Section 4: Accrual

This section covers general guidelines for accrual, screening, and enrollment procedures at the site. Additional information regarding participant accrual can be found in the MTN-008 Protocol Sections 4.4, 5, 7, 9 and 10.5.

4.1 Study Accrual Plan and Site Accrual Targets

Accrual for the entire study is expected to be completed in approximately 20 months. During this timeframe, accrual of 105 unique, evaluable mother-infant pairs will be recruited into 3 groups:

1. Pregnancy Cohort 1: Forty-five pairs randomized 2:1 to Tenofovir 1% gel: placebo gel
2. Pregnancy Cohort 2: Forty-five pairs randomized 2:1 to Tenofovir 1% gel: placebo gel
3. Lactation Cohort: Fifteen pairs, non-randomized, enrolled concurrently with Pregnancy Cohort

Study participants (both mothers and their infants) determined to be unevaluable will be replaced. This protocol defines unevaluable participants to be mothers who do not receive at least 4 doses of study gel, or who do not complete the Day 6 Visit, as described in Section 6.7 of this manual. The purpose of replacing participants is to preserve the power of the study in the cases of product discontinuation or non-adherence. For statistical utility, no more than 20% of each cohort should be replaced (total of no more than 9 participants will be replaced for each Pregnancy Cohort group and no more than 3 participants will be replaced for the Lactation Cohort, across the study at all sites).

Enrollment timelines include recruitment of additional participants to bring enrollment to the target number of evaluable participants. At study initiation, accrual for the Lactation Cohort and the Pregnancy Cohort: Group 1 will begin simultaneously. Accrual for the Lactation Cohort should be completed within 12 months, and accrual for the Pregnancy Cohort: Group 1 should be completed within 10 months following study initiation. Accrual for the Pregnancy Cohort: Group 2 will be contingent upon reassuring safety data obtained from Group 1, and is slated to begin approximately 10 months after study initiation and continue for an additional 10 months. Overall, each month, about 4 participants per site should be recruited. *Refer to the protocol sections 4.4 and 10.5 for additional information.*

Figure 4-1: MTN 008 Target Accrual Timeline (all sites combined)

Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Lactation Cohort	1	2	2	2	2	2	2	1	1	1~	1~	1~								
Pregnancy Cohort, Group 1	6	6	6	6	6	6	6	3	5~	4~										
Pregnancy Cohort Group 2*	Ongoing Group 1 Safety Review*										6	6	6	6	6	6	6	3	5~	4~

For each of the 3 categories of participants during the 20 month accrual phase

~ maximum additional participants required to yield participant number to reach evaluable target, if needed

* Written authorization from the Protocol Chair must be received prior to initiating recruitment into Group 2.

4.1.1 Accrual Status Reporting

For each site, accrual will begin after all applicable approvals are obtained and a site specific study activation notice is issued by the MTN Coordinating and Operations Center (CORE) at FHI. Once accrual is initiated, study staff will report the number of participants screened for and enrolled in the study to the CORE (FHI) on a weekly basis. Based on this information, the CORE (FHI) will distribute a weekly consolidated cross-site accrual report to the Protocol Team. In addition, the MTN Statistical and Data Management Center (SDMC) will post reports on their ATLAS portal listing the number of participants enrolled in the study based on data received and entered into the study database. Please see Section 15 of this manual for more information on the study reporting plan.

4.1.2 Site-specific Accrual Plan

Site staff is responsible for developing a standard operating procedure (SOP) for participant accrual and ensuring appropriate recruitment efforts are undertaken to meet site-specific accrual goals. The accrual SOP should minimally contain the following elements:

- Site-specific accrual goals
- Methods for tracking accrual goals versus actual accrual
- Recruitment methods and venues
- Methods for identifying the recruitment source of participants who present to the site for screening
- Methods for timely evaluation of the utility of recruitment methods and venues
- Pre-screening procedures (if any)
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

4.2 Pre-Screening

Sites may utilize facility electronic database resources or outside clinic referrals to identify prospective participants provided these systems are in documented compliance with all local HIPAA regulations and methods approved by the local IRB. Activities undertaken prior to obtaining informed consent are considered 'pre-screening' activities. Each site should specify in SOPs what specific pre-screening activities will be conducted. Site-specific SOPs should describe recruitment methods in detail, including what specific pre-screening activities will be conducted.

4.3 Screening Administrative Procedures

The term "screening" refers to all procedures performed to determine whether a potential participant is eligible to take part in MTN-008. No protocol-specified screening procedures or assessments may be undertaken until written informed consent for screening is obtained. Once informed consent for screening has been obtained, the study screening process can begin. During the Screening Visit, mothers screening for the Pregnancy or Lactation Cohorts will sign a screening informed consent. For infants in the Lactation Cohort, there will be a

single informed consent signed by the mother during her Screening Visit that will serve both as a screening and enrollment informed consent. Infants in the Lactation Cohort will not be reconsented at the Enrollment Visit. For further information, refer to Section 5, Informed Consent.

Study eligibility criteria are listed in protocol Sections 5.2 through 5.7.

It is the responsibility of the site Investigator of Record (IoR) and other designated staff to ensure that only participants who meet the study eligibility criteria are enrolled in the study.

4.3.1 Site-Specific Eligibility SOP

The study site must establish an SOP that describes how study staff will fulfill this responsibility. This SOP minimally should contain the following elements:

- Eligibility determination procedures, including:
  - During-visit eligibility assessment procedures
  - Post-visit eligibility assessment and confirmation procedures
  - Final confirmation and sign-off procedures prior to enrollment
  - Documentation
- Ethical and human subjects considerations
- Staff responsibilities for all of the above (direct and supervisory)
- Staff training requirements (if not specified elsewhere)
- QC/QA procedures related to the above (if not specified elsewhere)

Should site staff identify that an ineligible participant has inadvertently been enrolled in the study, the IoR or designee should alert the MTN-008 Study Management Team using the following email address: mtn008mgmt@mtnstopshiv.org and the MTN-008 Protocol Safety Review Team (PSRT) using the email address: mtn008PSRT@mtnstopshiv.org for guidance on the specific action to be taken.

