Section 5. Informed Consent

This section provides information on informed consent procedures for MTN-008. MTN-008 involves six types of informed consent:

Pregnancy Cohort:

1. Mother – informed consent for screening
2. Mother and Infant (to be born of the mother) – informed consent for enrollment

Lactation Cohort:

3. Mother – informed consent for screening
4. Mother – informed consent for enrollment
5. Infant – informed consent for screening and enrollment

Pregnancy and Lactation Cohorts, to be collected at enrollment:

6. Informed consent for long term specimen storage and possible future research testing for both mothers and infants

Potential study participants must provide written informed consent for screening in order to undergo protocol-specified procedures for determining eligibility. Potential participants who are found to be eligible must then provide written informed consent to enroll in the study. For infants in the Lactation Cohort, there is one informed consent form signed during the screening visit that serves to cover both screening and enrollment of the infant. For enrolled participants, informed consent for long term specimen storage and possible future research is optional. Participants may choose not to consent to long term specimen storage and possible future research testing and still be enrolled in the study.

This section contains general information and instructions applicable to all six types of informed consent required for MTN-008.

5.1 Overview of Informed Consent Requirements and Procedures

Informed consent is a process by which an individual voluntarily expresses her willingness to participate in research, after having been informed of all aspects of the research that are relevant to her decision. Informed consent is rooted in the ethical principle of respect for persons. It is not merely a form or a signature, but a process, involving information exchange, comprehension, voluntariness, and documentation. Each of these aspects of the process is described in greater detail below. Please also refer to Section 4.8 of the *International Conference on Harmonization (ICH) Consolidated Guidance for Good Clinical Practice* (GCP) and the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* for further guidance on the informed consent process and documentation requirements.

The US Code of Federal Regulations (45 CFR 46, Subpart A) specifies the elements of informed consent that must be conveyed to research participants through the informed consent process. It is the responsibility of the Investigator of Record (IoR) to ensure that all potential study participants are properly consented before any study procedures are initiated.

There are four main steps to a comprehensive informed consent process:

1. *Delivery* - Deliver all required information in a manner that is understandable to potential study participants

2. *Setting* - Assure that informed consent is obtained in a setting free of coercion and undue influence
3. *Comprehension* - Confirm that the participant comprehends the information
4. *Documentation* - Document the process

As a condition for study activation, the study site must establish an SOP for obtaining informed consent from potential study participants that ensures that all of the above-listed requirements are met. The SOP must be consistent with the DAIDS SOP for Source Documentation. FHI should approve this SOP prior to implementation for the study. IRB approval of this SOP is recommended. The SOP should contain certain recommended elements:

- The minimum legal age to provide independent informed consent for research at the study site
- Procedures for ascertaining participant identity and age
- Procedures for ascertaining participant literacy
- Procedures for providing all information required for informed consent to the participant
- Procedures for ascertaining participant comprehension of the required information
- Procedures to ensure that informed consent is obtained in a setting free of coercion and undue influence
- Procedures for documenting the informed consent process
- Considerations and requirements for illiterate participants, including specification of who may serve as a witness to the informed consent process, as applicable.
- Storage locations for blank informed consent forms
- Storage locations for completed informed consent forms
- Procedures for implementing a change in the version of the informed consent form used
- 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)

5.2 Informed Consent for Screening

At each site, the informed consent process for screening will be conducted according to site SOPs. Informed consent for screening must be obtained before performing any study screening procedures. For participants who do not consent to screening, no screening procedures should be performed and no data that can be linked to the participant's name or other personal identifier(s) should be recorded.

5.3 Informed Consent for Enrollment

At each site, the informed consent process for enrollment will be conducted according to site SOPs. However, site SOPs must reflect the standardized approach to the enrollment informed consent process that is described in this section. Informed consent for enrollment must be obtained before performing any "on-study" procedures. An overview of the standardized approach to the enrollment informed consent process is provided in Appendix 5-1. Additional details related to key steps in the process are provided in the remainder of this section.

For enrollment into the Pregnancy Cohort, the mother and infant (to be born of the mother) are consented for enrollment simultaneously on the same form. For enrollment into the

Lactation Cohort the mother signs one consent form for her enrollment, and a separate single consent form which provides consent for the infant's screening and enrollment.

