

Pre-Exposure Prophylaxis for HIV Prevention: State of the Art, State of the Science, and the Future

Raphael J. Landovitz, MD MSc

Associate Professor of Medicine

UCLA Center for Clinical AIDS Research & Education

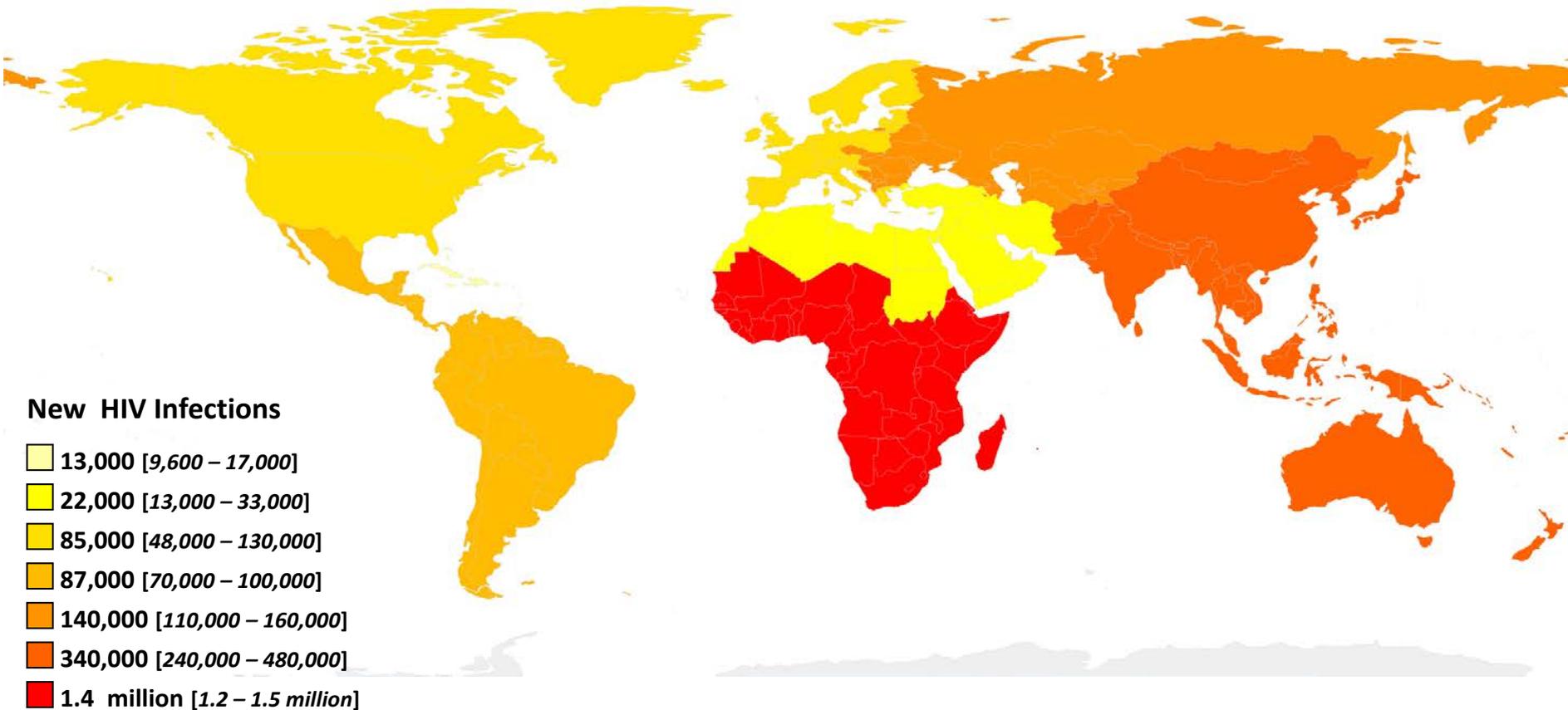
January 19, 2018

Disclosure

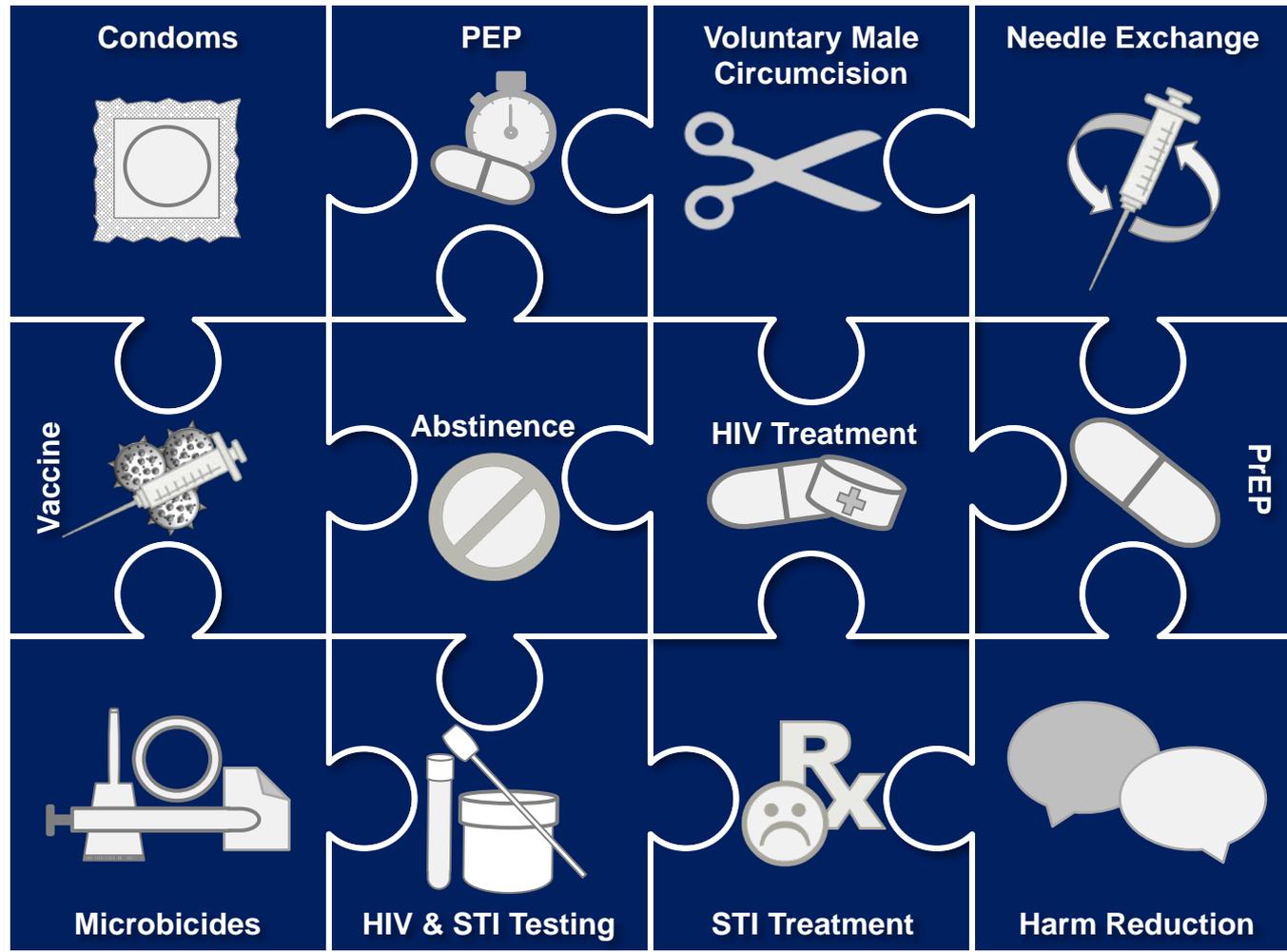
Raphael J. Landovitz has received research grants awarded to his institution from Gilead Sciences, has served as a consultant to Gilead Sciences.

