Section 6. Study Product Considerations for Non-Pharmacy Staff

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6. Introduction

This section provides information and instructions for non-pharmacy staff related to the ordering, transport, delivery and administration of MTN-034 study product for study participants. Associated instructions for pharmacy staff are provided in the MTN-034 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 two sequences of one VR containing 25 mg of dapivirine to be inserted monthly for 24 weeks and one Truvada® (200 mg FTC/300 mg TDF) oral tablet taken daily for 24 weeks. After completing the randomized sequence of two study product use periods, participants will then select one or neither of study products to use in the final 24 weeks of the study. Participants can change their study product choice (either or neither) during the third study product use period.

Table 6-1: Study Product Regimen

	N	Study Product Use Period 1: 24 Weeks	Study Product Use Period 2: 24 Weeks	Study Product Use Period 3: 24 Weeks	Dose, Route and Frequency
Sequence A	150	25 mg dapivirine VR	FTC/TDF oral tablets	Choice of 25 mg dapivirine VR or FTC/TDF oral tablets or neither	One 25 mg dapivirine VR inserted vaginally each month for 24 Weeks → followed by one FTC/TDF oral tablet taken by mouth daily for 24 Weeks → followed by participant's choice of either study product for 24 Weeks
Sequence B	150	FTC/TDF oral tablets	25mg dapivirine VR	Choice of 25 mg dapivirine VR or FTC/TDF oral tablets or neither	One FTC/TDF oral tablet taken by mouth daily for 24 Weeks → followed by one 25 mg dapivirine VR inserted vaginally each month for 24 Weeks → followed by participant's choice of either study product for 24 Weeks

6.2 Randomization Assignment

The MTN SDMC will generate and maintain the study randomization scheme. As shown in Table 6-1, study participants will be randomly assigned in equal numbers to one of two study product sequence regimens. Study sequence randomization will occur via the Medidata web-based system at the Enrollment Visit, as described in Section 12 (Data Collection) of this manual. After clinic staff has randomized a participant, they will need to view the participant randomization via Medidata to determine the product sequence. The product sequence must be completed on the prescription. Clinic staff complete a study prescription and send the original part to designated site pharmacy staff, as described in section 6.3 below, to notify the site pharmacist that the participant has been randomized and needs to be dispensed either a study VR or bottle of tablets.

6.3 Prescriptions and Dispensing Study Products at Initial Product Use Period Visits

One prescription must be completed at the initial visit of each of the three study product use periods (Visits 2, 9 and 16). Both the oral Truvada (FTC 200mg/TDF 300mg) tablet and the dapivirine 25mg VR are listed on the MTN-034 Prescription (Appendix 6-1). The prescription is sufficient to allow for product dispensing for the entire study product use period of the given study product regimen.

The prescription for the oral tablets and the VR indicates that the quantity dispensed at each visit will be sufficient to last until the next study visit. The pharmacist will dispense one bottle of 30 study tablets or 1 VR at the initial visit of the period and then monthly thereafter until the end of the respective study product use period (i.e. five subsequent months).

NOTE: A study prescription is used to communicate the initial dispensation request for each enrolled participant at the initiation of each study product use period (Period 1, 2 and 3), AND for switching between study products during Period 3.

6.3.1 In Clinic Prescription Procedures (C1-C5):

C1. After the participant is randomized (i.e., the Randomization CRF is completed), complete an MTN-034 Prescription per instructions on the prescription. The person who marks the informed consent check box is responsible for confirming the presence of a properly signed/marked and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

C2. The randomized product sequence (Sequence A or Sequence B) and study product use period (1, 2 or 3) must be completed. The box indicating the product to be dispensed must be checked.

C3. The bottom section of the prescription requires authorized prescriber name, signature, and date. This study staff member must be designated in the site's delegation of duties as an authorized prescriber of study product. This person also must be listed as an investigator (either the Investigator of Record or Sub-Investigator) on the current FDA Form 1572. This section requires documenting the assigned sequence and study period and the product to be dispensed.

