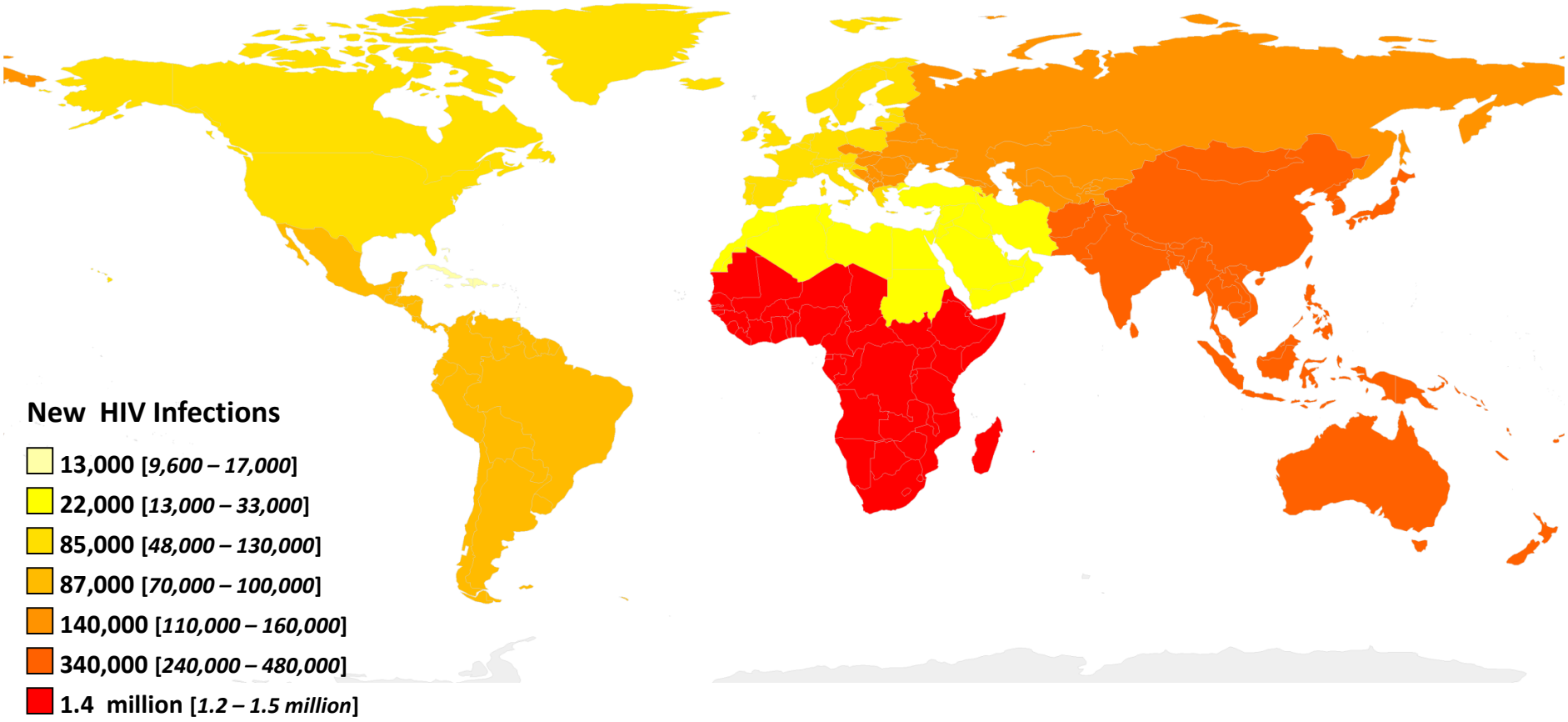
Biomedical Prevention: Where are we now? Where are we going?

Raphael J. Landovitz, MD MSc
Associate Professor of Medicine
UCLA Center for Clinical AIDS Research & Education
May 8, 2017

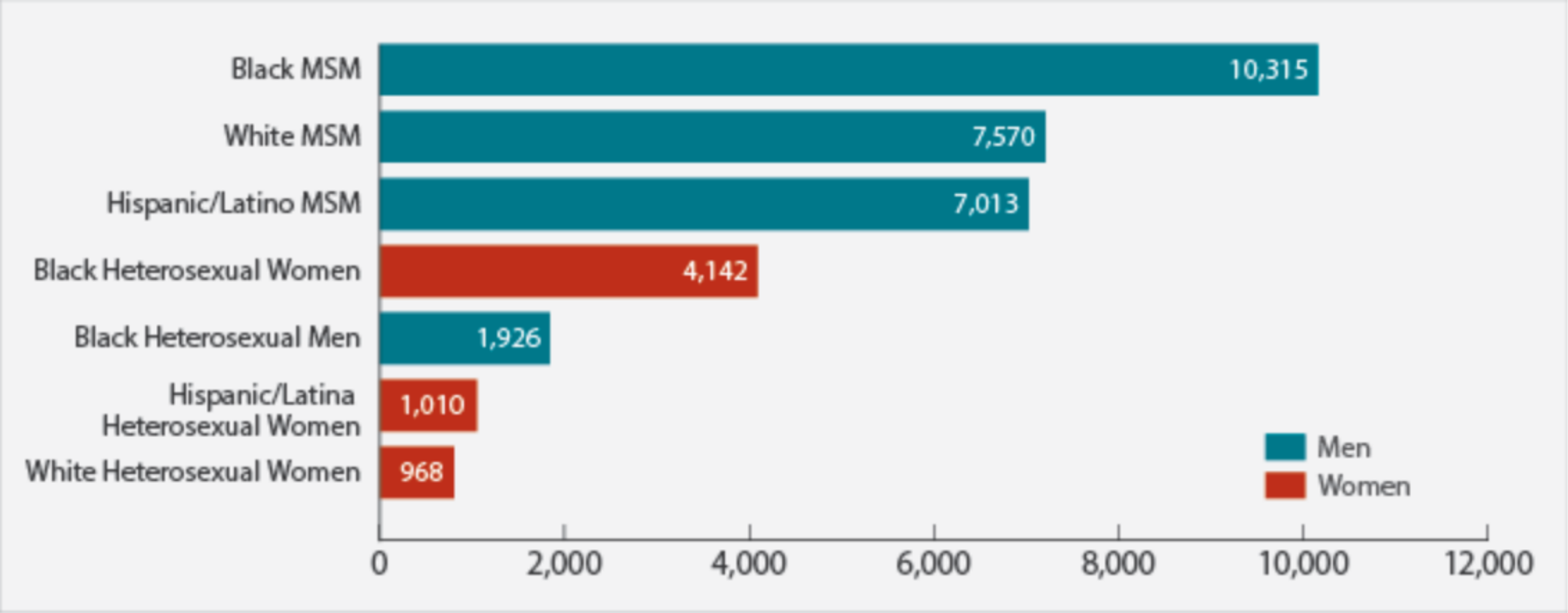
2.1 Million New Infections in 2015
5,600 New Infections per Day



