Microbicides for HIV Prevention

Janneke van de Wijgert
AMC-CPCD
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New HIV Prevention Technologies

- Microbicides (focus of this talk)
- Female barrier methods (e.g. diaphragm)
- Male circumcision
- Suppressive therapy for genital herpes
- Pre-Exposure Prophylaxis (PrEP)
- HAART treatment of partner
- HIV vaccines
# Comprehensive Approaches to HIV/AIDS

## Prevention

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

- Anti-retroviral therapies
- Opportunistic infection therapies
- Basic care
What is a Vaginal Microbicide?

Any substance that can substantially reduce transmission of HIV and/or other sexually transmitted infections (STI) when applied in the vagina.
Microbicide Formulations

A microbicide could potentially be produced in many forms such as gels, creams, suppositories, films, impregnated sponges or wipes, vaginal rings or something we haven’t thought of yet.
Microbicide Benefits

- Could be used by women who have difficulty negotiating safer sex with their male partner(s)
- Some are contraceptive, others are not contraceptive
- Are likely to be safe due to low dose of active ingredient and local action in vagina (limited systemic absorption)
- Some could protect against multiple STIs
- Some are not coitus-dependent (e.g. vaginal rings)
- Could have bidirectional effect
- Could have benefits for women who are already HIV positive
Sexual HIV Transmission Pathways

Several pathways and relative importance of each not yet clear:

- Cross epithelium by infecting or transcytosis through epithelial cells, epithelial transmigration of infected donor cells, uptake by Langerhans cells, and direct entry through epithelial disruptions.
- In submucosa, infect CD4+ T-cells, dendritic cells and macrophages using various receptors and co-receptors.
Biology of Microbicides

Source: R. Shattock, St. George’s Hospital Medical School
Development Approaches

Exploring compounds that:
- Inhibit pathogen entry or fusion
- Inhibit post-fusion activity such as viral replication
- Kill or inactivate pathogen
- Boost vagina’s natural defense mechanisms
- Are uncharacterized but seem promising
- For product info, see www.microbicide.org
## Products in Active Clinical Development by Mechanism of Action

<table>
<thead>
<tr>
<th>M of A</th>
<th>Products</th>
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<tbody>
<tr>
<td>Entry/fusion inhibitors (non-specific)</td>
<td>Carraguard gel, PRO-2000/5 gel, Invisible Condom</td>
</tr>
<tr>
<td>Entry/ fusion inhibitor (HIV-specific)</td>
<td>VivaGel</td>
</tr>
<tr>
<td>HIV replication inhibitors</td>
<td>TMC-120 gel and ring, Tenofovir gel, UC781 gel, PC-815 gel</td>
</tr>
<tr>
<td>Boost natural vaginal defenses</td>
<td>BufferGel, Acidform/Amphora gel</td>
</tr>
<tr>
<td>Uncharacterized</td>
<td>Praneem polyherbal vaginal tablet</td>
</tr>
</tbody>
</table>
# Ongoing Phase IIb/III Trials

<table>
<thead>
<tr>
<th>Product</th>
<th>Countries</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carraguard</td>
<td>South Africa (completed)</td>
<td>6,299</td>
</tr>
<tr>
<td>PRO-2000/5 (0.5% + 2%)</td>
<td>South Africa, Tanzania, Uganda, Zambia</td>
<td>9,673</td>
</tr>
<tr>
<td>PRO-2000/5 (0.5%) + BufferGel</td>
<td>Malawi, South Africa, USA, Zambia, Zimbabwe</td>
<td>3,220</td>
</tr>
<tr>
<td>Latex Diaphragm</td>
<td>South Africa and Zimbabwe (completed)</td>
<td>6,000</td>
</tr>
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### Other Potential Products by Mechanism of Action

<table>
<thead>
<tr>
<th>M of A</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Entry/fusion inhibitors (HIV-specific)</strong></td>
<td>CCR-5, CXCR4, and gp-41 blockers, soluble CD4, soluble DC-SIGN</td>
</tr>
<tr>
<td><strong>Other fusion inhibitors</strong></td>
<td>Cyanovirin-N (CV-N), other</td>
</tr>
<tr>
<td><strong>Maintaining normal vaginal flora</strong></td>
<td><em>Lactobacillus crispatus</em> suppository, CD4-expressing lactobacillus (MucoCept), other</td>
</tr>
<tr>
<td><strong>Fortify natural immune defenses</strong></td>
<td>Cytokines, monoclonal antibodies, other</td>
</tr>
<tr>
<td><strong>Kill or inactivate HIV</strong></td>
<td>Oxidants, lipids, surfactants, other</td>
</tr>
<tr>
<td><strong>New formulations</strong></td>
<td>Sustained release systems, biodegradable rings, smart polymers</td>
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How Effective Will They Be?

