Section 6. Study Product Considerations

6. Introduction

This section provides information and instructions for non-pharmacy staff related to the ordering, transport, delivery and administration of MTN-035 study product for study participants. Associated instructions for pharmacy staff are provided in the MTN-035 Pharmacist Study Product Management Procedures Manual, which will be made available to each site Pharmacist of Record (PoR) by the MTN LOC Pharmacist.

6.1 Study Product Regimens

Each study participant will be randomized to one of six study product administration sequences (Sequence A-F). Each sequence will consist of three four-week periods of study product administration, with one week between each four-week period. The total duration of product administration, including the two washout periods, is approximately 14 weeks. Each participant will receive study product that includes pericoital rectal administration of placebo inserts, placebo suppositories, and placebo (water) douches.

Figure 6-1 Study Regimen Sequences

Sequence	N	Period 1 (4 weeks)	Washout period (~1 week)	Period 2 (4 weeks)	Washout period (~1 week)	Period 3 (4 weeks)
A	35	Rectal insert	--	Rectal douche	--	Rectal suppository
B	35	Rectal douche	--	Rectal suppository	--	Rectal insert
C	35	Rectal suppository	--	Rectal insert	--	Rectal douche
D	35	Rectal insert	--	Rectal suppository	--	Rectal douche
E	35	Rectal douche	--	Rectal insert	--	Rectal suppository
F	35	Rectal suppository	--	Rectal douche	--	Rectal insert

As shown in Figure 6-1, study participants will be randomly assigned in equal numbers to one of six study regimen sequences.

6.2 Study Product Use Instructions

6.2.1 Placebo Rectal Inserts

During the rectal insert period of the study, participants will be instructed to place a single insert into the rectum prior to receptive anal intercourse (RAI). If a participant misses a dose, s/he must wait until the next RAI occurrence. If no other RAI activity occurs in that 7-day period, a dose should be inserted in the absence of RAI. If there is no RAI activity at all in a given 7-day period, participants should insert a dose on the seventh day. The pharmacist will provide lubricant with the inserts at dispensing, for ease of insertion.

Detailed product use instructions for the rectal insert can be found on the MTN-035 website.

6.2.2 Placebo Rectal Douche

During the placebo rectal douche period of the study, participants will be instructed to insert into the rectum the contents of a single water-filled enema bottle prior to RAI. If a participant misses a dose, s/he must wait to take a dose at the next occurrence of RAI, or if no other RAI activity occurs in that 7-day period, to take a dose in the absence of RAI. Furthermore, if no RAI activity occurs at all in a given 7-day period, participants will be instructed to take a dose on the seventh day in the absence of RAI.

Participants may use tap water for enema preparation. If the participant does not have access to an adequate water supply, the site will provide bottled water, if requested.

Detailed product use instructions for the rectal douche can be found on the MTN-035 website.

6.2.3 Placebo Rectal Suppositories

During the placebo rectal suppository period of the study, participants will be instructed to place a single suppository into the rectum prior to RAI. If a participant misses a dose, s/he must wait until the next RAI occurrence. If no other RAI activity occurs in that 7-day period, a dose should be inserted in the absence of RAI. The pharmacist will provide lubricant with the suppositories at dispensing, for ease of insertion.

Detailed product use instructions for the rectal suppository can be found on the MTN-035 website.

6.2.4 Study Product Concerns

Participants should be instructed to inform study staff of any problems or concerns regarding any of the study products. This includes (but is not limited to) a broken insert or suppository or issue with the douche bottle and/or tip. The product concern should be brought to the clinic at the next scheduled visit.

Clinic staff must notify the site pharmacist of any product-related issue(s) that a participant has brought to their attention. The returned product (if unused) or a photo should be provided to the pharmacist whenever possible. The pharmacist will relay the reported information to the MTN LOC Pharmacist for investigation.

6.3 Prescriptions and Dispensing Study Products at Initial Period Visits

The MTN Statistical and Data Management Center (SDMC) will generate and maintain the study randomization scheme. As shown in Figure 6-1, study participants will be randomly assigned in equal numbers to one of six product regimen sequences.

