Need for microbicides brought to light by leading women’s advocates

Zena Stein – 1990 article on “HIV Prevention: The Need for Methods Women Can Use”

IWHC, WHO, WAND – 1991-92 meetings articulating need for microbicides

IWHC & PopCouncil – Collaboration and creation of Women’s Health Advocates on Microbicides

ICRW – Key social behavioral research highlighted women’s vulnerability and need for a female-initiated tool to prevent HIV

GCM & AMD – Created in 1998, took advocacy on behalf of microbicide field to the global stage
## Past Microbicide Efficacy Trials

<table>
<thead>
<tr>
<th>Microbicide</th>
<th>Sponsors</th>
<th>Countries</th>
<th>Results / Reasons for Closure</th>
</tr>
</thead>
</table>
| **Nonoxynol-9** | NIH, AMFAR, FHI / Univ of Washington | Kenya | Sponge trial cancelled (1990)  
• More HIV+ in N-9 arm  
(not statistically significant) |
|  | USAID, NIH / FHI | Cameroon | Film trial completed (1996)  
• No efficacy against HIV |
|  | NIH / FHI | Kenya | Gel trial cancelled (1998)  
• Slow enrollment & follow up |
|  | WHO, UNAIDS | Thailand, Benin, Cote d’Ivoire, SA | Gel trial completed (2000)  
• Trend towards harm |
| **Savvy** | USAID / FHI | Ghana | Gel trial cancelled (2005)  
• Low HIV incidence  
• No safety concerns |
|  | USAID / FHI | Nigeria | Gel trial cancelled (2006)  
• Futility (no efficacy)  
• More HIV+ in Savvy arm  
(not statistically significant) |
## Past Microbicide Efficacy Trials (cont’d)

<table>
<thead>
<tr>
<th>Microbicide</th>
<th>Sponsors</th>
<th>Countries</th>
<th>Results / Reasons for Closure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cellulose Sulfate</strong></td>
<td>Gates, USAID, Polydex / CONRAD</td>
<td>Benin, India, SA, Uganda, Zimbabwe</td>
<td>Gel trial cancelled (2007) • More HIV+ in CS arm (not statistically significant)</td>
</tr>
<tr>
<td></td>
<td>USAID, Polydex / FHI</td>
<td>Nigeria</td>
<td>Gel trial cancelled (2007) • No safety concerns (precaution)</td>
</tr>
<tr>
<td><strong>Carraguard</strong></td>
<td>Gates, USAID / PopCouncil</td>
<td>South Africa</td>
<td>Gel trial completed (2007) • No efficacy against HIV • Good safety profile</td>
</tr>
<tr>
<td><strong>PRO 2000 (2%)</strong></td>
<td>UK MRC, DFID / MDP</td>
<td>SA, Tanzania, Uganda, Zambia</td>
<td>2% arm dropped (2008) • Futility (no efficacy) • Lower dose (0.5%) arm continues</td>
</tr>
<tr>
<td>Product / Study</td>
<td>Phase</td>
<td>Mechanism of Action</td>
<td>Sponsor / Developer</td>
</tr>
<tr>
<td>----------------</td>
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<td>---------------------</td>
</tr>
<tr>
<td>BufferGel &amp; PRO 2000 (0.5%)</td>
<td>2/2B</td>
<td>Defense Enhancer &amp; Entry Inhibitor</td>
<td>NIAID / HPTN (MTN)</td>
</tr>
<tr>
<td>HPTN 035</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRO 2000 (0.5%)</td>
<td>3</td>
<td>Entry Inhibitor</td>
<td>UK MRC, DFID / MDP</td>
</tr>
<tr>
<td>MDP 301</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Product / Study</td>
<td>Phase</td>
<td>Mechanism of Action</td>
<td>Sponsor / Developer</td>
</tr>
<tr>
<td>------------------</td>
<td>-------</td>
<td>---------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2B</td>
<td>ARV (NRTI)</td>
<td>DST (SA), USAID / CONRAD, CAPRISA</td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2B</td>
<td>ARV (NRTI)</td>
<td>NIAID / MTN</td>
</tr>
<tr>
<td>MTN 003/VOICE (Planned)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Lessons Learned from Prior Trials

<table>
<thead>
<tr>
<th>Lessons learned</th>
<th>What is being done differently</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prioritization</strong></td>
<td>• Adaptive design, multiple arms</td>
</tr>
<tr>
<td></td>
<td>• Advance best product only</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>• Early looks for harm and ability to stop</td>
</tr>
<tr>
<td></td>
<td>• Multiple data reviews during the trial</td>
</tr>
<tr>
<td><strong>Adherence</strong></td>
<td>• Longer acting formulations</td>
</tr>
<tr>
<td></td>
<td>• Product acceptability studies</td>
</tr>
<tr>
<td></td>
<td>• Daily contact with participants</td>
</tr>
<tr>
<td></td>
<td>• Smart applicator</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>• Epi studies conducted in advance</td>
</tr>
<tr>
<td><strong>Futility</strong></td>
<td>• Early stop if unlikely to show efficacy</td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>• Rigorous contraceptive requirements</td>
</tr>
<tr>
<td></td>
<td>• Family planning, including female condoms</td>
</tr>
<tr>
<td><strong>Trial locations</strong></td>
<td>• Diversify in terms of countries and sites</td>
</tr>
<tr>
<td></td>
<td>• Address co-enrollment concerns</td>
</tr>
</tbody>
</table>
### Early & Next Generation Microbicides

