



CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS
COLLABORATING CENTRE
FOR HIV PREVENTION RESEARCH

Women & HIV: The key to reaching the 3 zeros

Presented at the UNAIDS PCB, Geneva – December 2011

Quarraisha Abdool Karim, PhD

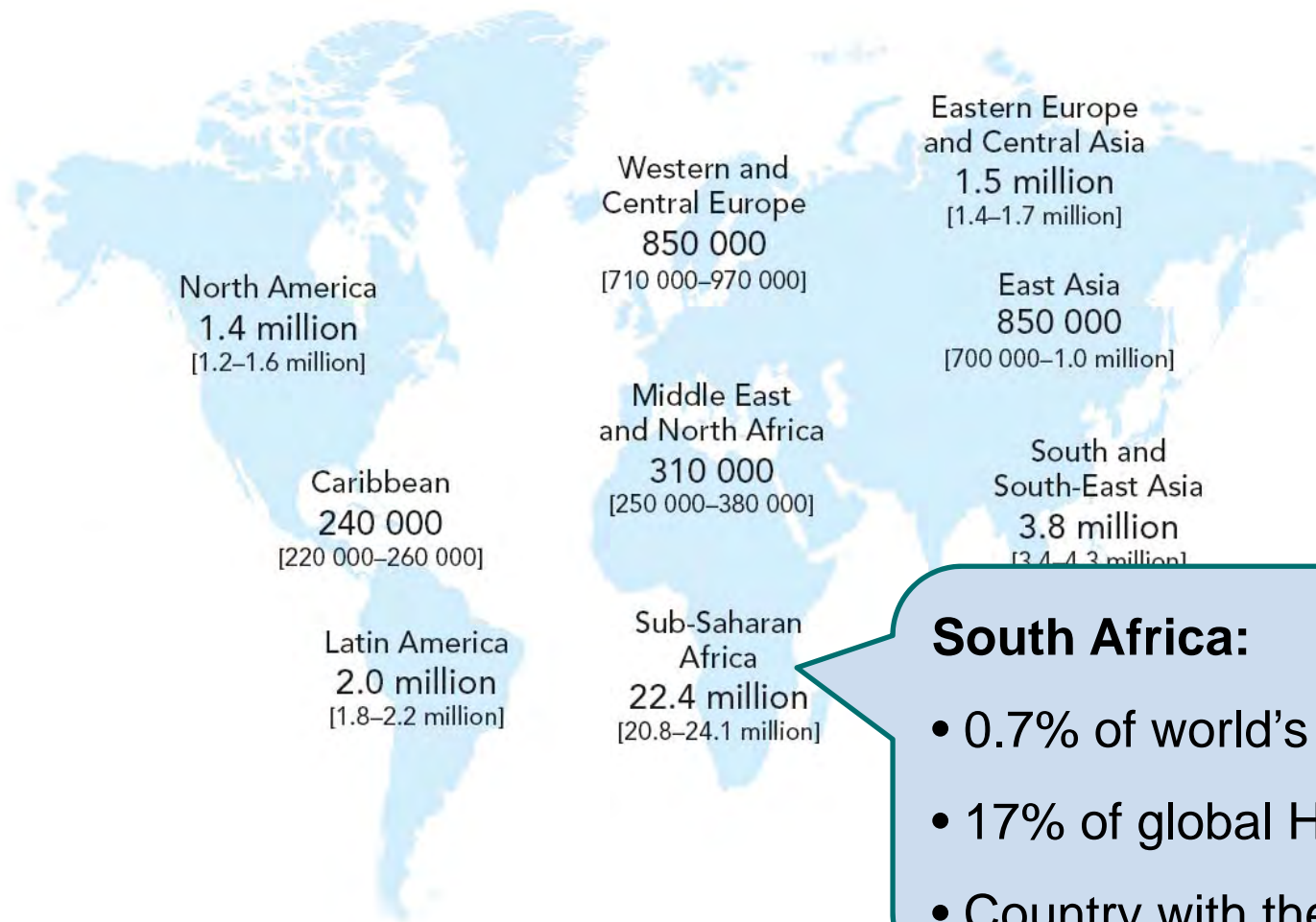
Associate Scientific Director, CAPRISA
Co-Chair HPTN & Associate Professor, Columbia University
Professor, Nelson R Mandela School of Medicine