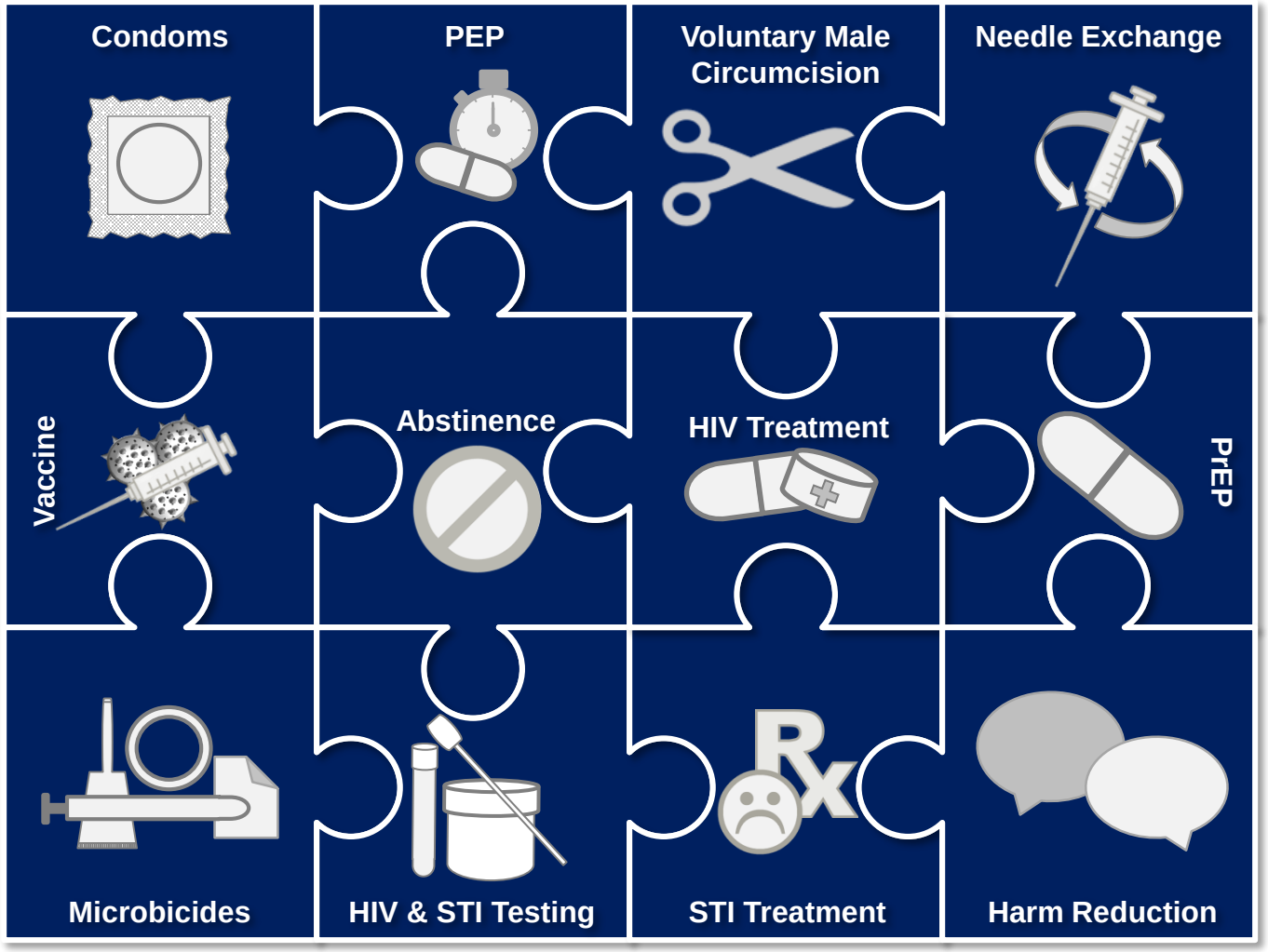
UNAIDS. Fact Sheet: 2015 Statistics; 2016.

But first, some (relatively) good news

Overall In 2015, new US diagnoses were down 19%



Prevention Modalities



Pre-Exposure Prophylaxis (PrEP)

- PrEP (Pre-exposure prophylaxis)
  - Strategy of administering ART to uninfected, at-risk individuals
  - Think of: Malaria prevention, birth control pill
- Tenofovir Disoproxil Fumarate (TDF) +/- Emtricitabine (FTC)
  - Safe and well-tolerated
  - Daily dosing of co-formulated tablet supported by PK/PD
  - Relatively high barrier to resistance
  - Rapid concentration in genital/rectal tissues
- Nonhuman Primate Models
  - Suggest TDF + FTC offers better protection than TDF alone
  - Effective protection from IV, rectal, and vaginal challenges
  - Lower concentrations in CV vs. rectal compartments with oral
  - Intermittent dosing may be possible

Garcia-Lerma JG *et al.* PLoS Med. 2008.
Hendrix CW *et al.* CROI. 2013.
Von Rompay KK *et al.* JID. 2006.
Lehman DA *et al.* JID. 2006.
Von Rompay KK *et al.* JID. 2012.
Grant RM *et al.* JID. 2015.
Subbarao S *et al* JID. 2006.
Garcia-Lerma JG *et al.* Transl Med. 2010.

Effectiveness of Daily TDF/FTC in Clinical Trials

iPrEx	FEM-PrEP	TDF2	VOICE	
(TDF/FTC)	(TDF/FTC)	(TDF/FTC)	(TDF)	(TDF/FTC)

