Update on Microbicide Development

Dr. Zeda Rosenberg

Mexico City, 3 August 2008
Microbicides in context
Products in the pipeline
Laying the foundation for access
Microbicides

- Topical products to prevent HIV transmission
- Could be delivered in many forms:
  - Gel applicator
  - Ring
  - Tablet, capsule, film

- Ideally safe, effective, low cost, user friendly
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
## Early Generation Microbicides: Ongoing Efficacy Trials

<table>
<thead>
<tr>
<th>Product / Study</th>
<th>Phase</th>
<th>Mechanism of Action</th>
<th>Sponsor / Developer</th>
<th>Countries</th>
<th>Estimated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>BufferGel &amp; PRO 2000 (0.5%) HPTN 035</td>
<td>2/2B</td>
<td>Defense Enhancer &amp; Entry Inhibitor</td>
<td>NIAID / HPTN (MTN)</td>
<td>Malawi South Africa Zambia Zimbabwe USA</td>
<td>July 2008 Results 2009</td>
</tr>
<tr>
<td>PRO 2000 (0.5%) MDP 301</td>
<td>3</td>
<td>Entry Inhibitor</td>
<td>UK MRC, DFID / MDP</td>
<td>South Africa Tanzania Uganda Zambia</td>
<td>March 2009 Results 2009</td>
</tr>
</tbody>
</table>
### Next Generation Microbicides: Ongoing/Planned Efficacy Trials

<table>
<thead>
<tr>
<th>Product / Study</th>
<th>Phase</th>
<th>Mechanism of Action</th>
<th>Sponsor / Developer</th>
<th>Countries</th>
<th>Estimated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir</td>
<td>2B</td>
<td>ARV (NRTI)</td>
<td>DST (SA), USAID / CONRAD, CAPRISA</td>
<td>South Africa</td>
<td>Q1 2010</td>
</tr>
<tr>
<td>CAPRISA 004</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results 2010</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>2B</td>
<td>ARV (NRTI)</td>
<td>NIAID / MTN</td>
<td>Malawi Uganda Zambia Zimbabwe South Africa</td>
<td>Q2 2011</td>
</tr>
<tr>
<td>MTN 003/VOICE (Planned)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Results 2011</td>
</tr>
</tbody>
</table>
## ARV-Based Microbicides in Development

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Developer</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNRTI</td>
<td>Dapivirine *</td>
<td>IPM / CONRAD, Population Council, ImQuest, Idenix</td>
<td>Phase 1/2, Phase 1, Phase 1, Preclinical, Preclinical</td>
</tr>
<tr>
<td></td>
<td>UC-781 *</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PC-815</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pyrimidinediones</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>S-DABO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRTI</td>
<td>Tenofovir *</td>
<td>IPM / CONRAD</td>
<td>Phase 1/2B</td>
</tr>
<tr>
<td>CCR5 blocker</td>
<td>Maraviroc *</td>
<td>IPM, Mintaka Foundation</td>
<td>Preclinical, Preclinical, Preclinical</td>
</tr>
<tr>
<td></td>
<td>Merck L-167, 872, 882 RANTES analogs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gp41 binder</td>
<td>Merck L-644</td>
<td>IPM</td>
<td>Preclinical</td>
</tr>
<tr>
<td>gp120 binder</td>
<td>BMS-793, Cyanovirin-N</td>
<td>IPM, Osel</td>
<td>Preclinical, Preclinical</td>
</tr>
<tr>
<td>Zinc finger inhibitor</td>
<td>NCp7’s</td>
<td>ImQuest</td>
<td>Preclinical</td>
</tr>
</tbody>
</table>

* Also being developed in combination
Topical Tenofovir

- NRTI
- Most advanced ARV microbicide in the pipeline
- Preclinical development began in late 1990s
- Proof-of-concept efficacy trials ongoing/planned
- Gilead license to CONRAD and IPM
- Viread® marketed as AIDS therapeutic
Dapivirine (TMC120)

- Highly potent NNRTI
- Developed by Tibotec, licensed to IPM
- Originally tested as oral therapeutic (11 studies)
- Multiple vaginal dosage forms in development (gels, rings, films, tablets, other)
- Phase 1/2 studies completed and ongoing; Phase 3 planned 2010
Highly potent NNRTI

