FOLLOW-UP VISIT CONSIDERATIONS

MTN-038 STUDY-SPECIFIC TRAINING | 11 SEPT 2018
Protocol Sections 7.4 (Follow-up) and 9.2-9.4 (Clinical Management)
- SSP Section 5: Study Procedures
- SSP Section 8: Clinical Considerations
- SSP Section 9: AE and Safety Reporting
- SSP Section 10: Laboratory Considerations
- SSP Section 11: Counseling Considerations
- SSP Section 12 Data Management
Scheduled Visits:
- First 2 Weeks of VR use:
  - Day 1, 7, & 14 (V3-5)
- Further follow-up:
  - Day 28, 42, 56, 91/PUEV (V6-9)
- Final Contact:
  - Day 92/V10 (24-72 hrs after PUEV)
- Split visits: permitted but not encouraged, V4-10; not permitted V2 or V3 (Day 1)

Interim visits: phone or clinic visits between scheduled visits
Procedures required will depend on the reason for the visit
- Make-up missed visit
- For administrative reasons
- For product-related reasons
- In response to AEs and/or SAEs.
- For additional STI counseling and testing in response to STI symptoms.
- For any needed HIV counseling and testing in response to participant report of symptoms consistent with acute infection or presumed exposure to HIV.
- For other reasons at participant request

Early Termination:
- Complete procedures per the Day 91/PUEV/Early Termination Visit Checklist
- Collecting the PK/PD blood, pelvic, and rectal specimens will be at management team discretion.
### VISITS 3-5 (DAY 1, 7, AND 14) PROCEDURES

<table>
<thead>
<tr>
<th>Administrative</th>
<th>Co-enrollment check, update locator, schedule next visit, provide reimbursement, <em>offer condoms</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>None</td>
</tr>
<tr>
<td>Counseling</td>
<td><em>HIV Pre-Post Test and STI Risk Reduction</em></td>
</tr>
<tr>
<td></td>
<td><em>Contraceptive Protocol Adherence</em></td>
</tr>
<tr>
<td>Clinical</td>
<td>Review/collect/update medical/menstrual/meds history</td>
</tr>
<tr>
<td></td>
<td>Assess AEs</td>
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<tr>
<td></td>
<td><em>Targeted Physical Exam</em></td>
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<tr>
<td></td>
<td>Pelvic Exam – Check for VR</td>
</tr>
<tr>
<td></td>
<td>Evaluate/provide findings; <em>RX/refer for RTI/UTI/STI</em></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Blood – TFV levels, <em>CBC w/ platelets/diff., serum creatinine, Syphilis, HIV</em></td>
</tr>
<tr>
<td></td>
<td>Pelvic – CVF for TFV levels and biomarkers, <em>cervical biopsies ‡, NAAT for Trich and GC/CT, wet mount w/ pH</em></td>
</tr>
<tr>
<td></td>
<td>Rectal fluid for TFV (Days 1 &amp; 14 only)</td>
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<tr>
<td></td>
<td>Urine – <em>Pregnancy/ dipstick/ Culture analysis</em></td>
</tr>
</tbody>
</table>

*If indicated
‡ per biopsy schedule
## VISITS 6-8 (DAY 28, 42 AND 56)

<table>
<thead>
<tr>
<th>Administrative</th>
<th>Co-enrollment check, update locator, schedule next visit, provide reimbursement, offer condoms*</th>
</tr>
</thead>
</table>
| Behavioral     | Ring Adherence CRF (Visit 6 & 8 only)  
Follow-up CASI questionnaire |
| Counseling     | HIV Pre-Post Test and STI Risk Reduction*  
Contraceptive Protocol Adherence |
| Clinical       | Review/update medical/menstrual/meds history  
Assess AEs  
*Targeted Physical Exam*  
Pelvic Exam- check for VR  
Evaluate findings; RX/refer for RTI/UTI/STI* |
<table>
<thead>
<tr>
<th>Laboratory Specimen Collection</th>
<th>Day 28/Visit 6</th>
<th>Day 42/Visit 7</th>
<th>Day 56/Visit 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urine for pregnancy test</td>
<td>X</td>
<td>If indicated</td>
<td>X</td>
</tr>
<tr>
<td>Blood for TVF</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CVF for TVF</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CVF for anti-HSV-2 activity</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CVF for biomarkers</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vaginal swabs for microbiota</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Vaginal Gram Stain</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>CVL for PK, PD and biomarkers</td>
<td>X</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Cervical Biopsies (‡ per sampling assignment)</td>
<td>X‡</td>
<td></td>
<td>X‡</td>
</tr>
<tr>
<td>HIV-1/2, urine dipstick/culture, AST/ALT, CDC w/ diff &amp; plat., creatinine, syphilis, NAAT for CG/ GT &amp; trich, wet mount w/ pH</td>
<td>If indicated</td>
<td>If indicated</td>
<td>If indicated</td>
</tr>
</tbody>
</table>
added swabs for microbiota. Also added ‘day 28 only’ for biopsies
Lisa Levy, 9/5/2017

ok
Tara McClure, 9/5/2017
VISITS 3-8: SPECIMEN COLLECTION PROCEDURES

During pelvic exam

**Blood for TVF**

**Rectal fluid for TVF (With anoscope)**

**CVF swabs**
- TVF
- Biomarkers
- Anti-HSV-2

**Vaginal fluid**
- Microbiota
- Gram stain

**CVL**

**Cervical Biopsies**

**Collect all specimens with the VR in place**

As close time proximity as possible for TVF samples (within 30 minutes)