4.3.2 Screening Window

Women being recruited for the Pregnancy Cohort should be consented in a reasonable timeframe prior to the participant's target gestational age window. Enrollment must occur within 28 days of obtaining screening consent, and therefore a suitable target for women preparing to enter into Pregnancy Cohort Group 1 (37 0/7 – 39 1/7 on study Day 0) would be when the participant is carrying a healthy infant with a gestational age of no less than 33 0/7 weeks. Women preparing to enter into Pregnancy Cohort Group 2 (34 0/7 – 36 6/7 on study Day 0) may begin screening no earlier than when the woman is carrying a healthy infant with a gestational age of 30 0/7 weeks.

Refer to Protocol section 5 for comprehensive inclusion/exclusion criteria listing and the SSP section 4.3.4 for information related to calculating gestational age and Appendix 4-4 of this section for breastfeeding requirements.

General considerations of the woman's and neonate's health based on prescreening activities can be used to determine if the full 28 days of screening would be necessary; it is possible that a participant could be screened successfully and enter the study one day or one week later, depending on site laboratory test result turnaround times.

Women being screened for the Lactation Cohort also have no more than 28 days between screening and study Day 0; however the eligible age range for infants spans 4 through 26 weeks (inclusive). Should a woman with an infant in the earlier age range not be currently eligible (either the woman or the infant), but have a condition that could be remedied, and then be eligible, she can be enrolled if she remains within the 28 day screening window. If more than 28 days have elapsed from signing the Screening Consent, she would need to be reconsented and rescreened for the study.

4.3.3 Screening Procedures

The study eligibility criteria for pregnant women, lactating mothers, and breastfeeding infants are listed in protocol Sections 5.2 – 5.7. Required screening procedures are described in Table 10 of the protocol. Protocol Section 7.2 and SSP Section 10, Clinical Considerations, lists procedures to be performed at the Screening Visit to determine participant eligibility for enrollment in the study. Refer to the site visit checklists for the chronology of procedures to be done at your site. Additionally, Appendix 4-2 lists Screening Procedures provided in the Protocol, and includes updates from LoA #1 in bold font**.**

Ascertainment of eligibility based on criteria included in sections 5.2 through 5.7 of the study protocol requires taking a medical history for mothers and infants, and conducting a physical and pelvic examination on maternal participants.

Documentation to address all of the eligibility criteria, including but not limited to, the clinical eligibility criteria above must be kept in the participant record. A blanket statement regarding all such inclusion criteria, such as, "The participant meets all inclusion criteria outlined in the protocol," is NOT adequate. Appropriate documentation includes, but is not limited to, a signed and dated chart note to address each negative criterion. For example, "Participant does not have any serious medical condition that would interfere with participation in the study" is an acceptable way to document that the criterion has been met.

If at any time during the screening process, the mother and/or infant is found ineligible for any reason, the screening process should be stopped and no further assessments undertaken. Any information related to the mother's or infant's health obtained during the screening process should be provided to her and explained. If indicated per site SOPs, further follow-up and/or referral for care should be offered to the woman and/or infant, and then fully documented in the study file.

4.3.4 Screening for Pregnancy Cohort Participants

To ensure preterm participants are not enrolled into the term cohort, site staff should confirm gestational age by at least one of the following categories:

1. Gestational age documented during first trimester:
    a. ascertain last menstrual period and confirm the fetus is clinically noted to be size equal to dates OR
    b. first trimester scan with estimated due date noted,
2. Gestational age documented during second trimester:
    a. second trimester scan with estimated due date noted, consistent with last menstrual period dates OR
    b. if gestational age is redated, confirm that the method used is consistent with ACOG Guidance.

The judgment of the Investigator should be documented thoroughly in participant chart notes.

Due to challenges related to establishing the normalcy and precise dating of the pregnancy, site staff should ensure no participants are recruited or enrolled if they entered prenatal care at greater than 31 weeks.

Known rupture of the amniotic membranes is an exclusion criterion or will result in product discontinuation if identified while enrolled. Diagnostic maneuvers may be performed in uncertain cases, specified by site investigator. Rupture of membranes is defined by the following criteria:

- Gross rupture of membranes
- Non-gross rupture of membranes
    - Positive pooling,
    - Positive nitrazine and/or positive ferning test by microscopy

4.3.5 Screening for Lactation Cohort Participants

During screening and during follow-up, all women in the lactation cohort should be counseled and encouraged to breastfeed in accordance with CDC guidelines and local and/or national guidelines applicable at the study site.

To be eligible, a woman should supply at least 75% of her infant's nutrition through breast feeding. Refer to Appendix 4-4, Infant Feeding Eligibility Criterion for Lactation Cohort and the Lactation Cohort Screening Visit Checklist in Section 7 of this manual.

The woman will be asked to collect 2 breast milk samples on each of 2 different days during her week of dosing at home. Appendices 4-5 and 4-6 are instructional references for the participant to use (with IRB approval) to document dates and times of trial-related activities performed at home between the Day 0 and Day 6 Visits. The Home Dosing Log (Appendix 4-5), used by participants in both Cohorts, and the Breast Milk Sample Collection Sheet (Appendix 4-6), used by participants in the Lactation Cohort only, should be returned to the clinic with the participant's breast milk samples at the Day 6 Visit. These logs should be filed with participant study records as source documentation for data entered on the Participant-Reported Home Dosing and Collection Form. Sites should supply a breast milk collection kit, comprised at minimum of what is required to collect study samples, plus at least one extra of collection supplies in case of contamination or damage at home:

- breast pump if needed, with new tubing
- breast milk pump collection bags/ bottles
- transfer pipettes (3)
- cryovials (5)
- ice packs/ cooler box for sample transport to the clinic
- cryovial labels, preprinted with the participant PTID
- Home Dosing Log (see Appendix 4-5)
- Breast Milk Sample Collection Sheet (see Appendix 4.6)

Study product should be provided to each participant at the Day 0 Visit after all required assessments are completed and an authorized clinician confirms that the participant is eligible to receive product. See Section 6.6 for more information on study product dispensation on Day 6.

4.3.6 Screening and Enrollment Logs

The DAIDS SOP for Essential Documents requires study sites to document screening and enrollment activity on screening and enrollment logs. Screening and enrollment logs may be maintained separately or combined into one log. Appendix 4-1 presents a sample screening and enrollment log suitable for use in MTN-008. Study sites are encouraged to reference the eligibility criteria item numbers from the corresponding non-DataFax eligibility forms underneath the log when recording the reason for screening failure/discontinuation on the screening and enrollment logs.

