



Biomedical HIV Prevention: Adherence Across Diverse Contexts and Cultures

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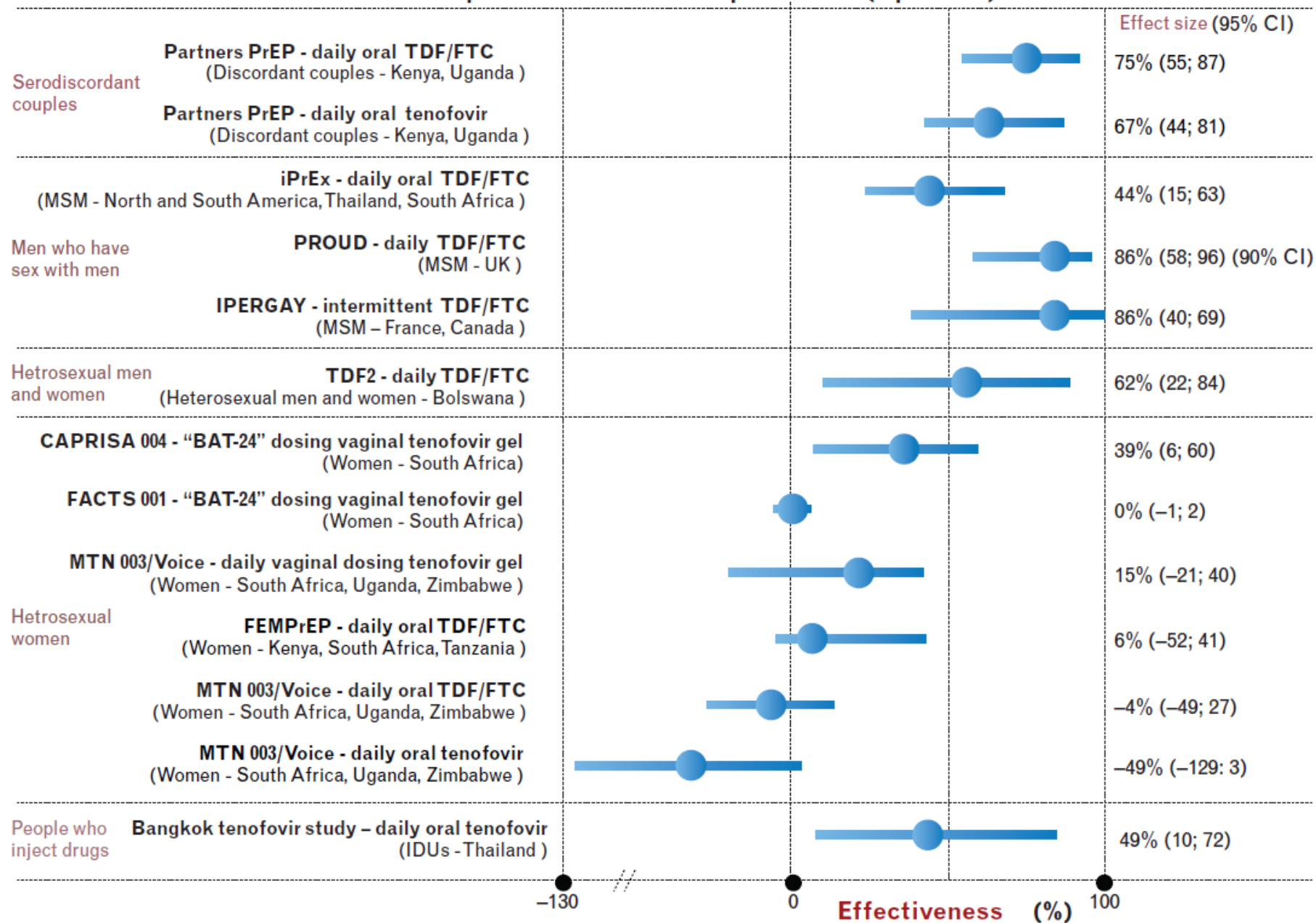
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Harvard Medical School and T.C. Chan School of Public Health
June 30th, 2015



Disclosures

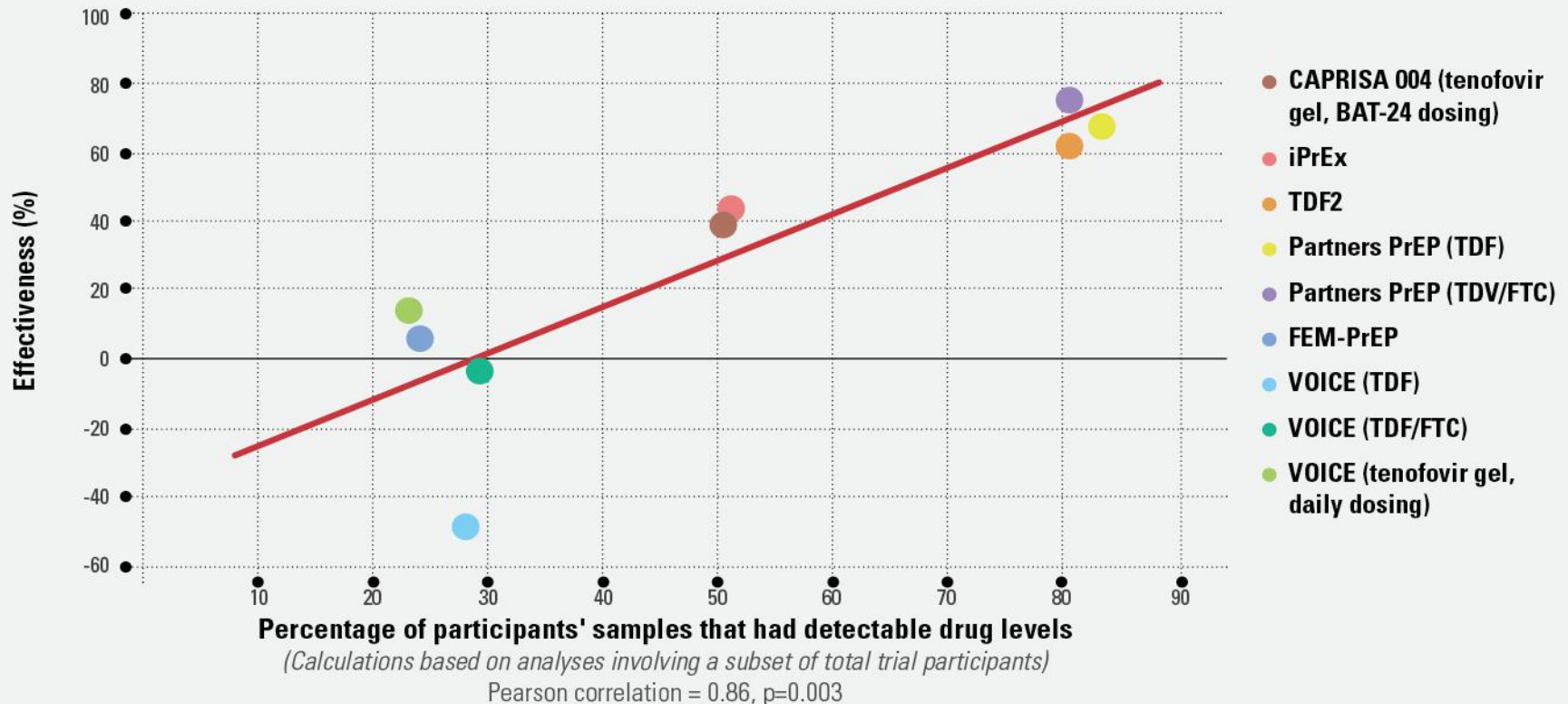
- Unrestricted educational and research grants from Gilead Sciences
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Clinical trial evidence for oral and topical tenofovir-based prevention (April 2015)



PrEP works, but adherence is key

➔ Effectiveness and Adherence in Trials of Oral and Topical Tenofovir-Based Prevention



Trials of oral and topical tenofovir-based PrEP show that these strategies reduce risk of HIV infection if they are used correctly and consistently. Higher adherence is directly linked to greater levels of protection.