1.8 Million New Infections in 2016

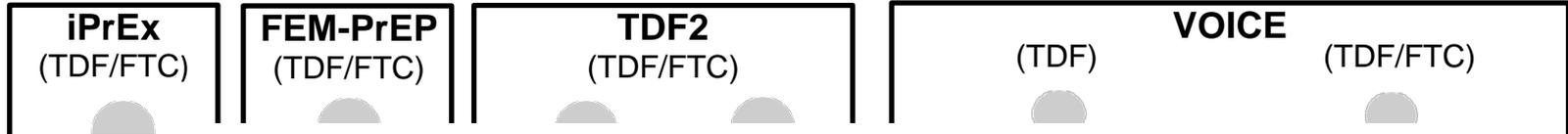
5,000 New Infections per Day



Prevention Modalities



Effectiveness of Daily TDF/FTC in Clinical Trials



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Preexposure Prophylaxis for HIV Infection among African Women

Lut Van Damme, M.D., Amy Corneli, Ph.D., Khatija Ahmed, M.Med., Kawango Agot, Ph.D., Johan Lombaard, M.B., Ch.B., Saidi Kapiga, M.D., Mookho Malahleha, M.B., Ch.B., Fredrick Owino, M.B., Ch.B., Rachel Manongi, M.D., Jacob Onyango, M.A., Lucky Temu, M.D., Modie Constance Monedi, Adv.Dip.Mid., Paul Mak'Oketch, B.Pharm., Mankalimeng Makanda, M.B., Ch.B., Ilse Reblin, B.Soc.Sc., Shumani Elsie Makatu, M.A., Lisa Saylor, B.A., Haddie Kiernan, B.S.N., Stella Kirkendale, M.P.H., Christina Wong, Ph.D., Robert Grant, M.D., Angela Kashuba, Pharm.D., Kavita Nanda, M.D., Justin Mandala, M.D., Katrien Fransen, M.S., Jennifer Deese, M.P.H., Tania Crucitti, Ph.D., Timothy D. Mastro, M.D., and Douglas Taylor, Ph.D., for the FEM-PrEP Study Group*

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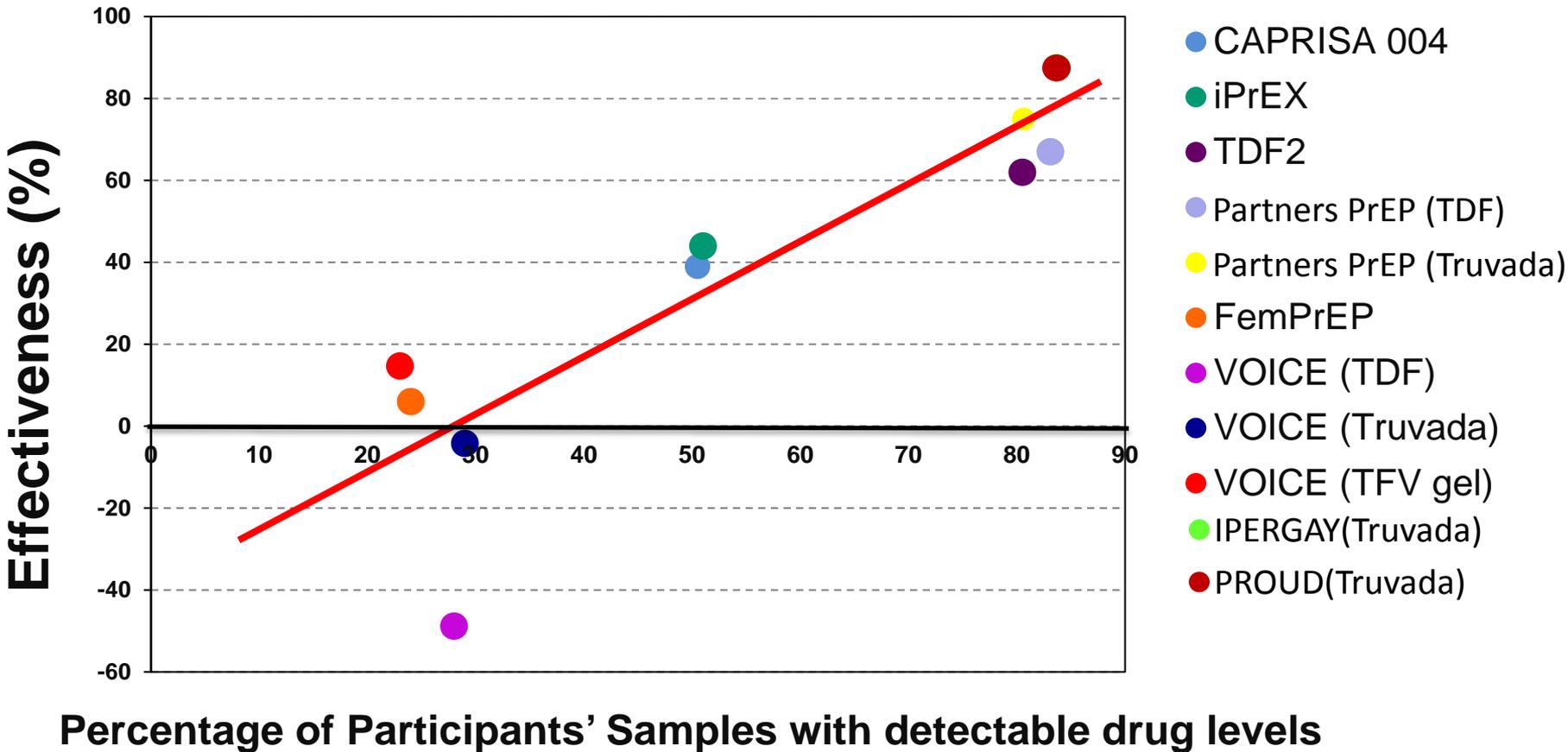
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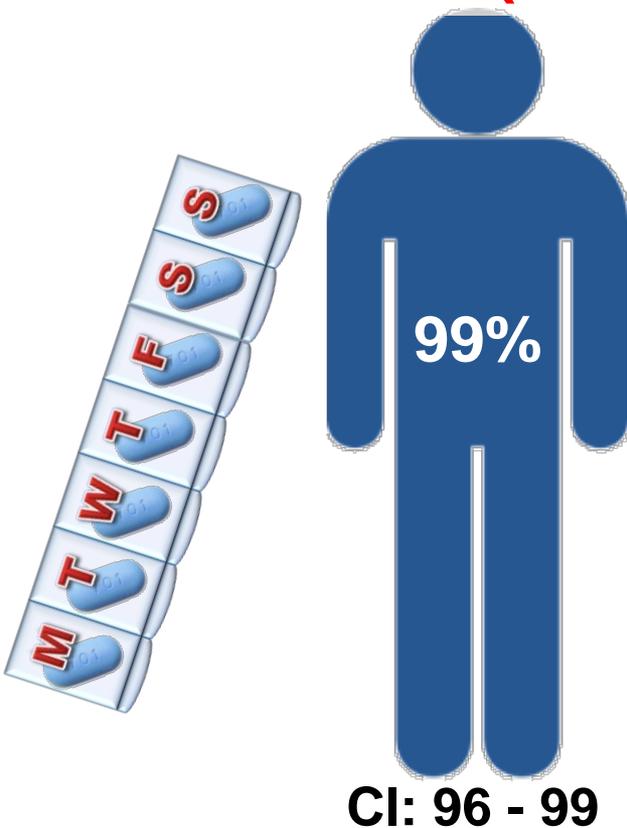
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to, M.Med.,
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Team*

