CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

CAPRISA IS A UNAIDS COLLABORATING CENTRE FOR HIV PREVENTION RESEARCH

CAPRISA 004

Safety & effectiveness of tenofovir gel for HIV and HSV-2 prevention in women

Salim S. Abdool Karim

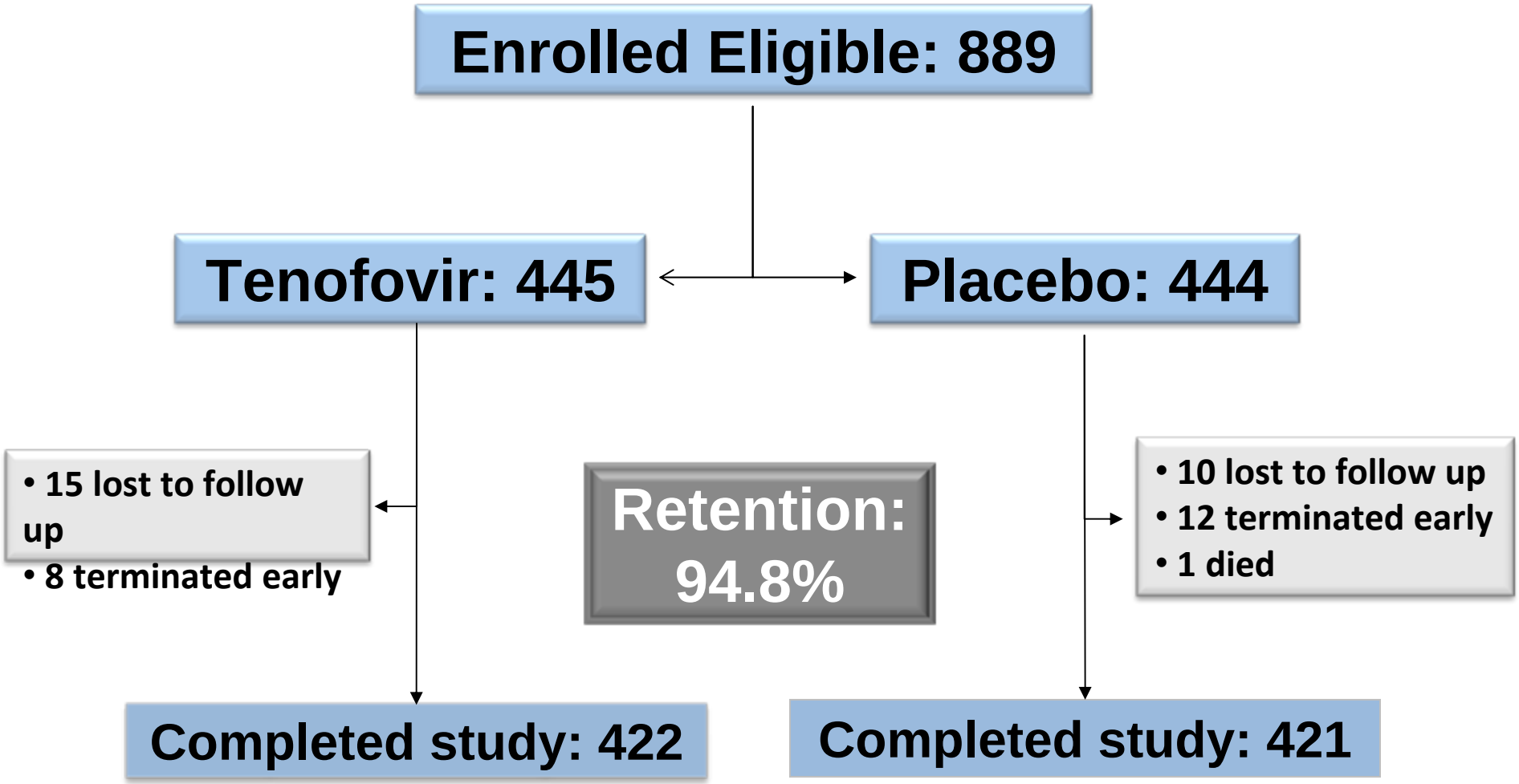
on behalf of the CAPRISA Study Group

MTN Regional Meeting – October 2010

Overview

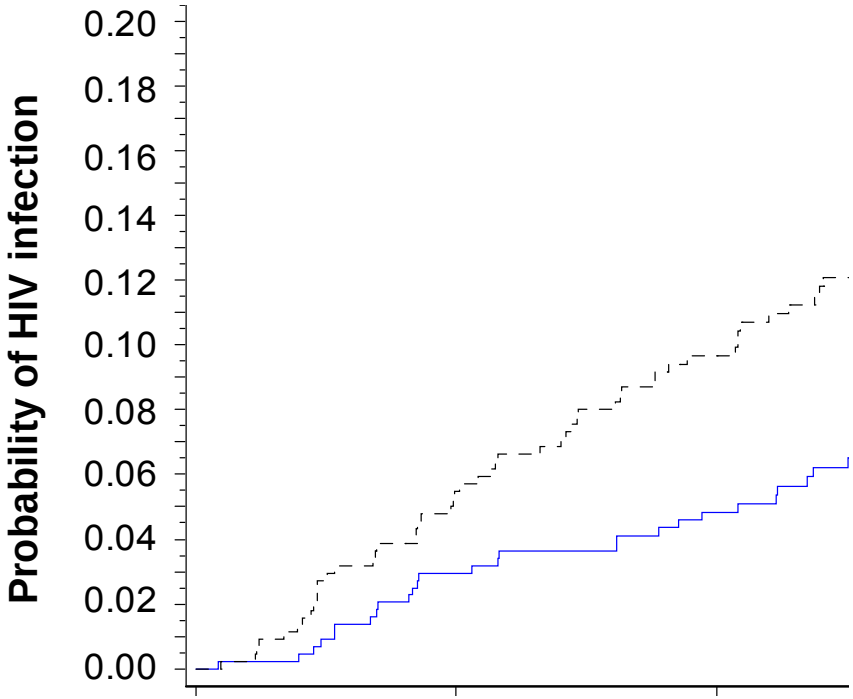
1. CAPRISA 004 effectiveness outcome
2. The challenge of adherence
3. How does the VOICE trial differ from CAPRISA 004?
4. Next steps

1. Study Overview: Enrollment & Retention



HIV infection rates in the tenofovir and placebo gel groups:

12 month Kaplan-Meier survival probability



Months of follow-up	6	12
Cumulative HIV endpoints	37	65
Cumulative women-years	432	833
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5
Effectiveness (p-value)	**47% (0.069)**	**50% (0.007)**

After 12 months of gel use:

