MTN 003D Overview: An Exploratory Study of Potential Sources of Efficacy Dilution in the VOICE Trial

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Outline

1. Stage 1
   - Background
   - Study Objectives
   - Study Sites & Sample
   - Study Design and Data Collection Tools

2. Stage 2
   - Background
   - Study Objectives
   - Study Sites & Sample
   - Study Design and Data Collection Tools
   - Study Timeline and Updates
   - Study Team & Key Roles
Stage 1
Background: Dilution of Efficacy*

- DSMBs futility results: tenofovir vaginal gel & oral tablet stopped

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* Masse et al., 2009
Sources of Efficacy Dilution

* Masse et al., 2009
Adherence

P24_1G. Please rate your ability, over the past 4 weeks, to insert gel exactly as you were instructed.

1. [ ] Very poor
2. [ ] Poor
3. [ ] Fair
4. [ ] Good
5. [ ] Very good
6. [ ] Excellent

We are most interested in knowing on how many days you inserted gel. So if you cannot remember which day(s) exactly you did insert gel, please guess. We prefer that you indicate that you missed some days, even if you cannot remember which exact days you missed.

NOTE: Q25aG repeats going backwards 7 days starting with yesterday.

25aG. Yesterday (x-day) did you insert gel?

1. Yes
2. No
3. Don’t remember
MTN 001 Trial: discrepancy between self report and plasma drug level

- After observed dosing, ALL had detectable plasma TFV
- After 6 weeks of home dosing:

**Daily TFV oral tablet**
- 38% of participants: had TFV plasma levels inconsistent with daily dosing
- BUT reported 100% adherence

**Daily TFV vaginal gel**
- 48% of participants: had undetectable TFV plasma levels
- BUT reported 100% adherence

*Minnis et al., 2012; van der Straten M2012*
MTN-001: Adherence to Vaginal Gel

- Those reporting 100% adherence were more likely to have undetectable plasma drug level ($p=0.02$)
Anal Sex

11. In the past 3 months how many times have you had anal sex? By anal sex we mean when a man puts his penis inside your anus.

Reported 1 or More Anal Sex Acts in the Past 3 Months?

Yes

No

Version 5.0   March, 30, 2009
Study Objectives

- **Primary:**
  - to explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants’ actual and reported product use
  - to explore the reasons, motivations, and context of engaging in receptive anal intercourse (and rectal use of gel among VOICE participants in the gel group)

- **Secondary:**
  - to explore participants’ risk perceptions and motivations to participate in VOICE and the association of these factors with product use or non-use in a prevention trial setting
Study Sites & Sample Size

- **Uganda**
  - Kampala (MU-JHU, n=22)

- **Zimbabwe**
  - Chitungwiza (Seke South and Zengeza, n=26)

- **South Africa**
  - Durban (Isipingo and Overport, n=40)
## Overall Stage 1 Sample

- Former VOICE participants

<table>
<thead>
<tr>
<th>Study group:</th>
<th>Gel Users</th>
<th>Tablet Users</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>All other women</td>
<td>20 [32]</td>
<td>23 [32]</td>
<td>43 [64]</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>43 [40]</td>
<td>45 [40]</td>
<td>88 [80]</td>
</tr>
</tbody>
</table>

*Target accrual numbers presented in brackets*
Relevant Stage 1 Findings

- Participants largely did not admit to non-adherence.
- Participants suggested that presenting women with blood test results would encourage honesty in reporting adherence.
Stage 2
Final VOICE Results

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+27-(0)73-323-0087 (through 7 March)
rossil@upmc.edu

FOR IMMEDIATE RELEASE

Daily HIV prevention approaches didn’t work for African women in the VOICE Study

Truvada found not an effective strategy in this population
Young, single women were least likely to use tablets or gel, and more likely to get infected at very high rates

ATLANTA, March 4, 2013 – Results of a major HIV prevention trial suggest that daily use of a product – whether a vaginal gel or an oral tablet – does not appear to be the right approach for preventing HIV in young, unmarried African women.

Of the three products tested in the VOICE Study – tenofovir gel, oral tenofovir and oral Truvada® – none proved to be effective among the 5,029 women enrolled in the trial; most participants did not use them daily as recommended. Drug was detected in less than a third of blood samples from women who were assigned to use either Truvada or oral tenofovir and in less than a quarter of samples from women designated to use gel. Moreover, those least likely to use their assigned products, single women under age 25, were also the most likely to acquire HIV. Incidence in these young women approached nearly 10 percent in some of the study sites in South Africa. a
# Tenofovir Detection During Study Participation*

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>FTC/TDF</th>
<th>TFV Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percent of <em>women</em> with TFV not detected in <em>any</em> samples</td>
<td>58%</td>
<td>50%</td>
<td>55%</td>
</tr>
</tbody>
</table>

* At routine quarterly visits among participants in the random sample of active arms
# Adherence from 3 Different Measures

<table>
<thead>
<tr>
<th></th>
<th>TDF</th>
<th>FTC/TDF</th>
<th>TFV Gel</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total percent of doses reportedly taken</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Returned Pill or Applicator Counts</td>
<td>87%</td>
<td>92%</td>
<td>86%</td>
</tr>
<tr>
<td>Self Report (7 days)</td>
<td>90%</td>
<td>91%</td>
<td>90%</td>
</tr>
<tr>
<td><strong>Adherence based on plasma TFV detection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percent of samples with TFV detected averaged across women (mean)</td>
<td>30%</td>
<td>29%</td>
<td>25%</td>
</tr>
</tbody>
</table>

