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)

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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

Sponsor/ Funder ***Study***	**Product/ Population**	**N**	**Sites**	**Expected Results**
CDC	TDF MSM	400	USA	2010
CDC *BTS*	TDF M&F IDUs	2400	Thailand	2010
CDC *TDF-2*	TDF/FTC M&F Hetero	1800-2000	Botswana	2010?

Ongoing PrEP Studies

Sponsor/ Funder ***Study***	**Product/ Population**	**N**	**Sites**	**Expected Results**
UCSF NIH BMGF *iPREX*	TDF/FTC MSM	3000	Peru Equador Brazil U.S. S Africa	2010
UW BMGF *Partners PrEP*	TDF TDF/FTC Discordant Hetero Couples	3900	Kenya Uganda	2011

Planned PrEP Studies

Sponsor/ Funder *Study*	**Product/ Population**	**N**	**Sites**	**Expected Start/ Results**
FHI USAID/ Gates *FEM-PrEP*	TDF/FTC Women	3900	Kenya Malawi South Africa Tanzania	2008/2012
MTN NIAID *VOICE*	TDF TDF/FTC TDF Gel Women	4200	Malawi South Africa Uganda Zambia Zimbabwe	2009/2012

Tenofovir and Truvada Trials

Women	12,050
Heterosexual men	2,950
MSM	3,400
IDU	2,400
TOTAL	**20,800**


VOICE
Vaginal and Oral Interventions to Control the Epidemic
Sponsor: NIAID/NIH
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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