

Section 7. Study Product Considerations for Non-Pharmacy Staff

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This section provides information and instructions for non-pharmacy staff (i.e., clinic staff) related responsibilities regarding blinding, transport, receiving the MTN-027 intravaginal ring (IVR) from pharmacy (dispensation of IVR from pharmacy staff to clinic staff), and delivery of the IVR to study participants (provision of IVR from clinic staff to study participant). Record keeping requirements for clinic staff are also provided. Associated instructions for pharmacy staff are provided in the MTN-027 Pharmacy Study Product Management Procedures Manual, which will be made available to each MTN CRS Pharmacy by the MTN LOC Pharmacist. Please refer to section 10 of this manual for product use instructions and guidance on study product adherence counseling.

7.1 Responsibilities and Obligations with Regard to Blinding

MTN-027 Investigators of Record (IoRs), and by delegation all MTN-027 study staff, are responsible for maintaining the integrity of the study’s single blinded design. The identity of the specific study product (VCV IVR, MK-2048 IVR, combination VCV/MK-2048 IVR, or placebo IVR) to which each participant is randomly assigned in a double-blinded manner, meaning that neither study participants nor study staff — including all members of the Protocol Team — will be provided information on the identity of the specific study product to which each participant has been assigned. However, if staff or participants were to visually compare study IVR types, then they might be able to discern that there are differences in appearance, and therefore, differences in study IVR type. For this reason, this study is deemed as single-blind.

Study documentation maintained by clinic staff — who are responsible for ascertaining primary and secondary study endpoints — will generate the randomization number to which each participant has been assigned, through an online randomization system. Study documentation maintained by pharmacy staff — who are excluded from ascertaining primary and secondary study endpoints — will include blinded

coded information indicating the specific sub-lot code(s) for the study IVR to which participants have been assigned, based on randomization number.

Blinding will be maintained throughout the study and until all study endpoint data have been verified and are ready for final analyses. There are no circumstances under which it is expected that unblinding a participant study product regimen assignment will be necessary to protect the safety of that individual. In the event that study staff becomes concerned that a participant may be put at undue risk by continuing use of study product, the IoR may temporarily hold or permanently discontinue product use by the participant. However, knowledge of the specific product to which the participant was assigned should not be necessary to guide further follow-up and/or treatment.

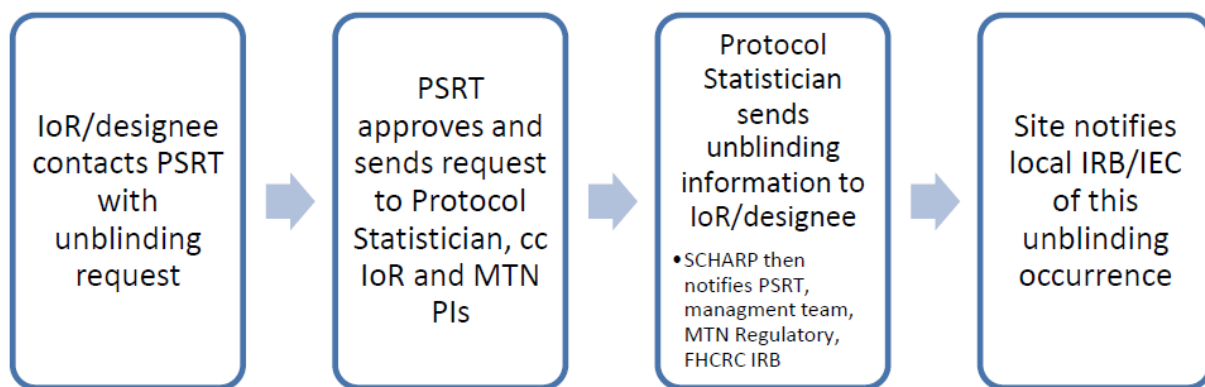
7.1.1 Emergency Unblinding Process

During the trial, an IoR/designee may request that a participant's study product regimen assignment be provided (unblinding), if it is essential to protect a participant's safety.