* Mean across all women’s proportion of adherence estimated by these measure
Tenofovir Detection with Plasma Testing:

- Assay is more sensitive for oral (tablets) than vaginal (gel) dosing
- Window of detection is longer for oral (tablets) than vaginal (gel) dosing
- Tablets: TFV detectable for up to ~7 days
- Gel: TFV detectable for up to ~3 days

No drug detected=

- Tablets: no dose taken in past week
- Gel: no dose taken in past 3 days
Study Objectives

- **Primary:**
  - to explore larger contextual issues and specific aspects of the VOICE trial that positively and negatively affected participants’ actual and reported product use
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- **Secondary:**
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Study Sites & Sample Size

- **Uganda**
  - Kampala (MU-JHU, n~≈48)

- **Zimbabwe**
  - Chitungwiza (Seke South and Zengeza, n~≈48)

- **South Africa**
  - Durban (Isipingo and Overport, n~≈48)
## Overall Stage 2 Sample

- Former VOICE participants (both MTN-003D naïve and experienced)

<table>
<thead>
<tr>
<th>Drug Detection Level**</th>
<th>Study Group</th>
<th>HIV(+)</th>
<th>HIV(-)</th>
<th>~Total FGDs/IDIs</th>
<th>~Total No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low drug detection per PK results</td>
<td>Gel</td>
<td>6 IDI</td>
<td>12 IDI 6 FGD△</td>
<td>24</td>
<td>54</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>6 IDI</td>
<td>12 IDI 6 FGD△</td>
<td>24</td>
<td>54</td>
</tr>
<tr>
<td>High drug detection per PK results</td>
<td>Gel</td>
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<td>12 IDI</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>6 IDI</td>
<td>12 IDI</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>24</td>
<td>60</td>
<td>84</td>
<td>144</td>
</tr>
</tbody>
</table>
## Stage 2 Sample per Location

<table>
<thead>
<tr>
<th>Drug Detection Level**</th>
<th>Study Group</th>
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<th>HIV(-)</th>
<th>~Total FGDs/IDIs</th>
<th>~Total No. of Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gel</td>
<td>2 IDI</td>
<td>4 IDI</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>2 IDI</td>
<td>4 IDI</td>
<td>6</td>
<td>6</td>
</tr>
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<td>Low drug detection per PK results</td>
<td>Gel</td>
<td>2 IDI</td>
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<td></td>
<td>Tablet</td>
<td>2 IDI</td>
<td>4 IDI</td>
<td>2 FGD△</td>
<td>18</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td>8</td>
<td>20</td>
<td>28</td>
<td>48</td>
</tr>
</tbody>
</table>
Stage 2 Design & Data Collection Tools

- Qualitative Exploratory Study
- Instruments:
  - Demographic survey
  - Discussion Guide [IDI & FGD]
- Available Tools:
  - Section A. MTN press release, educational sheet for study results; local press clippings
  - Section B. Timeline tool; PK visuals
  - Section C. Theme identification cards; pictures of prevention products
# Study Timeline and Updates

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>May 012</td>
<td>Protocol v1.0 approved</td>
</tr>
<tr>
<td>July 012</td>
<td>Qualitative training (Durban)</td>
</tr>
<tr>
<td>Sept 012</td>
<td>Full IRB approval (MRC)</td>
</tr>
<tr>
<td></td>
<td>First IRB approval (MUJHU)</td>
</tr>
<tr>
<td>1 Oct 012</td>
<td>Protocol specific training (Cape Town)</td>
</tr>
<tr>
<td>Oct 012</td>
<td>All sites activated</td>
</tr>
<tr>
<td></td>
<td>Stage 1 data collection starts</td>
</tr>
<tr>
<td>Mar 012</td>
<td>Stage 1 data collection ENDS</td>
</tr>
<tr>
<td>May 013</td>
<td>Protocol v2.0 approved</td>
</tr>
<tr>
<td>Oct 013</td>
<td>Stage 2 qualitative training (Durban)</td>
</tr>
<tr>
<td></td>
<td>Local IRB approvals obtained for Stage 2 and data collection begins</td>
</tr>
<tr>
<td>Dec 013</td>
<td>Stage 2 data collection ends</td>
</tr>
</tbody>
</table>
Study Team and Key Roles

Core/US
- **Chair**: Ariane van der Straten
- **Co-chairs**: Liz Montgomery, Barbara Mensch
- **Operations (FHI 360)**: Lisa Levy, Kristy Alston
- **Data coordination (RTI/WGHI)**: Miriam Hartmann
- **MTN Core**: Beth Galaska Burzuk
- **DAIDS**: Jeanna Piper

Site Teams
- **UZ-UCSF**: Nyaradzo Mgodi, Petina Musara, Imelda Makhala, Otilia Munaiwa
- **MU-JHU**: Clemensia Nakabiito, Juliane Etima, Teopista Tibaijuka, Josephine Nabukerra
- **MRC**: Sarita Naidoo, Kubashni Woeber, Funeka Mthembu, Nozipho Vilakazi

Behavioral Consultants
- **DTHF**: Zoe Duby, Thola Bennie
QUESTIONS?