Section 9. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the ordering and administration of MTN-008 study product for study participants. Associated instructions for the pharmacy staff are provided in the MTN-008 Pharmacist Study Product Management Procedures Manual, which will be made available to each site Pharmacist of Record (PoR) by the DAIDS Protocol Pharmacist. Please also refer to related information in Section 4 of this manual.

9.1 Responsibilities and Obligations with Regard to Blinding

MTN-008 Investigators of Record (IoRs), and by delegation all MTN-008 study staff, are responsible for maintaining the integrity of the study's blinded design. The identity of the specific vaginal product to which each participant is assigned is double-blinded, meaning that neither study participants nor study staff — including all members of the Protocol Team — will be provided information on the identity of the specific gel to which each participant has been assigned.

Study documentation maintained by pharmacy staff (such as the documents contained inside the Pharmacy Randomization Envelopes) will include coded information indicating the specific study product to which the participants have been assigned. Additional operational requirements to preserve blinding are as follows:

- Clinic staff should respond to participant questions about how to store product supplies and how to insert gel. Sample gel applicators should be stocked at all clinic locations for educational and counseling purposes. Actual study products may not be used for educational and counseling purposes.

- Clinic staff may observe and handle closed gel containers (cartons/bags) after dispensation by the PoR under specific circumstances when the study product is being administered in the clinic. The first dose (Day 0) and the seventh dose (Day 6) will be administered by the IoR or authorized clinician at the site. Other than the Day 0 and Day 6 doses, clinic staff may not open dispensed product or directly handle individual applicators.

- The unused product should be sent to the pharmacy with a completed MTN-008 Study Product Return document and placed in quarantine (see Appendix 9-1).

- In the event that a participant reports damage or other issues or problems with her study product — other than signs, symptoms, or other adverse events associated with product use — clinic staff should refer the participant to the PoR to further discuss and evaluate her report or concerns. In this type of event, clinic staff should not inspect study product in any way and under no circumstances should clinic staff dispense gel from any applicators. The first dose (Day 0) and the seventh dose (Day 6) will be administered by the IoR or authorized clinician at the site. Clinic staff may address questions or concerns regarding the study product during but not limited to these administrations. Clinic staff should also contact the PoR if they experience any issues or problems with the product during these observed administrations.

- If study product is damaged or requires the PoR to evaluate the participant's report, the PoR will collect the damaged supplies from the participant (if she has brought them with her). If the PoR identifies problems with the participant's applicators or gel, the PoR will immediately inform the DAIDS Protocol Pharmacist of the problem and take action per instructions received from the DAIDS Protocol Pharmacist. The DAIDS Protocol Pharmacist will inform the Pharmaceutical Co-Sponsors, MTN Pharmacist, MTN CORE (FHI) Clinical Research Managers, and SDMC Project Managers of the occurrence.

If the PoR has an interaction with a participant regarding study product s/he will document his/her interactions with participants, and any subsequent action taken, in signed and dated detailed notes that are retained in participant-specific pharmacy files. The PoR will forward copies of written documentation, containing no randomization assignment information, to clinic staff to provide information about the participant's report and resolution. Any issues requiring further interventions to reach resolution also should be communicated in writing to clinic staff.

If the PoR dispenses replacement study product supplies to a participant, the PoR will request that clinic staff provide a prescription in order to replace the unusable/damaged applicators. The pharmacist should refer to the participant's dispensing record and original prescription to confirm the correct replacement product.