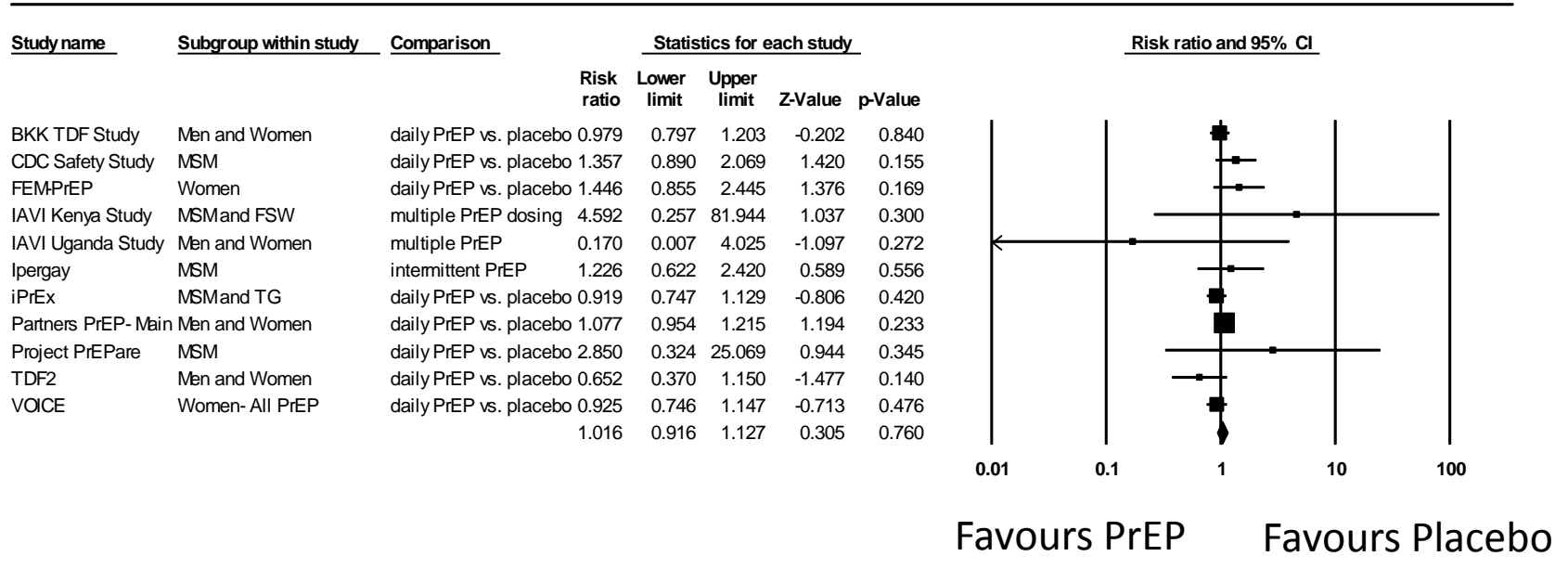
Source: Salim S. Abdool Karim, CAPRISA

Influences on PrEP Adherence and Protection

- Trial (lots of stated negatives) vs. real world
- Self-perception of risk
- Medical trust/mistrust
- Biology (“forgiveness” when missing doses)
- Support for adherence
- Integrating behavioral health with PrEP
- Modality (Next Gen PreP)

(Auerbach, Marrazzo, VanDamme, Van der Straten, Stadler, Tolley, Hendrix, Abdool Karim, Saethre, Corneli)

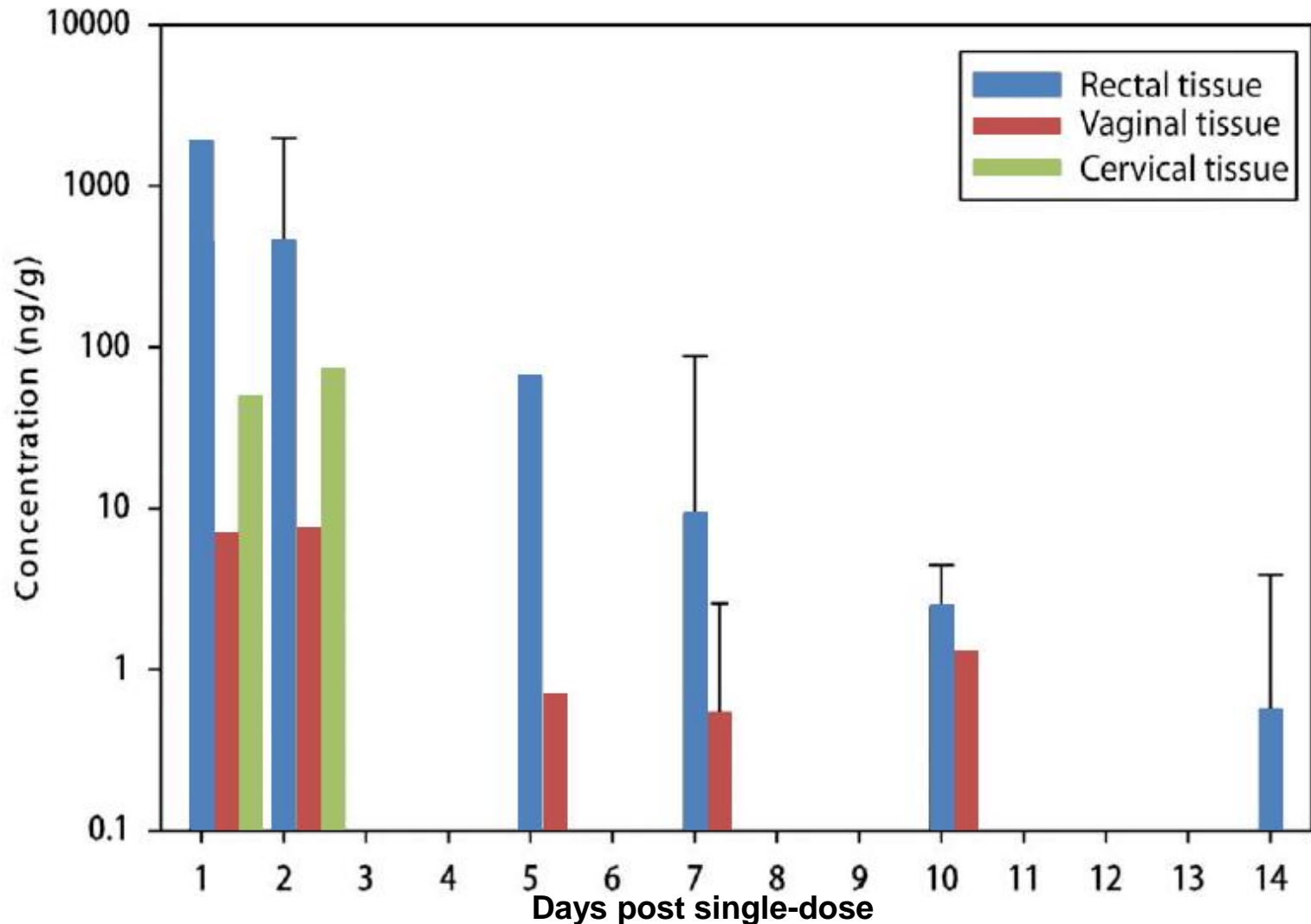
PrEP is well-tolerated, discontinuations rare because of AEs



- No difference in proportion of participants reporting any adverse event (RR=1.01, 95% CI: 0.99-1.03, p=0.27) or any grade 3 or 4 adverse event comparing PrEP to placebo study arms.
- Several studies noted subclinical declines in renal functioning and bone mineral density among PrEP users.

“Forgiveness”

Tenofovir Concentration: Rectal>Cervical>Vaginal



PrEP: Risk, Compensation, Adherence, Coverage

- **Best Case: “risky” person is highly adherent (good coverage)** →→ **No HIV transmission**
- **Worst case: “risky” person is not adherent (poor coverage)** →→ **HIV Transmission; selection for resistance**
- **Risk compensation? Not often relevant**
 - Possible, not often seen in studies to date
 - But what if condoms are never used?
- **Match counseling messages and prevention intervention to risk** →→ **Requires discussion with clinician**

Indirect adherence measures

- Self-report
- Pill count
- Medication possession ratio
 - ~90% adherence in PrEP trials by these measures
 - But trial efficacy 0% to 75%...



"Frankly, darling, I think your doctor is a little obsessive about this compliance thing."

© 2004 Diabetes Health

TFV plasma concentrations & adherence interpretation

- Concentration determines how far back yes/no applies
- Extensive knowledge of TFV PK represents “PK validated”.