To request the unblinding for a specific participant, the following steps are required:

1. IoR/designee must contact the Protocol Safety Review Team (PSRT) (412-641-8947 or mtn027psrt@mtnstopshiv.org).
2. If the PSRT rules that unblinding is required, the PSRT will send the unblinding request to the Protocol Statistician (Barbra Richardson; barbrar@scharp.org), and cc the IoR/designee from the site so that the statistician can send the information to the correct person at the site. The MTN PI and co-PI should also be copied on this request from PSRT.
3. The Protocol Statistician will provide the study product regimen assignment to the IoR/designee and will then notify the following: MTN PI and Co-PI, PSRT, the protocol management team and protocol chairs, MTN Regulatory and the Fred Hutchinson Cancer Research Center IRB that this has occurred.
4. The site IoR/designee must notify the local IRB in an expedited manner of this occurrence of unblinding.

Figure 7-1. Flow Chart of Emergency Unblinding Process



7.2 Randomization Assignment

- The MTN Statistical Data Management Center (SDMC) will generate and maintain the study randomization scheme and associated materials which consist of the MTN-027 Pharmacy Randomization List

MTN SDMC will conduct participant randomization via an online system with the Frontier Science & Technology Research Foundation, Inc. (FSTRF). After a participant has been confirmed as eligible and

has provided written informed consent to take part in the study, a clinic staff member will submit on the FSTRF website the required participant information for enrollment and randomization. After online submission, designated clinic staff and pharmacy staff will receive email notification that the participant has been randomized for this study – this email will include information that is necessary for clinic staff to complete a prescription (i.e., randomization number). Please refer to section 6 of this manual for detailed instructions for randomization participants using the FSTRF randomization system.

Clinic staff will print the randomization email notification and place in the participant clinic binder. The act of assigning a Randomization Number to a participant is considered the effective act of enrollment and randomization into the study. Once a Randomization Number is assigned, the participant is considered enrolled in the study. Note that the randomization number (or Code) will be displayed as a 4-digit number with a leading '0' in the email notification. The leading 0 should be deleted before transcription to other study documents.

Prescriptions (Appendix 7-1) will be produced as two-part no carbon required (NCR) forms. A bulk supply of prescriptions will be provided to the clinic staff by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional slips be needed during the study.

After recording CRS Name, CRS ID, CRS Location, PTID, Randomization Number, and other details on the prescription, clinic staff will separate the two sheets of the form, and the white original will be delivered to the pharmacy. The yellow copy will be retained in the participant's study notebook in the clinic. Only one prescription will be used for each participant. A prescription must be signed by an authorized prescriber as designated on FDA Form 1572.

7.3 Dispensing Study Product

Each participant is assigned to VCV IVR, MK-2048 IVR, combination VCV/MK-2048 IVR, or placebo IVR based on the randomization number provided in the randomization email notification from FSTRF.

Each IVR will be dispensed from the pharmacy in its original sealed pouch. The pharmacist/designee will also dispense a white participant IVR return bag. On the return bag label, the pharmacist/designee will complete the PTID and dispensation date, and clinic staff will complete a contact name and phone number. Clinic staff must be sure to provide the participant with the correct IVR and return bag. Clinic staff should instruct the participant that the IVR should be rinsed and dried and placed in the bag if the used IVR is removed prior to the next scheduled visit so that it can be returned to the clinic. Although participants are encouraged to not remove the ring, they may also rinse and dry the ring and place it in this bag for storage if there is a need to temporarily remove the ring. The ring should always be rinsed with clean water before reinsertion. Participants may request a new bag at clinic visits, as needed, if the bag is used or misplaced.