Relationship Between Effectiveness and Adherence in Microbicide & PrEP Trials



Maximizing the Potential Effectiveness

TDF/FTC (7x/week)

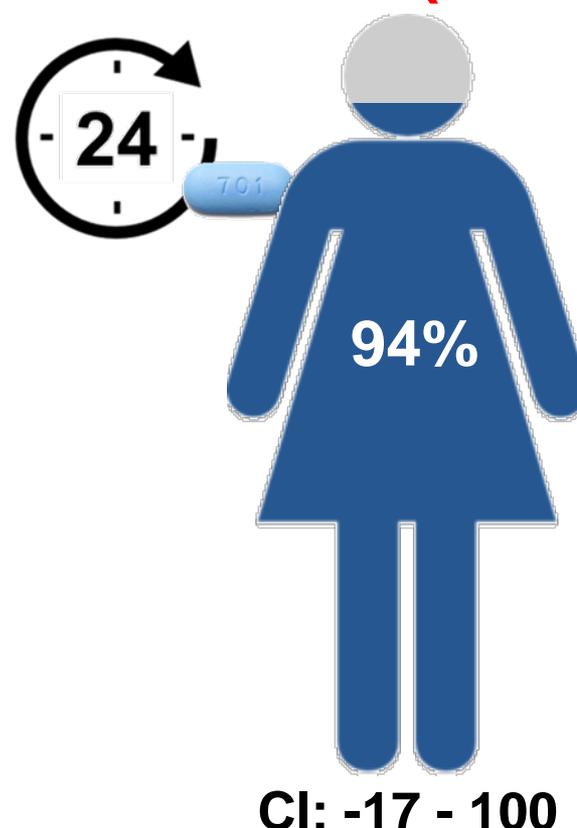


CI: 96 - 99

Some adherence forgiveness with retained protection

Anderson P *et al*, *Sci Transl Med*. 2012.

TDF/FTC (~1x/24^h)