- **1st generation – surfactants** – failed due to poor therapeutic index. Were tested because already on the market > 25 years as spermicides.

- **2nd generation – polyanions** – currently in Phase III trials. Cellulose sulfate failed (due to selective blocking of CXCR4 but not CCR5 co-receptor?) but Carraguard and PRO-2000 are still under evaluation. Low efficacy expected.

- **3rd generation – antiretrovirals** – currently in Phase I/II. Are likely to be more efficacious because they specifically target HIV.

- Efficacy may be improved by use with a barrier method or by combination products.
What is Needed to Get Product to Users?

- Discovery of product lead
- Pre-clinical and ongoing non-clinical testing (*in vitro*; animal models)
- Clinical testing in humans (ICH-GCP/GCLP):
  - Safety (Phase 1)
  - Expanded safety/dose-finding (Phase 1/2; 2; 2/3)
  - Efficacy (Phase 2/3; 3)
  - Bridging studies
- Manufacturing (ICH-GMP)
- Regulatory review, Licensing
- Introduction, Education, Access and Use
Basic Science Challenges

- Sexual transmission of HIV not fully understood; multiple pathways may have to be blocked simultaneously or sequentially.

- Human vagina and physiology of sexual intercourse not fully characterized.
  - Genital epithelial changes also caused by sex, reproductive tract infections, tampon use – what is normal?
Clinical Development Challenges

- Lack of well-established correlations between *in-vitro*, animal model, and clinical data regarding safety and efficacy.
  - Epithelial integrity and/or permeability changes, subclinical inflammation, increased immune activation, and/or decreased innate immunity could facilitate HIV transmission instead of preventing it.
  - Some changes invisible to the naked-eye – were missed in past microbicide trials? How best to monitor them in future trials?
  - Need validated biomarkers of safety and efficacy!
Clinical Trial Challenges (1)

- No perfect control group: Placebo may have lubricating, physical barrier, other anti-HIV, and/or local toxicity effects; no-product control arm cannot be blinded.

- In efficacy trials, HIV must be primary endpoint - large sample sizes needed in communities with high rates of sexual HIV transmission and low rates of other types of HIV transmission.

- HIV incidence in ongoing trials lower than expected; pregnancy rates higher than expected (most trials now providing family planning on-site).
Clinical Trial Challenges (2)

- Must measure microbicide effect over and above package of already proven HIV prevention interventions (VCT, condom promotion, treatment of curable STIs).
- Package may have to be expanded as new HIV prevention technologies prove to be effective (e.g. male circumcision)
- If product coitally-dependent, difficult to achieve full adherence for long periods of time.
- No reliable way to measure sexual behavior and product adherence. Biomarkers needed!
Clinical Trial Challenges (3)

- Logistics of recruiting and following large numbers of HIV-negative women are complex
- How best to achieve true informed consent, true community participation, and male involvement?
- Clinical care in HIV prevention trials versus standard of care in the community: Where does responsibility of researchers begin and end?
- Difficult to standardize procedures across trial sites
- Tension between local capacity-building needs and need to develop new prevention technologies as fast as possible
More Clinical Development Challenges

- ICH-GCP capacity constraints:
  - Trials done in countries with severe HIV epidemics; most have limited experience with ICH-GCP research
  - Each country has own drug regulatory system; some systems underdeveloped
  - Established trial sites should implement trials continuously to maintain skills, retain qualified staff, and minimize costs

- Selection of products to move forward:
  - Need for head-to-head comparisons and more coordination???
Concluding Remarks

The microbicides field needs more products in the pipeline, proof of concept, true placebos, and validated safety and surrogate efficacy endpoints.

Research on better collection of sensitive behavioral and adherence data should continue.

Research on delivery mechanisms should continue.

Despite challenges, microbicides field has grown significantly and first Phase 3 trials have been completed in 2007.