C4. Double-check the accuracy of all entries and then separate the two parts of the completed prescription. Retain the yellow (clinic) copy in the participant study notebook.

C5. Deliver the white (pharmacy) original prescription to the study pharmacy.

6.3.2 In Pharmacy Prescription Procedures (P1-P2):

P1. Designated site pharmacy staff will receive a Medidata alert via email that a given participant was randomized by the site clinic staff.

P2. Upon receiving the completed MTN-034 Prescription, the pharmacist will review the document for completion and accuracy. If a member of pharmacy staff identifies possible errors on the original prescription, he/she will return the original prescription to clinic staff for clarification(s) or correction(s). If corrections are required, the same corrections must be made on both the white original prescription and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both the white and yellow sheets. The same corrections and notes should be recorded on both the white original and yellow copy, on the same date, by the same person. Corrections to original study prescriptions should only be made by an authorized prescriber and fully documented in the participant's chart notes.

P3. Following review of the signed MTN-034 Prescription, pharmacy staff will complete the Pharmacy Dispensation CRF and will dispense the study VR or the Truvada tablets to clinic staff for participant use per instructions in the MTN-034 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy SOP(s).

6.4 Study Product Request Slip

The MTN-034 Study Product Request Slip is used by clinic staff to communicate to the study pharmacist the study product and quantity to be re-supplied, as well as clinic staff decisions to hold, resume, or permanently discontinue study product use (Appendix 6-2). The request slip will also be used to communicate to the pharmacist if a participant declines study product, terminates early from the study, or completes study product use. The slip will be produced as a two-part no carbon required (NCR) document. 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 complete the Request Slip per instructions on the slip. 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. When the request slip is used to request product for "RESUME" after a hold is resolved, the form MUST be signed by an authorized prescriber. It is anticipated that "RESUME" is only indicated following a "HOLD".

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 also should be recorded on both sheets. Identical corrections and notes should be recorded on both copies, on the same date, by the same person.

6.5 Study Product Re-Supply - Dispensing Study Products at follow-up Visits

The MTN-034 Study Product Request Slip (Appendix 6-2) will be used by clinic staff to communicate to the study pharmacist the study product (dapivirine VR or bottle of Truvada tablets) and the quantity to be re-supplied to each participant at each monthly visit or as needed. At visits, and any time additional product is needed (except to resume product use after a clinical product hold), mark the "RE-SUPPLY" box on the MTN-034 Study Product Request Slip. It is anticipated that when the request slip is used to resupply product at the scheduled follow-up visits, clinic staff will order a quantity of one VR or one bottle of 30 Truvada tablets. Clinic staff will indicate on the slip the type and amount of study product to be dispensed by indicating the quantity of Truvada tablet bottles or the quantity of dapivirine 25 mg VRs. However, if the participant is unable to attend her next scheduled visit, it is up to the discretion of the IoR/designee to allow the provision of additional study product. The reason for requesting >1 VR or bottle must be provided on the request slip. Oral Truvada tablets, however, must be ordered and dispensed only in bottles of 30 tablets. The IoR/designee will document approval of this additional dispensation on the request slip or the participant chart notes.

6.6 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-034 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 he/she 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 requirements. The "RESUME" box should only be checked if study product is being requested and dispensed following a product hold.

6.7 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., acquisition of HIV infection), mark the "PERMANENT DISCONTINUATION" box. 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 to that participant. Future slips will no longer be completed at the participant's remaining study visits.

6.8 Participant-Initiated Decline of Study Product

If a participant decides on his/her own to stop using the study product, and refuses to be re-supplied further study product, do not mark the "HOLD" box on MTN-034 Study Product Request Slip. Instead, mark the "PARTICIPANT DECLINE" box. Complete the slip and mark "PARTICIPANT DECLINE" at each subsequent visit during product period use in which the participant refuses study product. If the participant declines product at the onset of a product use period, no prescription will be sent. If the participant changes his/her mind and later decides to restart study product use during a product use period, complete the slip and mark "RE-SUPPLY". If the participant decides to continue product use at the beginning of a new product use period then a prescription should be completed.