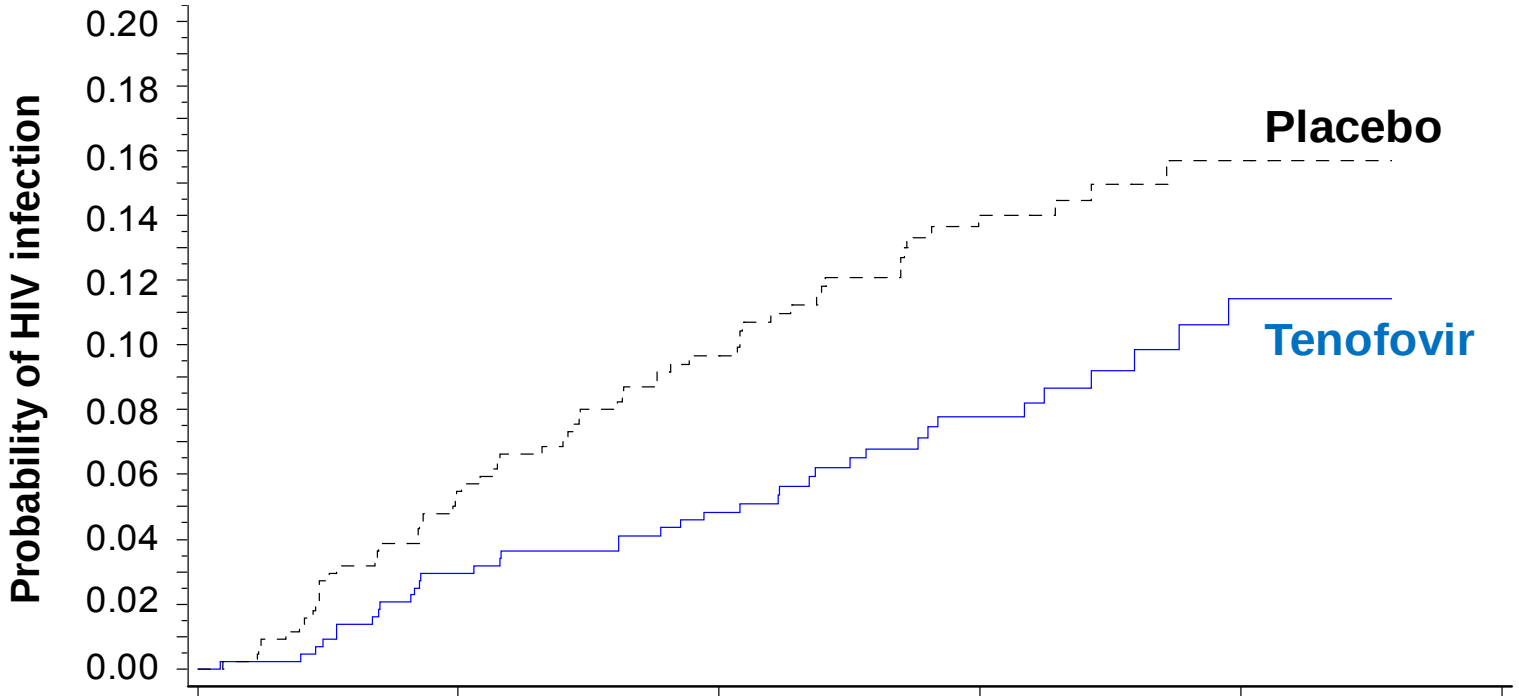
HIV endpoints: 65

Effectiveness: 50%

P-value: 0.007

HIV infection rates in the tenofovir and placebo gel groups:

24 month Kaplan-Meier survival probability



Months of follow-up	6	12	18	24	30
Cumulative HIV endpoints	37	65	88	97	98
Cumulative women-years	432	833	1143	1305	1341
HIV incidence rates (Tenofovir vs Placebo)	6.0 vs 11.2	5.2 vs 10.5	5.3 vs 10.2	5.6 vs 9.4	5.6 vs 9.1
Effectiveness (p-value)	**47% (0.069)**	**50% (0.007)**	**47% (0.004)**	**40% (0.013)**	**39% (0.017)**

Effectiveness of tenofovir gel in HIV prevention: Sensitivity analysis

	Effectiveness	CI	p
Protocol-defined endpoint (n=98)	**39%**	6 – 60	**0.017**
Incl HIV infection not meeting protocol definition (n=98+1 = 99)	**37%**	4 - 59	**0.023**
Per Protocol population (n=85)	**41%**	7– 63	**0.017**
Incl ineligibly enrolled (n=98+ 5=103)	**38%**	7 - 60	**0.015**
Incl post-trial infections (n=98 + 5 = 103)	**41%**	11 – 61	**0.015**
All HIV infections (n=119)	**45%**	19 - 63	**0.003**

Special tribute to the MTN

from the

CAPRISA 004 Study Team

NEWS

Research at this South African clinic includes a controversial microbicidal-gel trial.

HIV trial doomed by design, say critics

Controversy over a ground-breaking study of an experimental HIV prevention tool has underscored the field's need to revamp its approach to clinical trials.

On 23 May, researchers at the Centre for the AIDS Programme of Research in South Africa (CAPRISA) began a US$13.5-million study to test whether a microbicide gel containing the antiretroviral drug tenofovir prevents women from becoming infected with HIV during sex. The trial, funded by the US Agency for International Development (USAID), is the first to test a so-called second-generation microbicide — one that specifically targets the AIDS virus.

Researchers and advocates say that microbicides in the form of gels or creams, applied to microbicides, which make the vagina inhospitable to a range of microbes, have already failed efficacy trials, and two — cellulose sulphate and nonoxynol-9 — actually increased women's risk of infection (see *Nature* **446,** 12; 2007). Investigators are due to release the final analysis of the cellulose sulphate trial at the International AIDS Society meeting in Sydney, Australia, later this month. But scientists say the failure of that trial highlights the need to proceed cautiously with further microbicide studies.

The most controversial issue in the CAPRISA trial is the dosage schedule. This requires women to apply the gel once within 12 hours before sex and

"The microbicide development field cannot afford to take a further hit."

Critics say the proposed dosage regime will result in a poor trial outcome. "It will be hard to link the data to the way the gel is being used, which will potentially make it very difficult to make any interpretation of the data," says microbicide researcher Robin Shattock at St George's, University of London.