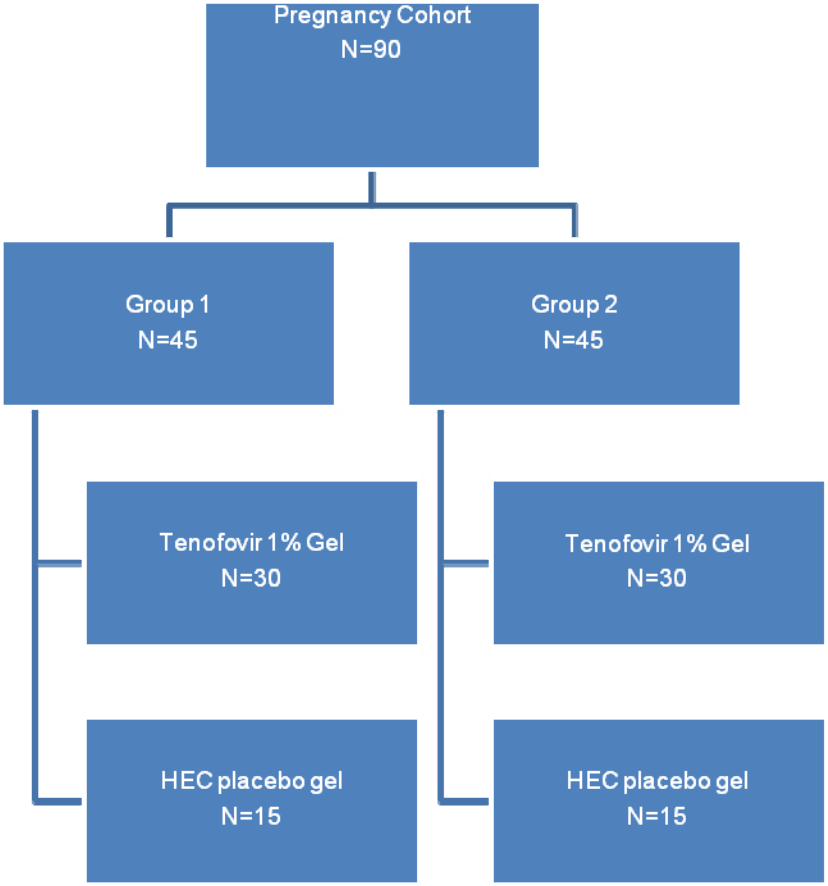
- Blinding will be maintained throughout the study, until all study endpoint data have been verified and are ready for final analysis. There are no circumstances under which it is expected that unblinding will be necessary to protect the safety of study participants. In the event that study staff become concerned that a participant may be put at undue risk by continuing use of her gel, the IoR may hold or discontinue product use by the participant; however, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment. If an IoR feels that product-specific information is necessary to protect participant safety, he/she should notify the MTN-008 Protocol Safety Review Team (PSRT).

9.2 Study Product Regimens

Participants in the Pregnancy Cohort will be divided into Group 1 or Group 2 based on gestational age. As shown in Figure 9-1, study participants in the Pregnancy Cohort will be randomized to one of two blinded study regimens and will receive either tenofovir 1% gel or placebo gel in a 2:1 ratio. Each participant will receive the contents of one applicator of tenofovir 1% gel or placebo gel vaginally for 7 consecutive days.

Each mother in the lactation cohort will receive the contents of one applicator of tenofovir 1% gel vaginally for 7 consecutive days.

Figure 9-1
MTN-008 Participant Randomization Scheme



9.3 Gel Use Instructions

The first dose (Day 0) and the seventh dose (Day 6) will be administered by the IoR or authorized clinician at the study site. Participants will insert the contents of one applicator at home on Days 1-5. Participants will be instructed to insert their gel at approximately the same time every day. If a daily dose is missed, the participant will be instructed to administer the missed dose as soon as possible, unless the next dose is due within 6 hours, in which case participants will be instructed to skip the missed dose and to take the next dose as originally scheduled.

9.4 Dispensing Study Products During On-Site Visits

Please refer to Sections 4 and 6 of this manual for further information on procedures for participant randomization and for initial ordering and dispensation of study products for enrolled participants. Instructions for completing MTN-008 Prescriptions are provided in those sections.

