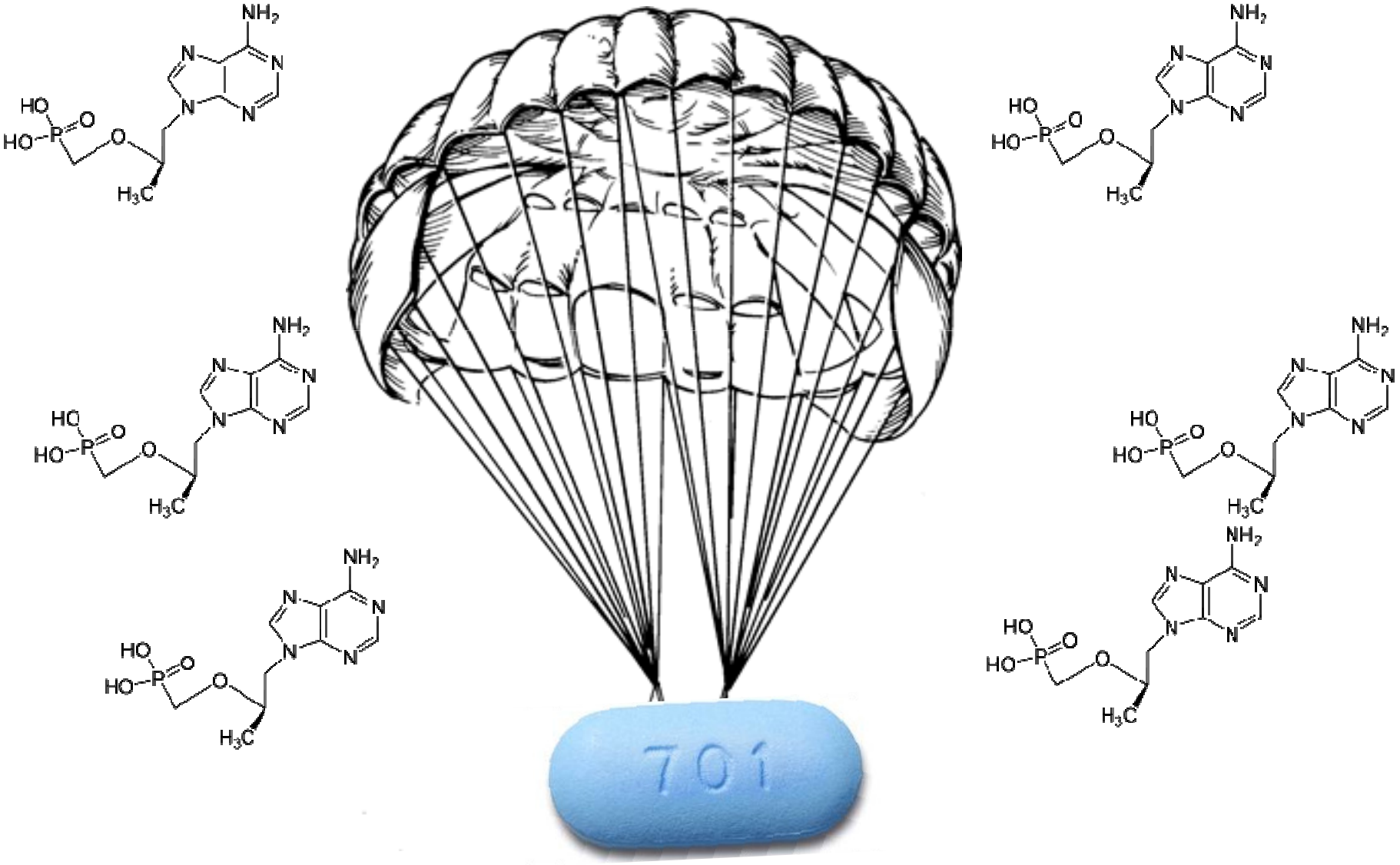



New biomedical technologies. Pre-exposure prophylaxis : Systemic and topical.

Linda-Gail Bekker
The Desmond Tutu HIV Centre
UCT
SA HIV Clnicians Society Conference 2012

Desmond Tutu HIV Foundation
Masibambane Ngezandla

And the last parachute goes to…..

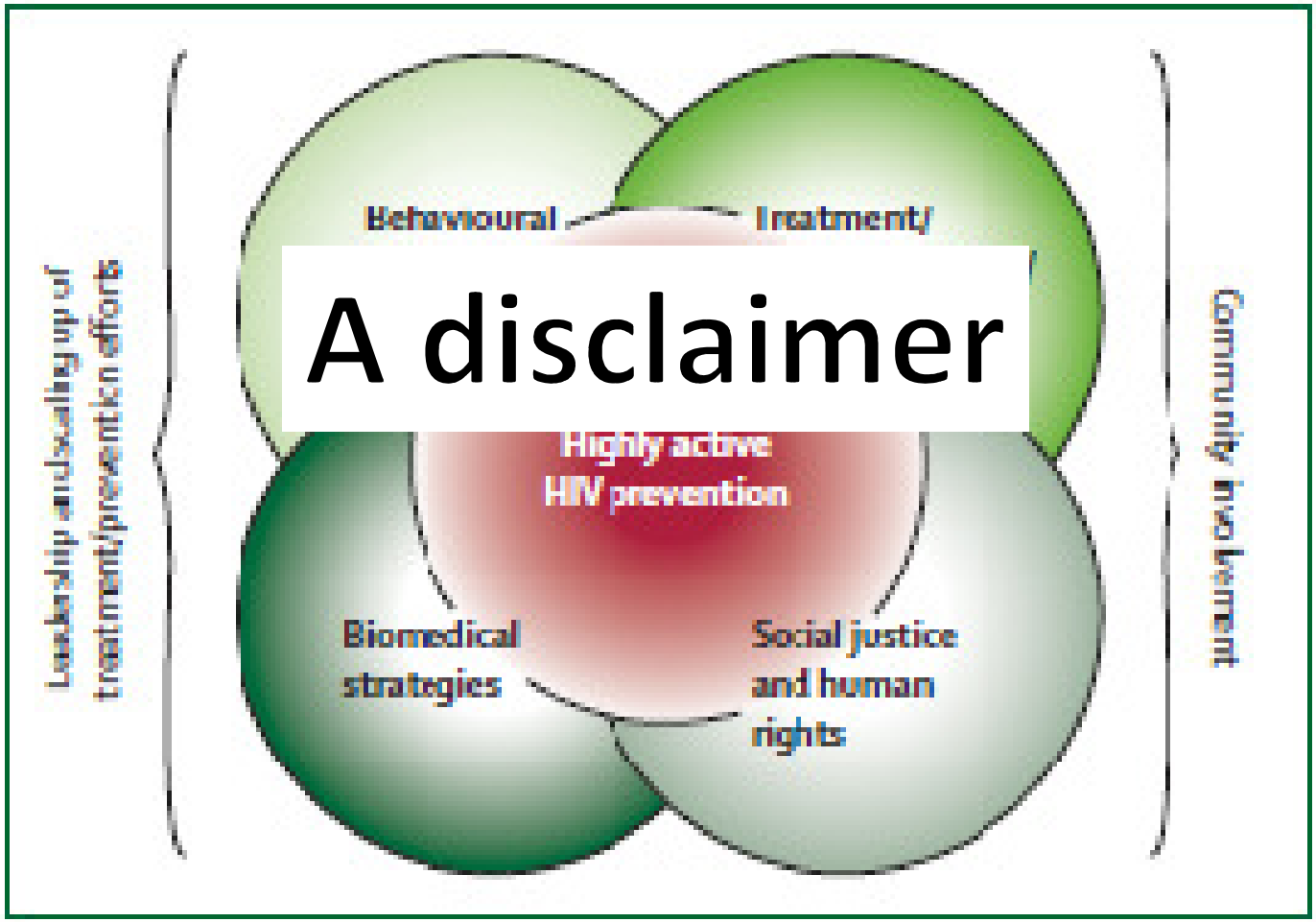


Why Tenofovir in prophylaxis?

- Protective in Animals
- Licensed for Treatment
- Excellent Safety Record PO
- Long Half Life (>48 hours)
- Enriched in Genital Fluids
- No interactions with tuberculosi treatment or hormonal contraception
- Relatively high barrier to resistance mutations

Highly active HIV prevention.

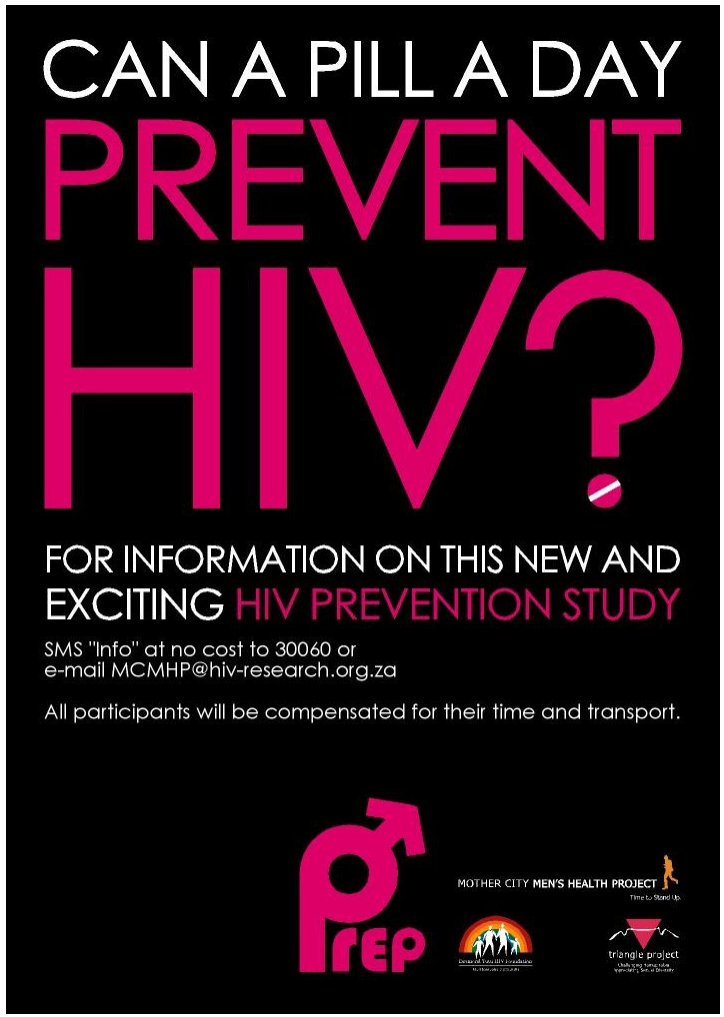
A term coined by Prof K Holmes, University of Washington School of Medicine, Seattle, WA, USA.5



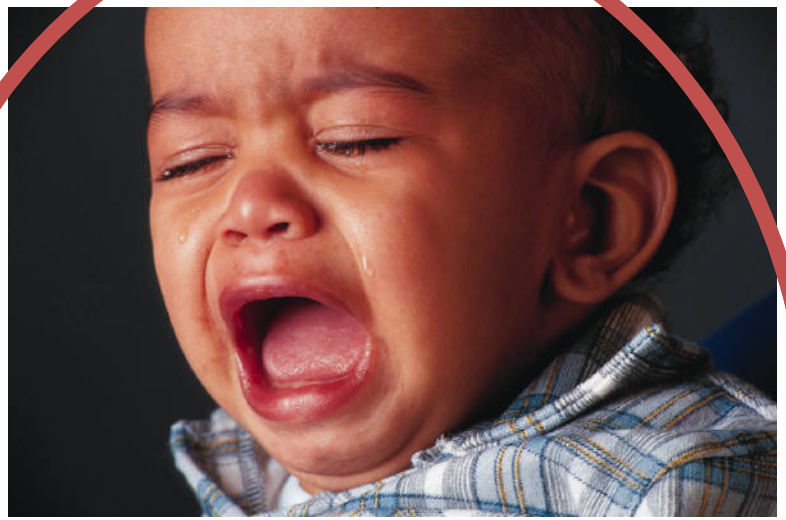
From Coates T et al 2008.

Targeted Prevention Packages

Antiretroviral therapy as Prevention?