The concern has led scientists and others, including Renee Ridzon of the Bill & Melinda Gates Foundation in Seattle, Washington, and Zeda Rosenberg of the International Partnership for Microbicides based in Silver Spring, Maryland, to call for the CAPRISA investigators to rethink their approach. Such

Special tribute to the MTN

- **Deepest gratitude to Sharon Hillier, our rainbow leader for her support when the CAPRISA 004 trial came under attack**
- **The CAPRISA 004 study team owe the MTN family our deepest appreciation for their unwavering support for the trial**
- **We share this result with you as our shared accomplishment as partners in the microbicide field**

Impact of tenofovir gel on HSV-2 incidence

	Tenofovir gel n=202*	**Placebo gel** n=224*
# HSV-2 infections	**29**	**58**
Women-years of follow-up	292.3	287.3
HSV-2 incidence per 100wy (95% CI)	**9.9** (6.6, 14.2)	**20.2** (15.3, 26.1)

**Note: Excludes equivocal HSV-2 results at study exit*

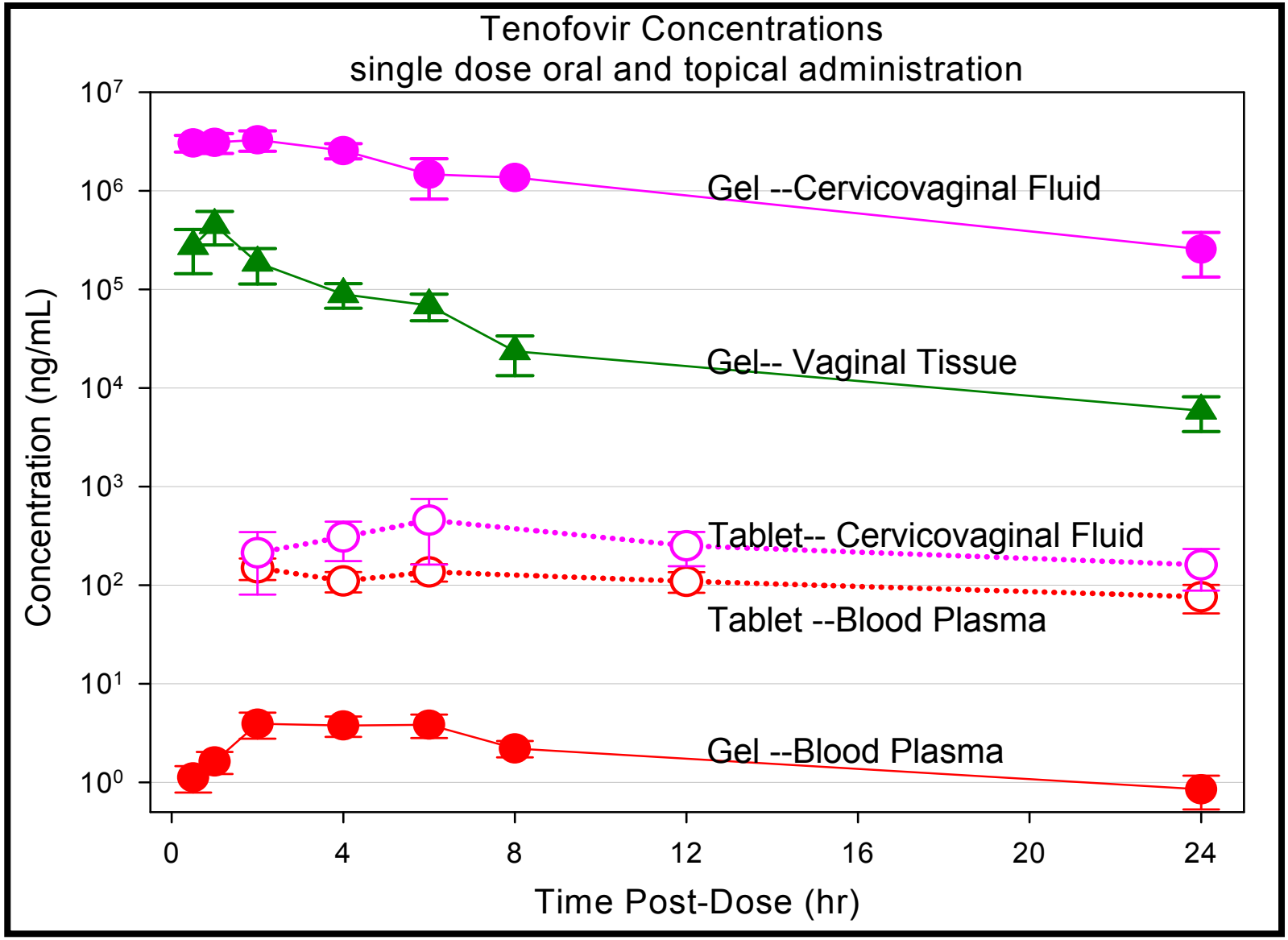
IRR = 0.49 (CI:0.30, 0.78); ***p* = 0.003**

51% protection against HSV-2 by tenofovir gel (CI: 22%-70%)

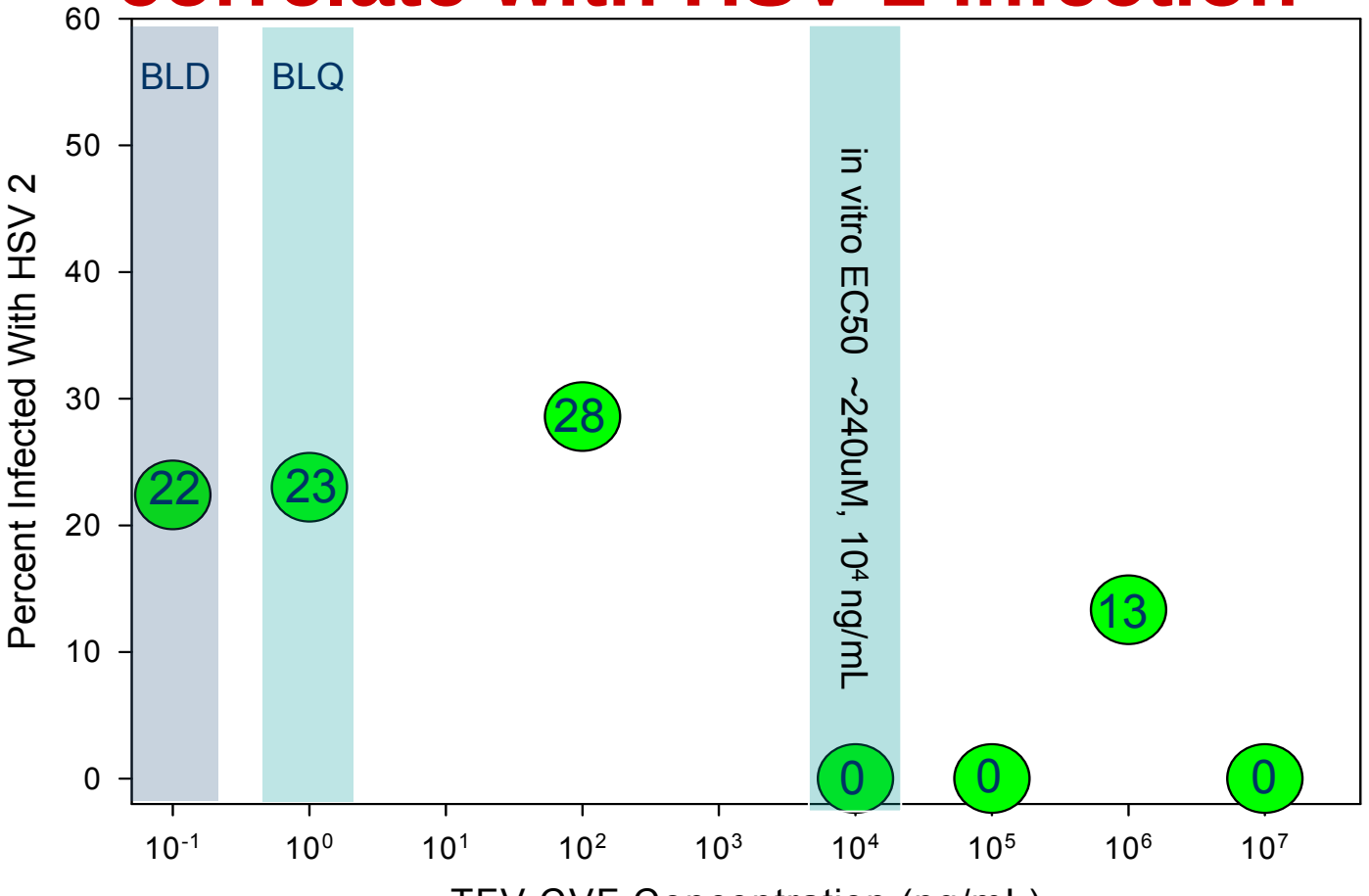
Antiviral activity of acyclic nucleoside phosphonates

