

CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS



Treatment as Prevention
and Pre-Exposure Prophylaxis

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Royal Garden Hotel, London

Sponsored by:

IATAC
INTERNATIONAL ASSOCIATION
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In partnership with:

British HIV Association
BHIVA

PrEP: Setting the Stage

**Kenneth Mayer, MD
Fenway Health**

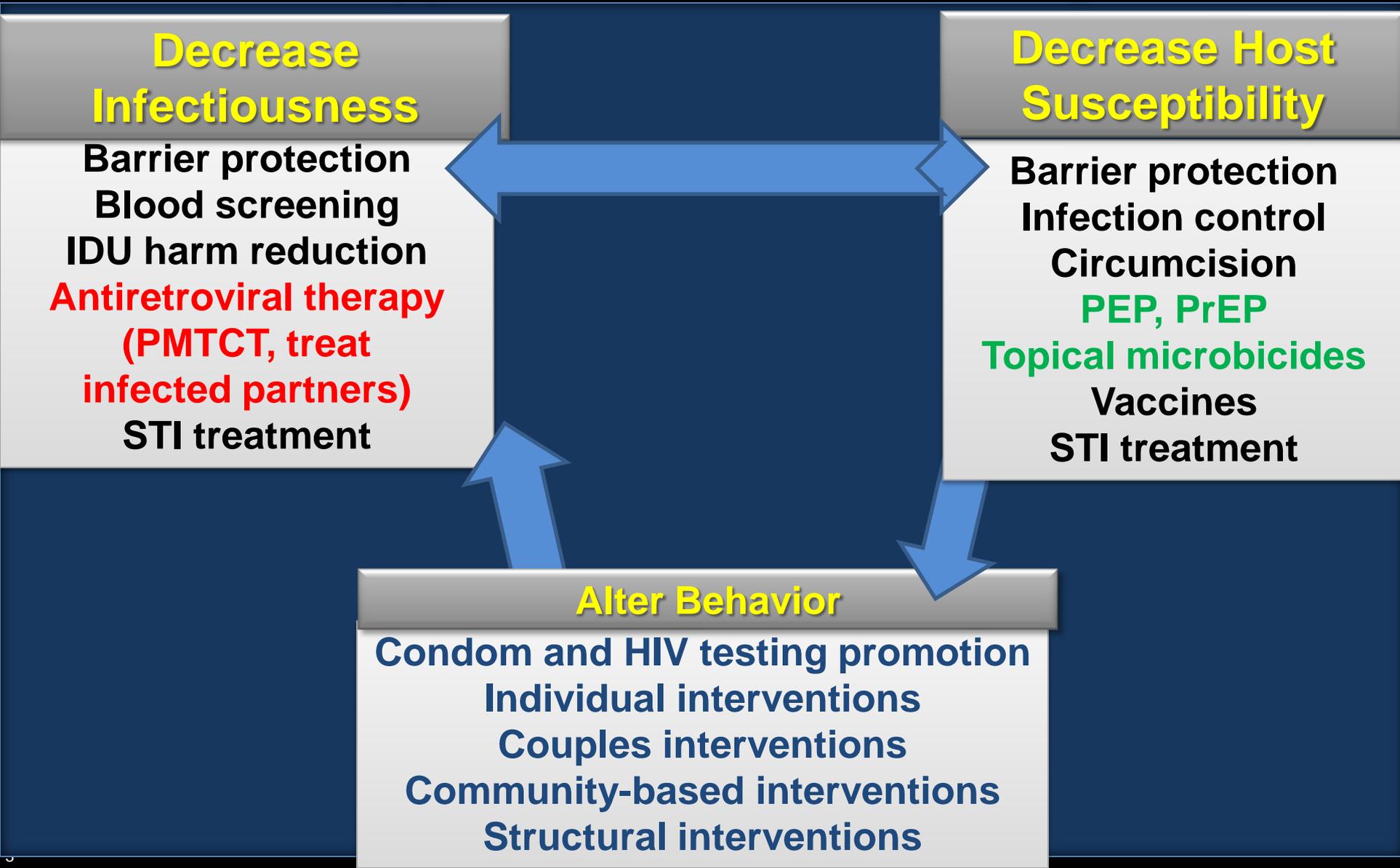
**Beth Israel Deaconess Medical Center
Harvard Medical School**



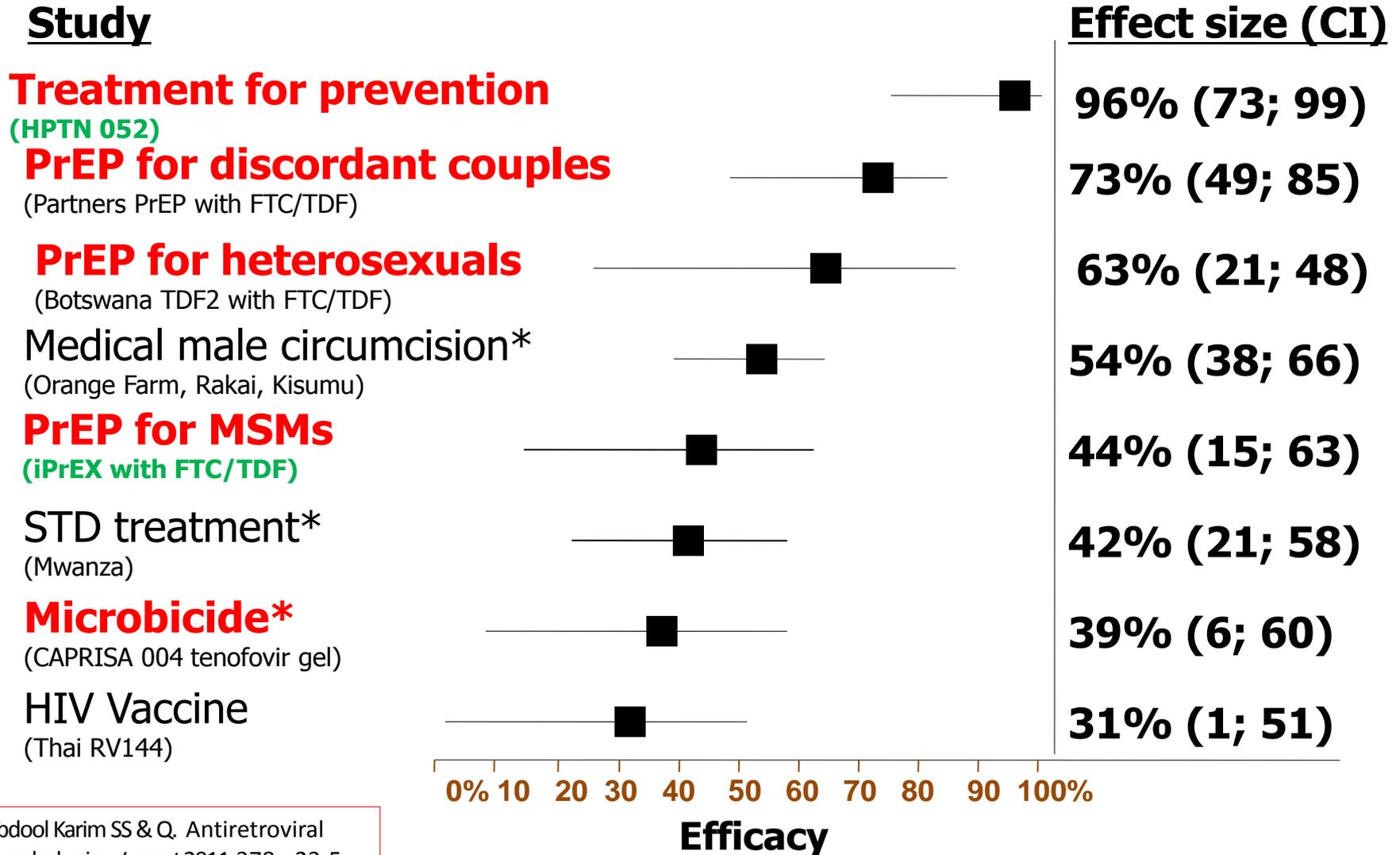
CONTROLLING THE HIV EPIDEMIC WITH ANTIRETROVIRALS
Treatment as Prevention and Pre-Exposure Prophylaxis

