MTN-003:
Overview of changes

- Increased sample size and length of follow-up
- Upper limit of age expanded
- Incorporated:
  - CMs and LoAs
  - Genital herpes acquisition endpoint
  - Information on results from other studies, including CAPRISA 004 and iPrEx
  - Changes based on updated package inserts and IBs
Overview of changes

• Reduced burden on procedures for seroconverters
• Updated lab QA procedures
• Clinical management guidance
• Statistical Considerations
• Appendix I: Schedule of Study Visits and Evaluation
• Updated Informed Consent Forms
Incorporated CMs and LoAs

Version 2.0

THE SCIENCE OF IMPROVING LIVES
Increased sample size and length of follow-up

Sample Size: The Bigger the Better
Increased sample size and length of follow-up

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 4,200</td>
<td>N = 5,000</td>
</tr>
<tr>
<td>Accrual = 21 Months</td>
<td>Accrual = 24 Months</td>
</tr>
<tr>
<td>Product use period:</td>
<td>Product use period:</td>
</tr>
<tr>
<td>• Minimum = 12 Months</td>
<td>• Minimum = 12 Months</td>
</tr>
<tr>
<td>• Maximum = 33 Months</td>
<td>• Maximum = 36 Months</td>
</tr>
<tr>
<td>Maximum length of Study</td>
<td>Maximum length of Study</td>
</tr>
<tr>
<td>Participation = 35 Months</td>
<td>Participation = 38 Months</td>
</tr>
</tbody>
</table>
HSV-1 and HSV-2 exploratory objective

• Based on CAPRISA 004 results
• To assess the incidence of genital herpes
• Tested at end of the study on enrollment and PUEV plasma archive specimens
• Participants will receive HSV tests results once these are available
Risks and Benefits

• Risks and benefits modified to reflect updates to package inserts and Investigator Brochures:
  – Phlebotomy may lead to greater than expected bleeding
  – Oral TDF Tablet:
    • depression
    • generalized weakness
    • possible damage to liver
    • bone pain and bone changes
# Inclusion and Exclusion Criteria

## Version 1.0

Upper age limit: 40

(PEP) for HIV infection

**Notes (lab abnormalities):**
- Exclusionary dipstick results could not be repeated
- [No provision regarding serum creatinine <LLN]

## Version 2.0

Upper age limit: 45

(PEP) for HIV **exposure**

**Notes (lab abnormalities):**
- Dipstick retesting allowable if results due to UTI or menses*
- Serum creatinine results <LLN will be repeated during the Screening period

*According to the judgment of the IoR/designee*
Section 6.7: Study Product Adherence

• Clarified that study product counts and self-reported data will not be reconciled
Section 7.4: Enrollment Visit

- Administration of Informed Consent for Enrollment may precede final confirmation of eligibility
  - Allows for single blood draw at enrollment (HIV testing, plasma archive)
  - SOPs must be updated
Section 7.5: Follow-Up Study Procedures

- All pelvic exams, scheduled and unscheduled, should include the following procedures:
  - Vaginal pH
  - Vaginal fluid swab for storage for biomarker analyses
  - Endocervical swab for biomarker analyses
  - Bimanual exam
- BV and candidiasis = only when clinically indicated (symptomatic)
- Clarified behavioral measures omitted when participant not exposed to study product
# Section 7.6.1: Reduced Procedures for Seroconverters

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HIV serology</td>
<td>• HIV serology</td>
</tr>
<tr>
<td>• Provision of study product, instructions, adherence counseling</td>
<td>• Provision of study product, instructions, adherence counseling</td>
</tr>
<tr>
<td>• Last dose recall</td>
<td>• Last dose recall</td>
</tr>
<tr>
<td></td>
<td>• ACASI</td>
</tr>
<tr>
<td></td>
<td>• Gram stain assessment</td>
</tr>
<tr>
<td></td>
<td>• Following a final test 8 weeks after product hold, the following tests will no longer be completed:</td>
</tr>
<tr>
<td></td>
<td>• Complete blood count with differential and platelets</td>
</tr>
<tr>
<td></td>
<td>• Phosphate, creatinine, AST and ALT</td>
</tr>
<tr>
<td></td>
<td>• Dipstick Urinalysis</td>
</tr>
<tr>
<td></td>
<td>• Plasma archive at Quarterly and PUEV visits</td>
</tr>
<tr>
<td></td>
<td>• Scheduled VOICE Termination Visit</td>
</tr>
</tbody>
</table>
Section 7.6.1: Changes Relating to MTN-015

For Seroconverters who delay or decline MTN-015:

• Deleted:
  – HBsAb test 6M after vaccine series

• Refer to SSP Section 6.10 for guidance
  – HBsAb testing will be performed for these participants, regardless of enrollment in MTN-015, at 1-2 months following vaccine series.