	DNA					RNA
	Papoviridae (HPV / polyomavirus)	Adenovirus	Pox virus	Herpes virus	Hepdadna virus	Retrovirus
	Polyomavirus Papillomavirus	Adenovirus	Variola virus Cowpox virus Monkeypox virus Camelpox virus Vaccinia virus	HSV-1 HSV-2 VZV CMV EBV HHV-6 HHV-7 HHV-8	HBV	HIV-1 HIV-2
Cidofovir 	■	■	■	■		
Adefovir 				■	■	■
Tenofovir 					■	■

Oral vs gel: CONRAD Tenofovir PK study



Tenofovir cervico-vaginal fluid concentrations correlate with HSV-2 infection



24%

6%

X^2 p = 0.03

Total # women	**27**	**22**	**14**	**4**	**10**	**15**	**5**
Number infected	6	5	4	0	0	2	0

2. The challenge of adherence…

1. Remove the barrel and the plunger from its wrapper

2. Put plunger into the barrel of the applicator, until it clicks

3. Unscrew the blue cap from the applicator

4. Hold the applicator with your thumb and middle finger at the grooves on the barrel. Place your forefinger on the plunger

5. Fold back the skin that covers the opening of your vagina with your other hand

6. Put rounded tip of the applicator into your vagina and push gently until your fingers touch your body

7. Use forefinger to push plunger all the way into the barrel

8. After all the gel has been inserted, gently pull out the applicator from the vagina

Addressing the challenge of adherence

- Explicit instructions on dosing, timing, mechanics of applicator use
- Monitoring product use by real-time monthly reconciliation of used & unused applicators
- Using real-time information on adherence for individual counselling and motivation
- Identify and address participant deficits in information, motivation, and behavioural skills
- Motivational techniques and structured one-on-one sessions, empower participants to pre-empt situations that lead to non-adherence

