MTN-042 Clinical Flow Sheets
General Guidance

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in protocol section 9.

- In general, the IoR/designee has the discretion to hold study product temporarily at any time if s/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary.
- Unless otherwise specified in protocol section 9, the IoR/designee should immediately consult the PSRT for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product.
- The IoR/designee will document all temporary product holds and permanent discontinuations on applicable CRFs.
- Syndromic management of genital symptoms is acceptable while awaiting laboratory results if such practice is in line with the local standards of care.
- Observed single dose treatment should be provided whenever possible, per clinician discretion.
- When clinically appropriate, investigators should use oral or parenteral (in the case of syphilis, for example) medications when at all possible.
<table>
<thead>
<tr>
<th>Condition</th>
<th>Temporary Hold</th>
<th>Permanent Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV Infection, PrEP or PEP Use</strong></td>
<td></td>
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<tr>
<td>Positive HIV Rapid Test Result</td>
<td>X</td>
<td></td>
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<tr>
<td>Confirmed HIV infection</td>
<td></td>
<td>X</td>
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<tr>
<td>Reported use of PrEP for HIV prevention prior to pregnancy outcome.</td>
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<td>X</td>
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<tr>
<td>Reported use of PEP for potential HIV exposure</td>
<td>X</td>
<td></td>
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<tr>
<td><strong>Delivery/Pregnancy Outcome Related</strong></td>
<td></td>
<td></td>
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<tr>
<td>Report of admission to care for labor and delivery management,</td>
<td></td>
<td>X</td>
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<tr>
<td>including induction of labor and cesarean delivery</td>
<td></td>
<td></td>
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<tr>
<td>Suspected onset of labor or rupture of membranes.</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Confirmed labor or rupture of membranes</td>
<td>X</td>
<td></td>
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<tr>
<td>Pregnancy Loss</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Other Conditions/Events Requiring Hold or Discontinuation</strong></td>
<td></td>
<td></td>
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<tr>
<td>Non-therapeutic injection drug use</td>
<td></td>
<td>X</td>
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<tr>
<td>Unable or unwilling to comply with required study procedures, or</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>otherwise might be put at undue risk to their/their infant’s safety and</td>
<td></td>
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<tr>
<td>well-being by continuing product use, according to the judgment of the</td>
<td></td>
<td></td>
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<tr>
<td>IoR/designee.</td>
<td></td>
<td></td>
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<tr>
<td>**Concurrent (consult PSRT regarding ongoing product use and other</td>
<td></td>
<td>X</td>
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<tr>
<td>potential safety considerations)**</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Holds/Discontinuations in Response to Adverse Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic Reaction to the study product</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Grade 3 AE Related to Study Product Use not in Section 9.5</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Grade 4 AE (regardless of relationship to study product)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
### Conditions Requiring Hold/Discontinuation (2)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Temporary Hold</th>
<th>Permanent Discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td>**Conditions Requiring Hold/Discontinuation for **oral Truvada Group <strong>Only:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acquisition of hepatitis B infection</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Initial result of ≥ Grade 2 creatinine clearance</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Confirmation</strong> of ≥ Grade 2 creatinine clearance after retesting within one week</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Initial result of ≥ Grade 2 glycosuria or proteinuria</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Confirmation</strong> of ≥ Grade 2 glycosuria or proteinuria after retesting within one week</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td><strong>Conditions Requiring Hold/Discontinuation for Vaginal Ring Group Only:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial epithelial disruption (abrasion/peeling) which has worsened after re-evaluation in 3-5 days</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Deep epithelial disruption (ulceration)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Symptomatic, localized erythema or edema (area &lt;50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation in 3-5 days</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Asymptomatic, localized erythema or edema (area &lt;50% of vulvar surface or combined vaginal and cervical surface) which has worsened after re-evaluation at the next scheduled visit</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Generalized erythema or severe edema (area &gt;50% of vulvar surface or combined vaginal and cervical surface)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>≥ Grade 2 genital bleeding (LoA#1)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Unexpected Grade 1 genital bleeding due to deep epithelial disruption (LoA#1)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cervicitis (inflammation and/or friability)</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>≥ Grade 2 chorioamnionitis (leading to referral for delivery per SOC) (LoA#1)</td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>
Product Use by Grade

• Grade 1 or 2 (not specifically addressed in protocol section 9.5), regardless of relatedness to study product may continue product use

• Grade 3 (not specifically addressed in protocol section 9.5), judged to be not related, continue product use

• Grade 3 (not specifically addressed in protocol section 9.5) judged to be related
  – Temporarily hold product
  – Reassess weekly x 2 weeks
  – If ≤ Grade 2 within 2 weeks, resume product
  – If not ≤ Grade 2 within 2 weeks, consult PSRT

• Grade 4, regardless of relationship, temporarily hold, consult PSRT
Product Use Management: HIV Infection

START

HIV rapid tests

no rapid test(s) positive

CONTINUE product.

one or more rapid tests positive

HOLD product pending confirmatory testing.

status after confirmatory testing = HIV uninfected

RESUME product.

status after confirmatory testing = HIV infected

PERMANENTLY DISCONTINUE product.

If confirmatory HIV testing is unclear; contact the Network Laboratory for guidance.