• Enrollment Informed Consent and Appendix I of the protocol updated to incorporate this change
Section 8.2: AE Definitions and Reporting

• Clarified that an AE is considered an untoward medical occurrence from the time of randomization through study termination

• Clarified that genital bleeding clinically assessed to be expected is not an AE

• Lab test abnormalities specified in the DAIDS Toxicity Table, not otherwise associated with a reported clinical AE, are reportable AEs

• SAE/EAE (rather than AE) must be reassessed by study staff 30 days after the participant’s study exit
Grade 3 AE - Related to Product

Not otherwise addressed in section 9

### Version 1.0

- No documentation of improvement to ≤ Grade 2 within 2 weeks, permanently discontinue
- Same Grade 3 AE reoccurs, Consult PSRT

### Version 2.0

- No documentation of improvement to ≤ Grade 2 within 2 weeks, **consult PSRT**
- Same Grade 3 AE reoccurs **deemed related to study product**, Consult PSRT
### Grade 3 AST and/or ALT Elevations (Oral)

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Temporarily hold</td>
<td>• Temporarily hold</td>
</tr>
<tr>
<td>• Repeat ALT/AST within 1 week</td>
<td>• Repeat ALT/AST within 1 week</td>
</tr>
<tr>
<td>• Follow weekly until Grade $\leq 1$, resume with concurrence from PSRT</td>
<td>• Follow weekly until Grade $\leq 1$, resume with concurrence from PSRT</td>
</tr>
<tr>
<td>• If no improvement to Grade $\leq 1$ within 3 weeks, permanently discontinue</td>
<td>• If no improvement to Grade $\leq 1$ within 3 weeks, consult the PSRT</td>
</tr>
</tbody>
</table>
### Grade 4 AST and/or ALT Elevations

#### Version 1.0
- Permanently discontinue
- Consult the PSRT
- Re-test at least weekly until both AST/ALT are grade $\leq 1$

#### Version 2.0
- **If RELATED**
  - Temporarily hold
  - Consult the PSRT
  - Re-test ALT/AST within 1 week
  - Follow weekly until Grade $\leq 1$, resume with concurrence from PSRT
- **NOT RELATED:**
  - Temporarily hold
  - Consult the PSRT
  - Re-test ALT/AST within 1 week
  - Follow weekly until Grade $\leq 1$, resume with concurrence from PSRT
# Creatinine (Oral)

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Temporarily hold for $\geq 1.5 \times BL$</td>
<td>• Temporarily hold for $\geq 1.5 \times BL$</td>
</tr>
<tr>
<td>• Re-test as soon as possible to within 1 week</td>
<td>• Re-test as soon as possible to within 1 week</td>
</tr>
<tr>
<td>• Resume product when improves to $\leq 1.3 \times BL$</td>
<td>• Resume product when improves to $\leq 1.3 \times BL$, <strong>in consultation with PSRT</strong></td>
</tr>
<tr>
<td>• If product is resumed and creatinine level increases to $\geq 1.5 \times BL$, permanently discontinue</td>
<td>• If product is resumed and creatinine level increases to $\geq 1.5 \times BL$, <strong>consult PSRT for further guidance on continuing product hold, or progressing to permanent discontinuation</strong></td>
</tr>
</tbody>
</table>
## Creatinine Clearance (Oral)

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• If clearance is $&lt; 50\text{mL/min}$ product should be held</td>
<td>• If clearance is $&lt; 50\text{mL/min}$ product should be held</td>
</tr>
<tr>
<td>• Re-test as soon as possible (at most within 1 week of receipt of results)</td>
<td>• Re-test as soon as possible (at most within 1 week of receipt of results)</td>
</tr>
<tr>
<td>• If level of $&lt; 50\text{mL/min}$ is confirmed with re-test, permanently discontinued</td>
<td>• If level of $&lt; 50\text{mL/min}$ is confirmed with re-test, permanently discontinued, in <strong>consultation with PSRT</strong></td>
</tr>
<tr>
<td>• If re-test cannot be done within 1 week plus 3 working days, permanently discontinue</td>
<td>• If re-test cannot be done within 1 week plus 3 working days <strong>will require PSRT consultation for further product management</strong></td>
</tr>
</tbody>
</table>
# Phosphate (Oral)

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Management of decreased phosphate was based on grading</td>
<td>• Management of decreased phosphate based on ranges for phosphate results</td>
</tr>
<tr>
<td>• Grade 1 and 2</td>
<td>• Phosphate $\geq 2.0$ mg/dL</td>
</tr>
<tr>
<td>• Grade 3 and 4</td>
<td>• Phosphate 1.4 - 1.9 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Phosphate 1.0 – 1.3 mg/dL</td>
</tr>
<tr>
<td></td>
<td>• Phosphate $&lt; 1.0$ mg/dL</td>
</tr>
</tbody>
</table>
Version 2.0 Phosphate Guidance (Oral)

• **Phosphate ≥ 2.0 mg/dL**
  – Continue product, unless other hold requirements apply
  – No recheck needed before the next scheduled phosphate test (e.g. Quarterly Visit)

• **Phosphate 1.4 mg/dL-1.9 mg/dL**
  – Manage as ≥ 2.0 mg/dL
  – Remind participant to eat a phosphate rich diet
Phosphate (Oral), cont.

