

Becoming an Independent Scientist: What does it take?

- **Good ideas – think local + global relevance**
- **Hard work**
- **Persistence**
- **Perseverance**
- **Patience**
- **A critical mass of skilled scientists**
- **A team with a common shared vision**
- **Good mentors and partners**
- **Be prepared for many failures and lots of criticism**
- **Enjoy the few successes**
- **No room for complacency**



Preventing HIV infection in Women – A Global Imperative!

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Director: CU-SA Fogarty AIDS Training Program

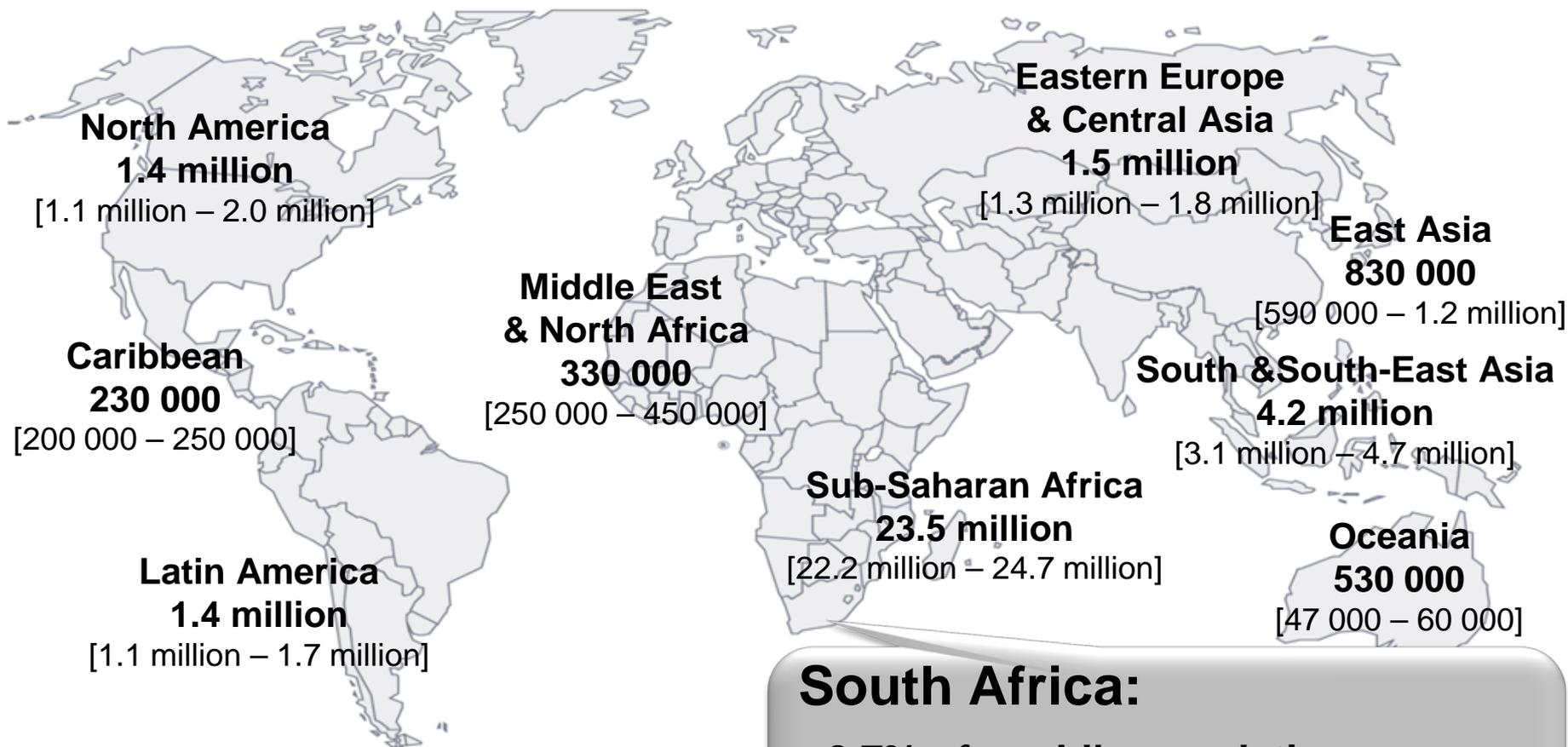
EMBLEM PI Workshop, Kenya, September 2014

Outline

- **Women & HIV in Africa**
- **Urgent need for HIV prevention in women**
- **Tenofovir gel : First HIV prevention technology to empower women against HIV**
- **Conclusion**

Global HIV epidemic - 2011

34.2 million living with HIV, 2.5 million new infections, 1.7 million deaths



South Africa:

- 0.7% of world's population
- 16% of global HIV burden (5.4m)
- Country with the most AIDS cases

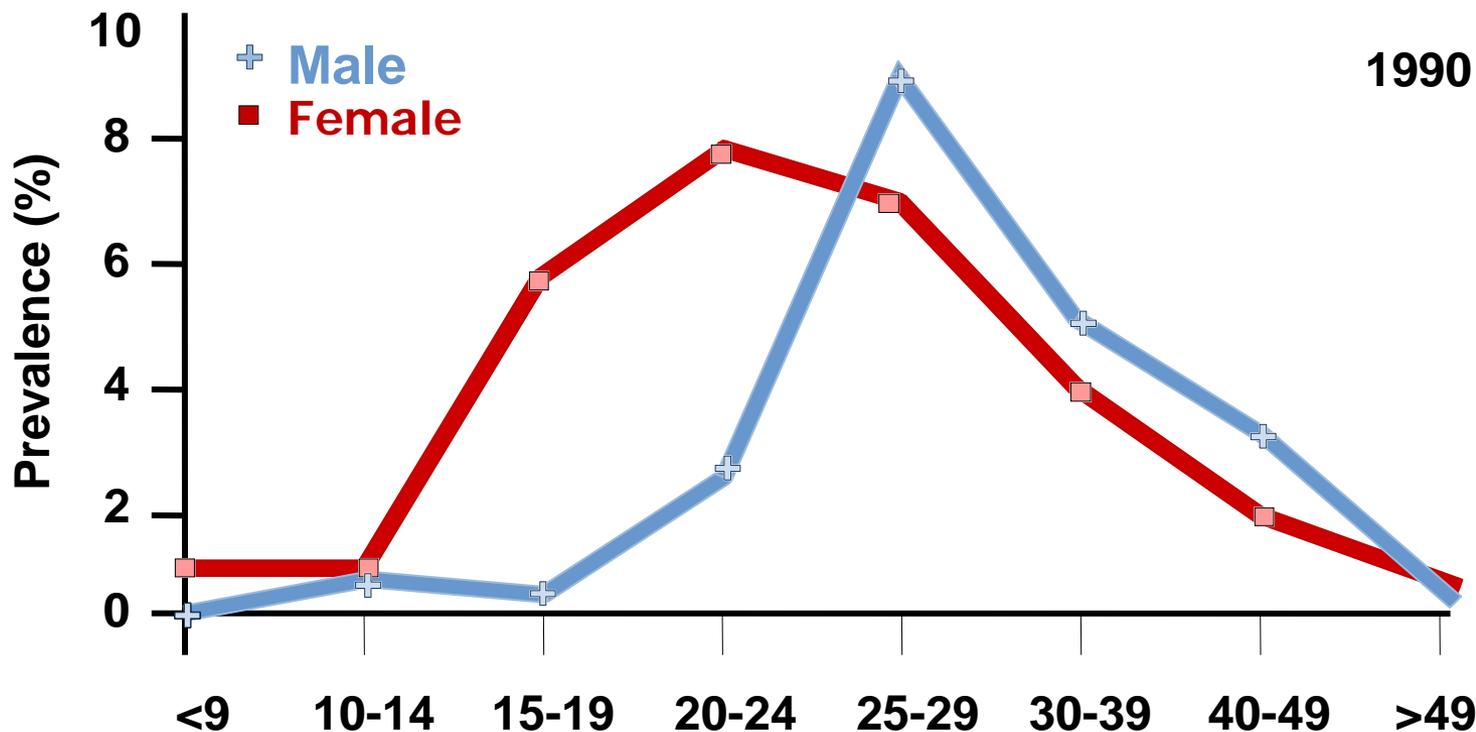
Why is the HIV epidemic so severe in South Africa?



Seroprevalence of HIV infection in rural South Africa

AIDS 1992, 6:1535-1539

Quarraisha Abdool Karim, Salim S. Abdool Karim, Bipraj Singh*, Richard Short† and Siphon Ngxongo‡