4 Phase 1 studies completed or in data analysis (Thailand, US) – vaginal and rectal

2 Phase 1 studies ongoing – vaginal and male tolerance

2 studies planned:
  • Single agent PK and expanded safety – planned early 2009
  • Combination UC-781/tenofovir safety – planned early 2010

Source: CONRAD
PC-815

- Carraguard + MIV-150 (NNRTI)

- In vitro activity
  - MIV-150 inactivates cell-free virus
  - MIV-150 and Carraguard are additive
  - EC50 of PC-815 is ~10X stronger than Carraguard
  - PC-815 is active against wide variety of HIV isolates
  - Seminal fluid does not impede activity

- HIV prevention studies ongoing in primate model

- Phase 1 clinical trials being planned

Source: Population Council
Topical Maraviroc

- CCR5 blocker
  - Pre-formulation ongoing

- Combination dapivirine/maraviroc
  - Silicone & EVA ring feasibility initiated
  - Gel initiated
  - Film to be initiated
  - Virology ongoing

- Preclinical assessment
  - 28-day vaginal rabbit dosing study ongoing

- PK and safety studies planned 2009-10

- Selzentry™ marketed as AIDS therapeutic
Microbicide Development Process

Research & Development
- IP rights
- Formulation
- Lab safety
- Community engagement
- Capacity building
- Incidence studies

Site Development
- Safety
- Efficacy
- Acceptability

Clinical Trials
- Clinical trials
- Licensure
- Post-licensure studies

Regulatory Approval

Launch & Access
- Manufacturing
- Service delivery
- Marketing
Criteria for Moving Forward: Pre-Clinical

- Compounds assessed to identify best candidates for clinic

**MECHANISMS OF ACTION**
- Earlier in life cycle is better
- New mechanism of action
- Comparison with other candidates with same mechanism of action

**LABORATORY STUDIES**
- Toxicity / Potency
- Pre-formulation

**COST & AVAILABILITY**
- IP access to compound
- Drug synthesis process
- Ease of manufacture
### Criteria for Moving Forward: Early Clinical Trials

- Candidates assessed in small numbers of volunteers

#### PHARMACOKINETICS
- Where drug goes in body, concentration, duration
- Preferred dosage:
  - Wide distribution in genital tract
  - Long duration
  - Sufficient concentration

#### ACCEPTABILITY
- Placebo formulations assessed in diverse populations
- Acceptability measured in all clinical trials

#### SAFETY
- Drug, formulation, delivery assessed for prolonged use
- Product safety evaluated in diverse populations
- Early clinical trials cannot fully predict risk of enhancing HIV transmission
Criteria for Moving Forward: Efficacy Trials

- Top candidates move into efficacy trials

BEST-IN-CLASS

- Essential criteria:
  - Potency
  - Safety
  - PK
  - Acceptable formulation

- Secondary criteria:
  - Mechanism of action
  - Cost
  - Ease of manufacture
  - Access / IP
Access Principles: Planning for Success

- Affordability
- Availability
- Accessibility
- Acceptability
## 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) Phase IIB (CONRAD / CAPRISA) 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

License provide for distribution on an affordable basis
Capacity Building at Research Centers

- Community engagement
- Referral networks for medical care/support
- Infrastructure and equipment
  - Build/purchase/lease and renovate space
  - Acquire medical and office equipment
- Staff development
  - Hire 15-20 per site with diverse expertise
  - Provide GCP, GCLP & study-specific training
- Communications, messaging and tools
- Financial management support
- HIV incidence studies
Ethical Guidelines for Clinical Trials

Many studies taking place in developing countries

Key issues
- Community engagement
- Monitoring social harms
- Informed consent process
- Risk reduction counseling
- Family planning / condoms
- Management of pregnancy
- STI screening and treatment
- Testing positive at screening
- Participants who seroconvert
- Treatment for physical harms
- Post-trial access to products

Guidelines
- UNAIDS/WHO ethical guidelines in HIV prevention trials, 2007
- UNAIDS/AVAC good participatory practices, 2007
- South Africa GCP guidelines, 2006
- IPM ethical guidelines, 2006
- Nuffield Council on Bioethics, 2005
- GCM consensus points, 2005
- CIOMS biomedical guidelines, 2002
- WMA Declaration of Helsinki, 2000
- ICH GCP, 1996
Illustrative Access Activities

- Acceptability studies
- Global manufacturing survey completed
- LSHTM modelling of microbicide introduction
  - India, South Africa, Tanzania
- Pharma lessons learned ARV treatment introduction
Discussion