Microbicide Trials Network: How are We Addressing HIV Prevention?

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MTN CORE
Overview

- Review the accomplishments from the MTN family since our previous regional meeting (May 2007)
- Reposition to face the challenges as we transition from HPTN 035 to VOICE
- Map the role of the MTN in the HIV prevention research landscape moving forward
Milestones

- May 2007: First MTN Regional Meeting
- June/July 2007: Approval of VOICE by the Strategic Working Group at Division of AIDS
- 26 July 2007: Completion of enrollment in HPTN 035
- October 2007: Face-to-face protocol development meeting for VOICE in Durban, SA
Milestones

- Dec 2007: VOICE PSRC review
- Feb 2008: Microbicides 2008 meeting in Delhi, India
  - 8 scientific oral presentations
  - 20 poster presentations
  - 2 book presentations
- Feb 2008: Site selection for VOICE study
Milestones

- April 2008: MTN Annual meeting, Washington DC
- May 2008: VOICE Version 1.0 approved by DAIDS and submitted to the FDA
- June 2008: MTN-001 and MTN-002 open for accrual
- July 2008: Community consultation for VOICE stopping rules and face-to-face protocol development meeting for VOICE community study (VOICE-C)
MTN Accomplishments

- Completion of full enrollment of 3100 women on HPTN 035 within 2 weeks of the timeline projected in May 2005
- Completion of HPTN 059 and presentation of the final study outcome at the Microbicides 2008 meeting in Delhi, India
MTN Accomplishments

- Development of a new collaboration with the International Partnership for Microbicides in evaluating the safety and acceptability of a vaginal ring for sustained delivery of microbicides
- Approval of two protocol concepts for pharmacokinetic and safety studies of tenofovir gel used as a rectal microbicide (MTN-006 and MTN-007)
The First Two Years of MTN

- Site teams can recruit and retain participants in a regulatory grade study of an investigational product with
  - High retention
  - Astonishing data quality
  - Quality laboratory testing
  - Appropriate follow-up of adverse events
  - Exceptional community and CAB input
The HPTN 035 Experience

- Has provided the foundation for success with the VOICE trial
- Has developed confidence within the site teams at every level
- Has built the NIH’s confidence in our ability to execute a high quality trial on time and within budget
- Has emerged as an example of a high quality team within the HIV prevention field
Informing Science in VOICE

- MTN-001: Comparison of oral tenofovir, vaginal tenofovir, and simultaneous use of both products
- Adherence
- Acceptability
- Pharmacokinetics
  - Blood
  - Cells in blood
  - Female genital tract
VOICE: A Flagship Study

- Phase IIb trial with five study groups testing two different HIV prevention approaches in women:
  - A once-a-day antiretroviral tablet (PrEP) TDF or TDF/FTC
  - A once-a-day application of a vaginal gel
- 4,200 women to be enrolled at 10 centers in Africa
- Target start date Feb/ March 2009
Maximizing What We Learn in VOICE

- VOICE-B
  - An exceptional opportunity to learn about potential effects on bone density in reproductive age women using oral PrEP

- VOICE-C
  - A unique collaboration between the community and the Behavioral Research Working Group
MTN-015: Seroconverter Study

Hypothesis:
Exposure to study agents in MTN clinical trials will not impact the natural history of HIV-1 infection as measured by the virologic, immunologic and clinical outcomes of participants with HIV-1 seroconversion during microbicide trials.
Microbicides and Pregnancy

- Prevent pregnancy through provision of contraception
- Proactively test microbicides and other prevention agents in pregnancy (MTN-002)
  - Phase I, open label, pharmacokinetic, placental transfer and safety evaluation – single site in Pittsburgh
  - Enroll 16 women at term
- MTN-016 – HIV Prevention Agent Pregnancy Exposure Registry
  - Protocol development in progress
MTN and VOICE: What is Different?