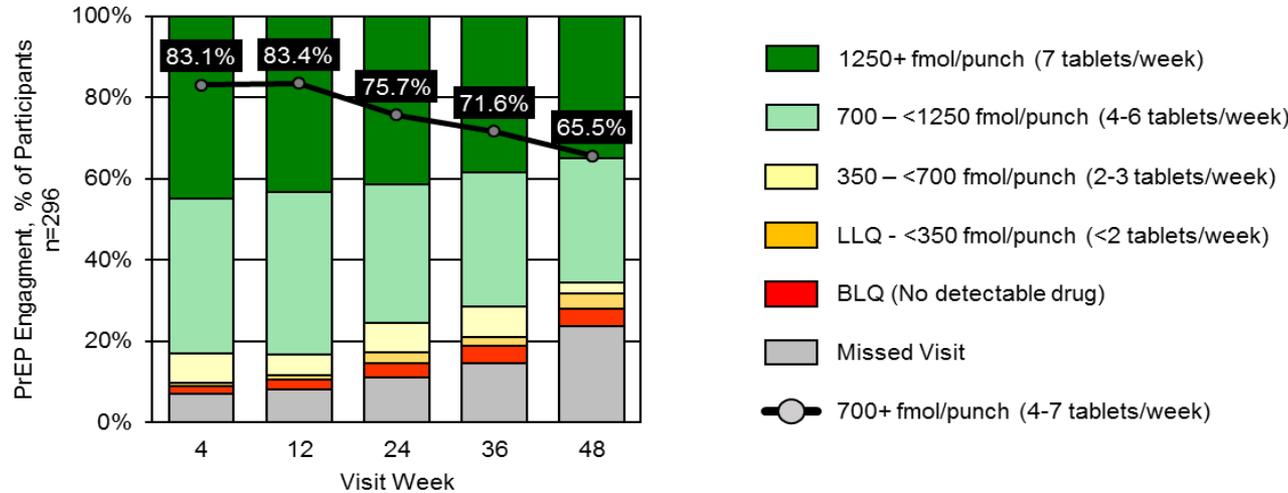
CI: -17 - 100

6-7 doses per week likely required

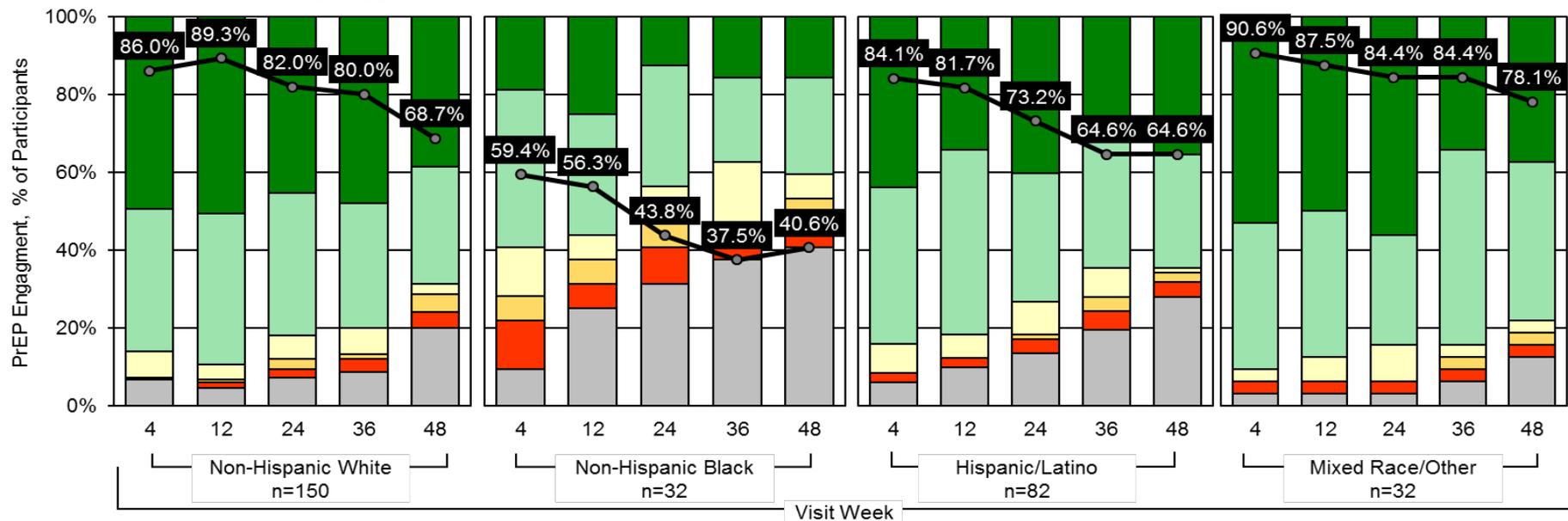
Donnell D *et al*, *JAIDS*. 2014.
Cottrell ML *et al*, *JID*, 2016.

