



CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA



CAPRISA IS A UNAIDS
COLLABORATING CENTRE
FOR HIV PREVENTION RESEARCH

Setting the stage: year in review and looking ahead

Joint Civil Society & MTN CWG meeting

Salim S. Abdool Karim

Pro Vice-Chancellor (Research): University of KwaZulu-Natal

Director: CAPRISA

Professor in Clinical Epidemiology, Columbia University

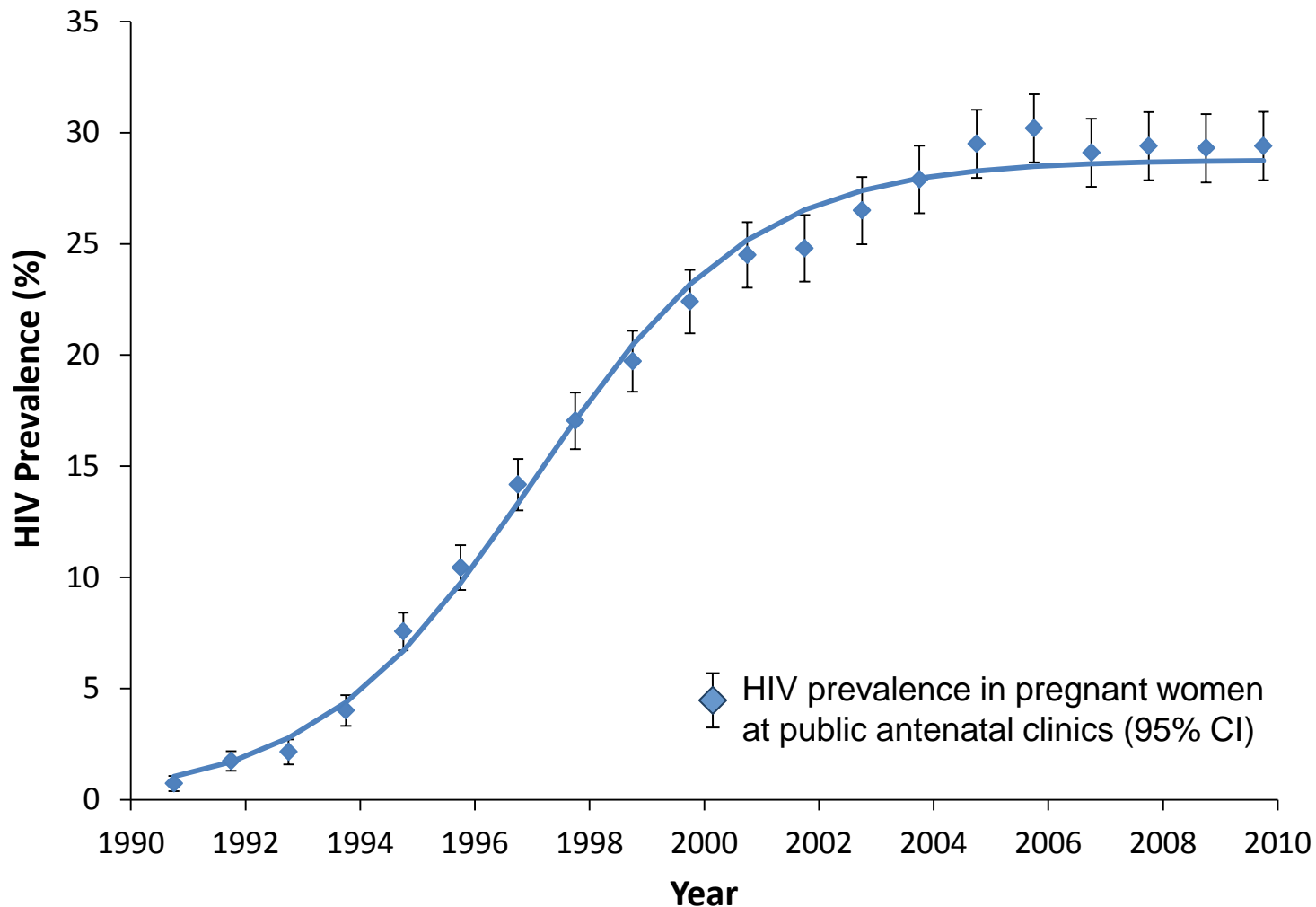
Adjunct Professor of Medicine, Cornell University