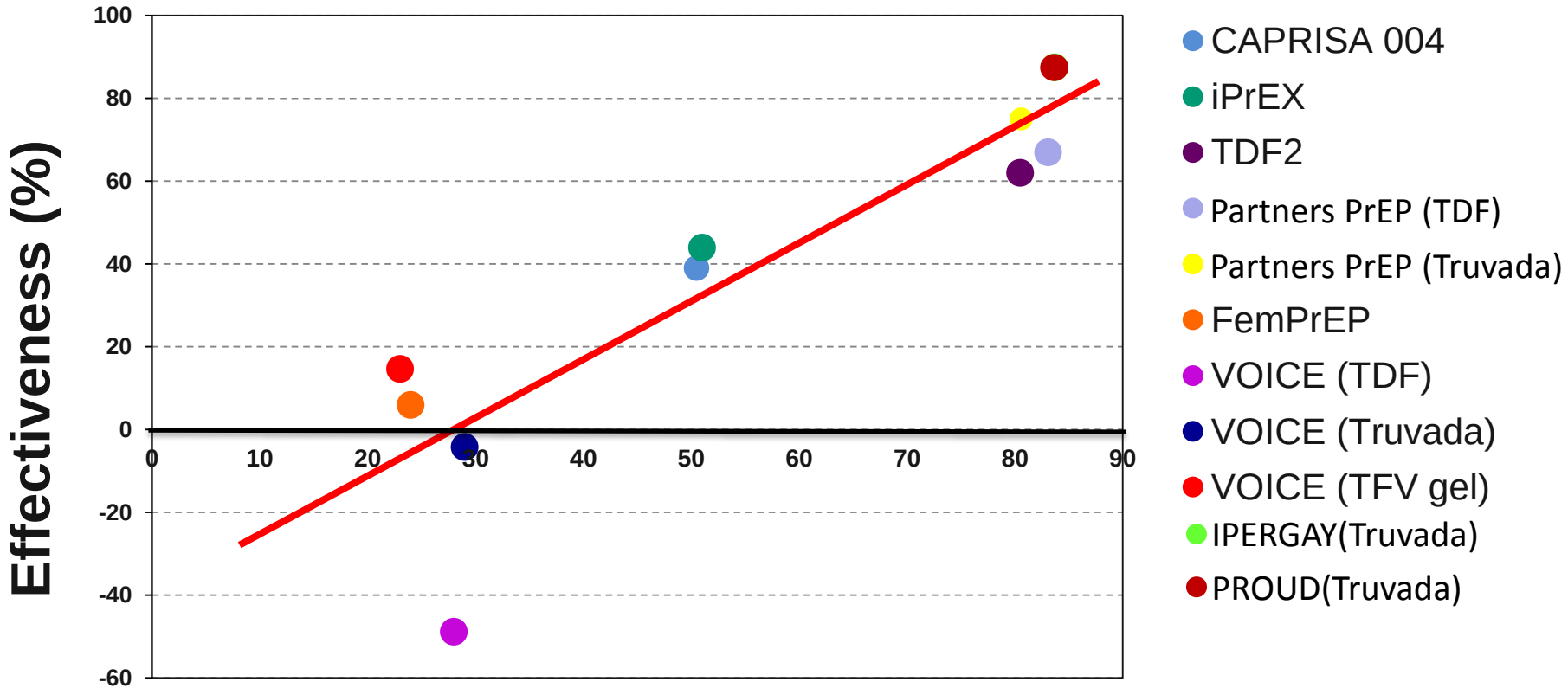
The NEW ENGLAND JOURNAL of MEDICINE

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*

Relationship Between Effectiveness and Adherence in Microbicide & PrEP Trials

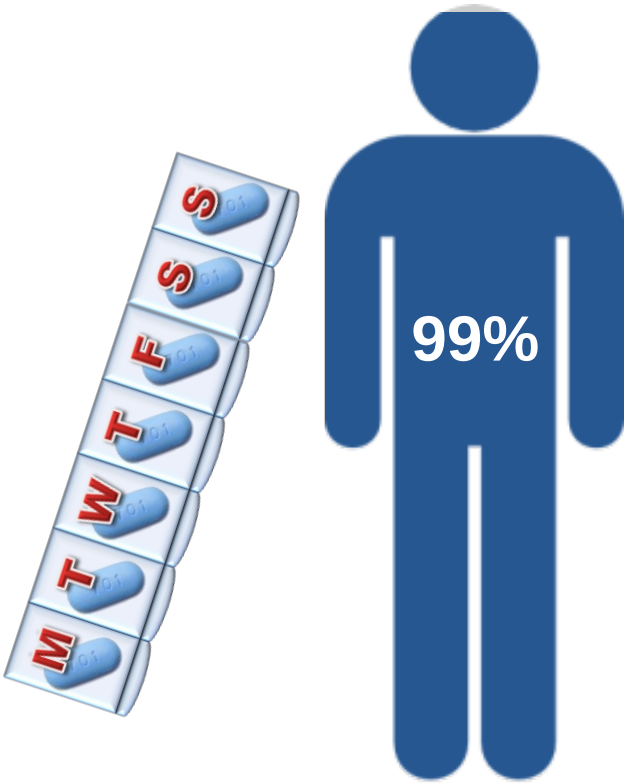


Percentage of Participants' Samples with detectable drug levels

SS Abdool Karim, personal communication

Maximizing the Potential Effectiveness

TDF/FTC (7x/week)

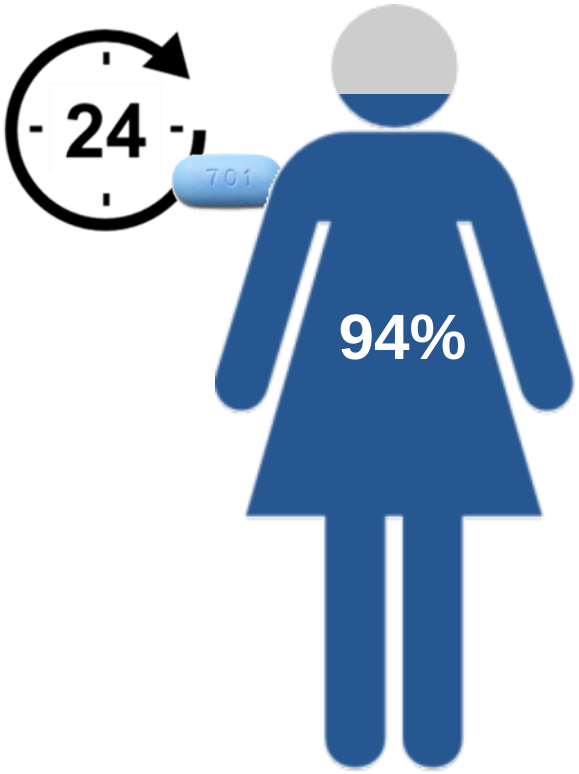


CI: 96 - 99

Some adherence forgiveness with retained protection

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

TDF/FTC (~1x/24°)

