Women & HIV: The key to reaching the 3 zeros

Presented at the UNAIDS PCB, Geneva – December 2011

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Co-Chair HPTN & Associate Professor, Columbia University
Professor, Nelson R Mandela School of Medicine
Outline

- HIV infection in women
- CAPRISA 004 results
- New hope for HIV prevention
- Impact of tenofovir gel on HIV infection rates in women
Southern Africa: Epicentre of the HIV pandemic

33.4 million living with HIV, 2.7 million new infections, 2 million deaths

Source: UNAIDS 2009

South Africa:
- 0.7% of world’s population
- 17% of global HIV burden (5.4m)
- Country with the most AIDS cases
The HIV epidemic in South Africa: 1990-2010

Source: Data from South African Department of Health Antenatal Surveys. www.doh.gov.za
HIV infection in South Africa: Young women - key to stopping the epidemic!

High HIV prevalence in Africa: the disproportionate burden in young women

Kenya

Malawi

Cameroon

Lesotho
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>
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<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
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<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>
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<tr>
<td>23-24</td>
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### High priority: Reducing HIV in young girls

HIV prevalence in Vulindlela schools by age and gender (grades 9 and 10)

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<th>Age Group</th>
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<tr>
<td></td>
<td>% (95% Confidence Interval)</td>
</tr>
<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>
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High priority: Reducing HIV in young girls
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Existing proven HIV prevention strategies - ABCCC:

- Abstinence
- Behaviour (Be faithful)
- Condoms
- Counsel & Test
- Circumcision

New strategy:
- ART for Prevention

Which of these are prevention tools for young women in Africa?

Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission.
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,2 Leila E. Mansoor,1 Ayesha B. M. Kharsany,2 Sengeziwe Sibeko,2 Koleka P. Mlisana,4 Zaheen Omar,1 Tanuja N. Gengia,1 Silvia Maarschalk,1 Natasha Arulappan,3 Mukelisiwe Mlotshwa,1 Lynn Morris,4 Douglas Taylor,5 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
CAPRISA 004 assessed the safety and effectiveness of 1% tenofovir gel

Use gel with sex (BAT 24):
- Insert 1 gel up to 12 hours Before sex,
- insert 1 gel within 12 hours After sex,
- no more than Two doses in 24 hours
Summary of CAPRISA 004 findings

- No safety concerns & no drug resistance
- Proof of concept that tenofovir gel can prevent HIV & HSV-2 infection in women
  - 39% protection against HIV overall
  - 54% effective in women who used gel consistently
  - 51% reduction in genital herpes (HSV-2)
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>HIV Prevalence 2005 - 2009</th>
<th>2015 - 2019</th>
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<tbody>
<tr>
<td>≤16</td>
<td>10.6%</td>
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New hope for zero new HIV infections in women

Presented at the UNAIDS PCB, Geneva – December 2011

Salim S. Abdool Karim

Pro Vice-Chancellor (Research): University of KwaZulu-Natal
Director: CAPRISA
Associate Member, Ragon Institute of MGH, MIT and Harvard
Professor in Clinical Epidemiology, Columbia University
Adjunct Professor of Medicine, Cornell University
Trial results finally show potential for microbicide HIV gel

Salim and Quansihia Abdool Karim, husband and wife, and co-principal researchers on the Centre for AIDS Programme of Research in South Africa (CAPRISA) trial, received a standing ovation at the recent International AIDS Society Conference in Vienna when they announced their results, which showed—for the first time—that the use of an antiretroviral microbicide gel can protect against HIV transmission. Mathematical modelling suggests that, in South Africa alone, this gel could prevent up to 3 million new infections and 8000 HIV-related deaths during the next 20 years.

The randomised double-blind, placebo-controlled trial followed 889 women without HIV infection in KwaZulu-Natal, South Africa, for 30 months. Women who used the 1% tenofovir gel applied no more than 12 h before vaginal sex and as soon as possible, but no later than 1 h, were 39% lower also empower women to negotiate condom use.

“Of course there are also many women who may want to use a microbicide covertly,” notes Pool, “there needs to be a whole range of products available for different tastes and scenarios.” Another trial, the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study, due in 2013, is

HIV/AIDS

At Last, Vaginal Gel Scores Victory Against HIV

Jon Cohen
Contributing correspondent, Science

Googolplex: While South Africa was in the spotlight for hosting the World Cup games, its AIDS researchers were quietly preparing for an announcement of a major milestone in their field. For the first time ever, a vaginal gel has unequivocally blocked the transmission of HIV.

