

Section 9. Study Product Considerations for Non-Pharmacy Staff

This section provides information and instructions for non-pharmacy staff related to the request, transport, and delivery of MTN 001 study products for study participants. Record keeping requirements for non-pharmacy staff also are provided. Associated instructions for pharmacy staff are provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks*, which will be made available to each study site Pharmacist of Record (PoR) by the DAIDS PAB Protocol Pharmacist. Please also refer to related information in Sections 4 and 6 of this manual.

9.1 Gel Use Instructions

During the 6-week gel only period, or dual use period, participants will be instructed to insert the gel — the entire contents of one applicator — into the vagina, once daily.

Vaginal administration of the study gel should occur before bedtime, or the longest period of rest. If a participant misses a dose, she must insert vaginally the missed dose as soon as possible, unless the next dose is estimated to be due within six hours. If the next dose is estimated to be due within six hours, the missed dose must be skipped. The next dose will be inserted vaginally as originally scheduled.

Detailed instructions for application of gel are listed in Figure 9-1 below. A listing of frequently asked gel use questions, and answers to these questions, is provided in Section Appendix 9-1.

Figure 9-1
Gel Use Instructions for MTN 001

Removing the Applicator: <ul style="list-style-type: none">• Tear open the opaque, plastic wrapper• Remove applicator from wrapper
Inserting the Applicator: <ul style="list-style-type: none">• Choose a comfortable position to insert the applicator, for example lying on your back with your knees bent or standing up with one leg raised and resting on an object• Hold the filled applicator about half-way along the barrel• Gently insert the filled 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 <p><i>* Note: Study Staff should inform participants that they may experience some minor gel leakage from the vagina, when inserting the filled applicator into the vagina</i></p>
Follow up Information: <ul style="list-style-type: none">• Dispose of the <i>used</i> applicator and plastic wrapper. If you can not dispose of your study supplies at your home or off site, you can bring your used applicators to the study clinic for disposal in accordance with applicable biowaste requirements (See SSP Section 9.5.2)• Bring all of your <i>unused</i> study gel tubes to your next visit

9.2 Tablet Use Instructions

During the 6-week tablet only period or dual use period, participants will be instructed to take one tenofovir disoproxil fumarate 300 mg tablet, by mouth, once daily for the six-week tablet only period and the six-week dual use period.

If a participant misses a dose, she must take 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, the missed dose must be skipped. The next dose will be taken orally as originally scheduled.

In the dual use period, both the pill and gel should be administered at approximately the same time, before the longest period of rest.

9.3 Observed dose of study product at End of Study Period Visits

Study staff will observe a single dose of study gel, tablet, or both gel and tablet, for participants at their End of Study Period Visits, to assess Pharmacokinetic measures. Each clinic will determine the appropriate method for the observation of the gel insertion. It is acceptable if the participant is given some privacy by placing a curtain between the study staff and the participant during gel insertion. When privacy is given, the study staff needs to ensure that the gel has been vaginally inserted. Please also refer additional information in Sections 6 and 7 of this manual. Study staff may permit participants to administer the gel dose behind a curtain while they remain in the exam room with the participant. Following the gel dose insertion, participants will be instructed to ambulate prior to conducting PK procedures, but taking into consideration the required timeframe between product use and PK procedures.

9.4 Distributing Study Product During Visits

Upon receipt of a completed and signed MTN 001 Prescription, or a completed and signed MTN 001 Study Product Re-Supply Slip (during mid-period visits), pharmacy staff will dispense product supplies for study participants as per the DAIDS Pharmacy Guidelines. Study gel cartons will be sealed with tamper-evident tape and labeled by the PoR in accordance with local requirements. In all cases, labeling will include the PTID of the participant for whom the supplies have been prepared and to whom they should be dispensed/delivered.