Study product sequence randomization will occur via the Medidata web-based system, as described in SSP Section 12 (Data Collection). After clinic staff have randomized a participant, they will need to view the participant randomization indicated on the Enrollment CRF in the Medidata Rave clinical database to determine the study product sequence assignment. Clinic staff must indicate the study product sequence (A-F) on the MTN-035 Prescription. Clinic staff will complete a study prescription and send the original part to designated site pharmacy staff, as described below, to notify the site pharmacist that the participant has been randomized and needs to be dispensed a study product.

There is only one prescription for all of the products in the study and this prescription is completed at the beginning of each product use period (Enrollment and Product Switch Visits /Visits 4 and 6). Each prescription is sufficient to allow for product dispensing for the entire period of the given study product regimen.

The completed prescription includes PTID; verification of signed informed consent; indication of the applicable product sequence, period and product; printed name and signature of the authorized prescriber and signature date. If corrections are needed, the same corrections must be made separately on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections should also be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.4 Study Product Request Slip

The MTN-035 Study Product Request Slip is used by clinic staff to communicate to the study pharmacist the quantity of study product to be re-supplied, as well as clinic staff decisions to hold, discontinue, or resume study product use (Appendix 6-2). The form will also be used to communicate to the pharmacist if a participant chooses to stop using study product and/or terminate early from the study. The slip will be produced as two-part no carbon required (NCR) sheets. Bulk supplies of the slips are available from the MTN Pharmacist and will be supplied to clinic staff throughout the course of the study. Clinic staff will record the PTID on the top of the form. When the form is used to request study product, the clinic staff name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up. Double-check the accuracy of all entries and then separate the two parts of the completed slip. Retain the yellow copy in the participant study notebook and deliver the white original to the pharmacy. If corrections are needed, the same corrections must be made separately on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections should also be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.4.1 Study Product Re-Supply - Dispensing Study Products at Mid-Period Visits

The MTN-035 Study Product Request Slip will be completed by clinic staff to communicate to the study pharmacist the study product and quantity to be re-supplied to a participant as needed during a product use period (and at interim visits, as needed).

Any time additional product is needed (except to resume product use after a clinical product hold), mark the “RE-SUPPLY” box on the MTN-035 Study Product Request Slip. Clinic staff will indicate on the slip the product and quantity of study product to be dispensed by checking one of the following boxes:

- Dispense 20 placebo rectal inserts
- Dispense 20 placebo rectal suppositories
- Dispense _____ empty enema bottles
- Dispense _____ enema tips.

Note: The placebo rectal inserts and suppositories are only dispensed in packages of 20. The specific quantity of enema tips (up to 20 at a time) and bottles (up to 4 at a time) to be resupplied must be specified on the Study Product Request Slip.

6.4.2 Product Hold/Resume

If a study clinician determines that a participant should temporarily hold study product use due to safety reason(s) (e.g., an adverse event), mark the “HOLD” box on the MTN-035 Study Product Request Slip. Record the reason for the hold on the adjacent “Reason” line. It is not necessary to complete any new slips at subsequent visits in which the hold is still in effect. Once a product hold is in effect, the site pharmacist will not dispense any study product to that participant until s/he receives a new request slip from the site clinic marked “RESUME”. Only clinic staff members who are authorized prescribers may mark the “RESUME” box. In all other circumstances, the slips are not required to be signed by an authorized prescriber; however site-specific pharmacy regulations may be more stringent than these requirements. All sites must comply with local and country requirements. The “RESUME” box should only be checked if study product is being ordered and dispensed following a product hold and resumption.

6.4.3 Permanent Discontinuation of Study Product

If a study clinician determines that a participant should permanently discontinue study product use due to safety reason(s) (e.g., grade 3 or higher hepatic toxicity), mark the "PERMANENT DISCONTINUATION" box on the MTN-035 Study Product Request Slip. Record the reason for the permanent discontinuation on the "Reason" line provided. Once a permanent discontinuation is in effect, the site pharmacist will not dispense any further study product for that participant. Future slips will no longer be completed at the participant's remaining study visits.