Prevention of MTCT



ART reduces VL
Reduce infectiousness

ART prophylaxis aborts potential infection

HIV transmission involves a discordant relationship…..

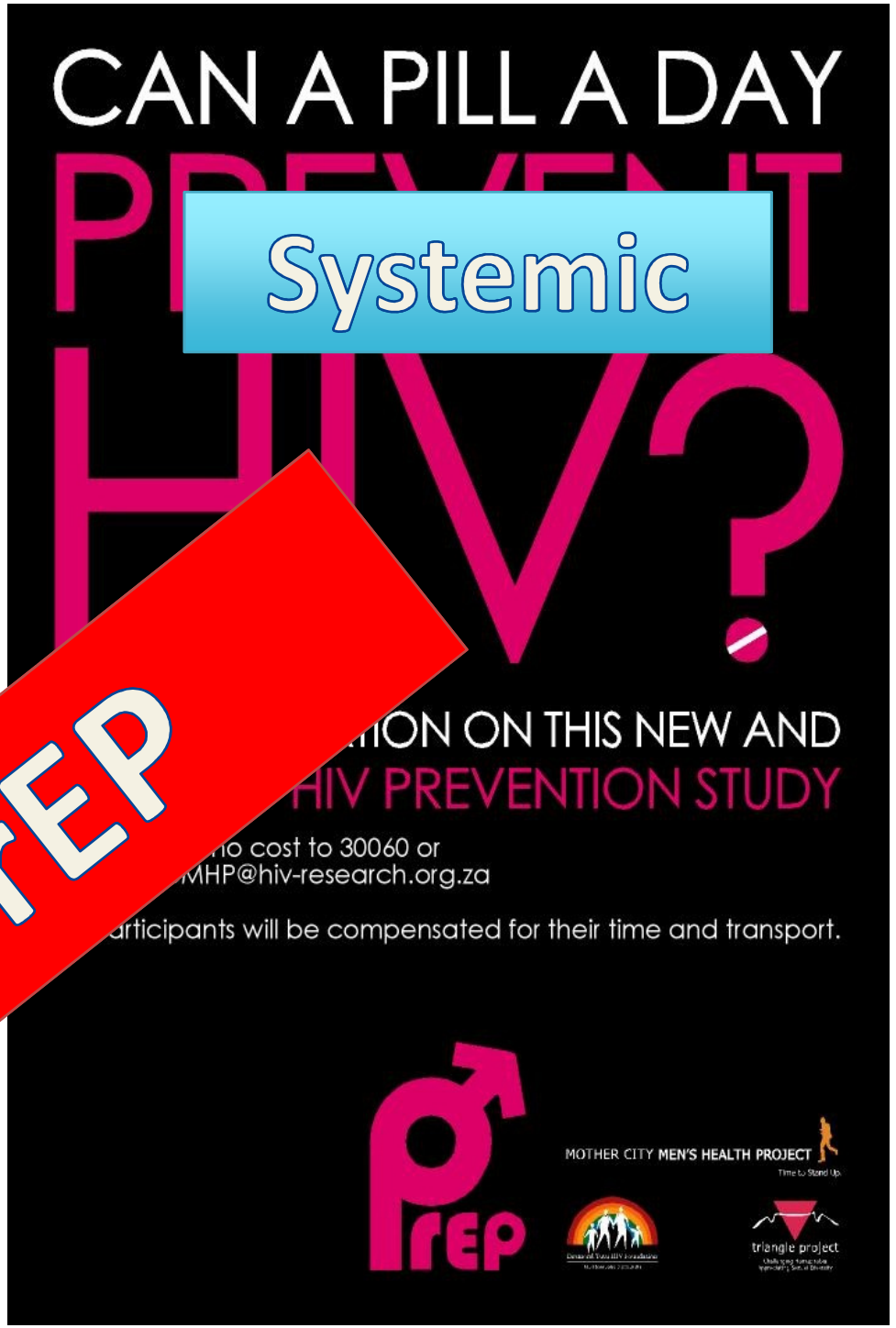
ART reduces VL
Reduce infectiousness

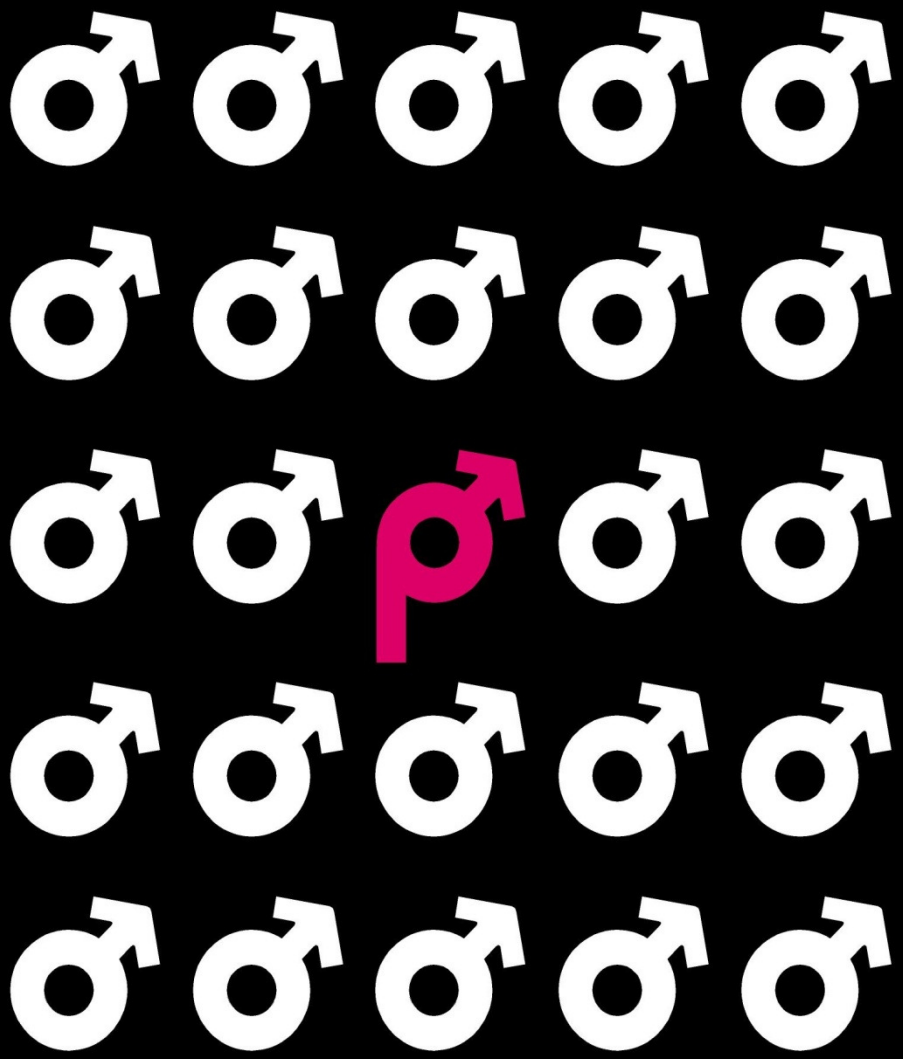
ART prophylaxis aborts potential infection

Systemic

Topical or microbicides

PrEP





CAN A PILL A DAY PREVENT HIV?

FOR INFORMATION ON THIS NEW AND EXCITING HIV PREVENTION STUDY

SMS "Info" at no cost to 30060 or
e-mail MCMHP@hiv-research.org.za

All participants will be compensated for their time and transport.

COMING 01-07-08

MCMHP@hiv-research.org.za

MOTHER CITY MEN'S HEALTH PROJECT
Time to Stand Up.

Desmond Tutu HIV Foundation

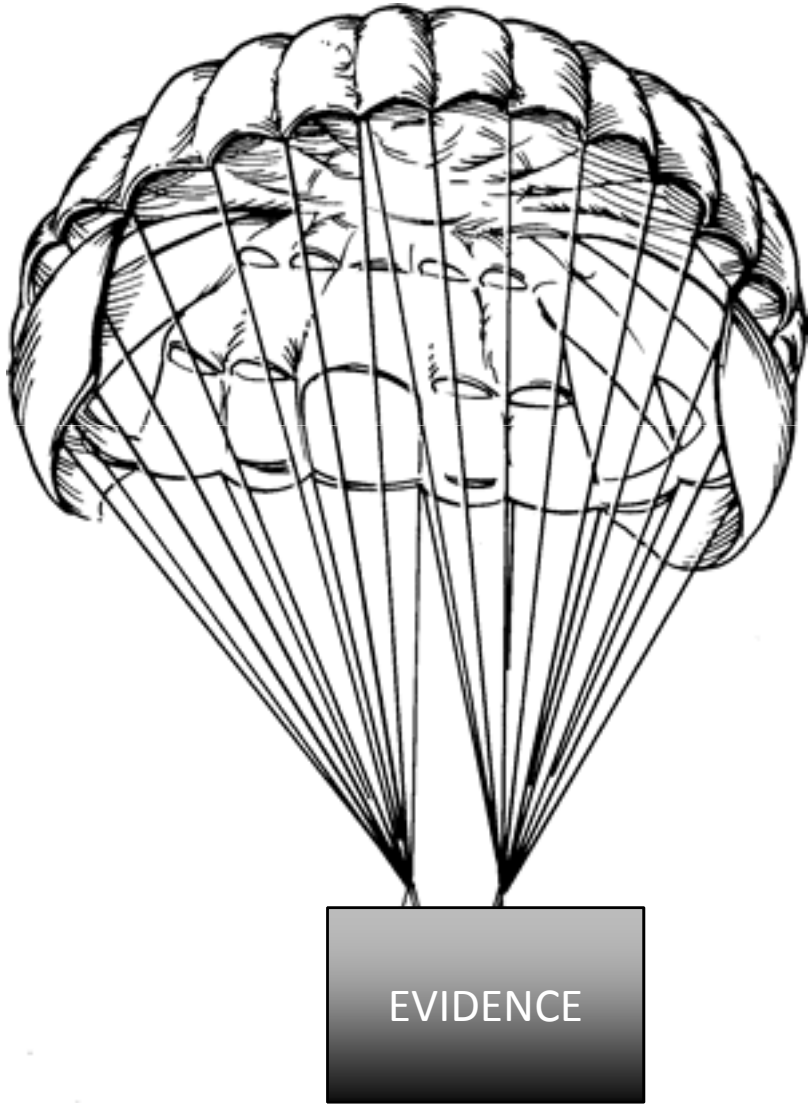
triangle project
Challenging Homophobia
Appreciating Sexual Diversity

PrEP

MOTHER CITY MEN'S HEALTH PROJECT
Time to Stand Up.

triangle project

And the last parachute goes to…..