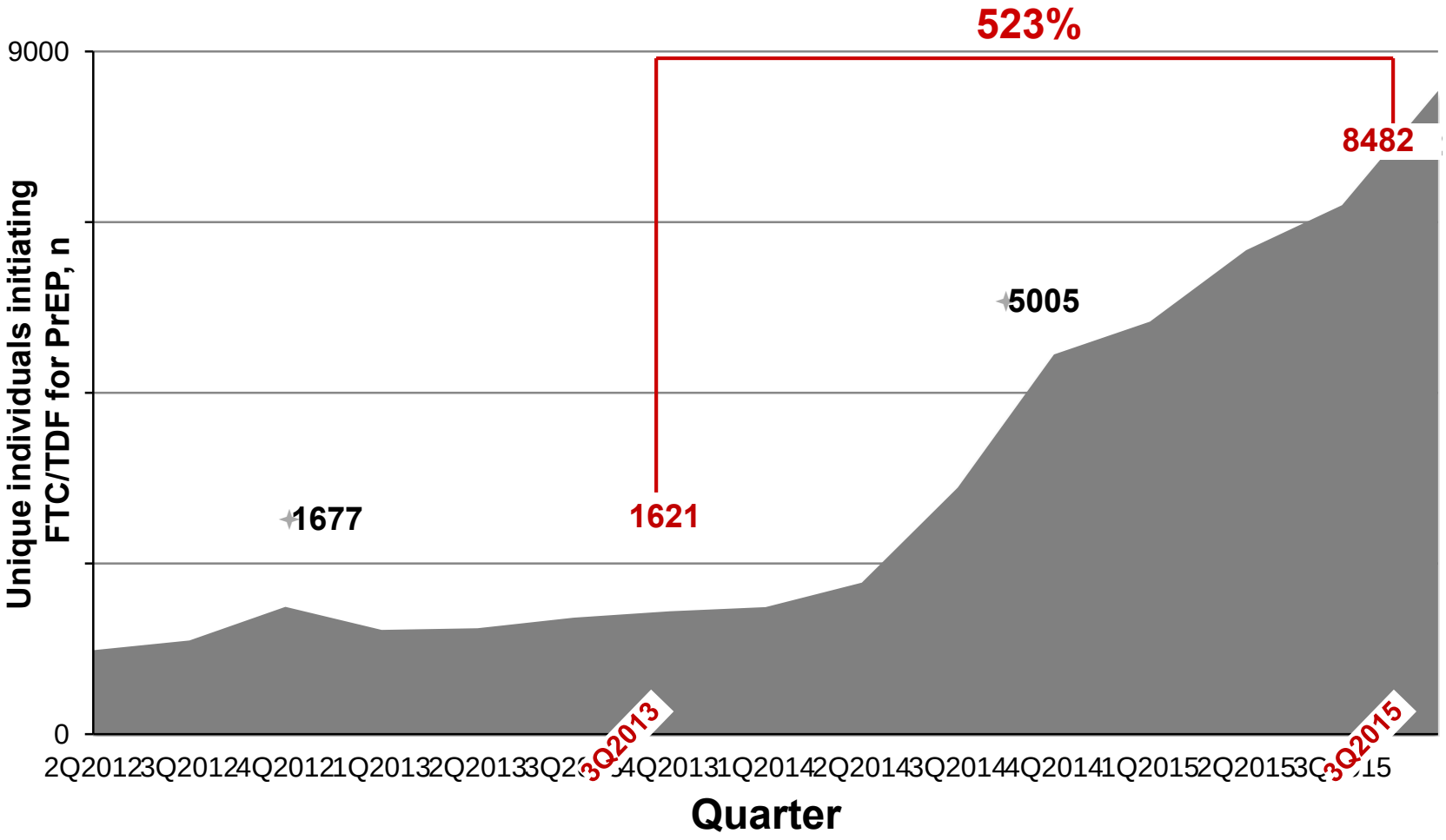


CI: -17 - 100

6-7 doses per week likely required

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

Total Incidence and Growth Trend of FTC/TDF for PrEP



49,148 Unique individuals initiated FTC/TDF for PrEP in the US 2Q2012 – 3Q2015

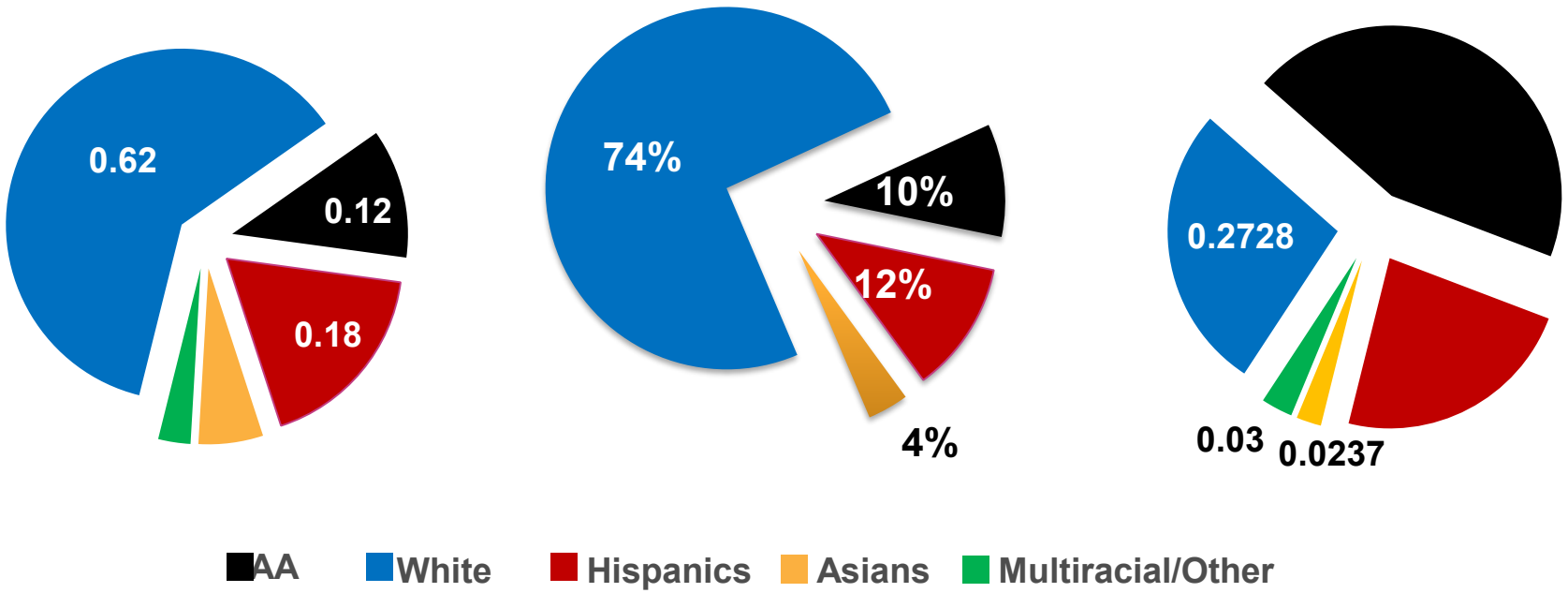
Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651

FTC/TDF for PrEP Utilization Compared With Population and New HIV Infections

Estimated Population Distribution by Race/Ethnicity, 2014, US[a]