HIV Prevention:

New Opportunities, New Challenges



Clinical Trial Evidence that Antiretroviral Drugs Prevent HIV Transmission

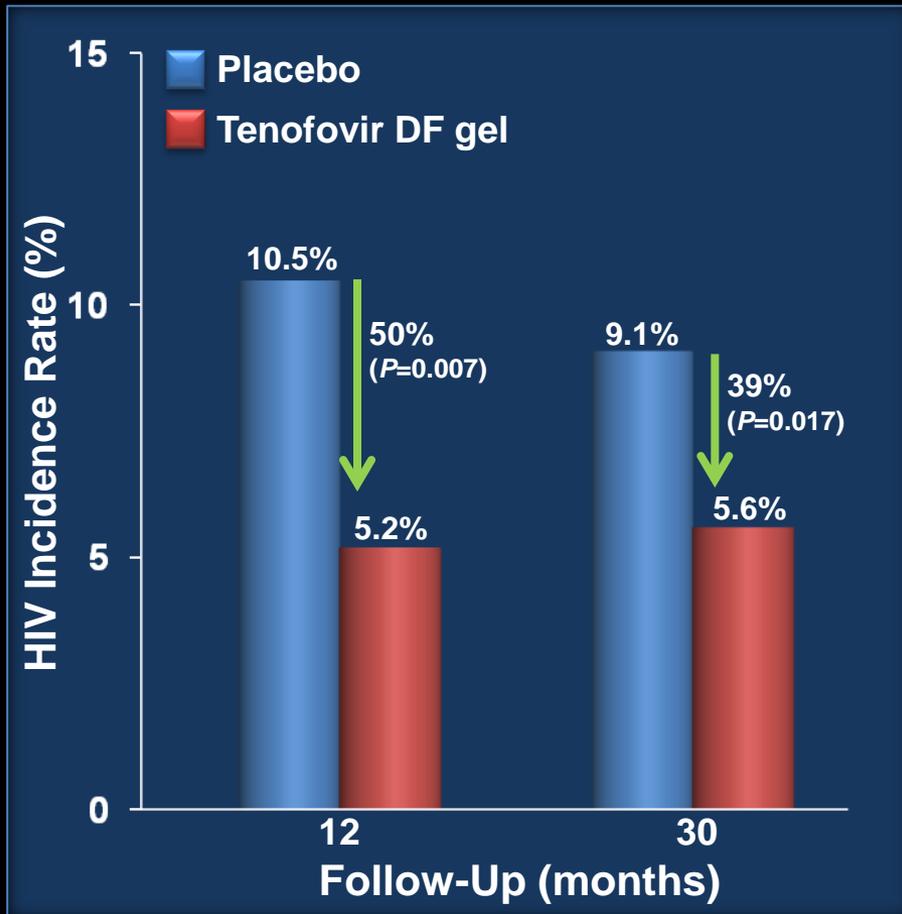


HPTN 052 Limitations

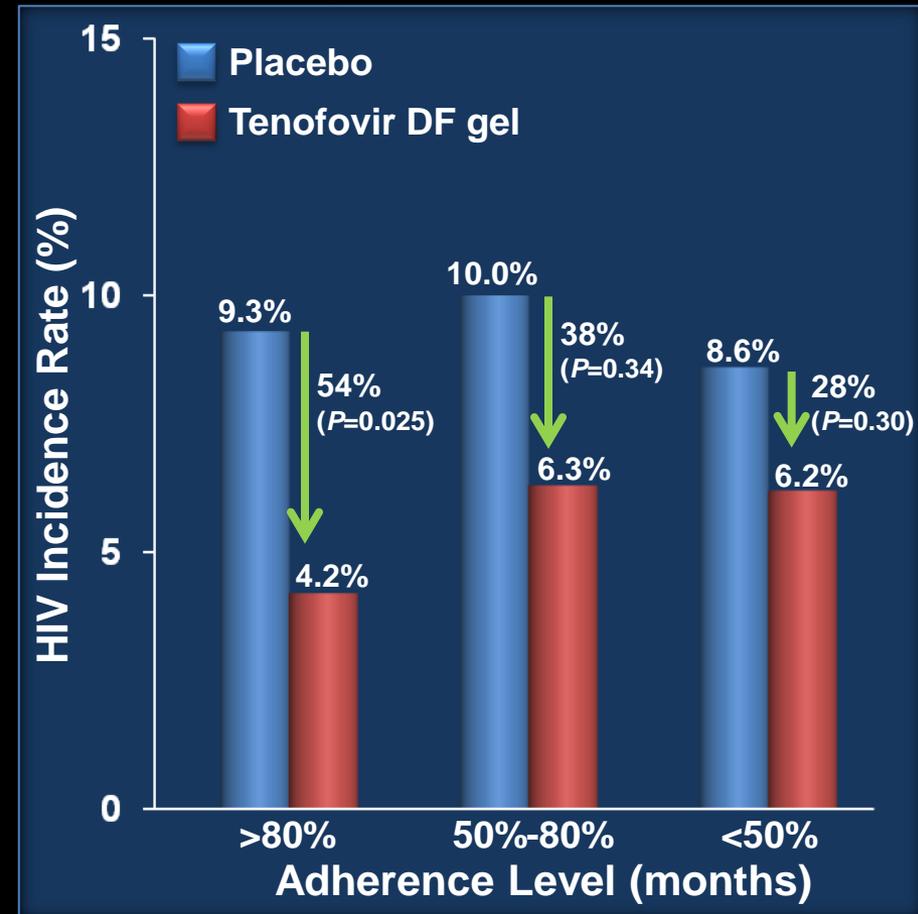
- Many couples are short-lived and do not disclose
- Some people may never disclose: MSM, SW
- Stigma about testing and revealing status
- Only 3% of couples in HPTN 052 were MSM
- **Not either, or.....**
- PrEP combined with ART for prevention can decrease epidemic more rapidly (Hallett, Walensky)
- **Can less frequent dosing or new agents be comparably effective?**
- **Can topical chemoprophylaxis lead to less frequent monitoring?**

