Welcome and MTN
State of the Network

Sharon Hillier PhD
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Directions

Where we were

Where we are

Where we are headed
Microbicide Trials Network

Reverse Site Visit

Washington D.C.

October 19, 2005
The mission of the Microbicide Trials Network is to reduce the sexual transmission of HIV through the development and evaluation of products applied topically to mucosal surfaces or administered orally. The goal is to conduct scientifically rigorous and ethically sound clinical trials of safety and effectiveness that will support licensure of topical microbicide products.
What MTN Will Do

• Develop and/or execute 14 separate clinical trials of microbicides over a 7 year period
• Maintain an extremely focused timeline driven research agenda
• Make tough decisions regarding both science and sites
• Not try to be all things to all people
# Product Pipeline in 2005*

<table>
<thead>
<tr>
<th>Stage</th>
<th>Membrane Disruption</th>
<th>Defense Enhancers</th>
<th>Entry Inhibitors</th>
<th>Replication Inhibitors</th>
<th>Other</th>
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<tbody>
<tr>
<td>Pre-Clinical</td>
<td></td>
<td></td>
<td>PSC-Rantes</td>
<td>MIV-150 TMC-125</td>
<td>Aptamers</td>
</tr>
<tr>
<td>Phase 1</td>
<td></td>
<td>Acidform™</td>
<td>Cellulose acetate VivaGel™</td>
<td>UC781 TMC 120 ring</td>
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</tr>
<tr>
<td>Phase 2/2B</td>
<td></td>
<td>Lactobacillus</td>
<td>Invisible condom™</td>
<td></td>
<td>Praneem Polyherbal</td>
</tr>
<tr>
<td>Phase 3</td>
<td>C31G</td>
<td>BufferGel™</td>
<td>Carraguard Cellulose Sulfate PRO 2000 (0.5%, 2%)</td>
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</table>

*Active planning, ongoing, or recently completed studies

Source: Alliance for Microbicide Development, October 2005
The MTN Portfolio
# Completed Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Product(s)</th>
<th>Route</th>
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<tbody>
<tr>
<td>HPTN-059</td>
<td>2</td>
<td>Tenofovir</td>
<td>V</td>
</tr>
<tr>
<td>HPTN-035</td>
<td>2/2B</td>
<td>PRO2000, BufferGel®</td>
<td>V</td>
</tr>
<tr>
<td>MTN-001</td>
<td>2</td>
<td>Tenofovir</td>
<td>O, V</td>
</tr>
<tr>
<td>MTN-002</td>
<td>1</td>
<td>Tenofovir</td>
<td>V</td>
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<tr>
<td>MTN-004</td>
<td>1</td>
<td>VivaGel®</td>
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<tr>
<td>RMP-02 / MTN-006</td>
<td>1</td>
<td>Tenofovir</td>
<td>R</td>
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<tr>
<td>MTN-007</td>
<td>1</td>
<td>Tenofovir</td>
<td>R</td>
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<tr>
<td>MTN-009</td>
<td>N/A</td>
<td>Resistance</td>
<td>N/A</td>
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<tr>
<td>MTN-012</td>
<td>1</td>
<td>Dapivirine Gel</td>
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# Ongoing Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
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<th>Route</th>
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<tbody>
<tr>
<td>MTN-003&lt;br&gt;MTN-003B&lt;br&gt;MTN-003C&lt;br&gt;MTN-003D&lt;br&gt;MTN-003-P01</td>
<td>2B</td>
<td>TVD/TDF/Tenofovir</td>
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<td>MTN-005</td>
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<td>Placebo ring</td>
<td>V</td>
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<tr>
<td>MTN-008</td>
<td>1</td>
<td>Tenofovir</td>
<td>V</td>
</tr>
<tr>
<td>MTN-013</td>
<td>1</td>
<td>Dapivirine, Maraviroc</td>
<td>V</td>
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<tr>
<td>MTN-015</td>
<td>Seroconverter</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>MTN-016</td>
<td>Pregnancy registry</td>
<td>N/A</td>
<td>N/A</td>
</tr>
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</table>
Gone but not Forgotten Studies

<table>
<thead>
<tr>
<th></th>
<th>Phase</th>
<th>Product(s)</th>
<th>Route</th>
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<tbody>
<tr>
<td>MTN-010</td>
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<td>UC781</td>
<td>V</td>
</tr>
<tr>
<td>MTN-019</td>
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<td>Tenofovir</td>
<td>V</td>
</tr>
<tr>
<td>MTN-021</td>
<td>1</td>
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## Studies in Preparation