6.4.4 Participant-Initiated Decline of Study Product

If a participant decides on his/her own to stop using study product, and refuses to be re-supplied with study product, do not mark the "HOLD" box. Instead, mark the "PARTICIPANT DECLINE" box on MTN-035 Study Product Request Slip. Complete the slip and mark "PARTICIPANT DECLINE" at each subsequent Product Switch Visit and during product use periods in which the participant refuses study product. If the participant changes his/her mind and later decides to restart study product use, complete the slip and mark "RE-SUPPLY".

6.4.5 Product Use Period Complete

When a participant has completed the study through their scheduled termination or withdraws from the study early, the box "Product Use Period Complete" should be checked and sent to the pharmacy. This serves as notification to the site pharmacist that the participant will have no further MTN-035 study visits, and thus will not require any additional study product dispensations. Note, staff should not complete a Request Slip with this box marked at each PUEV. If the participant desires to rejoin the study after a voluntary withdrawal, s/he may resume product use if applicable (see SSP Section 5 of this manual for further information).

6.5 Chain of Custody

6.5.1 Dispensing from the Pharmacy to Clinic Staff

Study product will be dispensed from the pharmacy to an authorized clinic staff member who will then deliver it to the participant. Each study site must develop an SOP on product dispensation and re-supply during study follow-up and include information on designating a Chain of Custody (dispensing method) for study product. The SOP should be developed with input from both pharmacy and clinic staff. It must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist.

Prescriptions and Study Product Request Slips should be delivered to the pharmacy by clinic staff or a runner, or faxed, followed by delivery of the original. Upon receipt of a correctly-completed and signed prescription or product request slip, the PoR will prepare the requested product and quantity of study product as documented on the prescription or request slip.

The MTN-035 Record of Receipt of Participant-Specific Study Product must be completed to document dispensation of study product to clinic staff for a given participant. For each Record of Receipt, pharmacy staff will complete the top section (CRS name, DAIDS site ID number, and study product lot number) and the first four columns in the body of the record. When receiving study product from the pharmacy for a participant, clinic staff will verify and record the PTID in the designated column, confirm the quantity of study product dispensed, as documented by the site pharmacist, and complete the remaining three columns in the body of the record. 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 site pharmacy.

Clinic staff are responsible for controlling access to the study products dispensed into their custody and ensuring that the products are delivered to the participant for whom they were dispensed. Clinic staff also must document delivery of the study products to a participant in the participant's study chart. Delivery may be documented in chart notes or on other source documents used for this purpose. In the event that all study products dispensed for a participant are not delivered to the participant, clinic staff will document this in the participant's study chart and return the study products to the pharmacy as soon as the participant's visit is completed, or as soon as clinic staff learn that the participant will not be completing his/her study visit on the scheduled date.

6.6 Unused Study Product Return and Retrieval

For chain of custody and accountability requirements, clinic staff will instruct each participant to bring all of his/her unused study product to the Product Use End Visit (PUEV, visits 3, 5 and 7). If product is not returned at the PUEV, participants should be instructed to return all unused study products prior to the next product use period (i.e. Product Switch Visits (Visits 4 and 6) and/or the Final/Early Termination Visit (Visit 8), or at an interim visit). Clinic staff will collect the unused inserts, suppositories and enema bottles and tips and return them to the pharmacy for quarantine and destruction. Upon the clinic staff returning the unused study product to the pharmacy, both the clinic staff member and the pharmacist will together complete the designated Record of Return of Study Product (Appendix 6-4).

Each time the clinic staff member returns participant unused study product to the pharmacy, s/he will complete the first four columns on the Record of Return including the date, time, PTID, product (insert, suppository, bottle or tip), the quantity returned, and clinic staff initials. When receiving the returned unused study product, the pharmacist will verify the PTID and complete the remaining columns on the Record of Return (date/time returned to the pharmacy and pharmacist initials). Comments may be recorded in the designated space, and if additional space is needed, on the back of the record. All Records of Return of Study Product will be retained in the site pharmacy.

Due to the frequency of routine unused product return, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur either by the participant returning the study product to study staff or by study staff conducting outreach, if permissible per local IRB requirements, to retrieve unused study product from the participant (e.g., at the participant's home).

