Microbicides

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Women as the Face of AIDS
Third Annual Summit
Iris House
12 June 2008
What is a Topical Microbicide?

An active agent or cocktail of active agents that prevents or reduces transmission of HIV and/or other Sexually Transmitted Infections when applied vaginally and/or rectally.
How would a Topical Microbicide be used?

Delivery could be in the form of a:
- gel
- film
- sponge
- intravaginal ring or diaphragm
- bio-engineered naturally-occurring vaginal bacterial species

Coitally associated or independent
NIAID Topical Microbicide Program

Ultimate Goal

To identify and support/facilitate development of safe, effective and acceptable topical microbicides to prevent HIV/AIDS and other STIs

Intervention Points for Microbicides in HIV Infection and Disease

DHHS/NIH/NIAID/DAIDS/PSP
Characteristics of an Ideal Microbicide

- Safe, even with frequent use
- Effective
- Acceptable to target populations
- Widely available (OTC), inexpensive
- Easy to use, store
- Stable
- Broad activity (HIV and STDs)
- Independent of coitus
- Contraceptive or non-contraceptive
Products: Purposes and Indications

Singular indication product, e.g., HIV microbicide

Combination sexual health product, e.g., HIV microbicide + contraceptive

Combination disease prevention product, e.g., HIV + HSV microbicide
Proposed Mechanisms for Cervicovaginal HIV Transmission

Migration thru Epithelium

Tear In Vaginal Epithelium

HIV+ lymphocyte

HIV+ Monocyte

Langerhan's Cell

Dendritic Cell

To Lymph Node
Possible Actions of Vaginally Administered Topical Microbicides

- *Gel/cream lubricate and create a physical barrier*
- *Maintain normal microflora*
- *Prevent other STDs*
- *Viral inactivation or neutralization*
- *Inhibition of binding and fusion*
- *Inhibition of reverse transcriptase*
- *Inhibition of HIV-1 uptake by or infection of dendritic cells*
What are the Potential Targets in the HIV Replication Cycle?

Block virus/cell gp120/CD4, gp41 and Coreceptor interactions:
SAMMA, PSC-RANTES, SCH-C, monoclonal antibodies, cyanovirin-N, SPL7013, T20,
Griffithsin, CMPD-167, BMS-806

RT Inhibitors: Block reverse transcriptase enzyme: PMPA (Tenofovir™),
UC781, SJ3366, TMC120 (Dapivirine™)

Non-specifically or specifically block virus-cell association:
Carraguard™, PRO2000, ISIS 5260

Entry

Coreceptor

Attachment

Reverse Transcription

Integration

Translation

Transcription

Protease

Genomic RNA

Multi-Spliced
Singly Spliced
Unspliced

Pr 160 gag/pol
Pr 55 gag

gp120/gp41

Immature Virion

Virus Inactivation: Nucleocapsid p7 Inhibitors

Pr 160 gag/pol

DHHS/NIH/NIAID/DAIDS

Reduced vaginal pH non-permissive for HIV replication:
BufferGel™, Acidform™
Successful Microbicide Strategy

Pipeline Development

Multiple activities driven by Milestones that may occur sequentially or simultaneously

Product Eliminated

Product recycled into Discovery

LEAD Discovery Preclinical Virology Preclinical Studies (Critical Path) Pilot Studies I II Clinical Studies III Deployment

The Microbicide Development Pipeline

DHHS/NIH/NIAID/DAIDS
What is needed for the Translation from Preclinical to Clinical?