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

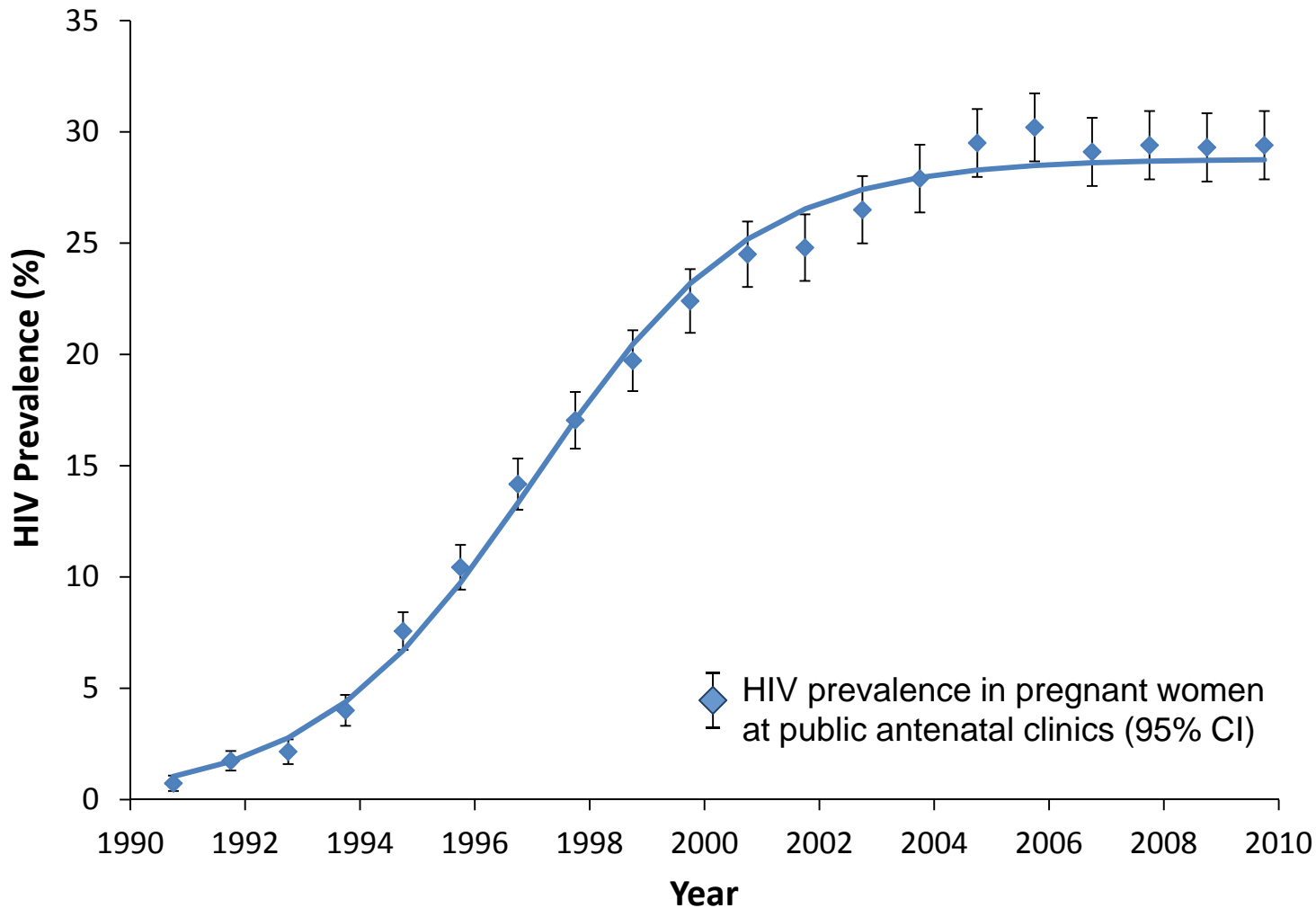
33.4 million living with HIV, 2.7 million new infections, 2 million deaths



South Africa:

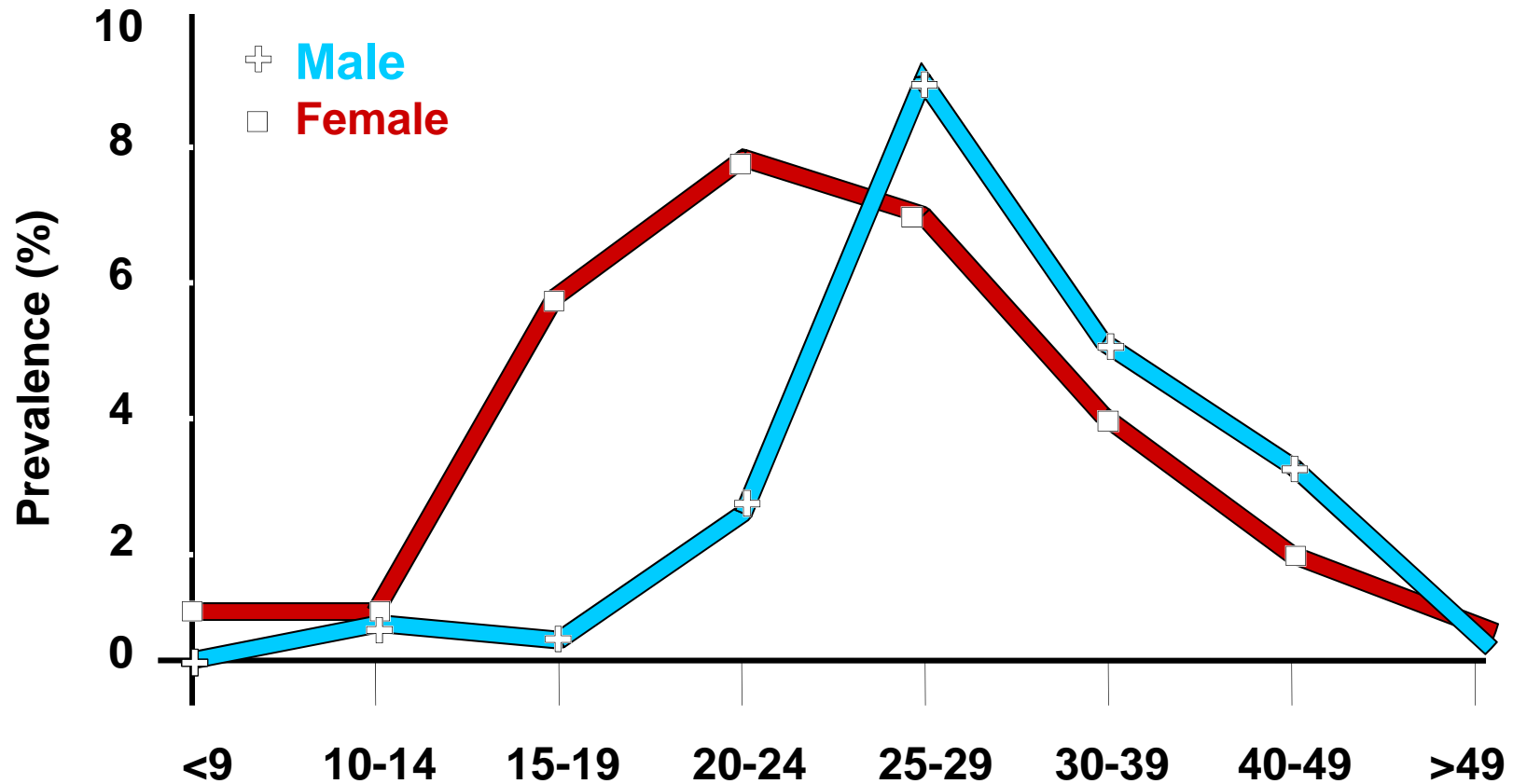
- 0.7% of world's population
- 17% of global HIV burden (5.4m)
- Country with the most AIDS cases

The HIV epidemic in South Africa: 1990-2010



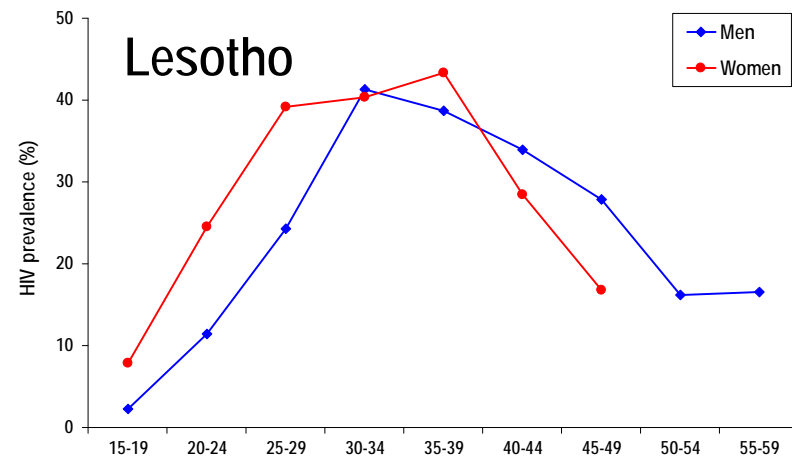
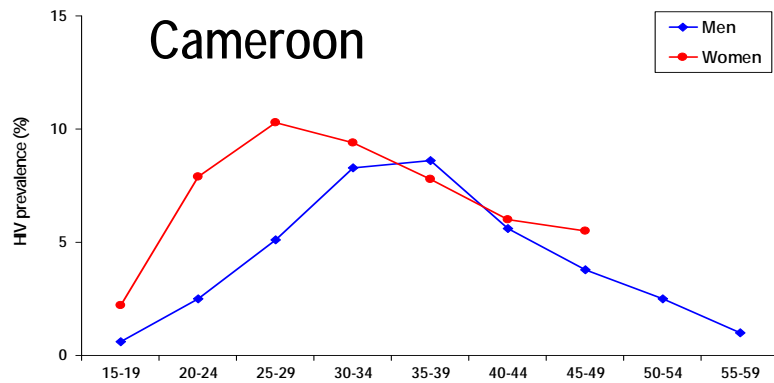
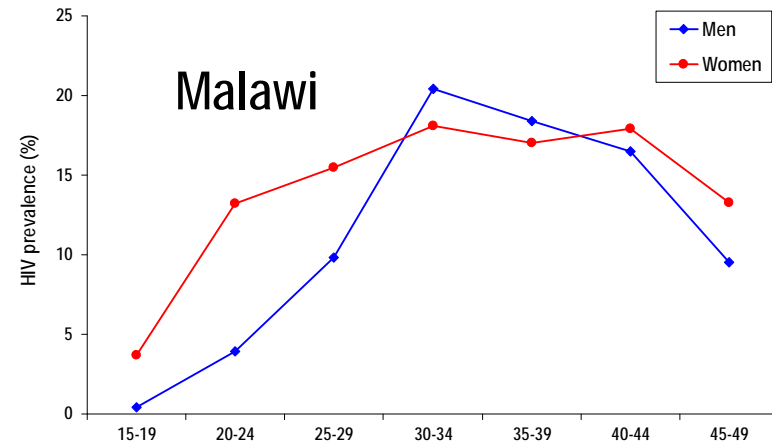
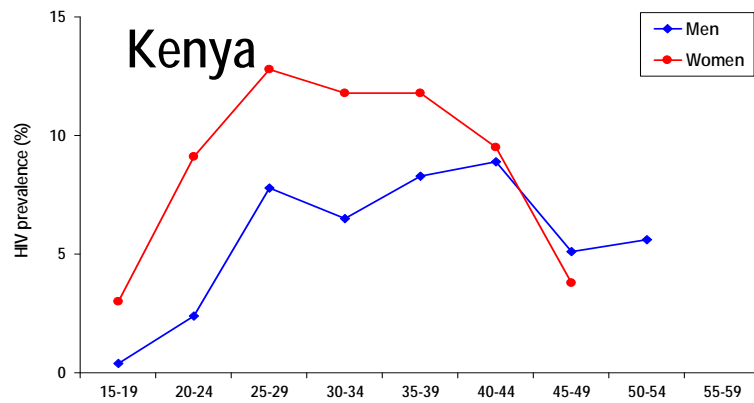
Source: Data from South African Department of Health Antenatal Surveys. www.doh.gov.za

