visits 5-13
5.5.5.1 Missed PPO Visits 5-13
5.5.6 Off-Site Visit Procedures 5-14
5.5.6.1 Off-Site Procedures Informed Consent 5-14
5.5.6.2 Reasons for Conducting Off-Site Visits 5-14
5.5.6.3 Permitted Locations, Visit Types, and Procedures 5-15
5.5.6.4 Off-Site Visit SOP Requirements 5-15
5.6 Procedures for Mothers Who Have a Positive Rapid HIV Test Result 5-17
5.6.1 Participants with a Positive Rapid HIV Test Who Are Confirmed as HIV-Uninfected 5-17
5.6.2 Procedures for Maternal Participants Who Become HIV-Infected 5-18
5.6.3 Procedures for Infant Participants Who Become HIV-Infected 5-20
5.7 Modified Procedures for Participants Who Experience a Pregnancy Loss 5-20
5.8 Modified Procedures for Participants Who Temporarily Hold or Permanently Discontinue Study Product Use 5-20
5.8.1 Temporary Hold 5-21
5.8.2 Permanent Discontinuation 5-21
5.9 Voluntary Withdrawal/Early Termination 5-21
5.10 Resumption of Study Participation After Voluntary Withdrawal 5-22
5.11 Product Use End and Information for Providers 5-23
5.12 Study Exit Visit 5-23
5.12.1 Participant Locator Information 5-24
5.12.2 HIV Counseling and Testing at the 6-week PPO visit 5-24
5.12.3 AE Management and Documentation 5-24
5.12.4 Final Study Contact 5-24
5.12.5 Referral to Non-Study Service Providers 5-25
5.12.6 Post-Study Contact 5-25

5 Introduction

This section provides information on requirements for study procedures in MTN-042, including screening and enrollment visits for mothers, and follow-up visits for mothers and infants.

5.1 Visit Location

Given the nature of the study procedures required to be performed during the MTN-042 study, all visit procedures are expected to be completed at the study clinic or by phone (for designated phone contacts). When necessary, follow-up visits may be conducted off-site at the participant's home or location suitable to the participant with documented consent and 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 mothers 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 mother 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-042 Management Team (mtn042mgmt@mtnstopshiv.org).

5.3 Screening Visit

The term "screening" refers to all procedures undertaken to determine whether a mother is eligible to take part in MTN-042. 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 (IC) should be reviewed to ensure that the mother clearly understands all information and is willing to participate in the study and is willing for her infant to be enrolled in the study once born. **It is strongly recommended that infant IC be obtained at the maternal screening or enrollment visit (i.e., before delivery).** 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-042 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 (or using the Informed Consent Coversheet (s), if preferred). See SSP section 4 for details about mother and infant IC.

In addition to the ICF and as part of the IC discussion, the participant should have the recommendations of the Interim Review Panel (IRP) meeting(s) from any prior cohorts explained to her to aid in her informed decision to participate in this subsequent cohort. Staff should refer to the operational guidance released with the IRP recommendations for specific counseling messages.

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

the entire screening process, beginning with the informed consent process. A new PTID will not be assigned to the mother or infant 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 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 (All cohorts)

Required screening procedures are reflected in the sample Visit Checklists available on the MTN-042 webpage. After provision of written informed consent, mothers will be assigned a PTID and undergo a series of behavioral eligibility assessments, clinical evaluations, and laboratory tests. The Infant PTID will be assigned once infant IC is provided. Further details on PTID assignment, structure, and related information are included in SSP Section 11.

Administrative procedures include:

- Collecting locator and demographic information
- Obtaining signed medical record release (if required per local laws/regulations) and antenatal care provider information
    - Mothers should be asked to bring any antenatal care records she has, including ultrasound records, to the screening visit.
    - If required per local laws/regulations, 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 7.1. 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 antenatal/obstetric care records prior to the mother's enrollment visit.
    - Note that the signed ICF and behavioral screening eligibility worksheet also confirms the participant's permission for access to her/her infant's medical records. These documents may serve as adequate source documentation in the place of a signed release, if one is not required by local laws/regulations.
- Obtaining planned location for delivery.
    - Sites may develop a site-specific source document to collect this information such as a log form, include in the medical records release form, other site-specific form, in chart notes and/or on the visit checklist. Planned delivery location should be actively reviewed at each visit prior to pregnancy outcome.
- If adequate records of a previous ultrasound are not available, performing or scheduling an ultrasound with results to be available for review prior to the enrollment visit,
    - Refer to SSP section 7.7 and 7.8 for details on required ultrasound elements for eligibility determination.
- If presumptively eligible, scheduling their enrollment visit
- Providing reimbursement

Behavioral eligibility criteria, based on self-report, should be evaluated using the Screening Behavioral Eligibility Worksheet provided on the MTN-042 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 is 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. Additionally, if infant informed consent is not conducted at screening per site SOP, the mother must verbally confirm at screening willingness for her infant to be enrolled in MTN-042.

