Antiretrovirals for HIV prevention: New hope and opportunity

2013 Biomedical HIV Prevention Forum

Salim S Abdool Karim

Director: CAPRISA
Chair: UNAIDS Scientific Expert Panel
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Pro Vice-Chancellor (Research): University of KwaZulu-Natal
Associate Member, Ragon Institute of MGH, MIT and Harvard
Adjunct Professor of Medicine, Cornell University
Outline

• Brief historical account

• Microbicides efficacy trials
  ▪ Early microbicides: Surfactants, blockers and buffers
  ▪ ARV based topical products

• Some Key Lessons

• Product pipeline

• Conclusion
People living with HIV

Children orphaned by AIDS in sub-Saharan Africa

The chronology above summarises the ‘BIG Picture’ of AIDS

1. The response to the HIV/AIDS epidemic has been global, incremental and is improving;
2. Despite this response, the epidemic has continued to grow in certain regions of the world, particularly Africa;
3. Major milestones & lessons have been achieved & learnt over this period through excellent scientific research e.g. the discovery of HIV in 1983;
4. We now know what works best and that which does not work in the epidemic; in both prevention & treatment e.g. that unsafe sex is a risk factor to global health;
5. Future challenges and obstacles both scientific & socio-cultural, are understood better as a result of this wealth of knowledge;
6. With this concerted, coordinated global approach, the global community is in a better state to control and ultimately manage the many facets of the epidemic better e.g. stigma, discrimination and HIV vaccine development.
The Global AIDS response pre-2010....

dearth of new prevention technologies
Clinical trial evidence for preventing sexual HIV transmission – July 2010

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical male circumcision</td>
<td>54% (38; 66)</td>
</tr>
<tr>
<td>Orange Farm, Rakai, Kisumu</td>
<td></td>
</tr>
<tr>
<td>STD treatment</td>
<td>42% (21; 58)</td>
</tr>
<tr>
<td>Mwanza</td>
<td></td>
</tr>
<tr>
<td>HIV Vaccine</td>
<td>31% (1; 51)</td>
</tr>
<tr>
<td>(Thai RV144)</td>
<td></td>
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Clinical trial evidence for preventing sexual HIV transmission – July 2011

**Study**

<table>
<thead>
<tr>
<th>Study</th>
<th>Effect size (95% CI)</th>
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<tbody>
<tr>
<td>Antiretroviral treatment for prevention HPTN 052 Africa, Asia, Americas(^1)</td>
<td>96% (73-99)</td>
</tr>
<tr>
<td>PrEP for discordant couples Partners PrEP Uganda, Kenya(^1)</td>
<td>73% (49-85)</td>
</tr>
<tr>
<td>PrEP for heterosexual men and women TDF2 Botswana(^2)</td>
<td>63% (21-84)</td>
</tr>
<tr>
<td>Medical male circumcision Orange Farm,(^6) Rakai,(^7) Kisumu(^8)</td>
<td>54% (38-66)</td>
</tr>
<tr>
<td>PrEP for MSMs iPrEX Americas, Thailand, South Africa(^4)</td>
<td>44% (15-63)</td>
</tr>
<tr>
<td>Sexually transmitted diseases treatment Mwanza Tanzania(^10)</td>
<td>42% (21-58)</td>
</tr>
<tr>
<td>Microbicide CAPRISA 004 South Africa(^3)</td>
<td>39% (6-60)</td>
</tr>
<tr>
<td>HIV vaccine RV144 Thailand(^11)</td>
<td>31% (1-51)</td>
</tr>
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</table>