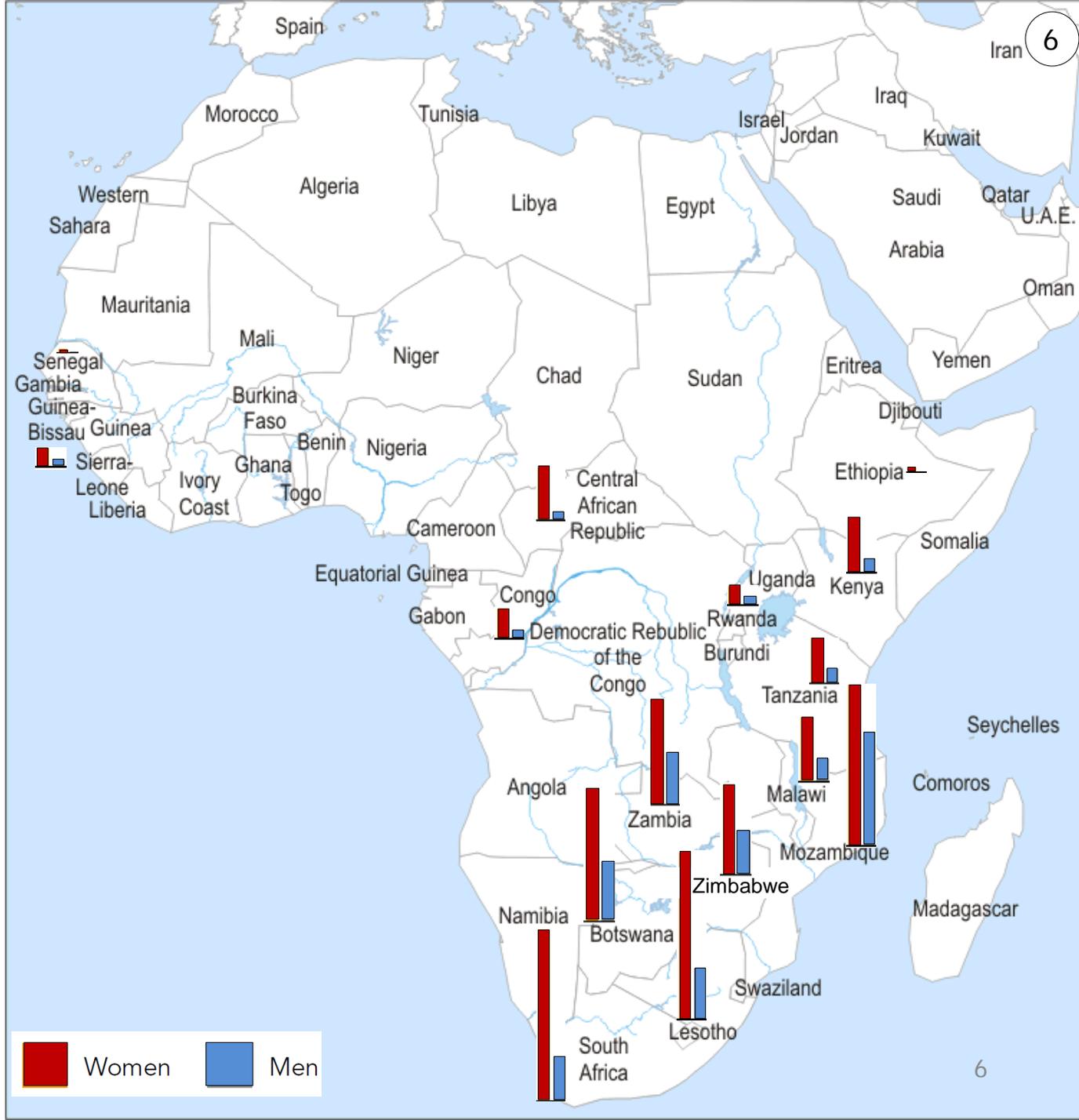


High rates of HIV among key populations: young women in Africa

HIV in 15–24 year men and women (2008–2011)

Young women have up to 8 times more HIV than men

Source: Adapted from UNAIDS 2012



Early studies of HIV epidemiology in women in South Africa



South Africa: host to a new and emerging HIV epidemic

Q ABDOOL KARIM
S S ABDOOL KARIM

**Sexually
Transmitted
Infections**



Unrecognized sexually transmitted infections in rural South African women: a hidden epidemic

D. Wilkinson,¹ S.S. Abdool Karim,¹ A. Harrison,¹ M. Lurie,¹ M. Colvin,¹
C. Connolly,¹ & A.W. Sturm²

**Bulletin of the World Health
Organization**



Reducing the Risk of HIV Infection among South African Sex Workers: Socioeconomic and Gender Barriers

Quarraisha Abdool Karim, MS, HED, Salim S. Abdool Karim, FFCH(SA), MMed(CH), MS, DipData, Kate Soldan, MS, and Martin Zondi



Sexual behaviour and knowledge of AIDS among urban black mothers

Implications for AIDS intervention programmes

Q. ABDOOL KARIM, S. S. ABDOOL KARIM, J. NKOMOKAZI



High HIV Incidence and Prevalence Among Young Women in Rural South Africa: Developing a Cohort for Intervention Trials