4.4 Assignment of Participant ID Numbers

Participant Identification (PTID) numbers will be assigned to each maternal participant who provides informed consent. The SDMC will provide the study site with a listing of mother PTIDs for use in MTN-008. Infant PTIDs, will correspond directly with the mother's PTID and will be assigned when the infant is enrolled in MTN-008. As shown in Figure 4-2, the listing will be formatted such that it may be used as the log linking PTIDs and participant names at each site (the PTID-Name Linkage Log). In addition, the list will include space to record which study cohort (Lactation or Pregnancy) and which Pregnancy Cohort Group (1 or 2) the participant is enrolled in.

Further information regarding the structure of PTIDs for MTN-008 can be found in Section 13. PTIDs will be assigned to all potential participants who provide written screening informed consent for the study, regardless of whether they enroll in the study. Only one PTID will be assigned to each potential participant.

Site staff is responsible for establishing SOPs and staff responsibilities for proper storage, handling, and maintenance of the PTID lists such that participant confidentiality is maintained, individual PTIDs are assigned to only one participant, and individual participants are assigned only one PTID.

Figure 4-2
Sample Site-Specific Mother PTID List for MTN-008

	PTID	Participant Name	Cohort/Group# circle one	Date	Staff Initials
1	XXX-0001-Y-0		L P1 P2		
2	XXX-0002-Y-0		L P1 P2		
3	XXX-0003-Y-0		L P1 P2		
4	XXX-0004-Y-0		L P1 P2		

4.5 Enrollment

At the Enrollment Visit, mothers will provide updated locator information, confirm continued eligibility, confirm availability for Days 1 and 3 telephone follow-up, and schedule the follow-up visit (Day 6 Visit). Disclosure of available test results will be provided to the participant, as applicable. If she continues to be willing, able, and eligible, she will be consented for enrollment. The signed enrollment informed consent will be obtained prior to conducting any study-related Enrollment Visit procedures, including the targeted physical exam, collecting laboratory specimens, or completing behavioral assessments. If the participant does not meet all eligibility criteria, enrollment will not occur.

Mothers in the Lactation Cohort will be considered enrolled in MTN-008 once the authorized clinician completes the study product prescription on Day 0.

Infants in the Lactation Cohort will be considered enrolled in MTN-008 at the same time their mothers are enrolled.

Mothers (and their unborn infants) in the Pregnancy Cohort will be considered enrolled in MTN-008 when the Clinic Randomization Envelope is assigned. Please refer to SSP sections 9.3.2 for additional details.

For replacement participants in both cohorts, the act of completing the MTN-008 replacement prescription ((Pregnancy Cohort) or new prescription (Lactation Cohort) serves as the act of randomization and enrollment in the study. Refer to 4.6 below for further information.

As the informed consent documents will be signed prior to delivery, eligibility criteria will not be assessed for infants in the Pregnancy Cohort. All infants born to mothers in the Pregnancy Cohort will be considered eligible, at birth. Please see protocol section 5.1.1 for details.

Refer to Appendix 4-2 of this manual for a list of Enrollment Visit Procedures provided in the Protocol, including updates from LoA #1 in bold font

The Enrollment Visit for both Pregnancy and Lactation Cohorts may take 9 hours or longer; sites must be prepared to keep the participant's comfort in mind. Because timing of the PK samples is critical to the success of this study, once participants have been administered study gel on Day 0 Visit and Day 6 Visit, they should remain at the clinical site until the last PK sample has been taken. Refer to Section 4.5.5 for collection windows acceptable for PK draws on Days 0 and 6 Visits.

Site staff should clearly convey to study participants that once they are in the clinic, they should anticipate remaining there until the completion of study procedures that day. Consider providing the participant with lunch, snacks, a comfortable place to rest, bathroom, beverages, reading materials, access to a phone, place for the breastfeeding infant to rest/play, place for an older child to play etc. as needed so that she can devote the entire day away from her usual activities. Consider participant dietary restrictions when providing meals. Remember that participants will return for the Day 6 Visit in a week and will go through the same routine again so their experience at enrollment is important for the retention of evaluable participants.

Confirm that any items provided to participants (like lunch) are specified in the informed consent form and approved by the IRB as they may be considered part of participant compensation.

4.5.1 Postponement of Enrollment

If, after initiation of the physical or pelvic exam, the mother is found to be ineligible for enrollment given the presence of certain conditions for which she would otherwise be eligible, enrollment may be postponed until the following findings have improved to a non-exclusionary severity grading or resolved, if resolution occurs within the 28 day of obtaining screening informed consent and she remains in the window for eligibility requirements:

- Pregnancy and Lactation Cohorts, exclusion criteria #5 and #8 respectively: Symptomatic vaginitis, including bacterial vaginosis and vulvovaginal candidasis (asymptomatic evidence of bacterial vaginosis and/or yeast is not exclusionary)

- Pregnancy Cohort, exclusion criterion #6: Clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff) at the Enrollment Visit.

- Pregnancy Cohort, exclusion criterion # 3:
    - Hemoglobin value of Grade 3 or higher according to DAIDS Toxicity Table

- Pregnancy Cohort, exclusion criteria #3 and Lactation Cohort, exclusion #6:
    - Serum creatinine greater than 1.0 mg/deciliter (dL)
    - AST and/or ALT greater than 1.5 upper limit of normal (ULN)

- Lactation Cohort exclusion criteria #9: On pelvic exam, any of the following findings:
    - Incomplete postpartum involution of the uterus
    - Clinically apparent Grade 2 or higher pelvic exam finding (observed by study staff)

- Lactation Cohort exclusion criteria #4: Participant report or clinical evidence according to the judgment of the IoR/designee of any of the following conditions:
    - Insufficient milk supply
    - Mastitis

In such a circumstance, the participant would be treated and offered the option of returning to the clinic to repeat and possibly continue with the Enrollment Visit (Day 0) procedures, once the condition had resolved. Note, however, that enrollment must occur within 28 days of signing the screening informed consent.

4.5.2 Randomization

Participants in the Lactation Cohort will not be randomized. Mothers in this cohort will all receive active tenofovir 1% gel, and require a completed prescription. Only mothers in the Pregnancy Cohort will be randomized. They will be assigned to either active tenofovir 1% gel or placebo gel in a 2:1 ratio. The study arms in the Pregnancy Cohort will be double-blinded to study gel assignment, meaning that both site staff and participants will not be provided information on the identity of the specific gels to which participants have been assigned. For each participant, random assignment will take place after the participant has been confirmed as eligible (and all required activities listed on the Day 0 Visit Checklist have been completed) and willing to take part in the study, as documented by her signing or marking the enrollment informed consent.

