

Section 7. Study Product Considerations for Non-Pharmacy Staff

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7. Introduction

This section provides information and instructions for non-pharmacy staff related to randomization, transport, delivery and administration of MTN-038 study product for study participants. Associated instructions for pharmacy staff are provided in the MTN-038 Pharmacy Study Product Management Procedures Manual, which will be made available to each site Pharmacist of Record (PoR) by the MTN LOC Pharmacist.

7.1 Study Product Regimens

Each participant will receive an IVR containing either 1.4 g TFV or matching placebo. Each study participant will be randomized to one of two study IVRs in a 2:1 ratio. Only the participants will not be told their assignment. The IVR is used continuously for approximately 91 days and will be removed by the participant (or clinician/designee, if necessary) at the product use end visit (PUEV/Early Termination Visit).

Table 7-1: Study Product Regimen

Group	N	Study IVR Description
A	32	TFV IVR containing 1.4 g TFV
B	16	Matching Placebo IVR

7.1.1 Randomization Assignment

The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme. As shown in Table 7-1, study participants will be randomly assigned in equal numbers to one of three study regimens.

Study IIVR 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 via Medidata to determine the study product assignment. Clinic staff must indicate the study product (IIVR containing either 1.4 g TFV or matching placebo) on the prescription. Clinic staff will complete a study prescription and send the original part to designated site pharmacy staff, as described in section 7.2 below, to notify the site pharmacist that the participant has been randomized and needs to be dispensed a study IVR.

7.2 Prescriptions and Dispensing IVR at Enrollment (Visit 2)

One prescription must be completed at the enrollment Visit (Visit 2). There is one MTN-038 Prescription for the IVRs including 1.4 g TFV or matching placebo (Appendix 7-1). The prescription is sufficient to allow for product dispensing for the entire study product use period. Bulk supplies of the prescriptions are available from the MTN pharmacist and will be supplied to site PoR to provide to clinic staff throughout the course of the study.

7.2.1 In Clinic Prescription Procedures (C1-C5):

C1. At Visit 2 (Enrollment Visit), the Inclusion Exclusion Criteria CRF and Randomization CRF must be completed by clinic staff for a participant to be enrolled/randomized into the study. A participant is considered officially enrolled after the completion of the Randomization CRF, as evidenced by the appearance of a randomization date and time on this CRF.

C2. After the participant is randomized, complete an MTN-038 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/signed and dated informed consent form for enrollment prior to recording his/her initials beside these boxes.

C3. The randomized product (1.4g TFV or placebo), as listed on the Randomization eCRF, must be indicated on the prescription, by checking the appropriate box.

C4. The middle section of the prescription requires the authorized prescriber's name, signature, and date. This study staff member must be designated in the site's DoA as an authorized prescriber of study product. This person also must be listed as an investigator (either the IoR or Sub-Investigator) on the current FDA Form 1572.

C5. 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.

C6. Deliver the white (pharmacy) original prescription to the study pharmacy.

7.2.2 In Pharmacy Prescription Procedures (P1-P2):

P1. At Visit 2, designated site pharmacy staff will receive an email notification from the Medidata system that a given participant was randomized by the site clinic staff. This communication will be printed and filed in the pharmacy binder.

P2. Upon receiving the completed MTN-038 Prescription, the pharmacist will review the document for completion and accuracy. The pharmacist will log into the Medidata database and, using the PTID recorded on the prescription, navigate to the participant's Pharmacy Dispensation CRF to determine the assigned IVR strength and for completion of this CRF.

P3. The assigned (auto-populated) IVR (1.4 g TFV or placebo) on the Pharmacy Dispensation CRF must match the IVR indicated on the prescription. If a member of the 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, 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.

P4. Following review of the signed MTN-038 Prescription, pharmacy staff will dispense the requested IVR for participant use per instructions in the MTN-038 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy SOP(s).

7.3 Vaginal Ring Request Slip

The MTN-038 Vaginal Ring Request Slip is used by clinic staff to communicate to the study pharmacist the study product and quantity to be re-supplied. Participants assigned to either the 1.4 g TVF or placebo study arms will receive one IVR at the enrollment visit to be used continuously for approximately 13 weeks; no re-supply is planned. Provisions for the dispensation of additional IVRs will be at the discretion of the IoR and in consultation with the PSRT as needed.