Protocol Reference: Section 9.3 and 9.6
Product Use Management:
Additional Conditions Requiring Product Hold

➢ Reported use of PEP for potential HIV exposure
➢ Suspected onset of labor or rupture of membranes.
➢ Unable or unwilling to comply with required study procedures, or otherwise might be put at undue risk to their/their infant’s safety and well-being by continuing product use, according to the judgment of the IoR/designee (consult PSRT)
➢ Co-enrollment (consult PSRT)

HOLD product. Consult PSRT if required per protocol.
Product Use Management:
Additional Conditions Requiring Permanent Discontinuation

➢ Acquisition of hepatitis B infection (for Truvada group only)
➢ Confirmation of ≥ Grade 2 creatinine clearance (for Truvada group only).
➢ Confirmation of ≥ Grade 2 glycosuria or proteinuria (for Truvada group only).
➢ Allergic Reaction to the Study Product
➢ Reported use of PrEP for HIV prevention prior to pregnancy outcome.
➢ Non-therapeutic injection drug use
➢ Confirmed labor or rupture of membranes
➢ Report of admission to care for labor and delivery management, including induction of labor and cesarean delivery
➢ Pregnancy Loss

PERMANENTLY DISCONTINUE product.
Product Use Management for **ORAL** Study Product:
≥ Grade 2 Creatinine Clearance, glycosuria, or proteinuria

START

≥ Grade 2 creatinine clearance, glycosuria, or proteinuria

HOLD product and notify the PSRT. Re-test within 1 week of receipt of result.

Retesting yields ≥ Grade 1

Continue HOLD and CONSULT PSRT.

Retesting confirms ≥ Grade 2

PERMANENTLY DISCONTINUE product.

No re-test within 1 week

Continue HOLD and CONSULT PSRT.

Protocol Reference: Section 9.5
CONTINUE product, unless permanent discontinuation guidelines apply. Consult the PSRT if a permanent discontinuation is deemed necessary and instituted by the IoR/designee.

Vaginally applied medications should not be used. Whenever possible, oral or parenteral medications should be used instead.

*Treat per local or current WHO guidelines, using observed single dose regimens whenever possible.
Product Use Management during **VAGINAL RING** use:
**Superficial epithelial disruption (abrasion/peeling)**

- **CONTINUE product.**
  - Perform naked eye exam.

- **Re-evaluate by speculum exam in 3-5 days.**
  - **Is it worse?**
    - **Yes**
      - **HOLD product and consult the PSRT.**
    - **No**
      - **CONTINUE product.**

**Protocol Reference:** Section 9.5
Product Use Management during VAGINAL RING use:
Deep epithelial disruption (ulceration)

- If confirmed by investigator, HOLD Product
- Re-evaluate by speculum exam in 3-5 days. Has it resolved?
  - Yes: RESUME product.
  - No: Re-evaluate by speculum exam in 2-3 days. Has it resolved?
    - Yes: RESUME product.
    - No: CONTINUE HOLD consult the PSRT re: discontinuation

If reoccurrence with no identified etiology, hold product and consult the PSRT regarding permanent discontinuation.

Protocol Reference: Section 9.5
Product Use Management during **VAGINAL RING** use:
Localized erythema or edema (area less than 50%)

CONTINUE product.
Perform naked eye exam.

Symptomatic?
Re-evaluate by speculum exam in 3-5 days.
Is it worse?

Asymptomatic?
Re-evaluate at next scheduled visit

Yes
HOLD product and consult the PSRT.

No
CONTINUE product.

Protocol Reference: Section 9.5
Product Use Management during VAGINAL RING use:
Generalized Erythema or Severe Edema (area more than 50%)

- **HOLD**
  - Product and perform naked eye examination

- **Re-evaluate by speculum exam in 3-5 days.**
  - **Has it resolved?**
    - Yes: **RESUME product.**
    - No: **CONTINUE**

- **Re-evaluate by speculum exam in 2-3 days.**
  - **Has it resolved?**
    - Yes: **RESUME product.**
    - No: **HOLD consult the PSRT re: discontinuation.**

If reoccurrence with no identified etiology, hold product and consult the PSRT regarding permanent discontinuation.

*Protocol Reference: Section 9.5*
Product Use Management during **VAGINAL RING** use: 
**Unexpected grade 1 genital bleeding**

- **CONTINUE** product (at clinician’s discretion) and perform naked eye examination
- **Due to deep epithelial disruption?**
  - yes: Follow guidance for deep epithelial disruption
  - no: Continue Product use

**NOTE:** recommended discretion be used to follow this management while approval is pending for LoA#1

Protocol Reference: Section 9.5, LoA#1
Product Use Management during **VAGINAL RING** use:
*Unexpected ≥ Grade 2 genital bleeding*

- **HOLD** Product and perform naked eye examination
  - **Due to deep epithelial disruption?**
    - **yes** Follow guidance for deep epithelial disruption
    - **no** PERMANENTLY DISCONTINUE product.

*NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1*

**Protocol Reference:** Section 9.5, LoA#1
Product Use Management during **VAGINAL RING** use: Cervicitis (including inflammation and/or friability)

**HOLD**
Product and evaluate for GC/CT; consider syndromic management, per clinician discretion

**Re-evaluate by speculum exam in 3-5 days.**

**Has it resolved?**

**Yes**
Regardless of etiology, **RESUME product.**

**No**
**CONTINUE HOLD** consult the PSRT regarding permanent discontinuation. Provide care per SOC.

**NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1**

Protocol Reference: Section 9.5, LoA#1
Product Use Management during **VAGINAL RING** use:
Genital petechia(e)/ genital ecchymosis

CONTINUE product and perform naked eye exam; further evaluation/treatment per clinician discretion

Protocol Reference: Section 9.5
Product Use Management:
≥ Grade 2 chorioamnionitis

Refer for delivery per local SOC; Permanently discontinue study product

NOTE: recommended discretion be used to follow this management while approval is pending for LoA#1