In a trial that involved nearly 900 South African women, those who received a vaginal gel that contains an anti-HIV drug had a 39% lower chance of becoming infected by the virus than those who received a placebo. “It is the first time any biological intervention against HIV transmission has ever shown convincing efficacy in a large trial,” says John Moore, who studies similar vaginal microbicides at the Weill Cornell Medical College in New York City. “It’s a clean-cut result with obvious protection of a meaningful level.”

More than 10 randomized controlled studies of microbicides, vaccines, and drugs to date have failed to thwart sexual transmission of HIV or have yielded such marginal success that researchers wound up bitterly debating the data for years after the trials were complete. But there’s no ambiguity about the data from this new microbicide study reported today online in Science and in a presentation at the 18th International AIDS Conference in Vienna: Of the 444 women who received a placebo gel, 66 became infected with HIV versus 34 infections in the 445 women who received the microbicide. The result was statistically significant, and no serious side effects occurred. “It’s a momentous moment for women,” says Pool. “It’s a game-changer—a huge step forward and a tremendous scientific achievement,” said Mitchell Warren, executive director of AVAC, a non-governmental organisation involved in global advocacy for HIV prevention. “We now have proof-of-concept for microbicides and that is a fundamental building block for the future.” He stresses the need to begin attempts, even at this early stage, to ensure that this successful clinical trial can translate into successful public health interventions: “no biomedical strategy, however effective, will have a lasting impact unless we also address stigma by using an evidence-based, human-rights focused approach. The proof-of-concept is actually the beginning and not the end of the road”.

The important issue is to make sure that vaginal microbicides do not acquire the negative connotations, such as promiscuity, disease as "commission as -"
July 2010: Global leaders comment...

Barack Obama, President of the United States
“Instead of just treating HIV/AIDS, we’ve invested in pioneering research to finally develop a way to help millions of women actually prevent themselves from being infected in the first place.”

Aaron Motsoaledi, South African Minister of Health
“CAPRISA is a step in the right direction…. Young women with this technique will be able to take their health into their own hands.”

Anthony Fauci, NIH
“…this finding is an important step toward empowering [women]…“

Jean-Francois Delfraissy, Executive Director: ANRS, France
"one of the greatest trials in the history of HIV"

Rajiv Shah, USAID Administrator
“…forefront of scientific innovation. [The study] is a model for future research in which clinical trials will be led by in-country investigators”
The CAPRISA 004 trial is in Science’s Top 10 Scientific Breakthroughs in 2010

Molecular Dynamics Simulations

Sometimes brute force is the way to go, particularly when computers can simulate chemical processes so finely. Such simulations are a computational nightmare.

Rats Redux

Today, most lab rats house mouse, but the number of rodents used in experiments is growing. Rats are more like us. The human heart, for example, beats about 70 times a minute, whereas an average, 100 kcal per minute, 900 South African women participated in the study, half receiving the microbicide and the others an inert gel. Among “high adherers,” women who used the microbicide exactly as instructed, its efficacy reached 54%

HIV Prophylaxis

From the start of the AIDS epidemic through 2009, only five of 37 large-scale studies that attempted to prevent HIV yielded positive results. Thus, the past July and November, two trials of different, novel HIV-prevention strategies unequivocally reported success. AIDS researchers all but danced with joy.

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The first result stole the show at the jam-packed XVII International AIDS Conference held in Vienna, Austria. A vaginal gel that contains the anti-HIV drug tenofovir reduced HIV infections in high-risk women by 39% over a 30-month period. Nearly 900 South African women participated in the study, half receiving the microbicide and the others an inert gel. Among “high adherers,” women who used the microbicide exactly as instructed, its efficacy reached 54%.
Since July 2010

New hope....
November 2010: Oral PrEP prevents HIV in MSM – iPrEx trial

131 infections after randomization

48 in FTC/TDF

83 in placebo

2499 Men who have sex with Men

Effect of daily TDF-FTC on HIV: 42% (CI: 15% - 63%)
May 2011: ART prevents HIV transmission from infected partners in discordant couples (HPTN 052)

1763 discordant couples in Africa & America

Effect on ART (HIV +ve) on HIV: 96% (CI: 73% - 99%)

EMBARGOED UNTIL RELEASE
Wednesday July 13, 2011, 2:00 a.m. Pacific Daylight Time

PIVOTAL STUDY FINDS THAT HIV MEDICATIONS ARE HIGHLY EFFECTIVE AS PROPHYLAXIS AGAINST HIV INFECTION IN MEN AND WOMEN IN AFRICA

Seattle, WA – In a result that will fundamentally change approaches to HIV prevention in Africa, an international study has demonstrated that individuals at high risk for HIV infection who took a daily tablet containing an HIV medication – either the antiretroviral medication tenofovir or tenofovir in combination with emtricitabine – experienced significantly fewer HIV infections than those who received a placebo pill. These findings are clear evidence that this new HIV prevention strategy, called pre-exposure prophylaxis (or PrEP), substantially reduces HIV.