PrEP Demonstration: High Adherence in STD/Community-Based Clinics

A



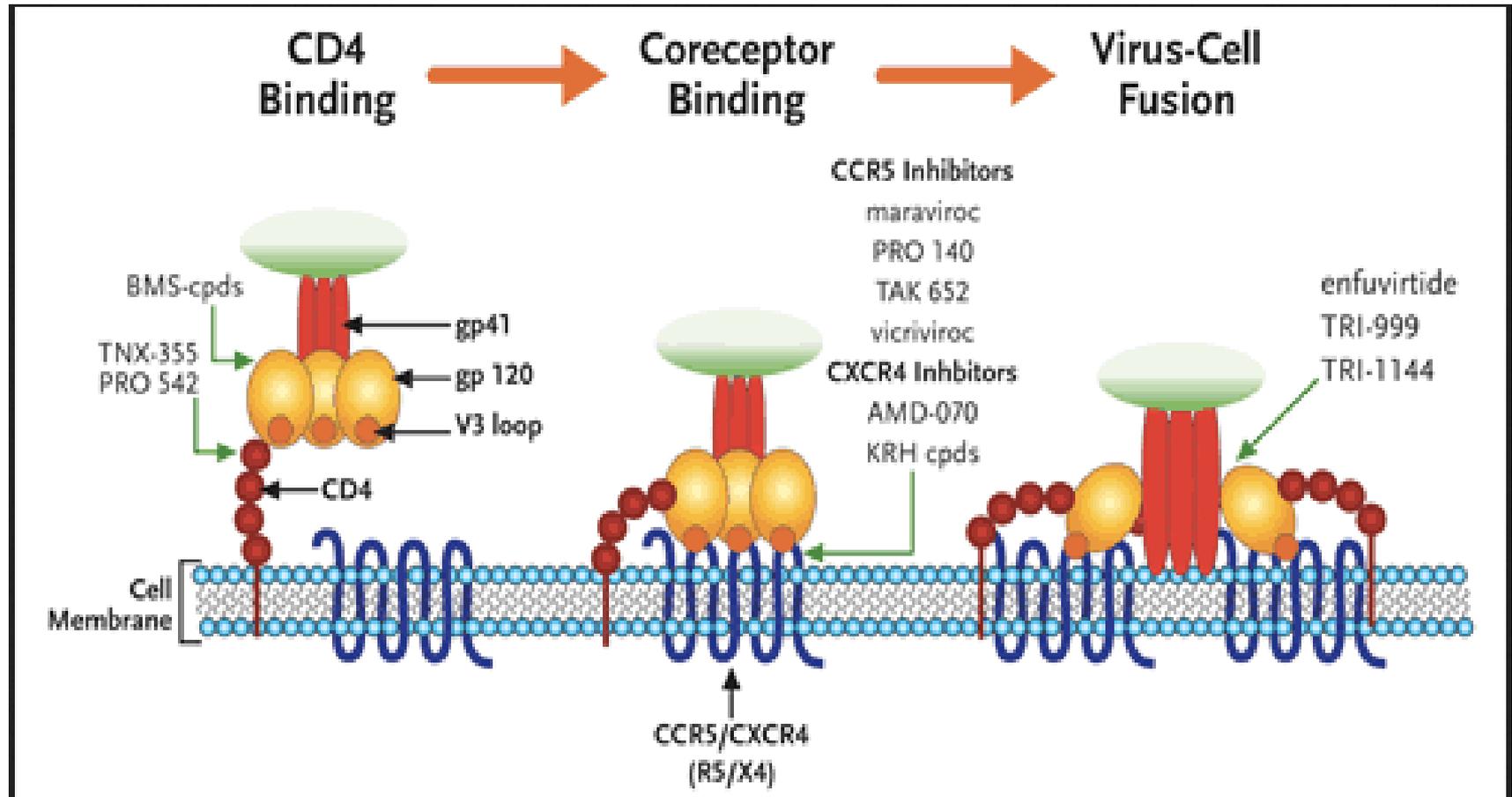
B



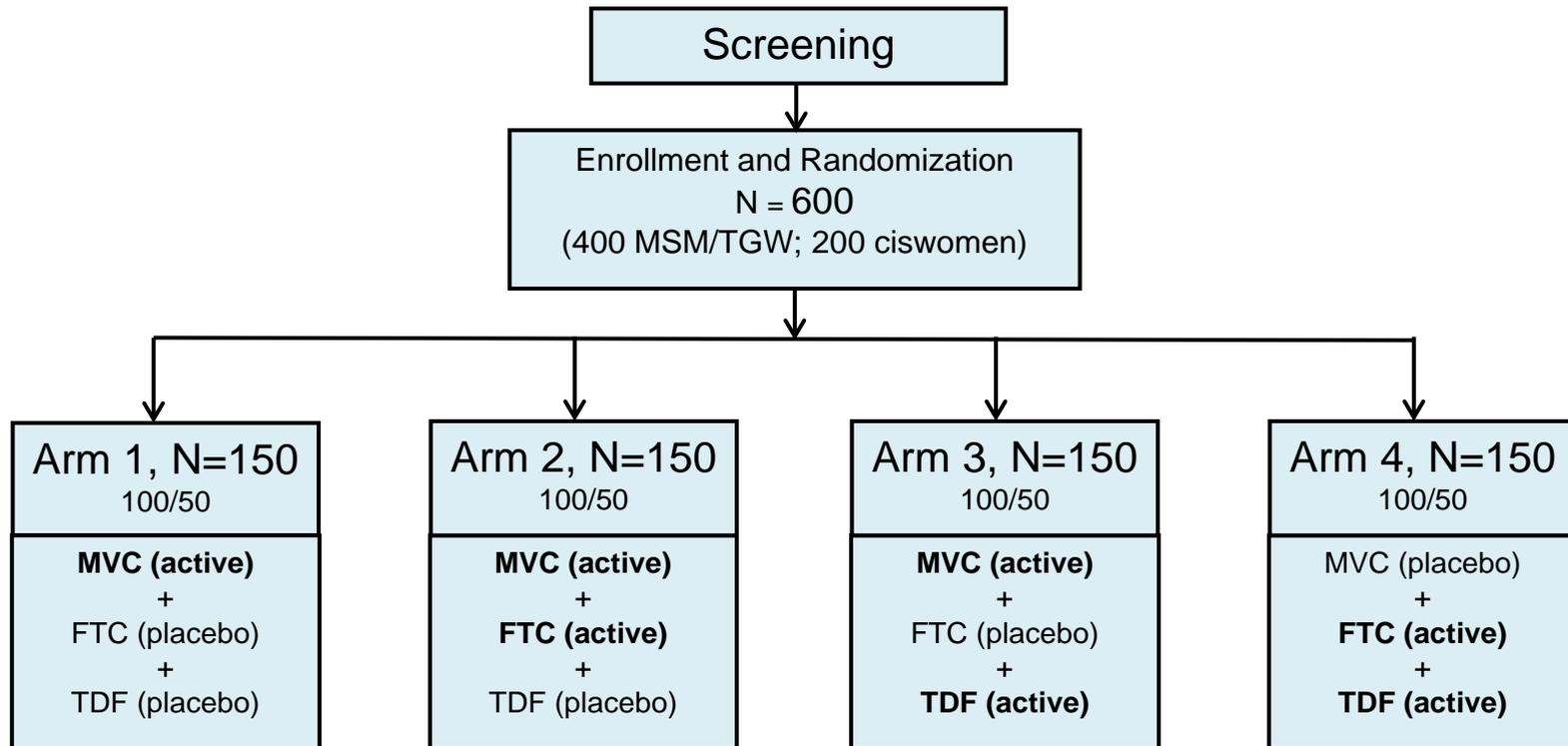
HPTN 069 / ACTG A5305

A phase 2 safety study designed to answer:
Could daily oral maraviroc, a CCR5 receptor
antagonist, be a next-gen PrEP agent for
men and/or women?

Maraviroc – HPTN 069/ACTG A5305



HPTN 069 / ACTG A5305



HPTN 069 / A5305: HIV Infections

- In MSM/TGW Cohort: 5 new HIV infections during the study
- Annual incidence rate 1.4% [95% CI: 0.8%, 2.3%]

#	Demos. (age, race/ethnicity, HIV risk)	Study arm	First reactive HIV+ test (week)	HIV RNA (cps/mL)	CD4 cells (/mm ³)	HIV tropism	Genotypic drug resistance	Plasma drug conc. at seroconversion visit (ng/mL)*
1	20, black MSM	MVC+ TDF	4	122,150	357	R5	none	MVC=0 [†] TFV=0
2	61, Asian MSM	MVC alone	16	981	294	R5	none	MVC=145
3	21, mixed MSM	MVC alone	24	106,240	325	R5	none	MVC=0 [†]
4	35, white MSM	MVC alone	32	13,626	828	R5	none	MVC=6.7
5	36, black MSM	MVC alone	48	52,191	804	R5	none	MVC=0.7