Evidence : Systemic PrEP

- 3 RPCTS involving 8457 HIV negative individuals
- 3 different populations
  - MSM, hetero (M +F), discordant couples (M`+ F)
- Both hetero and homo sexual risk
- Truvada (TDF/FTC), Tenofovir
- PE : 44-75%

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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 Chariyalertsak, 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., Ana I. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team*

Published online on November 23, 2010
Article and supplement available online
http://www.nejm.org/doi/full/10.1056/NEJMoa1011205
nejm.org/doi/suppl/10.1056/NEJMoa1011205/suppl_file/nejmoa1011

FDA approves TRUVADA as PrEP in July 2012

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 2, 2012 VOL. 367 NO. 5

Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

J.M. Baeten, D. Donnell, P. Ndase, N.R. Mugo, J.D. Campbell, J. Wangisi, J.W. Tappero, E.A. Bukusi, C.R. Cohen, E. Katabira, A. Ronald, E. Tumwesigye, E. Were, K.H. Fife, J. Kiarie, C. Farquhar, G. John-Stewart, A. Kakia, J. Odoyo, A. Mucunguzi, E. Nakku-Joloba, R. Twesigye, K. Ngure, C. Apaka, H. Tamooh, F. Gabona, A. Mujugira, D. Panteleeff, K.K. Thomas, L. Kidoguchi, M. Krows, J. Revall, S. Morrison, H. Haugen, M. Emmanuel-Ogier, L. Ondrejcek, R.W. Coombs, L. Frenkel, C. Hendrix, N.N. Bumpus, D. Bangsberg, J.E. Haberer, W.S. Stevens, J.R. Lingappa, and C. Celum, for the Partners PrEP Study Team*

ABSTRACT

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiretroviral Preexposure Prophylaxis for Heterosexual HIV Transmission in Botswana

Michael C. Thigpen, M.D., Poloko M. Kebaabetswe, Ph.D., M.P.H., Lynn A. Paxton, M.D., M.P.H., Dawn K. Smith, M.D., M.P.H., Charles E. Rose, Ph.D., Tebogo M. Segolodi, M.Sc., Faith L. Henderson, M.P.H., Sonal R. Pathak, M.P.H., Fatma A. Soud, Ph.D., Kata L. Chillag, Ph.D., Rodreck Mutanhaurwa, M.B., Ch.B., Lovemore Ian Chirwa, M.B., Ch.B., M.Phil., Michael Kasonde, M.B., Ch.B., Daniel Abebe, M.D., Evans Buliva, M.B., Ch.B., Roman J. Gvetadze, M.D., M.S.P.H., Sandra Johnson, M.A., Thom Sukalac, Vasavi T. Thomas, M.P.H., R.Ph., Clyde Hart, Ph.D., Jeffrey A. Johnson, Ph.D., C. Kevin Malotte, Dr.P.H., Craig W. Hendrix, M.D., and John T. Brooks, M.D., for the TDF2 Study Group*

ABSTRACT

Evidence : Topical PrEP

- Single trial
- RPCT
- One country – 2 sites
- 889 Heterosexual, high incidence HIV neg women
- 1% Tenofovir gel
- PE: 39%
- Led to second confirmatory study :
  - FACTS 001
  - RPCT
  - 1 country, numerous sites

Sciencexpress Report

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‡

[1]Centre for the AIDS Program of Research in South Africa (CAPRISA), Durban, South Africa. [2]Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, USA. [3]University of KwaZulu-Natal, Durban, South Africa. [4]National Institute for Communicable Diseases, Johannesburg, South Africa. [5]FHI, North Carolina, USA.

*These authors contributed equally to this work.

†To whom correspondence should be addressed. E-mail: caprisa@ukzn.ac.za

‡The members of the CAPRISA 004 Trial Group appear at the end of this paper.

The CAPRISA 004 trial assessed 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

region which accounts for 70% of global burden of Human Immunodeficiency Virus (HIV) infection (*1*). Current HIV prevention behavioral messages on abstinence, faithfulness and condom promotion have had limited impact on HIV

Where were we then: PrEP efficacy trial results, March 2012

Study	Population	N	Results
CAPRISA 004	Women	889	**39% efficacy vaginal TFV gel**
iPrEx	MSM	2499	**44% efficacy FTC/TDF**
TDF2 Study	Young men and women	1200	**62% efficacy FTC/TDF**
Partners PrEP Study	Heterosexual couples	4758	**67% efficacy TDF** **75% efficacy FTC/TDF**

However…..

Where are we now: PrEP efficacy trial results, March 2012

Study	Population	N	Results
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TDF2 Study	Young men and women	1200	**62% efficacy FTC/TDF**
Partners PrEP Study	Heterosexual couples	4758	**67% efficacy TDF** **75% efficacy FTC/TDF**
FEM-PrEP	High risk women	1950	**FTC/TDF = futility**
VOICE	Women	5029	**TDF = futility** **Vaginal TFV gel = futility** FTC/TDF ongoing
Bangkok Tenofovir Study	IDUs	2400	TDF ongoing
FACTS001	Women	2200	TFV gel enrolling

MMC already left with the second last parachute

Point efficacy…

- TasP

The New England Journal of Medicine

Prevention of HIV-1 Infection
with Early Antiretroviral Therapy

- 1763 discordant couples - hetero
- Treated immediately/deferred
- 39 infections : 27 vs 1 in linked transmissions
- 96% reduction in HIV transmission

Partners PrEP: 4758 couples

Group	TDF (1579)	TDF/FTC (1584)
Total	62 % (34-78)	73 % (49-84)
Women	68 % (29-85)	62 % (19-82)
Men	55 % (4-79)	83 % (49-94)

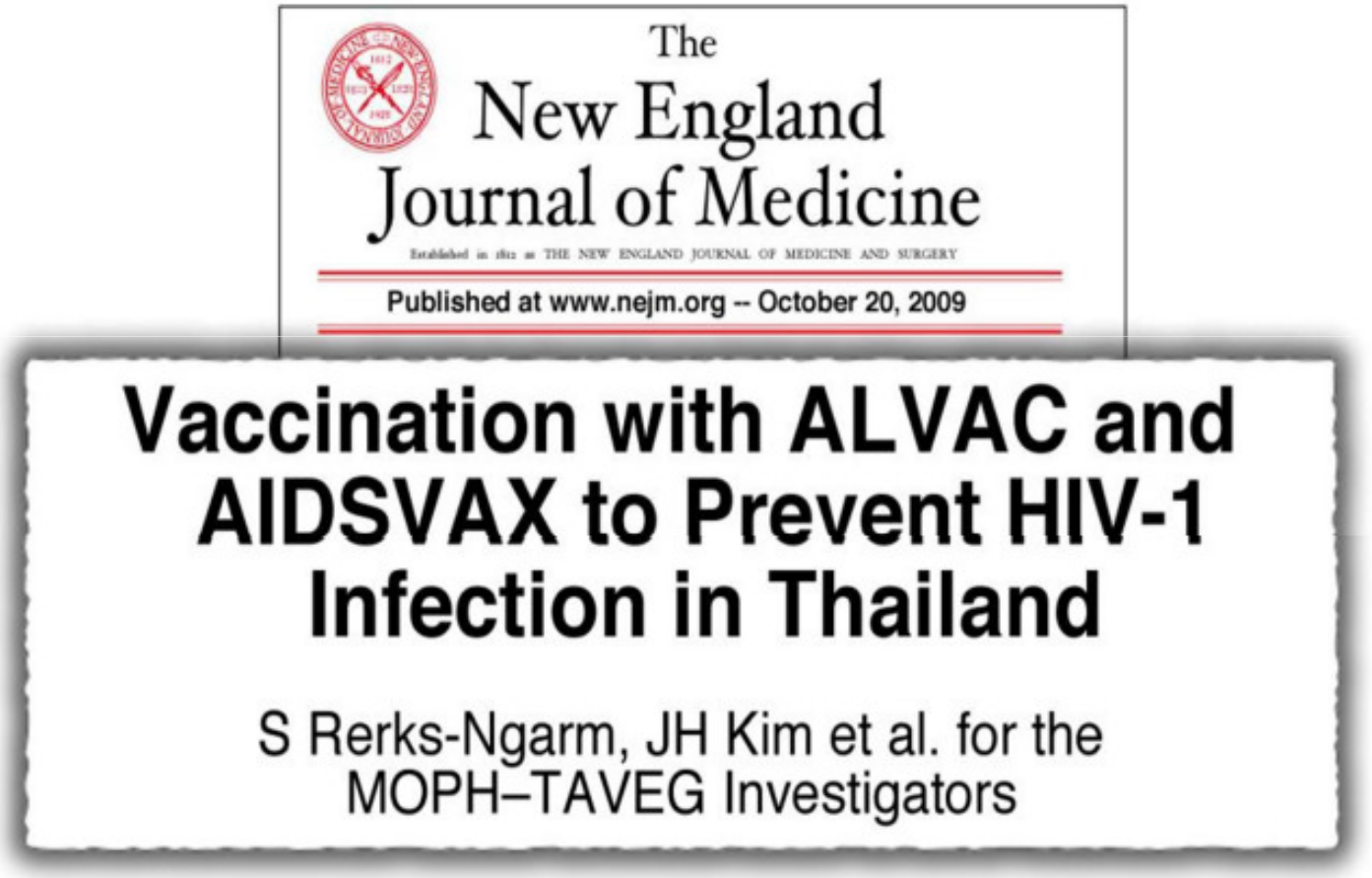
Discordant couples : “outside partners”

Study	Total N	Linked	Indeterm	Unlinked
Partners in Prevention	108	72%	2%	26%
HPTN 052	38	76%	5%	18%
Zambia cohort	149	87%	--	13%
Rakai cohort	57	50%	36%	14%

Even among stable serodiscodant couples, substantial % from outside partners

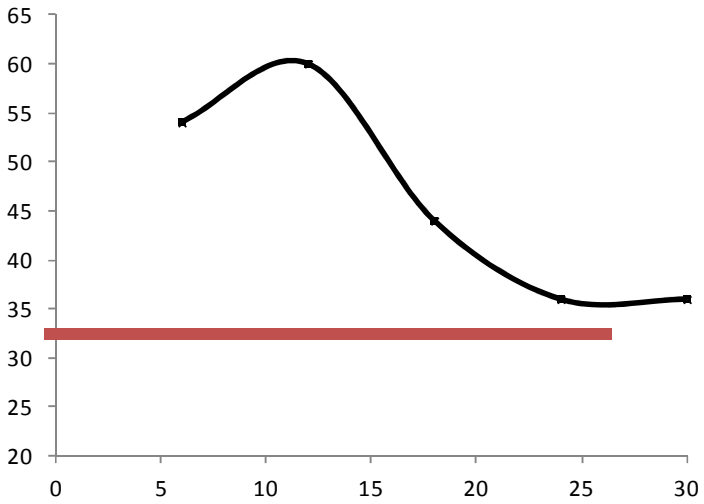
MMC already left with the second last parachute

First Signal of Efficacy in an HIV Vaccine Clinical Trial



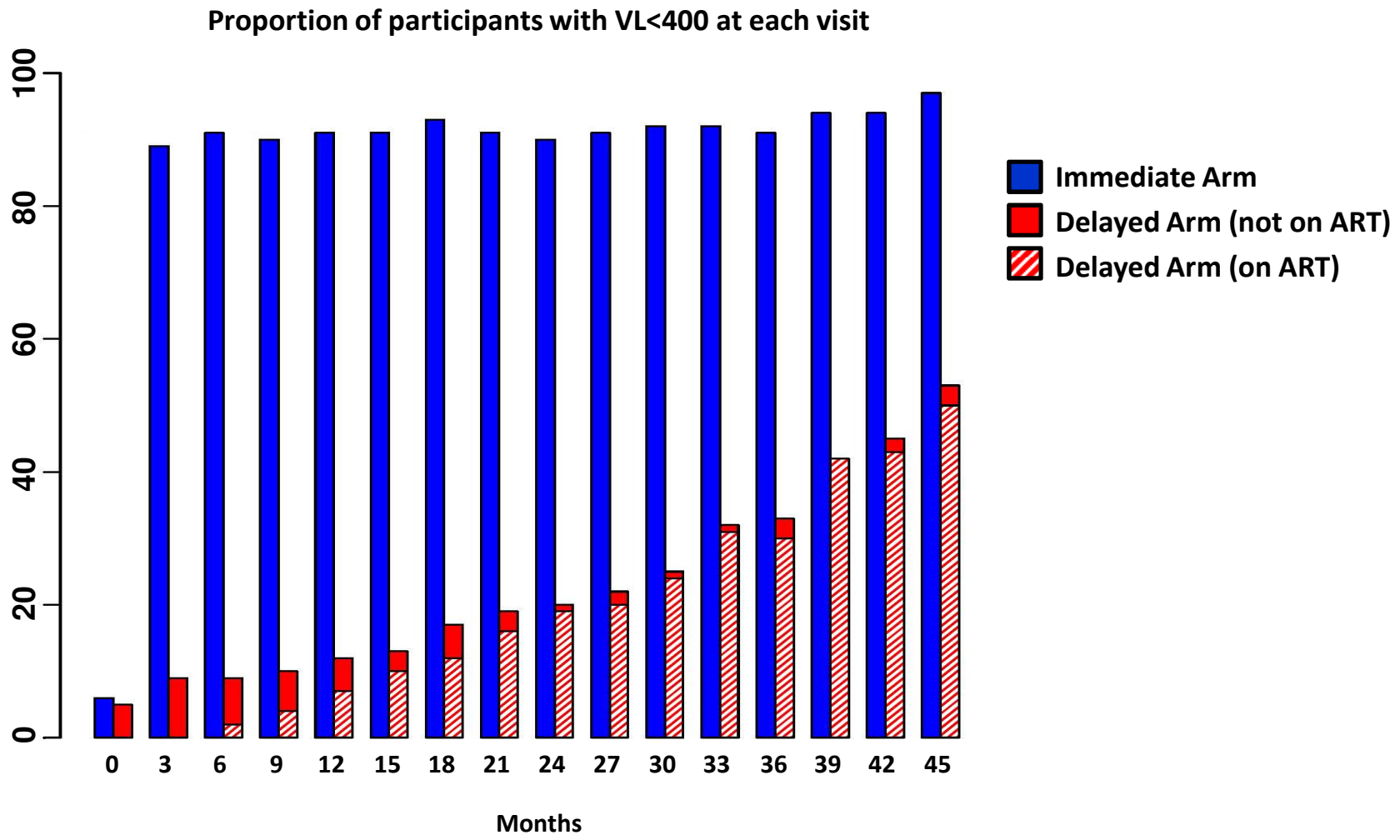
RV144 ALVAC Prime, AIDSVAX B/E Trial

31.2% Estimated Vaccine Efficacy



Adherence….