5.3.1 Informed Consent Support Materials

Sites may choose to use an informed consent visual aid during the informed consent process. These were developed to aid in introducing MTN-008 to potential study participants and in explaining some of the information contained in the screening and enrollment informed consent forms. The sheet contains information corresponding to schedule of visits to be conveyed in any informed consent discussion. The sheet does not substitute for the screening or enrollment informed consent forms, since additional site-specific details are provided in the informed consent form. Also, participants who decide to take part in the study must sign or mark the enrollment informed consent form (as described in Section 5.x). This sheet is not to be given to the participant to take home, but to be used in the clinic during the consenting process. See Appendix 5-3 for an example of an IC visual aid modeled from the Pittsburgh site's tool. Sites may use this template or modify it but it must reflect the content provided their visit checklists and informed consent forms.

Other suggested visual aids for each site to consider using are as follows:

- Calendar
- Male condoms
- Sample gel applicators
- Photographs of study products
- Sample randomization envelopes
- Breast milk sample log and collection materials for Lactation Cohort participants
- Tour the room where Visit Days 0 and 6 will occur, given the length of time the participants will spend at the clinic those days
- Home Dosing log
- Study Visit Schedule and Reminders sheet

5.3.2 Comprehension Assessment

The staff person conducting the informed consent process with a potential participant is responsible for determining whether the participant comprehends the information provided to her. There are five main elements to an effective comprehension assessment:

1 *Ask open-ended questions* - Ask questions to find out if the participant understands salient points of the protocol. If the participant is unable to respond correctly to any of the comprehension assessment questions, and cannot mention one or more of the salient points, follow-up with an open-ended probing question related to that particular point.

2 *Reinforce* - When responding to the various questions, potential participants may report back more information than is necessary. This is acceptable, as long as the required information is reported back. Briefly summarize the correct, key information she told you, reinforcing that this specific information is correct.

3 *Correct Misinformation* - If any misinformation is reported back, review the topics that were not clearly understood. Then, follow-up with open-ended questions to be sure she understands the correct information.

4 *Ask follow-up questions* - Even if a participant repeats back correct information, yet it is not clear that she really understands it, follow-up with another question to verify her understanding.

5 *Explain further* - There may be certain topics in the informed consent that remain unclear. Provide further explanation of these topics as needed to ensure that the participant is satisfied and clearly understands the information. It may be helpful to have a clinician or other staff member explain the information to the participant. The participant can tell you if that is something she would like. If necessary, further explanation or discussion can take place at a later point in time and screening/enrollment postponed until that visit.

5.4 Informed Consent for Specimen Storage and Possible Future Research Testing

At each study site, the informed consent process for specimen storage and possible future research testing will be conducted according to site SOPs among enrolled study participants. For participants who do not consent to specimen storage and possible future research testing, specimens collected and stored on-site per protocol will be retained until the study is completed and all protocol-specified testing has been done. Thereafter, any remaining specimens collected from these participants will be destroyed.

The MTN-008 informed consent form for the storage of specimens addresses both woman and infant in the same form and is to be collected at the enrollment visit. The woman may decline for both her and her infant, for her but not her infant, or for her infant but not for her. Refusal for one of the two participants should be fully documented both on the informed consent form and in the chart notes.

Women (and the infant's father, if participating in the consent process) should understand that declining their or their infant's specimen storage will not exclude them or their infant's ability to participate in the study.

5.5 Additional Elements of the Informed Consent for MTN-008

5.5.1 HIPAA Authorization

HIPAA authorization must be incorporated into the site specific informed consent process. This language may be added to the study consent forms or it may be a separate form, per individual IRB procedures for obtaining HIPAA authorization. However, written HIPAA authorization must be obtained at least at the time of the screening informed consent process, for all study participants, as required by the IRB.

5.5.2 Certificate of Confidentiality

Language for the Certificate of Confidentiality is included in the template informed consent forms as a multi-site Certificate of Confidentiality will be obtained from the National Institutes of Health (NIH) for this study. This certificate acts to protect study staff from being forced to tell people who are not connected with this study, such as the court system, about a subject's participation or information they give study staff for study purposes.

Once your site has obtained IRB approval, the final, approved informed consent forms and documentation of IRB approval of the study will be used for making the application for the certificate. Once NIH issues the certificate, you will be notified. Place a copy of the notification in your Regulatory Notebook.

As stated in the informed consent forms, although there will be a Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to the participant or others, study staff will be required to report this to the proper authorities. Additionally, applicable reportable diseases must be reported to the local health authorities.

5.5.3 IRB Assessment of Risk and Impact on Consent Process

Special Populations and documentation of risk/benefit category by IRB

For research projects including pregnant women, fetuses, neonates and children, documentation should be obtained from the IRB/EC stating the designation of a risk/benefit category from 45 CFR 46.204-205 and 46.404-407 and IRB/EC approval for involvement of these special populations based on the determination specified in that category. The documentation may be in the IRB/EC approval letter or in other official correspondence from the IRB/EC to the investigator. This documentation is needed to obtain protocol registration.