Total FTC/TDF for PrEP Utilization by Race/Ethnicity, Sept 2015, US[b]

Estimated New HIV Infections, 2014, US[c]



FTC/TDF for PrEP use among AA and Hispanics is low relative to the rate of new HIV infections

a. https://www.census.gov/quickfacts/table/PST045215/00

b. These data represent 43.7% (n=21,463) of unique individuals who have started TVD for PrEP from 2012-3Q2015.

c. Other indicates American Indian or Alaska Native, and Native Hawaiian or other Pacific Islander. CDC. *HIV Surveillance Report, 2014*

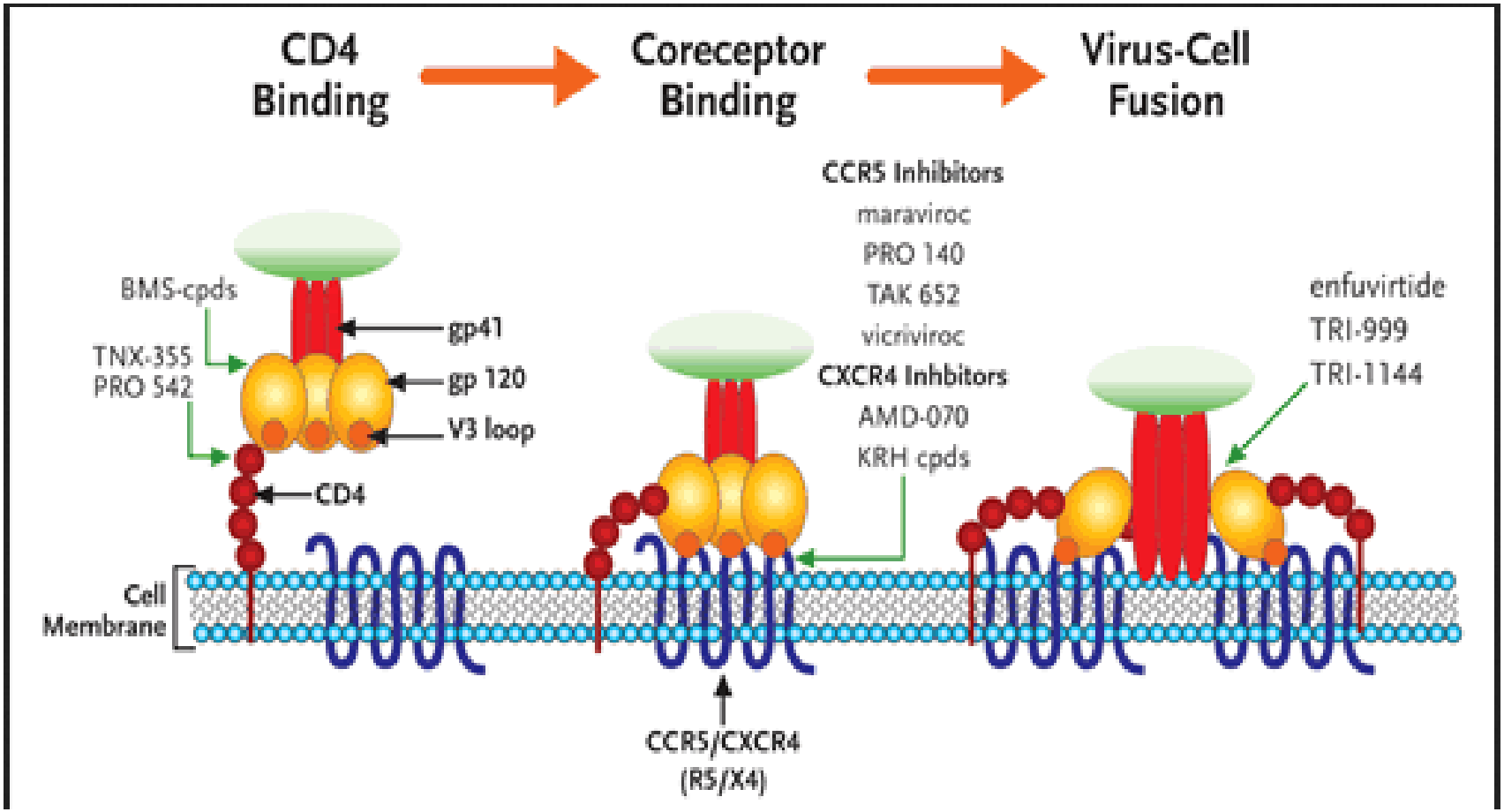
Bush S, et al. ASM/ICAAC 2016; Boston, MA. #2651

HPTN 069 / ACTG A5305

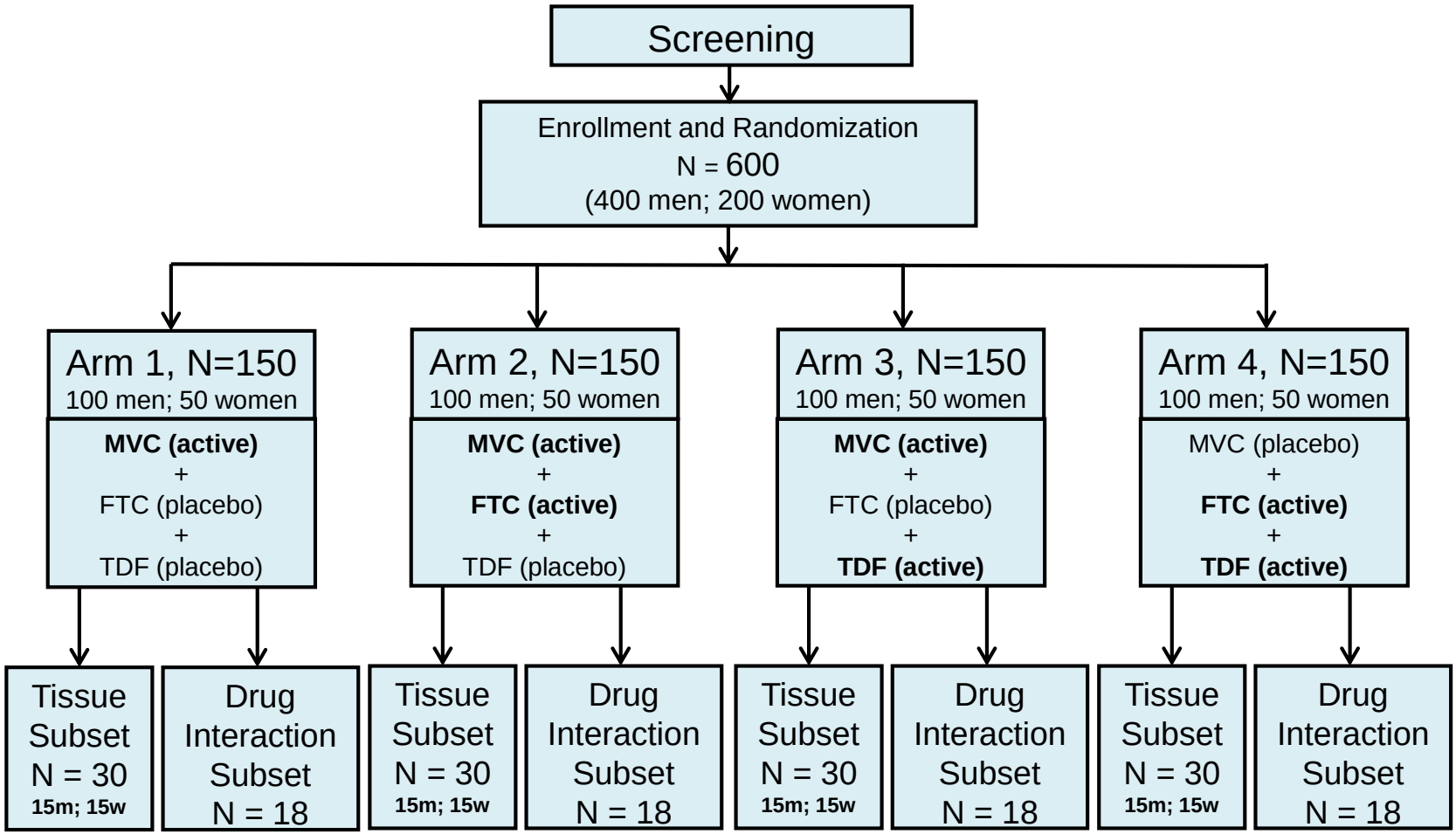
A phase 2 safety study designed to answer:

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



NEXT PrEP
AN HPTN/ACTG STUDY

HPTN 069 / A5305: HIV Infections

- 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 trop-ism	Geno-typic drug resis-tance	Plasma drug conc. at serocon-version 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

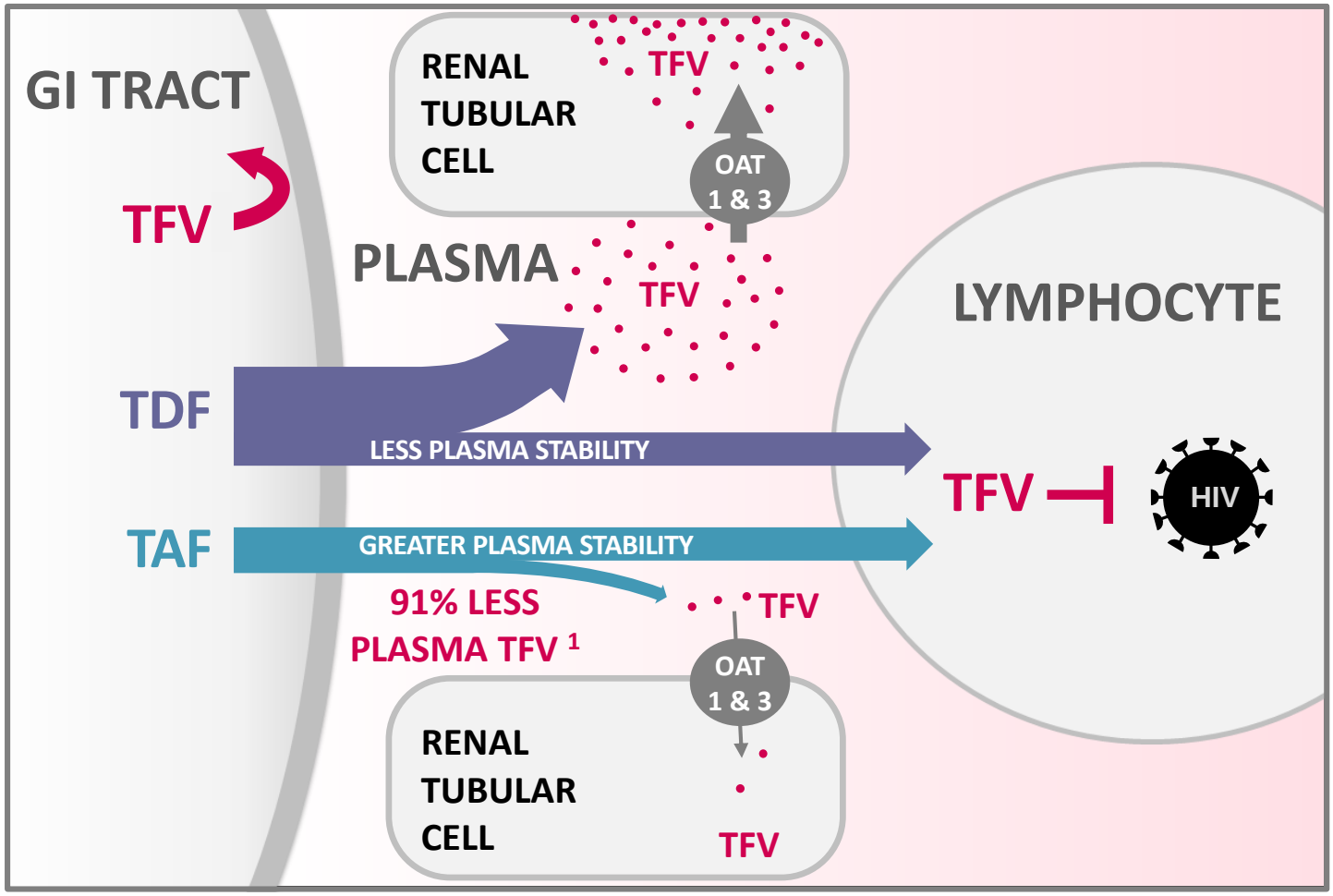
Pre-Clinical and Animal Models of TAF for PrEP

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.

