The State of Research and Development of Microbicides for the Prevention of HIV

Tucson, Arizona – October 12, 2005
Dr. Zeda Rosenberg
The Face of HIV Globally

- Increasingly female
  - 57% of adults living with HIV in sub-Saharan Africa are women aged 15-49
  - In South Africa – 1 in 4 women infected by age 22
  - In the Mekong Region – 30% of existing infections are in women; new cases are occurring at higher rates in women than men
  - In India – 22% of cases in housewives with single partner

- Married, monogamous
- Mothers
• Women account for 26% of AIDS cases, more than triple the rate from 20 years ago.

• Girls account for 57% of new HIV infections among youth aged 13 to 19.

• AIDS is now the leading cause of death for African-American women aged 25 to 34.
The Need for Women-initiated HIV Prevention Technologies

- Most HIV infections are spread by unprotected sex
- Current methods are male initiated and contraceptive
- Women have no means to protect themselves if their partners do not use male condoms or allow female condoms to be used
- Abstinence and being faithful are not likely to protect married women or those who are sexually abused
What is a Microbicide?

- Substance that can substantially prevent or reduce transmission of HIV when applied to the vagina

- Could potentially be made in many forms:
  - gel or cream
  - sponge
  - film
  - suppository
  - ring or diaphragm
# Comprehensive Approaches to HIV/AIDS

## Prevention

<table>
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<tr>
<th>Prior to Exposure</th>
<th>Time of Exposure</th>
<th>Treatment and Care</th>
</tr>
</thead>
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<tr>
<td>Vaccines</td>
<td>Male and female condoms</td>
<td>Anti-retroviral therapies</td>
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<tr>
<td>Pre-exposure prophylaxis</td>
<td>Anti-retroviral therapies (mother-to-child)</td>
<td>Opportunistic infection therapies</td>
</tr>
<tr>
<td>STI treatment</td>
<td></td>
<td>Basic care</td>
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<tr>
<td>Behavior change</td>
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## Treatment and Care

- Anti-retroviral therapies
- Opportunistic infection therapies
- Basic care

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Microbicides offer a woman-initiated method to reduce HIV transmission
Inhibition of HIV uptake by dendritic cells
- DC-SIGN mAbs
- Mannan

Inhibition of reverse transcriptive
- NRTIs - PMPA
- NNRTIs - UC781, TMC 120, DABO, MIV 150

Membrane Disruptive Agents
- C31G, SLS
- Cyclodextrins

Entry Inhibitors
- Polyanions
- Coreceptor antagonists
- Small molecule inhibitors
- CD4 mAbs
- BMS 806
- T-20
- Cyanovirin
- Plant lectins
Drug Delivery Formulations

- Delivery of active
  - Cervix/Vagina
    - Lumen
    - Surface
    - Intracellular
- Application frequency
  - Duration of activity
- Cost
- Manufacturing ease
- Other functions
  - Anti-inflammatory
  - Anti-STD
  - Spermicidal
- Stability
**Drug Development Process**

- **Pre-clinical** – formulation; *in vitro* and *in vivo*

- **Safety trials** – tens to hundreds of participants; drug absorption and distribution in the body; product delivery, dosage and duration; tissue coverage and tolerability; male and female product use acceptability; male tolerance

- **Large-scale efficacy trials** – multi-country; multi-site; thousands of women trial participants; conclusive effectiveness testing
<table>
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<tr>
<th>Candidate Microbicide</th>
<th>Mechanism of Action</th>
<th>Sponsor/Funder</th>
<th>Trial Location</th>
<th>Population Size</th>
</tr>
</thead>
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<tr>
<td>Carraguard</td>
<td>Entry Inhibitor</td>
<td>Population Council/Gates, USAID</td>
<td>Gugulethu, Isipingo, Durban, Gorkuwa, Shoshanguve South Africa</td>
<td>6,639</td>
</tr>
<tr>
<td>Cellulose Sulfate</td>
<td>Entry Inhibitor</td>
<td>Global Microbicide Program/Gates, USAID</td>
<td>Burkina Faso, Uganda India, Kenya South Africa</td>
<td>2,160</td>
</tr>
<tr>
<td>Cellulose Sulfate Trial 1</td>
<td>Entry Inhibitor</td>
<td>Global Microbicide Program/Gates, USAID</td>
<td>Port Harcourt, Lagos Nigeria</td>
<td>2,160</td>
</tr>
<tr>
<td>Cellulose Sulfate Trial 2</td>
<td>Entry Inhibitor</td>
<td>Global Microbicide Program/Gates, USAID</td>
<td>Mtubatuba, Durban, Johannesburg South Africa</td>
<td>11,920</td>
</tr>
<tr>
<td>PRO 2000</td>
<td>Entry Inhibitor</td>
<td>UK Medical Research Council/DFID</td>
<td>Harare, Chitungwiza Zimbabwe Lusaka Zambia Blantyre, Lilongwe Malawi Durban, Hlabisa South Africa</td>
<td>3,220</td>
</tr>
<tr>
<td>PRO 2000 Buffer Gel</td>
<td>Entry Inhibitor</td>
<td>NIAID</td>
<td>Masaka, Uganda Mwanza, Tanzania</td>
<td>3,220</td>
</tr>
<tr>
<td>PRO 2000 Buffer Gel</td>
<td>Entry Inhibitor</td>
<td>NIAID</td>
<td>Lagos, Ibadan Nigeria</td>
<td>2,140</td>
</tr>
<tr>
<td>PRO 2000 Buffer Gel</td>
<td>Vaginal Defense Enhancer</td>
<td>NIAID</td>
<td>Accra, Kumasi Ghana</td>
<td>2,140</td>
</tr>
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</table>
IPM’s mission is to prevent HIV transmission by accelerating the development and access of safe and effective microbicides for use by women in developing countries.
The Need for IPM