HIV infection in South Africa: Young women - key to stopping the epidemic!



Source: Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngxongo S. *AIDS* 1992; 6: 1535-9

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





HIV prevalence in pregnant women in rural Vulindlela, South Africa (2005-2008)

Age Group (Years)	HIV Prevalence (N=1237)
≤16	10.6%
17-18	21.3%
19-20	33.0%
21-22	44.3%
23-24	51.1%

High priority: Reducing HIV in young girls

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

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



The RHIVA Programme is conducted in collaboration with MiET Africa and DoE with funding from the Royal Netherlands Embassy



High priority: Reducing HIV in young girls

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

Age Group	HIV Prevalence (Oct/Nov 2010) % (95% Confidence Interval)	
	Male	Female
≤14	1.0 (0.0 – 3.0)	2.2 (0.3 – 4.0)
15-16	1.4 (0.4 – 2.4)	3.6 (2.2 – 5.0)
17-18	1.2 (0.2 – 2.2)	7.9 (5.0 - 11.0)
19-20	1.1 (0.0 – 2.7)	16.0 (9.2 – 22.0)



The RHIVA Programme is conducted in collaboration with MiET Africa and DoE with funding from the Royal Netherlands Embassy



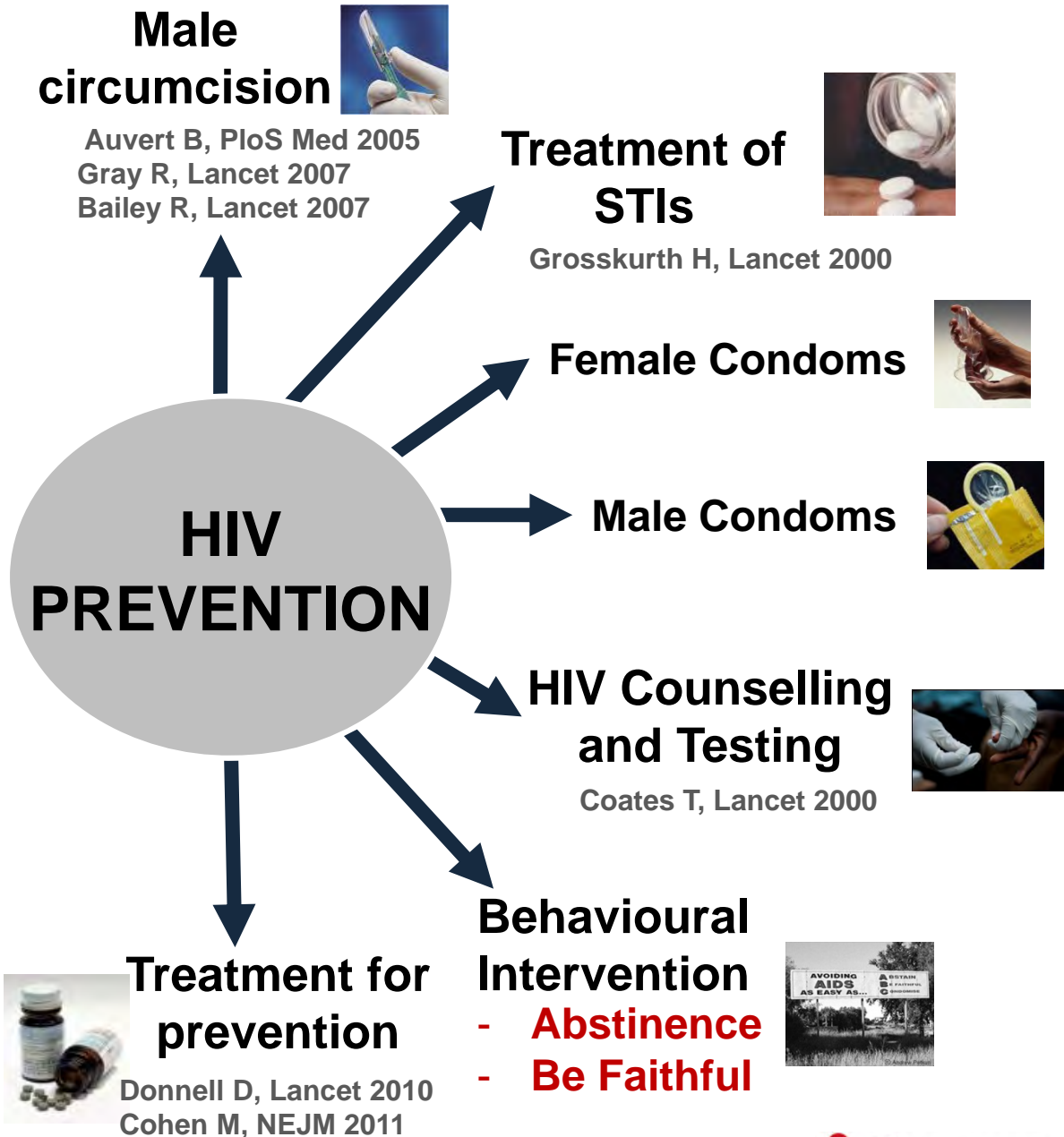
Existing proven HIV prevention strategies - ABCCC:

- **A**bstinence
- **B**ehaviour (Be faithful)
- **C**ondoms
- **C**ounsel & Test
- **C**ircumcision

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,¹ Leila E. Mansoor,¹ Ayesha B. M. Kharsany,¹ Sengeziwe Sibeko,¹ Koleka P. Mlisana,¹ Zaheen Omar,¹ Tanuja N. Gengiah,¹ Silvia Maarschalk,¹ Natasha Arulappan,¹ 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

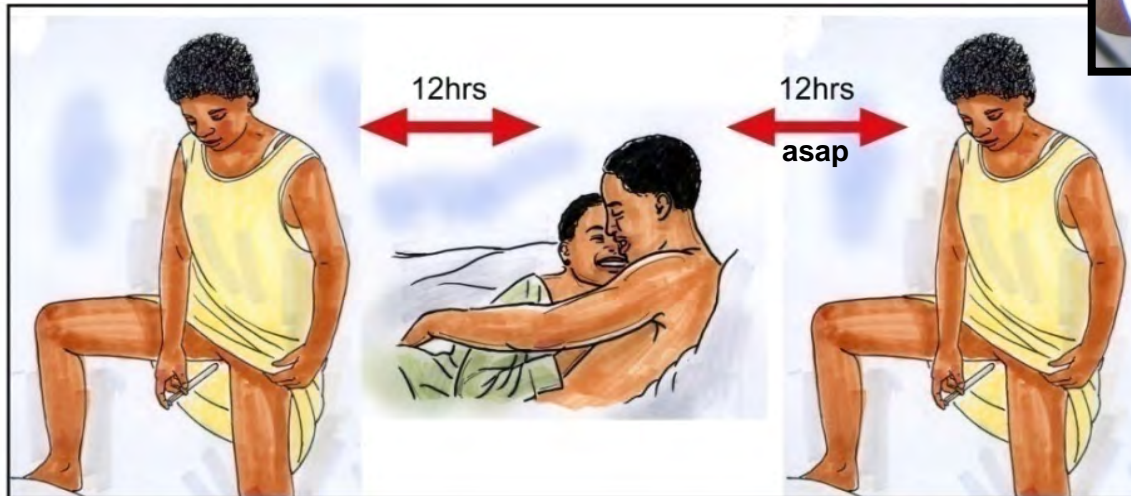


CAPRISA 004 assessed the safety and effectiveness of 1% tenofovir gel

Use gel with sex (BAT 24):

- Insert 1 gel up to 12 hours **B**efore sex,
- insert 1 gel within 12 hours **A**fter sex,
- no more than **T**wo doses in **24** hours

CAPRISA 004 tenofovir gel regimen



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



Age	HIV Prevalence	
(in years)	2005 - 2009	2015 - 2019
≤16	10.6%	±1%
17-18	21.3%	±1%
19-20	33.0%	±5%
21-22	44.3%	±10%
23-24	51.1%	±10%



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 microbicidal HIV gel

Salim and Quarraisha Abdool Karim, husband and wife, and co-principle 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 microbicidal gel can protect against HIV transmission. Mathematical modelling suggests that, in South Africa alone, this gel can prevent up to 1.3 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 vaginal gel, applied no more than 12 h before vaginal sex and as soon as possible, but no later than 12 h after sex, had a 39% lower

“It is 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



Salim Abdool Karim at the International AIDS Society Conference

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, is expected to start in 2013, is

For the CAPRISA tenofovir study see *Science* 2010; DOI:10.1126/science.1192748
For more on AVAC see <http://www.avac.org/>
For more on the Microbicides Development Programme see <http://www.mdp.rivm.ac.uk/>

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News

Success at last for anti-HIV gel

Vaginal gel cuts HIV infection in women by half.