6.9 Chain of Custody and Accountability

6.9.1 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 study product to the participant. Each study site must designate its Chain of Custody (dispensing method) for study product in MTN-034 SOPs for product dispensing and re-supply during MTN-034 follow-up. These SOPs should be developed with input from both pharmacy and clinic staff. They must be approved by the MTN Pharmacist prior to study activation and may only be modified after consultation with the MTN Pharmacist.

The pharmacist will dispense the study product to clinic staff who will then deliver the product to participants. Prescriptions and product request slips are expected to be delivered to the pharmacy by clinic staff or a runner or fax with original to follow. Upon receipt of a correctly completed and signed prescription or product request slip, the PoR will prepare the requested study product as documented on the prescription or request slip.

The MTN-034 Record of Receipt of Participant-Specific Study Product (Appendix 6-3) must be used to document dispensing of study product to clinic staff for a given participant. For each Record of Receipt, pharmacy staff will complete the PTID, assigned sequence, and the first four columns in the body of the record. When receiving study product from the pharmacy for a given participant, clinic staff will check to be sure the PTID and sequence are correct and confirm the study product and quantity of study product dispensed, as documented by the site pharmacist. Clinic staff will 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 participants for whom they were dispensed. Clinic staff also must document delivery of the study products to the designated participants in the participants' study charts. Delivery should be documented on the Participant-Specific Clinic Study Product Accountability Log (see below) and in chart notes or on other source documents used for this purpose. If all study products dispensed for a participant are not delivered to the participant, clinic staff will document this on the log and in the participant's study chart and return the unused study products to the pharmacy as soon as the participant's visit is completed or as soon as clinic staff know that the participant will not be completing her study visit on the scheduled date.

6.9.2 Participant-Specific Clinic Study Product Accountability Log

This log should be maintained and completed as outlined in the Clinic Study Product Accountability and Destruction SOP. A template of the SOP and the Study Product Accountability Log are available on the MTN-034 website. The SOP should define who is responsible for updating this log, when it is updated, where it is stored, how and when it will be QC'd and who is responsible for the QC procedures. It must be updated according to the site SOP for study product accountability and indicated in the Source Document SOP whether any of the data points will collect source data.

6.9.3 Clinic Study Product Destruction Log

This log (available on the MTN-034 website under Study Implementation Materials) should be completed to document the destruction of the used ring in the specific biohazard waste container/bin. This will be the final documentation required for documenting the accountability of any used ring that is not destined for further testing. If a ring is inserted in the clinic and then removed, during the same visit, due to an adverse event or error subsequently discovered, the ring would be placed in the container for destruction. When the container is sent for destruction a copy of the destruction must be sent to the site pharmacist and retained in the pharmacy study file.

6.10 Specimen Storage CRF

Site staff must document collection and storage of all returned used VRs *that are intended for testing* on the Specimen Storage CRF, as well as the Participant-Specific Clinic Study Product Accountability Log.

After documenting the return of used rings on the Specimen Storage CRF (if intended for testing) and clinic log, clinic staff should proceed to follow the directions outlined in SSP section 9. The placement of the used ring in the biohazard bag that is to be stored is documented on the Participant-Specific Clinic Study Product Accountability Log.

In the unusual event that a VR was dispensed but never inserted, the unused VR must be returned to the clinic and the event documented by study staff on a Protocol Deviation Log CRF and on the Participant-Specific Clinic Study Product Accountability Log. The unused VR should be returned to the pharmacy for quarantine. Only unused VRs (never inserted into the vagina) and Truvada tablets may be returned to the pharmacy. Clinic staff and pharmacy staff will complete the Pharmacy Record of Return of Site-Specific Unused VRs or Unused Truvada Tablets (Appendices 6-4a and 6-4b).