The SDMC will generate and maintain the study randomization scheme and associated materials, which consist of the following:

- MTN-008 Clinic Randomization Envelopes (Pregnancy Cohort only)
- MTN-008 Clinic Randomization Envelope Tracking Records (Pregnancy Cohort only)
- MTN-008 Pharmacy Randomization Envelopes (Pregnancy Cohort only)
- MTN-008 Pharmacy Randomization Envelope Tracking Records (Pregnancy Cohort only)
- MTN-008 Pregnancy Cohort Prescriptions

- MTN-008 Lactation Cohort Prescriptions
- MTN-008 Pregnancy Cohort Replacement Prescriptions
- MTN-008 Participant–specific Pharmacy Dispensing Records
- MTN-008 Study Product Return Documentation

MTN-008 Clinic Randomization Envelopes will be shipped from the SDMC to each study site. They will be stored in the clinic and assigned in sequential order to participants who have been confirmed as eligible and willing to take part in the study. Envelopes must be assigned in sequential order, and only one envelope may be assigned to each participant. Once an MTN-008 Clinic Randomization Envelope is assigned to a participant, it may not be re-assigned to any other participant, with the exception of replacement participants (see section 4.6, Replacement of non-evaluable Participants, below). All envelopes are sealed with blue security tape that, when opened, reveals the word "OPENED" in the residue of the tape (see Figure 4-5).

MTN-008 Clinic Randomization Envelope assignment to eligible participants will be documented on the MTN-008 Clinic Randomization Envelope Tracking Record (see Figure 4-6) that will accompany the randomization envelope shipment to each site. The act of assigning an MTN-008 Clinic Randomization Envelope to a participant is considered the effective act of randomization and enrollment for the Pregnancy Cohort in the study. Once an MTN-008 Clinic Randomization Envelope is assigned, the participant is considered enrolled in the study.

Each MTN-008 Clinic Randomization Envelope will contain an MTN-008 Pregnancy Cohort prescription (see Figure 4-8). MTN-008 prescriptions will be produced as a two-part no carbon required (NCR) form pre-printed with the CRS name, CRS location, and DAIDS site ID. In addition, the Pregnancy Cohort prescriptions will include the MTN-008 Clinic Randomization Envelope number. After recording the PTID and signature on the prescription, clinic staff will separate the two parts of the prescription form and deliver or fax the white original copy to the pharmacy. The original prescription must be delivered to the pharmacist in order for the study product to be dispensed. The MTN-008 Clinic Randomization Envelope (for Pregnancy Cohort participants) and the yellow copy of the associated prescription (for the Pregnancy and Lactation Cohorts) will be retained in the participant's study notebook. Each site will develop an SOP for writing study prescriptions and dispensing study gel to participants.

MTN-008 Pharmacy Randomization Envelopes for the Pregnancy Cohort will be shipped from the SDMC to each study pharmacy. Each MTN-008 Pharmacy Randomization Envelope will contain an MTN-008 Pregnancy Cohort: Participant-specific Pharmacy Dispensing Record, and will be used by pharmacy staff to document dispensation of study gel applicators to the participant. These records will be pre-printed with the CRS name, CRS location, DAIDS site ID, MTN-008 Pharmacy Randomization Envelope number, assigned bin code, and possible sublot codes for that corresponding bin code. The dispensing records will also contain a space to adhere the tear-off labels of dispensed applicators of study gel. Only site pharmacy staff will have access to the Participant-specific Pharmacy Dispensing Records.

Figure 4-3: Sample Clinic Randomization Envelope

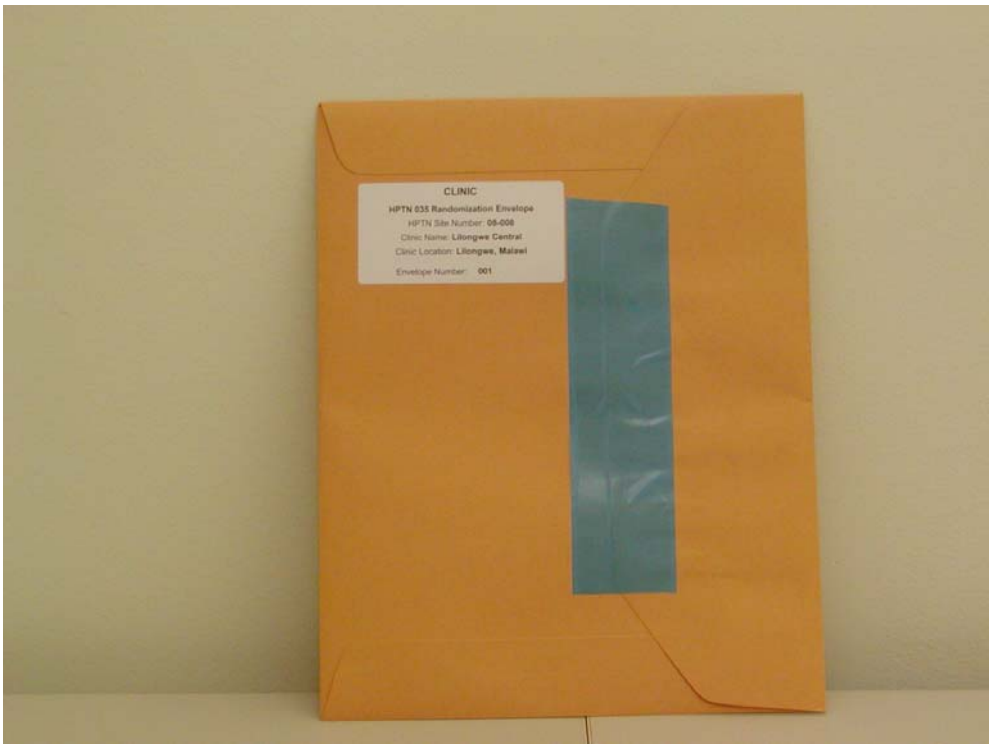


Figure 4-4: Sample Clinic Randomization Envelope–Close-up of MTN-008 Clinic Randomization Envelope Label

CLINIC – Pregnancy Cohort
GROUP 1
MTN-008 Randomization Envelope

DAIDS CRS ID: Pre-print

CRS Name: Pre-print

CRS Location: Pre-print

Envelope Number: Pre-print

Figure 4-5: Sample Opened MTN-008 Clinic Randomization Envelope

Figure 4-6: MTN-008 Pregnancy Cohort GROUP 1 Clinic Randomization Envelope Tracking Record

MTN-008 Pregnancy Cohort GROUP 1
Clinic Randomization Envelope Tracking Record

CRS Name:	Pre-print	DAIDS Site ID:	Pre-print
CRS Location:	Pre-print		

Instructions: Complete one row each time a clinic randomization envelope is assigned to an MTN-008 study participant. All entries must be made in blue or black ink. Corrections may be made by drawing a line through incorrect entries, entering correct information, and initialing and dating the correction.