Clinical trial evidence for preventing sexual HIV transmission – July 2013

<table>
<thead>
<tr>
<th>Prevention in injecting drug users</th>
<th>Effect size (95% CI)</th>
</tr>
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<tr>
<td>Bangkok tenofovir study: daily oral tenofovir (injecting drug users in Thailand)</td>
<td>49% (10 to 72)</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>Prevention of mother-to-child transmission</th>
<th>Effect size (95% CI)</th>
</tr>
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<tbody>
<tr>
<td>PACTG076: zidovudine to mother during pregnancy and labour and infant (HIV-positive pregnant women in USA and France)</td>
<td>58% (40 to 72)</td>
</tr>
<tr>
<td>Thal AZT trial: zidovudine to mother during pregnancy and labour (HIV-positive pregnant women in Thailand)</td>
<td>50% (15 to 71)</td>
</tr>
<tr>
<td>HIVNET 012: single dose nevirapine to mothers and infants (HIV-positive pregnant women in Uganda)</td>
<td>41% (15 to 59)</td>
</tr>
<tr>
<td>DREAMS: zidovudine to mother during pregnancy, labour, and post partum (HIV-positive pregnant women in Gite de l’Ivoire and Burkina Faso)</td>
<td>38% (5 to 66)</td>
</tr>
<tr>
<td>Africa AZT: zidovudine to mother during pregnancy and labour (HIV-positive pregnant women in Gite de l’Ivoire)</td>
<td>37% (-5 to 63)</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Sexual transmission prevention</th>
<th>Effect size (95% CI)</th>
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<tbody>
<tr>
<td>Partners FrEP: daily entricabine and tenofovir (serodiscordant couples in Kenya and Uganda)</td>
<td>70% (52 to 87)</td>
</tr>
<tr>
<td>Partners FrEP: daily oral tenofovir (serodiscordant couples in Kenya and Uganda)</td>
<td>67% (44 to 81)</td>
</tr>
<tr>
<td>TDF: daily entricabine and tenofovir (heterosexual men and women in Sotowana)</td>
<td>63% (72 to 82)</td>
</tr>
<tr>
<td>iPrEP: daily entricabine and tenofovir (men who have sex with men in the Americas, Thailand, and South Africa)</td>
<td>44% (15 to 61)</td>
</tr>
<tr>
<td>CAPRISA 004: citalotinovor gel (women in South Africa)</td>
<td>39% (0 to 90)</td>
</tr>
<tr>
<td>MN001V OICE: daily tenofovir gel (women in South Africa, Uganda, and Zimbabwe)</td>
<td>15% (-21 to 40)</td>
</tr>
<tr>
<td>FEM-PEP: daily entricabine and tenofovir (women in Kenya, South Africa, and Tanzania)</td>
<td>6% (-52 to 41)</td>
</tr>
<tr>
<td>MN003V OICE: daily entricabine and tenofovir (women in South Africa, Uganda, and Zimbabwe)</td>
<td>7% (-49 to 27)</td>
</tr>
<tr>
<td>MN003V OICE: daily tenofovir (women in South Africa, Uganda, and Zimbabwe)</td>
<td>-49% (-129 to 3)</td>
</tr>
</tbody>
</table>

*Source: Abdool Karim SS. Lancet 2013; 381(9883): 2060-2062*
Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission.
New hope for HIV prevention...

Preventing HIV Infection in Women: A Global Health Imperative
Quarraisha Abdool Karim,1,2 Sengeziwe Sibeko,1 and Cheryl Baxter1

Antiretroviral prophylaxis: a defining moment in HIV control
Salim S Abdool Karim, Quarraisha Abdool Karim

Epidemiological Impact of Tenofovir Gel on the HIV Epidemic in South Africa
Brian G. Williams, PhD,* Salim S. Abdool Karim, MBChB, PhD,† Quarraisha Abdool Karim, PhD,‡ and Eleanor Gouws, PhD§
A change in the discourse.....

zero new HIV infections
zero discrimination
zero AIDS-related deaths
Total annual resources available for AIDS, 2000–2010

- International assistance
- Domestic (public and private)
Antiretroviral Therapy coverage globally and by region

![Antiretroviral Therapy coverage graph](image)
Annual number of voluntary medical male circumcisions, 2009–2012
Estimated global number of new HIV infections and deaths due to AIDS 1990–2000
Estimated global number of new HIV infections and deaths due to AIDS 1990–2010
Number of people newly infected with HIV globally, 2001–2012

Number of people newly infected with HIV (thousands)

- High estimate
- Estimate
- Low estimate

Number of people newly infected with HIV (thousands)

2001 2012
But HIV continues to spread at high rates in some areas!