JAIDS JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES

*†David Wilkinson, *S. S. Abdool Karim, ‡Brian Williams, and *Eleanor Gouws

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

Age Group (Years)	HIV Prevalence (N=1029)
≤16	8.4
17-18	18.6
19-20	25.4
21-22	32.8
23-24	44.8



Stabilizing HIV prevalence masks high HIV incidence rates amongst rural and urban women in KwaZulu-Natal, South Africa

Quarraisha Abdool Karim,^{1,2} Ayesha BM Kharsany,^{1*} Janet A Frohlich,¹ Lise Werner,¹ May Mashego,¹ Mukelisiwe Mlotshwa,¹ Bernadette T Madlala,¹ Fanelesibonge Ntombela¹ and Salim S Abdool Karim^{1,2}



Stigma impedes AIDS prevention

Medical advances cannot help those who deny they are at risk of HIV and avoid HIV tests. **Salim S. Abdool Karim** describes how such attitudes may be overcome.



HIV and maternal mortality: turning the tide

Quarraisha Abdool-Karim, Carla AbouZahr, Karl Dehne, Viviana Mangiaterra, Jack Moodley, Nigel Rollins, Lale Say, Nathan Schaffer, James E Rosen, *Isabelle de Zoysa



Preventing HIV Infection in Women: A Global Health Imperative

Quarraisha Abdool Karim,^{1,2} Sengeziwe Sibeko,¹ and Cheryl Baxter¹



Screening for 'window-period' acute HIV infection among pregnant women in rural South Africa

ABM Kharsany,¹ N Hancock,² JA Frohlich,¹ HR Humphries,¹ SS Abdool Karim^{1,3} and Q Abdool Karim^{1,3}

¹Centre for the AIDS Programme of Research in South Africa (CAPRISA), Doris Duke Medical Research Institute, Nelson R



AIDS research must link to local policy

HIV research in South Africa is world class. To halt the country's epidemic, scientists need to shift focus from global problems to priorities at home, say **Salim Abdool Karim** and **Quarraisha Abdool Karim**.

High priority: Reducing HIV in young girls

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

Age Group (years)	HIV Prevalence (2010) % (95% Confidence Interval)	HIV Prevalence (2010) % (95% Confidence Interval)
	Male (n=1252)	Female (n= 1423)
≤15	1.0 (0.0 - 2.2)	2.6 (1.2 - 4.0)
16-17	1.1 (0.2 - 2.0)	6.1 (2.6 - 9.6)
18-19	1.5 (0 - 3.7)	13.6 (9.0 - 18.1)
≥20	1.8 (0 - 3.9)	24.7 (6.3 - 43.1)

Preventing the sexual spread of HIV:

- Existing accepted proven HIV prevention strategies - ABCC:
 - **A**bstinence
 - **B**ehaviour (Be faithful)
 - **C**ondoms (Male & Female)
 - **C**ircumcision (Medical Male)

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

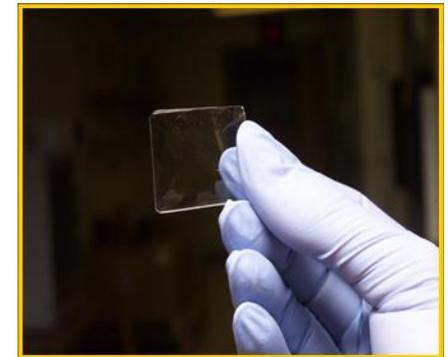
A microbicide is a product that can be applied to the vaginal or rectal mucosa with the intention of preventing the transmission of sexually transmitted infections including HIV