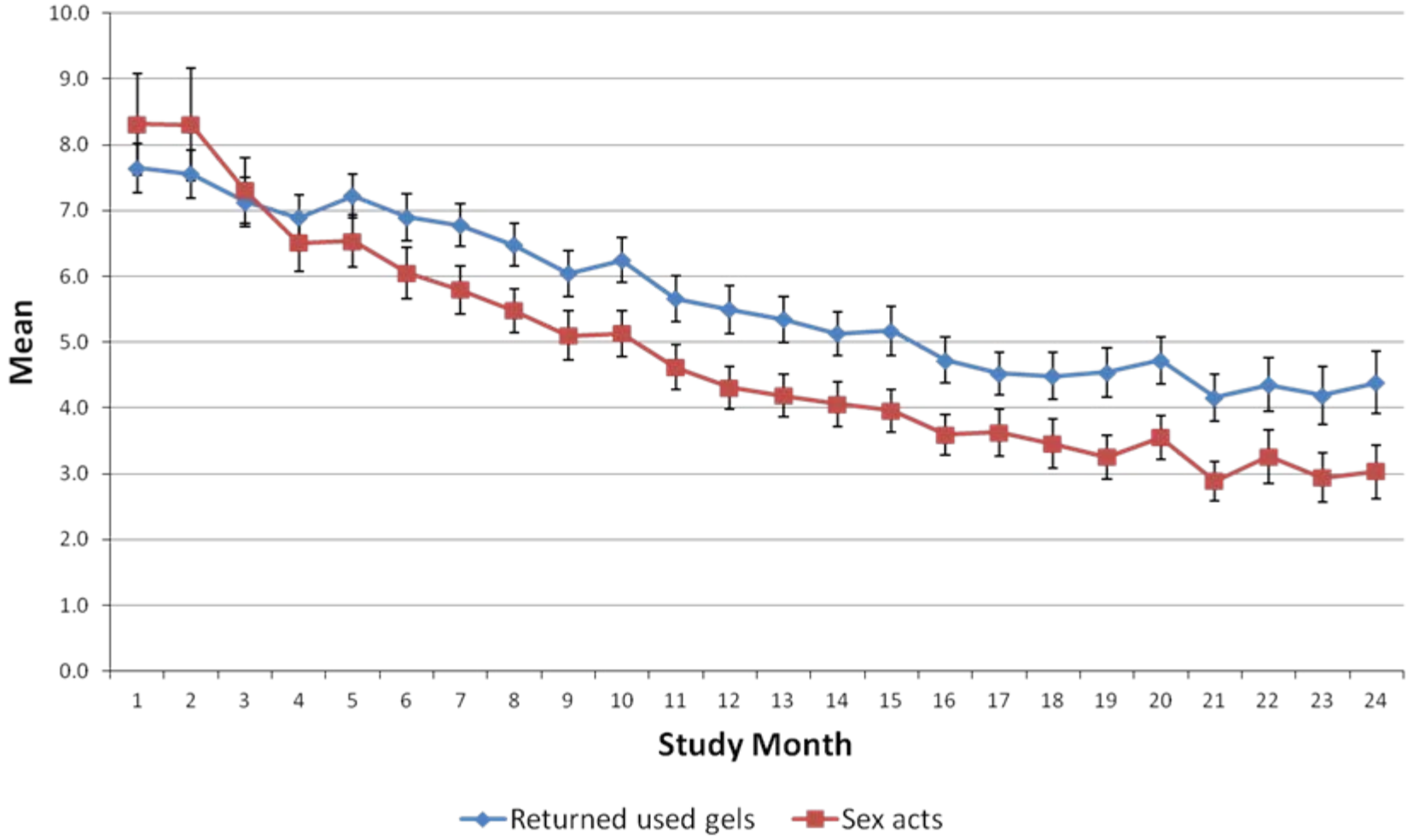
Applicators dispensed & returned

- # of applicators dispensed 181 340

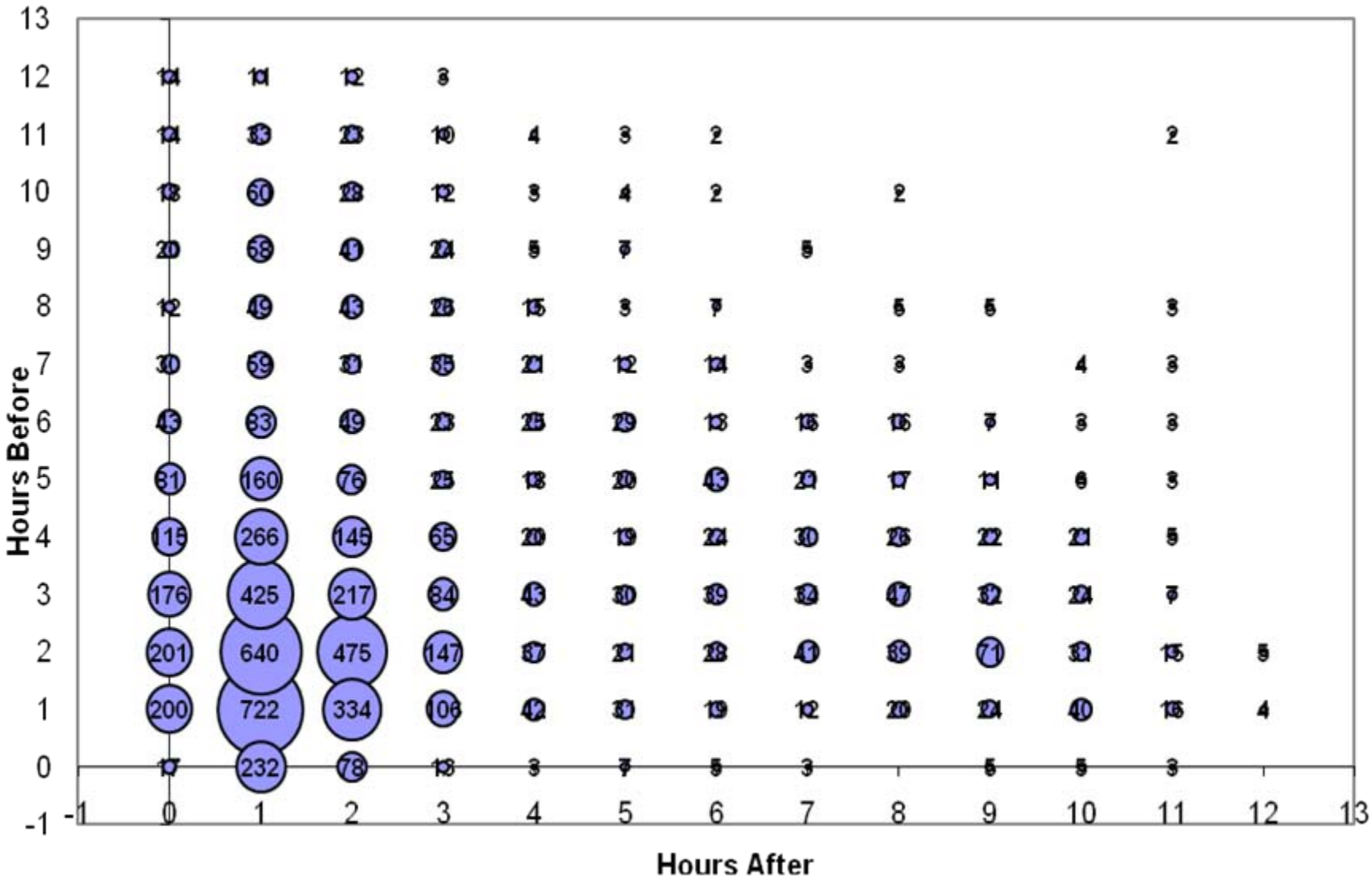
- # of used applicators returned 93 252
- # of unused applicators returned 79 528

- # of applicators returned 95.2%
- Applicators not returned (4.8%) 8 560

Mean number of returned used gels and self-reported number of sex acts



Self-reported timing of BAT 24 gel use



CAPRISA 004 adherence measures

1. % sex acts covered by 2 used returned applicators (median of all monthly estimates)

$$\frac{\text{\# empty applicators returned in month / 2}}{\text{\# sex acts reported in month}}$$

2. Frequency-based adherence – returned applicators as used each month

3. Self-reported adherence to BAT 24

$$\frac{\text{No. of self-reported adherent last coital acts}}{\text{Total no. of last coital acts}}$$