HIV prevalence in young pregnant women in rural Vulindlela, South Africa (2009-2012)

<table>
<thead>
<tr>
<th>Age Group (Years)</th>
<th>HIV Prevalence (N=1029)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤16</td>
<td>8.4</td>
</tr>
<tr>
<td>17-18</td>
<td>18.6</td>
</tr>
<tr>
<td>19-20</td>
<td>25.4</td>
</tr>
<tr>
<td>21-22</td>
<td>32.8</td>
</tr>
<tr>
<td>23-24</td>
<td>44.8</td>
</tr>
</tbody>
</table>
High rates of HIV among key populations: young women in Africa


Young women have up to 8 times more HIV than men

Source: Adapted from UNAIDS 2012
HIV prevalence among MSM in Africa

HIV prevalence in MSM:
Range: 6.2% in Egypt to 30.9% in Cape Town

A microbicide is a chemical product that is applied in the vagina or rectum with the intention of preventing the transmission of sexually transmitted infections including HIV.

Vaginal gel applicator

Vaginal ring

Vaginal film
History of microbicide effectiveness trials: Surfactants

Efficacy of Nonoxynol 9 Contraceptive Sponge Use in Preventing Heterosexual Acquisition of HIV in Nairobi Prostitutes

Phase 1 trial of nonoxynol-9 film among sex workers in South Africa

Effectiveness of COL-1492, a nonoxynol-9 vaginal gel, on HIV-1 transmission in female sex workers: a randomised controlled trial

SAVVY Vaginal Gel (C31G) for Prevention of HIV Infection: A Randomized Controlled Trial in Nigeria

SAVVY® (C31G) Gel for Prevention of HIV infection in Women: A Phase 3, Double-Blind, Randomized, Placebo-Controlled Trial in Ghana

- Safe but not effective
- Increased HIV infection
- Stopped for futility
- Safe and effective
History of microbicide effectiveness trials: Viral entry blockers and buffers

**Effectiveness of Cellulose Sulfate Vaginal Gel for the Prevention of HIV Infection: Results of a Phase III Trial in Nigeria**
Vera Nwokedi, Fanele Dlamini, Chilimba Chinde, Richert Turyabagye, Chima Nwodo, Nche Amba, Nchekah Asuquo, Nostra Cordo, Natale Holle, John Ume Osong, Jakob Olesen, Tarra Crutchfield, and Abdul Kafaralla

**Lack of Effectiveness of Cellulose Sulfate Gel for the Prevention of Vaginal HIV Transmission**
LaiVan Danne, MD, Rachel Goodrich, PhD, Florence M. Mongeza, MD, Bernard Gobah, MD, Sanovol Soled, MD, Nazaria Leek, MD, Juan Pedro, MD, Ineke van Staden, MD, and Jing Tu, PhD, for the CS Study Group

**Efficacy of Carraguard for prevention of HIV infection in women in South Africa: a randomised, double-blind, placebo-controlled trial**

**Safety and effectiveness of BufferGel and 0.5% PRO2000 gel for the prevention of HIV infection in women**

**PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 201): a phase 3, randomised, double-blind, parallel-group trial**

- **Safe but not effective**
- **Increased HIV infection**
- **Stopped for futility**
- **Safe and effective**
History of microbicide effectiveness trials: Antiretrovirals

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, Leila E. Mansoor, Ayeshia B. M. Khanyile, Sengeriwe Sibeko, Koleka P. Miliams, Jeanne Marrazzo, G Ramjee, G Nair, T Palanee, B Mkhize, C Nakabiito, M Taljaard, J Piper, K Gomez Feliciano, M Chirenje, and VOICE Study Team

Paper #26LB
Pre-exposure Prophylaxis for HIV in Women: Daily Oral Tenofovir, Oral Tenofovir/Emtricitabine, or Vaginal Tenofovir Gel in the VOICE Study (MTN 003)
Jeanne Marrazzo*, G Ramjee², G Nair³, T Palanee⁴, B Mkhize⁵, C Nakabiito⁶, M Taljaard⁷, J Piper⁸, K Gomez Feliciano⁹, M Chirenje¹⁰, and VOICE Study Team

HIV Prevalence (%) vs Year

- Safe but not effective
- Increased HIV infection
- Stopped for futility
- Safe and effective
## Current microbicide effectiveness trials

