CAPRISA 004 after Vienna: Advancing the tenofovir gel development agenda

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Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

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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
Summary of CAPRISA 004 findings

- No substantive safety concerns
- Proof of concept that tenofovir gel can prevent HSV-2 infection in women
  - 51% reduction in HSV-2
- Proof of concept that tenofovir gel can prevent HIV infection in women
  - 39% protection against HIV overall
  - 54% effective in women with high adherence

New hope and interest in microbicides and HIV prevention science
Changing the picture of HIV prevalence in pregnant women in rural S. Africa: Potential impact of tenofovir gel

<table>
<thead>
<tr>
<th>Age (in years)</th>
<th>2005 - 2009</th>
<th>2015 - 2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>19-20</td>
<td>33.0%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>21-22</td>
<td>44.3%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>23-24</td>
<td>51.1%</td>
<td>&lt;10%</td>
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</tbody>
</table>
Reducing HIV in women with tenofovir gel

- Regulatory
- Access
- Implementation
- Enhancing effectiveness of tenofovir gel
Meeting regulatory requirements for licensure of tenofovir gel

• What is needed – not known

• Dialogue with regulators
  ▪ FDA (CONRAD), TIA (MCC)

• What do regulatory bodies need?
  ▪ FDA: CAPRISA 004 & VOICE
    Safety & drug interaction studies
  ▪ MCC: Full dossier submission (?FACTS 001)
  ▪ EMA: Not known yet

• Regulatory document submissions
  ▪ Clinical Study Report for CAPRISA 004
  ▪ Regulatory dossier
Access to tenofovir gel

• **Normative Guidance (& Co-ordination)**
  - WHO / UNAIDS
  - Aug 2010: stakeholder consultation
  - June 2011: preparing for guidelines

• **Advocacy**
  - UNAIDS, USAID, DST, AVAC, GCM, TAC
  - Involving health service providers

• **Manufacture in Africa**
  - ProPreven (TIA, CIPLAMedpro, CONRAD)
Informing Implementation

• Integrating tenofovir gel into health services
  ▪ Family planning clinic integration – CAPRISA 008
  ▪ Assessing patient choices (oral vs topical) – MTN 018

• Consequences of exposure to tenofovir gel
  ▪ Potential impact of drug resistance – CAPRISA 009
    ◦ Disease Progression & Treatment Outcomes

• Toolkit to help clinics implement tenofovir gel
  ▪ MACAIDS toolkit – part of CAPRISA 008

• Community level impact
  ▪ Changing the course of the HIV epidemic – CAPRISA 010
Enhancing Effectiveness of Tenofovir Gel

- Adherence

- Drug Levels for Protection – Angela Kashuba presentation

- Biology
  - Correlates of Risk of Infection
## Adherence & effectiveness of tenofovir gel

<table>
<thead>
<tr>
<th># HIV</th>
<th>N</th>
<th>HIV incidence</th>
<th>Effect</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TFV</td>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>High adherers (&gt;80% gel adherence)</td>
<td>36</td>
<td>336</td>
<td>4.2</td>
<td>9.3</td>
</tr>
<tr>
<td>Intermediate adherers (50-80% adherence)</td>
<td>20</td>
<td>181</td>
<td>6.3</td>
<td>10.0</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>
# Impact of CASP on HIV Effectiveness

<table>
<thead>
<tr>
<th></th>
<th>Before CASP (&lt;01 Oct 08)</th>
<th>After CASP (&gt;01 Oct 08)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Detectable TNF</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (N=387)</td>
<td>34.6% (n=136)</td>
<td>46.4% (n=306)</td>
</tr>
<tr>
<td>Placebo (N=387)</td>
<td>46.4% (n=306)</td>
<td></td>
</tr>
<tr>
<td><strong># HIV infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tenofovir (N=418)</td>
<td>21</td>
<td>35</td>
</tr>
<tr>
<td>Placebo (N=410)</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>HIV incidence</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(per 100 women yrs)</td>
<td>7.5</td>
<td>4.8</td>
</tr>
<tr>
<td>Tenofovir (N=418)</td>
<td>9.9</td>
<td>8.4</td>
</tr>
<tr>
<td>Placebo (N=410)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>IRR</strong></td>
<td>0.75</td>
<td>0.57</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>25%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>CI (p-value)</strong></td>
<td>-45;61 (p=0.37)</td>
<td>2.4, 69 (p=0.03)</td>
</tr>
</tbody>
</table>
Do raised cytokines increase the risk of HIV acquisition?

<table>
<thead>
<tr>
<th></th>
<th>No ↑ cytokines</th>
<th>Elevated Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td># HIV infections</td>
<td>8</td>
<td>27</td>
</tr>
<tr>
<td>Women-years</td>
<td>81.2</td>
<td>130.9</td>
</tr>
<tr>
<td>HIV Incidence (per 100 women-yrs)</td>
<td>9.9</td>
<td>20.6</td>
</tr>
<tr>
<td>IRR (95% CI)</td>
<td>2.1 (0.9 – 5.3)</td>
<td></td>
</tr>
<tr>
<td>p-value</td>
<td>0.06</td>
<td></td>
</tr>
</tbody>
</table>
## Impact of elevated cytokines on Tenofovir effectiveness

<table>
<thead>
<tr>
<th></th>
<th>No ↑ cytokines</th>
<th>Elevated Cytokines</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BLD tenofovir</td>
<td>Detectable tenofovir</td>
</tr>
<tr>
<td># HIV infections</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Women-years</td>
<td>24.5</td>
<td>33.6</td>
</tr>
<tr>
<td>HIV Incidence (per 100 women-yrs)</td>
<td>20.4</td>
<td>38.7</td>
</tr>
<tr>
<td>RR (95% CI)</td>
<td>-</td>
<td>1.8 (0.8-4.2)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.05</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Werner et al.
Women who acquire HIV have higher levels of innate immune activation

- Systemic cytokines
- NK cell activation
- Vaginal cytokine profile
- (CD8 T-cell degranulation)
- (Platelet counts)

What drives activation?
- NOT
  - NK cell maturation stage (CD57)
  - KIR (reportoire/expression distribution)
  - Microbial Translocation (LPS, sCD14, I-FABP)
  - HSV-2 infection
- ? Host genetic factors
- Other infections- microbiome characterisation
Summary

• CASP approach effective in enhancing adherence - increased product effectiveness
  • Adherence in low users remains a gap
• Higher levels of inflammation in the genital tract prior to HIV infection associated with higher HIV acquisition rates
  • Role of high levels of genital tract inflammation in facilitating breakthrough HIV infections in women using tenofovir gel
• Understanding immune mechanisms that drive activation?
  ▪ Host genetics
  ▪ Role of other infections - microbiome characterisation
  ▪ Role of other triggers – exogenous hormones, semen...
Acknowledgements

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- **Trial Oversight Committee**:
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  - **FHI**: W Cates, L Dorflinger, and D Taylor
  - **USAID**: L Claypool, J Manning, J Spieler
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  - **Gilead Sciences**: J Rooney, Howard Jaffe
- **DSMB members**: K Mayer (Chair), E Bukusi, K Dickson, C Lombard & S Self. Independent DSMB statistician: M Chen
- **FHI Study monitors**: S Combes, C. Katz, L McNeil & A Troxler
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- Helen Rees (FACTS)
- Leila Mansoor (Adherence) Jo-Ann Passmore (Cytokine), Vivek Naranbhai (NK Cell)
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- Cohort administrators: PF Chonco, DP Magagula, PC Majola, T Ndlovu, L Ngobese, N Ngubane, NM Zwane
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