Setting the stage: year in review and looking ahead

Joint Civil Society & MTN CWG meeting

Salim S. Abdool Karim

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Director: CAPRISA
Professor in Clinical Epidemiology, Columbia University
Adjunct Professor of Medicine, Cornell University
Associate Member, Ragon Institute of MGH, MIT and Harvard
HIV prevention in mid-2010
Since then.. Good news & new hope
Big question at this time:
Do oral ARVs prevent HIV in women?
Key next Step: Back to Basics
What else is next…
The HIV epidemic in South Africa

HIV prevalence in pregnant women at public antenatal clinics (95% CI)

Source: Data from South African Department of Health Antenatal Surveys. www.doh.gov.za/
### 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>
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Clinical trial evidence for preventing sexual HIV transmission – July 2010

**Study**

- **Medical male circumcision**
  - (Orange Farm, Rakai, Kisumu)
  - Effect size (CI): 54% (38; 66)

- **STD treatment**
  - (Mwanza)
  - Effect size (CI): 42% (21; 58)

- **HIV Vaccine**
  - (Thai RV144)
  - Effect size (CI): 31% (1; 51)
Since July 2010
Good news leads to
New hope....
July 2010: ARV microbicide (topical PrEP) prevents HIV & HSV-2 in women - CAPRISA 004

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

Quarraisha Abdool Karim,1,2,† Salim S. Abdool Karim,1,2,3† Janet A. Froh Cheryl Baxter,1 Leila E. Mansoor,1 Ayesha B. M. Kharsany,1 Sengeziwe Sil Zaheen Omar,1 Tanuja N. Gengiah,1 Silvia Maarschalk,1 Natasha Arulappa Lynn Morris,4 Douglas Taylor5 on behalf of the CAPRISA 004 Trial Group

The Centre for the AIDS Programme of Research in South Africa conducted a randomized, double-blind, placebo-controlled, phase 2b trial to determine the effectiveness and safety of a 1% tenofovir gel, for the prevention of HIV infection in women. The study was conducted comparing tenofovir gel to a placebo gel among 997 women at high risk of HIV infection, who were recruited at 4 sites in South Africa. The median follow-up time was 22 months. The study population was 92% black and 83% of participants reported having sex with men who had sex with men in the past year. The study population had a median age of 27 years, 55% were married, and 49% were educated to Grade 10 or higher. The tenofovir gel was found to be effective in reducing the risk of HIV acquisition compared to the placebo gel. The 39% protection against HIV overall, 54% effective against HIV in high adherers, and 51% reduction in HSV-2.
November 2010: Oral PrEP prevents HIV in MSM – iPrEx trial

131 infections after randomization
- 48 in FTC/TDF
- 83 in placebo

- Primary HIV analysis (1 May): 44% protection
- At the end of the study: 42% (95% CI 18%-60%)
- No effect on HSV-2
  - TDF-DP drug levels in blood << EC50 for HSV
May 2011: ART prevents HIV transmission from infected partners (HPTN 052)

HIV treatment as prevention—it works

- 1763 discordant couples
- 13 sites in Africa, America & Asia
- ART at CD4 up to 550 vs only <250
- HIV incidence (placebo) = 2.2 per 100pys
- 28 matched HIV infn: 27 in delayed ART
- 96% effective (excl. non-matched viruses)
- Trial halted early for effectiveness

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 oral tenofovir or tenofovir plus emtricitabine had a significantly lower rate of HIV infections than those who did not. The new HIV prevention option reduces HIV incidence by more than 70%, according to the Partners PrEP Study, convened by the University of Washington International Clinical Research Center with support from the Bill & Melinda Gates Foundation.

4,758 HIV serodiscordant couples in Kenya and Uganda
Daily oral TDF or TDF/FTC or Placebo
HIV incidence (placebo group) = 1.9 per 100pys
78 HIV infections after randomization
- 18 in TDF arm (62% protection)
- 13 in FTC/TDF arm (73% protection)
- 47 Placebo
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

1219 heterosexual men & women enrolled in Botswana Daily oral TDF-FTC

HIV incidence rate (placebo) = 3.1 per 100pys

33 HIV infections after randomization

- 9 in FTC/TDF arm (63% protection)
- 24 in Placebo
Clinical trial evidence for preventing sexual HIV transmission – July 2010

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Clinical trial evidence for preventing sexual HIV transmission – July 2011

**Study**

- Treatment for prevention (Africa, Asia, America’s)
- PrEP for discordant couples (Partners PrEP)
- PrEP for heterosexuals (Botswana TDF2)
- Medical male circumcision (Orange Farm, Rakai, Kisumu)
- PrEP for MSMs (America’s, Thailand, South Africa)
- STD treatment (Mwanza)
- Microbicide (CAPRISA 004 tenofovir gel)
- HIV Vaccine (Thai RV144)