HPTN 052: Consistent Use of ART



Tenofovir levels and HIV-1 protection

- Objective adherence measures from trials show:

	% with tenofovir detected		HIV-1 protection: detection versus no detection of tenofovir	
	Seroconverters	**Non-seroconverters**	**Protection**	**p-value**
iPrEx	9%	51%	92%	<0.001
Partners PrEP FTC/TDF arm	25%	81%	90%	0.002

Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010

Tenofovir levels and HIV-1 protection

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  1) PrEP use was modest in iPrEx and high in Partners PrEP, consistent with overall efficacy

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Donnell et al CROI 2012 Abstract 30
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Tenofovir levels and HIV-1 protection

- Objective adherence measures from trials show:
  1) PrEP use was modest in iPrEx and high in Partners PrEP, consistent with overall efficacy
  2) When PrEP was taken, protection appeared to be very high

	% with tenofovir detected		HIV-1 protection: detection versus no detection of tenofovir	
	Seroconverters	Non-seroconverters	Protection	p-value
iPrEx	9%	51%	92%	<0.001
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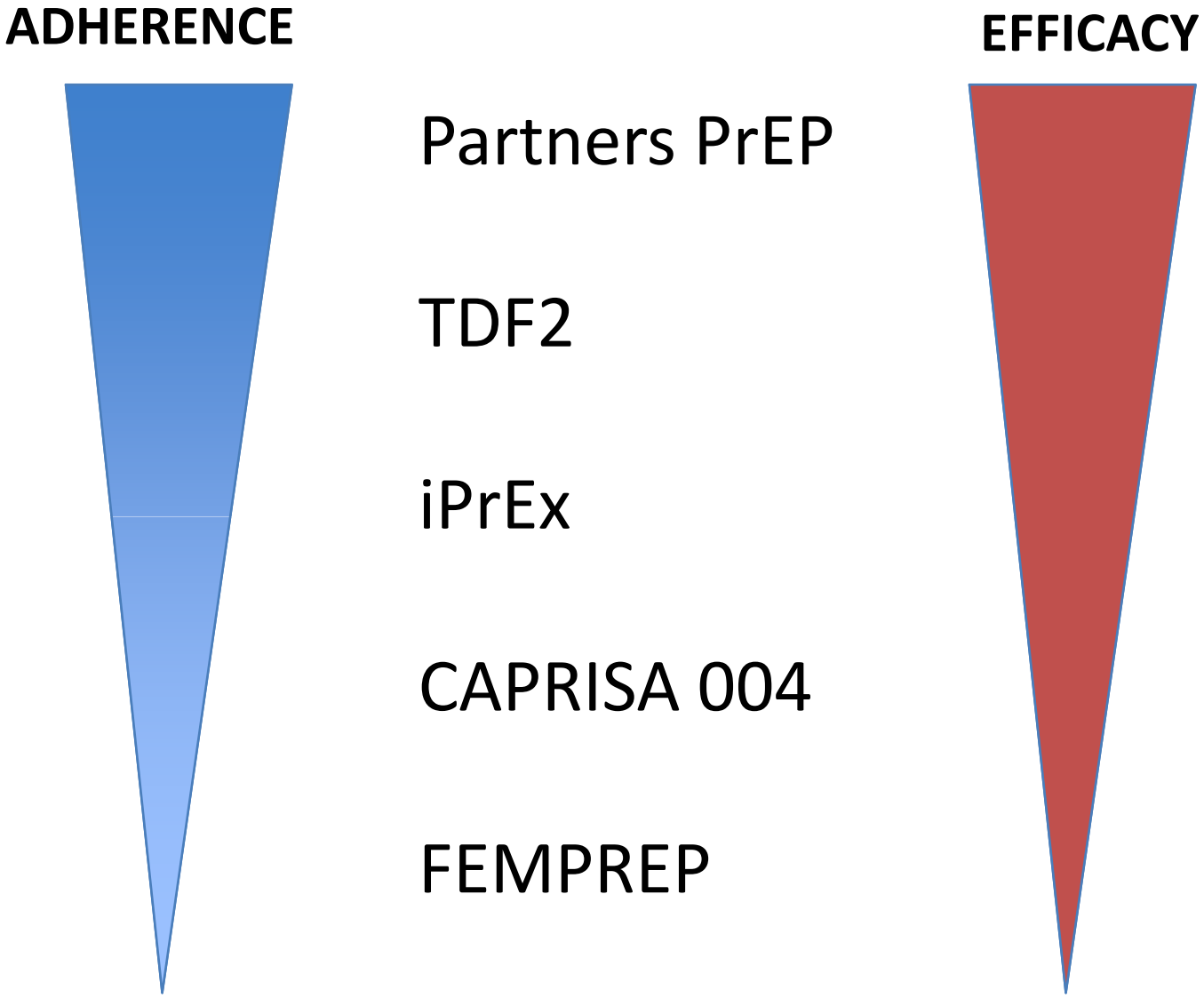
Donnell et al CROI 2012 Abstract 30
Grant et al N Engl J Med 2010

PrEP taken consistently or not at all

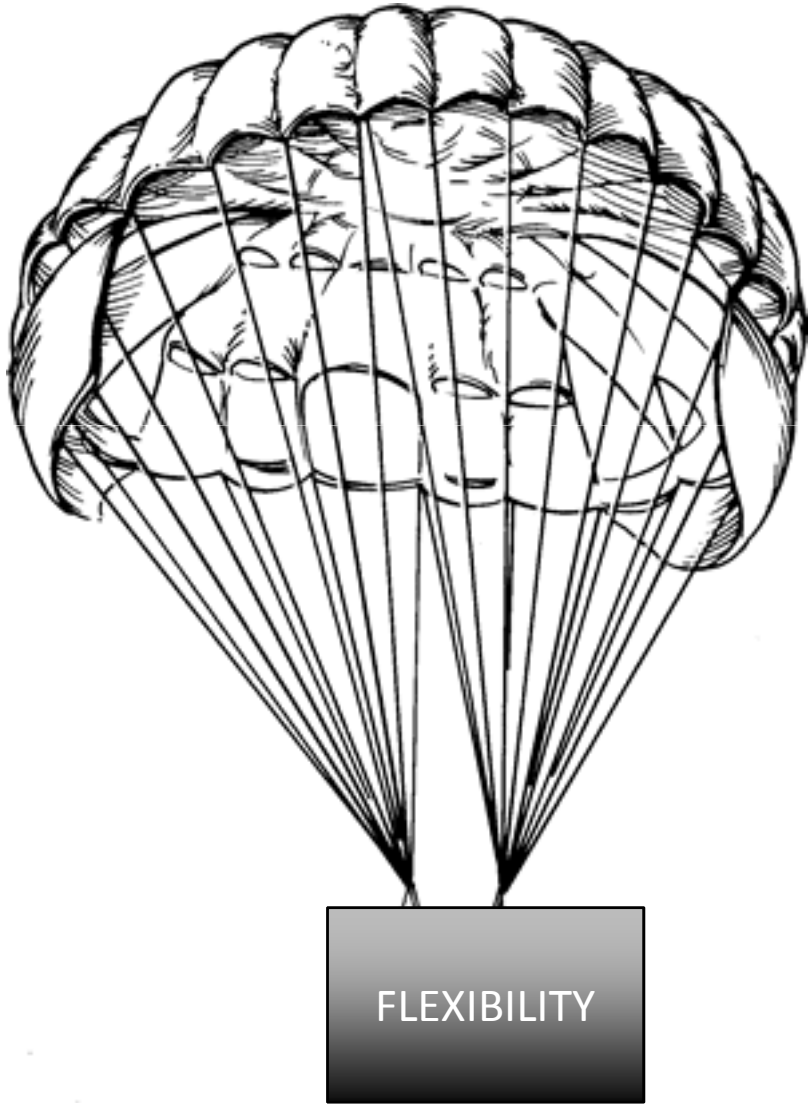
Partners PrEP Study

Serum tenofovir levels				
	Infected cases		Uninfected cohort	
Undetectable	20	**69%**	164	**18%**
0.3 - 10 ng/mL	1	**3%**	38	**4%**
≤10 – 40 ng/mL	1	**3%**	60	**7%**
≥ 40 ng/mL	7	**24%**	640	**71%**

Donnell, Abstract #30, CROI 2012


ADHERENCE
EFFICACY
Partners PrEP
TDF2
iPrEx
CAPRISA 004
FEMPREP

And the last parachute goes to…..