The Vaginal Ring Request Slip is also used to communicate to the pharmacist if a participant declines study product, terminates early from the study, or completes study product use (Appendix 7-2). 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 site PoR to provide to clinic staff throughout the course of the study.

Clinic staff will complete the site name, CRS Name, PTID, and study IVR on the top of the slip. When the slip 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 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.

7.3.1 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-038 Vaginal Ring 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.

7.3.2 Permanent Discontinuation of Study Product

If a study clinician determines that a participant should permanently discontinue study product use due to safety reason(s) (HIV acquisition, pregnancy), 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.

7.3.3 Participant-Initiated Decline of Study Product

If a participant decides on her own to stop using study product, and refuses to be re-supplied further study product, do not mark the "HOLD" box. Instead, mark the "PARTICIPANT DECLINE" box on the MTN-038 slip. Complete the slip and mark "PARTICIPANT DECLINE" at each subsequent visit 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."

7.3.4 Scheduled and Early Terminations

When a participant has completed her study participation, whether a scheduled or early termination, mark the "PRODUCT USE PERIOD COMPLETED" box on the MTN-038 slip. This serves as a notification to the site pharmacist that the participant will no longer be requiring any additional study product dispensations.

7.4 Chain of Custody and Accountability

7.4.1 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 develop SOPs for product dispensing and re-supply during study follow-up and include designating a Chain of Custody (dispensing method) for study product MTN-038. 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 site pharmacist will dispense the study product to clinic staff who will then deliver the IVR to the participant. Prescriptions and request slips are expected to be delivered to the pharmacy by clinic staff or a runner or via fax with original to follow. Upon receipt of a correctly completed and signed prescription or request slip, the PoR will prepare the requested IVR as documented on the prescription or request slip.

The MTN-038 Pharmacy Record of Receipt of Site-Specific Vaginal Rings must be used to document dispensing of IVRs from pharmacy staff to clinic staff for participants in MTN-038 (Appendix 7.3). For the Record of Receipt, pharmacy staff will complete the Date/time dispensed, PTID, IVR type, number of IVRs dispensed, and initials. When receiving study product from the pharmacy for a given participant, clinic staff will check to be sure the PTID, IVR type, and number of IVRs is correct, as documented by the site pharmacist. Clinic staff will complete the remaining two 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 IVRs 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 may be documented in chart notes or on other source documents used for this purpose. If all study product 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 know that the participant will not be completing her study visit on the scheduled date.

7.4.2 Site-Specific Clinic Study Product Accountability Log

This log should be maintained and completed as outlined in the site's Clinic Study Product Accountability and Destruction SOP. 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 at least daily and indicated in the Source Document SOP whether any of the data points will collect source data. The log is available on the MTN-038 website.

7.4.3 Clinic Study Product Destruction Log

This log should be completed to document the destruction of the used IVR in the specific biohazard waste container/bin. This will be the final documentation required for documenting the accountability of any used IVR that is not destined for further testing. If a IVR is inserted in the clinic and then removed, during the same visit, due to an adverse event or error subsequently discovered, the IVR would be placed in the container for destruction. The log is available on the MTN-038 website.

7.4.4 Ring Insertion and Removal CRF

Site staff must document collection and storage of all returned used IVRs *that are intended for testing* on the Ring Insertion and Removal CRF, as well as the Site-Specific Clinic Study Product Accountability Log.

After documenting the return of a used IVR on the CRF (if intended for testing) and clinic log, clinic staff should proceed to follow the directions outlined in SSP section 10. The placement of the used IVR in the original resealable foil pack in which it is to be stored should be documented on the Site-Specific Clinic Study Product Accountability Log.

In the unusual event that a IVR was dispensed but never inserted, the unused IVR must be returned to the clinic and the event documented by study staff on a Protocol Deviation Log CRF and on the Site-Specific Clinic Study Product Accountability Log. The unused IVR should be returned to the pharmacy for quarantine. Only unused IVR (never inserted into the vagina) may be returned to the pharmacy. Clinic staff and pharmacy staff will complete the Pharmacy Record of Return of Site-Specific Unused Vaginal Rings (Appendix 7.3a).

