Microbicides – Where are we?

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Co-Chair HPTN Leadership Group
Director: CU-SA Fogarty AITRP
A microbicide is a product that can be applied to the vaginal or rectal mucosa with the intention of preventing the transmission of sexually transmitted infections including HIV.

Microbicides containing antiretroviral drugs = Topical PrEP (Pre-exposure prophylaxis)
Past & Current Microbicide Clinical Trials

Zena Stein publishes seminal article “HIV prevention: the need for methods women can use”

1st class: Surfactants
- eg. N9, SAVVY
- Kenya N-9 sponge trial
- FHI N-9 film trial
- UNAIDS COL-1492 trial
- FHI SAVVY trial

2nd class: Polymers
- eg. PRO2000, Carraguard, Cellulose Sulfate (CS)
- CONRAD CS trial
- FHI CS Trial
- PopCouncil Carraguard trial
- HPTN PRO2000 & BufferGel trial
- MDP 0.5% PRO2000 trial
- 2% PRO2000 trial

3rd class: ARVs
- eg. Tenofovir gel, Dapivirine gel/ring
- CAPRISA Tenofovir gel trial
- MTN Tenofovir gel & tablet trial
- IPM Dapivirine gel & ring trial

4th class: Co-receptor Blockers
- eg. CD4 blocker, CCR5 Blockers

Safe but not effective
Increased HIV infection
Safe & effective
Stopped for futility

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Whither or Wither Microbicides?

Robert M. Grant,1 Dean Hamer,2 Thomas Hope,3 Rowena Johnston,4 Joep Lange,5 Michael M. Lederman,6 Judy Lieberman,7 Christopher J Miller,8 John P. Moore,9 Donald E. Mosier,10 Douglas D. Richman,11 Robert T. Schooley,12 Marty S. Springer,13 Ronald S. Veazey,14 Mark A. Wainberg15

After disappointing results from all efficacy trials conducted to date, the field of microbicides research now faces substantial challenges. Poor coordination among interested parties and the choice of nonvalidated scientific targets for phase III studies have hampered progress and created mistrust about the use of microbicides as a method to prevent HIV-1 sexual transmission. Although new promising strategies are available, there will need to be serious reappraisals of how decisions are made to advance the next generations of candidates into clinical trials, and the use of novel techniques in this process will be critical.

“Poor coordination among interested parties and the choice of nonvalidated scientific targets for phase III studies have hampered progress and created mistrust about the use of microbicides as a method to prevent HIV-1 sexual transmission.”
Global HIV epidemic, 2009

33.4 million living with HIV, 2.6 million new infections, 1.8 million deaths

Source: UNAIDS 2010

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Know your epidemic: The Evolving HIV Epidemic in Africa – a complex & dynamic mosaic

The evolving HIV epidemic in SSA: 1990-2005

Age and sex distribution of HIV
- Magnitude of the challenge

HIV Prevalence & Incidence rates in SA -2005

Current HIV prevention does not address prime source of new HIV infections

• Existing proven HIV prevention strategies - ABCCC:
  – Abstinence
  – Behaviour (Be faithful)
  – Condoms
  – Counselling and Testing
  – Circumcision

• Which of these HIV prevention strategies address the vulnerability in young women?
What works for HIV prevention: Results from RCTs -2009

• Review: 37 HIV prevention RCTs on 39 interventions:
  – PrEP: 1
  – Behavioural: 7
  – Microbicides: 12

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
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<tr>
<td>HIV Vaccine (Thai RV144)</td>
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<td>Circumcision (Orange Farm, Rakai, Kisumu)</td>
<td>57% (42; 68) M-A</td>
</tr>
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</table>

Number of intervention trials or studies anywhere in the world that have demonstrated a reduction in HIV incidence in adolescent women?