7.3.1 Chain of Custody

For MTN-027, the IVR and white return bag will only be dispensed from the pharmacy directly to a clinic staff member who will then provide the participant-specific study product to the participant. The pharmacist will record the PTID and date/time that the IVR is dispensed on the IVR pouch label (note that recording the last 6 unique digits of the PTID is sufficient, should space be limited). If staffing issues make it impossible for a clinic staff member to pick up the ring from the pharmacy, a designated transport staff member (runner or courier) may pick up the IVR and bag, and then transfer the study product to a designated clinic staff member who will then provide the participant the study product. The MTN-027 Chain of Custody (Pharmacy) SOP provides documentation regarding who receives the vaginal ring from the pharmacy. Responsibilities and procedures from the time of product receipt from the pharmacy until delivery to participant, including procedures for participant identity verification prior to ring provision,

should be outlined in the Clinic Study Product Accountability and Destruction SOP. This clinic SOP should be developed with input from both pharmacy and clinic staff to ensure smooth on-site clinic flow. This SOP must be approved by the MTN LOC Pharmacist prior to study activation and may only be modified after consultation with the MTN LOC Pharmacist.

The IVR should be vaginally inserted within 24 hours of the date/time indicated on the IVR pouch label. If administration does not occur within this time frame, the unused IVR must be returned to the pharmacy. Clinic staff can request another IVR for the given participant by marking RE-SUPPLY on an MTN-027 Intravaginal Ring Request Slip.

7.3.2 Initial Vaginal Ring Dispensing - Prescription Overview

All prescriptions will have the assignment “MTN-027 Intravaginal Ring (182mg of VCV; 30mg of MK-2048; 182mg of VCV and 30mg of MK-2048; or placebo)”, as all participants will be randomized to intravaginal ring. The randomization number pre-printed on participant’s randomization email notification from FSTRF will indicate to the pharmacy which IVR sub-lot code(s) can be dispensed to that given participant (MTN-027 Pharmacy Randomization List). Note that only one IVR may be dispensed at each visit.

The in-clinic procedures are listed below.

In Clinic (procedures C1-C5):

C1. Conduct participant randomization via the online FSTRF system. A randomization number will be generated for this participant. Note that the randomization number (or Code) will be displayed as a 4-digit number with a leading 0 in the FSTRF email notification to specified clinic and pharmacy staff. The leading 0 should be deleted before transcription to other study documents. Complete a prescription accordingly. 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.

C2. The middle section of the prescription must be completed by a study staff member 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.

C3. The bottom section of the prescription requires clinic staff initials and the date once all of the above is completed. This should be completed by the clinic staff member who verifies that the participant signed the informed consent form and completed the top part of the prescription.

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.

In Pharmacy (procedures P1-P3):

P1. Upon receiving the completed MTN-027 Prescription (at enrollment), the pharmacist will review the document for completion and accuracy. The pharmacist will print the FSTRF randomization email notification in order to double check prescription completeness and accuracy. This hard copy of the email will be placed in the participant pharmacy binder. In the event that pharmacy staff identifies possible errors on the original prescription, they will return the original prescription to clinic staff for clarification or correction. 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 copies. Identical

corrections and notes should be recorded on both copies, 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.

P2. Participant randomization and receipt of the MTN-027 Prescription will be documented on the Pharmacy Randomization List. Two pharmacy staff members (at minimum one pharmacist), will verify (by initialing and dating) the linking the participant's randomization number and possible IVR sub-lot codes. The PTID provided on the Prescription and verified on the FSTRF confirmation email will be entered on the Pharmacy Randomization List.

P3. Following review of the signed MTN-027 Prescription, pharmacy staff will dispense the study product for participants per instructions in the MTN-027 Pharmacy Study Product Management Procedures Manual and in accordance with the site pharmacy Chain of Custody SOP.

7.4 Study Product Accountability

Study product will be dispensed to clinic staff and provided to the participant in the clinic. **Used** study product will be returned by the participant and given to the clinic staff (rather than the pharmacy). Therefore, accommodation must be made to allow for documentation of distribution, collection, and removal of study product at the site clinic. A standardized process of tracking and accountability must be followed by all MTN-027 sites. A sample Participant-Specific Clinic Study Product Accountability Log is available on the MTN-027 website under Study Implementation Materials. This log includes tracking the date that the IVR is provided to the study participant, the date of IVR return to the clinic, and the final status of each ring (used ring for storage, used ring for destruction, unused ring to pharmacy, or ring not returned). Sites will be provided an SOP template which should be modified to reflect the specific processes at the site.