Rebecca Trager

An antiretroviral microbicide gel can cut HIV infection in women by more than 50% if used consistently.



The first successful trial of an HIV gel has shown that it may prevent transmission of the virus to women.

William Daniels/PANOS

Worldwide, an estimated 33 million people are living with HIV, roughly half of them women, according to UNAIDS. In South Africa, one in three women aged 20–34 is estimated to be infected with HIV. Because 60% of all new HIV infections in sub-Saharan Africa are in women, there is a sense of urgency surrounding the development of HIV-prevention tools for this group.

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- [Anti-HIV gel trial fails](#)
19 February 2008
- [HIV trial doomed by design, sav critics](#)
11 July 2007

Scienceexpress News of the Week

HIV/AIDS At Last, Vaginal Gel Scores Victory Against HIV

Jon Cohen
Contributing correspondent, *Science*

Gooodoo! 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-1 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 clear-cut result with obvious protection at a meaningful level.”

More than 30 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 hotly 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, 60 became infected with HIV versus 38 infections in the 445 women who received the microbicide. The result was statistically significant, and no serious side effects occurred. “It’s a moment we’ve been waiting for,” says Moore.



The New York Times

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A Promising Preventive

It is easy to understand why the results of a modest-size scientific study in South Africa were met with ecstatic applause on Tuesday at an international AIDS conference in Vienna. Researchers have shown that a vaginal gel cuts a woman’s risk of infection with H.I.V., the virus that causes AIDS, by almost 40 percent.

Those on the medicated gel were 39 percent less likely to contract H.I.V.; those who used it most regularly were 54 percent less likely. The only discouraging note was that effectiveness seemed to wane over time, possibly because women became less diligent in their use. The gel seems destined to take its place as a first-line prevention strategy.

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”



BREAKTHROUGH OF THE YEAR | NEWSFOCUS

www.sciencemag.org SCIENCE VOL 330 17 DECEMBER 2010

1607



Molecular Dynamics Simulations

Sometimes brute force is the way to go, particularly when using computers to simulate the gyrations proteins make as they fold. Such simulations are a combinatorial nightmare. Each two neighboring amino acids in a protein chain can bind to one another at two different angles, each of which can have three conformations. So a simple protein with 100 amino acids can fold in 3¹⁹⁸ different ways. Getting at the atomic detail is even scarier. Proteins sort through all these possibilities in milliseconds or less. Computers take far longer.

Protein-folding experts have long turned to supercomputers for help. But even these behemoths struggle to track the motions long enough to simulate the complete folding process. Two years ago, researchers in the United States unveiled a new supercomputer hardware with 512 computer chips tailor-made to speed the calculations of the way neighboring atoms in a protein and the surrounding water interact. That enabled them to gain another burst in speed. As a result, the group reported this year that they've been able to track the motion of atoms in a small protein 100 times longer than previous efforts could do—long enough to see the protein wind its way through 15 cycles of folding and unfolding. Next up, the group is already turning to novel machines with 1024 and 2048 chips to improve simulations of larger proteins.

However, physicists can tailor a quantum simulator to a particular Hamiltonian and let the experiment solve the theoretical problem. Five groups reproduced the results for four previously solved Hamiltonians. Three even mapped "phase diagrams" akin to the one that shows the temperatures and pressures at which water becomes a gas, liquid, or solid.

Physicists hope quantum simulators will crack Hamiltonians that have not been solved—such as one for high-temperature superconductors. But first they had to show that the things could reproduce known results. Check.



Rats Redux

Today, most lab cages house mice, but the tenant of choice used to be rats. The reason: Rats are more like us. The human heart, for example, beats about 70 times a minute; a rat's heart, 300 times; a mouse's, 700. Electrical signal patterns in rat and human hearts are also similar. Rats, being more intelligent than mice, might also be better models of human neural diseases such as Alzheimer's and Parkinson's. And rats are bigger and easier to handle for lab work.

Then, in 1989, researchers learned to delete specific genes to make "knockout mice." The technique they used, called homologous recombination of embryonic stem cells, didn't work in rats. So mice became the preferred

experimental animal in various developmental biology to drug

That too may pass. In 2009, researchers adapted to rats a method, previously used in fruit flies and zebrafish, that called for injecting nucleases to cut DNA. In August, another group announced that produced "knockout rat genetic trick used for knock this year, several groups reported using transposons, DNA sequences from one location to another to generate rats with genetic animals useful for development and disease research. As a result, knockout and genetic rats may soon displace their lab cages around the world.



HIV Prophylaxis

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

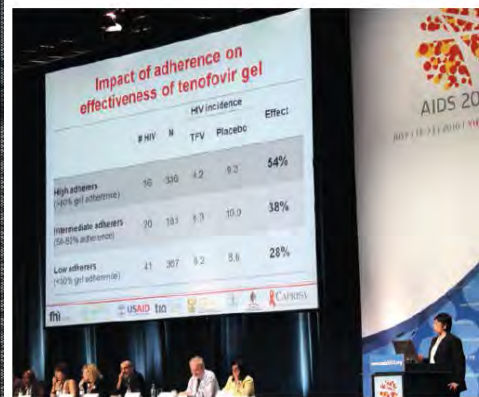
The first result stole the show at the jam-packed XVIII International AIDS Conference held in Vienna, Austria. A vaginal gel

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%.