Associate Member, Ragon Institute of MGH, MIT and Harvard

Outline

- **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)



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%

Clinical trial evidence for preventing sexual HIV transmission – July 2010

Study

Effect size (CI)

Medical male circumcision
(Orange Farm, Rakai, Kisumu)



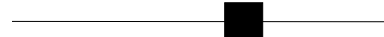
54% (38; 66)

STD treatment
(Mwanza)



42% (21; 58)

HIV Vaccine
(Thai RV144)



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

RESEARCH ARTICLES

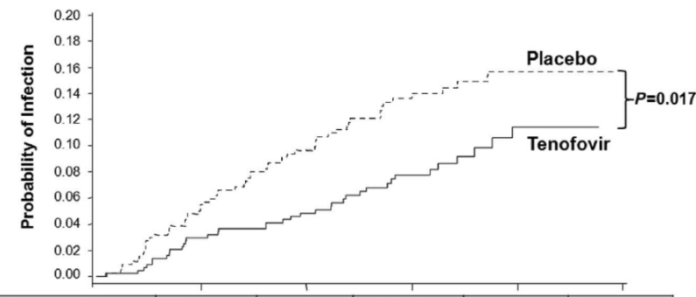


3 SEPTEMBER 2010 VOL 329 SCIENCE

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 Taylor,⁵ on behalf of the CAPRISA 004 Trial Group

The Centre for the AIDS Progr
effectiveness and safety of a 1
inhibitor, for the prevention o
was conducted comparing teno



39% protection against HIV overall

54% effective against HIV in high adherers

51% reduction in HSV-2



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

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 30, 2010

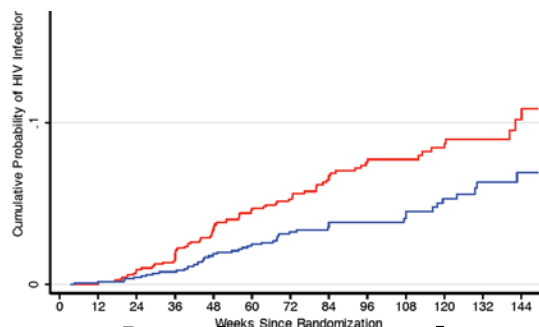
VOL. 363 NO. 27

131 infections after randomization

48 in
FTC/TDF

83 in
placebo

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



M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S.,
rgas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H.,
, Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc.,
, Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H.,
a-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D.,
mico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem.,
, Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D.,
D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D.,
, D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

- 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 \ll EC50 for HSV

May 2011: ART prevents HIV transmission from infected partners (HPTN 052)

Editorial

1719

www.thelancet.com Vol 377 May 21, 2011

THE LANCET

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

te group. Study informed of the appropriate care. All at least 1 more year. r results in both as a potentially ving the spread provide a new patient. Besides adherence to the





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

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

tenofovir or
infections than
few HIV
reduces HIV

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e other does
udy to date
f global health
PrEP Study.



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

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**

provide the
can reduce
sexual sex.

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3 percent
ategy of
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Clinical trial evidence for preventing sexual HIV transmission – July 2010

Study

Effect size (CI)

Medical male circumcision
(Orange Farm, Rakai, Kisumu)



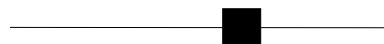
54% (38; 66)

STD treatment
(Mwanza)



42% (21; 58)

HIV Vaccine
(Thai RV144)



31% (1; 51)



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)

96% (73; 99)

73% (49; 85)

63% (21; 48)

54% (38; 66)

44% (15; 63)

42% (21; 58)

39% (6; 60)

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

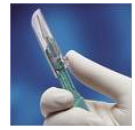
COMBINATION HIV PREVENTION



Microbicides for women

Abdool Karim Q, Science 2010

Male circumcision



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

Treatment of STIs



Grosskurth H, Lancet 2000



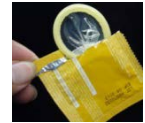
Treatment for prevention

Donnell D, Lancet 2010
Cohen M, NEJM 2011

Female Condoms



Male Condoms



Behavioural positive prevention



Fisher J, JAIDS 2004

HIV Counselling and Testing



Coates T, Lancet 2000

Oral pre-exposure prophylaxis



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

Post Exposure prophylaxis (PEP)



Scheckter M, 2002

Vaccines



Rerks-Ngarm S, NEJM 2009

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

Why did TDF/FTC not prevent HIV in these women?