7.4.1 Documentation of Ring Provision and Ring Collection

Participant-Specific Clinic Vaginal Ring Accountability Log

This log should be maintained and completed as outlined in the SOP for Clinic Vaginal Ring Accountability and Destruction (template is available on the MTN-027 website under Study Implementation Materials). This 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 when the IVR is provided to the participant or returned to the clinic and indicated in the Source Document SOP whether any of the data points will collect source data.

Ring Collection and Insertion CRF

Site staff must document all IVR returns on the Ring Collection and Insertion CRF, as well as the Participant-Specific Clinic Study Product Accountability Log described above.

After documenting the return of used or unused rings on the CRF and clinic log, clinic staff should proceed to follow the directions outlined in section 9.7.9 of this manual (Testing of Intravaginal Ring (IVR)). The placement of the used ring in the biohazard bag (supplied by Network Lab) that is to be stored is also documented on the Participant-Specific Clinic Study Product Accountability Log.

In the unusual event that a vaginal ring was dispensed but never inserted, the returned (unused) vaginal ring must be returned to the clinic and documented by study staff on the Ring Collection and Insertion CRF and the Participant-Specific Clinic Study Product Accountability Log. The unused vaginal ring should be returned to the pharmacy for quarantine. Only unused vaginal rings may be returned to the pharmacy; this can include study product in which the overwrap pouch was opened but the IVR was never vaginally inserted. Clinic staff and pharmacy staff will complete the Pharmacy Record of Returns.

Clinic Study Product Destruction Log

In the rare event that a ring must be destroyed, the Clinic Study Product Destruction Log (also available on the MTN-027 website under Study Implementation Materials) must be completed to document the destruction of the specific biohazard waste container/bin that contained the IVR to be destroyed. This will be the final documentation required for recording 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 specified biohazard container for destruction.

7.5 Duration of Use of Each IVR

Participants should be counseled to refrain from removing the IVR until scheduled Visit 9/Day 28 (approximately 28 days of IVR insertion), unless instructed otherwise by the study clinic. No replacement IVR is scheduled, given the protocol design.

Participants will receive an IVR to insert at their Enrollment Visit (Visit 2). Participants will be instructed to refrain from removing the IVR during the 28 day period, unless instructed otherwise by the study clinic. Ring removal is scheduled to occur at the participant's Day 28 visit. In the rare event a participant is not available to return to the clinic for the Day 28 visit to have the IVR removed, site staff should reschedule the visit within the visit window (i.e. no later than Day 29). If the participant is not able to return to the clinic within the Visit 9.0/Day 28 visit window, site staff should instruct the participant to remove the ring, rinse the ring with clean water (no soap), dry with a paper towel, and place in the re-sealable plastic bag provided or suitable substitute, until the participant is able to return to the clinic. All attempts made to contact the participant and retrieve the study product must be documented in the participants chart and the PSRT must be informed.

7.6 Vaginal Ring Re-supply During Follow-up or Interim Visits

While conducting all visit procedures for each scheduled visit is ideal, it is acknowledged that this might not always be possible. At a minimum, the following procedures must be conducted in order to dispense study product:

- AE assessment and clinical management, in accordance with section 8 of the protocol (verbal report of symptoms is acceptable; if symptoms indicate that further evaluation is necessary, this must be conducted prior to dispensing study product).
- Collection of used vaginal ring (and unused, if applicable), if available.
- Staff should also provide the associated product use adherence counseling and review vaginal ring use instructions with the participant, as needed.

If indicated, based on clinical discretion (e.g. participant reports risk behaviors and/or shows signs/symptoms of HIV or pregnancy), the following procedures may be conducted:

- A pregnancy test and/or HIV testing may be performed and must be negative prior to dispensing study product.

The MTN-027 Intravaginal Ring Request Slip, which will be produced as two-part NCR forms, (see Appendix 7-2) will be used by clinic staff to communicate to pharmacy staff that a new IVR should be resupplied to a participant.