7.5 Study Product Return and Retrieval

Protocol Section 6.4.4 specifies the circumstances under which the study IVR must be retrieved from participants. Although not likely, clinic staff should forward all unused study products to the site pharmacy. If IVRs are not returned at the end of the study product use period (PUEV – Visit 10), site staff will make every effort to encourage participants to return study product as soon as possible.

If the participant does not bring her study product(s) to this PUEV, study staff must arrange to retrieve the IVR(s) with five (5) business days. If the study product is not retrieved with that timeframe, then the MTN-038 PSRT must be informed.

Refer to the below table 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-038 PSRT must be notified.

Condition	Timeframe for Retrieval
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Permanent discontinuation or temporary hold due to potential HIV infection or pregnancy	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 IVR must be documented by clinic staff on the Ring Insertion and Removal CRF and the Site-Specific Clinic Study Product Accountability Log. If the IVR 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 Site-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.

7.6 Study Product Complaints

During the study, a problem or concern may be observed with a IVR. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (vaginal ring), packaging (overwrap pouch), 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 IVR was dispensed, IVR strength/lot #, 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. If the complaint/issue is concerning an unused IVR, then the unused product should be quarantined in the pharmacy. If the complaint/issue is concerning a used IVR, then the clinic staff should process/store the IVR per SSP Section 10.

Appendix 7-1: MTN-038 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. Deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

CRS Name:		CRS ID:		CRS Location:	
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Participant ID:

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Did the participant provide written informed consent for enrollment into MTN-038?	Yes <input type="checkbox"/>	No <input type="checkbox"/>	Clinic Staff Initials: _____
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<p>Check one: <input type="checkbox"/> 1.4 g tenofovir IVR <input type="checkbox"/> placebo IVR</p> <p>Sig: Insert one (1) ring into the vagina.</p> <p>Quantity: One vaginal ring. May be refilled as needed per request by designated clinic staff on MTN-038 Vaginal Ring Request Slip for duration of participation in the study.</p>
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<p>Authorized Prescriber Name (<i>please print</i>): _____</p> <p>Authorized Prescriber Signature: _____</p> <p>Date: <table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> - <table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table> - <table border="1" style="display: inline-table; border-collapse: collapse;"><tr><td style="width: 20px; height: 20px;"></td><td style="width: 20px; height: 20px;"></td></tr></table></p> <p style="text-align: center;"><i>dd</i> <i>MMM</i> <i>yy</i></p>								

Appendix 7-2: MTN-038 Vaginal Ring Request Slip

Participant ID: -

Instructions: Mark whether this is a study IVR re-supply, clinical hold, resume (after a clinical hold), participant decline, clinical permanent discontinuation, or product use period completion notification. Deliver the original white copy (labeled “Pharmacy”) to the pharmacy. File the yellow copy (labeled “Clinic”) in the participant’s study notebook.

REQUESTED IVR: (if indicated)	<input type="checkbox"/> 1.4 g tenofovir IVR	<input type="checkbox"/> placebo IVR
<input type="checkbox"/> RE-SUPPLY	→ Pharmacy: Dispense one (1) vaginal ring. Check requested IVR box above.	
<input type="checkbox"/> HOLD	→ Reason: _____ Pharmacy: Do not dispense further vaginal rings to the participant until another MTN-038 Intravaginal Ring Request Slip marked “RESUME” is received.	
<input type="checkbox"/> RESUME	→ Pharmacy: Dispense one (1) IVR. Only an authorized prescriber can indicate RESUME. Check requested IVR box above.	
<input type="checkbox"/> PARTICIPANT DECLINE	→ Pharmacy: Do not dispense at this visit - participant is refusing IVR.	
<input type="checkbox"/> PERMANENT DISCONTINUATION	→ Reason: _____ Pharmacy: Do not dispense any further IVRs to the participant.	
<input type="checkbox"/> PRODUCT USE PERIOD COMPLETE	→ Pharmacy: Do not dispense any further IVRs to the participant.	

Clinic Staff Name (*please print*): _____

Clinic Staff Signature: _____

Date: - -
 dd *MMM* *yy*