If a participant does not return remaining unused product on the day of the Final/Early Termination Visit, the remaining product should be retrieved within five working days. All efforts to retrieve remaining study product that has not been returned to the site should be documented in the participant's chart notes. If study product is not retrieved within the specified time frames noted above, this must be documented on the Protocol Deviation Log CRF. If the study product cannot be retrieved by the time the participant is terminated or withdraws from the study, this must be documented on the Protocol Deviation Log CRF. Related details and counseling around the need to ensure return of unused study product should be detailed in chart notes.

Section Appendix 6-1: MTN-035 Prescription

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

Participant ID: ☐☐☐ – ☐☐☐☐☐☐

Did the participant provide written informed consent for enrollment into MTN-035?	Yes ☐	No ☐	Clinic Staff Initials: _____

Sequence (check one):

	Period 1	Period 2	Period 3
☐ **A**	Rectal insert	Rectal douche	Rectal suppository
☐ **B**	Rectal douche	Rectal suppository	Rectal insert
☐ **C**	Rectal suppository	Rectal insert	Rectal douche
☐ **D**	Rectal insert	Rectal suppository	Rectal douche
☐ **E**	Rectal douche	Rectal insert	Rectal suppository
☐ **F**	Rectal suppository	Rectal douche	Rectal insert

Period (check one):

☐ Period 1 ☐ Period 2 ☐ Period 3

Study Product (check one):

☐ Insert ☐ Douche ☐ Suppository

Placebo Rectal Inserts, Suppositories and Enema Bottles/Tips

Sig: Use as directed.

Quantity: Sufficient to last until the end of the study period (as requested by designated clinic staff). May be refilled as needed for the duration of the study period.

MTN-035 Pharmacy Instructions:

Placebo Rectal Insert: Dispense one bottle of 20 inserts.*
Placebo Rectal suppository: Dispense 20 suppositories.*
Rectal Enema Bottles (empty): Dispense 4 empty enema bottles.
Rectal Enema Tips: Dispense 20 enema tips.
*Dispense with lubricant.

Authorized Prescriber Name *(please print)*:_____

Authorized Prescriber Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

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Pharmacy

Section Appendix 6-2: MTN-035 Study Product Request Slip

Participant ID: ☐☐☐ – ☐☐☐☐☐☐

Clinic Staff Instructions: Mark whether this is a re-supply (indicate product), clinical hold, resume (after a clinical hold), participant decline, permanent discontinuation or product use period completion notification. Only an authorized prescriber can indicate product resumption. Deliver the original white copy (labeled "Pharmacy") to the pharmacy. File the yellow copy (labeled "Clinic") in the participant's study notebook.

☐ **RE-SUPPLY** → **Pharmacy: (Check one)**
- ☐ Dispense 20 placebo rectal inserts*
- ☐ Dispense 20 placebo suppositories*
- ☐ Dispense _____ empty enema bottles
- ☐ Dispense _____ enema bottle tips

☐ **HOLD** → **Reason:** _____

Pharmacy: Do not dispense further MTN-035 study product to the participant until another MTN-035 Intravaginal Ring Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy: (Check one)**
- ☐ Dispense 20 placebo rectal inserts*
- ☐ Dispense 20 placebo suppositories*
- ☐ Dispense _____ empty enema bottles
- ☐ Dispense _____ enema bottle tips

☐ **PARTICIPANT DECLINE** → **Pharmacy: Do not** dispense at this visit – participant is refusing MTN-035 study product.

☐ **PERMANENT DISCONTINUATION** → **Reason:** _____

Pharmacy: Do not dispense any further study product to the participant.

☐ **PRODUCT USE PERIOD COMPLETED** → **Pharmacy: Do not** dispense any further study product to the participant.

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

*Dispense lubricant as needed.

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Pharmacy

Section Appendix 6-3: MTN-035 Study Product Record of Receipt

CRS Name:	**CRS ID:**

Instructions: Complete one row each time study product is dispensed to non-pharmacy staff for delivery to a study participant. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

PHARMACY STAFF				**CLINIC STAFF/RUNNER**			
Date/Time Dispensed by Pharmacy dd-MMM-yy (hh:mm) *24-hr clock*	PTID	Product(s) dispensed Incuding quantity	RPh Initials	PTID (Verify PTID)	Date/Time Received by Clinic Staff dd-MMM-yy (hh:mm) *24-hr clock*	Clinic Staff/ Runner Initials	Comments

Section Appendix 6-4: MTN-035 Record of Return of Study Product

CRS Name:	**CRS ID:**

Instructions: Complete one row each time study product is returned by non-pharmacy staff for delivery to the pharmacy. All entries must be made in dark ink. Corrections may be made by drawing a single line through incorrect entries, entering correct information, and initialing and dating the correction.