NOTE: Once the initial IVR has been vaginally inserted, the participant should not require additional IVRs. However, for example, in the unusual circumstance that the IVR has been expelled in such a way that the participant feels that it is not retrievable (e.g., during menses, in the toilet, etc.), then the participant should be instructed to notify the clinic, and a new IVR will be dispensed. The used IVR should be brought back to the clinic by the participant and given to clinic staff, preferably in the white IVR return bag.

The slip is also used to communicate clinic staff decisions to temporarily hold, permanently discontinue, or resume (after a temporary hold) IVR use. Further, the slip is used to communicate to the pharmacy of a participant's refusal to accept a new vaginal ring and to communicate when the product use period is completed. At minimum, one MTN-027 Intravaginal Ring Request Slip should be completed (white top sent to pharmacy and yellow copy stored in participant clinic binder) for each participant when she has completed use of study product – MTN-027 Intravaginal Ring Request Slip marked PRODUCT USE PERIOD COMPLETED.

A bulk supply of the slips will be provided to the clinic staff by MTN LOC Pharmacy. Sites will identify the individual responsible for receiving the slips and for contacting the MTN LOC Pharmacist should additional slips be needed during the study. Instructions for completion of the MTN-027 Intravaginal Ring Request Slips are printed on the slips themselves. Additional guidance for clinic staff is as follows:

- Record the CRS name, the participant's ID number (PTID) and the Randomization Number assigned to the participant in the boxes provided at the top of the slip.
- Mark the box for RESUPPLY, HOLD, RESUME, PARTICIPANT DECLINE, PERMANENT DISCONTINUATION, or PRODUCT USE PERIOD COMPLETED.
- If RE-SUPPLY or RESUME is marked, only one (1) vaginal ring is dispensed.
- Mark RESUME only after a HOLD has been lifted.
- Only mark the HOLD or PERMANENT DISCONTINUATION box for clinical (site-initiated) hold/permanent discontinuations. This includes any time the participant is directed by the clinician to remove the ring. Additionally, PERMANENT DISCONTINUATION should be marked for participants who decide to terminate from the study early. Record the reason for the hold or discontinuation on the line provided.
- If a participant declines to be issued a new vaginal ring for any reason, mark the PARTICIPANT DECLINE box. For participants who decline study product, a ring request slip should be completed in order to document the refusal. If the participant agrees to start receiving product again, mark the RE-SUPPLY box to indicate she is restarting product.
- At the scheduled Ring Removal Visit (Visit 9/Day 28), mark the PRODUCT USE PERIOD COMPLETED box. This will indicate that no more vaginal rings will be provided for the participant.
- The clinic staff printed name, signature, and signature date must be completed by a clinic staff member authorized to order study product for participants during follow-up. When marking RESUME, this clinic staff member must be an authorized prescriber. In all other circumstances, the slips do not need to be signed by an authorized prescriber; however site-specific pharmacy regulations and procedures may be more stringent. All sites must comply with their local requirements.
- Double-check the accuracy of all entries. The MTN-027 Intravaginal Ring Request Slip is a two-part NCR form. Retain the yellow copy in the participant study notebook, and deliver the white original to the pharmacy.
- The pharmacist must review the slip for completion and consistency. In the event that pharmacy staff identify possible errors on the slip, they will return the original slip to clinic staff for clarification or correction. If corrections are needed, the corrections must be made on both the white original sheet and the yellow copy. A signed and dated note explaining the corrections also should be recorded on both copies. Identical corrections and notes should be

recorded on both copies, on the same date, by the same person. Corrections should only be made by study staff authorized to complete the requested action on the original request slip. See above.

Once an IVR is provided to a participant, clinic staff will document on the Ring Collection/Insertion CRF the needed details regarding the provision of the vaginal ring. Staff will also document this action on the Participant-Specific Clinic Vaginal Ring Accountability Log as outlined in the SOP for Clinic Vaginal Ring Accountability and Destruction.