CAPRISA 004 Results: HIV Incidence

Overall



By Adherence





Nov 2010: Oral TDF/FTC PrEP prevents HIV in MSM – iPrEx trial

The NEW ENGLAND
JOURNAL of MEDICINE

ESTABLISHED IN 1812

DECEMBER 30, 2010

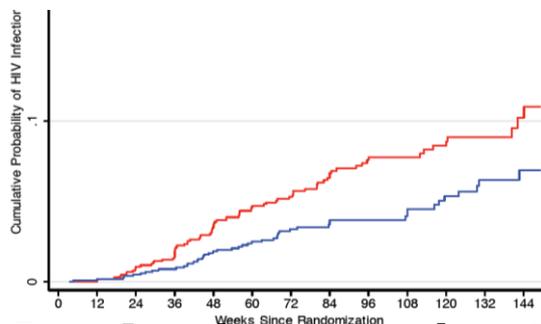
VOL. 363 NO. 27

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 << EC50 for HSV

Partners PrEP Study: Tenofovir Levels Correlate with HIV Protection

- Case cohort study of 30 seroconverters in active arms vs. 200 uninfected subjects randomly selected from active arms
- Plasma TDF levels at months 1, 3, 6, 12, 18, 24, 30, 36 + seroconversion visit

Subjects with Detectable Tenofovir Levels and Risk Reduction

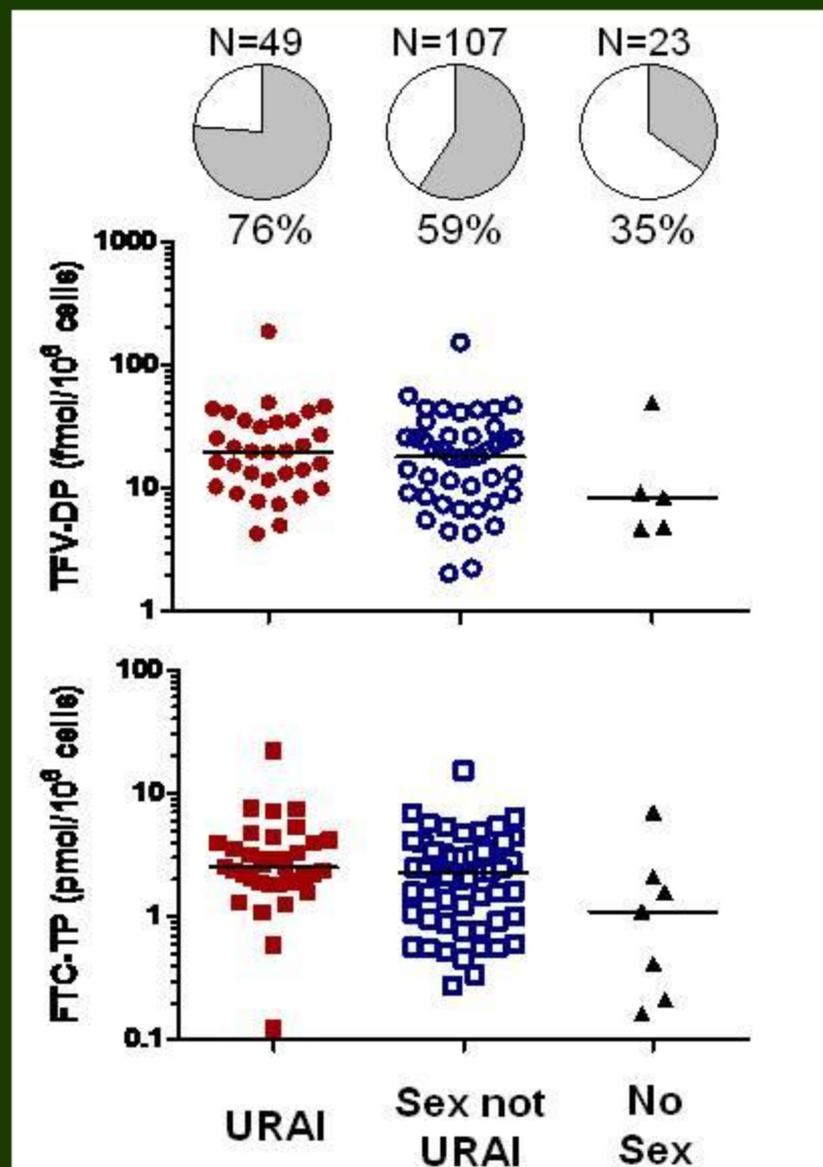
	Cases (TDF = 17, FTC/TDF = 12)				Cohort (N=198)	
	Visits prior to seroconversion		Seroconversion visits		All visits	
TDF	35/63	56%	6/17	31%	363/437	83%
FTC/TDF	20/36	56%	3/12	25%	375/465	81%

- Relative risk reduction associated with detectable tenofovir
 - TDF arm: 86% (95% CI: 57%, 95%)
 - FTC/TDF arm: 90% (95% CI: 56%, 98%)

Predictors of detection – Recent report of sex

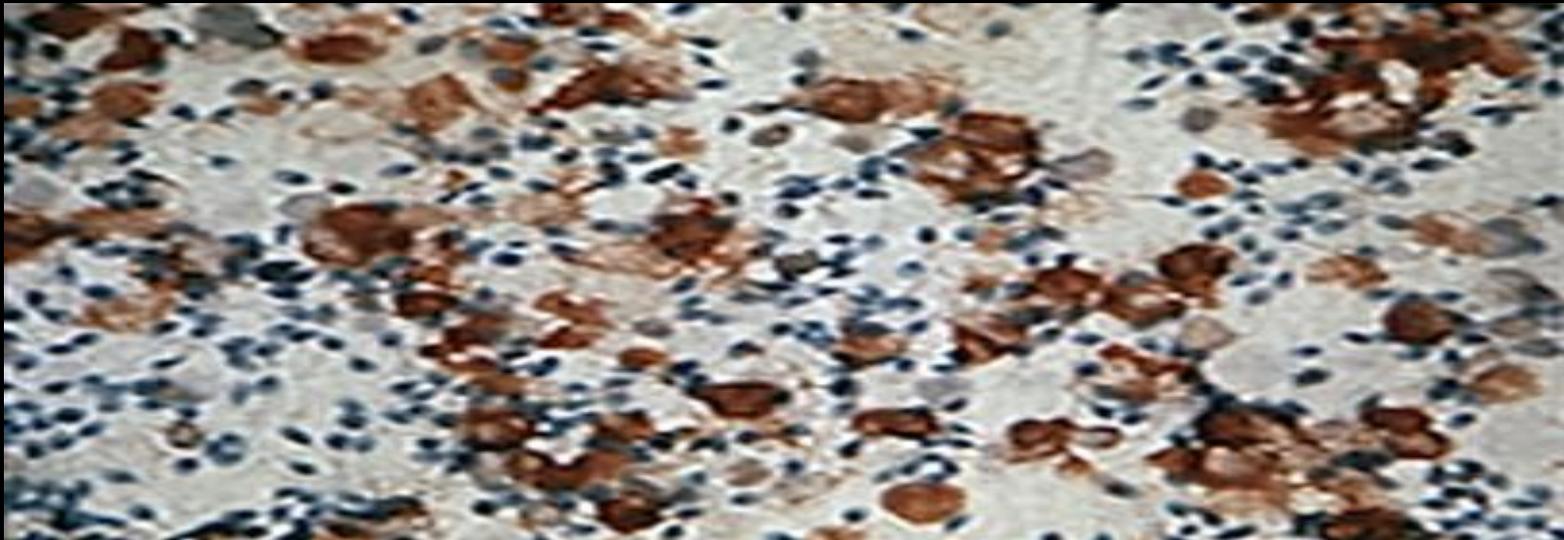
Anderson et al, CROI 2011

- 76% in those reporting URAI vs 59% reporting sex w/o URAI vs 35% reporting no sex in preceding 12 weeks (P=0.003).
- Trend suggests drug use associated with recent report of sex/URAI.