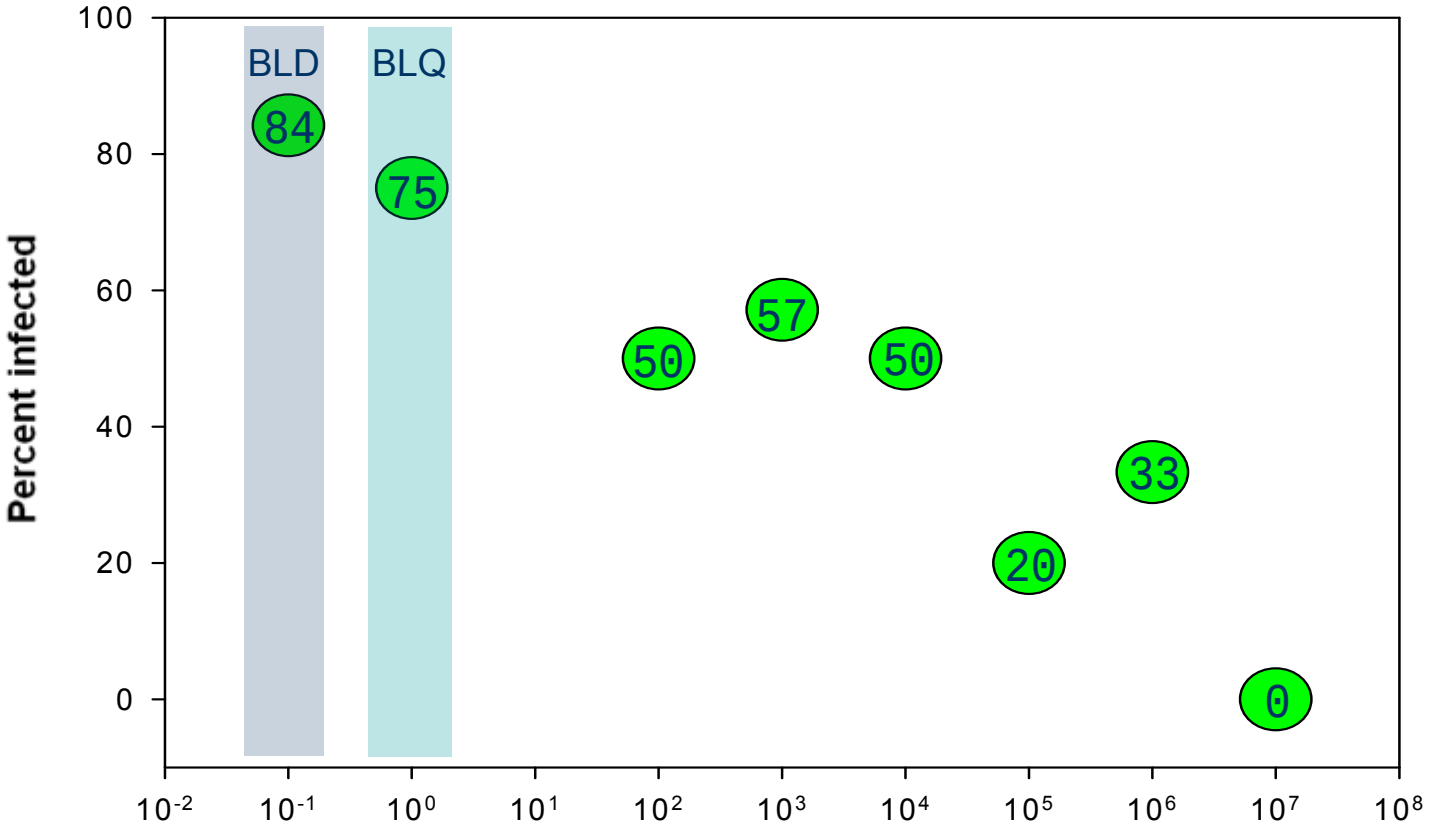
Adherence in CAPRISA 004

Primary adherence measure: Based on used applicators returned, % of sex acts covered by 2 applicators (gel/sex ratio):	**Mean: 72.2%** **Median: 60.2%**
Frequency based (Applicators used per month)	**5.5**
Self reported adherence to BAT 24	**90%**

Primary adherence measure on effectiveness of tenofovir gel

Adherence & HIV	Tenofovir	Placebo	Effect	p-value
High gel use: > 80% adherence	4.2	9.3	**54%**	**0.03**
Moderate gel use: 50 - 80% adherence	6.3	10.0	**38%**	0.29
Low gel use: < 50% adherence	6.2	8.6	**28%**	0.30

Tenofovir cervico-vaginal fluid concentrations correlate with HIV infection



Total # women	**19**	**8**	**6**	**7**	**2**	**5**	**6**	**1**
Number infected	16	6	3	4	1	1	2	0

CVF Concentration (ng/mL)

Acceptability of tenofovir gel

	Total N = 755	Rural n = 527	Urban n = 228
Liked study gel	**98%**	100%	94%
Found gel insertion difficult	**5%**	3%	7%
Gel insertion interrupts sex	**1%**	0.4%	4%
Gel provides too much lubrication	**10%**	3%	26%
Partner knew about gel use	**68%**	69%	68%
Partner did not like the gel	**4%**	4%	5%
Would use gel if it prevented HIV	**99%**	100%	98%

Polymorphisms & Resistance Mutations (n=93)

	Tenofovir	Placebo
Tenofovir related resistance mutations		
K65R or K70E	0	0
TAMS: M41L, D67N, K70R, L210W, T215Y/F, K219Q/E	0	0
Multi-NRTI/other: A62V, V75I, F77L, F116Y, Q151M, 69ins, N348I	0	0
Other mutations (Not related to tenofovir)		
E138A/K	3	7
V118I	2	3
V179A/D	0	3
K103N (*major NNRTI mutation*)	0	2
A98G or L210S	1	0
F77C, L100S, K103R or G190R	0	1

3. How does the VOICE trial differ from CAPRISA 004?

- **CAPRISA 004 and VOICE are complementary studies. Each is critical for advancing understanding about the safety and effectiveness of tenofovir gel**

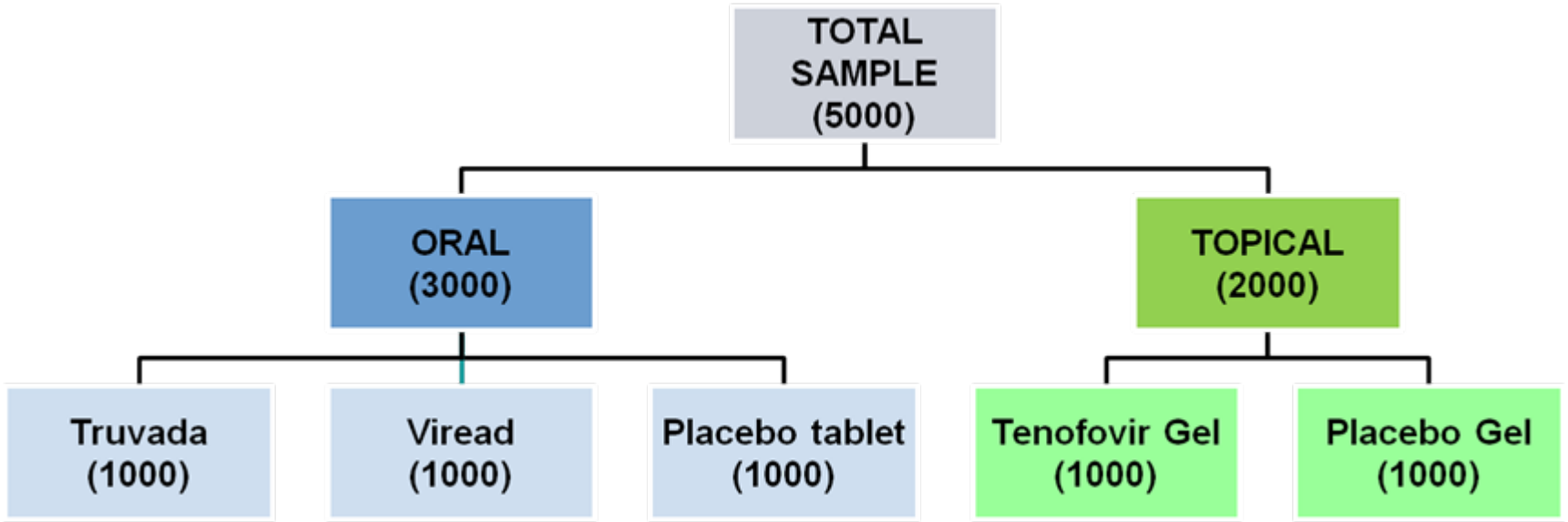
CAPRISA 004	VOICE
Dosing: BAT24 dosing	***Dosing***: Daily
Treatment: tenofovir gel vs placebo gel	***Treatment***: tenofovir gel vs placebo and two different oral ARV tablets, tenofovir and Truvada® , vs placebo
Population: 889 South African women from 2 sites in KwaZulu-Natal	***Population***: ± 5,000 women at sites in four countries in southern Africa.