Vaginal gel applicator



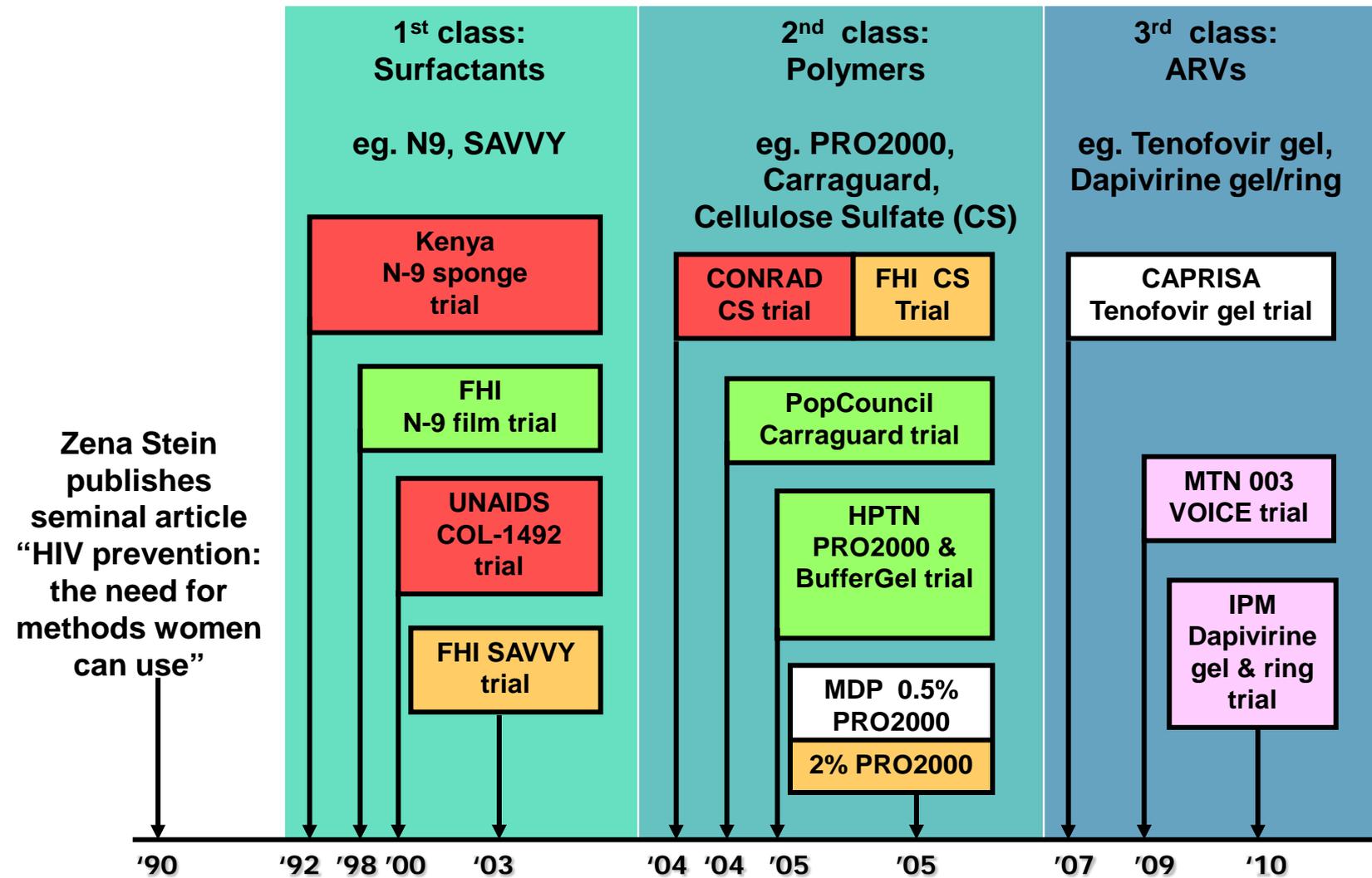
Vaginal ring



Vaginal film

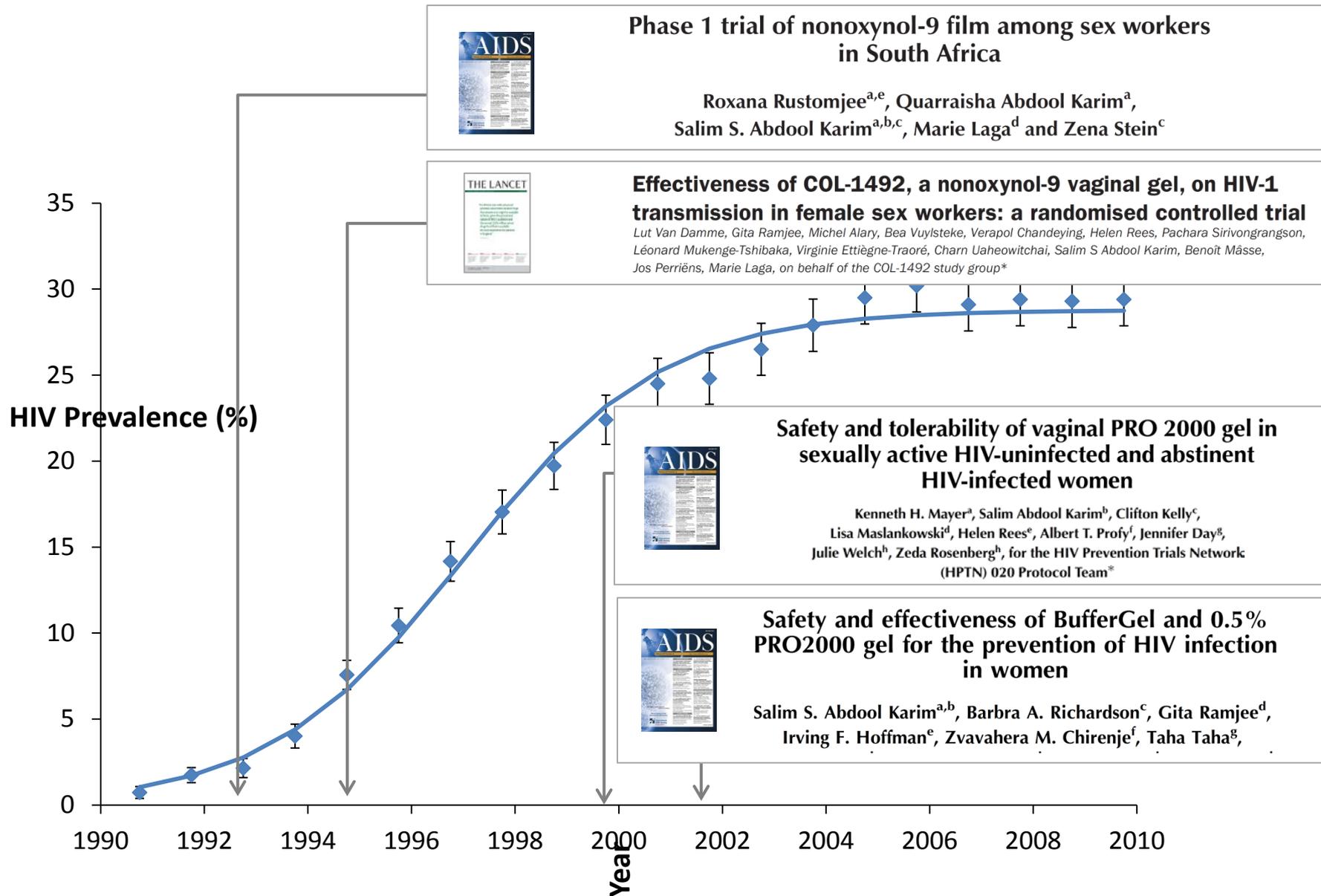
**Microbicides containing antiretroviral drugs =
Topical PrEP (Pre-exposure prophylaxis)**

Past & Current Microbicide Clinical Trials



■ Safe but not effective
 ■ Increased HIV infection
 ■ Stopped for fertility
 ■ Planned

A long road: Multiple disappointing microbicide trial results



Switching to antiretrovirals for HIV prevention in women...

Why Tenofovir?

- **Effective therapeutic agent**