**Preclinical Studies**

<table>
<thead>
<tr>
<th>Preclinical Virology</th>
<th>“Critical Path”</th>
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<tbody>
<tr>
<td>General Preclinical Virology</td>
<td></td>
</tr>
<tr>
<td>- Antiviral activity</td>
<td></td>
</tr>
<tr>
<td>- Toxicity Cell lines/Primary cells</td>
<td></td>
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<tr>
<td>- Range of Action--Subtypes</td>
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<tr>
<td>- Mechanism of Action</td>
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<tr>
<td>- Resistance</td>
<td></td>
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<tr>
<td>- Combination</td>
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<tr>
<td>- Relevant Matrices</td>
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<tr>
<td>Microbiology Specific</td>
<td></td>
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<tr>
<td>- Lab</td>
<td></td>
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<tr>
<td>- Condom Compatibility GLP</td>
<td></td>
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<tr>
<td>- Effect on Lactobacilli</td>
<td></td>
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<tr>
<td>- Effect of Matrices</td>
<td></td>
</tr>
<tr>
<td>- Seminal Plasma</td>
<td></td>
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<tr>
<td>- Cervical fluid</td>
<td></td>
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<tr>
<td>- Mucin</td>
<td></td>
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<tr>
<td>- Other STIs</td>
<td></td>
</tr>
<tr>
<td>- Cervical Explants</td>
<td></td>
</tr>
<tr>
<td>- NHP iVag transmission</td>
<td></td>
</tr>
<tr>
<td>Animal</td>
<td></td>
</tr>
<tr>
<td>- 10-14 day Rabbit Vaginal Irritation (RVI) GLP</td>
<td></td>
</tr>
<tr>
<td>- Systemic Absorption by iVag GLP</td>
<td></td>
</tr>
<tr>
<td>- Penile Irritation GLP</td>
<td></td>
</tr>
<tr>
<td>PK and Toxicology GLP</td>
<td></td>
</tr>
<tr>
<td>- Systemic Absorbance following iVag admin.</td>
<td></td>
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</table>

**Preformulation**

- Stability
- Sterility
- Homogeneity
- Purity

**Formulation**

- Stability, Sterility, Packaging, Storage

**Chemistry Manufacturing and Control (CMC)**

- Unformulated Drug Product
- Formulated gel

**GMP**

- Selection
- Labeling
- Acceptability Filling

DHHS/NIH/NIAID

Must be carried out in accordance with the CFR for GLP and GMP studies
Generalized GANTT Chart for Microbicide Product Development

Feasibility

Formulation
- Pre/generic Formulation
- Optimized Formulation

Manufacturing
- Analytical Method Development
- GMP Production
- Clinical Batches

Pre Clinical Studies
- (Acute Toxicology etc.)
- (Chronic Toxicity, Repo. Etc.)

Additional Toxicity studies

Pre IND / IND

Clinical Trial Activities
- Protocol Development
- Phase I
- Phase II
- Phase III

Years

GO/NO GO Decisions

Intermediate GO/NO GO Decisions
Microbicides: Where Are We?

No Proof-of-Concept for Microbicide Safety, Efficacy and Acceptability

Scenario building while waiting for data

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number</th>
<th>Candidates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preclinical</td>
<td>Multitudes</td>
<td>ZFI, Entry inhibitor, NNRTI, Nucleosides, Engineered Lactobacilli, Etc.</td>
</tr>
<tr>
<td>1</td>
<td>5</td>
<td>Vivagel™/SPI7013; TMC120 gel; UC-781; Tenofovir Gel (1%); Ethanol</td>
</tr>
<tr>
<td>1-2</td>
<td>3</td>
<td>Invisible Condom™; TMC120 gel; TMC120 vaginal ring</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Tenofovir Gel (1%)</td>
</tr>
<tr>
<td>2/2B</td>
<td>2</td>
<td>Tenofovir gel and PRO2000 (0.5%); BufferGel™ and PRO2000 (0.5%)</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>PRO2000 (0.5%)</td>
</tr>
</tbody>
</table>
Basic biomedical research
- Foster basic science and preclinical pipeline studies

Nonclinical product development
- Identify and advance the most promising approaches to clinical testing

Clinical evaluation
- Evaluate safety, efficacy and acceptability in populations most in need
Gaps in Knowledge for Microbicide Development

• Mechanism of mucosal infection by HIV--what are the cellular targets and their distribution?

• What are the infectious, physiologic and ecologic cofactors that influence HIV infection?

• How can we optimize the physical properties of a microbicide formulation to maximize safety, efficacy and acceptability?

• How does the immune or inflammatory responses triggered by a microbicide effect the safety of the product?

• What are the potential surrogate markers or safety and efficacy that can be validated by clinical evaluation?

• How should HIV resistance to ARVs influence microbicide candidate selection?