4. WHO/UNAIDS Consultation on next steps for tenofovir gel

- **Purpose of the consultation:**
  - **to develop consensus and plan for next steps with tenofovir gel following release of the CAPRISA 004 trial result**
- **Goal:**
  - **To speedily achieve implementation of tenofovir gel**
- **Next steps were defined as:**
  - **Priority 1: Phase IIb/III studies to confirm tenofovir effectiveness in preventing HIV infection**
  - **Priority 2: Phase IIIB / IV implementation science studies - assessing models for health service implementation**
  - **Priority 3: Phase I and II safety studies in adolescents, pregnancy, HBV, etc.**

Priority 1: MTN-VOICE phase IIb trial

- **V**aginal and **O**ral **I**nterventions to **C**ontrol the **E**pidemic
- **Five-arm, multi-site, randomized trial**



Priority 1: FACTS 001 Phase III trial

- *Purpose:* **To assess the safety and effectiveness of tenofovir gel for HIV and HSV-2 prevention**
- *Design:* **Multi-centre, 2-arm, double-blinded RCT**
- *Population:* **2,400 women aged 16 to 30 years**
- *Control arm:* **Placebo gel**
- *Intervention arm:* **Tenofovir gel (BAT 24 dosing)**
- *Primary outcome:* **HIV incidence**
- *Secondary outcome:* **HSV-2 incidence, CD4 counts, viral load, tenofovir resistance, HBV outcomes, adherence**

Priority 1: MDP 302 Phase III trial

- *Purpose:* **To assess the safety and effectiveness of coital use of tenofovir gel for HIV prevention**
- *Design:* **Multi-centre, 4-arm, double-blinded RCT**
- *Population:* **Several African countries**
- *Intervention 1:* **Tenofovir gel (BAT 24 dosing) (2:1 ratio)**
- *Intervention 2:* **Tenofovir gel (Single dose pre-sex) (2:1)**
- *Primary outcome:* **HIV incidence**
- *Secondary outcome:* **Viral load, tenofovir resistance, adherence**

H.I.V. Prevention Gel Hits Snag: Money

Joao Silva for The New York Times

Volunteers who took part in a trial of a microbicide listened to results in Vulindlela, Kwazulu-Natal Province, South Africa.

By CELIA W. DUGGER
Published: September 3, 2010

JOHANNESBURG — When scientists celebrated the announcement in July that a vaginal microbicide had finally been found that significantly reduced H.I.V. infections in women, there was still a prosaic — though essential — piece of the puzzle missing: money.

Donors have not committed enough money for even one of the two studies needed to confirm a promising South African trial of the microbicide and get it into women's hands. Only about $58 million of the $100 million needed for follow-up research has been pledged,

Priority 2: CAPRISA 008 - Implementation trial

- *Purpose:* **To assess the effectiveness of a sustainable tenofovir gel implementation strategy in a rural and urban South African clinic**
- *Design:* **Open-label randomized control trial**
- *Population:* **HIV negative CAPRISA 004 participants**
- *Control arm:* **Standard CAPRISA 004 trial processes for providing monthly tenofovir gel in CAPRISA clinic**
- *Intervention arm:* **Clinic processes (modelled on provision of Depo/OCs) for providing quarterly tenofovir gel in the family planning clinic**
- *Study duration:* **3 years (for sustainability assessment)**

Priority 2: CAPRISA 009 - Tenofovir treatment trial

- *Purpose:* **To assess the effectiveness of tenofovir-based cART compared to non-tenofovir cART**
- *Design:* **Open-label randomized control trial**
- *Population:* **HIV positive CAPRISA 004 participants**
- *Control arm:* **1st line cART that does not contain tenofovir (eg. DDI, 3TC and efavirenz)**
- *Intervention arm:* **1st line cART with tenofovir (eg. tenofovir, 3TC and efavirenz)**
- *Primary outcome:* **viral load at 12 months**
- *Secondary outcome:* **CD4 counts, viral load, tenofovir resistance, AIDS-defining illness, safety**

Additional studies

- **Priority 3: To establish safety for widespread use and facilitate routine implementation:**
  - **Pregnancy – see MTN agenda**
  - **Hepatitis B virus infection**
  - **Safety of multiple doses**
  - **Adolescents younger than 18 years**
  - **People with renal impairment**

- **Non-priority: To enhance implementation:**
  - **Packaging & marketing of gel**
  - **Improved cheaper applicator**

Summary of CAPRISA 004 findings

- **Safety**
  - **No substantive safety concerns**
  - **No tenofovir resistance or HBV flares identified**
  - **No evidence of risk compensation / behavioral disinhibition**
- **Proof of concept that tenofovir gel can prevent HSV-2 infection in women**
  - **51% reduction in HSV-2**
- **Proof of concept that tenofovir gel can prevent HIV infection in women**
  - **39% protection against HIV overall**
  - **54% effective in women with high adherence**

Conclusions

1. **Women, and young women in particular, bear the brunt of the HIV epidemic in Africa. Tenofovir gel potentially adds a new approach to empower women to take control of their own risk of HIV infection.**

2. **The CAPRISA 004 study was the first step – The VOICE and FACTS 001 studies are eagerly awaited as the highest priorities at the WHO/UNAIDS meeting**

3. **Once confirmed and implemented, tenofovir gel has the potential to alter the HIV epidemic. It is estimated that this gel could prevent 1.3 million new HIV infections and over 800,000 deaths over the next 20 years in South Africa alone.**