7.6.1 Vaginal Ring Hold and Resumption

Protocol Section 9 (Clinical Management) and section 8 of this manual specify the circumstances under which use of study product may be temporarily held or permanently discontinued. A product hold can occur for a number of reasons, as described throughout Protocol Section 9. Holds may be placed either in the clinic or over the phone.

If a product hold is instituted **during a clinic visit or over the phone**, an MTN-027 Intravaginal Ring Request Slip marked HOLD should be completed and delivered to the pharmacy, and a Product Hold/Discontinuation Log CRF should also be completed and faxed to DF/Net Research. A Product Hold/Discontinuation Log CRF should be completed for each clinical product hold, even if the participant is already on a hold for another reason. There is no need to send pharmacy an additional MTN-027 Vaginal Ring Request Slip if a product hold is already in place.

If product hold is instituted **over the phone**:

- Request that the participant remove the vaginal ring and place it in the study-provided white IVR return bag until further instructions are available.
- Follow-up as clinically appropriate per protocol, SSP and/or site SOPs.
- The participant should not resume IVR use until it is determined safe by the IoR/designee. IVR use may be resumed by asking the participant to come to the clinic for a new IVR.

An IVR should not be removed for a hold and later reinserted for reuse.

Once an MTN-027 Intravaginal Ring Request Slip is completed and a "HOLD" is marked, regardless of the reason or duration, no further rings will be dispensed for that participant until another slip is marked "RESUME" and signed by an authorized prescriber.

For the first dispensation after a hold, complete an MTN-027 Intravaginal Ring Request Slip marked RESUME. The Product Hold/Discontinuation Log CRF documenting the hold should be updated and re-faxed to DF/Net Research when the participant resumes study product.

7.6.2 Permanent Discontinuation

If it is determined by the site clinician that IVR use will be permanently discontinued, site staff will complete an MTN-027 Intravaginal Ring Request Slip marked PERMANENT DISCONTINUATION. No further Request Slips need to be completed for this participant after this visit. A Product Hold/Discontinuation Log CRF must also be completed and faxed to DF/Net Research. If the participant opts to remain in follow-up, follow guidance per section 4 of this manual regarding visit procedures for participants who have discontinued use of study product.

7.7 CYP3A4 Inhibitors and Inducers

VCV is a CYP3A4 substrate – it is extensively metabolized by CYP3A4. Despite only two of the four study products containing VCV, study staff must promote the avoidance of certain scheduled/routine CYP3A4 inhibitors and inducers (prescription medications, over-the-counter medications, herbal supplements, and nutritional supplements) via any route of administration, since this study is blinded. Appendix 7-3 outlines CYP3A4 inhibitors that participants should avoid using concomitantly in this study. Appendix 7-4 outlines CYP3A4 inducers to be avoided.

NOTE: single dose oral fluconazole for the treatment of vaginal fungal infections is permitted.

Information in Appendices 7-3 and 7-4 is adapted from:

<http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm#4>

If drug-drug interaction questions arise during the study that cannot be answered by any of the study-related materials provided (protocol, SSP, SOPs), please contact the MTN-027 PSRT (mtn027psrt@mtnstopshiv.org). Medications with unknown interactions will be dealt with on a case-by-case basis with input from the PSRT, as needed.

Other prohibited medications and practices can be found in Protocol Section 6.6 and section 8.5 of this manual.

7.8 Study Product Retrieval

Protocol Section 6.4.4 specifies the circumstances under which study product must be retrieved from participants who are required to hold or discontinue vaginal ring use. Because participants are expected to have the vaginal ring in place at the time of their clinic visit, the need for product retrieval is expected to be rare. When product retrieval is required, retrieval may occur by the participant returning the product to study staff. Only unused vaginal rings are brought to the pharmacy for quarantine.

Table 7-3 specifies the circumstances and timeframes with which vaginal rings must be retrieved. If the vaginal ring cannot be retrieved (i.e., participant disposed of it or product was lost after removal) this must be documented on the Ring Collection and Insertion CRF and the related details and counseling on the need to ensure return of product to site should be detailed in the participant's chart notes.

