

Section 6. Participant Follow-up

6.1 Study Follow-up Plan and Participant Retention Targets

Maternal participants in both the Lactation and Pregnancy Cohorts receive study drug for 7 consecutive days, starting on Day 0. Study sites will conduct follow-up phone calls on Day 1 and Day 3. Follow-up beyond study product dosing will include a Day 14 phone call, or clinic visit if necessary. Interim visits throughout follow-up are an additional option, if needed.

Women enrolled in the Pregnancy Cohort will be followed through the completion of their pregnancy, including a Delivery Visit and a Post-delivery Assessment. The post-delivery assessment visit is expected to occur approximately 14 days following delivery (+/- 7 days). Given the gestational age requirements for inclusion, total follow-up for a woman in the Pregnancy Cohort may last from 3-10 weeks. Follow-up phone calls and visits will include both women participants and their infants, once born.

For ease of reference throughout this section, visits are categorized as “mother and infant” to include the participating pair, unless further specified.

To minimize bias and ensure accuracy of study results, each study site will target a minimum retention rate of 95% for all enrolled study participants. Further information on MTN-008 retention definitions and procedures is provided in Section 8.

Mothers participating in the Pregnancy Cohort at participating MTN-016 sites will be encouraged to enroll themselves and their infants into MTN-016 (HIV Prevention Agent Pregnancy Exposure Registry: EMBRACE Study), for follow up during the first year of the infant’s life.

6.2 Types of 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. MTN-008 specifies follow-up visits for participants in both cohorts by telephone contact for the Days 1, 3, and 14 Visits, and in clinic for the Day 6 Visit. Women in the Pregnancy Cohort also have scheduled Delivery Visits and Post-delivery Assessments. All scheduled follow-up visits are pre-assigned a visit code for purposes of data management as described in Section 13.
- **Interim visits** are those visits that take place between scheduled visits or outside a visit window. Site staff may be required to assign visit codes to interim visits for purposes of data management as described in Section 13. Examples of reasons for an interim visit include follow-up on clinical management, repeat laboratory testing, or dispensation of additional study product,

Additional information related to the scheduling and conduct of scheduled and interim visits is provided in the remainder of this section.

6.3 Location of Follow-up Visits

All visits will be conducted at the site clinics. No study specific assessments may be completed off-site. The exceptions to this are the Day 1, Day 3 and Day 14 Phone Calls, and the Post-delivery Assessment (Pregnancy Cohort only) which may be by telephone, and the Delivery Visit, which will be conducted where the participant delivers.

6.4 Follow-up Visit Scheduling

All women (and infants enrolled in the Lactation Cohort) will be scheduled to complete follow-up visits throughout their participation in the study. For each participant, follow-up visits are targeted to take place based on the participant's enrollment (Day 0). Follow-up Visits include: Days 1, 3, and 14 telephone call or in-person visits to the clinic, if needed to assess clinical issues, and the Day 6 clinic visit.

Women in the Pregnancy Cohort, in addition to the above mentioned follow-up visits will have the following: 1) a Delivery Call, from the participant to notify staff about onset of labor, 2) a Delivery Visit, to occur as soon as possible from the time of delivery for staff to evaluate mother and baby and to collect a cord blood sample, before facility discharge, plus the Post-Delivery Assessment (by phone or in-person), approximately 14 days (+/- 7 days) after delivery. Enrolled participants should be scheduled for follow up to conform as closely as possible to the target dates.

Details of target visits and visit windows may be found in the MTN-008 SSP Section 13.3.2.

6.4.1 Target Visit Dates

Avoid scheduling Enrollment (Day 0) on a Monday, so that the Day 6 visit does not fall on a Sunday. Keep in mind staff scheduling given the length of the Day 0 and Day 6 clinic visits, ensuring qualified staff are available for the exams, laboratory specimen collection, and AE assessments throughout the duration of the visit.

For women in the Pregnancy Cohort, scheduling the follow-up visits may be impacted by the woman's labor and delivery. For example, the Delivery Visit may happen *before* the Day 14 Phone Call. Multiple visits may be conducted on the same day. In these types of cases, please contact FHI and SCHARP for specific guidance if needed.