Participant-specific study product supplies may be dispensed to participants in one of three ways:

- From the pharmacy directly to the participant
- From the pharmacy to authorized clinic staff who will then deliver the study product to the participant
- From the pharmacy to authorized transport staff (or “runners”) who will transfer the study product to authorized clinic staff who will then deliver the study product to the participant

Each study site must designate its dispensing method in MTN 001 standard operating procedures (SOPs) for participant randomization and product re-supply during follow-up. These SOPs should be developed with input from both pharmacy and clinic staff. Further information is provided in Sections 9.4.1-9.4.3 below.

9.4.1 Dispensing from the Pharmacy Directly to Participants

At sites choosing to dispense study product directly from the pharmacy to participants, prescriptions and study product re-supply slips are expected to be delivered to the pharmacy by the participants themselves, although this may be done by clinic staff or a runner. Upon receipt of a completed and signed prescription or study product re-supply slip, the PoR will prepare either two cartons of study gel (14 pre-filled applicators per carton) and/or one bottle of 30 tenofovir disoproxil fumarate tablets entered on the prescription or study product re-supply slip. Study product supplies may be prepared based on either original documents or faxed copies, but product will not be released to participants until the original prescription or request slip is received.

9.4.2 Dispensing from the Pharmacy to Clinic Staff

At sites choosing to dispense study product to clinic staff who will then deliver the product to participants, prescriptions and study product re-supply slips are expected to be delivered to the pharmacy by clinic staff or a runner. Upon receipt of a completed and signed prescription or study product re-supply slips, the PoR will prepare the study product entered on the prescription or re-supply slip. Study product may be prepared based on either original documents or faxed copies, but product will not be released to clinic staff until the original prescription or re-supply slip is received.

The MTN 001 Record of Receipt of Participant-Specific Study Product for Clinic Staff (see Section Appendix 9-2) must be used to document dispensing of participant-specific study product to clinic staff. Pharmacy staff will complete the top section (site name and site number,) and the first five columns on the Record of Receipt. When receiving study product from the pharmacy, clinic staff will verify the PTIDs, confirm the amount of product received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

Clinic staff are responsible for controlling access to the study product dispensed into their custody and ensuring that the product is delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of the study product to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that study product dispensed for a participant is not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining product to the pharmacy as soon as the participant's visit is completed.

9.4.3 Dispensing from the Pharmacy to Runners for Further Transfer to Clinic Staff

At sites choosing to dispense study product to runners who will transfer the product to clinic staff for subsequent delivery to participants, prescriptions and study product re-supply slips are expected to be delivered to the pharmacy by a runner. Upon receipt of a completed and signed prescription or product request slip, the PoR will prepare the number of participant-specific study product entered on the prescription or study product re-supply slip. Study product may be prepared based on either original documents or faxed copies, but product will not be released to a runner until the original prescription or study product re-supply slip is received.

The MTN 001 Record of Receipt of Participant-Specific Study Product for Runners (see Section Appendix 9-3) must be used to document dispensing of participant-specific study product to runners and transfers of the product to the clinic staff.

Pharmacy staff will complete the top section (site name and site number) and the first five columns on the Record of Receipt. When receiving study product from the pharmacy, runners will verify the PTIDs, confirm the amount of study product received for each PTID, and complete the remaining three columns on the Record of Receipt for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the record. All Records of Receipt will be retained in the pharmacy.

At the beginning of each work day, runners will complete the top section (site name, site number, clinic name, date) of their Daily Runner Logs. When receiving study product from the pharmacy, in addition to completing the Record of Receipt for each PTID, runners will complete the first four columns on the Daily Runner Log for each PTID.

Runners are expected to deliver participant-specific study product to authorized clinic staff directly after collecting the product from the pharmacy. Runners must control access to the product dispensed into their custody and deliver the product only to authorized clinic staff. Runners also must retain and control access to their Daily Runner Logs until the logs are returned to the pharmacy, at which time pharmacy staff assume responsibility for the logs. If completed logs are not returned to the pharmacy by the end of each work day, the PoR will notify appropriate clinic or pharmacy supervisory staff (per site SOPs) to ensure timely recovery of the logs. If completed logs are not recovered and delivered to the pharmacy within five calendar days, the PoR will notify the DAIDS PAB Protocol Pharmacist.