* expected pre-dose steady state MVC = 32 ng/ml

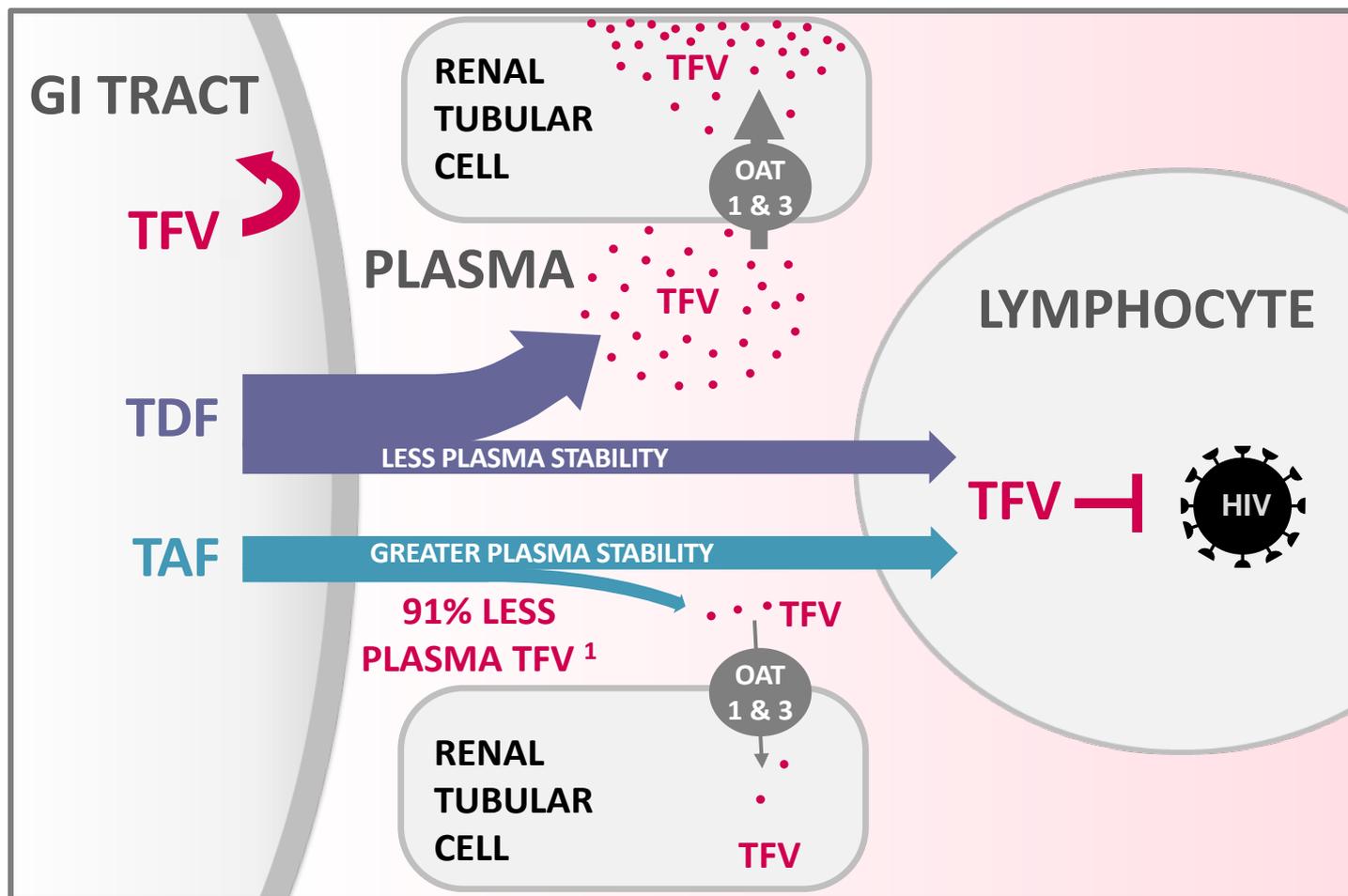
† undetectable plasma drug concentrations at every study visit

Pre-Clinical and Animal Models of TAF for PrEP

Will it be equi-efficacious as
TDF-based PrEP?

Perhaps
Perhaps not

Prodrug Pharmacology of TDF and TAF



TAF 25 mg results in >90% lower TFV plasma levels

Sax P, et al. Lancet 2015

Wohl D, et al. CROI 2016. Boston, MA. #681

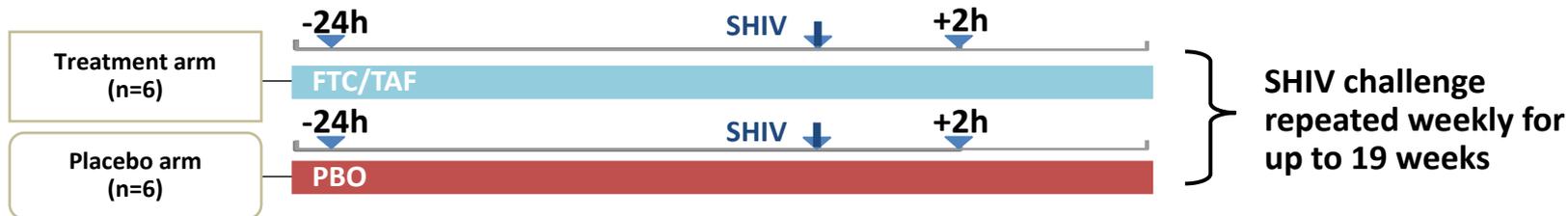
OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Concentrations of TFV and TFV-DP in Female Mucosal Tissues After Single Dose of TAF

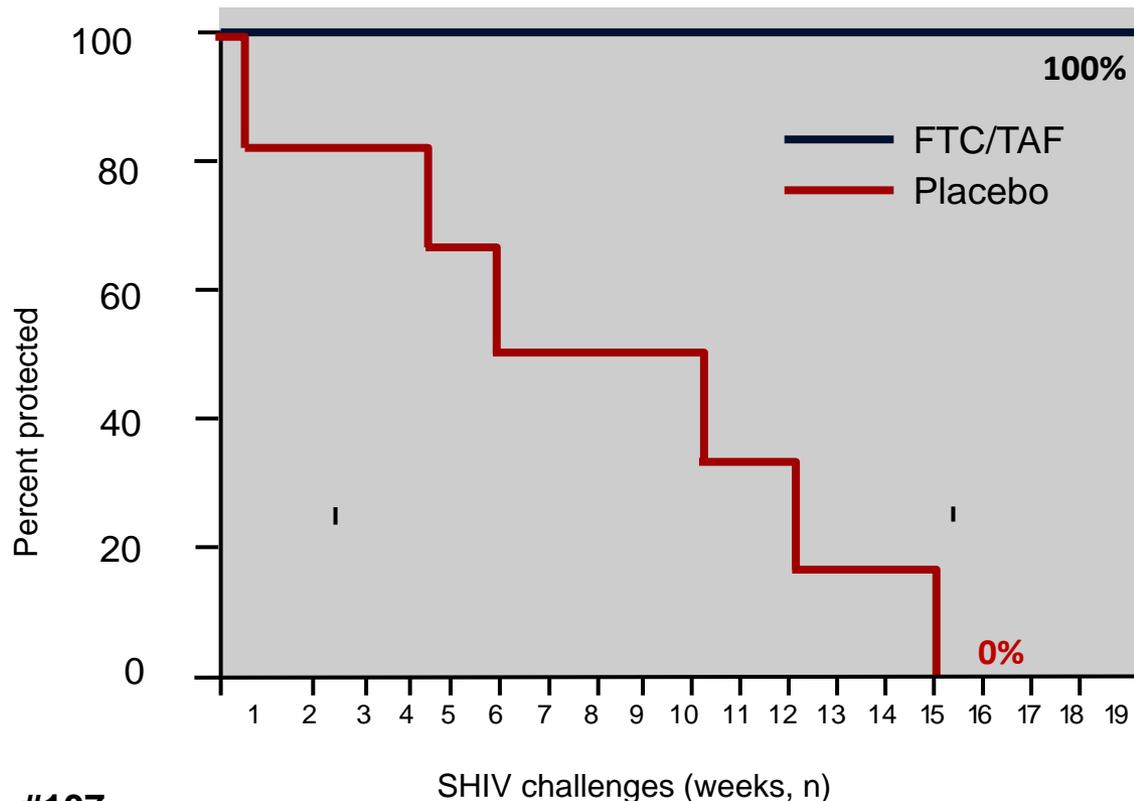
	TAF 25mg, Tissue Samples BLQ, %			TDF 300mg Tissue Samples BLQ, %		
	TFV	TFV-DP	<i>n</i>	TFV	TFV-DP	<i>n</i>
CVF	58	n/a	40	23	n/a	95
Genital Tissue	6	75	16	0	25	16
Rectal Tissue	0	63	8	0	0	8