4,758 HIV discordant couples in Kenya & Uganda

Effect of TDF on HIV: 67% (CI: 44% - 81%)
Effect of FTC/TDF on HIV: 75% (CI: 55% - 87%)
July 2011: Oral PrEP prevents HIV in heterosexual men & women (Botswana TDF2)

FOR IMMEDIATE RELEASE
Wednesday, July 13, 2011
5:00 AM EDT

CDC Trial and Another Major Study Find PrEP Can Reduce Risk of HIV Infection among Heterosexuals

CDC Assessing Data from All Heterosexual Trials to Develop Interim Guidance for Use

A new CDC study called the TDF2 study, along with a separate trial released today, provide the first evidence that a daily oral dose of antiretroviral drugs used to treat HIV infection can reduce HIV acquisition among uninfected individuals exposed to the virus through heterosexual sex.

The CDC TDF2 study, conducted in partnership with the Botswana Ministry of Health, found that

1219 heterosexual men & women in Botswana
Effect of TDF-FTC on HIV: 63%
Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission.
April 2011: FEM-PrEP trial stops: Truvada Tenofovir + FTC not effective in women

September & November 2011: VOICE stops tenofovir tablet and tenofovir gel arms: not effective

DSBM recommends halting tenofovir tablet and tenofovir gel arms: No protection against HIV
4 possible reasons for FEM-PrEP & VOICE results:

- Low adherence (If it is still in the tube, it cannot work)
- Inadequate drug levels at exposure (daily vs with sex)
- Biological activity of tenofovir hindered
- Chance findings (Statistical Type I & Type II errors)
False impression of PrEP & microbicides following VOICE & FEM-PrEP results
Actual situation with PrEP & microbicides following VOICE & FEM-PrEP results
Evidence that tenofovir gel works

1. Tenofovir gel reduced HIV by 39% (used with sex)

2. Tenofovir gel reduced genital herpes by 51%
   - Mechanism of action recently confirmed

3. Clear dose-response:
   - ↑ adherence = ↓ HIV (up to 54% reduction in HIV)

4. Tissue drug level correlates with HIV protection:
   - ↑ genital drug = ↑ HIV protection

5. Repeatedly highly effective in cell culture, explant tissues, mice & monkeys
“The HIV response faces a moment of truth.”

“This year, we have a unique opportunity to take stock of progress and to critically and honestly assess the barriers that keep us shackled to a reality in which the epidemic continues to outpace the response.”

UN General Assembly:
Implementation of the Declaration of Commitment on HIV/AIDS and the Political Declaration on HIV/AIDS - 2011
Oral PrEP & topical microbicides have the potential to alter the HIV epidemic in women
Conclusions

There is new hope in HIV prevention…

- Until 2010, skepticism in HIV prevention…lots of negative results
- Previously, little evidence that prevention can change epidemic
- More positive trials since July 2010 than in previous 29 years
- Treatment for prevention in particular provides huge hope

Microbicides and oral PrEP: Promising new HIV prevention technologies for women

- Gender dynamic is key to controlling HIV in Africa
- Tenofovir gel empowers women to directly control their HIV risk
- Urgent need to confirm gel effectiveness – FACTS 001 trial
- Estimated that tenofovir gel could prevent 1.3 million new HIV infections and over 800,000 deaths in women over the next 20 years in South Africa alone.
Acknowledgements

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  - US Centers for Disease Control and Prevention (CDC)
  - South African Department of Science and Technology (DST)
  - Fogarty International Center, NIH
  - European Commission - EDCTP
  - Doris Duke Charitable Foundation (DDCF)
  - National Research Foundation, South Africa (NRF)
  - Howard Hughes Medical Institute (HHMI)
  - Gilead Sciences (tenofovir API)
  - Royal Netherlands Embassy
  - MACAIDS Fund (via Tides Foundation)