6.11 Study Product Return and Retrieval

Protocol Section 6.5 specifies the circumstances under which study product must be retrieved from participants. Study participants will be instructed to return all study products (unused tablets and unused/used VRs) to the site at each scheduled study visit. Clinic staff should forward all unused study products to the site pharmacy.

Participants will be instructed to return all study products (unused tablets and used/unused VRs) prior to the next product use period. Specifically, for each participant, all VRs and/or oral tablets remaining in the participant's possession should be retrieved at Visit 9: Week 24 (Period 1: Study Product Use End), Visit 16: Week 48 (Period 2: Study Product Use End), and Visit 23: Week 72 (Period 3: Study Product Use End). If the participant does not bring her study product(s) to this visit, study staff must arrange to retrieve the VR(s) or tablet(s) with five (5) business days. Site staff will make every effort to encourage participants to return study products as soon as possible. If the study product is not retrieved with the above stated timeframe, then the MTN-034 PSRT must be informed.

Refer to Table 1 below for reasons for study product retrieval and timeframe of retrieval. If study product is not returned to the site within the time frames outlined, then the MTN-034 PSRT must be notified.

Table 6-2: Product Retrieval Timeframes

Condition	Timeframe for Retrieval
Permanent discontinuation due to pregnancy, potential HIV infection or Grade 3 or higher renal or hepatic toxicity	Within 24 hours
Permanent discontinuation for any other reason or IoR discretion	Within 5 working days
Temporary hold for reasons with expected duration of at least 7 days	Within 7 working days

The retrieved study product must be documented by clinic staff on the Specimen Storage CRF and the Participant-Specific Clinic Study Product Accountability Log. If the study product cannot be retrieved (i.e., participant disposed of it or it was lost after removal), this must be documented on the Protocol Deviation Log CRF and the Participant-Specific Clinic Study Product Accountability Log. Related details and counseling around the need to ensure return of study product to site should be detailed in the participant's chart notes.

6.12 Study Product Complaints

During the study, a problem or concern may be observed with either study product. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (VR or oral tablets), packaging (overwrap pouch, bottle), or other aspects of the study product. Clinic staff should make thorough record of complaints of participants and clinic staff. The clinic staff member will notify (via email) the site PoR and other designated site pharmacy staff of the study product complaint. This notification should include as much detail as possible. The following information should be provided in the email: PTID, date of the observed issue, date that the issue was reported, date study product was dispensed, whether an adverse event occurred, description of the nature of the issue, pictures (if relevant), and any other details deemed necessary.

The site PoR will forward (via email) this information to the MTN LOC Pharmacist. The MTN LOC Pharmacist will forward the study product complaint to IPM or Gilead. If the complaint/issue is concerning an unused study product, then the unused product should be quarantined in the pharmacy. If the complaint/issue is concerning a used VR, then the clinic staff should process/store the VR per SSP Section 9.

Appendix 6-1: MTN-034 Prescription

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:		CRS ID:		CRS Location:	

Participant ID: ☐☐☐ – ☐☐☐☐☐☐ **Visit #:** _____

Did the participant provide written informed consent for enrollment into MTN-034?	Yes ☐	No ☐	Clinic Staff Initials: _____

Indicate Sequence:

	Period 1	Period 2	Period 3
☐ A	Dapivirine VR	Truvada tablets	Choice
☐ B	Truvada tablets	Dapivirine VR	Choice

Indicate Study Product Use Period:

☐ Period 1 ☐ Period 2 ☐ Period 3 (Indicate choice):

☐ Dapivirine VR ☐ Truvada tablets ☐ No product

Indicate Study Product:

☐ **Dapivirine Vaginal Ring**	☐ **Truvada Tablets**
Sig: Insert one (1) ring into the vagina as directed. **Quantity:** One vaginal ring. May be refilled as needed per request by designated clinic staff on MTN-034 Study Product Request Slip for duration of indicated study product use period.	**Sig:** Take one (1) tablet by mouth once daily as directed. **Quantity:** One bottle of Truvada tablets (30 tablets/bottle). May be refilled as needed per request by designated clinic staff on MTN-034 Study Product Request Slip for duration of indicated study product use period.