At the Day 0 Visit, upon receipt of a completed and signed MTN-008 Prescription, pharmacy staff will dispense study product for participants per instructions in the MTN-008 Pharmacist Study Product Management Procedures Manual. On Day 0 participants will receive 7 pre-filled individually wrapped applicators of vaginal gel. One of these applicators will be administered on Day 0 at the clinic. The participant will take home 6 applicators. One applicator will be administered daily (Days 1-5). Participants will have one extra applicator at home should one of the doses become unusable for any reason. The applicators will be dispensed in a bag or other container which the PoR will label in accordance with US and local requirements. Labeling will include the PTID of the participant for whom the products were prepared. Upon receipt of the MTN-008 Study Product Return Documentation form the pharmacist will dispense one additional applicator on Day 6.This dose will be administered by the IoR or designated clinician.

Participant-specific study product may be dispensed directly to participants or to authorized clinic staff who will deliver the applicators to the participant.

9.5 Return of Unused Study Gel Supplies

If study staff determines that study gel will not be administered to the participant on the scheduled day, and study product already has been retrieved from pharmacy, it must be returned to the pharmacy as soon as possible.

- Participants will be instructed to bring all unused study product to the Day 6 visit. The clinic staff will count and document the returned unused study product on the Study Product Returns case report form as well as Study Product Return Documentation Form (Appendix 1). The top white copy of the Study Product Documentation Return Form must be sent to the pharmacy with the returned unused product. The yellow copy of this form should be retained in the participant's study record.

- It is anticipated that most participants will have one unused applicator to return. If a participant returns with no study product or more than one study applicator, detailed notes documenting the discrepancy should be included on the Study Product Return Documentation Form.

- Because participants are instructed to bring all unused study product to the Final Visit, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur either by the participant returning the product to study staff or by study staff conducting outreach to retrieve the product from the participant (e.g., at home).

If a participant does not return remaining unused product (in most cases this will be one applicator) on the day of the Final Clinic Visit, the remaining product should be retrieved within two business days. If the product is not retrieved within two business days, clinic staff must inform the PSRT.

If study product is returned following the Day 6 visit, the MTN-008 Study Product Return Documentation form must be accurately updated. This documentation should be recorded on the original white (pharmacy) form and the yellow (clinic (copy), both must be identical. The clinic staff is therefore required to bring the yellow copy to the pharmacy when returning the product. The white copy should be placed over the yellow and the note written and dated and then initialed by both the clinic staff and the pharmacist. The clinic (yellow) copy should be returned to the participant file and the white copy will remain in the pharmacy participant binder.

9.6 Instructions for Insertion of Study Gel for the Participant

Detailed instructions for insertion of study gel are listed in Figure 9-2 below and Appendix 9-2. For further reference, a listing of frequently asked questions related to product use, and answers to these questions, is provided in Appendix 9-3.

Appendix 9-1 MTN-008 STUDY PRODUCT RETURN DOCUMENTATION

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:	**Pitt CRS**	**DAIDS Site ID:**	**1001**
CRS Location:	**Pittsburgh, Pennsylvania**		

Clinic Randomization Envelope #:	

Participant ID: ☐☐☐–☐☐☐☐–☐–☐

Form Completion Date: ☐☐–☐☐☐–☐☐
dd *MMM* *vv*

Number of *unused* applicators returned: ☐
enter "0" if no unused applicators were returned

Clinic staff comments:

_____

_____

_____

_____

_____

_____

_____

Clinic Staff Initials: _____

_____

Pharmacy Staff Initials:

(Pharmacy copy only)

Figure 9-2

Gel Administration Instructions for MTN-008

Removing the Applicator:

- Tear open the wrapper
- Remove the applicator

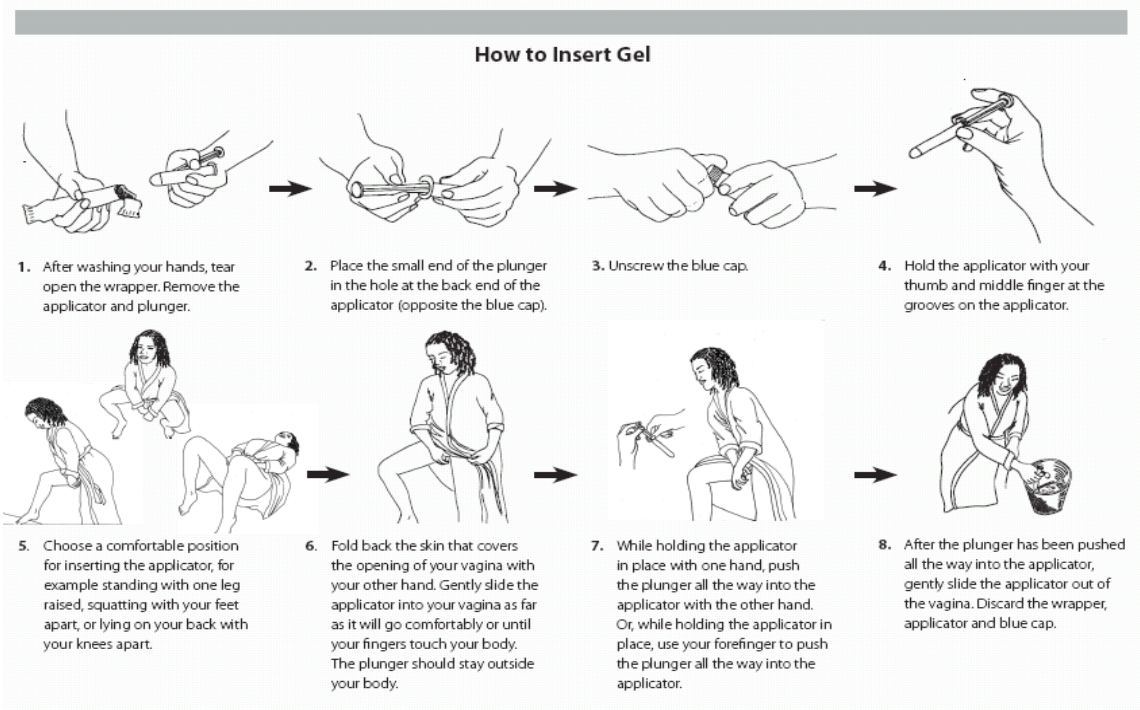
Inserting the Applicator:

- Hold the applicator containing MTN-008 study gel about half-way along the barrel
- Gently insert the applicator into the vagina as far as it will comfortably go
- Slowly press the plunger until it stops to deposit the gel into the vagina
- Withdraw the applicator from the vagina

Disposing the Applicator

- Discard the used applicator, plastic wrapper, and cap in accordance with applicable hospital policies.
- Do NOT return used applicators to the pharmacy

Appendix 9-2 Gel Use Instructions



Appendix 9.3 Product-Related Scenarios

9.3.1: What if the research study staff and/or authorized clinician think there is something wrong with the applicator?

A: If there seems to be something wrong with an applicator (for example, it is difficult to push the study gel out of the applicator, if study gel has leaked out, if the applicator appears to be empty or there is some other problem), do not use the applicator and notify the pharmacy. The unused applicator should be returned to the pharmacy when and if a new applicator is dispensed. The DAIDS Protocol Pharmacist should be notified as soon as possible by the Pharmacist of Record.

9.3.2: What is the best position to insert the gel?

A: Any position that is comfortable can be used to insert the gel. The positions that are recommended include sitting, standing, and lying down.

9.3.3: What should I do if it hurts when I use the applicator to insert the gel?

A: Inserting the gel should not be painful. If you have pain when inserting the gel, try another position (sitting, standing, or lying down). If you still have pain in the new position, perhaps you need to change the angle of the applicator. The applicator should be angled slightly upward, towards your back, when you insert it. If you try to change the angle, and you still feel pain on insertion, please contact the study clinic.

9.3.4: Where does the gel go to after I put it inside?

