MTN-001

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On behalf of the MTN001 Team
MTN-001

- Randomized, controlled, Phase II trial
- Comparing Adherence & Pharmacokinetics
- Once daily vaginal PMPA 1% gel
- Once daily oral tenofovir disoproxil fumarate (TDF) 300 mg tablet
MTN001 Rationale

- Head-to-head comparison of oral versus vaginal prevention dosing strategies
- Inform the design of 003 Tenofovir Efficacy Trial
  - Adherence estimates
  - Drug level estimates
- Activate new sites rapidly
Oral v. Vaginal Tenofovir

**Figure Legend**

<table>
<thead>
<tr>
<th>Route</th>
<th>Dose (mg)</th>
<th>Cmax (ng/mL)</th>
<th>Cmax per 100 mg</th>
<th>AUC (ng*hr/mL)</th>
<th>AUC per 100 mg</th>
<th>Relative F (Cmax, AUC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>270</td>
<td>618</td>
<td>2.29</td>
<td>3,372</td>
<td>12.5</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>135</td>
<td>240</td>
<td>1.78</td>
<td>2,093</td>
<td>15.5</td>
<td></td>
</tr>
<tr>
<td>Vaginal</td>
<td>40</td>
<td>3.4</td>
<td>0.09</td>
<td>46</td>
<td>1.2</td>
<td>&lt;4%, &lt;2%</td>
</tr>
</tbody>
</table>

270 mg PMPA QD PO
135 mg PMPA QD PO
68 mg PMPA QD PO
34 mg PMPA QD PO

[Barditch-Crovo AAC 2001]

40 mg PMPA (1%) single dose vaginal

[HPTN 050: N=6; Subj. w/ 3+ points]
Hypotheses

- Adherence and acceptability will be similar in both arms
- Tissue levels of PMPA will be similar irrespective of the route of administration
- Oral TDF will be associated with higher concentrations of PMPA in the blood compared to topical administration of PMPA
Study Schema

<table>
<thead>
<tr>
<th>Period A</th>
<th>W/O</th>
<th>Period B</th>
<th>F/U</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1-6</td>
<td>W7</td>
<td>Week 8-13</td>
<td>W14</td>
</tr>
</tbody>
</table>

**Arm 1 (60)**
- Oral TDF

**Arm 2 (60)**
- Vaginal PMPA

**Assessments**
- PK
- AA
- PK
- AA
Primary Objectives

- Comparison of oral tenofovir with vaginal PMPA in domains of:
  - Adherence
  - Acceptability
  - Pharmacokinetics (tissue)
Secondary Objectives

- Intracellular pharmacokinetics in blood
- Comparison of adverse effects
Procedures

- Adherence measures
- Behaviorally focused quantitative surveys
- Pharmacokinetic studies
  - Blood, vaginal fluid, vaginal biopsy*, intracellular*
- Laboratory measures of systemic safety

*PK Substudy Cohort only
Study Population

- Sexually active (weekly) women
- HIV-uninfected
- 18 to 45 years of age
- No active disease
Exclusion Criteria

- Acute or chronic hepatitis
- Renal disease (CrCl $>$ 70 mL/min)
- Any clinically relevant systemic disease
- History of pathologic fracture
- Pregnancy
- Breastfeeding
Sample size

- 120 women (60 in each arm)
- Paired analysis

Detect difference in adherence rate of Oral versus Vaginal regimen of

- 7.5% Difference, 83% Power, 0.0 rho*
- 5.0% Difference, 78% Power, 0.5 rho

*rho is magnitude of intra-individual correlation between arms.
Study Duration

- Approximately 98 days per participant
- Ten calendar months of accrual
- Eleven months total planned study duration
Sites

- Case Western Reserve University
- University of Pittsburgh
- University of Cape Town
- Makarere University/Johns Hopkins University
- TBD
- TBD