Consent consideration for research involving children

Based on the level of risk determined by the IRB, the procedures for consenting children may vary by site. With regards to including children in research, there are two types of determinations that your IRB is expected to consider:

- Consent by one or both parents as determined by the IRB: The signature lines on the template consent form are to be adjusted according to the IRB determination. File documentation of IRB determination with your essential documents. For this element, the IRB shall determine the extent that consent of parents or guardians is needed in accordance with §46.116 of Subpart A. If the IRB determines that the research involving children falls under §46.404 or §46.405, then the permission of one parent is sufficient for research to be conducted. If the IRB determines that the research is covered by §§46.406 and 46.407 and permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

5.5.4 Site-specific informed consent forms

The informed consent forms used at the site must be reviewed and approved by MTN CORE (FHI) before the site submits them to their IRBs/EC for approval. Prior to initiating the study, the site must obtain written approval by the IRBs/EC and DAIDS Protocol Registration Office prior to their use. After the forms are approved, the site is responsible for preparing supplies of their approved forms and for using only the currently approved versions of the forms. Further information on maintaining informed consent forms will be detailed in site SOPs.

5.5.5 Illiterate participants

If the participant is not literate, she is unable to participate in MTN-008. Literacy is required to complete CASI questionnaires.

5.6 Documenting the Informed Consent Process

US regulations require that informed consent be documented by "the use of a written informed consent form approved by the IRB/EC and signed and dated by the subject or the

subject's legally authorized representative at the time of consent."

Complete all name and date blocks - To fulfill this requirement, complete all signature and date blocks on the informed consent form in ink. Legal names should be used. Initials may not be used in place of a participant's surname and preferably, initials will not be used in place of a participant's first name.

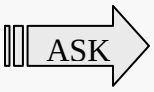
The DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials* lists detailed requirements and suggestions for documenting the informed consent process. All requirements listed in the DAIDS policy must be met. In order to also meet some of the suggestions listed in the DAIDS policy, site staff may use an informed consent "coversheet" similar to the sample included in Section Appendix 5-2. Sites choosing to use a coversheet should list the coversheet as a source document in their SOPs for source documentation for MTN-008 and should use the coversheet consistently to document all informed consent processes with all participants. The sample coversheet is available as a separate electronic file in the Study Implementation Materials section of the MTN-008 web page.

In addition to completing the documentation requirements on the informed consent form itself, each informed consent process must be documented in a signed and dated chart note. It is essential that the note and all other documentation (e.g., the informed consent form, the coversheet) document that informed consent was obtained before any study procedures were conducted. In particular, the documented date and end time of the informed consent process must precede the documented date and time of randomization. The chart note recorded to document the informed consent process should also document adherence to the requirements of the informed consent section of the DAIDS policy on *Requirements for Source Documentation in DAIDS Funded and/or Sponsored Clinical Trials*. If an informed consent coversheet is used, a chart note is still required, but it is not necessary to transcribe all information recorded on the coversheet into the chart note.

Finally, regulations require that participants be given a signed copy of the informed consent forms. If a participant opts not to receive a copy, document this in a chart note and offer the participant an alternate form of study contact information (e.g., a contact card or appointment card) in lieu of the full informed consent form.

Appendix 5-1
Overview of MTN-008 Enrollment Informed Consent Process

Briefly **describe the steps** in the enrollment consent process and tell the participant how long it takes to complete.



Does she have time to complete this today?

- If yes, proceed.
- If no, schedule return appointment.

Is she ready to have the **informed consent form** read to her or read it herself?

- If yes, proceed.
- If not, determine what she needs and provide information or schedule return appointment.

Read consent form, section by section, asking if she has questions and discussing as you go along.

Does she feel comfortable that she understands all aspects of the study?

- If yes, proceed.
- If not, determine what she needs and provide more information or schedule return appointment.

Administer **comprehension checklist.**

All questions/points on the checklist.

- If participant demonstrates comprehension of all required points, proceed.
- If not, discuss misunderstandings and probe problem areas with open-ended questions. Provide information and review protocol flow sheet charts, and any other IRB-approved materials as needed to resolve misunderstandings. Continue discussing until comprehension of all required topics is demonstrated.
- If participant is fatigued or requests more time, or if staff judge that participant needs more time, schedule return appointment and repeat steps in the process as needed.

After demonstrating comprehension, if the participant chooses to take part in the study, complete all name, signature, and date lines on the enrollment informed consent form. Offer participant a copy of the form. Document the process per DAIDS policy and site SOPs.

- If the participant chooses to take part in the study, proceed with enrollment.