<i>TFV plasma Concentration</i>	<i>Adherence Interpretation</i>
≥ 40 ng/mL	Dose within 24 hours
< 40 and ≥ 10 ng/mL	Dose ~48 hours ago
< 10 and ≥ 0.3 ng/mL	Dose ~ 7 days ago
BLQ	No dose within 7 days

Pros and Cons of dichotomous

Pros

- Confirms drug ingestion.
- Easy to collect.
- Potential for point of care testing.
- Plasma validated.



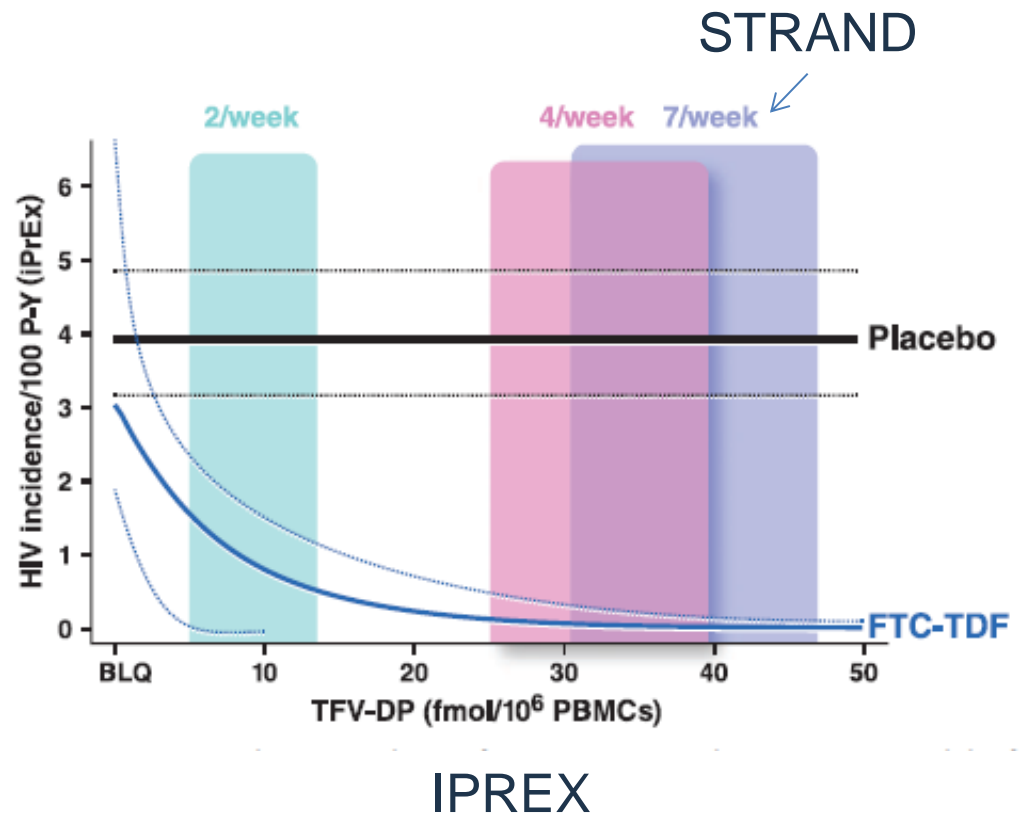
Cons

- Adherence information limited to most recent dose.
- White coat dosing.



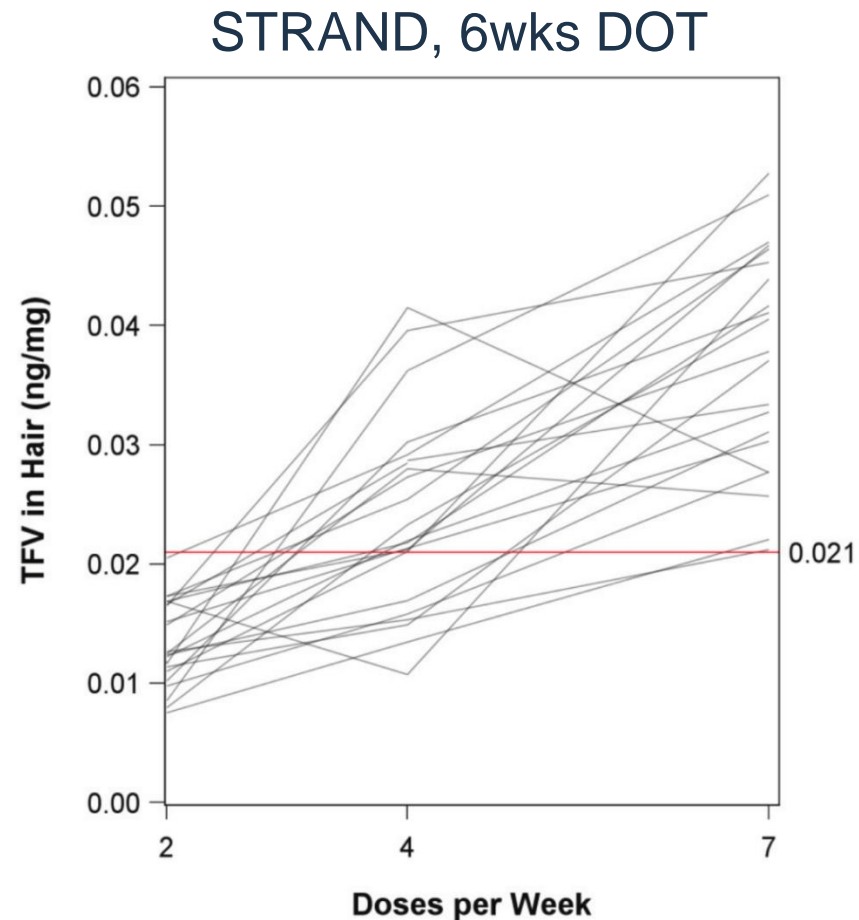
Long half-life examples - PBMC

- Tenofovir-diphosphate (TFV-DP) in PBMC (~3 day $t_{1/2}$)
- Clinically validated
 - iPrEx (MSM)
- PK validated
 - HPTN 066, STRAND



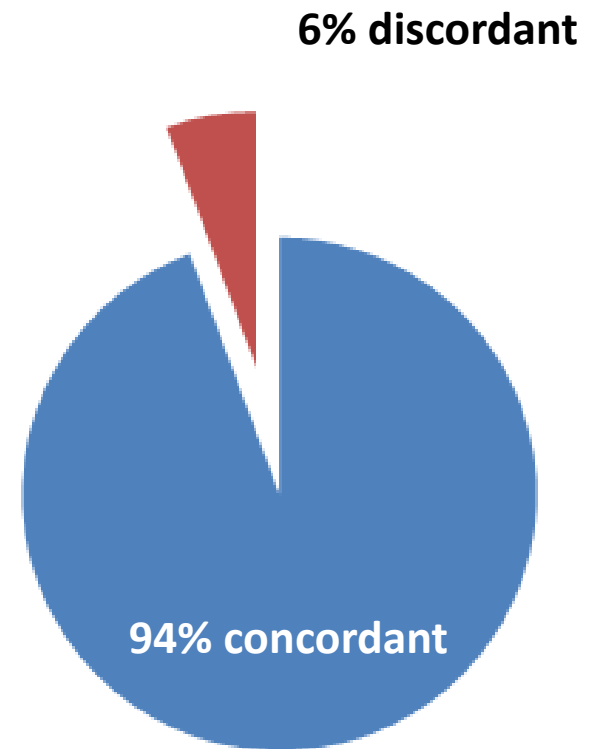
Long half-life examples - hair

- TFV in hair (~ 21 day $t_{1/2}$??).
- PK validated in dark-haired people in STRAND.



FTC-TP is also in RBC and DBS

- FTC-TP in DBS has similar $t_{1/2}$ to TFV/FTC in plasma.
- FTC-TP detection in DBS concordant with detection of TFV/FTC in paired plasma.
- TFV-DP informs cumulative dosing; FTC-TP detection informs dosing in last 48 hrs.



N=515 paired plasma:DBS

Pros and Cons of long half life moieties

Marker	Pro	Con
PBMC TFV-DP	<ul style="list-style-type: none">• Clinical and PK validated• Adherence over 1-2 weeks• Protective threshold identified	<ul style="list-style-type: none">• NOT easy to collect/process• Variable cell processing issues• Cold chain needed.
Hair TFV	<ul style="list-style-type: none">• Room temp storage, shipping• Adherence over long-term (?)	<ul style="list-style-type: none">• Baldness, acceptance• PK (?) and Variability (?)
DBS TFV-DP	<ul style="list-style-type: none">• Easy to collect and process• Adherence over ~8 weeks• Protective threshold identified• FTC-TP informs recent dosing	<ul style="list-style-type: none">• HCT abnormalities outside 35% to 50%?• Cold-chain needed.