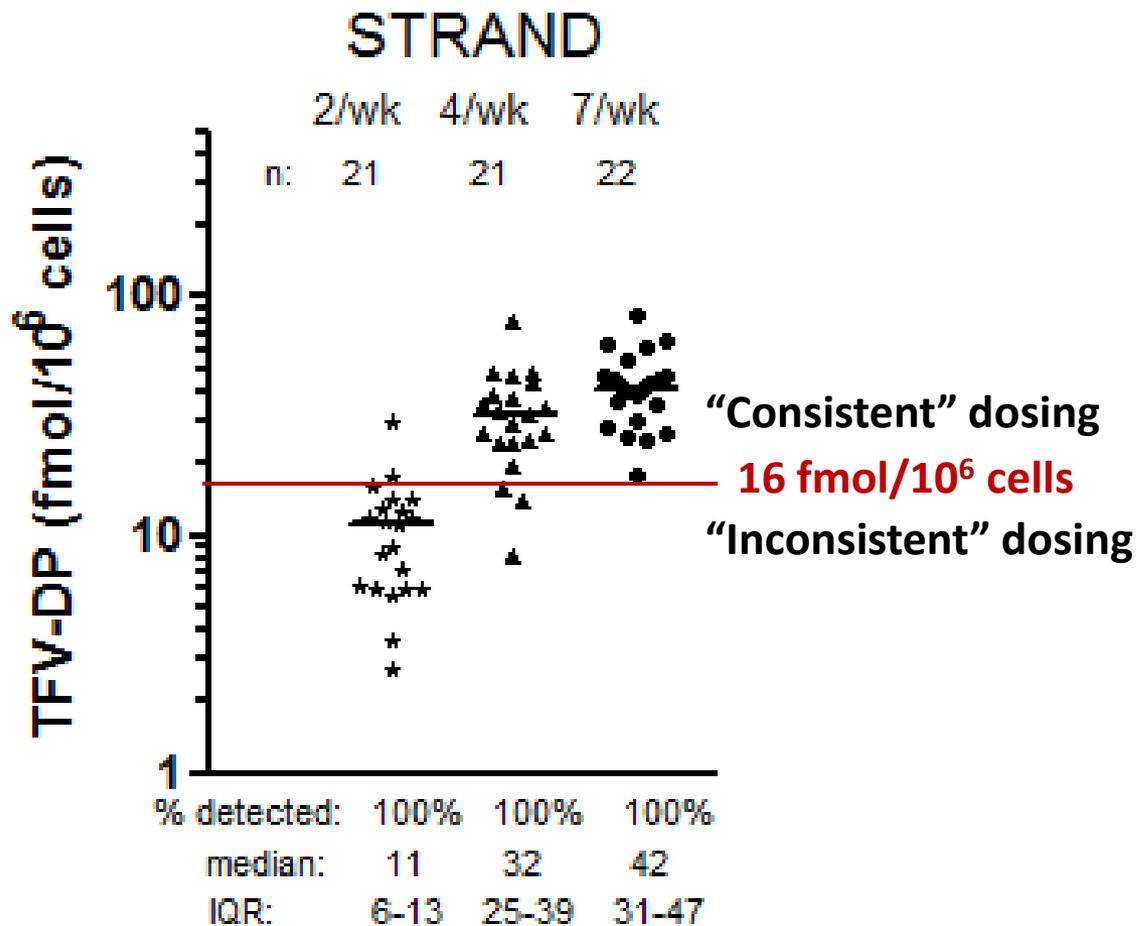
Why was oral and topical PrEP ineffective for some women?

- Adherence?
- Pharmacology?
- Genital Tract Inflammation, STDs?
- Viral challenge from partners?