- **Good safety profile**
- **Rapidly absorbed and long half-life**
- **Effective in suppressing viral load**
- **Protects against SIV in monkey studies**

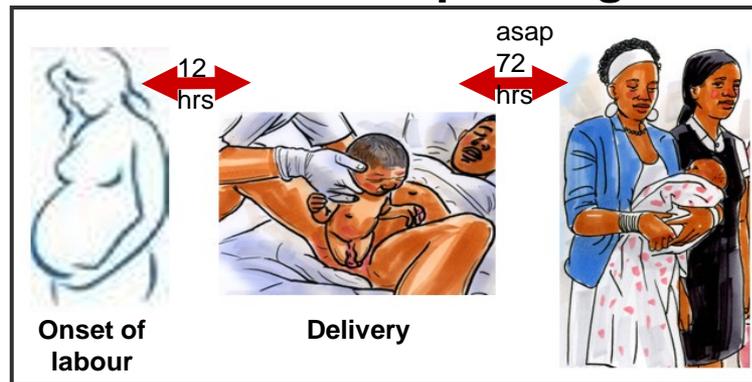
2003: Developed CAPRISA 004 to assess safety & effectiveness of tenofovir gel

• BAT 24 coitally-related gel use

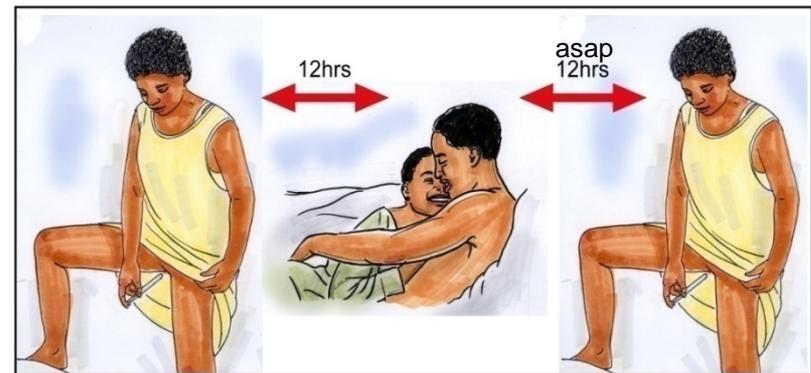
- Insert 1 gel up to 12 hours **B**efore sex,
- insert 1 gel as soon as possible within 12 hours **A**fter sex,
- no more than **T**wo doses in **24** hours