Acknowledgements

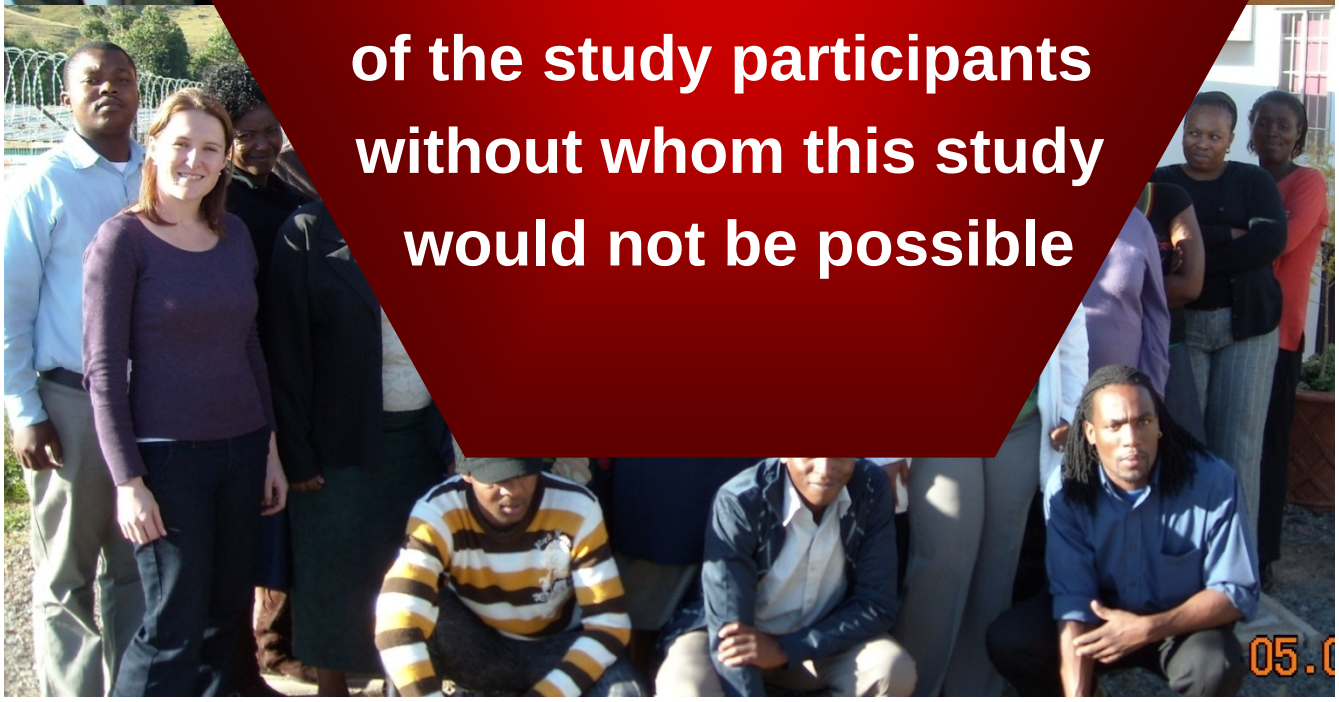
- **Financial support**: USAID & S African Dept of Science & Technology
- **Tenofovir & placebo gel:** Provided by CONRAD & Gilead Sciences
- **FHI Statistical & regulatory support:** S Cameron, D Sokal & D Taylor
- **Trial Oversight Committee**:
  - **CAPRISA**: Q Abdool Karim, SS Abdool Karim
  - **FHI**: W Cates, L Dorflinger, and D Taylor
  - **USAID**: L Claypool, J Manning, J Spieler
  - **CONRAD**: H Gabelnick
  - **LIFE*lab*** (TIA)*:* B Okole, C Montague
  - **Gilead Sciences**: J Rooney, Howard Jaffe
- **DSMB members**: K Mayer (Chair), E Bukusi, K Dickson, C Lombard & S Self. Independent DSMB statistician: M Chen
- **FHI Study monitors**: S Combes, C. Katz, L McNeil & A Troxler
- **Research infrastructure & training:** US NIH's CIPRA Program & the Columbia University - Southern African Fogarty Training Program

The CAPRISA 004 Trial Group

Principal Investigators:	Q Abdool Karim & SS Abdool Karim
Site Directors:	JA Frohlich, ABM Kharsany, KP Mlisana
Project coordinators:	C Baxter, LE Mansoor
Site co-ordinators:	NA Arulappan, S Maarschalk
Assistant site co-ordinators:	H Humphries, G Parker, J Richards, J Upton
Study Gynaecologist:	S Sibeko
Clinicians:	B Mdluli, N Miya, L Mtongana, N Naicker, Z Omar, D Sokal (FHI)
Nurses:	DD Chetty, F Dlamini, SD Gumede, Z Gumede, NE Khambule, N Langa, BT Madlala, N Madlala, N Mkhize, ZL Mkhize, M Mlotshwa, C Ndimande, N Ngcobo, C Ntshingila, B Phungula, TE Vumase
Counsellors:	NB Biyela, N Dladla, T Dlamini, CT Khwela, N Mayisela, MR Mlaba, J Mchunu, Z Msimango, D Nkosi, T Shange
Pharmacists:	L Chelini, TN Gengiah, A Gray, B Maharaj, GI Masinga, A Naidoo, M Upfold
Pharmacist's assistants:	B Moodley, Y Naidoo, C Ngcobo, T Nzimande, L Zondi
Statisticians:	AC Grobler, D Taylor (FHI), L Werner, N Yende
Data management:	R Lallbahadur, M Mdladla, K Naidoo, T Nala, C Pillay, P Sikakane, T Zondo
Quality assurance:	T Govender, N Mvandaba, F van Loggerenberg, I van Middelkoop
Laboratory:	J Naicker,V Naranbhai, N Ndlovu, N Samsunder, S Sidhoo, P Tshabalala J Ledwaba (NICD) & L Morris (NICD),
Behavioural Science:	J Fisher (UConn), K MacQueen (FHI)
Cohort co ordinators:	LR Luthuli, F Ntombela
Cohort administrators:	PF Chonco, DP Magagula, PC Majola, T Ndlovu, L Ngobese, N Ngubane, NM Zwane
Community outreach:	N Bhengu, P Buthelezi, PD Lembethe, BF Mazibuko, SF Mdluli, WN Mkhize, SP Ndlovu, S Ngubane, RM Ogle, RB Xulu
Administrative staff:	N Amla, SA Barnabas, T Malembe, M Matthews, YT Miya, A Mqadi, S Panday, S Sibisi, B Zulu, M Swart,

CAPRISA 004
eThekwini team

The CAPRISA 004 Protocol Team gratefully acknowledges the dedication and commitment of the study participants without whom this study would not be possible



CAPRISA 004
Vulindlela team