Table 7-3. Requirements for Retrieval of Study Product Due to Temporary Hold or Permanent Discontinuation

	Retrieve Study Product Within:
Permanent discontinuation or temporary hold due to potential HIV seroconversion	24 hours
Permanent discontinuation for any other reason or IoR discretion	5 working days
Temporary hold for reasons with expected duration of greater than 7 days	7 working days
End of Study (Visit 13/Day 35; Final Clinic Visit)	2 working days

For all product holds requiring product retrieval, if the IVR is not retrieved within the time frame listed in Table 7-3, the PSRT must be informed. The retrieved IVR must be documented by clinic staff on the Ring Collection and Insertion CRF and on the Participant-Specific Clinic Vaginal Ring Accountability Log as outlined in the SOP for Clinic Vaginal Ring Accountability and Destruction.

7.9 Study Product Complaints

During the study, a problem or concern may be observed with an IVR. A problem may be noted by the pharmacy staff, clinic staff, or the participant. These complaints may be about the dosage form (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 and pictures (if necessary). The following information should be provided in the email: date of the observed issue, date that the issue was reported, date IVR was dispensed, did an adverse event occur, description of the nature of the issue, 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 Merck. If the complaint/issue is concerning an unused IVR, then the unused IVR should be held in the pharmacy. If the complaint/issue is concerning a used IVR, then the clinic staff should process this IVR per standard operating procedures for used IVRs.

Appendix 7-1: MTN-027 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:		Randomization #:	<table border="1"> <tr> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> <td style="width: 20px; height: 20px;"></td> </tr> </table>			

Participant ID:

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Did the participant provide written informed consent for enrollment into MTN-027? Yes No Clinic Staff Initials _____

MTN-027 Intravaginal Ring
(182mg of VCV; 30mg of MK-2048; 182mg of VCV and 30mg of MK-2048; or placebo)

Sig: Insert one ring into the vagina.

Quantity: One intravaginal ring. May be refilled as needed per request by designated clinic staff on MTN-027 Intravaginal Ring Request Slip for duration of participation in the study.

Authorized Prescriber Name (please print): _____

Authorized Prescriber Signature: _____

Date:

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dd *MMM* *yy*

Clinic Staff Instructions: Complete all items on this prescription. After initialing and dating below, deliver original white copy (labeled "Pharmacy") to pharmacy. File yellow copy (labeled "Clinic") in participant study notebook.

Clinic Staff Initials: _____ Date:

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dd *MMM* *yy*

Appendix 7-2: MTN-027 Intravaginal Ring Request Slip

CRS Name:	
Participant ID:	Randomization Number:
<input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> <input type="text"/> - <input type="text"/>	<input type="text"/> <input type="text"/> <input type="text"/>
<p>Clinic Staff Instructions: Mark whether this is a study intravaginal ring re-supply, clinical hold, resume (after a clinical hold), clinical permanent discontinuation, participant decline, 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.</p>	
<input type="checkbox"/> RE-SUPPLY → Pharmacy: Dispense 1 intravaginal ring.	
<input type="checkbox"/> HOLD → Reason: _____ Pharmacy: Do not dispense further intravaginal rings to the participant until another MTN-027 Intravaginal Ring Request Slip marked "RESUME" is received.	
<input type="checkbox"/> RESUME → Pharmacy: Dispense 1 intravaginal ring. Only an authorize prescriber can indicate RESUME.	
<input type="checkbox"/> PARTICIPANT DECLINE → Pharmacy: Do not dispense at this visit – participant is refusing intravaginal ring.	
<input type="checkbox"/> PERMANENT DISCONTINUATION → Reason: _____ Pharmacy: Do not dispense any further intravaginal rings to the participant.	
<input type="checkbox"/> PRODUCT USE PERIOD COMPLETED → Pharmacy: Do not dispense any further intravaginal rings to the participant.	
Clinic Staff Name (please print): _____ Clinic Staff Signature: _____	

