MICROBICIDES AND OTHER PREVENTION TECHNOLOGIES

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Testing and treatment of genital infections (STIs)

Voluntary Counselling and Testing (VCT)

Behavioural Intervention (ABC)

Immunisation: Vaccines

HSV-2 Suppressive therapy

Microbicides

Cervical Barriers: vaginal diaphragms

Male circumcision

Exposure prophylaxis MTCT
PEP
PrEP

HIV PREVENTION

Voluntary Counselling and Testing (VCT)

Behavioural Intervention (ABC)

Immunisation: Vaccines

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Microbicides

Cervical Barriers: vaginal diaphragms

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Exposure prophylaxis MTCT
PEP
PrEP

HIV PREVENTION
Microbicides: Potential for HIV Prevention

- Chemical products applied in vagina to prevent HIV acquisition
- Female-initiated
- Early research on rectal application

Compelling evidence from monkey challenge studies:

- *0.5% PRO2000 – 0/7 macaques infected vs. 7/7 controls infected*
- **1% Tenofovir (48 hrs pre-challenge) – 0/10 macaques infected vs. 10/10 controls infected**

MICROBICIDES: POTENTIAL FOR HIV PREVENTION

- Gel/cream: Physical barrier, Lubrication
- Prevention of normal microflora
- Prevention of other STDs
- Viral disruption

- Inhibition of HIV uptake by dendritic cells (e.g., anti-DC-SIGN)
- Inhibition of reverse transcriptase
- Fusion/absorption inhibition (e.g., polyanions, co-receptor antagonists)

- Anti-HIV activity
- Toxicity
- Activity against other STIs
- Contraceptive/ non-contraceptive options

## MICROBICIDES: PRODUCTS IN PHASE IIIB/III TRIALS

<table>
<thead>
<tr>
<th>Product</th>
<th>Contraceptive</th>
<th>Specificity to HIV</th>
<th>Systemic Absorption</th>
<th>Coitally Dependent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acid Buffer BufferGel</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Entry Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS, PRO2000, Carraguard</td>
<td><strong>CS ++</strong></td>
<td>+</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Surfactants</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C31G (SAVVY)</td>
<td>++</td>
<td>+/-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td><strong>2nd Generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARV-containing</td>
<td>-</td>
<td><strong>++</strong></td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Tenofovir, TMC120</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Early-stage concepts
Pre-clinical development (30 - 40 candidates)
14 in early safety trials
5 in large-scale efficacy trials

Adapted from Alliance for Microbicide Development, Microbicide Watch 2006
MICROBICIDES: GLOBAL PHASE II B/III TRIALS

- **CARRAGUARD**
- **CELLULOSE SULFATE**
- **+ 2% & 0.5% PRO2000**
- **× BUFFERGEL & 0.5% PRO2000**
- **C31G (SAVVY)**

Countries participating in the trials:
- India
- South Africa
- Zimbabwe
- Malawi
- Uganda
- Tanzania
- Zambia
- Zimbabwe
- Ghana
- Burkin Faso
- Benin
- Nigeria
- Philadelphia, USA

PHASE IIB/III TRIALS

- CARRAGUARD
- CELLULOSE SULFATE
- 2% & 0.5% PRO2000
- BUFFERGEL & 0.5% PRO2000
- C31G (SAVVY)
# Microbicides: Where Are We Now?