HIVNET 012 nevirapine regimen



CAPRISA 004 tenofovir gel regimen



CAPRISA 004 Results

- **Tenofovir gel prevents HIV in women**
 - 39% protection against HIV overall
 - 54% effective in women with high adherence
 - 74% protection with high tenofovir levels
- **Tenofovir gel prevents HSV-2 infection in women**
 - 51% reduction in HSV-2 incidence

**First results to show that
antiretroviral drugs can prevent
sexual transmission of HIV & HSV-2**

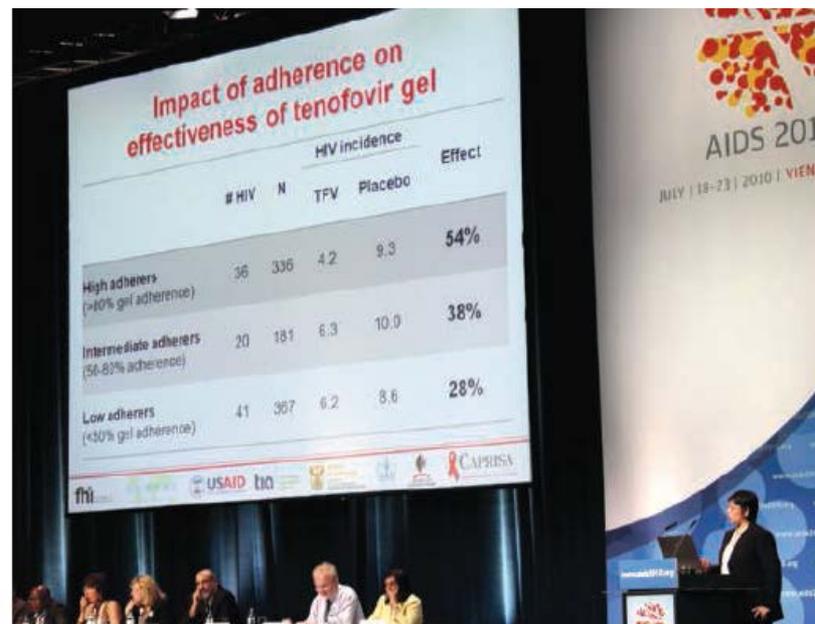
Tenofovir gel results at the 2010 International AIDS Conference & published online by Science at the same time



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





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 computer do the heavy lifting.

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 studies, from developmental biology to drug development.

That too may pass. In 2009, researchers adapted to rats a method, previously used in fruit flies and zebrafish, that uses enzymes called zinc finger nucleases to knock out genes. In August, another group announced a tweak that produced "knockout rats" by the same genetic trick used for knockout mice. Also this year, several groups reported advances in using transposons, DNA sequences that jump from one location to another within a genome, to generate rats with genetic mutations—animals useful for developmental biology and disease research. As a result of such techniques, knockout and genetically modified rats may soon displace their smaller cousins in lab cages around the world.



HIV Prophylaxis

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,

Downloaded from www.sciencemag.org on January 23, 2011

CAPRISA 004 was ranked among 2010's Top 10 Scientific Breakthroughs by Science



HIV Prophylaxis

From the start of the AIDS epidemic through 2009, only five 677 randomized studies that

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Comment

THE LANCET

The Lancet's paper of the year 2010

Between Jan 18 and Jan 31, *Lancet* readers voted for the research paper published in 2010 that they felt was most likely to influence practice and research. Two randomised trials led the field. Mark Loeb and colleagues' (figure)

CAPRISA 004 examined individual protection from HIV transmission in nearly 900 HIV-negative women aged 18–40 years in KwaZulu-Natal who were randomised to a 1% tenofovir vaginal gel or to a placebo gel to be



Adherence is essential & partnerships with the community enhances adherence

	# HIV	N	HIV incidence: TFV	HIV incidence: Placebo	Effect	p-value
High adherers (>80% gel adherence)	36	336	4.2	9.3	54%	0.03
Intermediate adherers (50-80% adherence)	20	181	6.3	10.0	38%	0.29
Low adherers (<50% gel adherence)	41	367	6.2	8.6	28%	0.30



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.”