A Lexicon of Intermittent PrEP

J. McConnell/AVAC

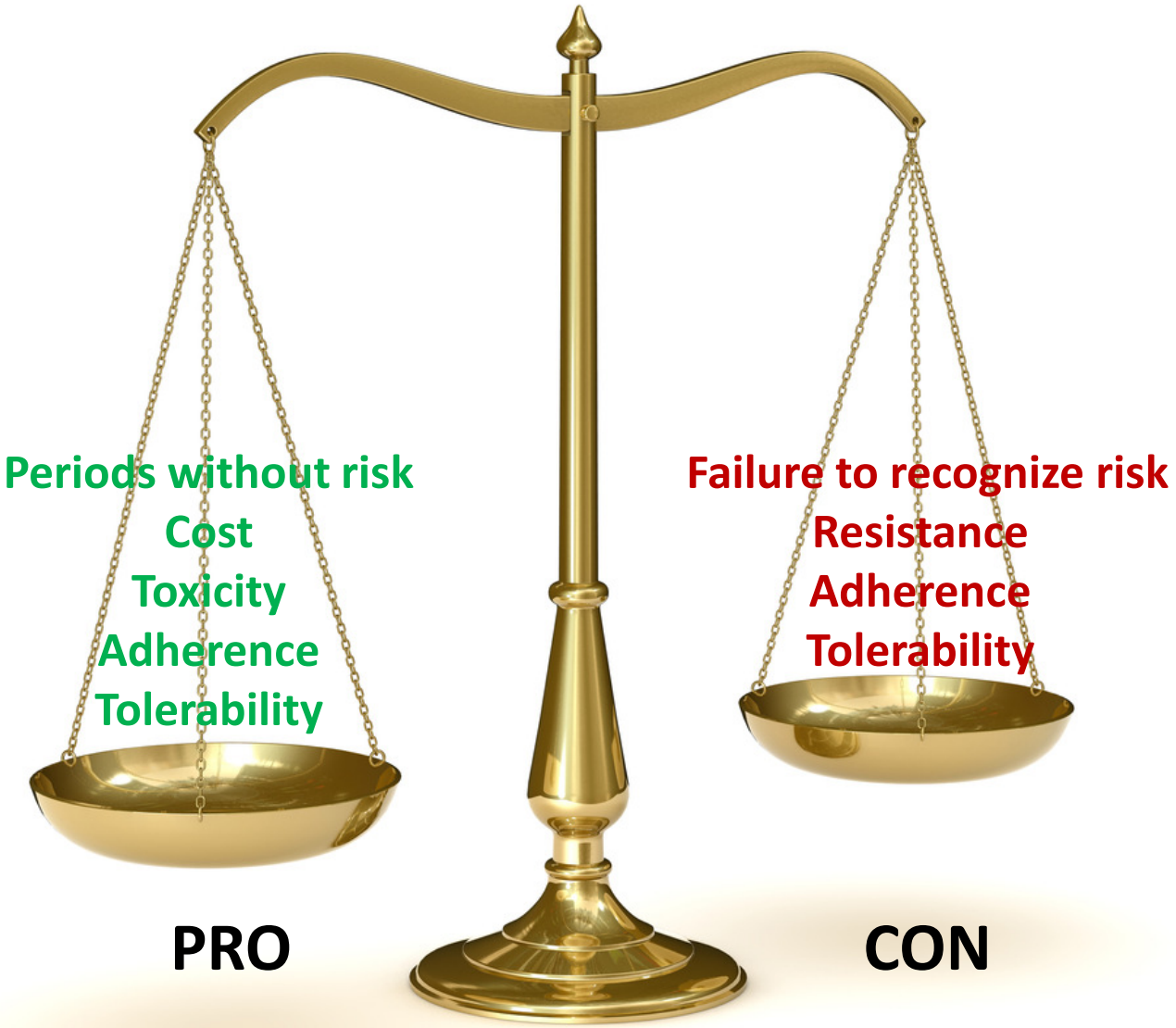
1. Fixed or time-based dosing

2. Event-based dosing

3. Time-based plus event-based dosing

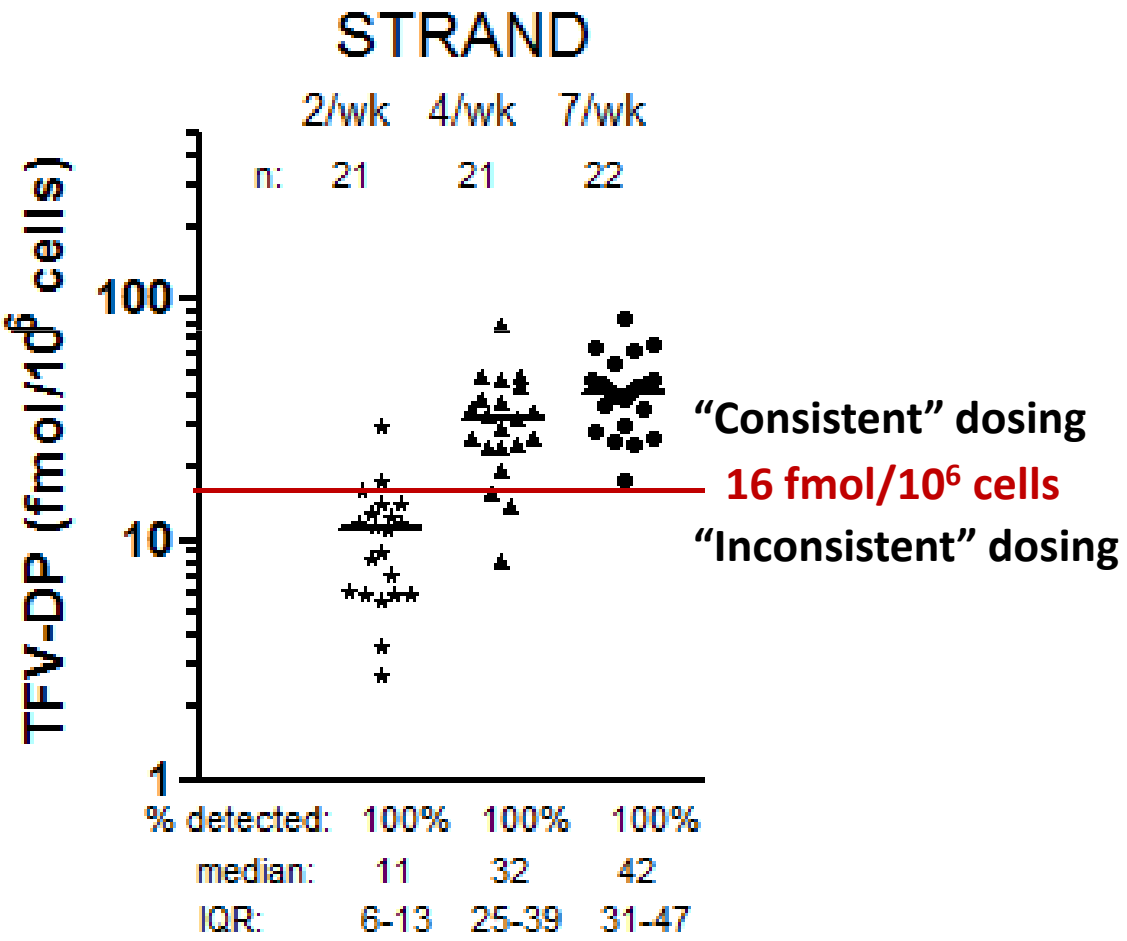
4. Periodic dosing

Why intermittent PrEP?



TDF-DP Levels in PBMC with 2-7 days DOT

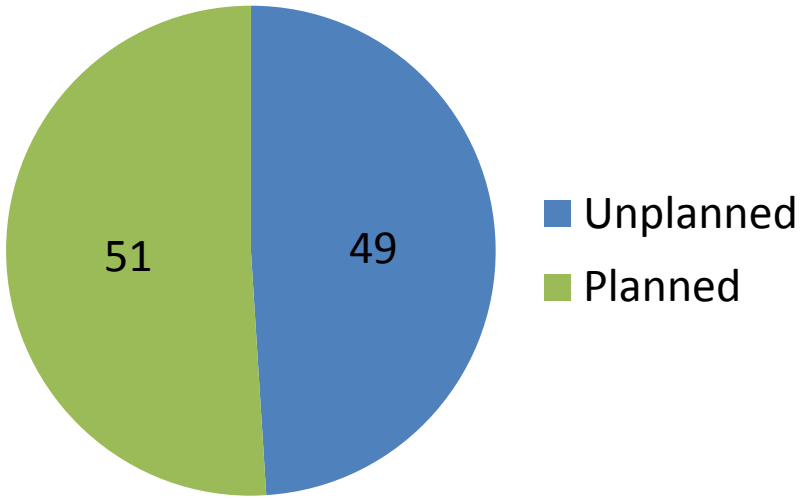
Understanding iPrEx results



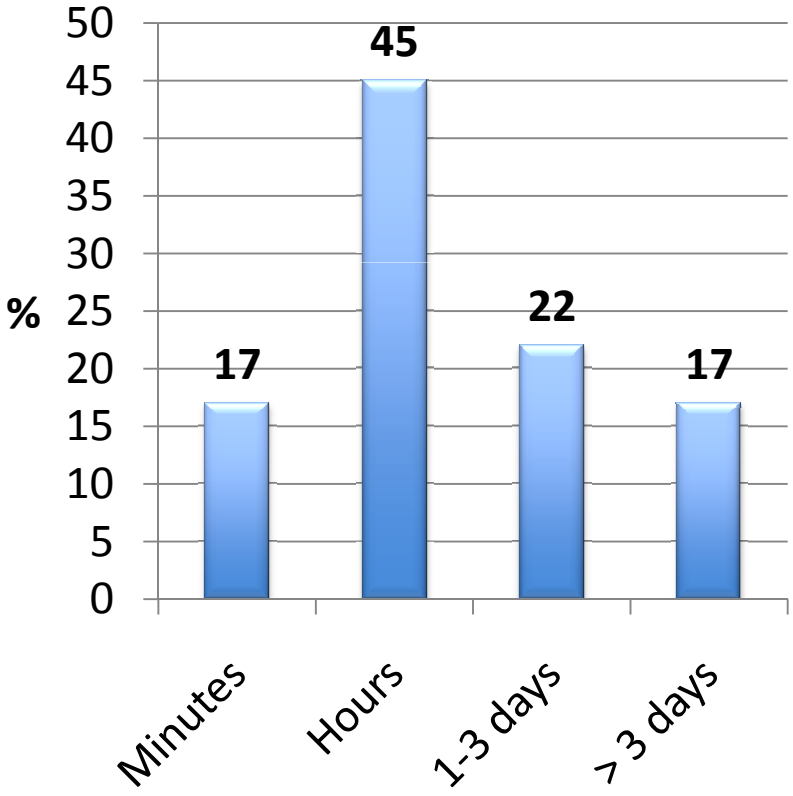
Planning for the pre-event dose

US online survey, 1013 MSM

Last anal sex planned?

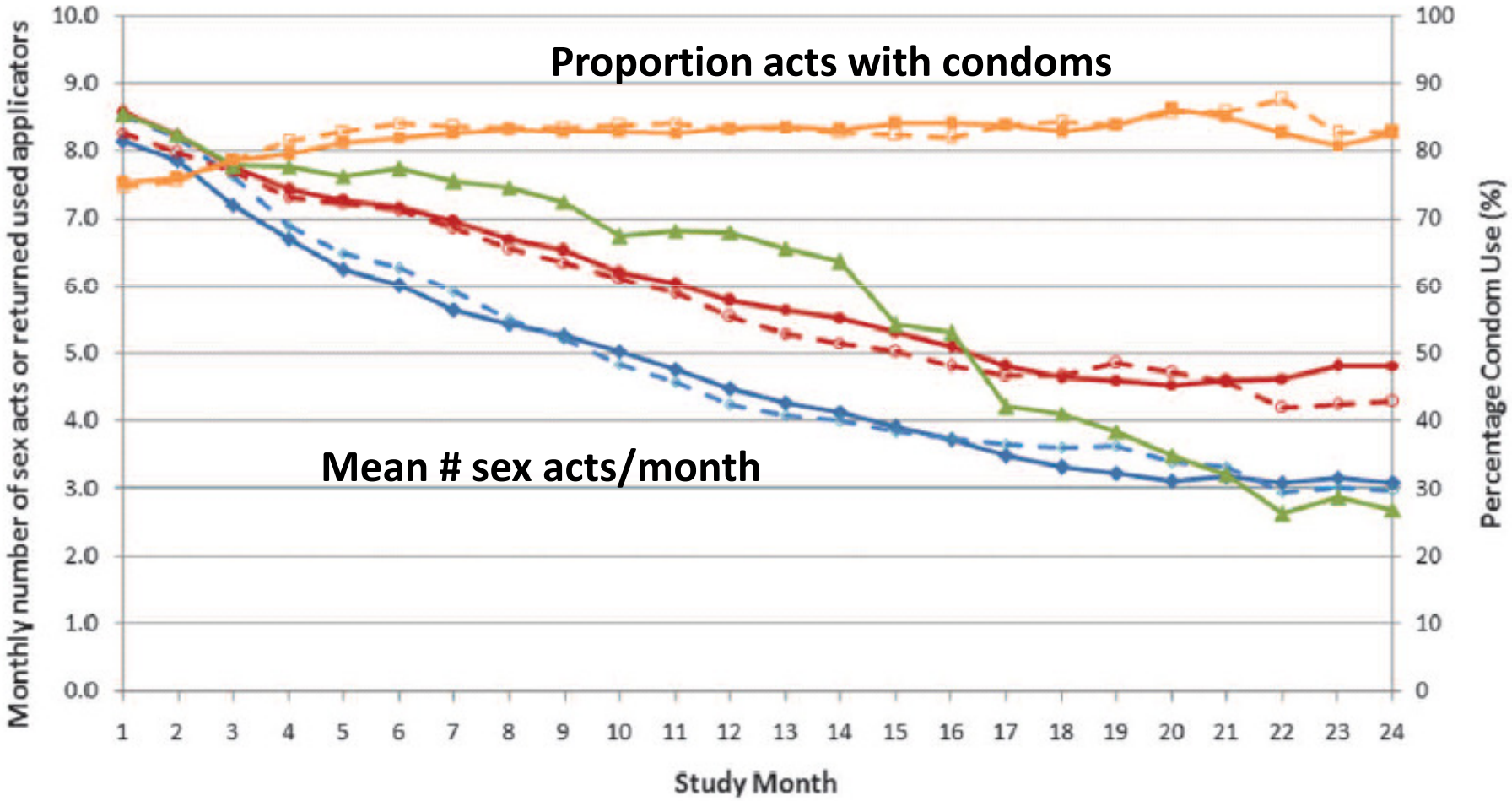


How far ahead planned?