6.4.2 Allowable Visit Windows

Acknowledging that it will not always be possible to complete follow-up visits on the targeted dates, MTN-008 allows for some visits to be completed within a visit window.

For each required study visit, there is an allowable visit window, to be used conditionally, specifying on which study days (post-enrollment) the visit is "allowed" to be completed.

- Enrollment (Day 0): within no more than 28 days of completing the screening informed consent.
- Day 1: within an additional 24 hours, or close of business on Day 2, if unable to reach participant with 3 documented attempts, using alternate locator information, on Day 1. If no contact is made within window, complete the Missed Visit form.
- Day 3: within an additional 24 hours, or close of business on Day 4, if unable to reach

participant with 3 documented attempts, using alternate locator information , on Day 3. If no contact is made within window, complete the Missed Visit form, but continue to attempt contact to complete all visit procedures as an interim visit.

- Day 6: within an additional 24 hours, or the morning of Day 7, if participant notifies staff she is unable to attend due to urgent reasons that have arisen since Day 0.
- Day 14: - 6/+7 calendar days.
- Delivery Visit: due to collection of maternal blood and cord blood samples, this visit must occur as soon as possible, but no more than 4 hours, after delivery.
- Post-delivery Visit: scheduled for 2 weeks post delivery, +/- 7 calendar days (i.e. 7-21 days after delivery).

Although the visit windows allow for some flexibility, the intent of the protocol-specified visit schedule is to conduct follow-up visits on the target date, and every effort should be made to do so. The MTN SDMC will provide the Protocol Team with routine visit adherence reports for purposes of monitoring adherence to the visit schedule (see Section 16).

6.4.3 Missed Visits

For participants who do not complete *any* part of a scheduled visit within the visit window, the visit will be considered “missed” and a Missed Visit case report form will be completed to document the missed visit. Section 13 gives detailed information regarding the completion of the Missed Visit form.

6.5 Follow-up Visit Procedures

Required follow-up visit procedures are listed in Protocol Sections 7.1 through 7.10, and in the SSP Section 7. Highlighted for reference below are the primary procedural requirements.

6.5.1 Mother and Infant Follow-up Procedures for Days 1 and 3 Phone Calls: Pregnancy and Lactation Cohorts

These visits will be by phone contact, but may occur in the clinic, if required for clinical follow-up and management of AEs.

- Administrative, Behavioral, and Regulatory
 - Update locator information
 - Schedule/confirm next study visit
 - Brief adherence assessment and counseling
- Clinical
 - Collect and update AEs for mothers and infants (if born)

6.5.2 Mother and Infant Follow-up Procedures for Day 6 Visit: Pregnancy and Lactation Cohorts

Refer to Figure 1 below, from MTN-008 Protocol, section 7.5, for a listing of procedures of the Day 6 Visit for both cohorts.

Prior to initiating the Day 6 Visit procedures, site staff will determine if the participant is evaluable (i.e. that a minimum of 3 doses and no more than 6 doses of study product were administered between Day 0 and Day 5). If the participant does not meet the criteria for being evaluable, site staff will complete a modified Day 6 Visit. In this dosing scenario, only safety and adherence/acceptability evaluations will be collected (see Section 7.2, Visit Checklists, Day 6 Visit Checklist procedures for items marked with an asterisk) at the Day 6 Visit.

Women participants should return to the Day 6 Visit with all unused study product applicators and the completed Home Dosing Log. Additionally, women enrolled in the Lactation Cohort should return with their breast fed infant, 2 frozen breast milk samples in 4 vials (see Section 12.8.3 for collection and storage instructions) and the completed Breast Milk Sample Collection log.

The IoR or designee will collect blood samples to confirm general health and liver function, collect a urine sample from women in the Lactation Cohort to confirm lack of pregnancy, and conduct a pelvic exam prior to the final dose of study gel administration.

Note that any symptoms of Chlamydia or gonorrhea should be tested via current CDC Guidelines.