Section Appendix 5-2

Sample Informed Consent Coversheet for MTN-008

Participant Name (or PTID):	
Name of study staff person completing informed consent process/discussion (and this coversheet):	
Is the participant of legal age to provide independent informed consent for research?	☐ Yes ☐ No ⇒STOP. Participant is not eligible
Date of informed consent process/discussion:	
Start time of informed consent process/discussion:	
Language of informed consent process/discussion:	
Was the informed consent process/discussion conducted according to site SOPs for MTN-008?	☐ Yes ☐ No ⇒Record and explain departures from site SOPs below.
Can the participant read?	☐ Yes ☐ No ⇒A literate impartial witness should be present during the entire informed consent process/discussion. Refer to site and DAIDS SOPs for specific instructions. Record name of witness here: Record relationship of witness to participant here:
Version number/date of informed consent form used during informed consent process/discussion:	
Was all information required for the participant to make an informed decision provided in a language that was understandable to the participant?	☐ Yes ☐ No ⇒ Explain below.
Were all participant questions answered?	☐ Yes ☐ No ⇒ Explain below.
Was the participant given adequate time/opportunity to consider all options before making her informed decision?	☐ Yes ☐ No ⇒ Explain below.
Did the participant accept a copy of the informed consent form?	☐ NA (participant chose not to provide informed consent) ☐ Yes ☐ No ⇒ Offer alternative form of study contact information to participant.
End time of informed consent process/discussion:	
Notes/Comments (continue on back if needed):	
Signature of study staff person completing informed consent process/discussion (and this coversheet):	

Name of IRB/PRO Approved:
Version 1.0

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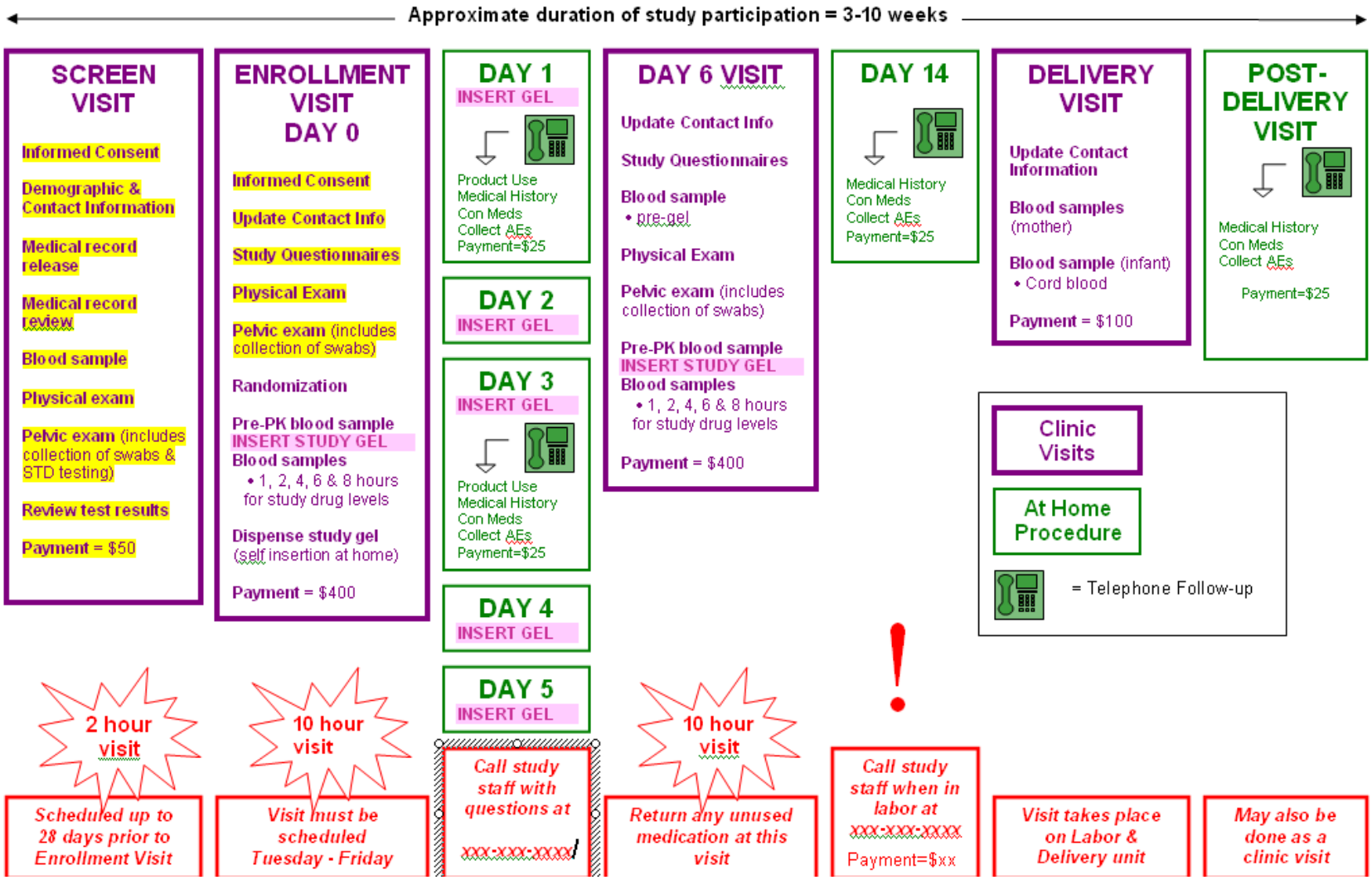
MTN 008: Pregnancy Cohort