Sexual frequency in women in CAPRISA 004

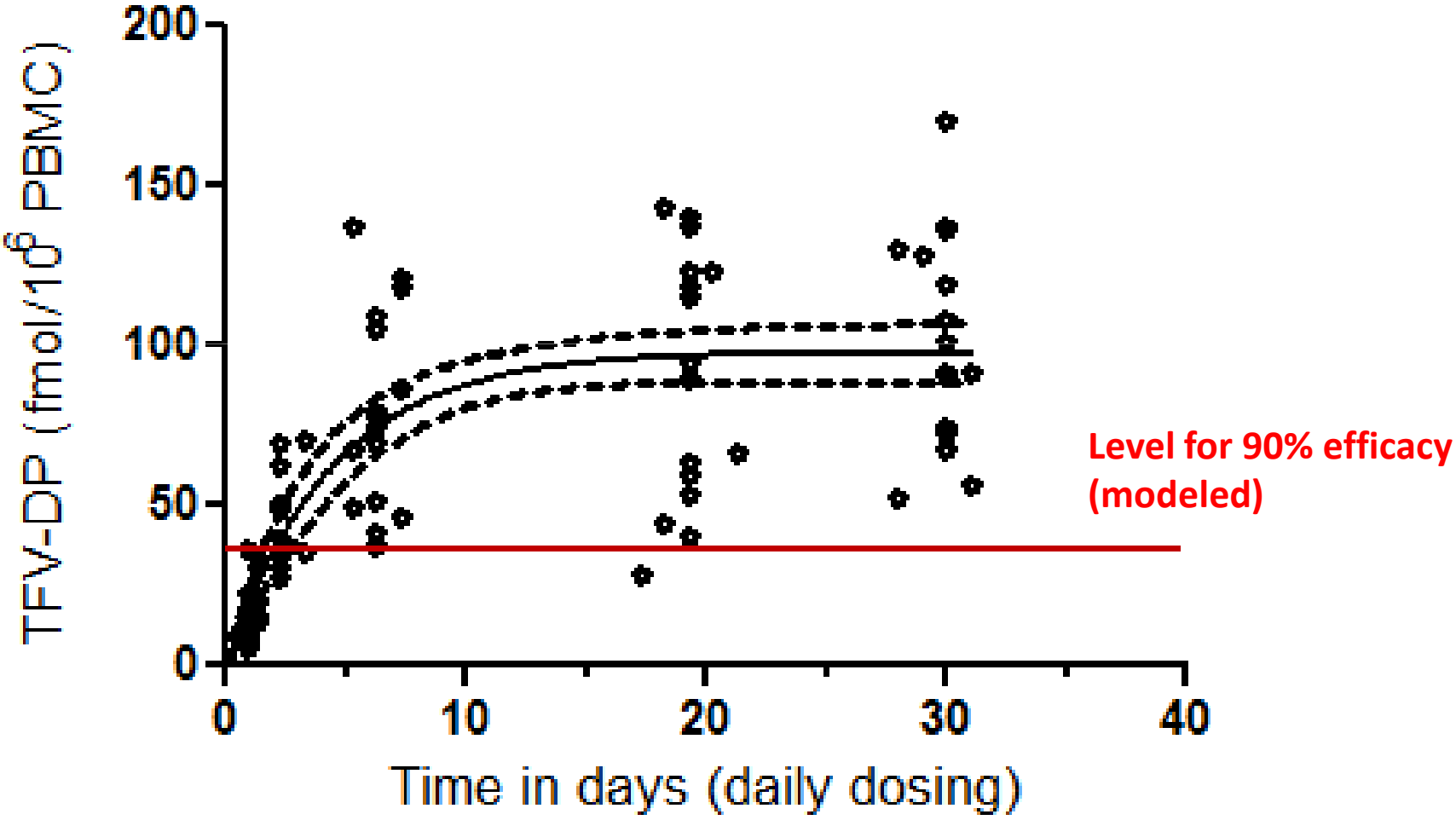
Incidence in placebo arm: 9.1/100wy



Abdool Karim, Science 2010

PBMC levels of TFV-DP (95% CI)

May need several (3-4) doses to get to protective level

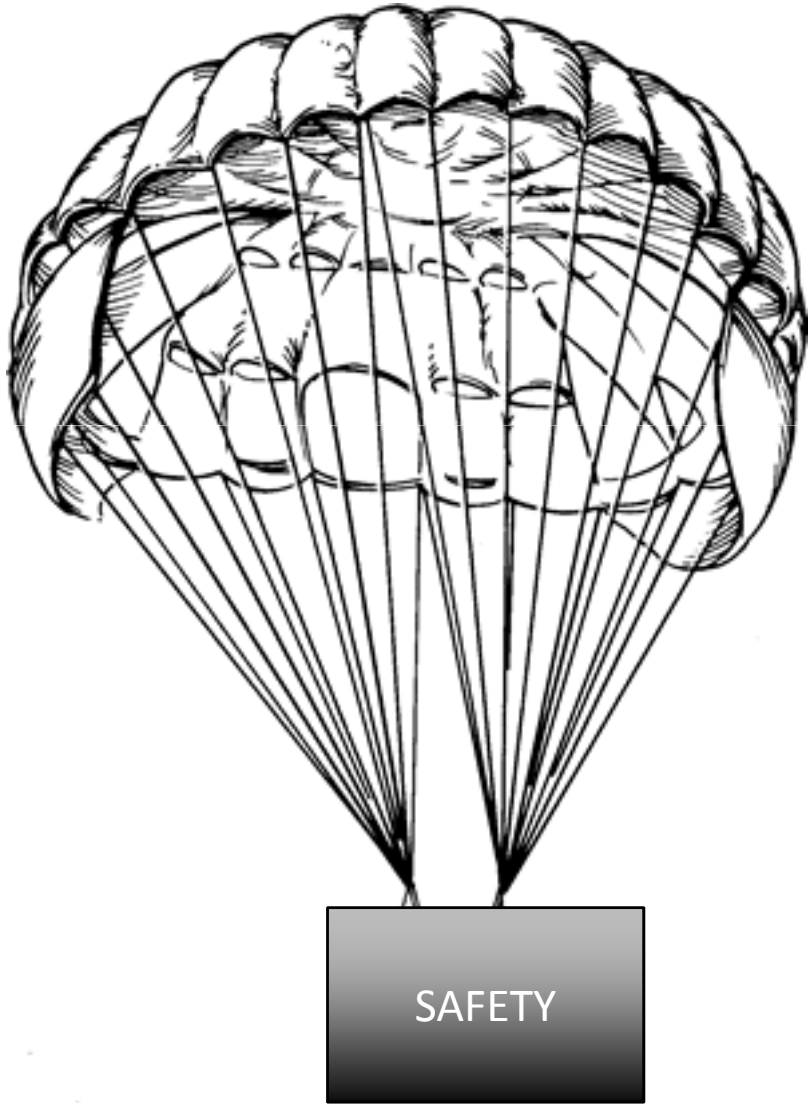


Anderson, Poster 587, CROI 2012

Lessons from NHP studies

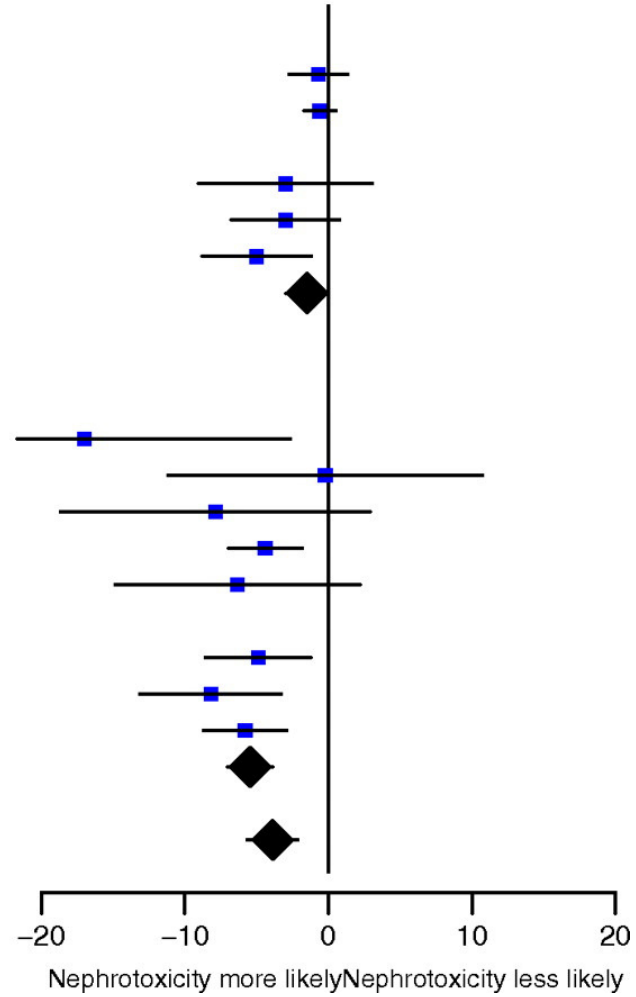
- PrEP can protect against repeated low-dose rectal challenge
- Systemic
  - Daily dosing protects at high levels
  - Event-based dosing protects with possible trend toward best if:
    - Pre-exposure dose 1-7 days pre-challenge
    - Post-challenge dose provided
  - Event-based dosing can protects against M184V strain
- Topical
  - Pre-exposure dose needed
- Great headway with closer replication to human challenge but **need human data to validate these models**

And the last parachute goes to…..



Safety:
Renal monitoring of PrEP users

Study/sub-category	Total	MD [95% CI], ml/min
RCT		
ART experienced		
BICOMBO 2009	333	−0.70 [−2.73, 1.33]
De Jesus 2009	300	−0.60 [−1.71, 0.51]
ART naive		
HEAT 2009	672	−3.00 [−9.06, 3.06]
Arribas 2008	458	−3.00 [−6.77, 0.77]
Gallant 2004	600	−5.00 [−8.80, −1.20]
Subtotal		−1.50 [−2.96, −0.005]
Cohort		
ART experienced		
Kinai 2009	63	−17.00 [−31.35, −2.65]
Goicoechea 2008 NNRTI	62	−0.22 [−11.18, 10.74]
Goicoechea 2008 RPI	84	−7.88 [−18.66, 2.90]
HOPS 2007	736	−4.40 [−6.97, −1.83]
Winston 2006	948	−6.33 [−14.85, 2.19]
ART naive		
Fux 2007	284	−4.90 [−8.58, −1.22]
Fux 2007 N	569	−8.20 [−13.13, −3.27]
Gallant 2005	658	−5.80 [−8.70, −2.90]
Subtotal		−5.45 [−7.02, −3.89]
Total		**−3.90 [−5.66, −2.14]**



Cooper, CID 2010

Renal fxn in PrEP studies

- Of 1251 pts receiving FTC-TDF in iPrEx,
  - 5 pts had elevated creatinine $\geq$ 2 sequential visits
  - All resolved when drug stopped
  - 4 re-challenged without problem
- Partners PrEP, TDF-2, Fem-PrEP
  - No significant difference between active, placebo arms
- Although nephrotoxicity not seen in this HIV negative population:
  - Excluded pts with baseline renal disease
  - Relatively small numbers, short follow-up

Resistance - Good news :

- In 4 published RCTs of PrEP:
  - Partners, iPrEx, TDF2, CAPRISA 004
- No infection on PrEP : **No RESISTANCE**
- No exposure to PrEP : resistance rare, but **INFECTION**