Clinic Randomization Envelope #	Envelope Assigned to Participant ID #	Date Assigned (dd-MMM-yy)	Time Assigned (hh:mm) (24-hour clock)	Clinic Staff Initials
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				
Pre-print				

Photocopying is not authorized

Figure 4-7: MTN-008 Prescription – Lactation Cohort

MTN-008 PRESCRIPTION – LACTATION COHORT

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	**Pre-print**	DAIDS Site ID:	**Pre-print**
CRS Location:	**Pre-print**		

Participant ID: ☐☐☐–☐☐☐☐–☐–☐

Did participant provide written informed consent for enrollment into MTN-008? ..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

TENOFOVIR 1% GEL

Sig: Insert the entire contents of one applicator vaginally at approximately the same time each day for seven (7) consecutive days.

Quantity: eight (8) pre-filled applicators of MTN-008 Tenofovir 1% gel

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense eight (8) applicators of MTN-008 Tenofovir 1% gel to participant. Applicators to be dispensed as follows:
- Day 0: 1 applicator for clinic administration
- Day 0: 6 applicators for home administration
- Day 6: 1 applicator for clinic administration

Clinic Staff Initials: _____ Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Figure 4-8: MTN-008 Prescription – Pregnancy Cohort

MTN-008 PRESCRIPTION – PREGNANCY COHORT

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	**Pre-print**	DAIDS Site ID:	**Pre-print**
CRS Location:	**Pre-print**	Clinic Randomization Envelope #:	**Pre-print**

Participant ID: ☐☐☐–☐☐☐☐–☐–☐

Did participant provide written informed consent for enrollment into MTN-008? ..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

MTN-008 Study Gel (Tenofovir 1% Gel or HEC Placebo)

Sig: Insert the entire contents of one applicator vaginally at approximately the same time each day for seven (7) consecutive days.

Quantity: eight (8) pre-filled applicators of study gel

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense eight (8) applicators of MTN-008 study gel to participant.
Applicators to be dispensed as follows:
- Day 0: 1 applicator for clinic administration
- Day 0: 6 applicators for home administration
- Day 6: 1 applicator for clinic administration

Clinic Staff Initials: _____

Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

Figure 4-9: MTN-008 Prescription – Pregnancy Cohort Replacement Participant

MTN-008 PRESCRIPTION – PREGNANCY COHORT REPLACEMENT PARTICIPANT

Instructions: All entries must be made in dark ink. Press firmly when completing this form. Corrections may be made by drawing a single line through incorrect entries, recording correct information, and initialing and dating the correction.

CRS Name:	**Pre-print**	DAIDS Site ID:	**Pre-print**
CRS Location:	**Pre-print**		

Participant ID: ☐☐☐–☐☐☐☐–☐☐–☐

Did participant provide written informed consent for enrollment into MTN-008? ..... *yes* ☐ *no* ☐ Clinic Staff Initials: _____

Clinic Staff Instructions: To complete the items below, obtain the MTN-008 Pregnancy Cohort prescription assigned to the ***participant being replaced***. Complete the information below based on the randomization information contained on that prescription.

Participant ID of participant being replaced: ☐☐☐–☐☐☐☐–☐☐–☐

Clinic Randomization Envelope # of participant being replaced: ☐☐☐

MTN-008 Study Gel (Tenofovir 1% Gel or HEC Placebo)

Sig: Insert the entire contents of one applicator vaginally at approximately the same time each day for seven (7) consecutive days.

Quantity: eight (8) pre-filled applicators of study gel

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Clinic Staff Instructions: Complete all items in this box. After initialing and dating, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Pharmacy: Dispense eight (8) applicators of MTN-008 study gel to participant. Applicators will be dispensed as follows:
- Day 0: 1 applicator for clinic administration
- Day 0: 6 applicators for home administration
- Day 6: 1 applicator for clinic administration

Clinic Staff Initials: _____ Date clinic envelope opened: ☐☐–☐☐☐–☐☐
dd *MMM* *yy*

Pharmacy

4.5.3 Participant-Specific Procedures: Pregnancy Cohort

For each participant in the Pregnancy Cohort, random assignment will take place after the participant has been confirmed as eligible and willing to take part in the study, as documented by her signing or marking the enrollment informed consent form. The in-clinic randomization procedures listed below will be performed for participants in the Pregnancy Cohort:

1. Obtain the next sequential MTN-008 Clinic Randomization Envelope and inspect it to verify that the correct envelope has been obtained and there is no evidence that the envelope has previously been opened or otherwise tampered with. Assign the envelope to the participant and document assignment on the MTN-008 Clinic Randomization Envelope Tracking Record by recording the PTID, date assigned, time assigned, and authorized clinic staff initials in the row corresponding to the assigned envelope number.

2. Open the assigned MTN-008 Clinic Randomization Envelope or, allow the participant to open it herself. Remove the prescription and confirm the information pre-printed at the top of the form. In particular, confirm that the envelope number printed on the prescription corresponds to the envelope number on the outside of the envelope. If the envelope does not contain a prescription, or if any information pre-printed on the prescription appears to be incorrect, contact the SDMC Project Manager and site Pharmacist of Record (PoR) immediately. The PoR will inform the DAIDS Protocol Pharmacist and MTN CORE Pharmacist. Do not proceed with randomization of this or any other participant until instructed to do so by the SDMC.