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

- Collecting medical, obstetric, and pregnancy history; review of available antenatal care records, including ultrasound records (per protocol participant must authorize site to obtain antenatal care records from provider), assessment of concomitant medications and vaginal products and practices; and conduct of a physical and obstetric abdominal examination, pelvic exam, if indicated, and ultrasound, if records are not available.
- Assessing for STI/RTI/UTIs, cervicitis, genital signs/symptoms, and overall general health.
- Calculating gestational age
    - For Cohort 3, the eligible gestational age limits are between 12 0/7 weeks – 29 6/7 weeks pregnant at the time of enrollment.
- Providing HIV pre/post-test and risk-reduction counseling and study approved condoms.
- Disclosing all available test results to the participant, as well as treatment or referrals for UTI/RTI/STIs if indicated.

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

- Receive testing for HIV, urinalysis (and/or culture, per SOC), Hepatitis B surface antigen, STIs (Syphilis, Gonorrhea, Chlamydia and Trichomonas), CBC with platelets, AST/ALT and serum creatinine (along with calculated creatinine clearance).
    - Vaginal swabs may be self-collected by the mother. Clinicians can assist with swab collection as needed.
    - 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, and vaginal pH test.

If the participant meets eligibility criteria at the end of the Screening Visit, she should be scheduled for her Enrollment Visit, making sure the enrollment visit takes place within the allowable 35-day time frame and the allowable cohort gestational range. Mothers should be provided with study informational materials, clinic contact information, and instructions to contact the clinic with any questions as needed prior to her scheduled Enrollment Visit. The participant should also be reminded to refrain from engaging in prohibited study practices beginning 24 hours prior to her enrollment visit.

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 and 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 Site Clinical Operations and Research Essentials (SCORE) Manual: Essential Documents and the 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-042, 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. For each cohort, a combined PTID Linkage Log will be maintained for mothers and infants. The PTID Linkage Logs must be stored in a secure location. Further details on the PTID Linkage Logs are included in SSP Section 11.

A sample Screening and Enrollment Log is available on the MTN-042 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 non-enrollment for the infant. Full completion instructions are within the log.

Note that a single Screening and Enrollment Log can be maintained for the MTN-042 study overall, or sites can choose to start a new log for each cohort. If a single log is maintained, sites should have clear organization such that cohorts are easily distinguished. For example, sites should insert a blank sheet of paper and/or a tab divider to indicate the start of screening and enrollment pages for a new cohort. Any unused lines on the last page from the previous cohort should be lined through, initialed, and dated.

5.3.3 Participants Found to be Ineligible (Screen Failures)

Screening procedures should be discontinued when the mother participant is determined to be ineligible. If the mother 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 mother screens out due to a clinical condition requiring follow-up, appropriate referrals should be provided to ensure the well-being of the mother and baby. 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.

For all screened-out mothers, 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.

Mothers -- Documentation for Eligible/Not Enrolled or Incomplete Screening:

If “Eligible/Not Enrolled” is marked on the Inclusion/Exclusion Criteria CRF for the mother, code N-1 should be entered for the participant on the Screening and Enrollment log and site staff should specify the reason on both the log and the CRF.

- Example: At enrollment, a mother who is eligible for the study reconsiders at the point immediately prior to randomization and decides not to enroll. “Mother declines enrollment” could be used to document the reason for this non-enrollment.

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

- Example: A mother completes her screening visit but is lost to follow-up and does not return for enrollment visit within 35 days.

Infant Not Enrolled Documentation:

Infants do not have set inclusion/exclusion criteria for MTN-042. Rather, their enrollment in the trial is determined by: their mothers being eligible, whether they have IC provided, and if they were born alive. If an infant is not enrolled, the appropriate reason should be provided through use of the infant

not enrolled codes (Z-1, Z-2, Z-3) on the Screening and Enrollment Log and corresponding entry be indicated on the Infant Inclusion/Exclusion Criteria CRF. While there is an "other" code available (Z-4) for infants not enrolled, it is expected this would be used rarely. The infant section of the entry row must be updated with the infant enrollment outcome for all enrolled maternal participants, even if the infant never receives a PTID.

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

- A participant with at least 1 positive HIV rapid test, no matter the outcome should be deemed ineligible per Exclusion Criteria 2 (E-2): At Screening or Enrollment, has a positive HIV test.
- A participant confirmed HIV-infected (i.e. has 2 positive rapids or discordant rapids with a positive confirmation) should be deemed ineligible per E-2 and Inclusion Criteria 4 (I-4): HIV-uninfected based on testing performed at Screening and Enrollment.