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 Data and Safety Monitoring Committee (IDMC) advised that the FEM-PrEP study was unable to demonstrate the effectiveness of Truvada [emtricitabine (FTC) and tenofovir fumarate (TDF)] in preventing HIV infection in the study population.

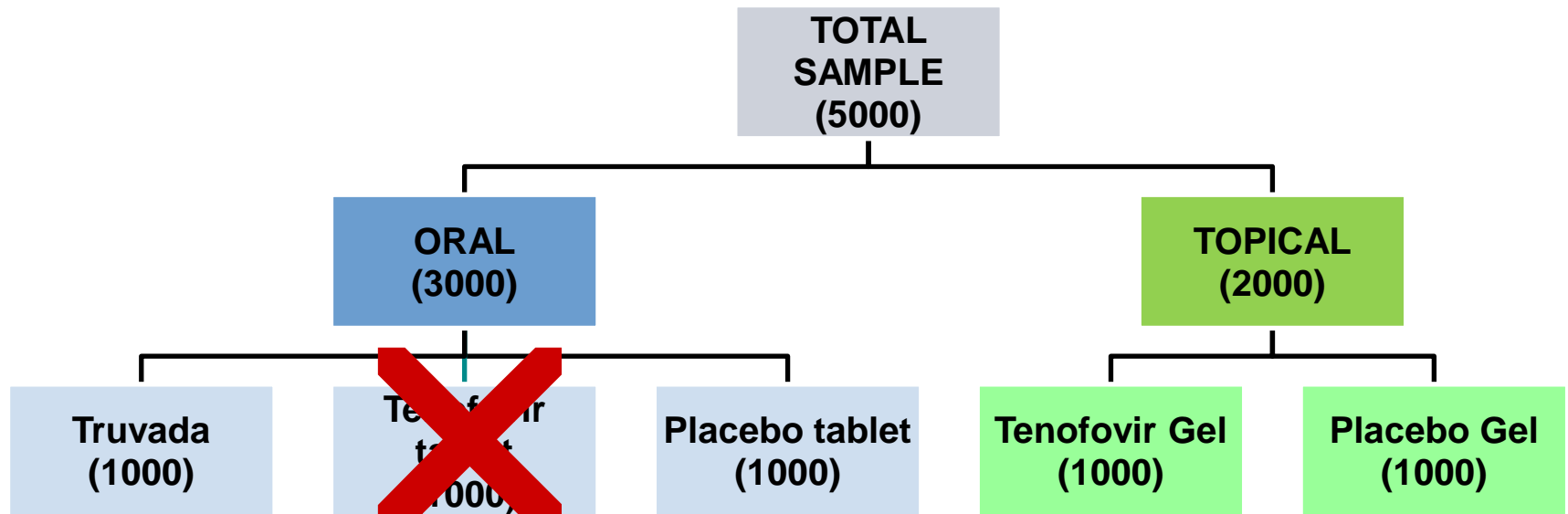
The IDMC's recommendation is in contrast to the originally planned conclusion. FHI subsequently concurred and has therefore decided to initiate an orderly closure of the study over the next few months. The final analyses have not yet been conducted. At this time, it cannot be determined whether or not Truvada works to prevent HIV infection in women.

- 1951 women enrolled
- Kenya, Tanzania & SA
- Daily oral TDF/FTC
- Both arms - 28 HIV infⁿ
- Zero effectiveness
- HIV incidence 5.1%
- Study halted for futility

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



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

Oral and topical PrEP in women: Results of Randomised Control Trials

Intervention and Study

Truvada (TDF/FTC) tablets

Partners PrEP

Botswana TDF2

FEMPrEP

VOICE



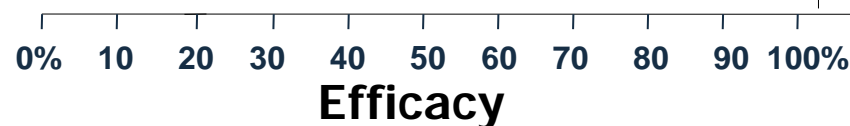
Effect size (CI)

73% (49; 85)

63% (21; 48)

0% (? ; ?)

?