Zero
Correlation between Viral Load and HIV Transmission


Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
ARVS for Prevention

Tenofovir

Truvada

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

Quarraisha Abdool Karim,†† Salim S. Abdool Karim,‡‡ Janet A. Frohlich,‡ Anneke C. Grobler,‡ Cheryl Baxter,‡ Lella E. Mansoor,‡ Ayeasha B. M. Kharsany,‡ Sengeziwe Sibeko,‡ Koleka P. Mlilana,‡ Zaheen Omar,‡ Tanuja Gengia,‡ Silvia Maarschalk,‡ Natasha Arulappan,‡ Mukelise Motsiwa,‡ Lynn Morris,‡ Douglas Taylor,† on behalf of the CAPRISA 004 Trial Group‡‡

The Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial assessed the effectiveness and safety of a 1% vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase inhibitor, for the prevention of HIV acquisition in women. A double-blind, randomized controlled trial was conducted comparing tenofovir gel (n = 445 women) with placebo gel (n = 444 women) in sexually active, HIV-uninfected 18- to 40-year-old women in urban and rural KwaZulu-Natal, South Africa. HIV serostatus, sexual behavior, and gel and condom use were assessed at monthly follow-up visits for 30 months. HIV incidence in the tenofovir gel arm was 5.6 per 100 women-years (person time of study observation) (36 out of 660.6 women-years) compared with 9.1 per 100 women-years (60 out of 660.7 women-years) in the placebo gel arm (incidence rate ratio = 0.61; P = 0.017). In high adherers (gel adherence > 90%), HIV incidence was 24% lower (95% CI = 0.025) in the tenofovir gel arm. In intermediate adherers (gel adherence 50 to 80%) and low adherers (gel adherence < 50%), the HIV incidence reduction was 38% and 28%, respectively. Tenofovir gel reduced HIV acquisition by an estimated 39% overall, and by 54% in women with high gel adherence. No increase in the overall adverse events rate was observed. There were no changes in viral load and no tenofovir resistance in HIV.

Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men


ABSTRACT

BACKGROUND
Antiretroviral chemoprophylaxis before exposure is a promising approach for the prevention of human immunodeficiency virus (HIV) acquisition.

METHODS
We randomly assigned 2499 HIV-seronegative men or transgender women who have sex with men to receive a combination of two oral antiretroviral drugs, emtricitabine and tenofovir disoproxil fumarate (FTC-TDF), or placebo once daily. All subjects received HIV testing, risk-reduction counseling, condoms, and management of sexually transmitted infections.

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
# RCT evidence of sexual HIV prevention interventions: 2011

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<td>Circumcision (Orange Farm, Rakai, Kisumu)</td>
<td>57% (42; 68) : M-A</td>
</tr>
<tr>
<td>Microbicide (CAPRISA 004 tenofovir gel)</td>
<td>39% (6; 60)</td>
</tr>
<tr>
<td>IPREX</td>
<td>44% (15; 63)</td>
</tr>
</tbody>
</table>

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Next Steps for Tenofovir Gel

• Confirmation of CAPRISA 004 – FACTS 001
• Licensure – CAPRISA 004 + VOICE
• Safety in adolescent women
• Implementation – CAP 008
• Enhancing understanding of acquisition and pathogenesis – CAP 009
• Identifying a TFV level as a surrogate of protection
• Informing new formulations, combinations, dosing
MTN-VOICE : Phase IIb Tenofovir gel Viread tablet & Truvada tablet trial

- Vaginal and Oral Interventions to Control the Epidemic
- Five-arm, multi-site, randomized trial
- Status: Accrual underway

TOTAL SAMPLE (4200)

ORAL (2520)
- Truvada (840)
- Viread (840)
- Placebo tablet (840)

TOPICAL (1680)
- Tenofovir Gel (840)
- Placebo Gel (840)

Information courtesy of MTN
Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Dapivirine (TMC120)

- NNRTI developed by Tibotec, licensed to IPM
- Developed originally as therapeutic - highly potent ARV
- Low toxicity
- Easily manufactured, stable & cheap
- Also as combination: Dapivirine + Maraviroc

Information courtesy of IPM
Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Dapivirine Clinical Development Pathway

<table>
<thead>
<tr>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPM Dapivirine gel PK</td>
<td>IPM Dapivirine gel safety (multiple studies)</td>
<td>IPM Dapivirine gel male tolerance</td>
<td>IPM Dapivirine ring PK</td>
<td>IPM Dapivirine ring safety &amp; PK</td>
</tr>
</tbody>
</table>