**Early Generation**
- First microbicides tested, some still in efficacy trials
- Not HIV specific
- Gel formulations
- To be applied vaginally within a few hours before sex
- No concern about potential resistance

**Next Generation**
- Newer products in different stages of preclinical and clinical research
- Specific to HIV (ARV-based)
- Various forms: gel, ring, film, tablet
- Longer duration of action: daily gels, monthly rings, etc.
- ARV resistance is a possible issue that needs to be investigated
Microbicidies in Product Development

Free virus

Attachment

Fusion

Reverse Transcription

Integration

Protein synthesis and assembly

Budding

Maturation

Lactin-V
Invisible Condom
NCp7’s
GM Biotics (Osel)

PRO2000
SPL7013 (VivaGel)
RANTES analogs
Cyanovirin-N

DS007 (Merck L’644)

S-DABO
Dapivirine
UC781
Tenofovir
PC-815

Pyrimidinediones (Samjin)

BufferGel

DS003 (BMS 793)
DS001 (Merck 167)
Maraviroc (Pfizer)

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SPL7013 (VivaGel)
RANTES analogs
Cyanovirin-N

S-DABO
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Pyrimidinediones (Samjin)

Early-generation compounds

Next-generation compounds
## Partnerships with Industry

<table>
<thead>
<tr>
<th>Compound</th>
<th>License</th>
<th>Year</th>
<th>Type/Stage</th>
<th>Development Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapivirine</td>
<td>Tibotec</td>
<td>2004</td>
<td>NNRTI</td>
<td>Phase I/II (vaginal gel, ring)</td>
</tr>
<tr>
<td>M167, M872, M882</td>
<td>Merck</td>
<td>2005</td>
<td>CCR5 blockers</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>BMS793</td>
<td>BMS</td>
<td>2005</td>
<td>gp120 binder</td>
<td>Early pre-clinical</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Gilead</td>
<td>2006</td>
<td>NRTI</td>
<td>Phase I PK (CONRAD / IPM)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase IIB (CONRAD / CAPRISA)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Phase IIB (MTN, planned)</td>
</tr>
<tr>
<td>Maraviroc</td>
<td>Pfizer</td>
<td>2008</td>
<td>CCR5 blocker</td>
<td>Pre-clinical</td>
</tr>
<tr>
<td>L’644 peptide</td>
<td>Merck</td>
<td>2008</td>
<td>gp41 binder</td>
<td>Early pre-clinical</td>
</tr>
</tbody>
</table>
Non-exclusive royalty-free licenses to develop, manufacture and distribute antiviral compounds as microbicides in developing countries.

Ongoing technical support from industry:
- Drug synthesis
- Site evaluation
- New compounds
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Countries</th>
<th>Study Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPM 001,</td>
<td>7 days</td>
<td>Belgium</td>
<td>• Reservoir ring safe and well tolerated</td>
</tr>
<tr>
<td>IPM 008</td>
<td>25 or 200 mg</td>
<td></td>
<td>• High drug levels (&gt; 1000 x EC50) well distributed in vaginal tissues &amp; fluids</td>
</tr>
<tr>
<td></td>
<td>N=25</td>
<td></td>
<td>• Low levels in plasma (&lt;50 pg/mL)</td>
</tr>
<tr>
<td>IPM 018</td>
<td>28 days</td>
<td>Belgium</td>
<td>• Both reservoir &amp; matrix rings safe and well tolerated</td>
</tr>
<tr>
<td></td>
<td>25 mg</td>
<td></td>
<td>• High drug levels (&gt; 4 logs x EC50), significantly more drug with matrix</td>
</tr>
<tr>
<td></td>
<td>N=24</td>
<td></td>
<td>• Low levels in plasma (&lt;2 ng/mL)</td>
</tr>
<tr>
<td>IPM 003,</td>
<td>42 days</td>
<td>Rwanda South Africa Tanzania</td>
<td>• Safe and well tolerated</td>
</tr>
<tr>
<td>IPM 005B</td>
<td>2.5 ml</td>
<td></td>
<td>• No drug-related SAEs</td>
</tr>
<tr>
<td>IPM 004</td>
<td>10 days</td>
<td>South Africa</td>
<td>• Safe and well tolerated</td>
</tr>
<tr>
<td></td>
<td>2.5 ml</td>
<td></td>
<td>• No drug-related SAEs</td>
</tr>
<tr>
<td></td>
<td>N=18</td>
<td></td>
<td>• PK data supports once-daily use</td>
</tr>
</tbody>
</table>
Product Acceptability Studies

- **Placebo gel formulations**
  - Completed 2006
  - Kenya, South Africa, Zambia

- **Placebo vaginal ring**
  - South Africa, Tanzania – ongoing
  - Kenya – follow up

- **Placebo vaginal tablet, film, soft gel capsule**
  - Planned 2008-09
  - Burkina, Mozambique, Tanzania, Zambia
Microbicide Donors

- Belgium
- Canada
- Denmark
- France
- Germany
- Ireland
- Netherlands
- Norway
- South Africa
- Sweden
- United Kingdom
- USA
- European Commission
- World Bank
- UNFPA
- Rockefeller Foundation
- Gates Foundation
What More Could Industry Do?

- $$$, €€€, £££, DKK …
- Linkages for formulations development
- Long-term seconded technical expertise
- Site development support in overlapping areas
- Support for access:
  - Sharing experience in resource limited settings
  - Product forecasting tools & procurement management
- Guidance on:
  - Relations with regulatory bodies for product approval
  - Issues of product liability and pharmacovigilance
  - Selecting outside technical expertise and vendors
  - Managing organizational growth