3. Provide appropriate information, instructions, and counseling to participant.

4. Complete the prescription, as follows:

- In the top section of the prescription, record the PTID and mark whether the participant provided informed consent to take part in the study. The staff member who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her staff initials beside these boxes.
- Complete the middle section of the prescription, which includes a space for the authorized prescriber's printed name, the authorized prescriber's signature, and the date. Only a site study staff member designated in the site's delegation of duties as an authorized prescriber of study gel may complete this section. This person also must be listed as an investigator (either the Investigator of Record or Sub-investigator) on the current FDA Form 1572. The date recorded in this section of the prescription is the date upon which the authorized prescriber signs the prescription.
- Complete the bottom section of the prescription, which includes a space for clinic staff initials and the date the Clinic Randomization Envelope was opened. The bottom section of the prescription may be completed by any clinic staff member authorized in the site's delegation of duties to determine the quantity of gel to be given to study participants.
- Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain and place the yellow copy in the participant study notebook. Also retain and place the MTN-008 Clinic Randomization Envelope in the participant study notebook. MTN-008 Clinic Randomization Envelopes may be hole-punched after they have been opened and their contents have been removed.
- Deliver the white original prescription to the study pharmacy, per site SOP, using one of the following options consistently:

- OPTION A: Give the original prescription to the participant to deliver to the pharmacy
- OPTION B: Deliver the original prescription to the pharmacy
- OPTION C: Fax a copy of the original prescription to the pharmacy for filling purposes only; deliver the original prescription to the pharmacy by the time of gel pick-up

Note: In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. If corrections are required, identical corrections must be made on both the white original prescription and the yellow copy. An identical signed and dated note explaining the corrections also must be recorded on both copies. Identical corrections and notes must be recorded on both copies, on the same date, by the same person. Corrections must only be made by study staff authorized to complete original prescriptions.

4.5.4 Participant-Specific Procedures: Lactation Cohort

Only steps 3 and 4 from the above participant-specific procedures apply to participants in the Lactation Cohort.

4.5.5 PK Collection Procedures: Both Cohorts

All MTN008 maternal participants, and infant participants in the Lactation Cohort, will contribute either blood or both blood and breast milk PK samples on the Days 0 and 6 clinic visits. Collection of blood specimens for pharmacokinetic (PK) analysis should be performed for both cohorts at a pre-gel time point and then 1, 2, 4, 6, and 8 hours following gel insertion. In addition, for the Lactation Cohort, breast milk collection should be collected at 2, 4, and 6 hours after gel insertion. All collections should occur within a +/- 15 minute window at each target time point. Document all PK collection times on the Maternal Pharmacokinetics CRF, Infant Pharmacokinetics CRF (as appropriate), and LDMS tracking sheet. All specimen collections should be drawn as closely as possible to the proscribed target time point, and if not at the proscribed time point, collections should be drawn within the +/- 15 minute window.

In the rare instance that a sample is not drawn within the expected time window, the sample still should be collected. However, if the collection time runs into the next collection time point (75% of the temporal distance to the next scheduled time) then that initial time point is considered missed.

Any samples collected outside the +/- 15 minute windows, which are not attributed to participant concern, will be documented as a protocol deviation for specimen collection outside +/- 15 minute window.

Below are tables outlining the time points and allowable windows for collection of blood and breast milk samples for both Cohorts.

Note that the exception to these time restrictions is the final PK collection of the day, i.e., PK hour 6 for breast milk collection in Lactation Cohort, and PK hour 8 for Blood Collection in both Pregnancy and Lactation Cohorts) should be collected even if beyond the expected windows.

Pregnancy Cohort

PK Dose (Time 0)	Sample Collected	Allowable Collection Window (+/- 15 minutes from target PK collection times)	Absolute Collection Timeframe from Time 0
Pre-gel	Blood	N/A	N/A
Hour 1 post gel insertion	Blood	45 min – 1 hr 15 min	Up to 1 hr 45 min
Hour 2 post gel insertion	Blood	1 hr 45 min – 2 hr 15 min	Up to 2 hr 45 min
Hour 4 post gel insertion	Blood	3 hr 45 min – 4 hr 15 min	Up to 5 hr 30 min
Hour 6 post gel insertion	Blood	5 hr 45 min – 6 hr 15 min	Up to 7 hr 30 min
Hour 8 post gel insertion	Blood	7 hr 45 min – 8 hr 15 min	No limit

Lactation Cohort

PK Dose (Time 0)	Sample Collected	Allowable Collection Window (+/- 15 minutes from target PK collection times)	Absolute Collection Timeframe from Time 0
Pre-gel	Blood Only	N/A	N/A
Hour 1 post gel insertion	Blood Only	45 min – 1 hr 15 min	Up to 1 hr 45 min
Hour 2 post gel insertion	Blood/ Breast Milk	1 hr 45 min – 2 hr 15 min	Up to 2 hr 45 min
Hour 4 post gel insertion	Blood/ Breast Milk	3 hr 45 min – 4 hr 15 min	Up to 5 hr 30 min
Hour 6 post gel insertion	Blood/ Breast Milk	5 hr 45 min – 6 hr 15 min	Up to 7 hr 30 min (Blood); No limit (Breast Milk)
Hour 8 post gel insertion	Blood Only	7 hr 45 min – 8 hr 15 min	No limit

Once specimens have been collected on Enrollment (Day 0), the same time intervals for each PK specimen collection should be used to calculate targeted time points for the Day 6 PK collection. For example if at the Day 0 Visit, the 1 hour specimen was collected 65 minutes after dosing (time 0), then at the Day 6 Visit, the 1 hour specimen should also be drawn 65 minutes post-dose. The collection targeted time points and windows for all Day 6 Visit samples should be adjusted according to actual sample collection times at the Day 0 Visit. A PK collection timing tool is available on the MTN website under Study Implementation Materials to help calculate Day 0 and Day 6 sample collection target times and collection windows.

Women in both Cohorts will be asked to document dates and times of trial-related activities performed at home between the Day 0 and Day 6 Visits. The Home Dosing Log (Appendix 4-5), used by participants in both Cohorts (if IRB approved), should be returned to the clinic at the Day 6 Visit.

Additionally, women in the Lactation Cohort will be asked to collect 2 breast milk samples on each of 2 different days during her week of dosing at home. Appendix 4-6 is an instructional reference for the participant to use (with IRB approval) to document dates and times of breast milk sample collection between the Day 0 and Day 6 Visits. The Breast Milk Sample Collection Sheet (Appendix 4-6) should be returned to the clinic with the participant's breast milk samples at the Day 6 Visit.