Source: Abdool Karim S, Abdool Karim Q, Nature, 446; 2007



Source of data in table: Abdool Karim Q, Abdool Karim SS, Frolich J, et al. Science 2010

Unique features of CAPRISA 004

- 1. First microbicide trial funded by a developing country**
 - Trial funded by both South African and US governments
- 2. Trial was a joint US-SA partnership**
 - Joint venture by US (FHI, CONRAD & USAID) and South African (CAPRISA, TIA & DST) organizations.
- 3. Trial led by African scientists**
 - Trial designed, conducted and analysed in South Africa
- 4. Royalty-free license for SA govt. secured up-front to manufacture and distribute tenofovir gel in Africa**

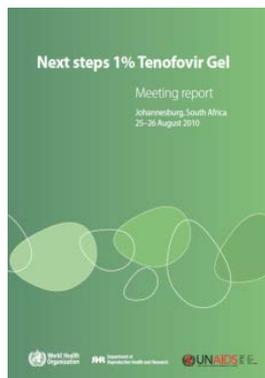
Progress on tenofovir gel



Confirmatory trial (FACTS 001) on Tenofovir gel started October 2011 in South Africa – funded 50-50 by the SA and USA governments



WHO developing policy and guidelines for tenofovir gel implementation



SA Government (TIA) owns the licence for tenofovir gel and is planning a factory to manufacture tenofovir gel in South Africa

Over 20 years, the use of tenofovir gel in South Africa could avert up to 2 million new infections and 1 million AIDS deaths (*Williams et al. Journal of AIDS, 2011*)

ARV prophylaxis

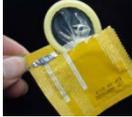
Male circumcision 

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 Counselling and Testing 

Coates T, Lancet 2000

Behavioural Intervention

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



Treatment for prevention 

Donnell D, Lancet 2010
 Cohen M, NEJM 2011



Microbicides for women 

Abdool Karim Q, Science 2010

Oral pre-exposure prophylaxis 

Grant R, NEJM 2010 (MSM)
 Baeten J, 2011 (Couples)
 Paxton L, 2011 (Heterosexuals)
 Choopanya K, 2013 (IDU)

Post Exposure prophylaxis (PEP) 

Scheckter M, 2002

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

Future Plans: Developing the next generation combination tenofovir gel

**Tenofovir +
Anti-
inflammatory
Gel**

**A high efficacy
combination gel?**

- Identifying source of cytokines & genital inflammation
- Understanding immune mechanisms by which raised genital cytokines increase the risk of HIV infection
- Identifying which anti-inflammatory agents suppress genital inflammation and can be added to tenofovir gel
- Assessment of candidates for clinical testing

**Failure to prevent HIV
infection in young women**

equals

**Failure to control HIV in
southern Africa**

Conclusion

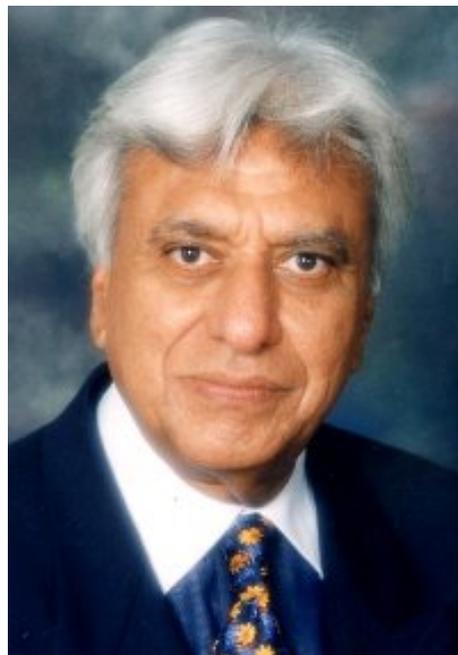
There is new hope in HIV prevention...

- **Several studies have now shown that antiretroviral drugs prevent HIV infection**
- **Treatment for prevention in particular provides huge hope**
- **Tenofovir gel: Promising new HIV prevention technology that can empower women to protect themselves from HIV**
- **Gender dynamic is key to controlling HIV**

Special thanks to my mentors



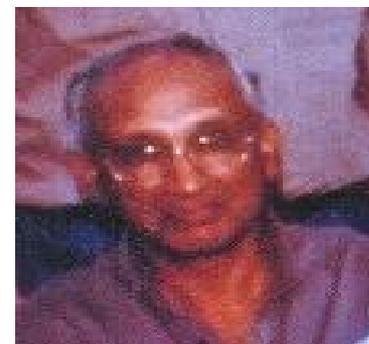
**Mervyn Susser
&
Zena Stein**



Jerry Coovadia



Patricia Berjak



Jack Moodley



Acknowledgements



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- 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:

- National Research Foundation, South Africa (NRF), CHAVI, SAAVI, European Commission – EDCTP, Johap – Oxfam, Doris Duke Charitable Foundation (DDCF), Global Fund against AIDS, TB & Malaria (GFATM)