At the Day 6 Visit, the CASI Follow-Up Acceptability and Adherence Questionnaire should be administered approximately 1 hour after dosing of study product, after the PK1 sample is collected. The Gel Use Experience (GUE) Questionnaire should be administered by a staff member immediately after the participant completes her CASI interview. Site staff should administer the GUE Questionnaire to participants in a private location. At the end of the visit, on the same day as the questionnaire is completed, clinic staff should enter the GUE data from the participant's form into the GUE database, stored on the same computer as the CASI instruments. Refer to MTN-008 SSP section 13 for detailed CASI and GUE completion instructions. Protocol Section 7.18 specifies the different behavioral assessments to be performed at different time points throughout follow-up.

Maternal participants in the Pregnancy and Lactation Cohorts and infant participants in the Lactation Cohort will have blood specimens collected for PK analysis of tenofovir blood levels. Maternal participants will have samples drawn prior to study gel administration, and at 1, 2, 4, 6, and 8 hours after the Day 6 Visit study product application. Infant participants will have one heel stick to collect blood approximately 6 hours following maternal dosing, **and** within 1-4 hours of breastfeeding.

In addition to the blood PK analysis, women enrolled in the Lactation Cohort will have breast milk samples collected for PK analysis. Clinic research sites will provide a breast pump, bags, and any other needed materials. Women participants will provide breast milk samples at the clinic prior to study gel administration, and at 2, 4, and 6 hours after study product administration. Breast milk samples may be collected after the blood PK samples are drawn. Breast milk samples should be stored in the freezer immediately as each sample is collected, after labeling each sample with MTN-008 study labels provided by the SDMC. Refer to MTN-008 SSP Manual Section 12.8.3 for further details.

Figure 1: MTN-008 Day 6 Visit Procedures

Day 6 Visit: Pregnancy and Lactation Cohorts			
Component	Pregnancy Cohort Procedure/Analysis (Mothers)	Lactation Cohort Procedure/Analysis (Mothers)	Lactation Cohort: Procedure/Analysis (-Infants)
Clinical and Study Product	<ul style="list-style-type: none"> • Medical history • Concomitant medications • Targeted physical exam • Pelvic exam • Vaginal and cervical swabs • Urine collection* • Single dose of study gel to be administered by IoR/designee at clinic • Insert saline lock** • Blood collection at PK time points (target pre-gel and 1, 2, 4, 6, and 8 hours) • Collect AEs • Collect unused study gel • Disclosure of results* 	<ul style="list-style-type: none"> • Medical history • Concomitant medications • Targeted physical exam • Pelvic exam • Vaginal and cervical swabs • Urine collection‡ • Single dose of study gel administered by IoR/designee at clinic • Insert saline lock** • Blood collection at PK time points (target pre-gel and 1, 2, 4, 6, and 8 hours) • Breast milk collection (target pre-dose and 2,4, 6 hours) • Collect AEs • Collect unused study gel • Disclosure of results‡ • GC/CT* • Urine HCG • CBC with differential (pre-gel) • Serum creatinine • AST and ALT • HIV serology* • HBsAg* • Maternal blood tenofovir level (target pre-gel, 1, 2, 4, 6, and 8 hours) • Breast milk tenofovir levels (target pre-dose and 2,4, 6 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal/cervical biomarkers • Quantitative vaginal culture • Vaginal Gram stain • Trichomonas test* • Wet prep* • Herpes culture* 	<ul style="list-style-type: none"> • Medical history • Feeding history • Concomitant medications • Collect AEs • Blood collection via heel stick (target 6 hours <u>following maternal dosing</u>) + • Blood tenofovir levels +
Laboratory	<ul style="list-style-type: none"> • GC/CT* • CBC with differential (pre-gel) • Serum creatinine • AST and ALT • HIV serology* • HBsAg* • Maternal blood tenofovir level (target pre-gel, 1, 2, 4, 6, and 8 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal/cervical biomarkers • Quantitative vaginal culture • Vaginal Gram stain • Trichomonas test* • Wet prep* • Herpes culture* 	<ul style="list-style-type: none"> • GC/CT* • Urine HCG • CBC with differential (pre-gel) • Serum creatinine • AST and ALT • HIV serology* • HBsAg* • Maternal blood tenofovir level (target pre-gel, 1, 2, 4, 6, and 8 hours) • Breast milk tenofovir levels (target pre-dose and 2,4, 6 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal/cervical biomarkers • Quantitative vaginal culture • Vaginal Gram stain • Trichomonas test* • Wet prep* • Herpes culture* 	<ul style="list-style-type: none"> • Blood tenofovir levels +

*if indicated ** if applicable

+ Optimally, blood will be drawn about 1-4 hours following the start time for a nursing session. While the study team anticipates that all infants would nurse during this interval, infant blood draw and blood tenofovir levels would not be performed if the infant did not nurse following maternal dosing and prior to final departure from the study visit.