Screening HIV Rapid Test Results	Final HIV Diagnosis (confirmation)	Eligibility Criteria	
		I-4	E-2
Dual Negative	NA	No	No
Discordant	Infected	Yes	Yes
	Uninfected	No	Yes
Dual Positive	NA	Yes	Yes

5.4 Enrollment Visit (All Cohorts)

Enrollment procedures are specified in Protocol Section 7.3 and reflected in the sample Enrollment Visit Checklist available on the MTN-042 study website. A mother is considered enrolled in the study when she is randomized via the MTN-042 Medidata Rave clinical database. All baseline samples and examinations must be collected/completed 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 mothers. 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 an 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 participant cannot complete enrollment within her Screening to Enrollment window, she should be considered a screen fail.

In brief, procedures occurring before and after randomization are noted below.

5.4.1.1 Procedures Completed PRIOR to Randomization

The mother should undergo the following procedures before randomization:

- Confirm the informed consent form(s), as applicable, have been signed and dated and the mother remains willing and able to participate in the study, and is willing her infant to enroll once born.
    - Note: it is strongly recommended that infant IC be obtained before maternal enrollment; this can be done at the maternal enrollment visit if not already captured during screening and is recommended to occur before randomization.

- Confirm the 35-day screening window has not been exceeded and mother is within gestational age range for currently enrolling cohort (including re-dating of GA as needed based on Ultrasound results per protocol section 7.13 and SSP section 7.7 and 7.8).
- 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, obstetric, and pregnancy history that was first collected at the Screening Visit, including review of any antenatal care records or ultrasound records obtained. Assess for new vaginal practices.
- Administer the Edinburgh Postnatal Depression Scale CRF and calculate score; refer for counseling/support, if needed. (See SSP section 7.2.7 for more information)
- Assess for STI/RTI/UTIs or cervicitis signs/symptoms.
- Collect urine for urinalysis (and/or culture, per site SOC).
- Collect blood for HIV testing, AST/ALT, CBC with platelets, creatinine clearance and 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-042 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.
- If indicated, conduct a physical exam to confirm the mother is in good general health.
- Perform ultrasound if no previous ultrasound results are available.
- Conduct an obstetric exam, and conduct pelvic exam and pelvic sample collection per Pelvic Exam Checklist
- Disclose all participant's available test results and, if indicated, provide treatment or referrals for STI/RTI/UTIs/cervicitis.

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 participant eligibility have been completed by designated site staff, the participant may be randomized to a study product arm, at which point she will be considered officially enrolled in the study.

Participants may be selected for an IDI based on criteria outlined in SSP section 14. If a participant is selected for an IDI, clinic staff should inform her of selection, explain the IDI process, confirm verbally the participant's willingness to participate in an IDI and schedule the IDI (or inform her that someone

will contact her to schedule). Note that final eligibility for the IDI will be determined on the day of the interview. Document the IDI selection outcome on QPL and the Enrollment CRF.

After randomization, the following procedures should be completed:

- 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 required behavioral assessments (COVID, Baseline Behavioral Assessment)
- 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. For further detailed guidance on first product use, refer to SSP section 9.2.
- 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.
- 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.
- 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:

- 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 appropriate gestational age window, if possible and the participant is willing. All enrollment visit procedures should be redone on the day of rescheduled enrollment.
- 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 and documentation guidance. **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 (Cohort 3)

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 follow-up visits that are pre-pregnancy outcome (pre-PO) for the mother and post-pregnancy outcome (PPO) for the mother and infant, if enrolled.

Participants will have the following follow-up visits for cohort 3:

Note: Expected completion of these visits will depend on the participant's GA at enrollment. The Cohort 3 Visit Calendar Tool will generate a visit schedule for each participant based on their gestational age at enrollment.

Pre-PO (up until PO or 41 6/7 weeks of gestation, whichever comes first):

- 2-week visit
- 4-week visits through 36 weeks gestation

- Pre-PPO phone contacts
    - 1-week and 3-week Pre-PPO phone contacts
    - Every odd numbered week after enrollment starting from 36 weeks GA until PO
- Bi-weekly visits starting from 36 weeks gestation– every even numbered week after enrollment once the participant is 36 weeks GA until PO

In the case when both a bi-weekly and 4-week visit are indicated in the 36th week for a participant, the 4-week visit should be conducted.