HIV-1 Drug Resistance from PrEP

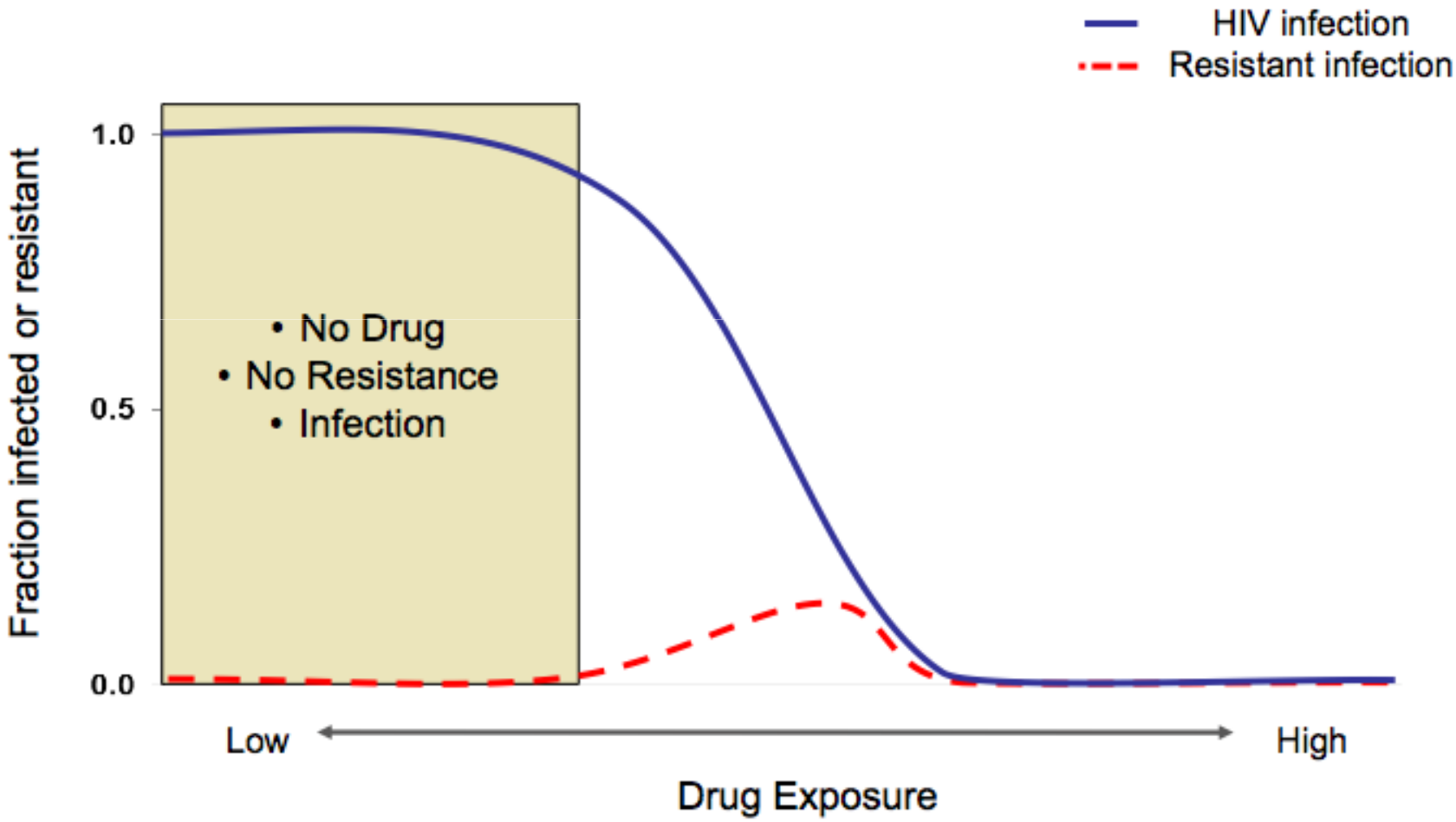
- **Infrequent** cases of drug resistance among PrEP study participants who seroconverted while receiving active drug

Study	Infections on Study	
	# infected	# resistant to FTC or TDF
iPrEx	131	None
Partners PrEP	82	None
TDF2	33	1 placebo (K65R <1%)*
FEM-PrEP	68	1 placebo (M184V)* 4 FTC/TDF (M184V/I)**

* Transmitted (primary) resistance can occur independent of PrEP, which likely explains resistance in the placebo arm

** 1 probable and 2 possible transmitted resistance; 1 uncertain timing of infection (HIV RNA detectable at first follow-up visit)

Theoretical Infection-Exposure-Resistance Relationships



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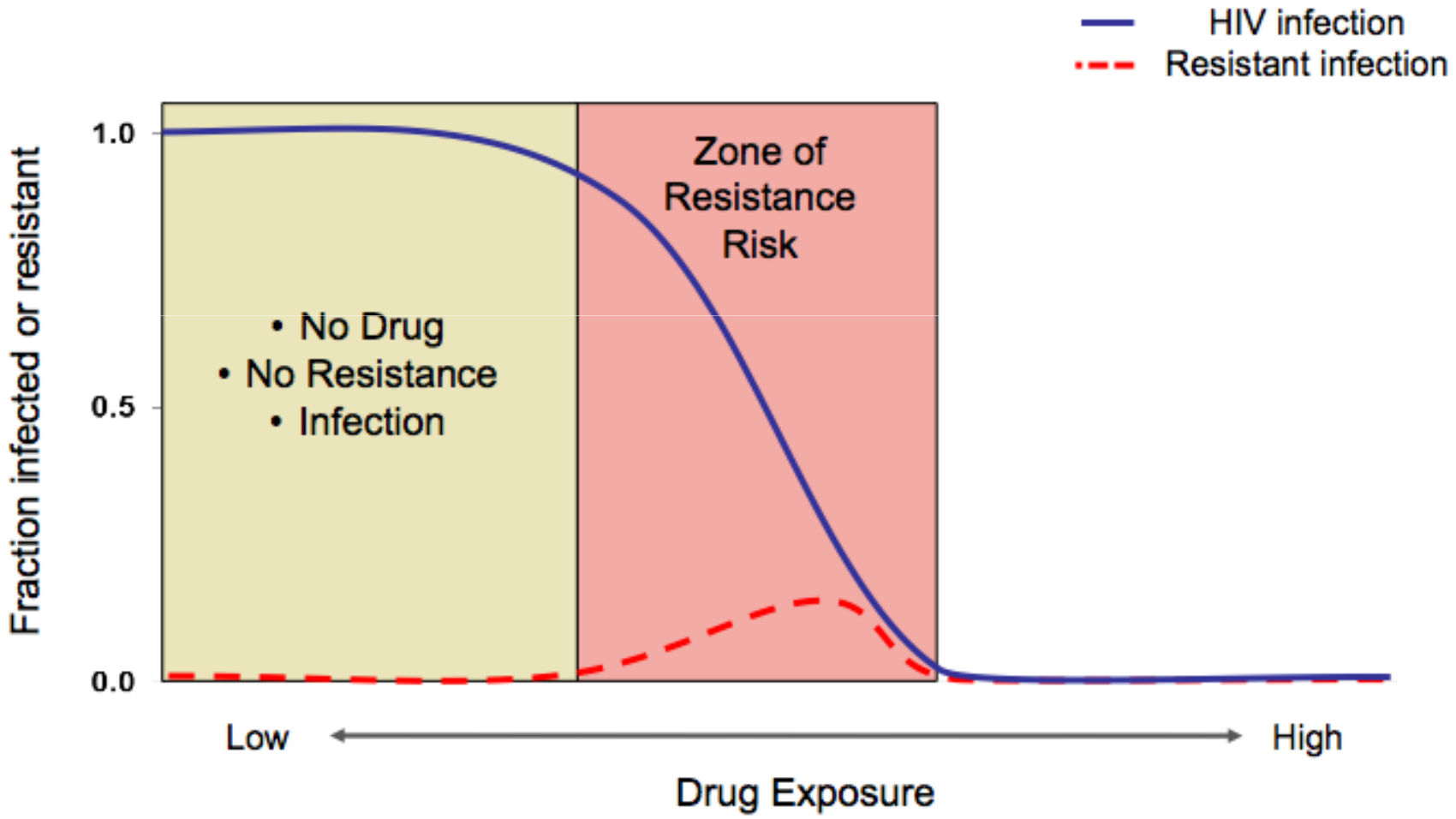

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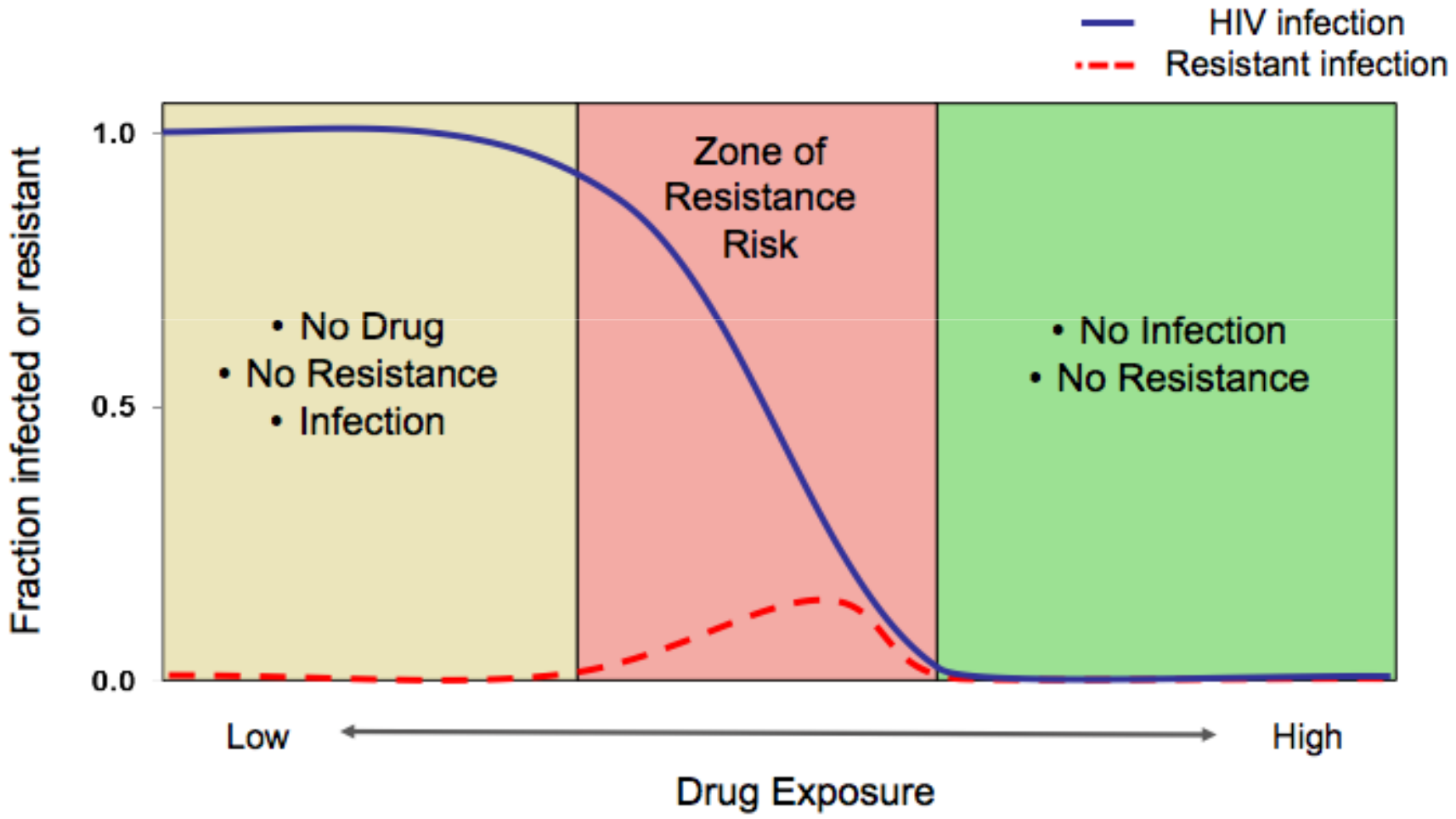


Bad news :

- Resistance risk increased if PrEP started during unrecognised acute HIV infection….