Oral and topical PrEP in women: Results of Randomised Control Trials

Intervention and Study

Effect size (CI)

Tenofovir (TDF) tablets

Partners PrEP

VOICE

?



62% (34; 78)
0% (? ; ?)

0% 10 20 30 40 50 60 70 80 90 100%
Efficacy

Oral and topical PrEP in women: Results of Randomised Control Trials

Intervention and Study

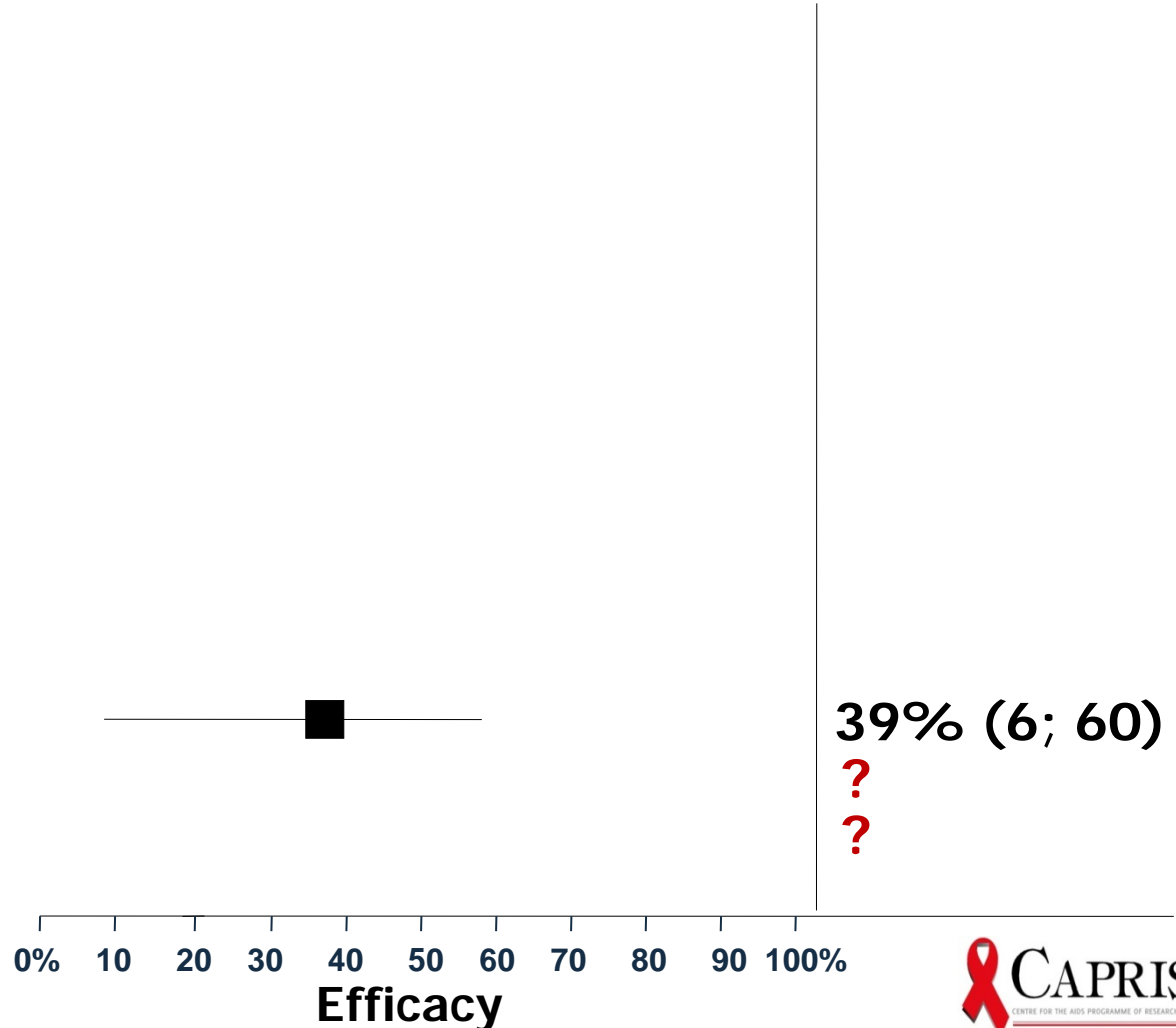
Effect size (CI)