CORRELATES OF PREP PROTECTION

(GRANT ET AL, LANCET ID, 2014)

TABLE 2

	BLQ	LLOQ to <350 fmol per punch	350-699 fmol per punch	700-1249 fmol per punch	≥1250 fmol per punch
Estimated dose (tablets per week)	None	<2	2-3	4-6	7
Follow-up (% of visits)	25%	26%	12%	21%	12%
HIV infections (n)	18	9	1	0	0
Person-years per infection	384	399	179	316	181
HIV incidence (95% CI)	4.70 (2.99-7.76)	2.25 (1.19-4.79)	0.56 (0.00-2.50)	0.00 (0.00-0.61)	0.00 (0.00-1.06)
HR vs previous placebo (95% CI)*	1.55 (0.88-2.56)	0.69 (0.32-1.32)	0.19 (0.01-0.88)	0.00 (0.00-0.25)	0.00 (0.00-0.50)
HR vs concurrent off-PrEP (95% CI)†	1.25 (0.60-2.64)	0.56 (0.23-1.31)	0.16 (0.01-0.79)	0.00 (0.00-0.21)	0.00 (0.00-0.43)

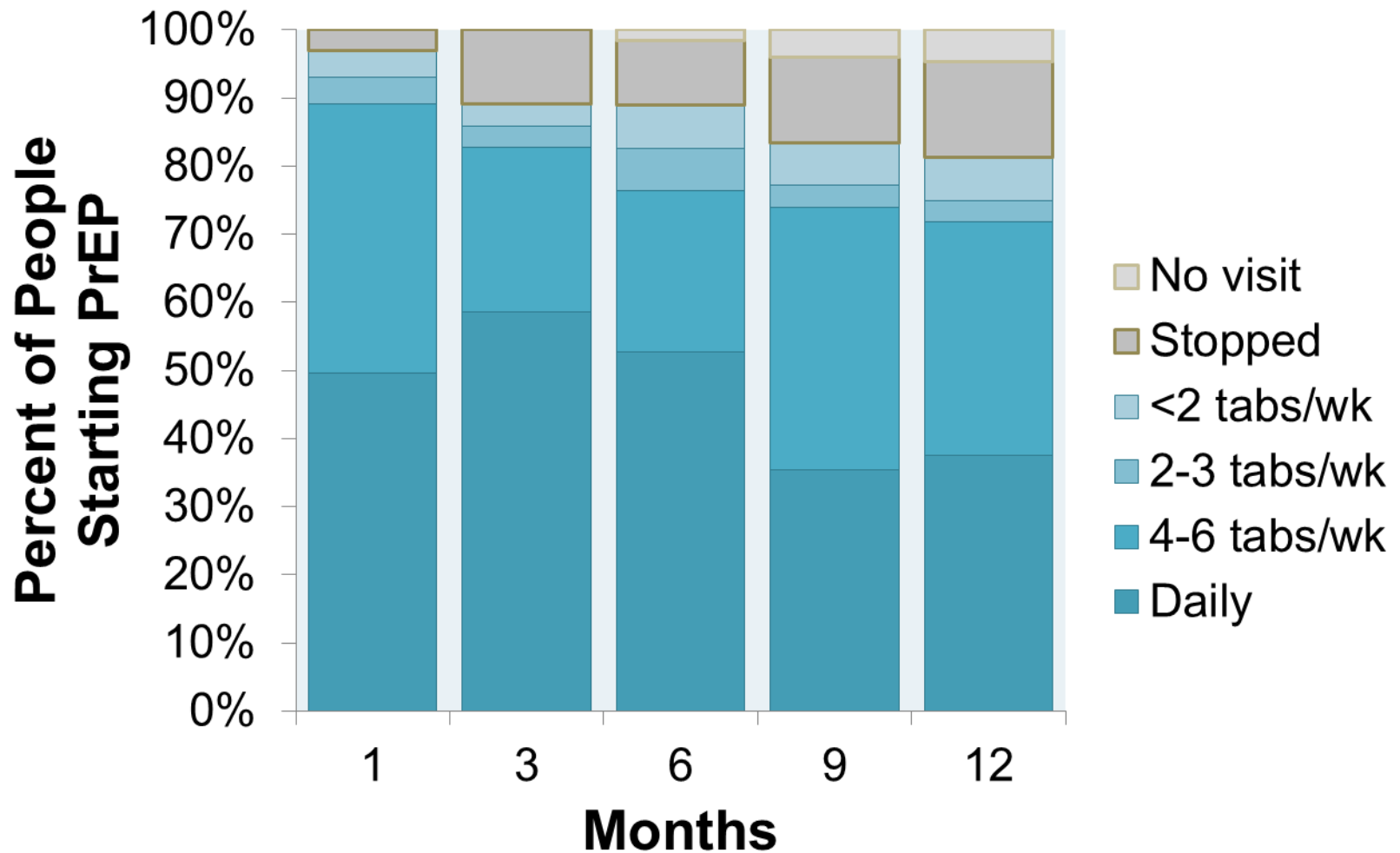
HR=hazard ratio. PrEP=pre-exposure prophylaxis. BLQ=below limit of quantification. LLOQ=lower limit of quantification. *Adjusted for study site. †Adjusted for study site, age, number of sexual partners, non-condom receptive anal intercourse, and syphilis. Drug concentration measurements were not available for 5% of visits.

Table 2: Effect of tenofovir diphosphate in dried blood spots on HIV infection

iPrEx Open Label PrEP in San Francisco:

81% still on PrEP at 12 months,¹

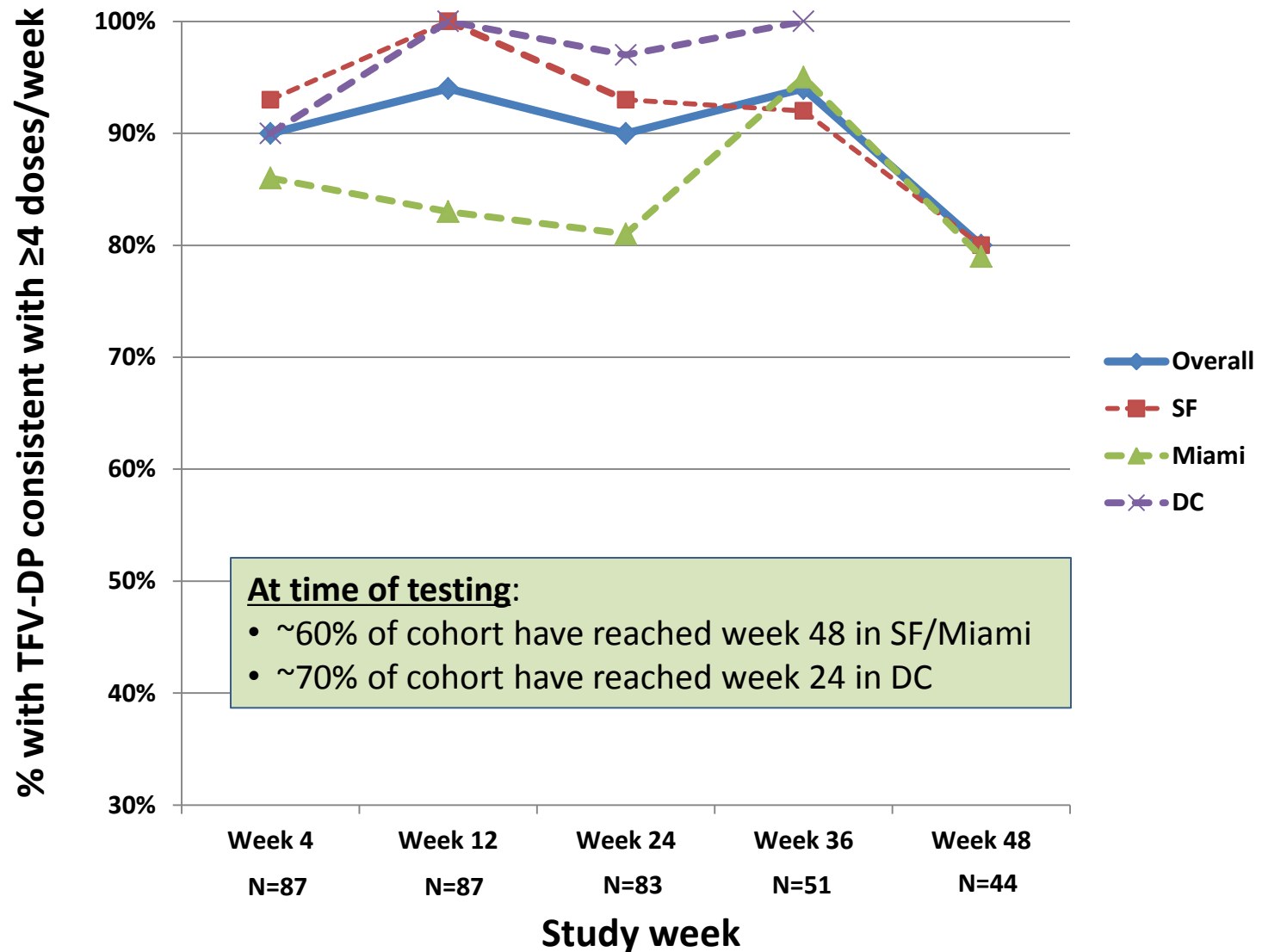
92% on PrEP use 4+ tablets per week.²



1. Grant *Lancet ID* 2014 14(9):820-9;

2. Estimated from dried blood spots in iPrEx OLE in San Francisco.

Proportion with estimated ≥ 4 doses/week in longitudinal cohort (N=90), overall and by site SF Demo Project, Al Liu et al



New technologies and PrEP adherence

- ↑ treatment adherence with text messaging (Lester, Lancet, 2010)
- Wisepill: used in Life-Steps HAART adherence intervention modified for PrEP, including daily SMS with pts (Mayer/Safren)
- Next step counseling in iPrEX Ole, augmented by electronic diary in SF and Chicago was associated with ↑ adherence (Amico/Hosek)
- Feedback on drug levels been studied as adjunct to counseling (Landovitz)
- SexPro App including diary features and adherence support, tested in NYC, SF, Lima and Rio (Buchbinder)



COGNITIVE BEHAVIORAL THERAPY (CBT) PREP ADHERENCE INTERVENTION

(SAFREN/MAYER, NIMH R34)

- 4 weekly hour-long sessions
- Booster sessions at 2 and 3 months
- Based on Life-Steps*
- Nurse delivered
- Incorporates:
 - Problem Solving
 - Motivational Interviewing
 - Mindfulness and Relaxation
- 84% had TFV levels c/w daily use at 6 months

*Safren SA, et al. Two strategies to increase adherence to HIV antiretroviral medication: life-steps and medication monitoring. Behav Res Ther. 2001 Oct;39(10):1151-62.

Psaros C, et al. An intervention to support HIV preexposure prophylaxis adherence in HIV-serodiscordant couples in Uganda. J Acquir Immune Defic Syndr. 2014 Aug 15;66(5):522-9.

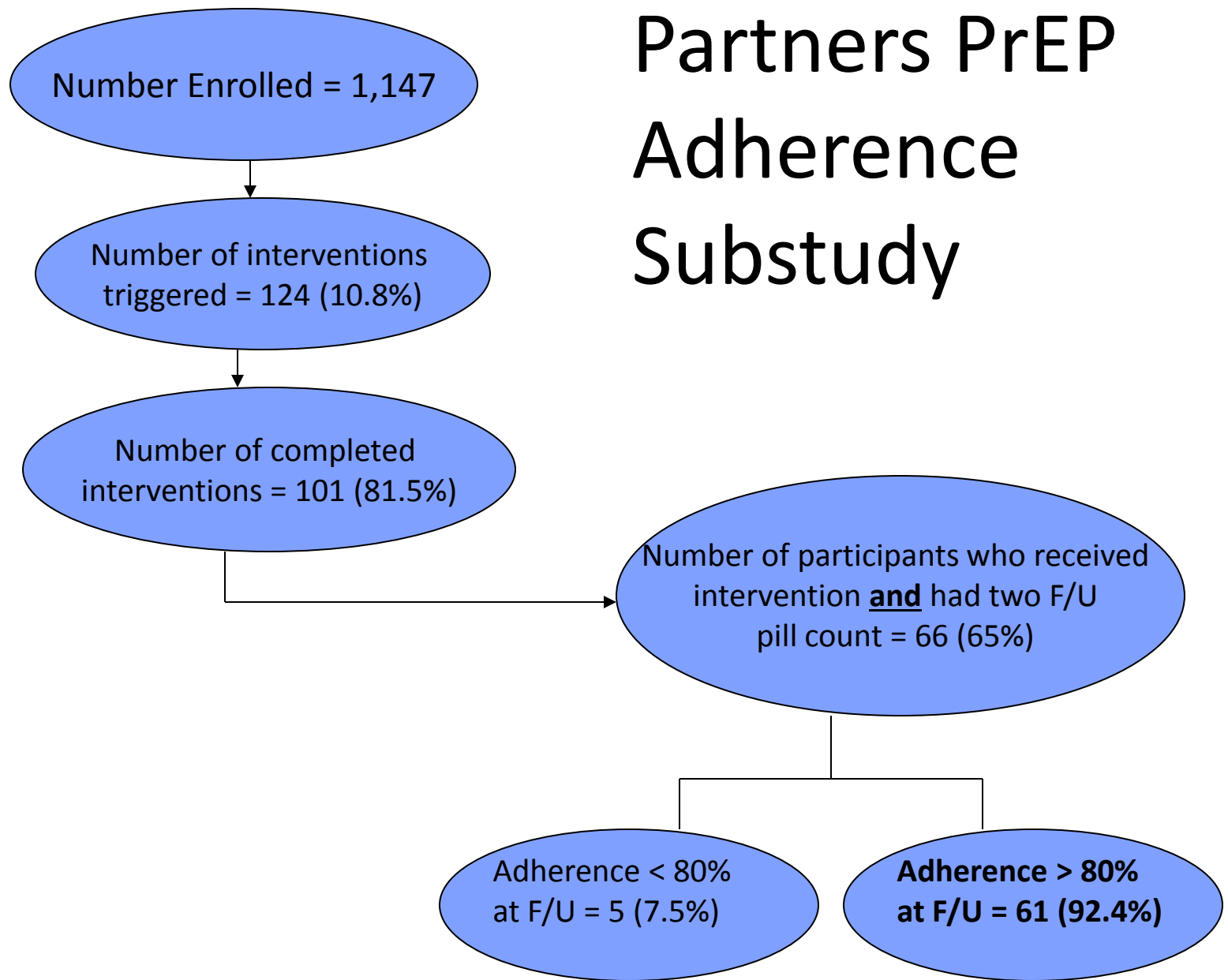
Partners PrEP: Ancillary Adherence Study

(Haberer et al)

- Intervention based on principles of Cognitive Behavioral Therapy (CBT) and Motivational Interviewing (MI) targeted to HIV-negative participants with low (<80%) unannounced pill count adherence
 - To improve adherence through the duration of the study
 - To examine process of intervention delivery and predictors of intervention success
- Intervention in progress based on the work of Safren et al on adherence to ART (*Safren et al., 1997; 2001; 2007*)
- Modular / checklist format:
 - Standardized provision of information while still tailoring counseling messages to individual needs
 - Delivery by a variety of study staff members with various levels of training
 - Provides a reference for future counseling sessions