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
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<tbody>
<tr>
<td>MTN-011</td>
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<td>Tenofovir</td>
<td>V</td>
</tr>
<tr>
<td>MTN-014</td>
<td>1</td>
<td>Tenofovir</td>
<td>V, R</td>
</tr>
<tr>
<td>MTN-017</td>
<td>1</td>
<td>Truvada, Tenofovir</td>
<td>O, R</td>
</tr>
<tr>
<td>MTN-018</td>
<td>3B</td>
<td>CHOICE</td>
<td>O</td>
</tr>
<tr>
<td>MTN-018B</td>
<td>3B</td>
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<tr>
<td>MTN-018C</td>
<td>3B</td>
<td></td>
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<td>3</td>
<td>Dapivirine ring</td>
<td>V</td>
</tr>
<tr>
<td>MTN-022</td>
<td>2</td>
<td>Tenofovir, Truvada HIV vaccine</td>
<td>V</td>
</tr>
<tr>
<td>MTN-023</td>
<td>1</td>
<td>Dapivirine ring</td>
<td>V</td>
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<tr>
<td>MTN-024</td>
<td>1</td>
<td>Dapivirine ring</td>
<td>V</td>
</tr>
</tbody>
</table>
Protocol Summary in 2012

Initial MTN Target: 14
MTN Productivity by 2012: 32
MTN’s Contributions to HIV Prevention
MTN Contributions

- Preclinical evaluation of candidate microbicides
  - Comparative evaluation core
- Phase 1 pharmacokinetic / pharmacodynamic studies
- Clinical evaluation of candidate microbicides
  - Vaginal
  - Rectal
- Behavioral research agenda
- Pregnancy
- Antiviral resistance
Preclinical Evaluation

Colorectal explant infection product evaluation

Day of Culture

HIV-1 p24 (pg/ml)
PK / PD Studies

Viral infection in rectal biopsies

Oral Dose
Single Rectal Dose
Multiple Rectal Dose

Drug concentration in the biopsies

RMP-02/MTN-006
Clinical Evaluation of Microbicide Candidates
Which is effective?
Is each safe?
Which will women use?
VOICE Related Studies

- Pregnancy (MTN-016)
- Resistance (MTN-009)
- HIV Seroconverters (MTN-015)
- Bone health (VOICE-B)
- Community Perceptions (VOICE-C)
Rectal Microbicides
Anorectal Anatomy
Populations Needing RM

![Image of two people holding hands](image)

![Bar chart showing percentage of Women and RAI in Seattle, St. Louis, and New Orleans](chart)

**PROJECT ARM**
AFRICA FOR RECTAL MICROBICIDES
MTN Rectal Microbicide Portfolio

- **RMP-02/MTN-006**
  - Phase 1 rectal safety study of vaginal 1% tenofovir gel

- **MTN-007**
  - Phase 1 rectal safety study of reduced glycerin 1% tenofovir gel
Mucosal Safety

- Epithelial sloughing
- Histopathology
- Mucosal mononuclear cell phenotype by flow cytometry
- Cytokines
  - RT-PCR
  - Microarray
  - Luminex
- Fecal calprotectin
- Rectal microflora

Data from Charlene Dezzutti MTN Core Laboratory
Behavioral Research Agenda

- Integration of behavioral scientists into all MTN studies
- Ancillary behavioral studies
  - MTN-003C, MTN-003D
- Development and use of new approaches and technology
  - ACASI, Wisebags, VASP counseling
- Increased integration of biomedical and behavioral approaches to adherence monitoring
Pregnancy
MTN-002

- Single dose study of tenofovir gel prior to elective CS
- Maternal pharmacokinetics and placental transfer of tenofovir 1% vaginal gel
- Study completed
  - Pittsburgh, PA

Maternal tenofovir PK
MTN-008

- Expanded safety of tenofovir 1% gel in pregnancy and lactation
- Study sites
  - Pittsburgh, PA
  - Birmingham, AL
- Study ongoing
MTN-016

- MTN pregnancy registry for women who become pregnant during MTN studies
- Primary objectives
  - Pregnancy loss: mothers exposed/not exposed to an active study agent
  - Major malformations: infants exposed/not exposed to active study agent *in utero*
Sustained Release Products
MTN-005

- Safety and acceptability of a non-medicated intravaginal ring
  - Bronx-Lebanon, NY
  - Birmingham, AL
  - Pune, India

- Study ongoing in the US and India
MTN-013

- Phase 1 safety and PK/PD of vaginal rings:
  - Dapivirine
  - Maraviroc
  - Dapivirine & Maraviroc
  - Placebo