A: The gel will come out of the vagina (through the same opening where it was inserted) over the next day. Sometimes when the gel comes out it looks clear. Sometimes it has a white color, and sometimes it has white clumps. This has been seen in other studies of the gels and it is normal. It is not normal to see a yellow or green discharge from the vagina, or a discharge with a bad odor, or with pain or itching. If this happens, it could mean you have an infection, in which case you should contact the study clinic.

9.3.5: Can the applicator get lost inside me?

A: No, the applicator cannot get lost inside you. When you use the applicator, hold it with your fingers about half-way along the barrel, and insert it until your fingers touch your body. Half of the barrel of the applicator should go inside your body. The other half should stay outside the body.

9.3.6: What should I do if I have trouble applying the gel with the applicator?

A: The applicators should be easy to use. If you have difficulty using the applicators, please contact the study clinic, as the clinic staff may be able to show you different ways that you can insert the gel, which might make it easier.

9.3.7: What happens if I press the plunger too early and most of the gel comes out on my outside? Can I put more in?

A: Yes. If most of the gel comes out on your outside, discard that applicator and use a new applicator to insert another dose of gel.

9.3.8: If I have my period, should I use the gel?

A: Yes. You should use the gel daily, even during your period.

9.3.9: What happens if the applicators get wet before I use them?

A: If only the wrapper gets wet, the applicator can still be used. Dry the wrapper off before taking out the applicator. If the applicator itself gets wet, it should not be used, but this might only happen if the wrapper is already open.

9.3.10: What should I do if the wrapper is already open when I want to use the gel?

A: You should only use applicators with sealed wrappers, so you should always open the wrapper right before inserting the gel. If you notice an applicator with a wrapper that is not sealed, do not use that applicator. Use a different applicator with a sealed wrapper instead. Discard the applicator with the open wrapper. When you return for the next scheduled visit and you should inform the study staff of any applicators you had to discard because the wrapper was not sealed. If you find that more than one wrapper is not sealed, please contact the clinic immediately to discuss obtaining a resupply of study product.

9.3.11: What should I do if I forget to use the gel?

A: If you miss a dose you should insert the missed dose as soon as possible, unless the next dose is estimated to be due within 6 hours. If the next dose is estimated to be due within six hours, you should skip the missed dose. The next dose should be inserted as originally scheduled.

9.3.12: Will the gel affect my partner's ability to father children?

A: No. The ingredients in the gel are not known to have any effect on male fertility.

9.3.13: What should I do if my partner has a reaction to the gel?

A: Contact the study clinic and ask their advice. They might ask your partner to go to the clinic to be assessed and receive treatment if needed.

9.3.14: What should I do if I have a reaction to the gel (e.g., unusual itching, stinging)?

A: Contact the study clinic.

9.3.15: Can I have sex straight away after inserting gel, or do I need to wait?

A: You don't need to wait to have sex after inserting gel.

9.3.16: Does it matter what brand condoms we use?

A: Ideally, you should use the condoms given to you by the study clinic staff. However, if you do not have one of those condoms, and you have a different condom, use that condom. Condoms are the only known way to protect against HIV and other sexually transmitted diseases (STDs), so it is always better to use any condom (even if it was not given to you by the study) than to use no condom.

9.3.17: What should I do if the gel leaks out?

A: It is likely that some gel will leak out. This is normal and you don't need to do anything about it. You should always apply the full amount contained in the applicator. It may be helpful to wipe yourself on the outside with a dry cloth/tissue if you have been standing for a minute or two after you applied the gel, if you find that a small amount leaks out. The study staff will give you panty liners to help catch the gel if it leaks out.

9.3.18: Can my partner insert the gel for me?

A: It is preferable that you insert the gel yourself, but if you are happy that your partner knows how to do it in a way that won't cause you discomfort, then this is acceptable. It is better for your partner to insert the gel for you than not to use the gel at all.

9.3.19: Can I continue to take my birth control pills?.

A: You are requested as part of this study to continue your oral contraception as discussed with the study staff.