**Effect size (CI)**

- Treatment for prevention: 96% (73; 99)
- PrEP for discordant couples: 73% (49; 85)
- PrEP for heterosexuals: 63% (21; 48)
- Medical male circumcision: 54% (38; 66)
- PrEP for MSMs: 44% (15; 63)
- STD treatment: 42% (21; 58)
- Microbicide: 39% (6; 60)
- HIV Vaccine: 31% (1; 51)
The 4 key recent changes in HIV prevention

- There is new hope in HIV prevention…
  - Until 2010, skepticism in HIV prevention…lots of negative results
  - Little evidence that prevention can change the epidemic

- The new technologies provide new hope for women
  - Gender dynamic is key to controlling HIV in Africa
  - TFV gel - new target population: women & health services

- New HIV prevention is fundamentally dependent on HIV status
  - Pre-circumcision, HIV messages were generic – same message for HIV-ve & HIV+ve ie. safe sex
  - HIV testing now a key to HIV prevention

- Combination prevention now offers hope
  - Always had combination prevention - now targeted combinations
  - Key is – can now reduce HIV in young women
Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission
FHI Statement on the FEM-PrEP HIV Prevention Study

FHI to Initiate Orderly Closure of FEM-PrEP

Monday, April 18, 2011

Following a scheduled interim review of the FEM-PrEP study data, the Independent Data Monitoring Committee (IDMC) advised that the FEM-PrEP study was unable to demonstrate the effectiveness of Truvada [emtricitabine and tenofovir disoproxil fumarate (TDF)] in preventing HIV infection in the study population, which was originally planned conclusion. FHI subsequently concurred and has therefore decided to initiate an orderly closure of the study over the next few months. The final analyses have not yet been conducted. At this time, it cannot be determined whether or not Truvada works to prevent HIV infection in women.
Sept 2011: VOICE stops oral tenofovir arm: Tenofovir not effective & trial has no chance of showing it prevents HIV (futility)

VOICE - Vaginal and Oral Interventions to Control the Epidemic

TOTAL SAMPLE (5000)

ORAL (3000)

- Truvada (1000)
- Tenofovir tablet (1000)
- Placebo tablet (1000)

- DSBM recommends halting tenofovir tablet (VIREAD) arm due to futility

TOPICAL (2000)

- Tenofovir Gel (1000)
- Placebo Gel (1000)
Oral and topical PrEP in women: Results of Randomised Control Trials

Effect size (CI)

Truvada (TDF/FTC) tablets
- Partners PrEP: 73% (49; 85)
- Botswana TDF2: 63% (21; 48)
- FEMPrEP: 0% (? ; ?)
- VOICE: ?

Intervention and Study

0%    10     20    30     40     50    60    70     80     90  100%
Oral and topical PrEP in women: Results of Randomised Control Trials

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**Tenofovir (TDF) tablets**

- Partners PrEP
- VOICE

**Effect size (CI)**

- 62% (34; 78)
- 0% ( ? ; ?)
Oral and topical PrEP in women: Results of Randomised Control Trials

### Intervention and Study

- **Tenofovir gel**
  - CAPRISA 004
  - VOICE
  - FACTS 001

### Effect size (CI)

- **39% (6; 60)**
- ?
- ?
Oral and topical PrEP in women: Results of Randomised Control Trials

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Big scientific question at this time…

- Do oral antiretrovirals prevent HIV infection in women?
- 2 trials show protection & 2 trials do not show protection
- Such dramatic differences in trials are unusual
- Why the conflicting results?
  - Just plain bad luck?
  - Inadequate adherence to daily tablets in FEM-PrEP & VOICE?
  - Different populations with different risks and biology?
- While awaiting detail data - plan studies on biology now!
- To establish biological differences: Back to Basics
- Translational research: from bench to patient & from patient to bench
Key next step.....

- Need to go back to the lab to better understand the basics of the biology of genital tract pathogenesis, drug levels & virus-drug interaction in these trial populations

- Collect specimens to address potential hypotheses
  - HIV Clade? Kenya & Uganda different from South Africa & Botswana
  - Geography? Type of epidemic? Stage of epidemic?
  - Age? Nature of partnerships? Number of partners (multi-antigens)?
  - Level of activated CD4 cells in vagina? Genital inflammation?
  - Adequate drug for viral challenge? PK? Viral load in partners?

- If we do not understand why the trials differed – how do we plan the next PrEP trials?
What else is next…..

- Status of current trials – next results:
  - Voice – next DSMB in about a month’s time (November)
  - FACTS 001 – just started enrolling

- Next oral / topical PrEP effectiveness trials:
  - Effectiveness of ring technologies – IPM’s dapivirine ring
  - Effectiveness in rectal compartment
  - Implementation effectiveness

- Combination prevention:
  - Based on a foundation of increased HIV testing & T4P
  - Aims for synergy in the combination for impact on epidemic
  - For impact on young women – PrEP is critical
  - Moving beyond the individual to community level impact
  - We need to establish if combination prevention is a step towards stopping the epidemic in a Community