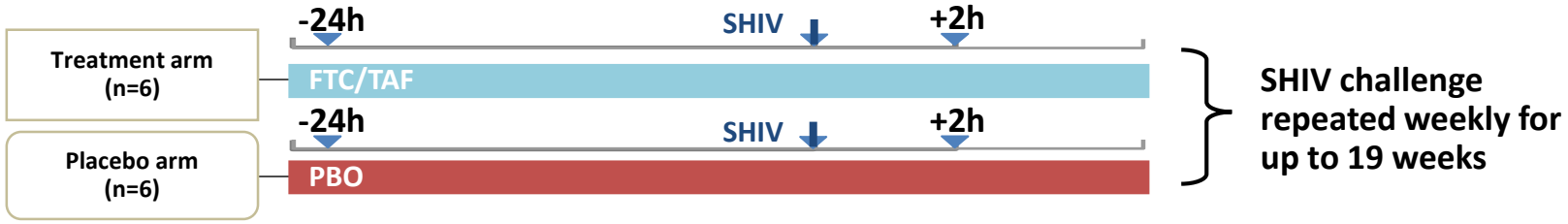
Concentrations of TFV and TFV-DP in Female Mucosal Tissues After Single Dose of TAF

	TAF 25mg, Tissue Samples BLQ, %		*n*	TDF 300mg Tissue Samples BLQ, %		*n*
	TFV	TFV-DP		TFV	TFV-DP	
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

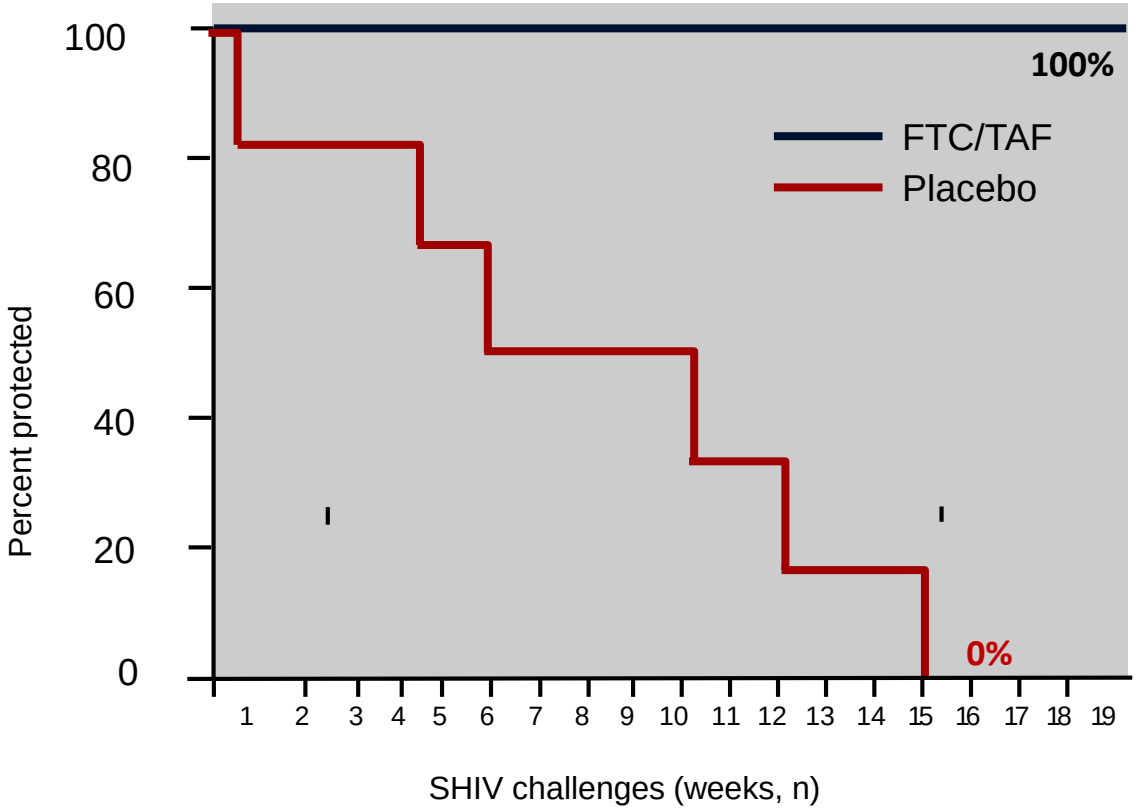
BLQ=below the level of quantification. 0=all the samples had detectable TFV (none were BLQ)

Garrett K, et al. CROI 2016. Boston, MA. #102LB

F/TAF for PrEP in SHIV-Challenged Macaques



- F/TAF prevents rectal SHIV infection in macaques to a degree similar to that previously found with F/TDF but with a substantially reduced TFV dose[1]
  - F/TAF protected 100% of macaques (N=6) challenged with SHIV in a similar, pre-clinical trial[2]



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

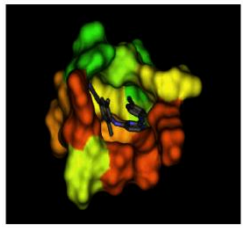
RILPIVIRINE: HPTN 076

A phase 2 safety study designed to answer:

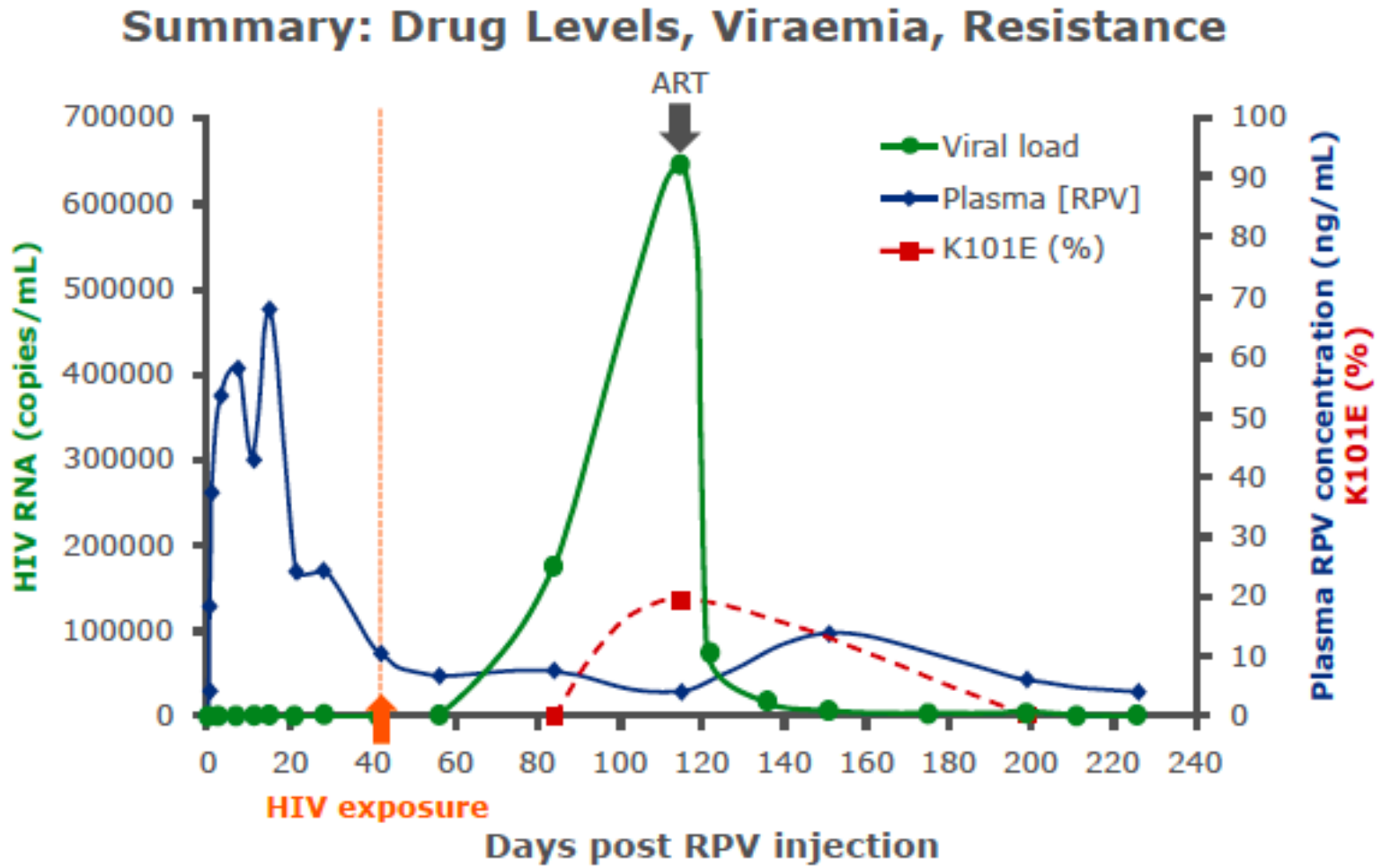
Could injectable rilpivirine, a FDA-approved NNRTI in its oral formulation, be a useful sustained-release PrEP agent?