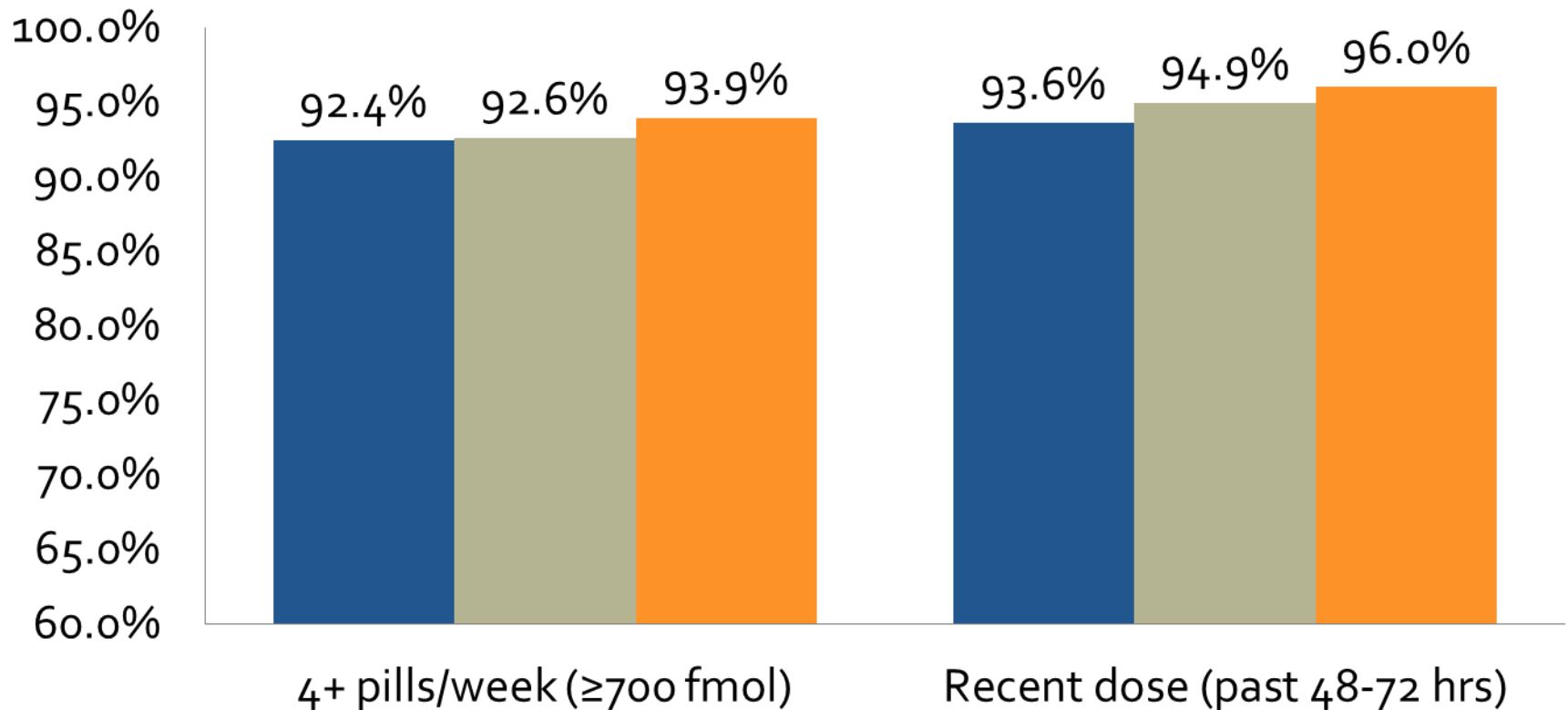
Partners PrEP Adherence Substudy



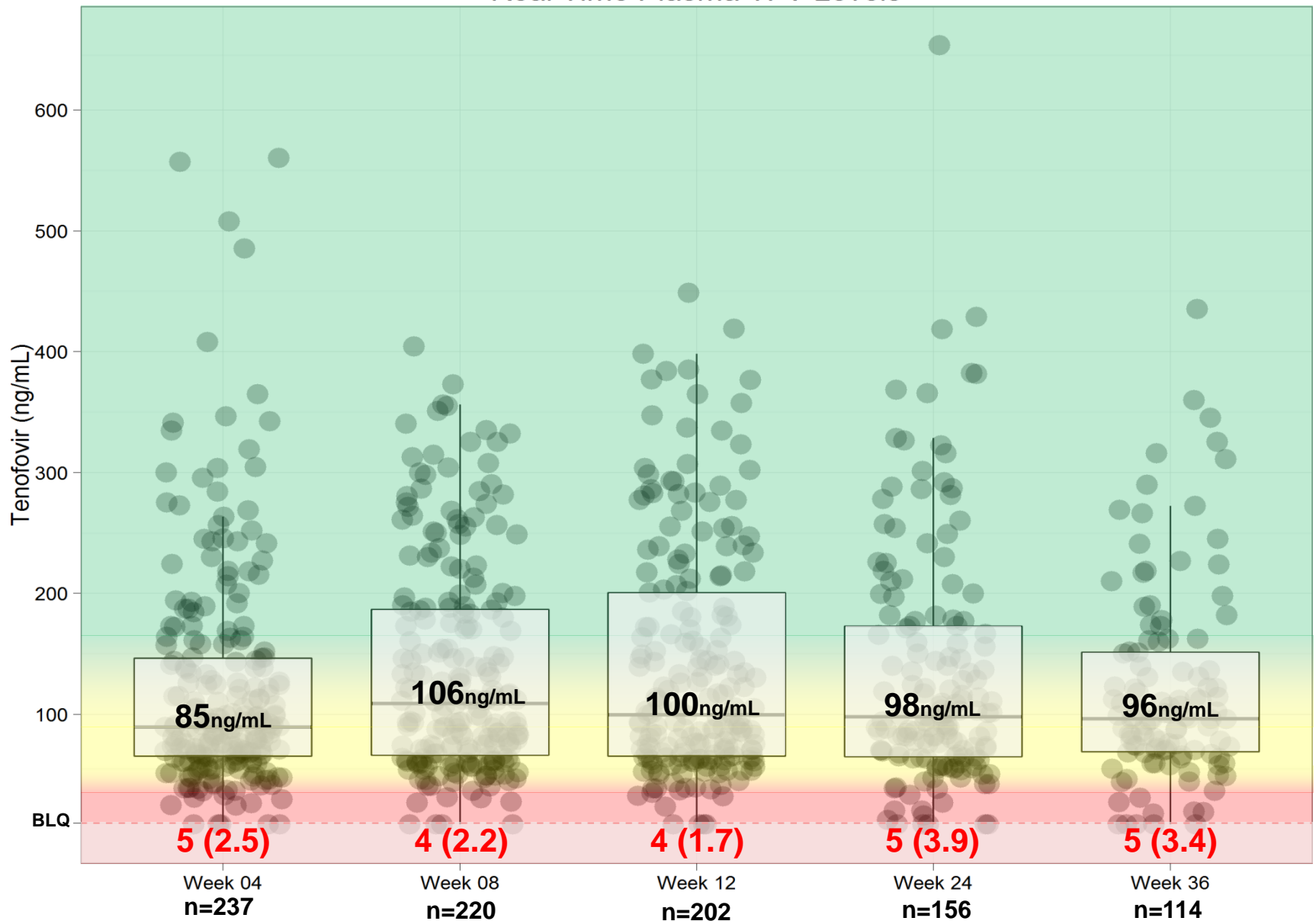


Preliminary DBS Adherence Data (06/15/15)

■ 3M (n = 171) ■ 6M (n = 136) ■ 12M (n = 49)



Real Time Plasma TFV Levels



*BLQ – 30: No drug/up to a single dose in the past 48 hours.

60 – 80: Trough concentration at steady state with daily dosing for at least 48 hours.

200 – 300: Peak concentration at steady state with daily dosing for at least 48 hours.

Landovitz et al

How To Improve Chemoprophylaxis Effectiveness?

New Oral PrEP Drugs and Dosing Strategies



Novel Adherence Strategies



Alternative Delivery Systems and Formulations



**Vaginal & Rectal
Microbicides**



Intravaginal rings



**Injectables:
ARVs and mAbs**

Impact of age on adherence

- iPrEX sub-study (*Liu, JAIDS, 2014*)

TABLE 4. Proportion and Factors Associated With Sometimes and Always (vs. Never) Drug Detection Over Time*

Characteristics	Never Detected, %	Sometimes Detected, %	Always Detected, %	OR (Some vs. Never) (95% CI)	<i>P</i>	OR (Always vs. Never) (95% CI)	<i>P</i>
Age							
≤20	58	29	13	Ref		Ref	
21–25	28	45	27	4.04 (1.66 to 9.85)	0.002	6.32 (2.09 to 19.09)	0.001
26–30	32	44	24	3.42 (1.21 to 9.67)	0.02	4.74 (1.26 to 17.76)	0.021
>30	16	29	55	5.13 (1.87 to 14.07)	0.001	33.24 (9.91 to 111.45)	<0.001


- Partners PrEP sub-study
 - AOR 1.7 (1.3–2.1, $p=0.01$) for <80% MEMS adherence (*Haberer, PLoS Med, 2013*)

Tailoring PrEP for Key Populations

HPTN 073 Black MSM

Client-centered care
coordination (C4)

(Wheeler/Fields)



