CAPRISA 004

Effectiveness & safety of vaginal microbicide 1% tenofovir gel for prevention of HIV infection in women

Quarraisha & Salim S Abdool Karim
on behalf of the
CAPRISA 004 Trial Group
### HIV prevalence in pregnant women in rural Vulindlela, South Africa (2005-2008)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1237)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
</tr>
<tr>
<td>17-18</td>
<td>21.3%</td>
</tr>
<tr>
<td>19-20</td>
<td>33.0%</td>
</tr>
<tr>
<td>21-22</td>
<td>44.3%</td>
</tr>
<tr>
<td>23-24</td>
<td>51.1%</td>
</tr>
</tbody>
</table>
HIV Prevention: The Need for Methods Women Can Use

Zena A. Stein, MA, MB, BCH

Abstract: Efforts to prevent heterosexual transmission of HIV (human immunodeficiency virus) infection have thus far focused on modifying sexual behaviors and the use of condoms. While the experience of family planners, particularly in those countries most threatened by heterosexual HIV transmission, has shown that the most effective measures of pregnancy prevention have relied on women, little attention has been given to barriers to HIV transmission that depend on the woman and are under her control. Tactics which interrupt transmission of the virus should be considered in their own right and separated from those that interrupt pregnancy, for insurance, the diaphragm. Greater emphasis is urged for research on preventive methods women could use, including the possibility of a topical virucide that might block transmission through the vaginal route. (Am J Public Health 1990; 80:460-462.)

Introduction

At present, the sole physical barrier promoted for the prevention of sexual transmission of human immunodeficiency virus (HIV) infection from men to women is the condom. With condoms, active male cooperation is crucial. The proposition of this paper is that the empowerment of women is crucial for the prevention of HIV transmission to women. It follows that prophylaxis must include procedures that rely on the woman and are under her control. A wider condom is used in the prescribed manner. Efficacy is not easy to establish. One working estimate suggests that condoms reduce risk by a factor of 10. Combined with spermicidal lubricants, they may be considered more efficacious.

The effectiveness of a program based on condom use must be measured against the public health objective, which is to prevent the spread of the AIDS (acquired immunodeficiency syndrome) epidemic in the population by blocking transmission of virus in individual sexual encounters. Effective
Why Tenofovir Gel?

- Effective therapeutic agent
- Very good safety profile
- Prevents mother-to-child transmission
- Gel rapidly absorbed and long half-life
- Very low systemic absorption – therefore expect fewer side effects
- Protects against SIV in monkey studies
CAPRISA 004 assessed the safety and effectiveness of 1% tenofovir gel

- BAT 24 coitally-related gel use
  - Insert 1 gel up to 12 hours Before sex,
  - insert 1 gel as soon as possible within 12 hours After sex,
  - no more than Two doses in 24 hours

HIVNET 012 nevirapine regimen
- Onset of labour
- Delivery

CAPRISA 004 tenofovir gel regimen
- 12hrs
- asap 72 hrs
- 12hrs
- asap 12hrs
Methods

• Proof of concept double-blinded, randomized, placebo-controlled trial

• Enrolled high risk HIV uninfected women reporting two coital acts in past 30 days – known high risk populations from pre-trial feasibility studies

• Endpoint driven trial (92 HIV endpoints)

• HIV infection is primary safety & effectiveness endpoint:
  ▪ HIV negative: 2 negative rapid HIV tests
  ▪ HIV endpoint: PCR+ in 2 separate blood specimens
    Positive Western blot

• Intent-to-treat analysis except for adherence analysis
CAPRISA 004: Urban and Rural sites

**CAPRISA Vulindlela Clinic**
KwaZulu-Natal Midlands

**CAPRISA eThekwini Clinic**
Durban City Centre
Ethics and regulatory approvals

• Informed Consent process informed by community consultation and engagement

• Informed consent process:
  ▪ Step 1: General information session for volunteers
  ▪ Step 2: Assessment of language choice, literacy levels & cognitive ability for autonomous decision-making
  ▪ Step 3: Completion of comprehension quiz on study goal, trial concepts, obligations and rights as research participants

• Ethics approval – UKZN & FHI

• South African Medicines Control Council approval

• Protocol Safety Review meetings bi-monthly

• Independent DSMB
Screening and Enrollment

1075 excluded:
- 536 HIV positive
- 142 did not return
- 132 not sexually active
- 51 pregnant or planning a pregnancy
- 37 participating in other research
- 33 refused participation
- 26 not keen to use contraceptives
- 24 allergic to latex
- 23 planning to relocate
- 23 medical condition
- 19 unable to attend study visits
- 14 unable to provide informed consent
- 15 other reasons