Long Acting Rilpivirine (TMC278) HPTN 076: Phase 2 Safety

- TMC278 LA is a novel poloxamer 338-containing formulation of TMC278. TMC278 LA is long-acting suspension and well-suited for delivery via IM injection
- HPTN 076 enrolling at 4 sites, low-risk HIV-uninfected women (NY, NJ, Zim, SA)
- Fully enrolled, Data available 2017



SSAT040: Seroconversion Event During Washout of 300 mg



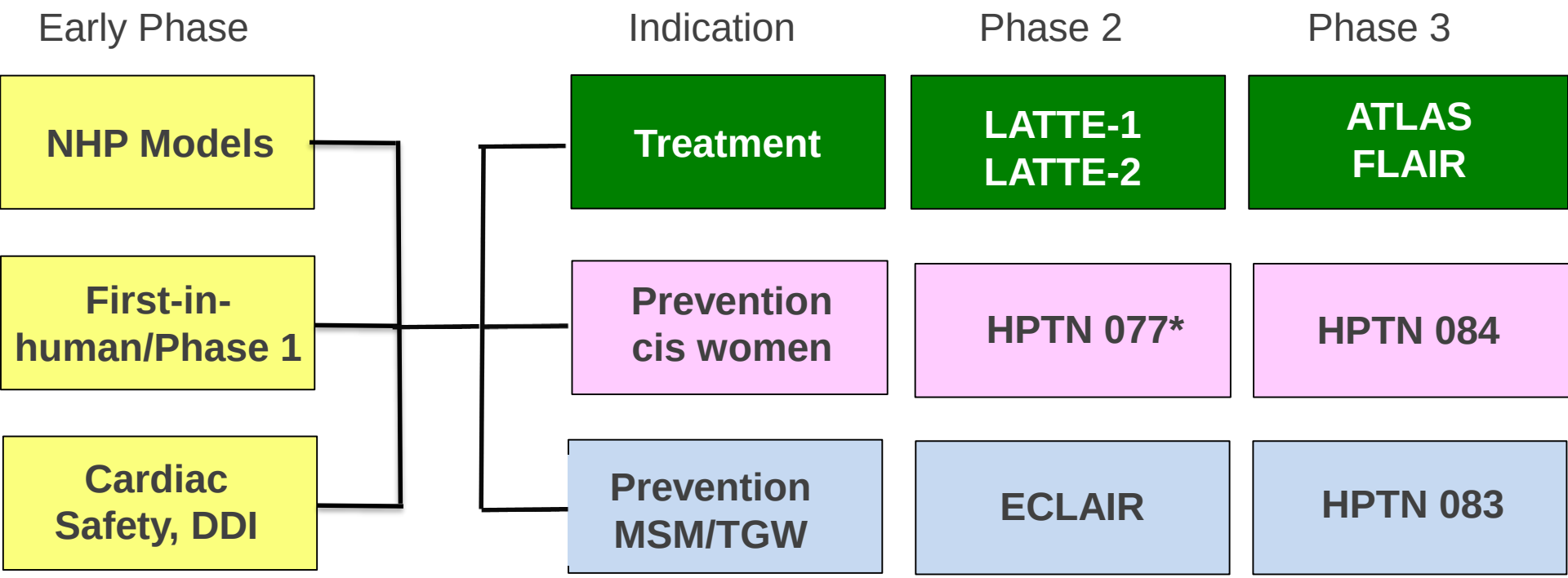
ART = antiretroviral therapy

Penrose K, et al. HIVR4P 2014. Abstract OA27.01

CABOTEGRAVIR

Formerly known as GSK1265744
Or “744”

Cabotegravir (GSK 1265744) development



*INCLUDES BOTH MEN AND WOMEN

HPTN 083

HPTN
HIV Prevention
Trials Network

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

ClinicalTrials.gov Identifier: NCT02720094

Immunotherapies: VRC01

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

The AMP Study (HVTN 704/HPTN 085)

AMP is the first trial to assess if antibodies can be used to prevent HIV infection, similar to how antibodies are used to prevent other infectious diseases.

AMP Study Research Sites

Reading the Tea Leaves: My Top 10 List of Things to Watch

1. Long Acting Injectables
2. Implants
3. Weekly/Monthly Tablets
4. Subcutaneous broadly-neutralizing antibodies
5. Gels, Films, and Threads for Women and Men
6. Combination rings for women/girls
7. Point of care viral load testing
8. Point of care STD testing
9. Point of care drug-level testing
10. It's no longer "Test and Treat" – from NOW it's "Test and START" (as in "immediately. Same day as diagnosis.")

Conclusions

- **We did not stop with drug development when we had AZT for HIV treatment**
  - **We have only experienced "first generation PrEP" to date**
  - **The many exciting pharmaco-chemical and bio-engineering/delivery opportunities are being investigated**
- **We need better insights into how to market, equally (appropriately) deploy, and scale up these interventions**

Thank you, Funders

Thank you! Questions?

rlandovitz@mednet.ucla.edu