Post-pregnancy outcome (PPO):

- PPO visit (V 101/Mother and V201/Infant) – within 2 weeks of delivery
- 1-week PPO phone contact (V102/Mother and V202/Infant), as needed
- 6-week PPO/ Mother Study Exit Visit (SEV) (V103/Mother and V203/Infant)
- 6-month PPO (V204/Infant)
- 12-month PPO/Infant SEV (V205/Infant)

Figure 1: Study Visit Schedule – Cohort 3

Cohort 3	Screening
Enrollment Window 12 0/7 weeks of gestation – 29 6/7 weeks of gestation	Enrollment
	1-week (phone, home or clinic as needed per local standard of care)
	2-week
	3-week (phone, home or clinic as needed per local standard of care)
	4-week and every 4 weeks through 36th week of gestation
	Every odd-numbered week starting from 36th week of gestation (e.g., follow-up weeks 19, 21, 23) until pregnancy outcome (phone, home or clinic as needed per local standard of care)
	Every even-numbered week including and after 36th week of gestation (e.g., follow-up weeks 20, 22, 24) until pregnancy outcome
Infants enroll →	Post-pregnancy outcome visit (delivery hospital/facility or clinic)
	1-week post-pregnancy outcome (phone, home or clinic as needed per local standard of care)
Mothers exit →	Approximately 6 weeks post-pregnancy outcome
	Approximately 6 months post-delivery
	Approximately 12 months post-delivery

Sites will need to track the mother closely near the time of her expected delivery date to ensure they are aware of her delivery and can prepare for her to transition to the PPO portion of the study follow-up and follow-up of her infant (for live births).

Sites should attempt to bring in the mother and infant (if born alive) for the PPO visit (V101/V201) as soon as possible after the PO. If the PPO visit cannot be scheduled within a week of the PO, sites should attempt to have the 1-week PPO phone contact (V102/V202) with the mother and infant during this timeframe. The PPO visit (V101/201) and the 1-week PPO phone contact (V102/202) have overlapping windows that close 14 days after the confirmed date of the mother's pregnancy outcome. If the PPO Visit occurs before the PPO 1-week phone contact, the phone contact may be skipped; this will not be considered a missed visit. If a mother cannot complete the PPO Visit within the window, the site should make all attempts to bring her and her infant in as soon as possible for an interim visit to capture pregnancy outcome information and complete PPO procedures, if applicable (See section 5.5.5.1). When a mother notifies the site of the delivery, it is recommended that sites chart note any relevant PO information provided in case the mother becomes lost to follow-up before either the PPO Phone contact or PPO visit is completed, as this information may serve as the only PO data able to be captured. Note that if a participant calls to report she has delivered and reports an AE, the contact should be considered an Interim Visit so that the AE can reported on the AE Log CRF.

Should a mother deliver prior to completion of any of her scheduled pre-PO visits, these visits will not be made up nor considered missed. She will proceed to the PPO portion of her visit schedule. See SSP section 11 for details on transitioning in the study database to the PPO visit portion of the visit schedule. Her infant will be enrolled at birth, or at the time infant IC is provided if not signed before delivery. See section 5.5.2 for infant enrollment information. If the mother experiences a pregnancy loss, she will continue her regular visit schedule with modified procedures. See Section 5.7 for details.

Pre-PO bi-weekly visits and phone contacts will cease after 41 and 6/7 weeks gestation. Product should be discontinued at pregnancy outcome, or a max of 41 and 6/7 weeks gestation. As needed, an interim visit should be conducted for product resupply especially for participants using oral Truvada to ensure they have no lapse in supply to cause missed doses leading up to their PO or 41 and 6/7 weeks gestation, whichever comes first.

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 Phone Contact Visits

Mothers are to complete phone contacts prior to pregnancy outcome per the schedule described in section 5.5 above. These are required study visits for all mothers. The primary purpose of these contacts is to review medical history, assess for any AEs or address any issues or concerns with product use or study participation, receive any needed counseling, confirm planned delivery location, and disclose available results. The 1-week PPO Phone Contact has similar procedures but is focused on assessing the mother and infant in context of her pregnancy outcome and may be omitted if the PPO visit has already occurred. Mothers may choose to come to the clinic for these visits if preferred. See the Sample Phone Contacts Visit Checklists (maternal and infant) on the MTN-042 website for full list of procedures.

5.5.2 Infant Enrollment

Infants are enrolled in MTN-042 at birth, or at the time infant IC is provided if not signed before delivery. There are no set protocol inclusion/exclusion criteria for infants. All sites are strongly encouraged to obtain infant IC during the maternal screening or enrollment visit (i.e., before delivery). However, for rare instances where infant IC is not obtained prior to delivery, infant IC may be obtained at any time up until closure of the infant's month 12 visit window. If the mother chooses to withdraw her own consent for participation at any point, she may still choose to keep her infant enrolled in the study. Sites should be mindful to explain this option and clearly assess and document the mother's decision in this regard. In summary, infants must meet the following conditions to be enrolled:

- Born alive (to mothers enrolled in MTN-042)
- Infant IC has been provided

The date of infant enrollment will be the date of birth, or the date infant IC is signed if obtained after delivery. See SSP Section 11 (Data Collection) regarding further details regarding form completion in the event an infant is not enrolled.