Screened: 2160

Enrolled & randomized: 1085

196 excluded:
- 135 co-enrolled
- 50 in other study <1 year ago
- 1 <18 years (ineligible age)
- 8 pre-existing HIV (PCR+)
- 2 no follow up HIV test

Enrolled eligible: 889

Vulindlela: 611
eThekwini: 278
Enrollment & Retention

Enrolled Eligible: 889

Tenofovir: 445

- 15 lost to follow up
- 8 terminated early

Retention: 94.8%

Completed study: 422

Placebo: 444

- 10 lost to follow up
- 12 terminated early
- 1 died

Completed study: 421
## Comparability of the study arms at baseline: Selected sexual behavioral characteristics

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir N=445</th>
<th>Placebo N=444</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at sexual debut</td>
<td>17.4</td>
<td>17.4</td>
<td>0.78</td>
</tr>
<tr>
<td>Mean # of sexual partners</td>
<td>3.0</td>
<td>3.6</td>
<td>0.78</td>
</tr>
<tr>
<td>Vaginal sex only (past month)</td>
<td>92.8%</td>
<td>92.3%</td>
<td>0.99</td>
</tr>
<tr>
<td>Any Anal sex (past month)</td>
<td>0.4%</td>
<td>0.5%</td>
<td>1.00</td>
</tr>
<tr>
<td>Coital frequency (past month)</td>
<td>8.6</td>
<td>8.2</td>
<td>0.49</td>
</tr>
<tr>
<td>Condom use always</td>
<td>28.8%</td>
<td>29.5%</td>
<td>0.99</td>
</tr>
</tbody>
</table>
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

After 12 months of gel use:

<table>
<thead>
<tr>
<th>Months of follow-up</th>
<th>6</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative HIV endpoints</td>
<td>37</td>
<td>65</td>
</tr>
<tr>
<td>Cumulative women-years</td>
<td>432</td>
<td>833</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>
</tr>
<tr>
<td>Effectiveness (p-value)</td>
<td>47%</td>
<td>50%</td>
</tr>
<tr>
<td></td>
<td>(0.069)</td>
<td>(0.007)</td>
</tr>
</tbody>
</table>

HIV endpoints: 65
Effectiveness: 50%
P-value: 0.007
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>

Effectiveness:
- Tenofovir: 47% (p=0.069)
- Placebo: 50% (p=0.007)

HIV infection rates:
- Tenofovir: 5.6 vs 9.1 (p=0.017)
Relationship between effectiveness & mean number of returned empty applicators

- Effectiveness:
  - HIV-: 47%
  - HIV+: 50%

- Mean number of returned used gels over time:
  - HIV-: Blue line with error bars
  - HIV+: Red line with error bars

- P values:
  - Slope over time in HIV-: <0.0001
  - Slope over time in HIV+: <0.0001
  - Overall difference between HIV- and HIV+: 0.43
## Impact of adherence on effectiveness of tenofovir gel

<table>
<thead>
<tr>
<th>Adherence Level</th>
<th># HIV</th>
<th>N</th>
<th>TFV</th>
<th>Placebo</th>
<th>Effect</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>
<td>54%</td>
</tr>
<tr>
<td>Intermediate adherers (50-80% adherence)</td>
<td>20</td>
<td>181</td>
<td>6.3</td>
<td>10.0</td>
<td>38%</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>
<td>28%</td>
</tr>
</tbody>
</table>
## Sensitivity analysis: HIV infections in CAPRISA 004

<table>
<thead>
<tr>
<th></th>
<th>Window period</th>
<th>During study</th>
<th>Post study</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only protocol definition HIV endpoints of 2 positive PCRs</td>
<td></td>
<td>96 + 2 = 98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV infections not meeting protocol definition of 2 PCRs</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Post study HIV infections</td>
<td></td>
<td>5</td>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Window period HIV infections</td>
<td>8</td>
<td>5</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td>HIV infections in ineligibly enrolled women</td>
<td>2</td>
<td>5</td>
<td></td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>10</strong></td>
<td><strong>104</strong></td>
<td><strong>5</strong></td>
<td><strong>119</strong></td>
</tr>
</tbody>
</table>
Effectiveness in HIV prevention: Sensitivity analysis