• What is the role for combinations of actives as a microbicide strategy?
The Integrated Preclinical Clinical Program for HIV Topical Microbicides (IPCP-HTM)

Integrated multi-project programs in collaboration with industry partners to create “mini-pipelines” for development

- Stimulate and support a diverse preclinical base of single and combination microbicides for vaginal and/or rectal use
- Support translation of new microbicides and microbicide strategies from preclinical studies to pre-Phase I clinical trials,
- Facilitate entry of new methods and expertise for determining microbicide safety, efficacy and acceptability into microbicide development

DHHS/NIH/NIAID/DAIDS/PSP
IPCP-HTM Scientific Profile

**Microbicide Targets**
- CD4
- gp120
- gp120/CD4 interaction
- gp41
- Coreceptor
- NNRTI
- HIV p7 nucleocapsid Inhibitor

**New Concepts/Strategies**
- Combinations
  - Dual
  - Triple
  - Multi-mechanism inhibitors
- Lactobacilli delivery of microbicides
- siRNA – *virus and cell targets*
- Integration of formulation and acceptability
- Biomarkers and coital effects on microbicidal efficacy
- Rectal microbicide development
  - Establishment of preclinical algorithm
  - Vaginal formulation delivered rectally
  - Specific rectal formulation
- New imaging modalities for safety assessment:
  - Optical Coherence Tomography
- Coital disassociated microbicide delivery
  - Vaginal rings
  - Smart gels

DHHS/NIH/NIAID/DAIDS/PSP
• **Mission:** Reduce HIV transmission through development and evaluation of topically applied microbicides

• **Goal:** Conduct scientifically rigorous and ethically sound efficacy trials to support licensure of microbicide products
  
  ✓ Pharmaceutical model---Advances microbicides with an existing IND.
  ✓ Implement standardized preclinical criteria for the rational selection of microbicide products to advance
  ✓ Rapidly implement emerging safety assessment tools into phase 1 & 2 trials
  ✓ Behavioral Research Committee – to develop the scientific agenda and priorities
Microbicide Evolution

1st Generation  
Nonoxynol-9

2nd Generation  
Nonspecific inhibitors

3rd Generation  
HIV specific inhibitors  
✓ NRT  
✓ NNRT  
✓ CCR5

4th Generation  
Combination Inhibitors

DHHS/NIH/NIAID/DAIDS/PSP
## Results: 1\textsuperscript{st} and 2\textsuperscript{nd} Generation of Microbicides

<table>
<thead>
<tr>
<th>Product</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>N-9 Gel (52.5 mg)</td>
<td>Trial completed, evidence of harm</td>
</tr>
<tr>
<td>N-9 Film (70 mg)</td>
<td>Trial completed, no evidence of harm or benefit</td>
</tr>
<tr>
<td>Savvy (C31G) - Nigeria</td>
<td>Trial stopped due to futility; trend toward harm</td>
</tr>
<tr>
<td>Savvy (C31G) - Ghana</td>
<td>Trial stopped due to futility, increased reproductive tract AEs</td>
</tr>
</tbody>
</table>
# Results and Update: 2nd Generation of Microbicides

<table>
<thead>
<tr>
<th>Product</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose Sulfate - CONRAD</td>
<td>Trial stopped, trend toward harm</td>
</tr>
<tr>
<td>Cellulose Sulfate - Family Health International</td>
<td>Trial stopped, no harm</td>
</tr>
<tr>
<td>Carraguard® - Population Council</td>
<td>Trial completed, no evidence of harm or benefit</td>
</tr>
<tr>
<td>0.5% PRO2000 Gel/P-Microbicides Development Programme</td>
<td>Ongoing</td>
</tr>
<tr>
<td>0.5% PRO2000 Gel/P and BufferGel</td>
<td>Enrollment complete, participants exiting, results expected Q1/2009</td>
</tr>
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HPTN 035: Phase II/IIb Trial of Vaginal Microbicides for the Prevention of HIV Infection in Women

**Phase II**
- Feb 2005
- Jul 2006

**Phase IIb**
- **M3**
- Durban & Hlabisa, SA
- Lilongwe, Malawi
- Harare, Zimbabwe
- Blantyre, Malawi
- Lusaka, Zambia

**Visit**
- M1
- M2
- M3

**Participant follow-up:** 12-30 mos.

**DSMB ≤ 12 mos.**

**M1, M2, M3 Monthly Visits:**
- Pelvic exam, safety labs with pregnancy and HIV tests (colposcopy for subset)

**Quarterly Visits:**
- Pelvic exams and HIV tests
- Monthly Visits: Pregnancy test

**Treatment regimen:**
- Apply a single dose of the product intravaginally up to 60 mins before each act of vaginal intercourse

**Primary endpoints:**
- Safety
- HIV infection

**Secondary endpoints:**
- BV
- Chlamydia infection
- Genital ulcer disease
- Gonorrhea infection
- HSV-2 infection
- Pregnancy
- Syphilis infection
- Trichomoniasis