## Phase IIb/III Clinical Trial Update

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Trial</th>
<th>Recruited</th>
<th>HIV Prevalence %</th>
<th>Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>USAID Gates Foundation</td>
<td>CONRAD Cellulose Sulphate</td>
<td>959/2600</td>
<td>10 - 55</td>
<td>Dec 2009</td>
</tr>
<tr>
<td>USAID</td>
<td>FHI Cellulose Sulphate</td>
<td>1395/2160</td>
<td>9 - 20</td>
<td>May 2008</td>
</tr>
<tr>
<td>DfID</td>
<td>MDP 0.5% and 2% PRO2000</td>
<td>1312/9673</td>
<td>20 - 38</td>
<td>Dec 2009</td>
</tr>
<tr>
<td>NIH</td>
<td>HPTN 035 BufferGel &amp; 0.5% PRO2000</td>
<td>1191/3220</td>
<td>17 - 28</td>
<td>Apr 2009</td>
</tr>
<tr>
<td>USAID Gates Foundation</td>
<td>Population Council Carraguard</td>
<td>6299/6629</td>
<td>18 – 43</td>
<td>Dec 2007</td>
</tr>
<tr>
<td>USAID</td>
<td>FHI SAVVY (C31G) - Ghana</td>
<td>2142/2142</td>
<td>9</td>
<td>Study terminated</td>
</tr>
<tr>
<td>USAID</td>
<td>FHI SAVVY (C31G) - Nigeria</td>
<td>2070/2142</td>
<td>12</td>
<td>Sept 2007</td>
</tr>
</tbody>
</table>
ARV-containing Microbicides

- More specific
- Longer acting

Vaginal Rings

- 30+ days of drug delivery
- Potentially reduces compliance burden
- Easy to use

Ref: International Partnership for Microbicides
MICROBICIDES: KEY CHALLENGES

- Lack of markers of protection
- Adherence to product use
- Trial conduct: pregnancy, retention, HIV incidence, cost
- Ethics and care obligations

Note: Many of the same challenges in other prevention trials
The MDS was initiated by the Microbicide Donors Committee.

Year-long consultative process with key players in microbicide research and development.

Purpose: To take stock of the current status of the field, identify gaps, and build consensus on current R&D priorities.

Available at: Microbicide Alliance Booth Exhibition Hall Space #H-489, and at www.microbicide.org
CERVICAL BARRIERS: POTENTIAL FOR HIV PREVENTION

- Women-initiated method
- Proven safe, effective and acceptable contraceptive
- Upper genital tract may be more susceptible to HIV infection – covering cervix may ↓ HIV infection
- Observational studies – reduced STI infection

  ➢ E.g: Rosenberg et al - Reduced risk of Gonorrhoea among diaphragm users, [OR, 0.32; CI: 0.16-0.45]
CERVICAL BARRIERS: VAGINAL DIAPHRAGM CLINICAL TRIAL

<table>
<thead>
<tr>
<th>Trial No.</th>
<th>No. of Sites</th>
<th>HIV Prevalence @ Screening</th>
<th>Recruited</th>
<th>Trial Duration</th>
<th>End Date</th>
<th>Expected Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIRA</td>
<td>Durban</td>
<td>32%</td>
<td>5045</td>
<td>12-24 months retention rate = 87-92%</td>
<td>September 2006</td>
<td>June 2007</td>
</tr>
<tr>
<td>Vaginal Diaphragm with Replens</td>
<td>Johannesburg Harare</td>
<td>N = 5045</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: Challenges similar to microbicide trials
MALE CIRCUMCISION: POTENTIAL FOR HIV PREVENTION

- Biological data on HIV risk reduction
  - Removal of HIV target cells from foreskin
  - Keratinisation of skin surface – rapid drying ↓ STI

- Epidemiological evidence
  - HIV prevalence ↓ in circumcised men

- Meta analysis (Weiss et al, 2000)
  - 38 (mainly African) studies – circumcision ↓ risk of HIV
Auvert et al: HIV incidence: 0.85/100py (n = 20) in circumcised men vs. 2.1/100py (n = 49) in control; RR = 0.40 (95% CI: 0.24 – 0.65); p <0.001 – 60% protection