<table>
<thead>
<tr>
<th>Phase</th>
<th>Trial name</th>
<th>Candidate(s)</th>
<th>Countries</th>
<th>Number of women</th>
</tr>
</thead>
<tbody>
<tr>
<td>III</td>
<td>MTN 020</td>
<td>Dapivirine vaginal ring</td>
<td>Malawi, South Africa, Uganda, Zambia, Zimbabwe</td>
<td>3476</td>
</tr>
<tr>
<td></td>
<td>IPM 027</td>
<td>Dapivirine vaginal ring</td>
<td>Malawi, Rwanda, South Africa,</td>
<td>1650</td>
</tr>
<tr>
<td></td>
<td>FACTS 001</td>
<td>Tenofovir gel (coital)</td>
<td>South Africa</td>
<td>2900</td>
</tr>
<tr>
<td>IIIb</td>
<td>CAPRISA 008</td>
<td>Tenofovir gel (coital)</td>
<td>South Africa</td>
<td>700</td>
</tr>
</tbody>
</table>
Outline

• Brief account of history

• Microbicides efficacy trials
  ▪ Early microbicides: Surfactants, blockers and buffers
  ▪ ARV based topical products

• Some Key Lessons

• Product pipeline

• Conclusion
Lesson 1: Persistence amidst obstacles: [CAPRISA 004 took 8 years]

Decided to pursue the idea of studying Tenofovir gel. (Initially with PRO2000)

Visit to Gilead - study gets the nod and plans move ahead

SA Govt / LIFElab grant award for the trial

USAID Grant Award for trial

CAPRISA 004 protocol v 1.0 finalised and approved July 2006

First patient screened May 2007

Co-enrolment discovered

CAPRISA 004 Tenofovir Gel Trial completed.

July 2010: Results presented in Vienna & Published simultaneously in Science

2003 2004 2005 2006 2007 2008 2009 2010
Lesson 2: Partnering for success

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

Quarraisha Abdool Karim,1,2,† Salim S. Abdool Karim,1,2,3,† Janet A. Frohlich,1 Anneke C. Grobler,1 Cheryl Baxter,1 Leila E. Mansoor,1 Ayesha B. M. Kharsany,1 Sengezile Sibeko,1 Koleka P. Mlisana,1

3 SEPTEMBER 2010 VOL 329 SCIENCE

UNIVERSITY OF KWAZULU-NATAL
INUYESI YAKWAZULU-NATALI

CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH
Key Lesson 3: Adherence is essential

<table>
<thead>
<tr>
<th></th>
<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></td>
<td>TFV</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>High adherers</td>
<td>36</td>
<td>336</td>
<td>4.2</td>
<td>9.3</td>
<td>54%</td>
</tr>
<tr>
<td>(&gt;80% gel adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate adherers</td>
<td>20</td>
<td>181</td>
<td>6.3</td>
<td>10.0</td>
<td>38%</td>
</tr>
<tr>
<td>(50-80% adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low adherers</td>
<td>41</td>
<td>367</td>
<td>6.2</td>
<td>8.6</td>
<td>28%</td>
</tr>
<tr>
<td>(&lt;50% gel adherence)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


CAPRISA 004 was developed… …”after extensive consultation with international scientific experts and review of monkey challenge data.”

“Just as importantly, it followed detailed consultation with the communities involved.”

Adherence is essential: Effectiveness by adherence in PrEP trials

Pearson correlation = 0.86, p=0.003

Adherence by drug levels

- CAPRISA 004
- iPrEX
- TDF2
- PartnersPrep (TDF)
- PartnersPreP (FTC)
- FemPrEP
- VOICE (TDF)
- VOICE (Truvada)
- VOICE (TFV gel)
Key Lesson 4: Correlate of HIV risk
Genital inflammation increases risk of HIV

Principal component analysis (PCA) was used to cluster women according to their cytokine concentration profiles

Key Lesson 5: Correlate of protection
Genital concentrations of drug

Drug concentrations after topical and oral antiretroviral pre-exposure prophylaxis: implications for HIV prevention in women
Salim S Abdool Karim, Angela DM Kashuba, Lise Werner, Quarraisha Abdool Karim

Probability of HIV infection

Placebo gel
Tenofovir gel
TFV ≤1000ng/ml
Tenofovir gel
TFV >1000ng/ml

p=0.01*
*comparing women with tenofovir concentration >1000ng/ml vs placebo. Adjusted p=0.03
Key Lesson 6: Serendipity in science
Discovering how antibody kills HIV