- **Phosphate 1.0 - 1.3 mg/dL**
  - Continue product, unless other hold requirements apply
  - Remind participant to eat a phosphate rich diet
  - May offer two week course of phosphate supplements*
  - Retest phosphate at the next study visit. If on recheck:
    - $\geq 2.0 \text{ mg/dL}$: follow $\geq 2.0 \text{ mg/dL}$ guidance
    - 1.0 - 1.9 mg/dL: remind participant to eat a phosphate rich diet; may offer two week course of phosphate supplements.*
    - Phosphate level should be rechecked at the next study visit.
    - $< 1.0 \text{ mg/dL}$: follow guidance on Phosphate level $< 1.0 \text{ mg/dL}$

*According to the judgment of the IoR/designee*
Phosphate (Oral), cont.

- **Phosphate < 1.0 mg/dL**
  - Temporary product hold
  - Advise participant to eat a phosphate rich diet
  - May offer two week course of phosphate supplements*
  - Retest within 2 weeks of the receipt of the results

- If improvement to ≥ 1.0 mg/dL is documented within two weeks, product may be resumed and guidance related to ≥ 1.0 mg/dL followed, depending on the phosphate level result
  - If not, continue hold and consult PSRT

*According to the judgment of the IoR/designee*
## Proteinuria (General)

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• <strong>1+</strong> finding, confirm with a second urine dipstick no earlier than 1 week but no later than 2 weeks from detection</td>
<td>• <strong>Greater than trace</strong> finding, should prompt serum creatinine and phosphate testing on day of detection</td>
</tr>
<tr>
<td>• <strong>2+ or greater</strong> does not need to be confirmed at a separate visit</td>
<td>• <strong>1+</strong> requires a repeat dipstick 1-2 weeks after initial detection</td>
</tr>
<tr>
<td></td>
<td>• <strong>2+ or greater</strong> does not need to be confirmed at a separate visit</td>
</tr>
</tbody>
</table>
# Proteinuria (Oral)

## Detection of 1+

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hold product if detection of 1+ confirmed on two separate visits</td>
<td>• Product held only if creatinine or phosphorus results obtained at time of detection meet hold criteria</td>
</tr>
<tr>
<td>• Product should only be held if creatinine or phosphorus results obtained at time of detection meet hold criteria</td>
<td>• Detection of 1+ alone should not lead to product hold</td>
</tr>
</tbody>
</table>
# Proteinuria (Oral)

## Detection of 2+

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hold product until serum creatinine or phosphorus results obtained at time of detection are available</td>
<td>• Hold product until serum creatinine or phosphorus results obtained at time of detection are available</td>
</tr>
<tr>
<td>• Continue product hold if hold criteria outlined for creatinine and/or phosphate are met</td>
<td>• Continue product hold if hold criteria outlined for creatinine and/or phosphate are met</td>
</tr>
<tr>
<td>• If neither value meet hold criteria, study product should be resumed</td>
<td>• If neither value meet hold criteria, study product should be resumed</td>
</tr>
</tbody>
</table>
## Proteinuria (Oral)

### Detection of 3+ or greater

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Hold product regardless of serum creatinine or phosphorus result obtained at time of detection</td>
<td>• Hold product and consult PSRT regarding further testing and product management</td>
</tr>
<tr>
<td>• Urine dipstick, creatinine and phosphate testing should be performed monthly for at least 3 months</td>
<td></td>
</tr>
</tbody>
</table>
Proteinuria (Oral)

Resuming product following a hold

<table>
<thead>
<tr>
<th>Version 1.0</th>
<th>Version 2.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Product use may be resumed following resolution of proteinuria no earlier than 3 months after product cessation</td>
<td>• Product use may be resumed following the resolution to &lt; 2+, and approved by PSRT</td>
</tr>
<tr>
<td>• If product resumed and protienuria increases to 2+ or greater, product use must be permanently discontinued</td>
<td>• If product resumed (in the setting of 3+ or greater), and proteinuria increases to 2+ or greater, product use must be held, and PSRT consulted</td>
</tr>
</tbody>
</table>
Glycosuria (Oral)

**Version 1.0**

- Clinical management based on:
  - Detection of 1+
  - Detection of 2+
  - Detection of 3+ or greater

**Version 2.0**

- \(1+ \rightarrow\) confirmed \(\geq 1+\):
  - temporarily hold product and test serum creatinine and phosphorus
- \(\geq 2+ \rightarrow\) Temporarily hold product and test serum creatinine and phosphorus
- PSRT must be consulted for further guidance regarding product management
Updated Informed Consent Forms

• Increased sample size
• Increased study duration
• Increased age limit (site specific)
• Added CAPRISA 004 and iPrEx results
• Updated risks
• Added HSV testing
• Clarified HIV resistance, and Hepatitis B testing
• Enrollment IC may precede final confirmation of eligibility to reduce number of blood draws
Other Updates

- Appendix III: Follow-up HIV Testing Algorithm was updated to include guidance to consult NL for participants whose Sample 1 WB are indeterminate or negative.
- Appendix IV: Algorithm for Hep B Management was modified to include that vaccination may also follow local guidelines.
Thank you!

What are your questions?