Resistance More Likely if PrEP is Given During Unrecognized Acute Infection*

Study	Baseline Infections	
	# infected	# resistant
iPrEx	10	2/2 active (M184V/I) 1/8 placebo (M184V)
Partners PrEP	14	2/8 active (1 K65R, 1 M184V)
TDF2	3	1/1 active (K65R, M184V, A62V)
FEM-PrEP	2	0/1 active

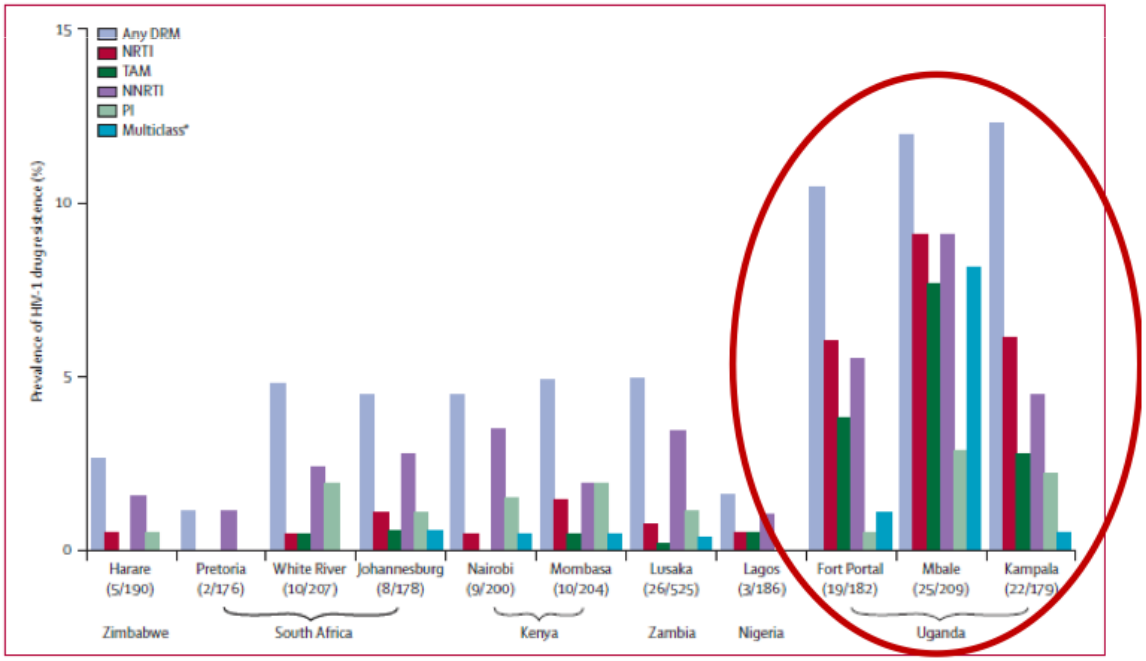
*Infection + incomplete suppression of replication selects resistance

Transmitted (primary) resistance can occur, independent of PrEP, which likely explains resistance in the placebo arm

Good news:

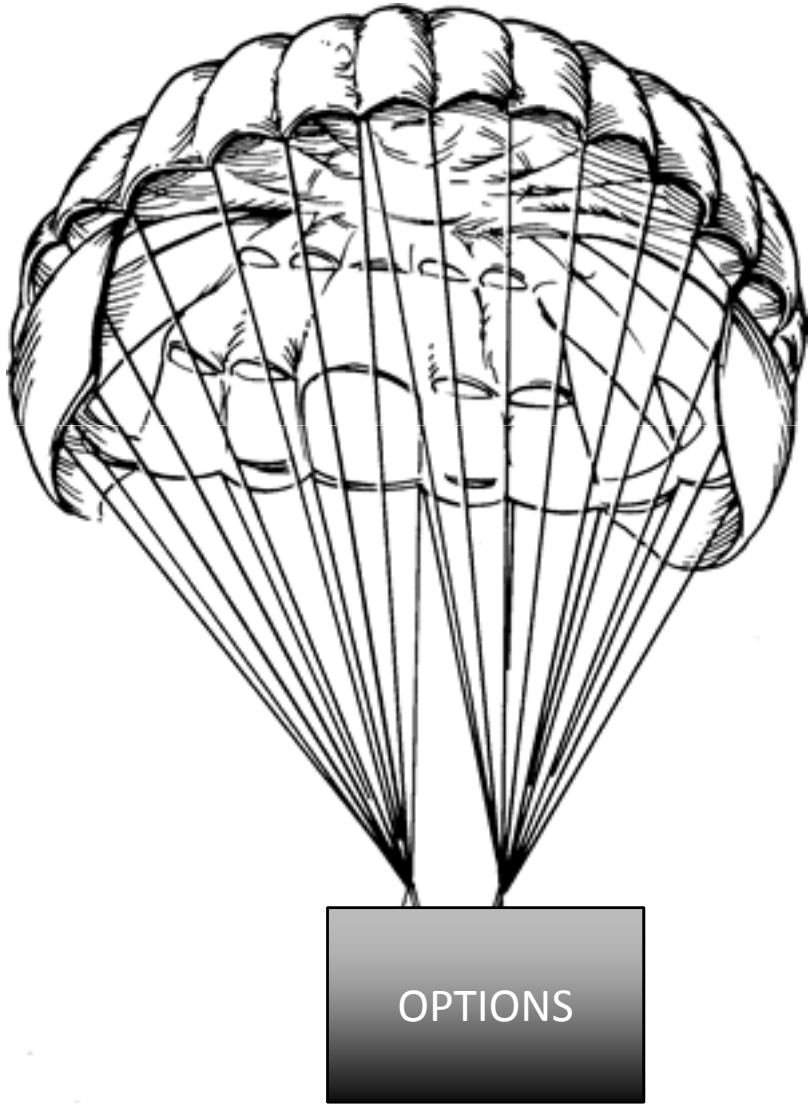
- Resistance NOT seen in topical PrEP
- CAPRISA 004 (Tenofovir gel)
- No minor or major resistance

- Resistance from ART is common
  - 15-20% of first-line therapy
  - Evidence of spread: prevalence pretherapy has increased in some countries from <5% to >12%
  - Uganda, Cameroon



Hamers et al., Lancet Infectious Dis 2011

And the last parachute goes to…..



Tenofovir as a first-generation PrEP agent

Pill

Gel

Vaginal film

Vaginal ring

Injectable

Great things in the pipeline…….

The Microbicide Pipeline?

Partial Listing of API

RT Inhibitors:
Tenofovir
Dapivirine
MIV-150
UC781
IQP-0528
DABO

Protease Inhibitors:
Darunivir
Lopinavir
Ritonavir
Sequinivir

Lectins:
Cyanovirin N
Griffithsin
BanLec
Actinohivin

Food Products:
Praneen
Green Tea Extracts
Pomergranate Juice

Entry Inhibitors:
Maraviroc
Dendrimers (Vivagel)
Defensins (RC101)
DS003 (BMS793)
PSC Rantes
ß cyclodextrin
IQP-0831 (Isis 5320)
SAMMA
mABs
HNG-156
T1249
C52L
L'167
L'872
L'882
L'644

Nucleic Acids:
Aptamers
siRNA

Other:
GML
Lactobacillus
Top. Estrogen
Zinc
Thiolesters

The Microbicide Pipeline?

Possible Dosage Forms

Vaginal Rings:

Silicone	Matrix
EVA	Reservoir
PU	Insert

Single Use:

Gels
Creams
Films
Tablets
SGC

Other Devices:

Diaphragm
Duet
Non-woven
Female Condom





The Microbicide Pipeline?
Combinations and MPT

Combination HIV Prevention Products	
Dapivirine-Maraviroc Vaginal Ring	IPM
Dapivirine-Maraviroc Gel	IPM
Maraviroc-Tenofovir Film	IPM
Dapivirine-Tenofovir Vaginal Ring	IPM
MIV-150-Zn Acetate-Carageenan Gel	Pop Council

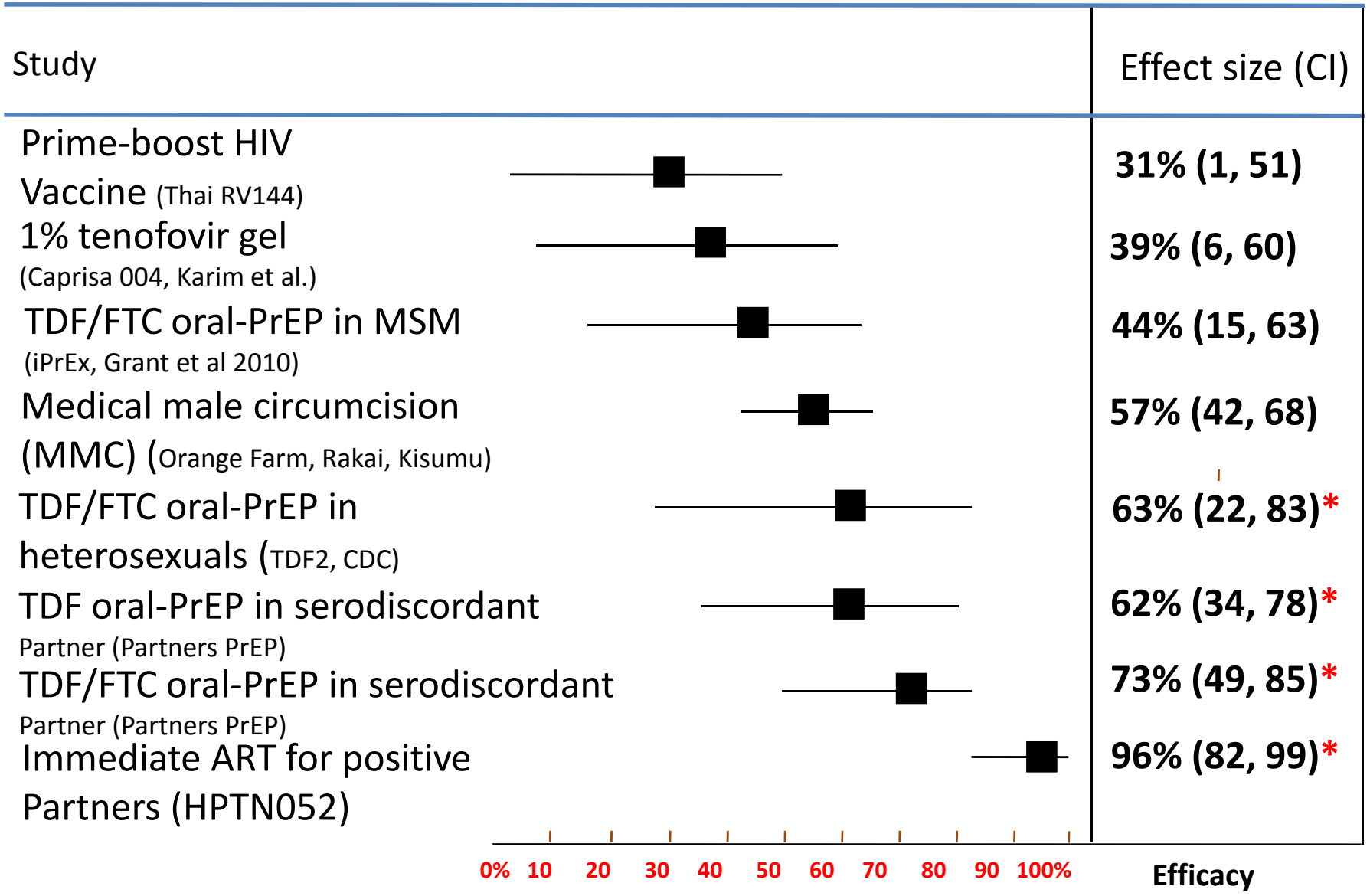
Multi-Purpose Prevention Technologies	
Tenofovir Gel	Gilead
Tenfovir-Levonorgestrel Vaginal Ring	CONRAD
ARV-Hormone Vaginal Ring	IPM/Pop Council
Tenofovir-Acyclovir Vaginal Ring	CONRAD
CV-N Expressing Lacto/Mucocept	Osel
Barrier De i es + ARV	Vario s

Highly active HIV prevention.

A term coined by Prof K Holmes, University of Washington School of Medicine, Seattle, WA, USA.5

From Coates T et al 2008.

New biomedical intervention strategies



*Provisional

Prevention plane is on track to land safely

Not going to need parachutes at all……

Thanks

- Prevention divisions at DTHF
- John Mellors
- Jared Baeten
- Connie Cellum
- Susan Buchbinder
- Bob Grant
- Slim and Quarraisha Kariem
- HVTN, MTN, HPTN,FACTS, iPrEx (OLE).

Desmond Tutu HIV Foundation

Masibambane Ngezandla