No procedures for the infant many occur until the infant ICF form is signed. See SSP Section 4 for details about infant IC. Once IC is confirmed, generate the infant PTID in Medidata and complete the column for Infant PTID on the PTID Name Linkage Log (*note: infant name can be left blank until after birth, when known*). Update the Screening & Enrollment Log next to the mother's entry with the infant PTID. At the time of confirmed live birth or signing of the infant IC if obtained after delivery (or, at the time of confirmation that the infant will *not* be enrolled, e.g. fetal death/stillbirth, withdrawal of consent/IC not provided, mother not enrolled), update the Screening & Enrollment Log with the outcome of the infant's enrollment.

If an infant is deemed too ill to undergo study procedures, the IoR/designee may opt to omit specific study procedures. Participant mothers will be strongly encouraged to complete one year of follow-up for their infants but can decline further participation at any time. Should the infant not enroll in the study due to consent withdrawn by/not obtained from the mother, no infant procedures should be

done. The mother should continue with study participation on her regular schedule if willing. See section 5.7 for guidance on mothers who experience a pregnancy loss.

For visits post-pregnancy outcome where both mother and infant will have study procedures, 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 to attend the semi-annual visits with the infant for her to provide and receive relevant medical information about the infant. If mother is no longer caring for the child due to the mother's death or other domestic separation scenario, the legal caretaker/guardian for the infant (per site SOP) should be responsible for the remainder of infant follow-up to the extent possible. Sites must specify in SOPs, procedures in the event of the death of the parent, as well as definitions and procedures for guardianship identification.

5.5.3 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 Cohort 3 Sample Visit Checklists available on the MTN-042 website.

As a general guide, clinic visit procedures may include:

<u>Mothers</u>

All visits:

- 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*
- 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.
- Medical/obstetrical 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.
- 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.
- Performing a physical exam, pelvic exam, and testing for UTI/RTI/STIs or other clinical condition, as required/indicated.*
- Collection and storage of blood and pelvic specimens for drug level testing/storage and safety and/or STI testing.*
    - Note: no real-time drug level feedback will be provided in this study

*Required or if indicated designation will vary across visits.

Pre-PO visits only:

- Collect/review antenatal care records; confirm planned delivery location
- Perform obstetrical exam
- Provision of product use and product adherence counseling

- If indicated, collection of used VR for storage and future testing, or unused oral Truvada for destruction.*
- If indicated, 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. Note that DOD of the first study tablet at product resupply visits is required per protocol Appendix I.*
- Administration of behavioral assessments *
- Assessment/review of social impacts* (spontaneously self-reported socials harms by the mother at any visits should be appropriately documented and counseled)

Post Pregnancy Outcomes (PPO) visits only

- Administration of Post-PPO behavioral questionnaires at PPO and SEV.
- Collect/review delivery records and postpartum care
- At PPO Visit: Collection of used VR for storage and future testing, or unused oral Truvada for destruction, if not already returned.
- Study Exit Visit: Assessment/review of social impact and benefits (spontaneously self-reported socials harms by the mother at any visits should be appropriately documented and counseled)

*Required or if indicated designation will vary across visits.

Note: participants selected for an IDI in cohort 3 will have the interview scheduled around their 36th week of gestation after 4 weeks of product use has been confirmed (see SSP section 14).

Infant:

PPO visit through 12-month PPO visit:

- Review/confirmation of locator information, visit scheduling and provision of reimbursement (may be combined with mother's procedures, when applicable)
- Review of health, anthropometry, feeding history (including administration of Infant Feeding Assessment CRF) including recording/updating any adverse events (AEs) and concomitant medications
- Review/update infant health care records
- Performing a physical exam (targeted after PPO visit)
- If indicated, HIV testing (mother to receive pre- and post-HIV test counseling for infant)
    - HIV testing required for infants born to HIV-infected mothers
- Collection and storage of blood for drug level testing/storage and safety testing
    - At PPO Visit only, DBS for TFV-DP and FTC-TP or plasma for DPV drug levels
    - Creatinine serum required the PPO and 6-week PPO visit (all infants/both study arms, per protocol appendix II), and only if clinically indicated at all other visits.
- Provision of all available infant test results to mother; offer condoms to mother.

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 7.5.3 and are included in the Early Termination Sample Visit Checklist for the mother. Infant early termination procedures are incorporated on the infant Month 12 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. 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.

5.5.4 Visits Conducted Over Multiple Days: Split Visits Procedures

All procedures specified by the protocol to be performed at a follow-up visit, ideally, will be completed at a single visit on a single day. If all required follow-up procedures cannot be completed on a single day (e.g., because the participant must leave the study site before all required procedures are performed), the remaining procedures 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-042.

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 and vaginal swabs for biomarkers) must be collected on the same day to avoid complicating interpretability of the data.

At a minimum, all the following procedures must be conducted during split or interrupted visits to dispense study product:

- 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).
- If scheduled per protocol, HIV testing, HIV pre- and post-test counseling
- If applicable, collection of used rings or unused study tablets.