**Note:** Perform procedures as required per study visit
### Visit 9/ PUEV (Day 91)/ Early Termination

<table>
<thead>
<tr>
<th>Administrative</th>
<th>Co-enrollment check, update locator, schedule next visit, provide reimbursement, <em>offer condoms</em></th>
</tr>
</thead>
</table>
| Behavioral    | Ring Adherence CRF  
Exit CASI questionnaire  
IDI (if selected/agreed at enrollment)* |
| Counseling    | HIV Pre-Post Test and STI Risk Reduction  
Contraceptive  
Protocol Adherence |
| Clinical      | Review/update medical/menstrual/meds history  
Assess AEs  
*Targeted Physical Exam*  
Pelvic Exam – check for VR  
Evaluate findings; *RX/refer for RTI/UTI/STI*  
VR removal |

*Serves as Early Study Termination Visit: Complete all procedures and Study Discontinuation CRF*
### VISIT 9/ PUEV (DAY 91) / EARLY TERMINATION, CON’T

#### Pre-Ring Removal

<table>
<thead>
<tr>
<th>Urine</th>
<th>Blood</th>
<th>Rectal</th>
<th>Pelvic</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Pregnancy</td>
<td>• HIV-1/2</td>
<td>• Rectal fluid for TFV</td>
<td>• CVF for TFV</td>
</tr>
<tr>
<td>• <em>Dipstick/culture analysis</em></td>
<td>• CBC w/ diff &amp; plat.</td>
<td></td>
<td>• CVF for biomarkers</td>
</tr>
<tr>
<td></td>
<td>• Creatinine</td>
<td></td>
<td>• Vag swab for microbiota</td>
</tr>
<tr>
<td></td>
<td>• AST/ALT</td>
<td></td>
<td>• Gram stain</td>
</tr>
<tr>
<td></td>
<td>• TFV</td>
<td></td>
<td>• Cervical biopsies for PK and PD</td>
</tr>
<tr>
<td></td>
<td>• <em>Syphilis</em></td>
<td></td>
<td>• <em>NAAT for CG/CT &amp; Trich</em></td>
</tr>
</tbody>
</table>

**4 hrs Post-Ring Removal for TFV samples:**

- blood → rectal fluid → CVF

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MTN-038 SITE-SPECIFIC TRAINING | 11SEPT2018- FOLLOW VISIT CONSIDERATIONS
VISIT 9/PUEV: SPECIMEN COLLECTION AND VR PROCEDURES

Pre-VR Removal
- Blood
- Rectal fluid • With anoscope

During pelvic exam
- CVF swabs • Prior to speculum placement
- Vaginal fluid
  - Microbiota
  - Gram stain
  - (w/ speculum)
- Cervical Biopsies (w/ speculum)

As close time proximity as possible (within 30 minutes)

Post-VR Removal
*Collect TFV samples within 30 minutes
- Blood
- Rectal fluid
- CFV
# VISIT 10/ FINAL CONTACT (IN-CLINIC)

<table>
<thead>
<tr>
<th>Administrative</th>
<th>Update locator, provide results from last visit, schedule next visit if needed, provide reimbursement, offer condoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral</td>
<td>None</td>
</tr>
<tr>
<td>Counseling</td>
<td><strong>HIV Pre-Post Test and STI Risk Reduction</strong></td>
</tr>
<tr>
<td>Clinical</td>
<td>Review/update medical/menstrual/meds history&lt;br&gt;Assess AEs&lt;br&gt;<em>Targeted Physical Exam</em>&lt;br&gt;Evaluate findings; <em>RX/refer for RTI/UTI/STI</em></td>
</tr>
<tr>
<td>Laboratory</td>
<td>Blood – TFV levels, <em>CBC w/ platelets/Diff, creatinine</em>&lt;br&gt;Rectal - fluid for TFV levels&lt;br&gt;Pelvic – CVF for TFV levels, <em>wet mount w/ pH</em>&lt;br&gt;Urine – <em>Pregnancy, dipstick/ Culture analysis</em></td>
</tr>
</tbody>
</table>

Schedule 24-72 hours after Day 91/PUEV
STUDY PROCEDURE EXCEPTIONS OF NOTE

- **Condoms offered** per site SOP/practice. Meant to provide exemption for when condoms use is not applicable such as if a participant has sex exclusively with women or is abstinent per the protocol inclusion criteria requirements.

- **Pregnancy test and contraceptive counseling** not required for participants who have undergone supracervical hysterectomy or bilateral oophorectomy verified by medical records.

- If **HIV test results** will not be available during the visit, post-test counseling may occur upon provision of test results over the phone or in person as part of a split visit or at an interim visit, if indicated per local standard of care.
MISSED VISITS

- Visits not completed within the allowable visit window are considered “missed”
- Missed Visit CRF must be completed. If the visit is made-up outside of the visit window, log a PD with this reason selected.
- Follow your site-specific retention SOP for procedures to be done and proper documentation of efforts to contact participant

If Visits 3-10 (Days 1, 7, 14, 28, 56, and/or Day 91/PUEV) are missed:

- Make up the missed visit and required study procedures (as soon as possible) at an interim visit, and

- Retain the participant for her remaining scheduled study follow-up visits.
  - Note: If Day 91 is missed, the visit should be made-up as soon as possible and the Final Contact Visit should be schedule based on the actual PUEV (interim visit).
QUESTIONS? COMMENTS?