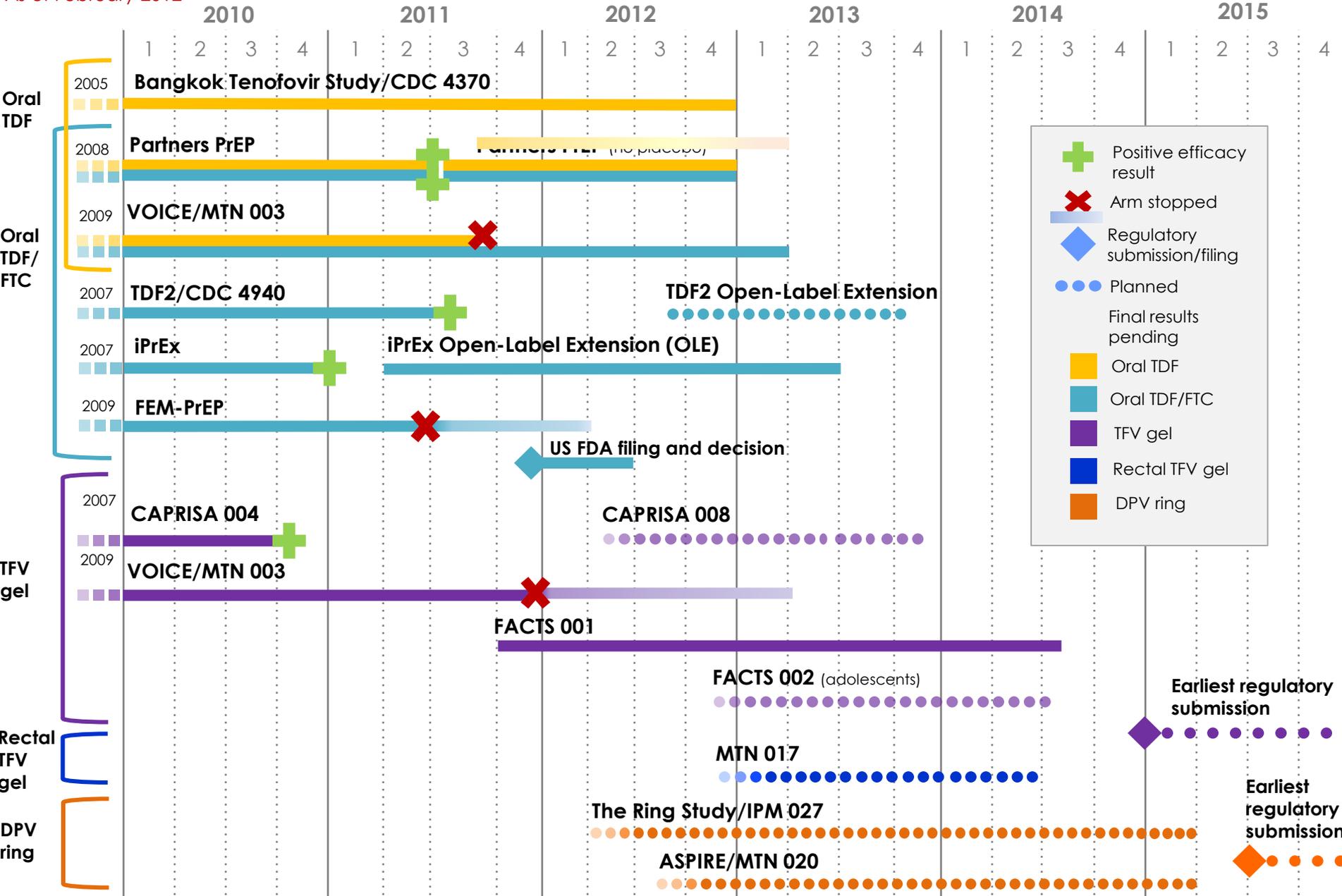
TDF-DP Levels in PBMC with 2-7 days DOT

Understanding iPrEx results



ARV-based HIV Prevention Timeline

As of February 2012

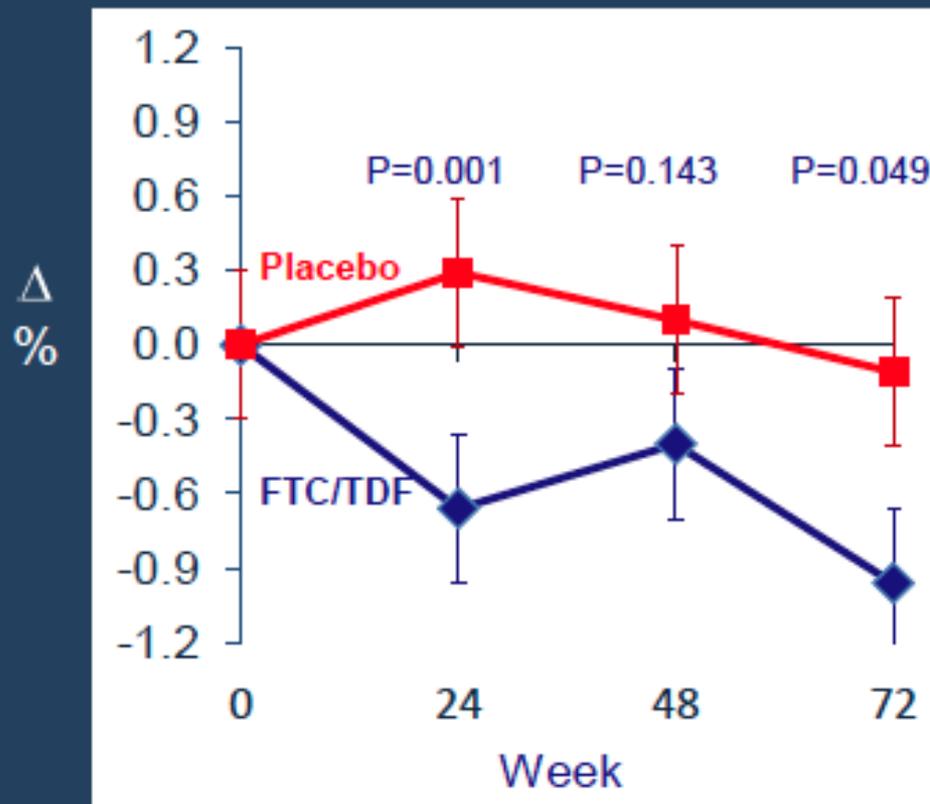


* Trial end-dates are estimates; due to the nature of clinical trials the actual dates may change. For full trial details, see www.avac.org/trials.

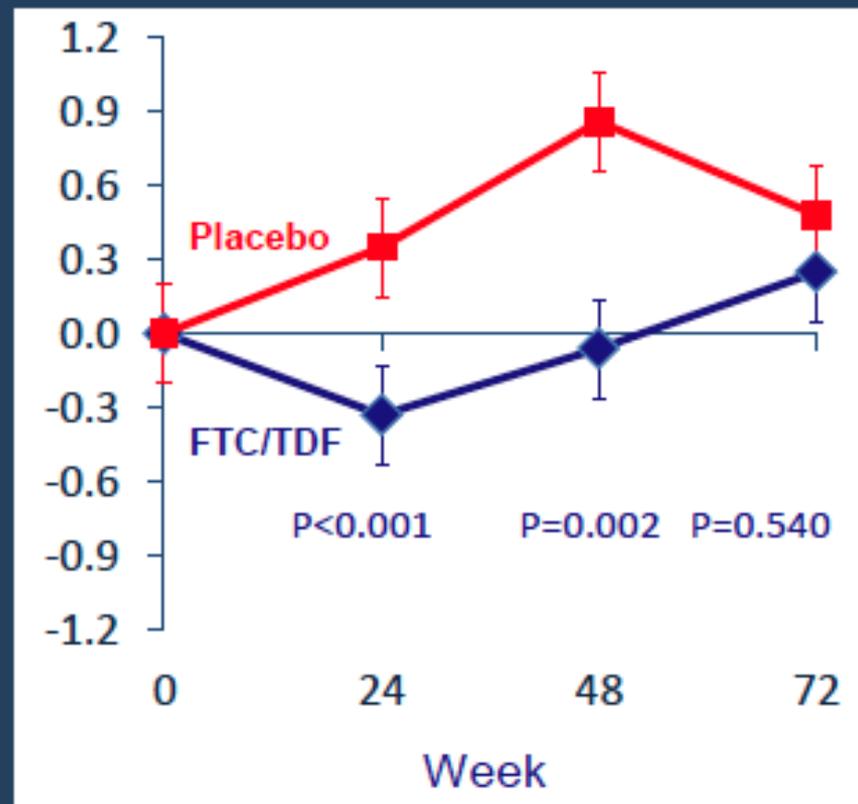
** Not all trials included are effectiveness trials. Trials included on this list are mainly phase II/IIb, III/IIIb and IV trials.

PERCENT CHANGES FROM BASELINE IN BMD BY RANDOMIZATION GROUP

SPINE (L1-L4)