**N = 200~605**
- **BufferGel**
- **0.5% PRO2000 Gel**
- **Placebo**
- **No treatment**

**N = 100**
- Philadelphia, PA

**N = 700**
- Durban & Hlabisa, SA
- Lilongwe, Malawi
- Harare, Zimbabwe
- Blantyre, Malawi
- Lusaka, Zambia

**N ≈ 220**

**N ≈ 2200**

192 incident infections

33% protective effect

DHHS/NIH/NIAID/DAIDS/PSP
3rd Generation Microbicide Update

1. Tenofovir Gel (1%)
   - Dosed prior to and after intercourse - within 24 hour time frame
2. Tenofovir Gel (1%); Viread; Truvada
   - Dosed daily

1. Ongoing in South Africa
2. Expected to start Q4 2008/Q1 2009 at multiple sites in Africa
MTN-003: The VOICE Study
Vaginal and Oral Interventions to Control the Epidemic
Phase 2B, Safety and Effectiveness Study
1% Tenofovir (PMPA) Gel
Tenofovir DF (TDF) Tablet
TDF/FTC (emtricitabine) Tablet
General Rationale

• Safe and effective PrEP is essential
• Strong opinions about….
  – Topical vs. Oral
  – Single Drug vs. Combinations
  – Safety
  – Acceptability/Adherence
  – Effectiveness
  – Consequences of Resistance
  – Overall Risk/Benefit

• No human data!
MTN-003: The VOICE Study

TOTAL SAMPLE (4200)

ORAL (2520)
- FTC/TDF (840)
- TDF (840)
- ORAL PLACEBO (840)

TOPICAL (1680)
- PMPA GEL (840)
- PLACEBO GEL (840)
PMPA Gel: Following a Classic Drug Development Paradigm

<table>
<thead>
<tr>
<th>2006</th>
<th>2007</th>
<th>2008</th>
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<tbody>
<tr>
<td>HPTN 050 Phase I Safety</td>
<td>HPTN 059 Phase II Expanded Safety</td>
<td>Male Tolerance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tissue PK</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTN-002 Pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTN-001 Oral vs. Topical PK</td>
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<td></td>
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<td>MTN-003 VOICE STUDY</td>
</tr>
</tbody>
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Why a Head-to-Head Trial?

- Theoretical reasons to favor either approach for safety, acceptability, efficacy and/or selection of resistance
  - vaginal use may confer less systemic toxicity and less resistance
  - vaginal use may be more culturally acceptable
  - oral use is less closely linked to sexual practices, and can be administered by the woman without knowledge of her partner
  - NO HUMAN DATA

- Only head-to-head trial will answer questions
Study Objectives

• Primary Objectives
  - Estimate effectiveness of 1% tenofovir gel, oral TDF, and oral FTC/TDF in preventing HIV infection among at-risk women.
  - Evaluate extended safety of daily 1% tenofovir gel, oral TDF, and oral FTC/TDF in women at risk for sexually transmitted HIV infection.
Challenges

• Development of optimal formulations

• Assessment of safety
  - Preclinical
  - Clinical

• Biomarkers/Surrogate markers
  - Safety
  - Efficacy

• Clinical trial implementation
  - Incidence
  - Risk reduction counseling

DHHS/NIH/NIAID/DAIDS
Clinical Trial Sites in 2008

THE AMERICAS:
- United States: Phase I, II, IIB
- Puerto Rico: Phase I
- Dominican Republic: Phase I

WEST AFRI CA:
- Cameroon: Phase I, II

EUROPE
- Belgium: Phase I

ASIA
- India: Phase II
- Thailand: Phase I

SUB-SAHARAN AFRI CA:
- Kenya: Phase I
- Malawi: Phase II, IIB
- Rwanda: Phase I/II
- South Africa: Phase I, IIB, III
- Tanzania: Phase I, I/II, III
- Uganda: Phase III
- Zambia: Phase IIB, III
- Zimbabwe: Phase I, II, IIB

Source: Alliance for Microbicide Development
Controlling the Pandemic

Prevention

Vaccines
HIV
Other STIs

STI Reduction
HSV-2

Microbicides
HIV
Other STIs
Combinations

Antiretroviral Therapy
Pre-exposure Prophylaxis (PrEP)

Intervention Strategies
Risk reduction
Voluntary counseling (VCT)

Perinatal
Mother-to-child Transmission (MTCT)

Ultimate Goal:
Multi-Component Prevention Strategy