5.5.5 Missed Visits

To the extent possible mother and infant should complete their PPO and 6-week PPO visits together. However, 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 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 conduct a limited set of procedures, such as resupply rings/tablets and/or to conduct associated safety assessments and counseling as needed (see minimum procedures required to dispense rings/tablets outlined in SSP Section 5.5.2 above). Except for the PPO visit (see section 5.5.5.1), visits that are missed should NOT have the full complement of visit procedures "made up" outside of the protocol-specified visit windows.

5.5.5.1 Missed PPO Visits

In the event the PPO visit is missed, an interim visit should be completed to capture pregnancy outcome data and complete PPO visit procedures, if possible.

For the mother, this visit will focus on capture of the pregnancy outcome and should include:

- Review of medical/delivery/postpartum care records
- Medical/obstetrical history review including recording/updating any adverse events (AEs) and concomitant medications
- A physical exam, if indicated
- Completion of the pregnancy outcome CRF
- Collection of any study product and documentation of product discontinuation
- Note that samples for drug levels (DBS for TFV-DP and FTC-TP in Truvada group or plasma for DPV in DPV ring group) ***can be omitted*** for the mother given the time that will have passed

since discontinuation of product use (≥14 days). Sites should contact the management team with if unsure about sampling requirements.

All procedures as outlined in the PPO visit for infants, including collection of samples for drug levels and creatinine testing, should occur.

5.5.6 Off-Site Visit Procedures

MTN-042 protocol Section 7 specifies that visit procedures may be conducted off-site with participant consent. 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.

5.5.6.1 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/or 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.

5.5.6.2 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-042 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

5.5.6.3 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. interim, pre-PO, Post-PO study exit/termination) 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.

5.5.6.4 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-042 Community Working Group and Sites Community Advisory Board or Group as relevant with regard to conducting off-site 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

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-042 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-042 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 (if Pre-PO)
- 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-042 HIV Confirmation and Seroconversion Guide. See SSP section 5.6.2 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 (if pre-PO) 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 or is scheduled to change to a new 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 Maternal Participants Who Become HIV-Infected

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 (if pre-PO).** 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 next regularly scheduled clinic visit immediately following confirmation, and every three months thereafter from the point of seroconversion for the remaining follow-up period, or as indicated. Refer to the Seroconverter Schedule Tool (within the Visit Calendar Tool) available on the MTN-042 website.
- **HIV-1 RNA PCR or HIV-1 genotyping** may be performed on the stored plasma closest to the time of 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.

If a participant misses the first visit following seroconversion, contact the MTN-042 Management Team for guidance on the missed laboratory procedures.

Maternal participants who acquire an HIV infection will continue in regular study follow-up with a modified procedure schedule for a minimum of twelve months. In order to accommodate protocol-specified laboratory evaluations, these visits/procedures will be quarterly from the point of seroconversion. The participant will follow her original protocol-outlined schedule of follow-up visits (with plasma collection, CD4+ T cell count and HIV-1 RNA PCR labs added quarterly) until the point of her 6-week PPO visit. After this point, she will switch to a quarterly schedule of seroconversion visits as defined by her seroconversion date. Visit windows on quarterly seroconversion visits will be contiguous. Sites should use the Seroconversion Scheduling Tool to determine target dates and visit windows for quarterly seroconversion visits.

For mothers who remain in follow-up, the following procedures will be discontinued during all regularly scheduled visits up to and including her 6-week PPO visit:

- 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 adherence and product acceptability assessments.

The following visit procedures should be conducted during the mother's quarterly seroconversion visits which occur after the 6-week PPO visit:

		Quarterly Seroconversion Visits
ADMINISTRATIVE AND REGULATORY		
Collect/review/update locator information		X
Provide reimbursement (sites to reference SOPs)		X
Schedule next visit/contact		*
BEHAVIORAL		
HIV/STI risk reduction counseling (modified to address secondary prevention needs)		X
Social Harms Reporting		*
CLINICAL		
Review/update medical history and postpartum care records		X
Review/update concomitant medications, including ARVs		X
Physical exam		*
Pelvic exam		*
Treat RTI/UTI/STIs		*
Disclose available test results		X
Collect AEs		X
Referral for further management/care		X
	LABORATORY	
URINE	Dipstick UA (and/or culture)**	*
	Offer pregnancy testing	*
BLOOD	CD4+ T cell count	X
	HIV RNA	X
	AST/ALT	*
	Creatinine	*
	CBC with platelets	*
	Syphilis serology	*
	Plasma archive	X
	HIV-1 Genotypic Resistance Test	*
PELVIC	NAAT for GC/CT/Trich	*
	Wet prep/KOH wet mount for candidiasis and/or BV	*
	Vaginal pH	*

The MTN-042/DELIVER 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-042 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. A sample Seroconverter Follow-Up Visit Checklist is available on the MTN-042 study website.

5.6.3 Procedures for Infant Participants Who Become HIV-Infected

This section provides infant HIV testing and follow-up guidance as outlined protocol section 7.7.1.