<table>
<thead>
<tr>
<th>Primary outcome (n=98)</th>
<th>Effectiveness</th>
<th>CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39%</td>
<td>6 – 60</td>
<td>0.017</td>
</tr>
<tr>
<td>Incl HIV infection not meeting protocol def (n=98+1 = 99)</td>
<td>37%</td>
<td>4 - 59</td>
<td>0.023</td>
</tr>
<tr>
<td>PP population (n=85)</td>
<td>41%</td>
<td>7– 63</td>
<td>0.017</td>
</tr>
<tr>
<td>Incl ineligibly enrolled (n=98+ 5=103)</td>
<td>38%</td>
<td>7 - 60</td>
<td>0.015</td>
</tr>
<tr>
<td>Incl post-trial infections (n=98 + 5 = 103)</td>
<td>41%</td>
<td>11 – 61</td>
<td>0.015</td>
</tr>
<tr>
<td>All HIV infections (n=119)</td>
<td>45%</td>
<td>19 - 63</td>
<td>0.003</td>
</tr>
</tbody>
</table>
Impact of tenofovir gel on initial HIV viral load in seroconvertors

<table>
<thead>
<tr>
<th></th>
<th>Tenofovir</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of events</td>
<td>38</td>
<td>60</td>
</tr>
<tr>
<td>Log mean viral load</td>
<td>4.65</td>
<td>4.30</td>
</tr>
<tr>
<td>Range (IQR)</td>
<td>4.04 - 5.39</td>
<td>3.56 – 5.17</td>
</tr>
<tr>
<td>p-value</td>
<td>p=0.15</td>
<td></td>
</tr>
</tbody>
</table>
Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

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*These authors contributed equally to this work.

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‡The members of the CAPRISA 004 Trial Group appear at the end of this paper.

The CAPRISA 004 trial assessed 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 region which accounts for 70% of global burden of Human Immunodeficiency Virus (HIV) infection (1). Current HIV prevention behavioral messages on abstinence, faithfulness and condom promotion have had limited impact on HIV

Available for download from: http://www.sciencemag.org/scienceexpress/recent.dtl
Impact of tenofovir gel on Herpes Simplex Virus Type-2 infection
Global epidemic of HSV-2 infection

- High prevalence of HSV-2 infection
  - ~ 20% in sexually active adults globally
  - ~ 50 - 60% in South African sexually active adults
  - ~ 80% in HIV infected men and women globally

- Commonest cause of genital ulcer disease

- HSV-2 infection almost entirely asymptomatic
  - up to 90% of HSV-2 positive have no prior GUD

- Acyclovir & other antivirals effective HSV-2 treatment (viral suppression) but do not prevent or cure HSV-2
(S)-1-(3-Hydroxy-2-phosphonomethoxypropyl)cytosine (HPMPC, cidofovir, Vistide®).

- Adefovir dipivoxil (Hespers®).

- Tenofovir disoproxil fumarate (TDF, Viread®).
Purpose

To assess the impact of coitally related tenofovir gel on HSV-2 acquisition in high risk women in South Africa

Methods

• Samples for HSV-2 testing
  ▪ Stored sera (or plasma, if serum unavailable) tested
  ▪ Enrolment and study exit visit or last available visit

• Kalon HSV-2 type specific EIA
  (Kalon Biological Ltd, United Kingdom)
  ▪ Sensitivity = 96.4% (CI 89.8% - 99.3%)
  ▪ Specificity = 99.1% (CI 96.8% - 99.5%)
HSV-2 status at enrolment and study exit