TOTAL HIP



Placebo	247	199	124	59
FTC/TDF	256	203	124	59

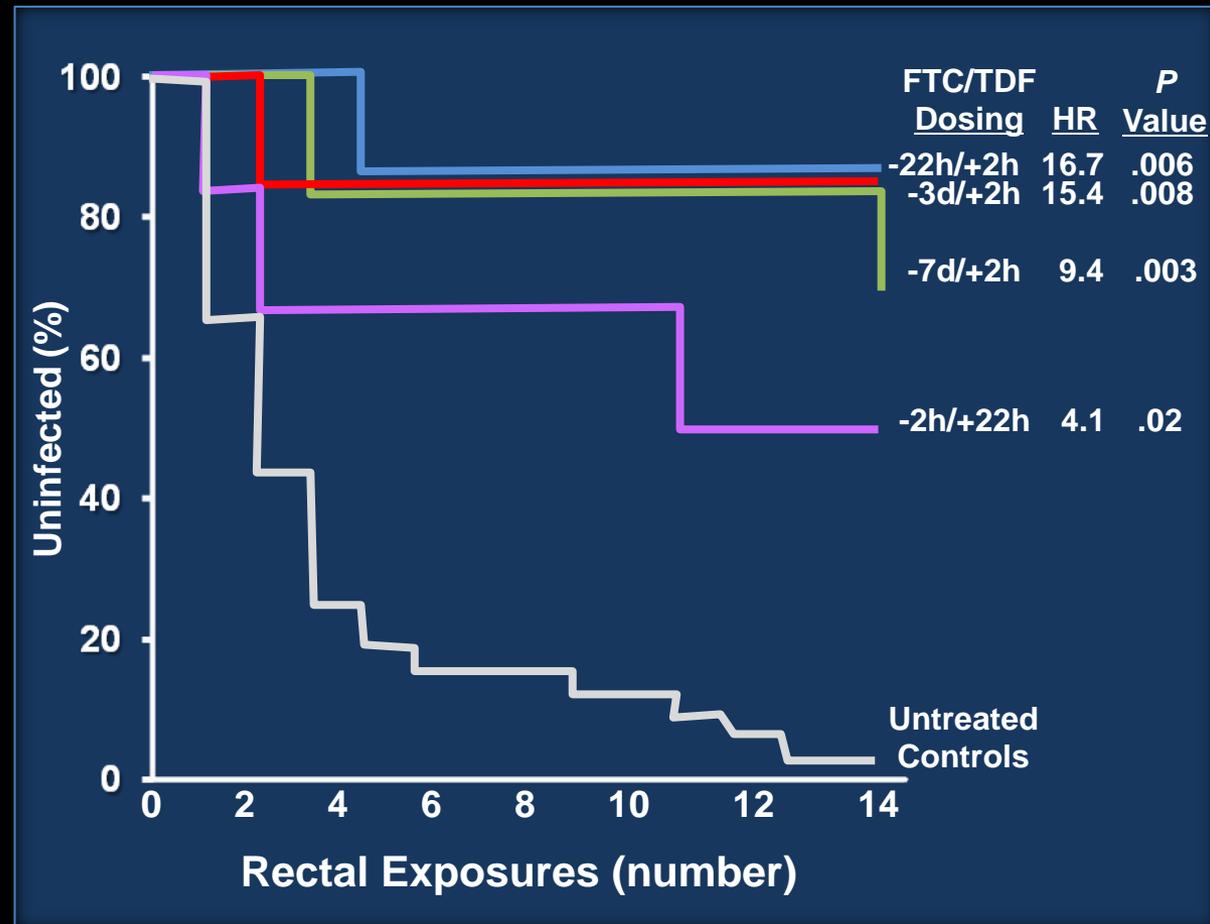
247	199	124	59
256	202	125	59

Mean, SE and P-values by linear mixed model

Peri-Exposure Prophylaxis in Macaques With Oral FTC/TDF

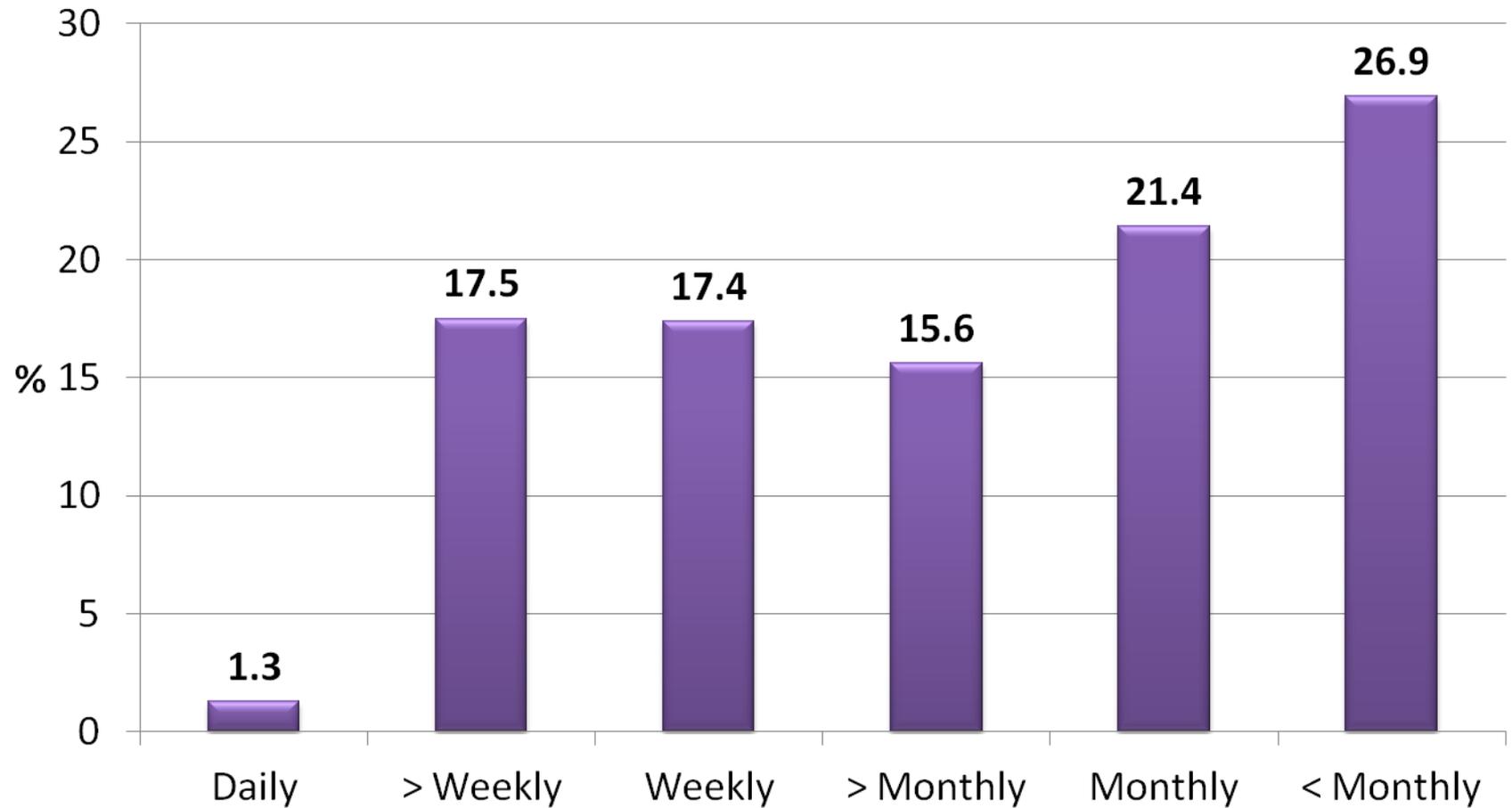
- Macaque model of rectal transmission of HIV
 - Rectal exposure with R5 virus inoculum (10 TCID₅₀)
- 2 doses of FTC/TDF
 - Before SHIV exposure (-)
 - After SHIV exposure (+)
- Extended window of protection
 - Associated with extended long intracellular persistence of drug
- No drug resistance in macaques failing PrEP