Last month, the first-ever study of oral pre-exposure prophylaxis made headlines with results even more encouraging. The subjects, 2499 men and transgender women who have sex with men, were recruited from six countries. Half were asked to take Truvada, a combination of tenofovir and emtricitabine, each day. After an average of 1.2 years, the treated group had 43.8% fewer infections than the group that took a placebo. Again, better adherence equaled better efficacy: In a small substudy, efficacy increased to 92% in participants who had measurable levels of Truvada in their blood.

Neither approach is a magic bullet, AIDS researchers say. But in combination with other measures, they could usher in a new era of HIV prevention.

The CAPRISA 004 trial is in Science's Top 10 Scientific Breakthroughs in 2010



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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**



Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Charialertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D.,

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)

Editorial

www.thelancet.com Vol 377 May 21, 2011

1719

THE LANCET

HIV treatment as prevention—it works

Last week any doubts around treatment as an approach to halt the spread of the HIV epidemic were allayed. An international study showed that antiretroviral treatment can prevent the sexual transmission of HIV among heterosexual couples in whom one partner is HIV-infected and the other is not. UNAIDS described the result as a “serious game changer” for HIV prevention.

The phase 3 clinical trial, HPTN 052, was done by the HIV Prevention Trials Network and funded by the US National Institutes of Health. It was due to run until 2015, but

group versus three cases in the immediate group. Study participants and investigators have been informed of the results and all participants offered the appropriate care. All study participants will be followed for at least 1 more year.

Clearly, treating sooner rather than later results in both a clinical benefit for the individual and has a potentially enormous public health benefit in slowing the spread of infection. These results are likely to provide a new level of dialogue between physician and patient. Besides emphasising the benefit of medication adherence to the



Corbis

1763 discordant couples in Africa & America

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



July 2011: Oral PrEP prevents HIV transmission in discordant couples (PartnersPrEP)



UNIVERSITY OF WASHINGTON
INTERNATIONAL CLINICAL RESEARCH CENTER
PARTNERS PrEP STUDY

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)



CENTERS FOR DISEASE CONTROL AND PREVENTION

FOR IMMEDIATE RELEASE

Wednesday, July 13, 2011
5:00 AM EDT

Media Contact:

National Center for HIV/AIDS,
Viral Hepatitis, STD, and TB Prevention

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%

**ARV
prophylaxis**

**Male
circumcision**



Auvert B, PloS Med 2005
Gray R, Lancet 2007
Bailey R, Lancet 2007

**Treatment of
STIs**

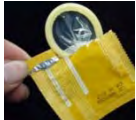


Grosskurth H, Lancet 2000

Female Condoms



Male Condoms



**HIV
PREVENTION**

**Oral pre-exposure
prophylaxis**



Grant R, NEJM 2010 (MSM)
Baeten J, 2011 (Couples)
Paxton L, 2011 (Heterosexuals)

**HIV Counselling
and Testing**



Coates T, Lancet 2000

**Post Exposure
prophylaxis (PEP)**



Scheckter M, 2002

**Treatment for
prevention**



Donnell D, Lancet 2010
Cohen M, NEJM 2011

**Behavioural
Intervention**

- **Abstinence**
- **Be Faithful**



Note: PMTCT, Screening transfusions, Harm reduction, Universal precautions, etc. have not been included – this is focused on reducing sexual transmission

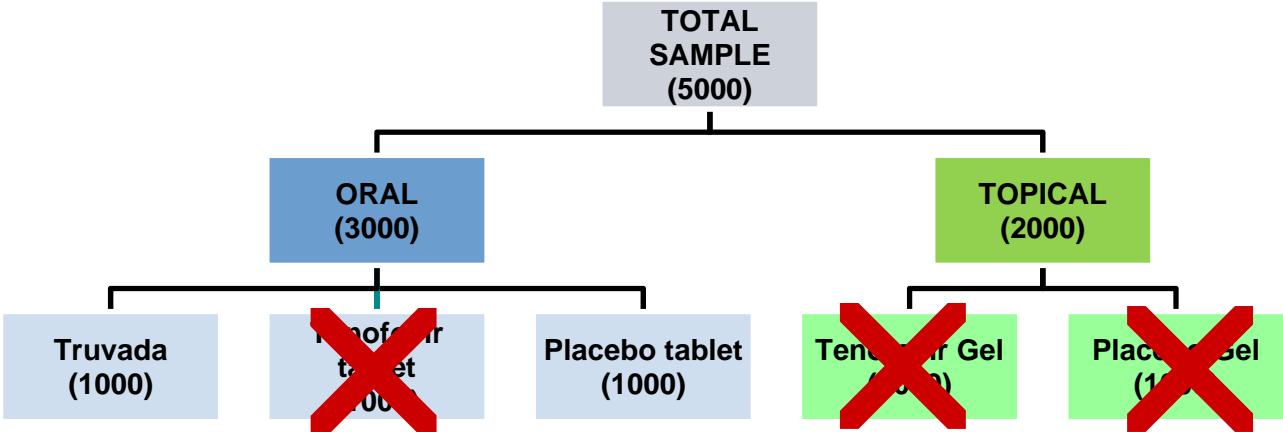




**April 2011: FEM-PrEP trial stops: Truvada
Tenofovir + FTC not effective in women**



**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**

Reasons for VOICE & FEM-PrEP results

“...whether adherence, our daily dosing strategy, inflammation, or other factors could explain the lack of oral and vaginal tenofovir effectiveness..”