When receiving study product from runners, clinic staff will verify the PTIDs, confirm the amount of product received for each PTID, and complete the remaining two columns on the Daily Runner Log for each PTID. Comments may be recorded in the designated column and, if additional space is needed, on the back of the log.

Clinic staff are responsible for controlling access to the study product transferred into their custody, ensuring that the product is stored appropriately while in their custody, and ensuring that the product is delivered to the participants for whom they were dispensed. Clinic staff also must document delivery of study product to designated participants in the participants' study charts. Delivery may be documented in chart notes, on visit checklists, or on other source documents designated for this purpose by clinic staff. In the event that study product dispensed for a participant is not delivered to the participant, clinic staff will document this in the participant's study chart and return the remaining product to the pharmacy as soon as possible after the participant's visit is completed.

9.5 Return of Study Product Supplies

Study participants will be instructed to return all unused study products to the site at each scheduled study visit. Study staff will be required to collect unused product at the Mid-Study Period and End of Study Period Visits. The unused study product collected at these scheduled visits will not be reissued to the participants. New prescriptions must be completed and additional study product will be dispensed. As indicated, study staff will collect unused products at all other unscheduled visits. If the participant is going to continue the study, the study product may be returned to the participant at the unscheduled visit. In the event that unused study products are not returned at the end of each study period visit, study staff members will make every effort to encourage participants to return study product as soon as possible.

9.5.1 Unused Product Supplies

Participants who are permanently discontinued from study product use will be instructed to return all unused study product to the site. The PoR will store returned unused study products in designated areas within the study pharmacy

In the event that a participant becomes infected with HIV, or has a severe (Grade 3 or higher) renal or hepatic toxicity, every effort should be made to collect unused applicators or tablets remaining in her possession within 24 hours. In the event that a participant becomes pregnant, infected with Hepatitis B, or experiences an adverse event that requires permanent discontinuation of gel or tablet use (per protocol Section 9), any unused pre-filled applicators or tablets remaining in her possession should be collected from her as soon as possible, within five working days, and returned to the pharmacy on the day of collection. It is not necessary to collect remaining study product from participants for whom product use is temporarily held. However, study product must be collected from such participants within five working days, to protect their safety, if it is suspected that the participant may not comply with clinic staff instructions to refrain from product use for the duration of the temporary hold.

In the event that an issue or problem is identified that would necessitate collection of unused product from all participants, detailed instructions for collection and handling of the study product, and documentation thereof, will be provided in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* and from the DAIDS PAB Protocol Pharmacist. Other associated operational and/or data collection instructions also may be provided by the MTN CORE and/or MTN SDMC. Clinic and pharmacy staff will follow all such instructions.

Finally, any unused product remaining in a participant's possession at the time of study exit must be collected from the participant and returned to the pharmacy on the day of collection. When planning and scheduling study exit visits, clinic staff should instruct participants to bring all remaining unused product to their exit visits. For participants who do not bring their remaining product to their exit visits, arrangements should be made to collect the product as soon as possible and document all such efforts in the participants' study charts. For participants for whom all reasonable efforts fail, guidance should be sought from the MTN 001 PSRT.

Unused study product collected from participants for any reason should be returned to the pharmacy on the day of collection. When study product is collected by clinic staff, the staff may return the collected applicators or tablets to the pharmacy themselves or, if product runners are utilized at the site, clinic staff may transfer the collected product to a runner for return to the pharmacy. In such cases, the MTN 001 Daily Runner Log should be used to document transfer of the collected study product into the custody of the runners and subsequent return to the pharmacy, with notations in the “comments” column of the log indicating that the study product is being returned by, rather than received by, clinic staff.

9.5.2 Used Gel Supplies

Participants will be instructed to dispose of used applicators off-site (e.g., at their homes) whenever possible and allowed per local biowaste requirements. When this is not possible or allowed, participants may return their used applicators to the study clinic for disposal in accordance with applicable biowaste requirements. Clinic staff should provide participants with plastic bags or other suitable containers in which to store their used applicators between visits. Clinic staff also may wish to consider installing easily accessible biowaste containers near the clinic doorway and/or in other common areas within the clinic. Clinic staff should not return used applicators to the pharmacy.