Enrolled in HIV trial: 889 (CAPRISA 004) → 1 missing
454 HSV-2 positive

At risk for HSV-2: 434

Tenofovir: 208

Placebo: 226

3 missing
3 equivocal exit results

Completed study: 202

Completed study: 224

1 missing
1 equivocal exit result
# 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%)
Impact on HSV-2 outcome: sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th># HSV infection</th>
<th>N</th>
<th>Incidence rate</th>
<th>IRR</th>
<th>Effect</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tenofovir</td>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Effectiveness of tenofovir gel by HSV-2 indeterminate results</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate excluded</td>
<td>87</td>
<td>426</td>
<td>9.9 (6.6, 14.2)</td>
<td>20.2 (15.3, 26.1)</td>
<td>0.49</td>
<td>51</td>
<td>0.30, 0.78</td>
</tr>
<tr>
<td>Indeterminate treated as negative</td>
<td>87</td>
<td>430</td>
<td>9.7 (6.5; 14.0)</td>
<td>20.1 (15.3; 26.0)</td>
<td>0.48</td>
<td>52</td>
<td>0.30; 0.77</td>
</tr>
<tr>
<td>Indeterminate treated as positive</td>
<td>91</td>
<td>430</td>
<td>10.8 (7.4; 15.3)</td>
<td>20.5 (15.6; 26.4)</td>
<td>0.53</td>
<td>47</td>
<td>0.33; 0.83</td>
</tr>
<tr>
<td><strong>Analysis adjusted for: site, age, condom use, STI, contraceptive use, # sexual partners, and parity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indeterminate excluded</td>
<td>87</td>
<td>426</td>
<td>0.53</td>
<td>47</td>
<td>0.33; 0.83</td>
<td>0.005</td>
<td></td>
</tr>
</tbody>
</table>
Summary of Safety Findings

- No tenofovir resistance in women infected while using tenofovir gel
- No increase in the overall rate of side effects
  - Noted a small increase in mild diarrhoea (17% vs 11%, p=0.015)
  - No kidney toxicity (tenofovir excreted through kidney)*
- No safety concerns in pregnancy – noting that gel use was discontinued early in pregnancy
- No liver side effects in people with Hepatitis B virus infection
- No increase in HIV risk behaviour while using gel

* Note: the study excluded women with low creatinine clearance at enrollment
Summary of CAPRISA 004 findings

- **Safety**
  - No substantive safety concerns
  - No tenofovir resistance identified
  - Safe in Hepatitis B virus infected women
  - No evidence of risk compensation / behavioral disinhibition

- **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
  - 50% reduction in HIV after 1 year of tenofovir gel use
  - 54% effective in women with high adherence
Conclusions

1. Women, and young women in particular, bear the brunt of the HIV epidemic in Africa.

2. Tenofovir gel potentially adds a new approach to HIV prevention as the first that can be used and controlled by women. It could help empower women to take control of their own risk of HIV infection.

3. The CAPRISA 004 study is the first step - additional studies are urgently needed to confirm and extend the findings of the CAPRISA 004 trial.

4. Once confirmed and implemented, tenofovir gel has the potential to alter the HIV epidemic. It is estimated that this gel could prevent 1.3 million new HIV infections and over 800,000 deaths in South Africa alone.
Acknowledgements

• **Financial support:** USAID & S African Dept of Science & Technology

• **Minister of Health and special thanks to Premier Zweli Mkhize**

• **Tenofovir & placebo gel:** Provided by CONRAD & Gilead Sciences

• **FHI Statistical & regulatory support:** S Cameron, D Sokal & D Taylor

• **Trial Oversight Committee:**
  - CAPRISA: Q Abdool Karim, SS Abdool Karim
  - FHI: W Cates, L Dorflinger, and D Taylor
  - USAID: L Claypool, J Manning, J Spieler
  - CONRAD: H Gabelnick
  - LIFElab (TIA): B Okole, C Montague
  - 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

• **Research infrastructure & training:** US NIH’s CIPRA Program & the Columbia University - Southern African Fogarty Training Program
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- Assistant site co-ordinators: H Humphries, G Parker, J Richards, J Upton
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- Clinicians: B Mdluli, N Miya, L Mtongana, N Naicker, Z Omar, D Sokal (FHI)
- Nurses: DD Chetty, F Dlamini, SD Gumede, Z Gumede, NE Khambule, N Langa, BT Madlala, N Madlala, N Mkhize, ZL Mkhize, M Mlotshwa, C Ndimande, N Ngcobo, C Ntshingila, B Phungula, TE Vumase
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- Pharmacist’s assistants: B Moodley, Y Naidoo, C Ngcobo, T Nzimande, L Zondi
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- Data management: R Lallbahadur, M Mdladla, K Naidoo, T Nala, C Pillay, P Sikakane, T Zondo
- Quality assurance: T Govender, N Mvandaba, C van Loggerenberg, I van Middelkoop
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- Behavioural Science: J Fisher (UConn), K MacQueen (FHI)
- Cohort co ordinators: LR Luthuli, F Ntombela
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- Community outreach: N Bhengu, P Buthelezi, PD Lembethe, BF Mazibuko, SF Mdluli, WN Mkhize, SP Ndlovu, S Ngubane, RM Ogle, RB Xulu
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