Sharon Hillier, 25 November

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:**
 - \uparrow adherence = \downarrow HIV (up to 54% reduction in HIV)
- 4. Tissue drug level correlates with HIV protection:**
 - \uparrow genital drug = \uparrow HIV protection
- 5. Repeatedly highly effective in cell culture, explant tissues, mice & monkeys**

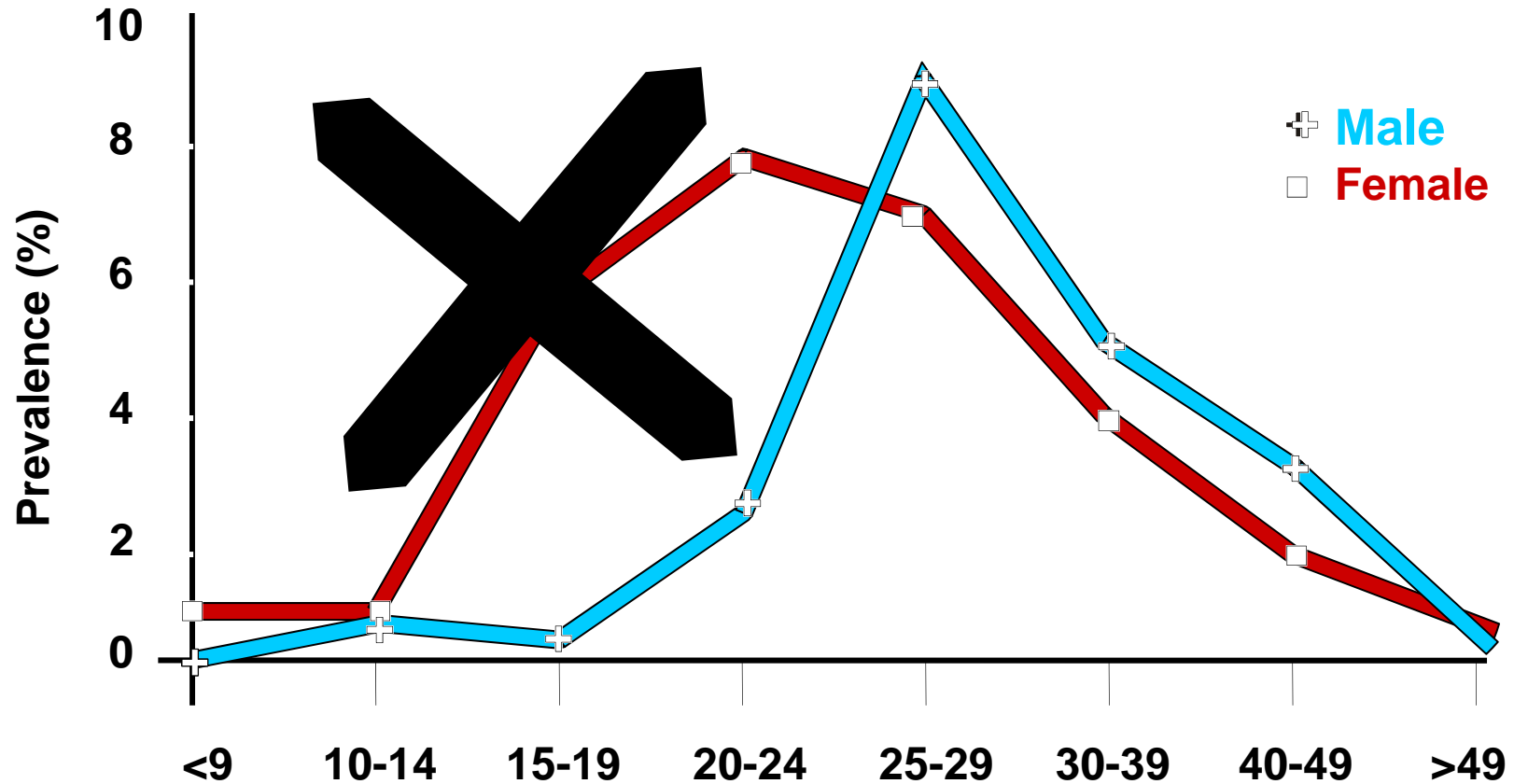
“The HIV response faces a moment of truth.”

“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



Source: Abdool Karim Q, Abdool Karim SS, Singh B, Short R, Ngxongo S. *AIDS* 1992; 6: 1535-9

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.



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