BLQ=below the level of quantification. 0=all the samples had detectable TFV (none were BLQ)

TAF/FTC for PrEP in SHIV-Challenged Macaques



- TAF/FTC prevents rectal SHIV infection in macaques to a degree similar to that previously found with TDF/FTC but with a substantially reduced TFV dose¹
 - TAF/FTC protected 100% of macaques (N=6) challenged with SHIV in a similar, pre-clinical trial²



1. Massud I, et al. CROI 2016. Boston, MA. #107
2. Heneine W, et al. CROI 2006. Denver, CO. #32LB

HPTN 076

A phase 2 safety study designed to answer:
Could injectable rilpivirine, a FDA-approved
NNRTI in its oral formulation, be a useful
sustained-release PrEP agent?



HPTN 076: Safety and acceptability of injectable rilpivirine(TMC278 LA) for PrEP

136 HIV-uninfected, women ages 18-45 years

WEEKS

4



52



76



ARM 1
N = 91

**Daily oral
TMC278**

**Six injections of TMC278 LA
1200 mg every 8 weeks**

ARM 2
N = 45

**Daily oral
placebo**

**Six injections of TMC278 LA
placebo every 8 weeks**

**Follow-up phase
(tail phase)**

HPTN 076: Phase 2 Safety Results

- Safe and well-tolerated
- Acceptable to women
- Cold chain required
- Unclear interest of sponsor in pursuing PrEP indications
- Concern about cross-resistance to agents used as first line in LMIC

CABOTEGRAVIR

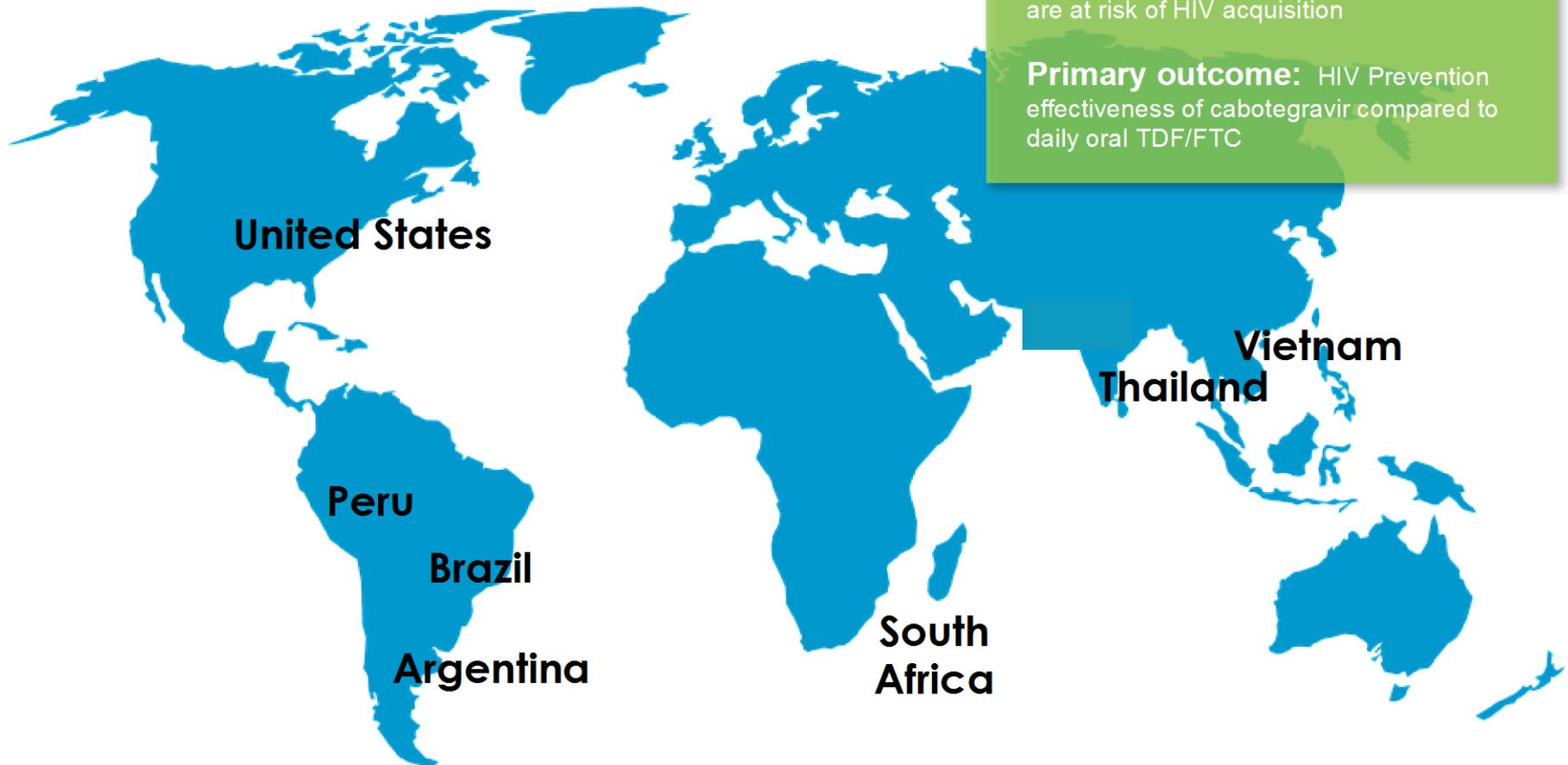
Formerly known as GSK1265744
Or "744"