- HIV-1 testing (including confirmation of HIV infection) is if indicated at all scheduled infant visits or can occur at an interim visit as needed. HIV testing of the infant should occur at the PPO visit or as soon as possible following birth from an HIV-infected mother, and at any timepoint point during the infant's follow-up upon a reported seroconversion of the mother (whether found via study testing or report from external testing), especially if the infant is breastfeeding, or as clinically indicated. Infant HIV-1 testing (including confirmation of HIV infection) will be done per local standard of care, generally including HIV RNA and/or DNA assays, and may occur at a scheduled visit or an interim visit. Contact the MTN Virology Core (mtnvirology@mtnstopshiv.org) immediately when performing infant HIV testing.
- Upon confirmation of infant HIV infection the following procedures are performed on the infant if agreed to by the participant:
    - Immediately following confirmation of HIV infection, perform plasma collection, CD4+ T cell count, HIV-1 RNA PCR test, and HIV-1 genotyping.
    - Facilitate rapid referral of the infant for appropriate further management including necessary blood tests, urgent ART initiation, and adherence counselling and follow up for the mother/guardian.
    - At all subsequent scheduled clinic visits until the infant is one year old, perform **plasma collection, CD4+ T cell count and HIV-1 RNA PCR**. HIV-1 RNA PCR or 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).

If an infant misses the first visit following seroconversion, contact the MTN-042 Management Team for guidance on the missed laboratory procedures. Refer to the MTN-042/DELIVER HIV Confirmation and Seroconverter Guide for a summary of infant follow-up and modified procedures.

5.7 Modified Procedures for Participants Who Experience a Pregnancy Loss

If a mother experiences a pregnancy loss after the Enrollment Visit, she will discontinue product use (as a scheduled end of use due to pregnancy outcome) and attend routine post-pregnancy outcome visits with the following procedures performed at her next clinic visit:

- CBC with platelets
- AST/ALT
- Blood creatinine and calculation of creatinine clearance
- Collection of blood for drug level and vaginal swab for biomarker specimens

For participants who have a pregnancy loss, a Pregnancy Outcome CRF must be completed to report the loss. Whenever possible, pregnancy outcomes should be collected from medical records or other written documentation from a licensed health care practitioner. When medical records cannot be obtained, outcomes may be based on participant report. Participants should receive counseling and referral for medical care, if needed, and support to help her cope with her loss.

If a participant has a pregnancy loss, site staff should complete a Study Product Request Slip, if indicated, (i.e., for participants who have ever had a prescription completed) to notify the Pharmacy (mark 'permanent discontinuation') to indicate the participant was permanently discontinued, complete the Product Discontinuation CRF.

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 vaginal ring 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 born to participants 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 and SSP Section 8.17.

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 clinic 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 blood for drug level and vaginal swab for biomarker specimens

For those participants who permanently discontinue study product use for reasons other than seroconversion or loss of pregnancy and who remain in MTN-042 follow-up, protocol-specified procedures for MTN-042 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 blood for drug level and vaginal swab for biomarker specimens
- Behavioral and product acceptability assessments
- Provision of product adherence counseling

Note that Adherence CRFs should be completed one final time at the visit where product is being discontinued to capture data related to product adherence in the previous 4 weeks, and then stopped at subsequent visits. Similarly, collection of used rings or any unused tablets should occur one final time at the visit product is being discontinued and stopped thereafter. If a participant is being discontinued at a visit where a behavioral assessment is scheduled to be administered (e.g., for cohort 3 maternal participants at the 4-week visit), then sites should proceed to administer this form and then discontinue subsequent behavioral assessments (including COVID-19 and any Follow-up or Post-PO Behavioral Assessments).

5.9 Voluntary Withdrawal/Early Termination

Mothers may voluntarily withdraw themselves and/or their infants from the study (withdraw consent) and terminate their study participation for any reason at any time. In cases of maternal withdrawal, site staff should ask the mother if she would be willing to complete one final study visit, which would count as her early termination visit. If the participant is willing, early termination procedures will be done per Protocol Section 7.5.3 (6-Week PPO Visit). At the minimum, 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 is available on the MTN-042 website. At the time of maternal withdrawal, site staff should confirm if the mother wishes to withdraw consent for both herself and her infant or herself alone. Infant participation should be encouraged and is permitted so long as the mother was ever enrolled in the study and consent remains on file. If an infant is withdrawn early/terminated that early termination procedures will be done per the infant 12-month PPO procedure schedule. 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).

5.10 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. If such cases arise, study staff are advised to contact the MTN-042 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:

Mothers:

- 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, if she has not had her pregnancy outcome.
- Prior to performing any study procedure, the participant must re-consent to document that she 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.
- For participants who are still pregnant and will be resuming product use, a pelvic exam should be performed if indicated (i.e. if the participant was previously placed on hold for a pelvic exam finding, and confirmation that the finding has resolved is needed) prior to re-instating product use.
- 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.