Both of these logs should be filed with participant study records as source documentation for data entered on the Participant-Reported Home Dosing and Collection Form.

Study product should be provided to each participant at the conclusion of the Day 0 Visit, after all required assessments are completed (refer to procedures listed on the Visit Checklists, Section 7 of this manual) and, an authorized clinician confirms that the participant is eligible to receive product for administration at home. See Section 6.6 for more information on study product dispensation on Day 6.

For Lactation Cohort participants, sites also should supply a breast milk collection kit, comprised at minimum of what is required to collect study samples, plus at least one extra of collection supplies in case of contamination or damage at home:

- breast pump if needed, with new tubing
- breast milk pump collection bags/ bottles
- transfer pipettes (3)
- cryovials (5)
- ice packs/ cooler box for sample transport to the clinic
- cryovial labels, preprinted with the participant PTID
- Home Dosing Log (see Appendix 4-5)
- Breast Milk Sample Collection Sheet (see Appendix 4.6)

4.6 Replacement of Unevaluable Participants

Once it has been determined that a particular participant is unevaluable (refer to Section 6.6 of this manual to define evaluability) and requires replacement, the site will begin procedures for enrolling the replacement participant. For replacement participants in the Pregnancy Cohort, site clinic staff will not assign a new Clinic Randomization Envelope to replacement participants, but instead the replacement participant will inherit the randomization assignment of the participant being replaced. The site clinic staff will complete the applicable MTN-008 Prescription for the Pregnancy Cohort Replacement Participant by transcribing the randomization information from the original MTN-008 prescription completed for the participant being replaced onto the replacement prescription.

For replacement participants in the Lactation Cohort, a new MTN-008 Prescription for the Lactation Cohort will be completed. There are no MTN-008 Lactation Cohort Replacement

Prescriptions for this cohort because these participants are not randomized and everyone receives tenfovir 1% gel.

For replacement participants in both cohorts, the act of completing the MTN-008 replacement prescription ((Pregnancy Cohort) or new prescription (Lactation Cohort) serves as the act of randomization and enrollment in the study. Once the applicable MTN-008 replacement/new prescription is completed, the replacement participant is considered enrolled in the study.

4.7 Product Use Instructions

After enrollment has been completed, participants will be provided with detailed instructions for daily use of their assigned product, followed by adherence counseling. Participants also will complete their first product use at the clinic during their enrollment visits. Study product should be provided to each participant at the Day 0 Visit after all required assessments are completed and an authorized clinician confirms that the participant is eligible to continue product use. See MTN-008 SSP Manual Section 6.7 for more information on study product re-supply and re-issue.

A copy of the Home Dosing Log (2 sided) will be given to the participant to log each instance of study product dosing. Refer to Appendix 4-5 to see a copy of this form. Clinic staff will complete the dates for Day 1 through Day 5 using the MMM/dd/yy format, and will instruct participants to record the time that product is inserted each day. Participants will be instructed to record comments or notes about additional or missed dosing in the comment section on the back of the page. Staff will ask participants to return to the Day 6 Visit with this completed form, and will review the form as part of the confirmation of appropriateness of conducting the Day 6 Visit procedures. Follow-up use of this form is described in Section 6 of this manual. Further guidance related to product use instructions, first product use, and adherence counseling is provided in Section 12 of this manual.

Appendix 4-1
Sample Screening and Enrollment Log for MTN-008

	Cohort L P -1 P-2	Screening Attempt	Screening Date (s)	Participant ID	Enrollment Date (or NA if not enrolled)	Screening Failure Date (or NA if enrolled)	Reason for Screening Failure (or NA if enrolled)
						Refer to non-Datafax Eligibility forms for Screen Failure Codes	
1 (M)							
2 (I)							
3 (M)							
4 (I)							
5 (M)							
6 (I)							
7 (M)							
8 (I)							

Lactation and Pregnancy Cohorts
(M): Mothers
(I): Infants

Appendix 4-2
Screening Visit: Pregnancy and Lactation Cohorts

Screening Visit: Pregnancy and Lactation Cohorts		
Component	**Procedure/Analysis (Mothers)**	**Lactation Cohort: Procedures/Analysis (Infants)**
Administrative, Behavioral, and Regulatory	• Informed consent for screening • Demographic information • Locator information • Eligibility assessment • Obtain signed records release* • Assign participant identification number (PTID) • HIV pre- and post-test counseling • Reimbursement • Schedule next visit* • Provision of condoms and pantyliners*	• Assign participant identification number (PTID) • Eligibility assessment
Clinical	• Medical eligibility information (including exclusionary medical conditions and medications) • Medical history • Concomitant medications • Review medical records • Blood collection • Urine collection (Lactation Cohort) • Targeted physical exam • Pelvic exam • Vaginal swabs • Cervical swabs • Treatment for reproductive tract infection (RTI)/urinary tract infection (UTI) or mastitis* • Provision of contraception and contraception education* • Disclosure of available test results	• Medical eligibility determination • Medical history
Laboratory	• Test for chlamydia and gonorrhea (GC/CT) • Urine HCG (Lactation Cohort) • CBC • HIV serology • Serum creatinine • Hemoglobin • AST • ALT • Syphilis serology if not documented within past year • HBsAg test if not documented within past year • Trichomonas test • Pap smear* • Wet prep and vaginal pH* • Vaginal and cervical biomarkers (Pregnancy Cohort) • Quantitative vaginal culture (Pregnancy Cohort) • Gram stain (Pregnancy Cohort) • Herpes culture*	