- Evaluation of **oral drugs** for treatment of HIV
  - Greater risk of toxicity associated with systemic drugs = greater need for enhanced pharmacovigilance
  - Need for site physicians to continue building expertise in recognizing serious toxicity (lactic acidosis, Nephrotoxicity) which will require an established referral system for acute care by specialists
  - Greater need to perform laboratory testing urgently to rule out toxic effects
Evaluation of Oral Drugs

- Enhanced communication with communities regarding the use of oral ARV's for prevention - a new concept
- The need to exclude breastfeeding women to prevent ARV exposure to infants
- Need for careful management of study product to prevent exposure of HIV-infected individuals to oral drug, which could induce resistance
Repositioning the MTN for VOICE

- Evaluation of **vaginal gels** which contain tenofovir
  - Systemic absorption, although only 1% of oral dose, but may be associated with greater systemic toxicity than for PRO 2000 or BufferGel
  - Use of products daily rather than with coitus
  - Concerns about emergence of ARV resistance
  - Daily use gel products create huge storage challenges for the sites (and potentially for our participants) because of the sheer volume of study to be stored
In the meantime......

- All women who have seroconverted during participation in HPTN 035 must be offered enrollment on MTN-015
- MTN-016 must be completed and provided to the sites for implementation so that eligible women and infants from HPTN 035 can be enrolled
- New CRSs will join the US sites in completing MTN-001
Transitions……

- Are always a time of uncertainty and anxiety
- Provide us the opportunity to reflect on what has gone well and to identify ways that we can do better in the future
- Present opportunities for growth and development of individuals and organizations
Transitional Challenges

- To maintain the high quality study teams at the sites
- For MTN CORE and the NIH to better understand the challenges at the sites and what we can do to assist during the transition
- To think strategically about how we can implement our 035 closeout plans, launch the 015 and 016 studies, and get VOICE into the field as quickly as possible
In Other Words……

- There are a million reasons we could fail due to the sheer complexity of the work we are trying to do
- We have to find a million and one more ways to make it all work
## Ongoing PrEP Studies

<table>
<thead>
<tr>
<th>Sponsor/ Funder Study</th>
<th>Product/ Population</th>
<th>N</th>
<th>Sites</th>
<th>Expected Results</th>
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<tbody>
<tr>
<td>CDC</td>
<td>TDF MSM</td>
<td>400</td>
<td>USA</td>
<td>2010</td>
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<tr>
<td>CDC BTS</td>
<td>TDF M&amp;F IDUs</td>
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<td>Thailand</td>
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<tr>
<td>CDC TDF-2</td>
<td>TDF/FTC M&amp;F Hetero</td>
<td>1800-2000</td>
<td>Botswana</td>
<td>2010?</td>
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## Ongoing PrEP Studies

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<th>N</th>
<th>Sites</th>
<th>Expected Results</th>
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<tbody>
<tr>
<td>UCSF NIH BMGF iPREX</td>
<td>TDF/FTC MSM</td>
<td>3000</td>
<td>Peru, Equador, Brazil, U.S. S Africa</td>
<td>2010</td>
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<tr>
<td>UW BMGF Partners PrEP</td>
<td>TDF, TDF/FTC Discordant Hetero Couples</td>
<td>3900</td>
<td>Kenya, Uganda</td>
<td>2011</td>
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# Planned PrEP Studies

<table>
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<tr>
<th>Sponsor/ Funder Study</th>
<th>Product/ Population</th>
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<th>Sites</th>
<th>Expected Start/ Results</th>
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<tbody>
<tr>
<td>MTN NIAID VOICE</td>
<td>TDF TDF/FTC TDF Gel Women</td>
<td>4200</td>
<td>Malawi South Africa Uganda Zambia Zimbabwe</td>
<td>2009/2012</td>
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## Tenofovir and Truvada Trials

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<tr>
<th>Group</th>
<th>Participants</th>
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<tr>
<td>Women</td>
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<tr>
<td>Heterosexual men</td>
<td>2,950</td>
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<tr>
<td>MSM</td>
<td>3,400</td>
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<tr>
<td>IDU</td>
<td>2,400</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>20,800</strong></td>
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Vaginal and Oral Interventions to Control the Epidemic

Sponsor: NIAID/NIH
For VOICE, The Time is Now

- HPTN 035 taught us that the results of other studies can impact our study, even if it is a different product.
- There are 7 other studies of oral or topical tenofovir/Truvada underway or planned.
- There is a window of opportunity to do the VOICE trial - but the results of other tenofovir gel, oral tenofovir and Truvada studies being done in similar or other populations will impact what happens during the VOICE trial.
Fulfilling Our Promise?

- A **lot** of people will have to do everything possible to maintain the timelines
- We must value efficiency
- We have to find common goals and shared values
- We must believe that we can make a difference in this epidemic, and treat every day of delay as a lost opportunity