Protection From SHIV



Anal sex frequency

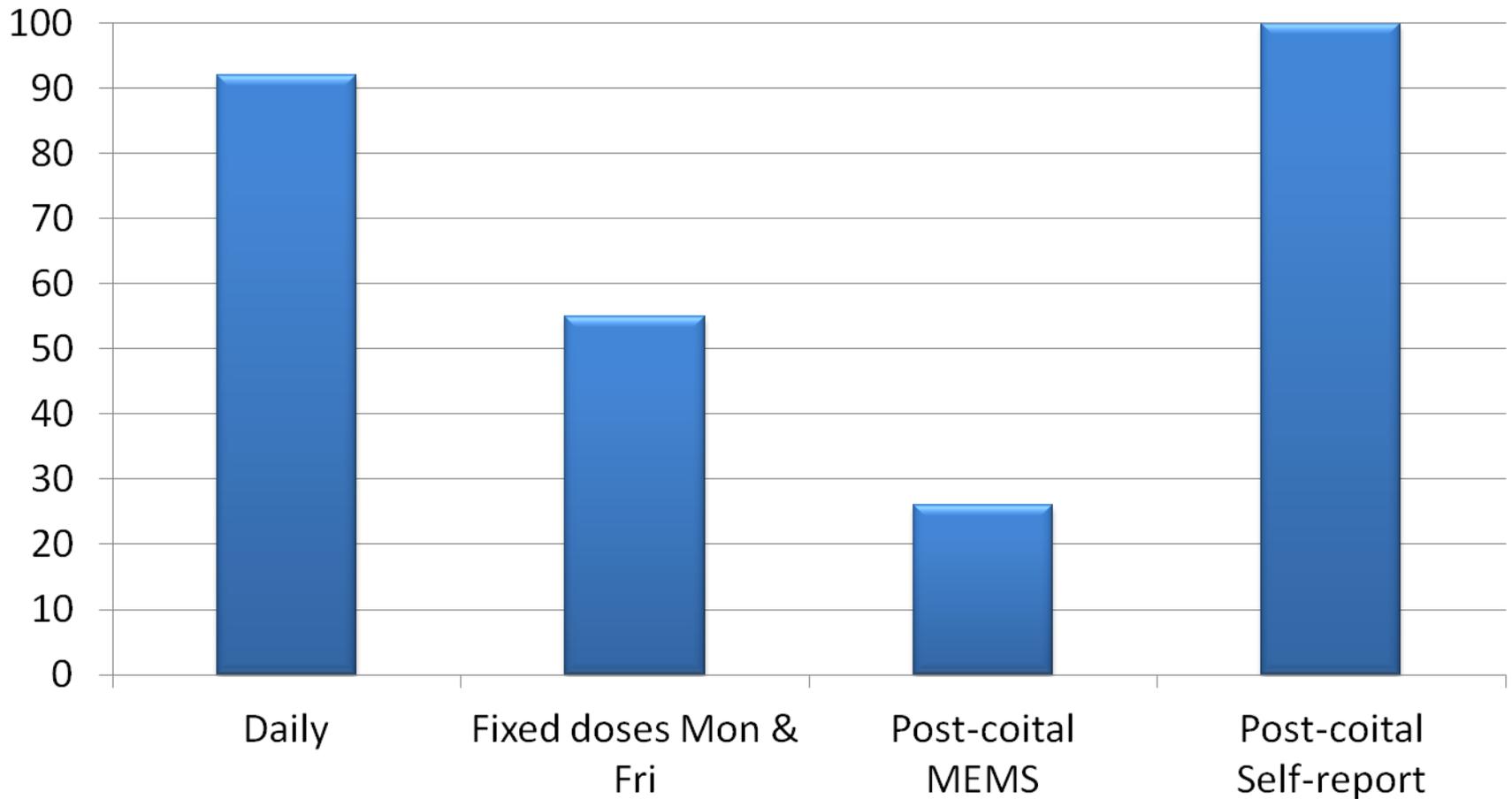
Thai MSM



What about intermittent PrEP?

- **IAVI** studies in East Africa: MSM and FSW, small size, but many missed post-coital doses
- **HPTN 066**: dose proportionality study of weekly TDF/FTC, twice weekly, and double dose twice weekly. DOT. Sampling blood, mucosal secretions and tissues.
- **HPTN 067**: MSM in Bangkok and NYC, and high risk women in Capetown, to compare adherence to coitally dependent vs. fixed intermittent PrEP.
- Ipergay: getting underway

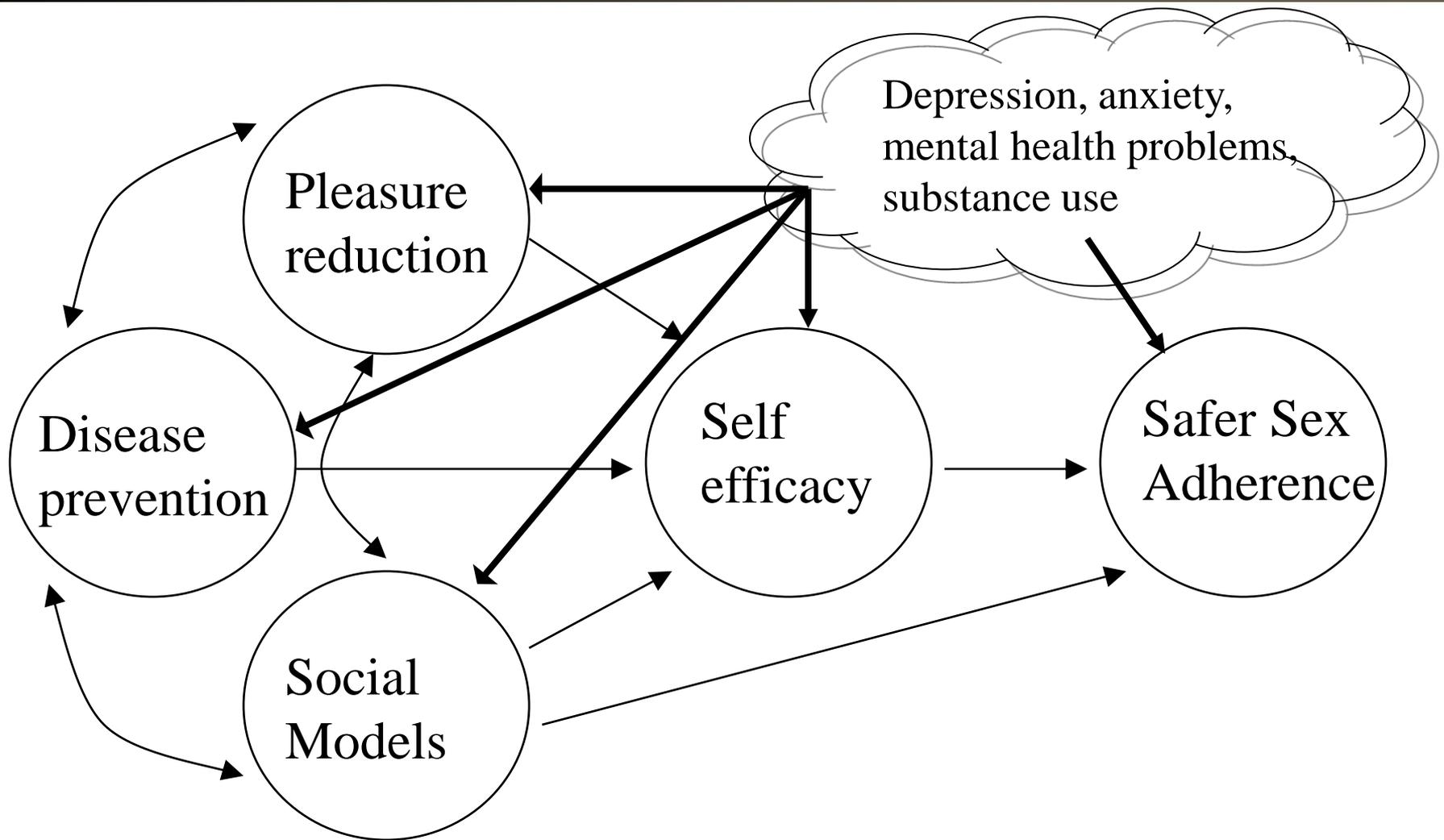
Adherence to different PrEP dosing, MEMs RCT in Kenya MSM and FSW