- International organization dedicated to microbicide development
- Identify and support promising new microbicide candidates through the development process
- Raise sufficient resources to fund rapid development of microbicide candidates for product licensure
- Prepare for availability and adoption of microbicides in resource-poor areas
Guiding Principles as a PDP

- Not business as usual
- Reduce time to licensure
  - The faster microbicides are approved, the faster women will have access to them
  - Rapid development of safe and effective microbicides means more lives saved
- Provide resources to microbicide developers
  - Infrastructure
  - Financial
- Identify best practices from both public and private sectors
- Collaborate with both public and private sector partners
- Maintain open dialogue with communities
- Protect women’s health
Opportunities For Action

Help ensure widespread availability & adoption

BASIC RESEARCH ➔ DISCOVERY ➔ PRE-CLINICAL ➔ CLINICAL TRIALS ➔ LICENSURE ➔ LAUNCH

- Help identify the “next generation” of microbicides
- Assess and fund across the microbicide portfolio
- Provide common capabilities or supports for the field
- Maximize clinical trial capacity
- Help create regulatory pathways and capacity

- Multiple mechanisms/targets/products
- Formulation capacity
- In vitro and in vivo models
- Regulatory
- Manufacturing
Other candidates also exist including many proteins with multiple mechanisms of action and other redundant small molecules including NNRTIs and NRTIs.
Donors

- Canada
- Denmark
- European Commission
- Ireland
- Norway
- The Netherlands
- Sweden
- United Kingdom
- United States
- The Bill and Melinda Gates Foundation
- The Rockefeller Foundation
- World Bank
- UNFPA
2004 International Collaborators and Partners

R&D:
- Biosyn, Inc., USA
- European Microbicide Project, United Kingdom
- GlaxoSmithKline, United Kingdom
- ImQuest BioSciences, USA
- National Institute of Allergy and Infectious Diseases, USA
- Particle Sciences, USA
- Population Council, USA
- Queen’s University of Belfast, Northern Ireland
- St. George’s Hospital Medical School, United Kingdom
- Tibotec BVBA, Belgium
- Tibotec Pharmaceuticals, Ltd., Ireland
- University of Utah, USA
- Warner Carslot, Northern Ireland facility

Access:
- EngenderHealth, USA
- Health and Development Africa, South Africa
- JHPIEGO, Zambia
- Population Council, USA
- University of Cape Town, South Africa

Clinical Sites and Studies:
- CONRAD, USA
- Family Health International, USA
- FARMOVIS-Panoxel, South Africa/Multinational
- Harvard School of Public Health, USA
- Imperial College, United Kingdom
- International Antiviral Therapy Evaluation Center, The Netherlands
- Kilimanjaro Reproductive Health Programme, Tanzania
- Microbicide Development Programme, United Kingdom
- MRC/UVRI Uganda Research Unit, Uganda
- Project Ubumwe, Rwanda
- Quintiles, South Africa
- SOS-Medisearch International N.V., Belgium
- Triclimum, South Africa
- University of Ghent, Belgium
- University of the Free State, South Africa
- University of the Witwatersrand,
  Reproductive Health and HIV Research Unit, South Africa
- University of York, United Kingdom

Global Advocacy:
- AIDS Fondet, Denmark
- Alliance for Microbicide Development, USA
- DSW, Germany
- Global Campaign for Microbicides, USA
- Interagency Coalition on AIDS and Development, Canada
- National AIDS Trust, United Kingdom
- UNAIDS’ Global Coalition on Women and AIDS, Switzerland

Regulatory Affairs:
- Social & Scientific Systems, Inc., USA
- Triclimum, South Africa
- World Health Organization, Switzerland
Collaborators in the U.S.

- Alliance for Microbicide Development
- Biosyn, Inc.
- CONRAD
- EngenderHealth
- Family Health International
- Global Campaign for Microbicides
- Harvard School of Public Health
- ImQuest BioSciences
- National Institute of Allergy and Infectious Diseases (NIAID)
- Particle Sciences
- Population Council
- Social & Scientific Systems, Inc.
- University of Utah
Funding for Microbicides

- Funding in 2004 – US$140 million

- United States
  - NIH – 71%
  - USAID – 25%
  - CDC – 4%

- UK

- Netherlands

- Ireland

- European Commission

- Bill and Melinda Gates Foundation

- Other

- $72 million Development

- $65 million Research

- $3 million Advocacy
In 2004, US$140 million was spent on microbicide research, development and advocacy
- $65 million on research + $72 million on development + $3 million on advocacy

In 2005 and subsequent five years, this amount must increase to US$280 million
- $130 million on research + $120 million on development + $20 million on site development + $10 million on advocacy
Conclusion

With leadership, sufficient financial resources, collaborative efforts and product development expertise, women in developing countries should have access to effective microbicides within the next 5 to 10 years.
Visit our website at:
www.ipm-microbicides.org

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