Appendix 4-3
Enrollment Visit: Pregnancy and Lactation Cohorts

Enrollment Visit (Day 0)			
Component	**Pregnancy Cohort: Procedure/Analysis (Mothers)**	**Lactation Cohort: Procedure/Analysis (Mothers)**	**Lactation Cohort: Procedure/Analysis (Infants)**
Administrative, Behavioral, and Regulatory	• Informed consent for enrollment • Locator information • Eligibility confirmation • Randomization • Baseline acceptability questionnaire • Coital log • Adherence counseling • Reimbursement • Schedule follow-up visits/calls • Disclosure of available test results* • Provision of condoms and panty liners* • Education/ distribution of Home Dosing Log	• Informed consent for enrollment • Locator information • Eligibility confirmation • Baseline acceptability questionnaire • Coital log • Adherence counseling • Participant education on collection of 2 breast milk samples at home (target 4 hours post dosing on two different days when study product was inserted) • Supplies for breast milk collection • Reimbursement • Schedule follow-up visits/calls • Disclosure of available test results* • Provision of condoms and panty liners* • **Education/ distribution of Home Dosing Log and Breast Milk Sample Collection log**	• Eligibility confirmation
Clinical	• Review medical records • Medical history • Concomitant medications • Targeted physical exam • Pelvic exam • Vaginal swabs • Cervical swabs • Insert saline lock** • Blood collection at PK time points (pre-gel, 1, 2, 4, 6, and 8 hours) • Supply 7 pre-filled study product applicators • Single dose of study gel to be administered by IoR/designee at clinic • Collect AEs	• Review medical records • Medical history • Concomitant medications • Targeted physical exam • Pelvic exam • Vaginal swabs • Cervical swabs • Urine collection • Insert saline lock** • Blood collection at PK time points (target pre-gel, 1, 2, 4, 6, and 8 hours) • Breast milk collection at PK time points (target 2,4,6 hours) • Supply 7 pre-filled study product applicators • Single dose of study gel to be administered by IoR/designee at clinic • Collect AEs	• Medical history • Concomitant medications • Collect AEs (self-reported, medical records, direct evaluation) • Blood collection via heelstick (target 6 hours <u>following maternal dosing)</u>

Laboratory	• CBC with differential (pre-gel) • **Plasma Archive** • Maternal blood tenofovir level (pre-gel, 1, 2, 4, 6, and 8 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Vaginal pH • Vaginal and cervical biomarkers • Quantitative vaginal culture • Gram stain • Wet prep* • Trichomonas* • Herpes culture*	• Urine HCG • CBC with differential (pre-gel) • **Plasma Archive** • Maternal blood tenofovir levels (pre-gel, 1, 2, 4, 6, and 8 hours) • Flow cytometry (pre-gel)*** • PBMCs*** • Breast milk tenofovir level(target pre-gel, 2,4,6 hours) • Vaginal pH • Vaginal and cervical biomarkers • Quantitative vaginal culture • Gram stain • Wet prep* • Trichomonas test* • Herpes culture*	• Blood tenofovir levels

* if indicated ** if applicable *** if site capacity allows

Appendix 4-4
MTN-008 INFANT FEEDING Eligibility Criterion for Lactation Cohort

For women being considered for the Lactation Cohort, determine what proportion of their feedings are mother's milk versus formula using the questions below and maintain with source documentation. This inclusion criterion requires breastfeeding of at least 75% of infants nutrition at enrollment, with intention to sustain this through the Day 6 Visit, to meet eligibility.

Discuss with the mother:

1. How are you feeding your baby?
   Mother's milk
   Formula
   Both

2. If breast or both: What percent of the feedings you are currently giving your baby is mother's milk? _____%

If mother states at least 75%, use categories below to determine status more completely:

a. 75-80% mother's milk (2-3 out of every 10 feedings are formula or solids or 14-16 ounces/day formula)
b. 80% mother's milk combined with less than 20% formula/solids
c. exclusively mother's milk (at breast or expressed)

Participant ID

			–					–		0

Home Dosing Log

You will insert 1 applicator of study gel into your vagina each day for the next 5 days at home, starting the day *after* enrollment. Please bring this log with you to your Day 6 Visit on _____/_____/_____.

For each day, please record the time you inserted the study gel. The date has been pre-filled by study staff.

- Please be sure to mark the "AM" or "PM" box for each recorded time
- If you **did not** insert study gel on a specific day, please mark the box for "I did not insert study gel today"

Optional: Record any comments or notes about additional or missed dosing on the back of this page.

DAY 1

Date: MMM / dd / yy **Time:** hr : min ☐ AM ☐ PM

OR ☐ I did not insert study gel today

DAY 2

Date: MMM / dd / yy **Time:** hr : min ☐ AM ☐ PM

OR ☐ I did not insert study gel today

DAY 3

Date: MMM / dd / yy **Time:** hr : min ☐ AM ☐ PM

OR ☐ I did not insert study gel today

DAY 4

Date: MMM / dd / yy **Time:** hr : min ☐ AM ☐ PM

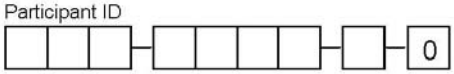
OR ☐ I did not insert study gel today

DAY 5

Date: MMM / dd / yy **Time:** hr : min ☐ AM ☐ PM

OR ☐ I did not insert study gel today

Participant ID



Additional comments and notes

Appendix 4-6
Breast Milk Sample Collection Sheet

Participant ID

									0

Home Collection of Breast Milk Specimens

Note: Place the ice packs provided to you in your freezer so they will be frozen when you need them.

You will collect **TWO** breast milk samples at home this week – on **TWO DIFFERENT** days.

On the days you collect your breast milk sample, please carefully follow these instructions:

1. Four hours after you put the study gel into your vagina, pump milk from one breast until the breast is empty. Use a clean container to collect the sample.
2. **GENTLY** swirl the container of breast milk. **DO NOT SHAKE**.
3. Using the provided dropper, place approximately 2 milliliters (mL) of breast milk into 2 of the small tubes provided. You will have 2 small tubes with 2 mL of breast milk each.
4. Write the **COLLECTION DATE** and **COLLECTION TIME** on two of the provided labels. Also record the date and time of collection below.
   - For the date, use the following format: MMM / dd / yy. For example, February 06, 2010 will be recorded as FEB / 06 / 10.
   - Please be sure to mark the "AM" or "PM" box for each recorded time
   - If you did not collect the breast milk sample, please mark the "none collected" box
5. Place one label on each small tube.
6. Immediately place both labeled small tubes in your freezer, away from the door or sides.
7. Any remaining milk in the container may be used to feed your baby, as long as it is stored properly.

Repeat steps 1 – 7 on the second day you collect your breast milk sample. You will have a total of 4 small tubes in your freezer. **Bring all 4 tubes with you to your next study visit using the cooler and ice packs provided to you.**

Call the study staff at _____ - _____ - _____ if you have any questions or concerns about collecting, storing, or transporting your breast milk samples.