Evolution of an HIV glycan–dependent broadly neutralizing antibody epitope through immune escape

Penny L. Moore1,2, Elin S Gray1, C Kurt Wibmer3,4, Jinal N Bhiman1,2, Molati Nonyane1, Daniel J. Sheward3, Tandile Hermanus1, Shringkhala Bajimaya4, Nancy L. Tumba1, Melissa-Rose Abrahams5, Bronwen E. Lamison1, Nthabeleng Ranchobe1, Lihua Ping5, Nobuhelo Ngandu3, Quarraisha Abdool Karim6, Salim S. Abdool Karim6, Ronald I. Swanstrom3, Michael S. Seaman4, Carolyn Williamson3 & Lynn Morris1,2

“Researchers at the CAPRISA consortium, discovered broad neutralizing antibodies against HIV....”

....State of the Nation Address by President Jacob Zuma on 14 February 2013
Microbicide product pipeline

• Intravaginal rings (IVRs) with tenofovir or other antiretroviral agents:
  – Maraviroc, MIV-150 (NNRTI), Tenofovir

• Microbicide film formulations:
  – Multiple ARV being evaluated in early stage development as vaginal films
    • Dapivirine, tenofovir, maraviroc, IQP-0528, RC-101

• Long acting injectables
  – TMC278 (Rilpivirine): NNRTI developed by Tibotec (Janssen) for treatment of HIV infection
Multi-purpose Prevention Technologies

- A single product, configured for at least two SRH prevention indications:
  - Contraception
  - Protection against HIV
  - Protection against other STIs eg. BV, HSV-2

- **Vaginal Rings**
  - Tenofovir and levonorgestrel (LNG)
  - Dapivirine and levonorgestrel

- **MIV-150 Products- Pop Council**
  - MIV-150 (NNRTI), Zinc acetate, LNG, carrageenan in IVR or gel

- **Barrier microbicides**
  - SILCS diaphragm with microbicide
## Major Gap: Options to reduce HIV infection in adolescent women

HIV prevalence in school boys and girls in a rural South African district (grades 9 and 10)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>HIV Prevalence (Oct/Nov 2010) % (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>≤14</td>
<td>1.0 (0.0 – 3.0)</td>
</tr>
<tr>
<td>15-16</td>
<td>1.4 (0.4 – 2.4)</td>
</tr>
<tr>
<td>17-18</td>
<td>1.2 (0.2 – 2.2)</td>
</tr>
<tr>
<td>19-20</td>
<td>1.1 (0.0 – 2.7)</td>
</tr>
</tbody>
</table>

RHIVA collaboration with MiET Africa and DoE with funding from the Royal Netherlands Embassy
### Major Gap: Options to reduce HIV infection in adolescent women

**HIV prevalence in school boys and girls in a rural South African district (grades 9 and 10)**

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</tr>
</tbody>
</table>
Conclusion

• Concept of microbicides now proven - 20 years after first proposed & 18 years after first human trials

• Results of FACTS 001 (confirmatory trial) eagerly awaited - next step towards licensure of tenofovir gel

• Antiretroviral based microbicides (women-initiated technology) can alter the course of the HIV epidemic

• New formulations (eg dapivirine ring) & multipurpose technology approaches to improve adherence

• Several new products are in the pipeline while the effort to get tenofovir gel to women is in progress
Acknowledgements

- CAPRISA was established as part of the Comprehensive International Program of Research on AIDS (CIPRA) of the National Institutes of Health (NIH) (grant# AI51794)

- CAPRISA is funded by:
  - DAIDS, NIAID, National Institutes of Health
  - US Agency for International Development (USAID) via FHI and CONRAD
  - President’s Emergency fund for AIDS Relief (PEPFAR)
  - US Centers for Disease Control and Prevention (CDC)
  - South African Department of Science and Technology (DST)
  - Fogarty International Center, NIH
  - Howard Hughes Medical Institute (HHMI)
  - Gilead Sciences (Tenofovir API)
  - Royal Netherlands Embassy and MIET
  - MACAIDS Fund (via Tides Foundation)
  - Technology Innovation Agency (LIFELab)

- Past Funders:
Quarraisha & Salim Abdool Karim receive the inaugural Olusegun Obasanjo Prize for Scientific Discovery and Technological Innovation from The African Academy of Sciences