New Antiretrovirals for Prevention

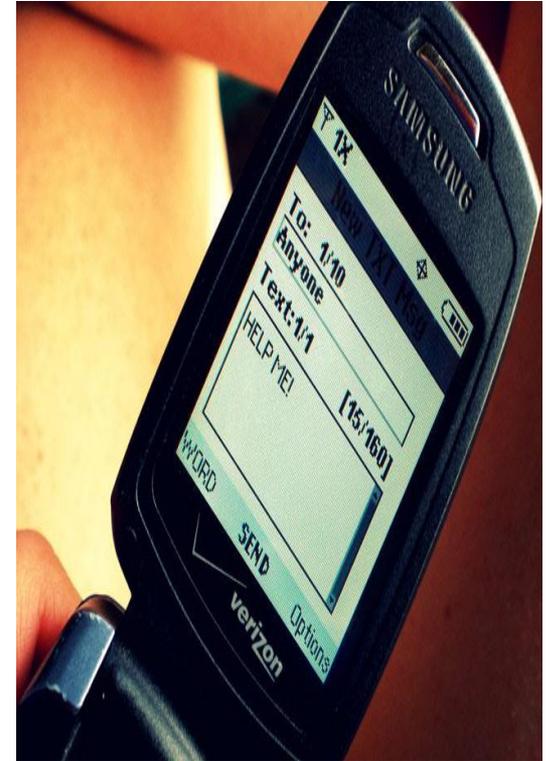
	Mechanism	Status	Developers/ Sponsors
Dapivirine (gel and ring)	NNRTI	Phase 1/2 (gel ring)	Tibotec/IPM
UC-781 (gel)	NNRTI	Phase 1/2	CONRAD MTN
MIV-150 (gel)	NNRTI	Phase 1	Population Council
BMS-793 (?)	gp120 inhibitor	Pre-clinical	BMS/IPM
L644 peptide (?)	gp120 inhibitor	Pre-clinical	Merck/IPM
Maraviroc (oral and ring)	CCR5 inhibitor	Phase 1	ViiV/IPM HPTN/MTN
TMC278 (injectable)	NNRTI	Phase 1	Tibotec

Social Cognitive Model



Demo Projects to Enhance Adherence

- In Weltel study (Kenya), weekly SMS message and phone support reported adherence and rates of virologic suppression
- SF adapting this for use in PrEP with weekly SMS messages to check in
- Fenway: 2 new projects:
- R34 (Mayer/Safren) to develop evidence-based adherence intervention
- R21 (Mimiaga/Mitty) to study stimulant using MSM to develop PreP package



Youth

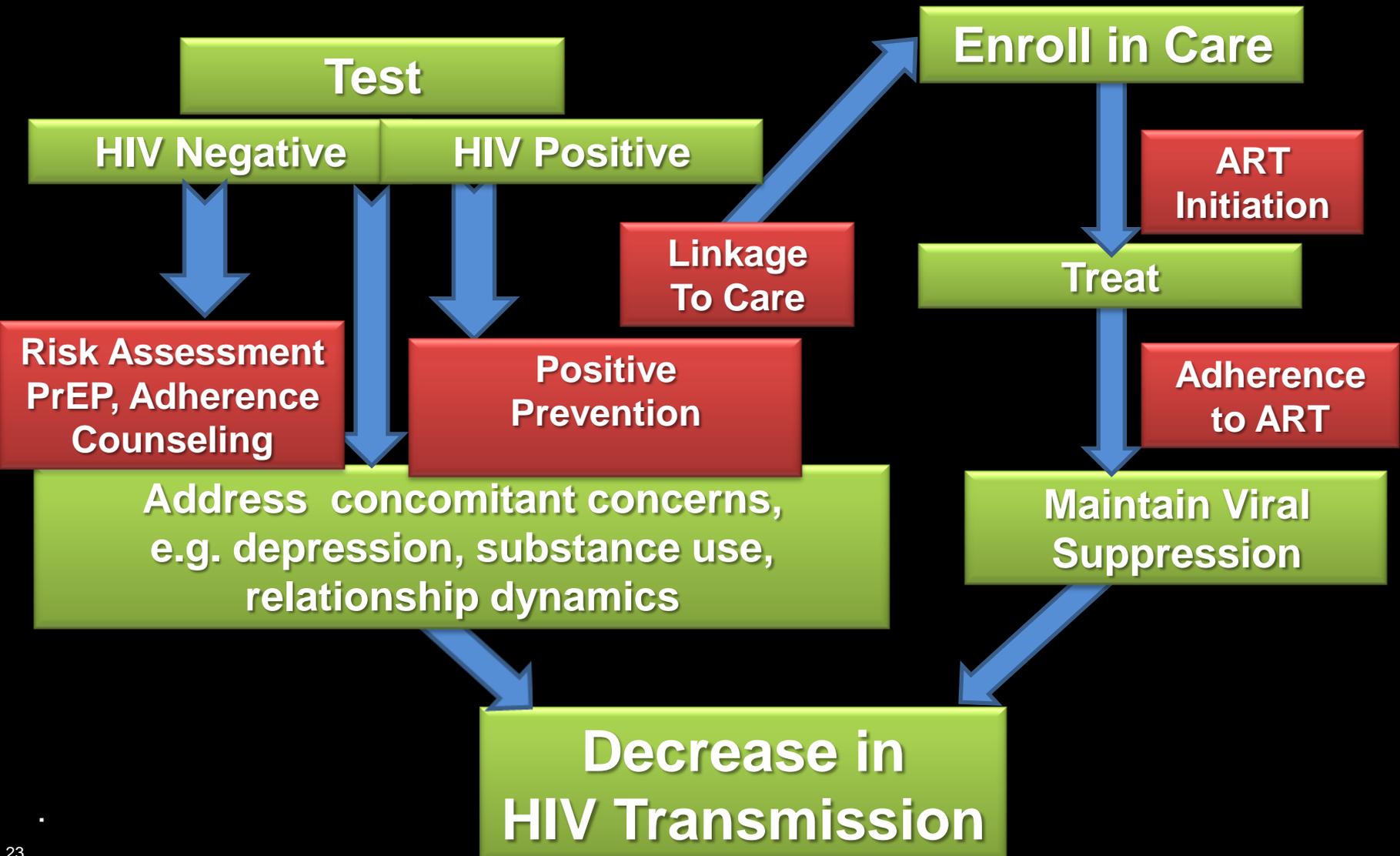
- ATN 082: 58 young MSM In Chicago randomized to PrEP vs placebo
- 46 enrolled in iPrEX OLE, 70% used PrEP
- Of PrEP users, blood levels indicate about 50% adherence, comparable to self-report
- Youth enjoyed integrated Next Step Counseling
- Lots of interim visits for social issues
- No seroconversions
- ATN 110/113: PrEP demo projects for youth, ages 15-18 and 18 and above, getting underway

Antiretrovirals for Prevention 6/12

- Clinical trials provided proof of concept, but...
- How do we optimize effectiveness?
- Integration of treatment as prevention with other services (e.g. mental health)
- Define best drugs for each indication
- Define the role of intermittent dosing
- Define whether oral or topical is preferable
- Affordability and Scalability
- Optimize Prevention Packages

Combination Antiretroviral Prevention

Interventions to Increase Testing



Thank You

**Fenway Clinical,
Epidemiological and
Behavioral Research Teams
Fenway Medical Department**

Susan Buchbinder

Connie Celum

Mike Cohen

Wafaa El-Sadr

Bob Grant

Trip Gulick

Steve Safren

Dawn Smith

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www.thefenwayinstitute.org