<table>
<thead>
<tr>
<th>Population</th>
<th>HIV Prevalence (%)</th>
<th>Site</th>
<th>Recruited</th>
<th>End Date/Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV (-) men</td>
<td>7.3</td>
<td>Kenya</td>
<td>2,784</td>
<td>September 2007</td>
</tr>
<tr>
<td>HIV (-) men</td>
<td>9</td>
<td>Uganda</td>
<td>5000</td>
<td>Interim analysis Dec06</td>
</tr>
<tr>
<td>HIV (+) men</td>
<td>9</td>
<td>Uganda</td>
<td>780</td>
<td>2008</td>
</tr>
<tr>
<td>Women partners from both cohorts</td>
<td>12</td>
<td></td>
<td>4,035</td>
<td></td>
</tr>
</tbody>
</table>

**Challenges**

- Safety and Ethical Challenges
- Cultural and religious acceptability
- From evidence to public health action

Ref: Auvert et al. PLoS Med 2: e298. DOI: 10.1371/journal.pmed.0020298
PRE-EXPOSURE PROPHYLAXIS (PrEP): POTENTIAL FOR HIV PREVENTION

- Proof of concept, e.g. malaria, PMTCT

- Candidates: Tenofovir & Truvada
  - Good safety profile in AIDS treatment
  - Once a day regimen
<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Product</th>
<th>Site</th>
<th>Enrolled</th>
<th>Study Population</th>
<th>End date</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDC</td>
<td>Oral Tenofovir (TDF)</td>
<td>Thailand (N = 1600)</td>
<td>1200</td>
<td>Male &amp; Female IDU</td>
<td>2008</td>
</tr>
<tr>
<td>CDC</td>
<td>Oral Tenofovir (TDF)</td>
<td>USA (N = 400)</td>
<td>211</td>
<td>MSM</td>
<td>2008</td>
</tr>
<tr>
<td>CDC</td>
<td>Truvada (FTC/TDF)</td>
<td>Botswana (N = 1200)</td>
<td>71</td>
<td>Heterosexuals</td>
<td>2008/9</td>
</tr>
<tr>
<td>NIAID</td>
<td>Truvada (FTC/TDF)</td>
<td>Peru (N = 1400)</td>
<td>Not yet recruiting (6 July 06)</td>
<td>MSM</td>
<td>21 months</td>
</tr>
<tr>
<td>Gates</td>
<td>Oral Tenofovir (TDF)</td>
<td>West Africa (N = 1200)</td>
<td>400 Ghana, 400 Cameroon, 136 Nigeria</td>
<td>High risk women</td>
<td>Ended</td>
</tr>
</tbody>
</table>

Safety and preliminary effectiveness of tenofovir disoproxil fumarate (TDF) for prevention of HIV infection in women

PrEP: KEY CHALLENGES

- Implications of breakthrough infections with resistant viruses for future therapy options
- Level of adherence required?
- Monitoring for adverse events
- Acceptability of chronic medication for healthy people?
- Potential for abuse of PrEP among those who cannot/will not use condoms
HSV-2 SUPPRESSIVE THERAPY: POTENTIAL FOR HIV PREVENTION

- HSV-2 increases risk of HIV acquisition
  - 2-fold increased rate (Celum et al, 2004)

- HSV-2 ↑ risk of transmission
  - 5-fold increase in per-contact risk due to GUD (Wald et al, 2004, Corey et al, 2004)

- HIV impacts on natural history of HSV-2 – frequent sub-clinical occurrences

- HSV-2 associated with ↑ HIV viral load
  - 0.3 log ↑ plasma HIV viral load in early HIV (Duffus et al, 2005, Schacker et al, 2001)
**HSV-2 SUPPRESSIVE THERAPY: CLINICAL TRIALS**