Information courtesy of IPM

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
IPM: Phase III trial design

- Adaptive trial design with multiple arms
  - Only the best in class moves forward
- Strong focus on safety (early looks for harm)
- Early stop for futility
- Powered for licensure
- Improved adherence
  - Daily participant contact
  - Smart applicator
  - Longer-acting formulations
- Anticipated start date: mid 2010

Information courtesy of IPM
Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
UC-781

- Licensed to CONRAD
- NNRTI with potent anti-HIV activity
- Low toxicity
- Also as combination: UC-781 + Tenofovir
UC-781 Clinical Development Pathway

2006
- Phase I Safety

2007
- Phase 1 Safety (14 day)
- Male Tolerance

2008
- Vaginal pK and safety
- Rectal Safety

Information courtesy of CONRAD

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
MIV-150

- NNRTI licensed to the Population Council
- Combination (PC-815): MIV-150 + Carraguard
- Trials starting in 2008/9:
  - Phase 1 safety and PK
  - Male tolerance

*Information courtesy of Population Council*

Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
Maraviroc

- Licensed to IPM
- Being developed as a gel and ring as combination product: Dapivirine + Maraviroc
- Currently in pre-clinical assessment:
  - Animal vaginal dosing studies ongoing

Information courtesy of IPM
Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
### IPM pipeline: other compounds

<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>M167, M872, M882</td>
<td>Merck</td>
<td>2005</td>
<td>CCR5 blockers</td>
<td>Pre-clinical (on hold)</td>
</tr>
<tr>
<td>BMS793</td>
<td>BMS</td>
<td>2005</td>
<td>gp120 binder</td>
<td>Early 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>

*Information courtesy of IPM*
Challenges in ARV microbicide trials

• Criteria for selection of candidates:
  – No validated animal model - so multiple criteria used
  – Promising new approach: ex-vivo challenge model

• No surrogate markers of safety & protection
  – HIV endpoint: only gold standard for safety & efficacy
  – ? Tenofovir gel levels

• Real world adherence to daily or coital use esp. over years (eg. daily acyclovir use at 12 months = 34.5%)#

• Potential for drug resistance - will this affect their subsequent care and choice of ARV treatment?

• Trial design challenges (IOM report)


Presented at the 1st Int workshop on HIV & Women, 10 – 11 January 2011, Washington DC
# Effectiveness of tenofovir gel in preventing HIV infection

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV infections</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>Women-years (# women)</td>
<td>680.6 (445)</td>
<td>660.7 (444)</td>
</tr>
<tr>
<td>HIV incidence (per 100 women-years)</td>
<td>5.6</td>
<td>9.1</td>
</tr>
</tbody>
</table>

Incidence rate ratio: 0.61 (CI: 0.4 to 0.94); \( p = 0.017 \)

39% lower HIV incidence in tenofovir gel group
HIV infection rates in the tenofovir and placebo gel groups: Kaplan-Meier survival probability

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative HIV endpoints</td>
<td>37</td>
<td>65</td>
<td>88</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>Cumulative women-years</td>
<td>432</td>
<td>833</td>
<td>1143</td>
<td>1305</td>
<td>1341</td>
</tr>
<tr>
<td>HIV incidence rates (Tenofovir vs Placebo)</td>
<td>6.0 vs 11.2</td>
<td>5.2 vs 10.5</td>
<td>5.3 vs 10.2</td>
<td>5.6 vs 9.4</td>
<td>5.6 vs 9.1</td>
</tr>
<tr>
<td>Effectiveness (p-value)</td>
<td>47% (0.069)</td>
<td>50% (0.007)</td>
<td>47% (0.004)</td>
<td>40% (0.013)</td>
<td>39% (0.017)</td>
</tr>
</tbody>
</table>

p=0.017
# Impact of adherence on effectiveness of tenofovir gel

<table>
<thead>
<tr>
<th></th>
<th># HIV</th>
<th>N</th>
<th>HIV incidence</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>TFV</td>
<td>Placebo</td>
</tr>
<tr>
<td>High adherers (&gt;80% gel adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate adherers (50-80% adherence)</td>
<td>36</td>
<td>336</td>
<td>4.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Low adherers (&lt;50% gel adherence)</td>
<td>41</td>
<td>367</td>
<td>6.2</td>
<td>8.6</td>
</tr>
</tbody>
</table>