Date: - -
 dd *MMM* *yy*

Appendix 7-3: CYP3A4 Inhibitors to Avoid

Strong Inhibitors ≥ 5-fold increase in AUC or > 80% decrease in CL	Moderate Inhibitors ≥2 but < 5-fold increase in AUC or 50-80% decrease in CL	Weak Inhibitors ≥ 1.25 but < 2-fold increase in AUC or 20- 50% decrease in CL
<p><u>Antibiotics:</u> clarithromycin, telithromycin</p> <p><u>Antidepressants:</u> nefazodone</p> <p><u>Azole Antifungals:</u> ketoconazole, itraconazole, posaconazole, voriconazole</p> <p><u>Pharmacokinetic Enhancers:</u> cobicistat</p> <p><u>Protease Inhibitors:</u> ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, saquinavir, boceprevir, telaprevir</p> <p><u>Reverse Transcriptase Inhibitors:</u> delavirdine</p> <p><u>Vasopression Receptor Antagonists:</u> conivaptan</p>	<p><u>Antiarrhythmics:</u> dronedaron</p> <p><u>Antibiotics:</u> erythromycin, ciprofloxacin</p> <p><u>Antiemetics:</u> aprepitant</p> <p><u>Antineoplastics:</u> imatinib</p> <p><u>Azole Antifungals:</u> fluconazole, miconazole</p> <p><u>Calcium Channel Blockers:</u> verapamil, diltiazem</p> <p><u>Protease Inhibitors:</u> atazanavir, darunavir/ritonavir, fosamprenavir</p>	<p><u>Antiandrogens:</u> bicalutamide</p> <p><u>Antianginals:</u> ranolazine</p> <p><u>Antiarrhythmics:</u> amiodarone, quinidine</p> <p><u>Antibiotics:</u> azithromycin</p> <p><u>Antidepressants:</u> fluoxetine, fluvoxamine</p> <p><u>Antihyperlipidemics:</u> atorvastatin</p> <p><u>Anti-inflammatory (asthma):</u> zileuton</p> <p><u>Antineoplastics:</u> nilotinib</p> <p><u>Antituberculars:</u> isoniazid</p> <p><u>Anxiolytics:</u> alprazolam</p> <p><u>Calcium Channel Blockers:</u> amlodipine, felodipine</p> <p><u>Herbal Supplements:</u> ginkgo biloba, goldenseal</p> <p><u>Histamine H2 Antagonists:</u> cimetidine, ranitidine</p> <p><u>Immune Suppressants:</u> cyclosporine</p> <p><u>Platelet Aggregation Inhibitors:</u> cilostazol</p> <p><u>Protease Inhibitors:</u> tipranavir/ritonavir</p>

Appendix 7-4: CYP3A4 Inducers to Avoid

Strong Inducers ≥ 80% decrease in AUC	Moderate Inducers 50-80% decrease in AUC	Weak Inducers 20-50% decrease in AUC
<u>Anticonvulsants/Mood Stabilizers:</u> phenytoin, carbamazepine <u>Anticonvulsants/Barbiturates:</u> primidone <u>Antituberculars:</u> rifampin <u>Barbiturates:</u> phenobarbital, butalbital <u>Glucocorticoids:</u> dexamethasone <u>Herbal Supplements:</u> St. John's wort [^] <u>Protease Inhibitors:</u> tipranavir (alone)	<u>Antibiotics:</u> nafcillin <u>Antihypertensives:</u> bosentan <u>Antituberculars:</u> rifabutin <u>CNS Stimulants:</u> modafinil <u>Reverse Transcriptase Inhibitors:</u> efavirenz, etravirine, nevirapine	<u>Anticonvulsants:</u> oxcarbazepine, rufinamide <u>Antidiabetics:</u> pioglitazone <u>CNS Stimulants:</u> armodafinil <u>Glucocorticoids:</u> prednisone <u>Herbal Supplements:</u> echinacea [^] <u>Protease Inhibitors:</u> amprenavir

[^]The effect of St. John's wort and echinacea varies widely and is preparation-dependent.

AUC: Area under the curve in a plot of concentration of drug in blood/systemic circulation versus time. AUC (from zero to infinity) represents the total drug exposure over time.

CL: Clearance