Section Appendix 9-1
Frequently Asked Gel Use Questions

Q1: 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.

Q2: 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.

Q3: 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.

Q4: 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.

Q5: 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.

Q6: What should I do if I think there is something wrong with an applicator or its gel?

A: If an applicator does not seem to be working properly (for example, you find it difficult to push the gel out of the applicator, or if gel has leaked out, or you think there is some other problem), do not use the applicator. Use another applicator instead. Keep the applicator that had something wrong and bring it to the study pharmacy at your next study visit. If you think that something is wrong with all of your applicators, contact the study staff as soon as possible (i.e., do not wait until your next visit) so the staff can make sure you have enough working applicators to use for the study period.

Q7: 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.

Q8: If I have my period, should I use the gel?

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

Q9: Can I use tampons at the same time as the gel?

A: You can use tampons while taking part in this study. If you use tampons, you should take out the tampon when you insert the gel, and put another tampon in an hour after you inserted the gel.

Q10: What if I have bleeding between periods?

A: Please contact the study clinic.

Q11: How do I store the gel?

A: Store the gel in a cool, dry place.

Q12: 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.

Q13: 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 they return for the next scheduled visit and they should inform the study staff of any applicators they had to discard because they were not sealed.

Q14: What should I do if I forget to use the gel?

A: If you miss a dose (gel or tablet), 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 will be inserted as originally scheduled.

Q15: Is the gel contraceptive?

A: The study gel is not a way to prevent pregnancy. If you wish to avoid pregnancy, you should use known reliable methods of contraception (such as tablets, and injections) while you are in this study.

Q16: 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.

Q17: 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.

Q18: What should I do if I have a reaction to the gel (e.g., unusual itching, stinging)?

A: Contact the study clinic.

Q19: What should I do if I think I am pregnant?

A: Contact the study clinic immediately. The clinic staff will give you a pregnancy test to find out if you are pregnant or not.

Q20: 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.

Q21: 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.

Q22: 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 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.

Q23: Can I use herbs or other substances for tight or dry sex while I am using the gel?

A: Herbs or other substances could damage the inside of the vagina. These substances also could interfere with the study gels. Therefore we recommend that you do not use herbs or other substances in the vagina. If you feel you must use these substances, please do not use them from one hour before you insert the gel. This will help make sure the substances do not interfere with the gel.

Q24: 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 to not use the gel at all.

Q25: Will I have access to the gel if it is shown to be effective?

A: If the gel is shown to be safe and effective, it will take some time for the gel to be allowed to be sold in the shops, but we will try to make sure this happens as quickly as possible.

Q26: What happens if I spill my tablets accidentally?

A: If any of the tablets become lost or unusable before the next scheduled visit, inform the clinic staff immediately so that they make arrangements for replacement tablets to be dispensed.

Q27: Do I need to eat before taking my tablets?

A: No, you may take the tablet with or without a meal.

Q28: What if I throw up immediately after taking a tablet?

A: If you throw up immediately after taking your tablet, wait approximately 30 minutes and take another tablet. If you throw up again, skip the dose until the next scheduled does.

Q29: What if I have trouble swallowing the tablet?

A: If you have trouble swallowing the pill, take a sip of water and relax. Place the pill on the back of your tongue and swallow with water. You may try drinking the water with a straw as this may help to swallow the tablet.

Q30: What if I forget to take the tablet?

A: If you forget to take your tablet, take the missed dose as soon as possible unless the next dose is due within 6 hours. If the next dose is due within 6 hours, the missed dose will be skipped and the next dose will be administered as originally scheduled.

Q31: What if I am taking oral contraception?

A: You may continue your oral contraception.

Q32: What are the side effects?

A: The most common side effects are: diarrhea, nausea, vomiting and intestinal gas. Other side effects that have been reported include: weakness, low phosphate, dizziness, shortness of breath, and rash.