**Captured via CASI and GUE form

Items in **bold** reflect LoA updates

6.5.4 Day 6 Visit for Unevaluable Participants in both Pregnancy and Lactation Cohorts

Completion of the Day 6 Visit procedures will be based on participant evaluability as defined by the protocol. Participants will be considered unevaluable in the following cases:

- mother-infant pairs in which the mother did not receive at least 4 doses of study product, OR
- mother-infant pairs in which the mother did not complete the Day 6 Visit (refer to Section 6.6.1 below).

There are additional situations which may require a modified Day 6 Visit. A modified Day 6 Visit, comprised only of safety and adherence/acceptability assessments, will be completed if:

- the participant successfully self-administered fewer than 2 doses of study product between Day 0 and Day 6,
- the participant successfully self-administered all 6 doses of study product between Day 0 and Day 6, OR,
- the participant self-administered the most recent dose of study product within 6 hours of her Day 6 Visit, **and** is unable to return within 24 hours for her Day 6 Visit procedures.

Refer to section 7 of this manual for a worksheet preceding the Day 6 Visit Checklist.

Maternal Participants: Women who meet the definition of “unevaluable” will not receive further study product dosing or have PK samples drawn at the Day 6 Visit. However, a safety assessment must be performed. This assessment should include:

- Pelvic exam
- AE review and update
- Medical history review and update
- Concomitant medications review and update
- Safety laboratory evaluation
 - Serum Creatinine
 - CBC
 - AST/ALT
- Urine hCG (Lactation Cohort only)
- Follow-up acceptability and adherence questionnaire via CASI
- Administration of GUE Questionnaire
- Collection of Home Dosing Log
- If indicated:
 - GC/CT
 - HIV Serology (with pre- and post-counseling)
 - HBsAG test
 - Trichomonas test
 - Herpes culture
 - Wet prep
 - Gram stain

Infant Participants (Lactation Cohort): Infants of maternal participants who meet the definition of unevaluable should not have the heel stick PK sample drawn. However, safety assessments must be performed and should include:

- AE review and update
- Concomitant medications review and update

Refer to Section 6.6 of this SSP for more information regarding replacement of unevaluable participants.

6.5.5 Mother and Infant Follow-up Procedures for Day 14 Phone Call: Pregnancy and Lactation Cohorts

These visits will be conducted by phone, but may occur in the clinic, if required for clinical follow-up and management of AEs.

- Administrative, Behavioral, and Regulatory
 - Update locator information
 - Schedule/confirm next study visit, if applicable
- Clinical
 - Collect and update AEs for mothers and infants (if born)
 - Collection of interim medical history and concomitant medications for mothers and infants (if born)

6.5.7 Delivery Phone Call: Pregnancy Cohort Only

The participant must contact research staff when she thinks she may be in labor, or if she is admitted with anticipation of delivery. Site staff should remind the participant of this call each time they speak with the participant, during all scheduled and interim visits.

Note: there are no required CRFs for this visit. If any data are collected during the phone call, it will be considered an Interim Visit.

6.5.8 Delivery Visit: Pregnancy Cohort Only

- Administrative
 - Update locator information
 - Reimbursement
 - Assign infant PTID
- Clinical
 - Cord blood collection
 - Blood collection (mothers, single time point when cord blood is taken)
 - Collection of concomitant medications for mothers and infants
 - Collect AEs for mothers and infants
 - Targeted physical exam for mothers, as needed to evaluate a reported AE
- Laboratories
 - Details about labs to be obtained as part of MTN-008 can be found in Section 12 (Laboratory Considerations). In brief:
 - Cord blood tenofovir levels
 - Maternal blood tenofovir level
 - CBC with differential
 - PBMCs
 - Flow cytometry

6.5.9 Post-delivery Assessment: Pregnancy Cohort only

These visits may be conducted by phone or in-person.