Authorized Prescriber Name *(please print)*:_____

Authorized Prescriber Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Version 1.0: 22JAN2018 **Pharmacy**

Appendix 6-2: MTN-034 Study Product Request Slip

Instructions: Complete the CRS name, ID # and location. Complete the PTID and circle the sequence and study product use period. Indicate the visit #. Mark whether this is a study product re-supply (if so, indicate which study product and quantity), clinical hold, resume (after a clinical hold), participant decline, clinical permanent discontinuation, or product use 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.

CRS Name:		**CRS ID:**		**CRS Location:**	

Participant ID: ☐☐☐ – ☐☐☐☐☐☐ **Sequence:** A or B **Period:** 1 2 or 3 **Visit #:** ____

☐ **RE-SUPPLY** → **Pharmacy: (Check one)**
- ☐ Dispense _____ dapivirine vaginal ring(s)*
- ☐ Dispense _____ bottle(s) of Truvada tablets (30 tablets/bottle)*

* Reason > 1 VR or bottle: _____

☐ **HOLD** → **Reason:** _____

Pharmacy: Do not dispense study product to the participant until another MTN-034 Study Product Request Slip marked "RESUME" is received.

☐ **RESUME** → **Pharmacy: (Check one)**
- ☐ Dispense one (1) dapivirine vaginal ring
- ☐ Dispense one (1) bottle of Truvada tablets (30 tablets/bottle)

Only an authorized perscriber can indicate RESUME.

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

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

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

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

Clinic Staff Name *(please print)*: _____

Clinic Staff Signature: _____

Date: ☐☐ – ☐☐☐ – ☐☐
dd *MMM* *yy*

Version 1.0: 22JAN2018 **Pharmacy**

Appendix 6-3: MTN-034 Record of Receipt of Participant-Specific Study Product

Participant ID: ☐☐☐ – ☐☐☐☐☐☐ **Assigned sequence:** A or B

PHARMACY STAFF				CLINIC STAFF/RUNNER		
Date/Time dispensed from pharmacy dd-mm-yy (hh:mm) 24 hr clock	**Indicate dapivirine VR or Truvada Tablets**	Number of VRs or Bottles Dispensed by Pharmacy	Pharmacist Initials	Date/Time received from pharmacy dd-mm-yy (hh:mm) 24 hr clock	Clinic Staff/ Runner Initials	Comments

Instructions: Complete one row each time a VR or bottle of tablets 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

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Appendix 6-4a: MTN-034 Record of Return of Site-Specific Unused Dapivirine VRs

CRS Name:	**CRS ID:**

CLINIC STAFF				**PHARMACY STAFF**				
Date Returned to Pharmacy (dd-MMM-yy)	PTID	**No. of VRs**	Clinic Staff/ Runner Initials	Date Received by Pharmacy (dd-MMM-yy)	PTID (verify)	Reason for Return	RPh Initials	QA against Destruction Form Pharmacy Staff Initials

Instructions: Complete one row each time an unused VR is returned by the participant to non-pharmacy staff for subsequent return to the site 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.

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Appendix 6-4b: MTN-034 Record of Return of Site-Specific Unused Truvada Tablets

CRS Name:	**CRS ID:**

CLINIC STAFF				**PHARMACY STAFF**				
Date Returned to Pharmacy (dd-MMM-yy)	PTID	**No. of Tablets**	Clinic Staff/ Runner Initials	Date Received by Pharmacy (dd-MMM-yy)	PTID (verify)	Reason for Return	RPh Initials	QA against Destruction Form Pharmacy Staff Initials

Instructions: Complete one row each time unused tablet(s) are returned by the participant to non-pharmacy staff for subsequent return to the site 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.

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