HPTN 083

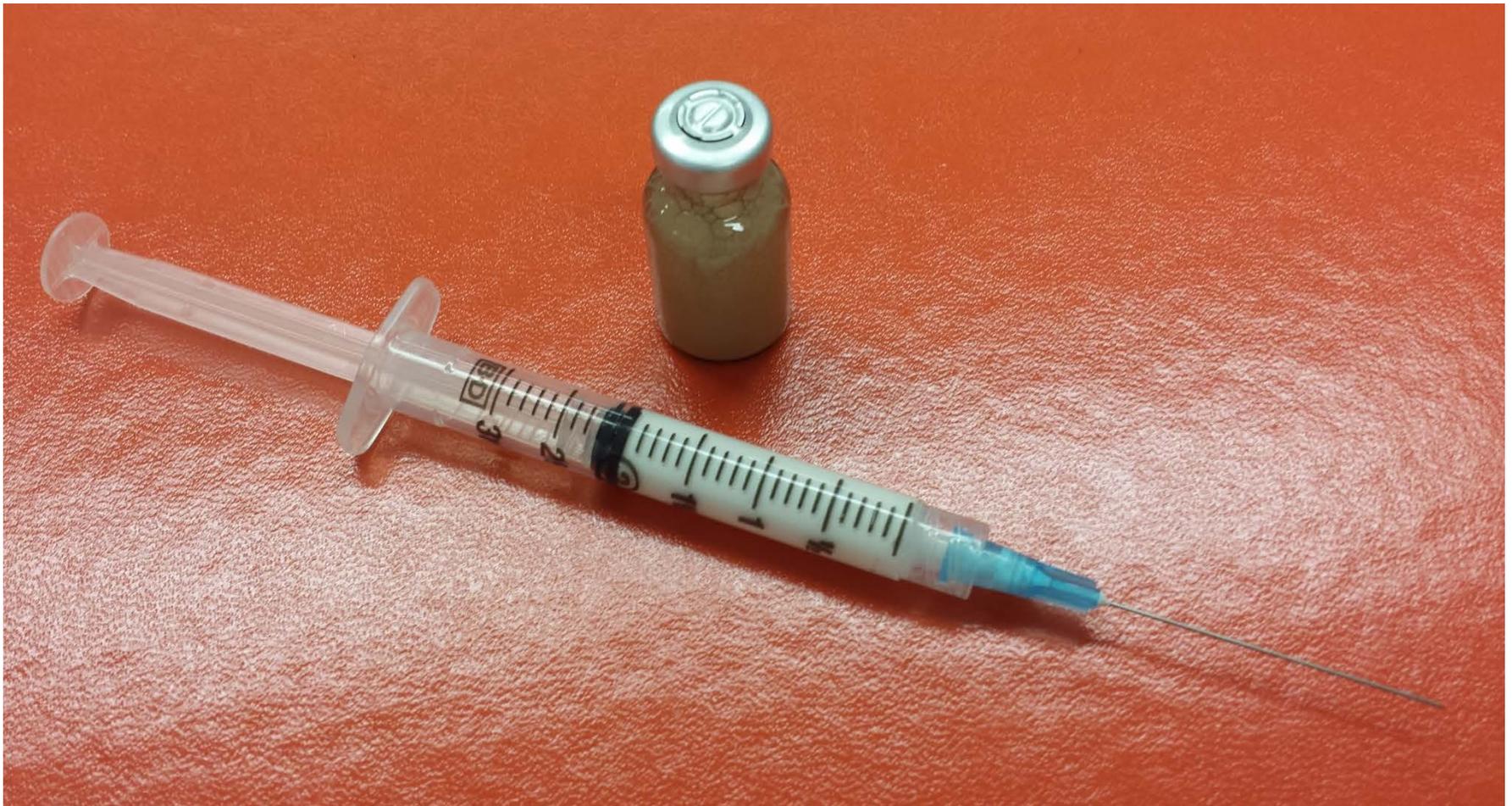
A Phase 2b/3 Double Blind Safety and Efficacy Study of Injectable Cabotegravir Compared to Daily Oral TDF/FTC, for Pre-Exposure Prophylaxis in HIV-Uninfected Cisgender Men and Transgender Women who have Sex with Men

Target enrollment: 4,500 HIV-uninfected cisgender men and transgender women who have sex with men and who are at risk of HIV acquisition

Primary outcome: HIV Prevention effectiveness of cabotegravir compared to daily oral TDF/FTC



Cabotegravir



Cabotegravir and Intralipid





AMP
STUDY

The logo consists of a stylized bar chart with ten vertical bars of varying heights, each composed of horizontal segments in shades of purple and green. Below the chart, the letters 'AMP' are written in a large, bold, purple font with a green outline. The word 'STUDY' is written below 'AMP' in a smaller, green, sans-serif font.

Slides adapted from Shelly Karuna/HVTN and Phil Andrew/HPTN

Study Schema for The



Study



**MSM & TG in the
Americas**



**Women in
sub-Saharan Africa**

REGIMEN

TOTAL

REGIMEN	MSM & TG in the Americas	Women in sub-Saharan Africa	TOTAL	
VRC01 10 mg/kg	900	500	1300	10 infusions total & Infusions every 8 weeks
VRC01 30 mg/kg	900	500	1300	
Control	900	500	1300	
Total	2700	1500	4200	Study duration: ~22 months

Subcutaneous PrEP Implants

Modeled After Implanon/Nexplanon Contraception



- Simple insertion AND removal
- Long-acting (months to years)
- PrEP + contraception?
- Current development:
 - TAF, CAB, EFdA (MK-8591)

Topical agents for PrEP: As Good as Systemic PrEP?

Commentary

HIV Prevention: The Need for Methods Women Can Use

ZENA A. STEIN, MA, MB, BCH

“...a less efficacious barrier (one that fails more often than another on each sexual encounter), if frequently used, might serve the public health as well or better than a more efficacious but less frequently used barrier, and **could in the end play an important role in preventing transmission at the population level.**”

(Am J Pub Health, 1990)

Thank you!



California HIV/AIDS
Research Program