Infants:

- The infant's original PTID and follow-up visit schedule will remain unchanged.
- Prior to performing any study procedure, the mother (or guardian) must re-consent to document that they are voluntarily agreeing to have the infant rejoining the study. Site staff should document in the infant participant's chart notes their resumption of study follow-up.

5.11 Product Use End and Information for Providers

Mothers will be randomized to start using either the VR or Oral Truvada at the Enrollment visit and are to continue use until she goes into labor i.e., starts contractions, water breaks, admitted to delivery facility/hospital or up to a maximum of 41 and 6/7 weeks gestation. Product use will not continue after the mother's pregnancy outcome and all product is expected to be returned to the clinic at the Mother's PPO Visit by the mother. If the study product is left in the possession of the delivery facility and the mother is not able to retrieve and return product herself, the site should attempt to arrange pick-up from the facility or document loss or inability to retrieve the product (i.e., because it has been disposed). At each visit prior to the mother's pregnancy outcome, staff should review with the participant the study instructions and expectations for when she goes into labor, including stopping use and return of study product, and notifying the site of her delivery, as part of protocol counseling. See SSP 9.2 (Counseling) for information.

As mothers will be receiving antenatal care and will deliver at facility/hospital that may or may not be designated by the site, it is essential to ensure medical care providers that the mother comes in contact with during her study participation are aware of her participation in the MTN-042 study and are primed on pertinent information relevant to her care and study product use. An MTN-042/DELIVER Provider Guide is available on the MTN-042 study website that can assist with disseminating this information to providers. Sites may choose how best to distribute this guide per site SOP. A suggested approach would be for site staff to contact facilities and providers with this information as soon as sites are aware of delivery facilities and antenatal care providers identified by participants. The site may also arrange for the participants to give the DELIVER Provider Guide to providers or keep a copy with her to provide to any new providers she may come in contact with i.e. seek care or delivery at an unplanned location.

5.12 Study Exit Visit

The mother and infant will exit the study at different points during follow-up in MTN-042. The mother is scheduled the study at the 6-Week PPO Visit (V103). The infant will remain in the study and exit at the 12-Month Visit (V205). The respective scheduled SEV serves as the final follow-up visit for the mother and infant. 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 of the mother and ends when the mother and infant SEV visits are completed, respectively. Should a participant miss their SEV visit, the AE reporting period ends when their SEV visit window closes.

During the mother's PPO Visit, site staff should discuss with the participant what procedures will be conducted during the 6-week PPO Visit and how follow-up will continue with the infant until the infant's 12-Month visit. Depending on results from labs collected during PPO or if this visit is missed,

plans may need to change. It may be necessary for the participant to present to the clinic for specific safety testing, return study product, etc.

At each the mother's and infant's SEV, staff should complete the respective MTN-042/DELIVER Maternal Study Exit Worksheet or MTN-042/DELIVER Infant 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. The log should be first completed at the maternal SEV and updated as needed at the infant SEV. Samples of the Study Exit Worksheets and Permission to Contact Log are available on the MTN-042 website.

LoA#1 to protocol version 2.0 specifies that if maternal participants are unable to return to the clinic to complete their SEV within the window, that staff should attempt to complete as many of the visit procedures as possible over the phone. Conduct of any SEV visit procedures via phone should still occur within the specified SEV visit window. Sites should try and complete as many procedures as feasible over the phone, prioritizing follow-up on participant safety outcomes (i.e., to capture or update AEs). A protocol deviation should be submitted that summarizes any required SEV procedures that were omitted due to the nature of the phone contact (e.g., sample collection, physical exams).

If the SEV visit window closes and no SEV procedures have been completed (either in-clinic or by phone), then the SEV is considered missed and a **Missed Visit CRF** should be completed.

5.12.1 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, especially since the infant will continue in follow-up. Locator information will continue to be actively reviewed with the mother for her and her infant through the infant's 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.

5.12.2 HIV Counseling and Testing at the 6-week PPO visit

HIV testing will be performed at the 6-Week PPO Visit (V103) 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 at the 6-Week PPO Visit (V103). or have ambiguous HIV testing results (i.e., positive or discordant rapid tests and negative or indeterminate Geenius), study termination should be postponed until the algorithm is completed and all necessary samples are collected.

5.12.3 AE Management and Documentation

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

5.12.4 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:

- Participants who are HIV infected (must be followed for a minimum of 12 months after seroconversion confirmation
- Participants with certain types of AEs that are ongoing at study exit (see SSP Section 8)

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.

5.12.5 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, access to a HIV prevention product, 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. 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).

5.12.6 Post-Study Contact

It is expected that all mothers will be re-contacted by study staff when study results are available for dissemination. Sites should maintain documentation of contact made with participants to disseminate study results.

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 who 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.