<table>
<thead>
<tr>
<th></th>
<th>HPTN 039 (NIH)</th>
<th>Partners in Prevention (Gates Foundation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective</strong></td>
<td>Effect of HSV-2 on HIV susceptibility</td>
<td>Effect of HSV-2 on HIV infectiousness</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>&amp; Daily Acyclovir or placebo</td>
<td>&amp; Daily Acyclovir or placebo</td>
</tr>
<tr>
<td></td>
<td>&amp; HIV-, HSV2+ MSM &amp; women</td>
<td>&amp; HIV discordant couples (HIV+ partner is HSV-2+)</td>
</tr>
<tr>
<td></td>
<td>&amp; 9 sites (US, Peru, Africa)</td>
<td>&amp; 14 sites in Africa</td>
</tr>
<tr>
<td><strong>Sample size</strong></td>
<td>3277 participants</td>
<td>3000 HIV discordant couples (6000 participants)</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>HIV acquisition</td>
<td>HIV transmission</td>
</tr>
<tr>
<td><strong>Status of enrollment</strong></td>
<td>100% (3277 participants)</td>
<td>70% (2100 couples)</td>
</tr>
<tr>
<td><strong>Anticipated completion</strong></td>
<td>2007</td>
<td>2008</td>
</tr>
</tbody>
</table>
HSV-2 SUPPRESSIVE THERAPY:
KEY CHALLENGES

- Adherence
- Continuous vs. episodic treatment
- Potential for emergence of HSV-2 resistance
IMPACT OF NEW TECHNOLOGIES ON HIV PREVENTION

- **Microbicides** – 60% effective product could avert 2.5 million new HIV infections in middle to low income countries\(^{(1)}\)
- **Male circumcision** – widespread implementation in Sub-Saharan Africa could avert 2 million new HIV infections over the next 10 years\(^{(2)}\)
- **Cervical barriers** – inexpensive, registered, women-initiated – impact on reduction of HIV among women
- **PrEP** – reduction of HIV in high risk individuals
- **Herpes suppressive therapy** – lower HIV acquisition and transmission

Ref: 1. Public Health working group: model projects 2002
FUTURE CHALLENGES IN NEW HIV PREVENTION TECHNOLOGIES

PUBLIC HEALTH
- Contextualize policy development for appropriate local action
- Link to scale-up of VCT
- Managing the behavioural disinhibition
- Maintaining high levels of adherence

IMPLEMENTATION
- Operational research and feasibility
- Regulation and licensure
- Access and Affordability
- Acceptability
- Service provider education
- Monitoring and evaluation

FUTURE RESEARCH
- Promote collaboration to ensure optimal use of resources
- Prioritizing research with promising public health impact
- Addressing future clinical trial design
  - Choice of control interventions
  - Ethical issues
PROVEN PREVENTION METHODS

- BEHAVIOURAL CHANGE
- VCT
- BARRIER METHODS (Male & Female Condoms)
- MTCT
**Impact on HIV Epidemic**

Leadership & scaling up of treatment/prevention efforts

Community involvement

Enhanced by synergistic use of social, behavioural, biomedical and barrier methods

- **Barrier Methods (Male & Female Condoms)**
- **Microbicides**
- **HSV-2 Suppressive Therapy**
- **BEHAVIOURAL CHANGE**
- **CERVICAL BARRIERS (Vaginal Diaphragms)**
- **PrEP**
- **VCT**
- **MTCT**

**Male Circumcision**
Abstain
Be Faithful
Condomise & Testing
Circumcision
Diaphragm
Exposure prophylaxis (pre- and post)
Female-controlled microbicides
Genital tract infection control
HSV-2 suppressive treatment
Immunity
ACKNOWLEDGEMENT

**Microbicide Clinical Trials**
- Population Council
- HPTN 035
- Microbicides Development Programme (MDP)
- CONRAD
- Family Health International (FHI)

**Vaginal Diaphragm Trial**
- University of California, San Francisco

**Male Circumcision**
- Bertran Auvert
- Stephen Moses
- Ron Gray
- Maria Wawer

**PrEP Trials**
- Centers for Disease Control (CDC)
- Family Health International

**HSV-2**
- Connie Cellum

**Salim Abdool Karim**, Tom Coates, Ward Cates, Renee Ridzon
THANK YOU

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