Informed Consent Visual Aid



MTN 008: Lactation Cohort

Informed Consent Visual Aid

Approximate duration of study participation = 3 weeks

SCREEN VISIT

- Informed Consent
- Demographic & Contact Information
- Medical record release
- Medical record review
- Blood sample
- Physical exam
- Pelvic exam (includes collection of swabs & STD testing)
- Review test results
- Payment = $60

2 hr visit

Scheduled up to 28 days prior to Enrollment Visit

ENROLLMENT VISIT - DAY 0

- Informed Consents
- Update Contact Info
- Study Questionnaires
- Physical Exam
- Pelvic exam (includes collection of swabs)
- Blood sample, pre-gel
- INSERT STUDY GEL
- Blood samples
  - 1, 2, 4, 6 & 8 hours
- Breast Milk samples
  - 2, 4 & 6 hours
- Dispense study gel (self insertion at home for days 1-5)
- Payment = $xxx + pump

INFANT
Bring to Enrollment Visit

- Heel stick
- Payment = $xxx

9+ hr visit

Visit must be scheduled Tuesday - Friday

DAY 1
INSERT GEL

Product Use
Collect AEs

Payment = $xx

DAY 2
INSERT GEL

DAY 3
INSERT GEL

Product Use
Collect AEs

Payment = $xx

DAY 4
INSERT GEL

DAY 5
INSERT GEL

During TWO days of study gel use, you will collect breast milk samples at home 4 hours after dosing with gel.

DAY 6 VISIT

- Update Contact Info
- Study Questionnaires
- Blood sample
  - pre-gel
- Physical Exam
- Pelvic exam (includes collection of swabs)
- INSERT STUDY GEL
- Blood samples
  - 1, 2, 4, 6 & 8 hours
- Breast Milk samples
  - 2, 4 & 6 hours
- Payment = $300

INFANT
Bring to Day 6 Visit

- Heel stick
- Payment = $xxx

9+ hr visit

Return any unused medication and breast milk samples at this visit

DAY 14

Collect AEs

Payment = $xx

Clinic Visits

At Home Procedure

= Telephone Follow-up

Section Appendix 5-4
Sample MTN-008 Informed Consent Comprehension Assessment: Screening Pregnancy Mother

1. The main purpose of this study is to find out if using vaginally applied tenofovir gel is safe for you and your baby during the end of pregnancy and during breastfeeding. True
2. Tenofovir gel is an "experimental" gel that is being studied for prevention of HIV infection (in other studies). True
3. Tenofovir gel has been tested in one other study in pregnant women so far. True
4. As part of this study, you will be asked questions about your health history, family history and current medications, but you will not have a pelvic exam or any blood work done. False
5. We will call you every 8 hours after you go home to see how you are doing. False
6. You will have an HIV blood test as part of the screening for this study. True
7. You may choose to withdraw from this study at any time with no consequence to your continued health care. True
8. The screening part of the study is expected to take approximately xx hours and if you are eligible and agree to be enrolled in the study, the first and last day's procedures, are expected to last approximately 9-10 hours. True

- ❑ Study participant passed the assessment by answering all questions correctly → proceed to signing informed consent document

- ❑ Study participant missed at least one question → complete the following:

    - o Review the question(s) that were answered incorrectly with the participant.
    - o Review the necessary sections of the informed consent with the participant to ensure understanding.
    - o If the participant can demonstrate understanding of the questions she had previously answered incorrectly on the 2nd attempt, document and proceed with signing the informed consent document.
    - o If after the second attempt, the participant is still unable to answer the questions correctly, participant is ineligible. End informed consent process and document fully.

Notes_____
_____
_____
_____

Staff signature _____ Date_____