CLINIC STAFF/RUNNER				**PHARMACY STAFF**			
Date/Time Received by Clinic dd-MMM-yy (hh:mm) *24-hr clock*	PTID	Product(s) returned Including quantity	Clinic staff/runn-er Initials	PTID (Verify PTID)	Date/Time Received by Pharmacy Staff dd-MMM-yy (hh:mm) *24-hr clock*	Pharmacy Staff Initials	Comments

Section Appendix 6-5: Frequently Asked Product Use Questions

Q1. What is the best position to insert the rectal insert or suppository?

Find the position that feels most comfortable. Many people already have a position they prefer (kneeling, squatting, etc.). If you do not have a preferred position, we recommend that you lie on your left side or on your back. See Product Use Instructions.

Q2. What should I do if it hurts when I insert the rectal insert, suppository or douche tip?

Inserting any of the study products should not be painful. If you have pain when inserting one of the products, try another position. The douche tip should be easy to use; the tip is supplied slightly lubricated. The insert and suppository may be lubricated with the lubricant provided by the clinic staff. If you have difficulty using the products, please contact the study clinic, as the clinic staff may be able to show you different ways that you can insert the study product, which might make it easier.

Q3. Where does the study rectal insert or suppository go after I put it inside?

The study insert and suppository stay in the rectum and slowly dissolve.

Q4. What should I do if I think there is something wrong with one of the products?

If there seems to be something wrong (for example, you find it difficult to remove the suppository from the wrapper, or if the study douche bottle leaks, or you think there is some other problem), do not use the product. Use another insert, suppository or bottle supplied by the study instead. Keep the product that had something wrong with it and return it to clinic staff at your next study visit. If you think that something is wrong with the entire supply of one of your products, contact the study staff as soon as possible (i.e., do not wait until your next visit) so that they can make sure you have enough useable product.

Q5. What happens if I drop a product? Can I still use it?

If one of the products falls on the floor or in a place that you can retrieve it and wipe it off, you may use the product or use another insert, suppository or new enema bottle/tip in your current supply. If all of your product is lost or becomes unusable before your next scheduled visit, inform the clinic staff immediately so that they may make arrangements for replacement products to be dispensed.

Q6. How do I store the study products?

Store all the study products in a cool, dry place at room temperature and not in the sun. Keep them out of the reach of children.

Q7. What should I do if I have a reaction to the insert, suppository or douche/tip (e.g., unusual itching, stinging)?

Contact the clinic staff and ask their advice. They might ask you to go to the clinic to be assessed and receive treatment, if needed.

Q8. Does it matter what brand of condoms we use?

Ideally, you should only use the condoms given to you by the clinic staff. However, if you do not have one when needed but you have a different condom, use that one. If you use non-study provided condoms, inform the study clinic staff of the change. It is always important when having anal sex to use condoms that do not contain nonoxynol-9 (N9) lubricant, as this may damage the rectum. Condoms are the only known way to protect against both HIV and other sexually transmitted diseases (STIs), 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.

Q9. What lubricant should I use to insert the products? Can I use herbs or other substances for anal sex while I am using the products?

You will be provided lubricant when you receive the inserts and suppositories. The enema tips are already lubricated. It is recommended that you use the specific study provided lubricant (Good Clean Love) for product administration. If lubricant is desired at other times during the study, you may use your usual practice or request lubricant from the clinic.

Q10. Can my partner insert the study product for me?

It is preferable that you insert the study product yourself, but if you are confident 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 study product for you than to not use the study product at all.

Q11. What if I forget to use the study product?

If you forget to use the product with RAI activity, the dose will just be missed. If no RAI activity occurs at all in a given 7-day period, or if you forget to use the study product prior to RAI, you should take a dose on the seventh day in the absence of RAI.