Tenofovir gel

CAPRISA 004

VOICE

FACTS 001



Oral and topical PrEP in women: Results of Randomised Control Trials

Intervention and Study

Effect size (CI)

Truvada (TDF/FTC) tablets

Partners PrEP

Botswana TDF2

FEMPrEP

VOICE

Tenofovir (TDF) tablets

Partners PrEP

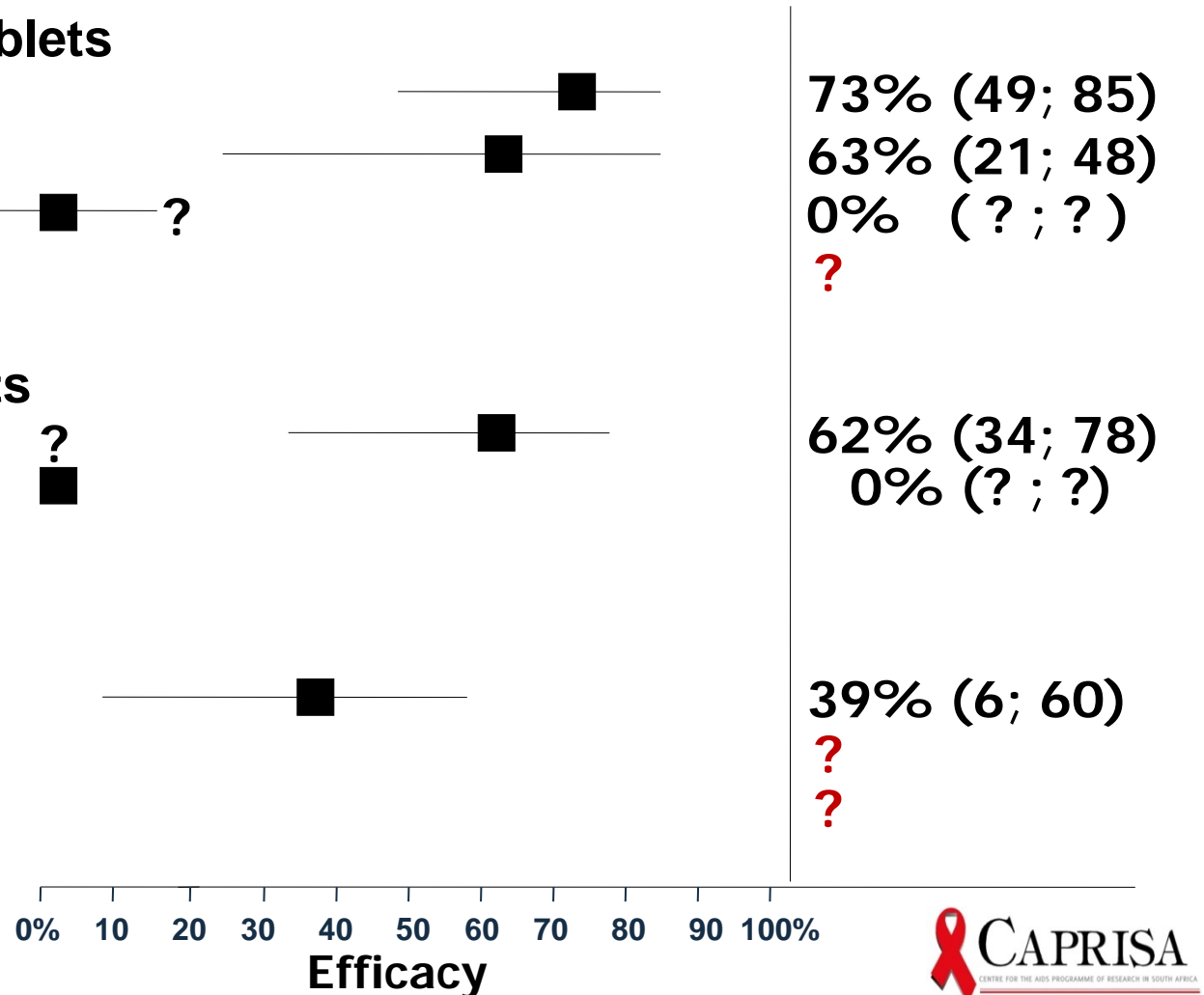
VOICE

Tenofovir gel

CAPRISA 004

VOICE

FACTS 001



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