- Administrative
- Update locator information
- Reimbursement
- Clinical
 - Collect/ update AEs for mothers and infants
 - Collect/ update medical history for mothers and infants
 - Collect/ update concomitant medications for mothers and infants

6.5.10 Interim Visit: Pregnancy and Lactation Cohorts

An interim visit may occur at any time during study participation for several reasons. See Section 13.3.2 for possible reasons for an Interim Visit and protocol section 7.10 for further information.

6.6 Replacement of Unevaluable Participants: Both Cohorts

It is possible that not all participants will be able to receive a minimum of 4 doses of study product or complete the Day 6 Visit (see Section 6.6.1 below) within the allowable visit window.

Clinic staff will evaluate participants on the Day 6 Visit to confirm that participants are evaluable and should receive the final dose of study gel application. Protocol Section 9.3 – 9.9 lists conditions under which participants should be discontinued from study gel use, either temporarily or permanently. The site Investigator of Record (IoR) is responsible for ensuring these protocol specifications are followed for all participants. Should a participant in either Cohort not receive at least 4 doses of study product (the Days 0 and 6 doses, plus 2 doses at home in the intervening week) OR not complete the Day 6 Visit within the visit window (either by not returning to the clinic or not completing all PK tests per protocol) OR if the participant self-administered 6 doses in the intervening week after the Day 0 Visit, she is not considered statistically “evaluable.” Non-evaluable participants will be replaced per MTN-008 Protocol section 4.5 and MTN-008 SSP section 4.6.

The IoR should consult the PSRT for guidance for all temporary or permanent product discontinuations.

6.6.1 Completion of the Day 6 Visit

Once a woman meets criteria for evaluability and presents for her Day 6 Visit, it is expected that she will complete all procedures on that day. In the rare event of an urgent or emergent situation such that the woman must leave prior to completion of all procedures, if site staff can complete the following, at minimum, the participant is considered evaluable:

- Physical exam
- Pelvic exam
- Assessment for AEs
- Collection of all safety labs
- Collection pre-gel PK sample
- Placement of gel

For the lactation cohort, in addition to all the above:

- Collection of pre-gel breast milk sample
- Collection of breast milk sample at 2 hours post-dose

6.7. Procedures for Participants Who Discontinue Product

Regardless of the participant retention methods undertaken at each study site, participants may voluntarily withdraw from the study for any reason at any time.

Participants who discontinue study gel because of safety concerns or participants enrolled in the Lactation Cohort who become pregnant will receive no further study product and will be encouraged to remain in the study if they are willing, for safety and adherence evaluations according to the Day 6 Visit checklist (see SSP section 7). Study pharmacy staff must be informed of the product discontinuation in writing using the Study Product Return form. Participants are instructed to return all unused study product to the clinic at the Day 6 Visit or should the Day 6 Visit not occur, within 5 days of the scheduled visit.

6.8 Premature Study Discontinuation for an Individual Participant

Under some circumstances it may be appropriate for the investigator to prematurely discontinue a participant from study participation. These are:

- Failure to attend the Day 6 Visit within window,
- Participant report at the Day 6 Visit of successful self-administration of fewer than 2 doses or more than 5 doses between the Day 0 and Day 6 Visits,
- Request by participant to withdraw,
- Lactation Cohort participants with positive hCG at the Day 6 Visit,
- Request of IoR if the study is no longer in the best interest of the participant
- Clinical management is required for:
 - Pregnancy Cohort participants who have suspected rupture of membranes or are admitted for labor,
 - Participant report and clinician evaluation of allergic reaction resulting in local or systemic toxicity,
 - Grade 2 or 3 AE judged to be related to study product, if the IoR deems study withdrawal in the best interest of the participant, and in consultation with the PSRT,
 - Any Grade 4 AE that cannot be attributed to anything other than study product, and,
 - AST and/or ALT elevations that cannot be attributed to:
 - Preeclampsia
 - Alcohol consumption
 - Non-study medication drug toxicity
 - Herbal agents
 - Viral hepatitis

Refer to SSP Section 10 for detailed description of clinical consideration. All product discontinuation for reasons other than the participant being unevaluable by protocol definition, must be discussed with the MTN-008 PSRT.