- Sites
  - Pittsburgh, PA
  - Boston, MA
  - Birmingham, AL
Objective Measures of Ring Use
Challenges
Discordant PrEP/Microbicide Results

- Evidence of efficacy
  - CAPRISA 004, Partners in Prevention, CDC TDF2, and iPrEx

- Futility
  - FEM-PrEP, VOICE

- Reasons for PrEP failure in FEM-PrEP and VOICE
  - Not known yet
  - Possibilities include population characteristics, adherence, PK, or biology
Hormonal Contraception and HIV

- Hormonal contraception may be associated with modest increase in risk of HIV acquisition
  - Heffron R et al. Lancet Infectious Diseases, 2012
- Recent WHO guidance* is for women to continue using hormonal contraception + condoms to avoid unwanted pregnancy and HIV infection
- MTN needs to consider dual protection strategies as part of the MTN portfolio

Combination Prevention

Conventional HIV Prevention Package + PrEP

± HIV Vaccine
Additional Research Challenges

- Development / optimization of biomarkers for use in clinical trials
  - Sexual exposure, adherence, safety, and efficacy
- Designing trials without placebo arms
- Bridging between the end of PrEP effectiveness trials and community availability of PrEP agents
- Managing concerns around antiviral resistance
- Developing and managing the PrEP pipeline
Looking Towards the Future
Sustained Delivery Products

3,476 Women

HIV prevention package

Placebo ring
1,738 women

HIV prevention package

Dapivirine ring
1,738 women
Rectal Microbicide Development

- MTN-017
- Phase 2 rectal safety study of tenofovir gel
- International sites
  - United States
  - Thailand
  - South Africa
  - Peru

Endpoints
- Safety
- Adherence
  - Self report
  - Objective measures
- Acceptability
- PK/PD

Initiation Q1 2013
<table>
<thead>
<tr>
<th></th>
<th>8 weeks</th>
<th>8 weeks</th>
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<tbody>
<tr>
<td><strong>BL</strong></td>
<td>TNF Gel Daily</td>
<td>TNF Gel With sex</td>
<td>Oral Truvada</td>
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<tr>
<td><strong>BL</strong></td>
<td>TNF Gel With sex</td>
<td>TNF Gel Daily</td>
<td>Oral Truvada</td>
</tr>
<tr>
<td><strong>BL</strong></td>
<td>Oral Truvada</td>
<td>TNF Gel With sex</td>
<td>TNF Gel Daily</td>
</tr>
</tbody>
</table>
Vaccine PrEP Interactions

- MTN-022 / HVTN-095
- Exploration of potential interactions between oral/topical PrEP and HIV vaccine
  - DNA NYVAC prime boost
  - Truvada
  - Vaginal tenofovir gel
- Primary objectives
  - Safety
  - Acceptability
  - Systemic immunogenicity
Sustained Delivery Injection

- Rilpivirine NNRTI
- IM nanosuspension
- Potential for 1-3 month delivery
- Phase 1 PK/PD studies ongoing
  - Colorectal explants
  - Cervicovaginal explants
- MWRI-01*
  - University of Pittsburgh
  - Liverpool University

*Funded by the Bill and Melinda Gates Foundation
New Drug Targets
MTN Network Recompetition

- RFA released
  - 27th January, 2012
- Submission due date
  - 29th September, 2012
- Next steps
  - Defining the research agenda for the MTN
  - Preparing the submission
MTN Strategic Priorities

- Continued development of sustained delivery products for HIV prevention
  - Phase 1 – Phase 3
  - Access / implementation studies during licensure review period

- Vulnerable populations
  - Pregnancy, adolescence, MSM, mature women

- Partner with other agencies to facilitate product development
  - DAIDS Networks, CONRAD, Bill and Melinda Gates Foundation, Corporate Sponsors
Summary

- Development of safe and effective PrEP agents including microbicides remains a critical focus for HIV prevention research.
- Increased interest in sustained delivery products.
- Rectal microbicide development important for both domestic and international MSM and others at risk of infection through RAI.
- Innovative trial design will be needed to sustain prevention research agenda.
## MTN Presence at M2012

<table>
<thead>
<tr>
<th>Type of Presentation</th>
<th># Accepted</th>
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<tbody>
<tr>
<td>Oral presentations</td>
<td>12</td>
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<tr>
<td>Oral poster discussions</td>
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<tr>
<td>Posters</td>
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<td><strong>Total # of presentations</strong></td>
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<tr>
<td><strong>M2012 scholarships</strong></td>
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