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Tenofovir cervico-vaginal fluid concentrations correlate with HIV infection

<table>
<thead>
<tr>
<th>CVF Concentration (ng/mL)</th>
<th>Total # women</th>
<th>Number infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>BLD</td>
<td>19</td>
<td>16</td>
</tr>
<tr>
<td>BLQ</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>10^-2</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>10^-1</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>10^0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10^1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>10^2</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>10^3</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>10^4</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>10^5</td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

Kashuba ADM, Vienna Presentation

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# Impact of tenofovir gel on HSV-2 incidence

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir gel n=202*</th>
<th>Placebo gel n=224*</th>
</tr>
</thead>
<tbody>
<tr>
<td># HSV-2 infections</td>
<td>29</td>
<td>58</td>
</tr>
<tr>
<td>Women-years of follow-up</td>
<td>292.3</td>
<td>287.3</td>
</tr>
<tr>
<td>HSV-2 incidence per 100wy (95% CI)</td>
<td>9.9 (6.6, 14.2)</td>
<td>20.2 (15.3, 26.1)</td>
</tr>
</tbody>
</table>

*Note: Excludes equivocal HSV-2 results at study exit

IRR = 0.49 (CI:0.30, 0.78); \( p = 0.003 \)

51% protection against HSV-2 by tenofovir gel (CI: 22%-70%)
### Epidemiology of herpes simplex virus type 2 infection in US

CDC's National Health and Nutrition Examination Surveys (NHANES)

<table>
<thead>
<tr>
<th></th>
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<th></th>
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</thead>
<tbody>
<tr>
<td>National estimate (14-49 )</td>
<td>21.0</td>
<td>17.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Females</td>
<td>25.2</td>
<td>22.8</td>
<td>20.9</td>
</tr>
<tr>
<td>Males</td>
<td>17.0</td>
<td>11.2</td>
<td>11.5</td>
</tr>
<tr>
<td>Blacks</td>
<td>43.2</td>
<td>41.7</td>
<td>39.2</td>
</tr>
<tr>
<td>Whites</td>
<td>16.5</td>
<td>13.0</td>
<td>12.3</td>
</tr>
<tr>
<td>Black females</td>
<td>51.3</td>
<td>46.1</td>
<td>48.0</td>
</tr>
<tr>
<td>White females</td>
<td>23.4</td>
<td>18.6</td>
<td>15.9</td>
</tr>
<tr>
<td>Black males</td>
<td>27.5</td>
<td>24.2</td>
<td>29.0</td>
</tr>
<tr>
<td>White males</td>
<td>14.6</td>
<td>9.2</td>
<td>8.7</td>
</tr>
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</table>

\(^{(1)}\) Xu et al/ Trends in Herpes Simplex Virus Type 1 and Type 2 Seroprevalence in the United States JAMA. 2006;296:964-973

\(^{(2)}\) Morbidity and Mortality Weekly Report Seroprevalence of Herpes Simplex Virus Type 2 Among Persons Aged 14-49 Years -- United States, 2005—2008 Weekly April 23, 2010 / 59(15);456-459
Conclusion

- Preventing HIV transmission is complex - control of viral replication is important for preventing transmission
- Proof of concept for prophylactic use of ARVs for preventing sexual transmission established – CAPRISA 004 & IPREX
  - Tenofovir gel well on its way towards licensure – VOICE, FACTS 001
  - Access models being developed – CAP008
  - Understanding impact on pathogenesis and treatment outcomes – CAP009
  - Safety data in adolescent women – FACTS
- UC781 & Dapivirine are well along in the clinical development pathway – IPM-009
- IPM ring formulation – important advance
- Two other ARVs (MIV-150: NNRTI) and (Maraviroc: CCR5 inhibitor) are in advanced pre-clinical testing
- Combination microbicides are being developed
Meeting the diverse needs of women: The Future Face of Microbicides?

- Physical Barrier
- Implant
- Vaginal ring
- Pills
- Gel
- Long-Acting Injectable
- Film

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Acknowledgements

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