*We've launched a new PrEP demonstration project
for Black men who have sex with men.*

Participate in the live Twitter chat on

#HPTN073 **Wednesday, August 14** #PrEPChat
at 10 am PT / 1 pm ET

With our guests: @JonPaulLucas and @cchauncey
Be sure to follow @HIVptn

Join the HPTN 073 Webinar:

"Introducing HPTN 073: A BMSM PrEP Demonstration Study"
at 11 am PT / 2 pm ET
by registering at
<http://bit.ly/073Webinar>

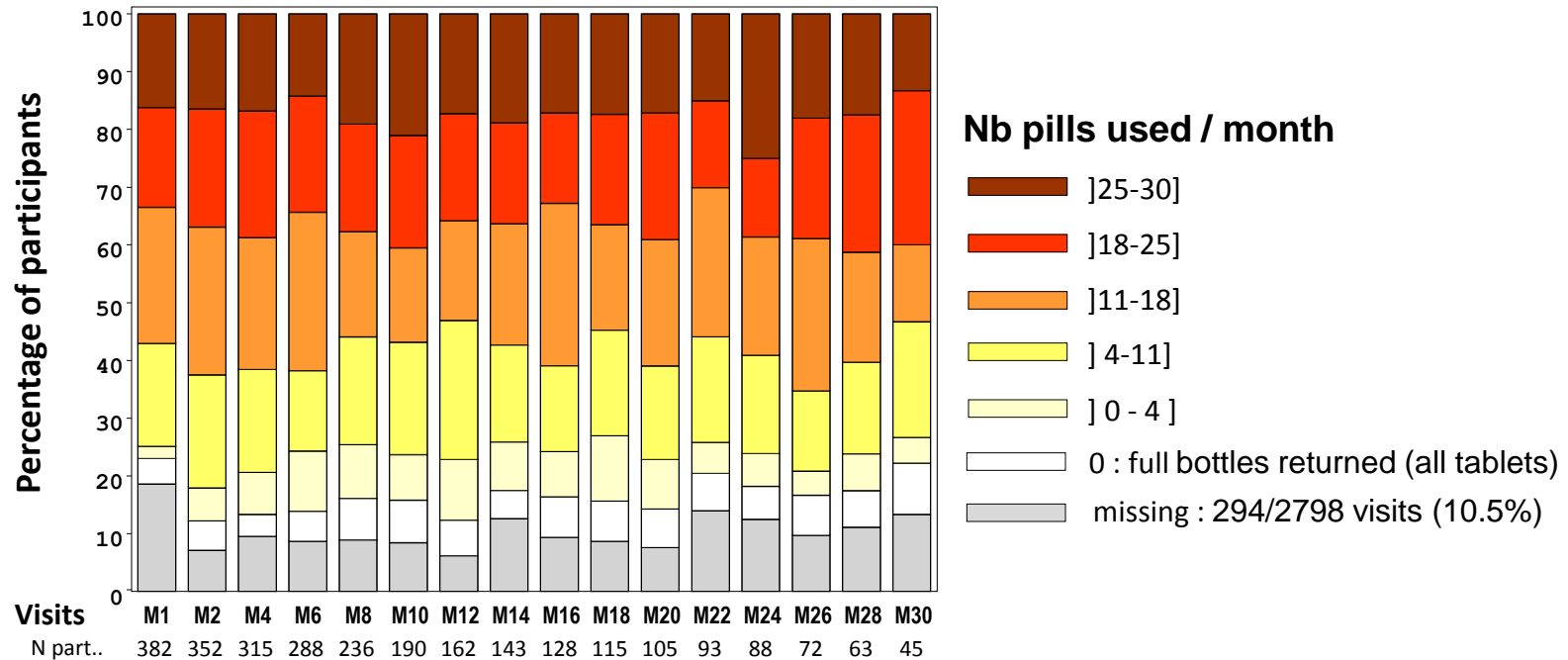
Find out more about HPTN 073 at

ATN 110/113

- YMSM 15-22 y.o.
- PreP + Individual vs.
group EBI behavioral
intervention (Hosek et al)

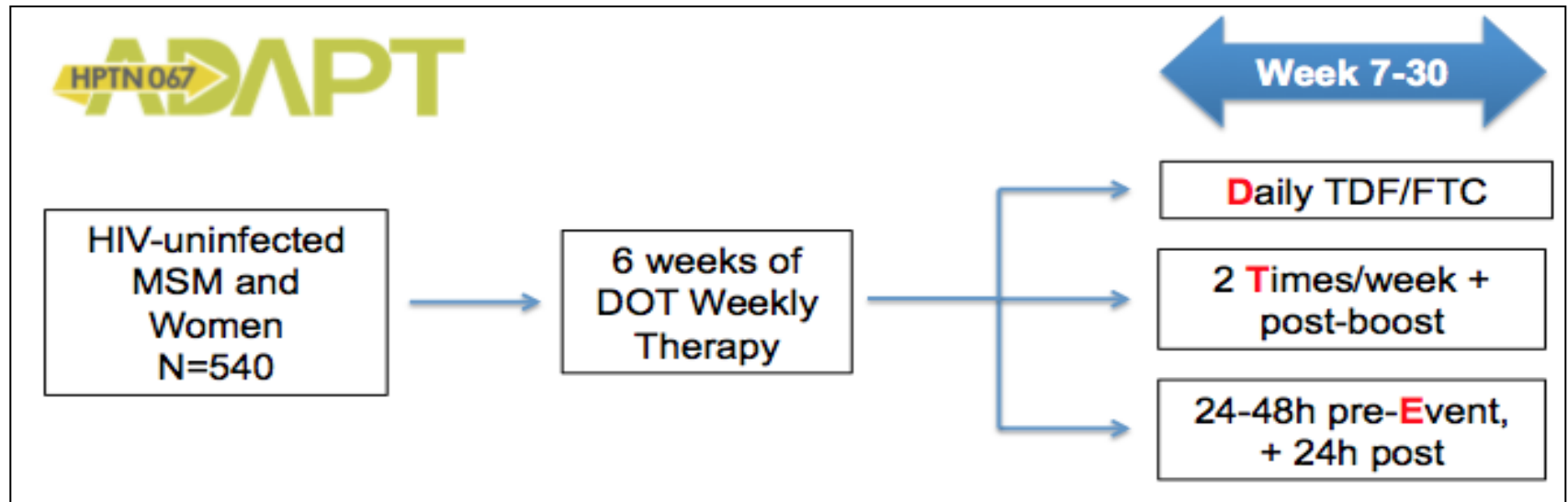


iPERGAY TDF/FTC Usage



- **Median number of pills/month (IQR):** 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm ($p=0.84$)
- **48 participants (12%) received PEP**
25 (13%) in the TDF/FTC arm and 23 (11%) in the placebo arm ($p=0.73$)

HPTN 067: Women



Dosing Regimen	<u>Drug detected in Plasma</u>		Coverage
	Week 10	Week 30	
Daily	93%	79%	75%
Time-driven	87%	63%	56%
Event-driven	78%	53%	52%

Low rates of adverse events, no difference in rates of (rare) seroconversion

HPTN 083 Study schema

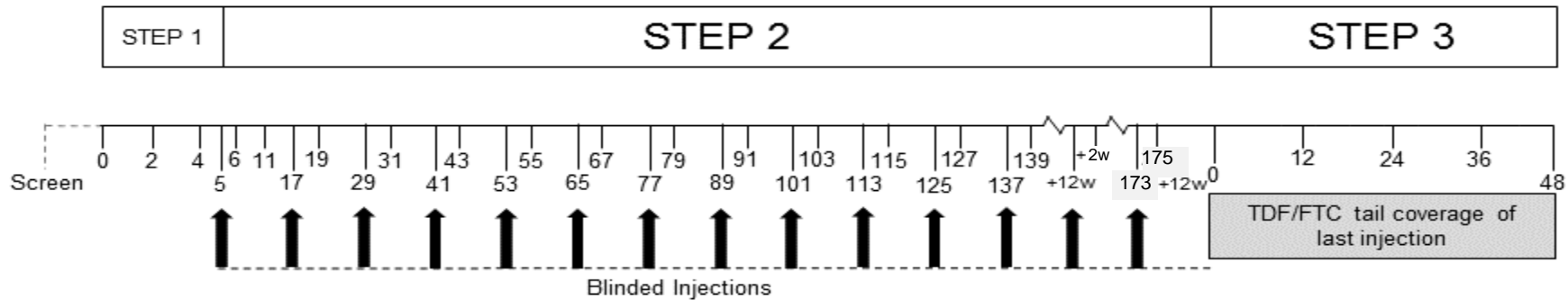
4500 HIV-uninfected MSM/TGW in Asia, North & South America will be randomized 1:1 to:

Step 1: Oral TDF/FTC or Cabotegravir 30 mg daily x 5 weeks (DB)

Step 2: Oral TDF/FTC daily or IM Cabotegravir 800 mg every 3 months (DB)
Continues until required number of seroconversions reached (mean 2.5y)

Step 3: Open label TDF/FTC daily to cover PK “tail”

Post-trial access under discussion



ARM A
1:1
ARM B

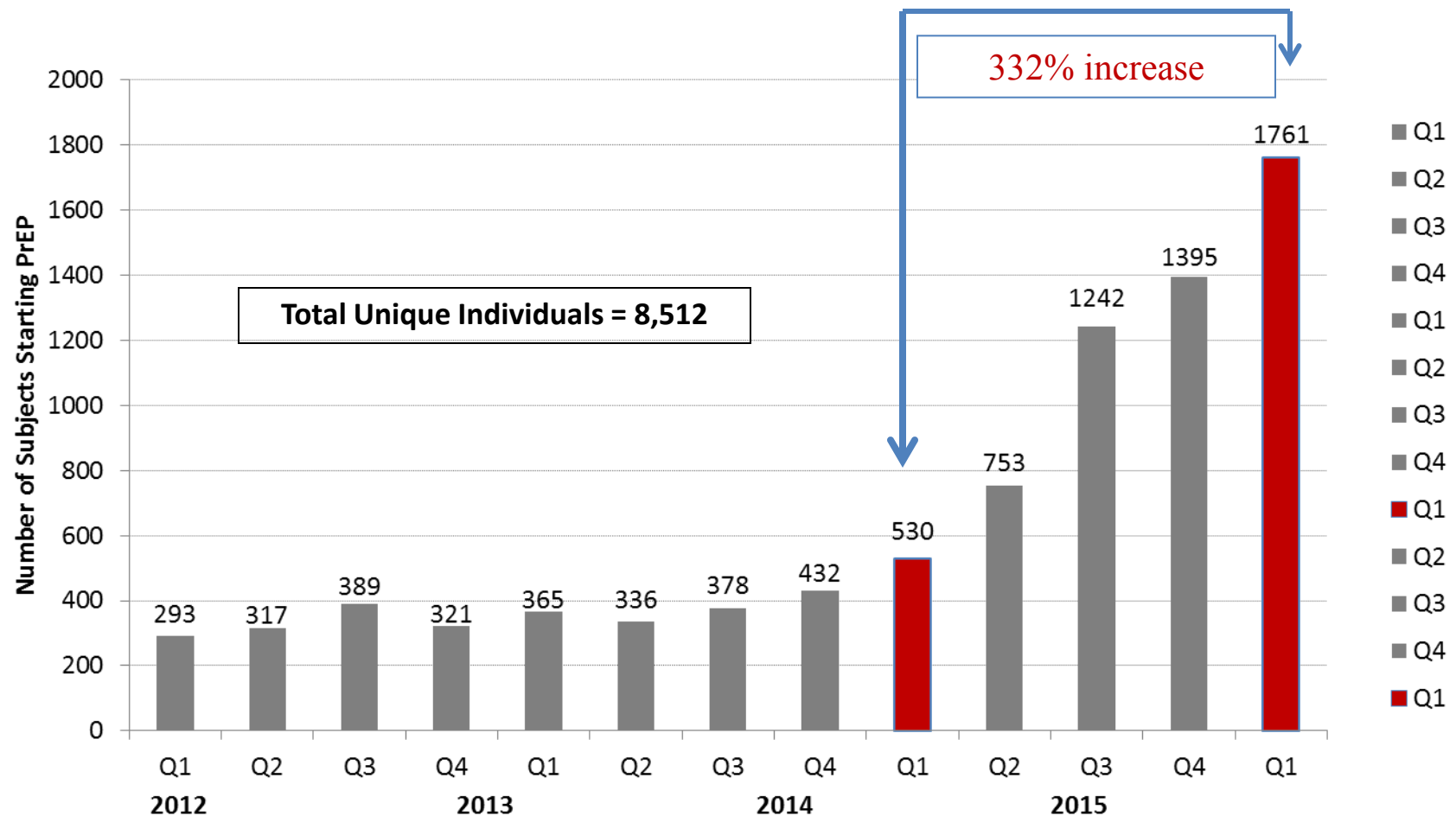
Oral CAB 30 mg PO QD	CAB LA 800 mg IM Q12Weeks + TDF/FTC PBO PO QD	Open label TDF/FTC PO QD
TDF/FTC PBO QD		
TDF/FTC PO QD	TDF/FTC PO QD + PBO IM Q12Weeks	Transition to local HIV prevention services
Oral CAB PBO PO QD		

Blinded study duration 65-185 Weeks

PK “tail” coverage

Arm A participants will begin Step 3 approximately 12 weeks after final injection

New PrEP Starts per Quarter



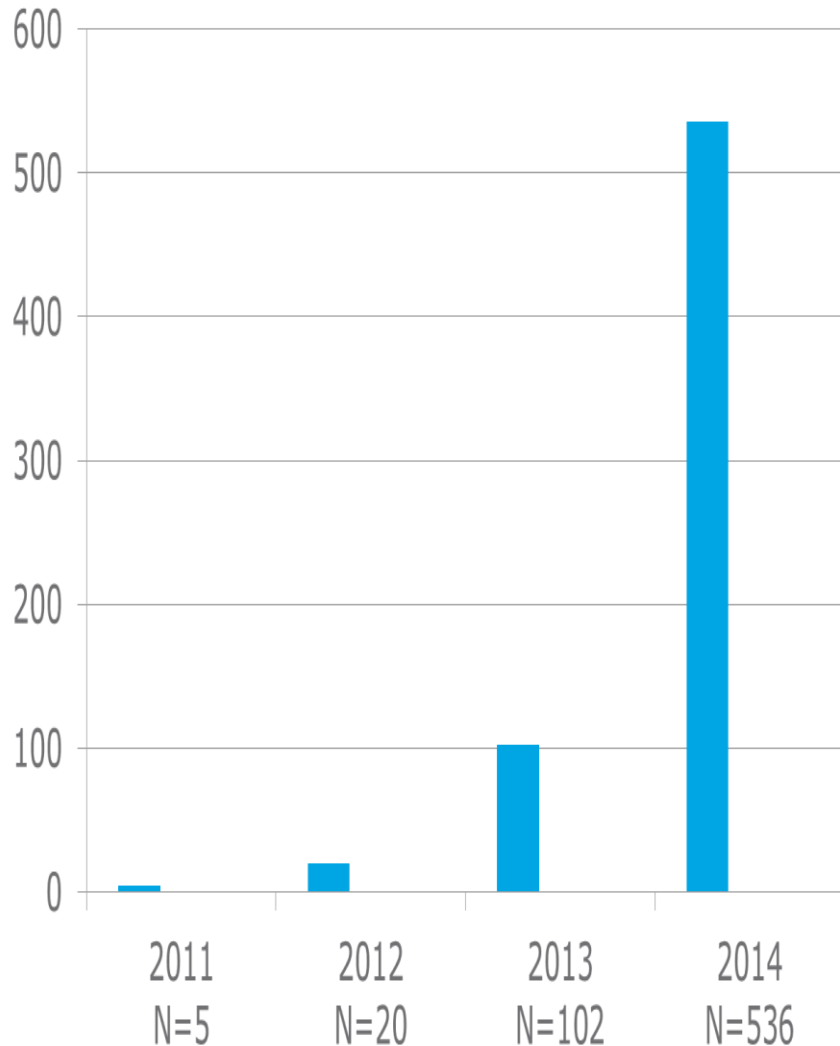
IMS National Prescription Database accounts for approx. 39% of all TVD prescriptions

PrEP Eligibility and Use in SF

Group	People
HIV negative at substantial risk:	
MSM with 2+ non-condom anal sex (ncAI) partners ¹	12,589
MSM with 0 ncAI and an STI in the last year ²	2,325
Female partners of HIV+ MSM ³	653
Trans women ⁴	522
TOTAL estimated PrEP eligibility	16,089
TOTAL reporting any PrEP in past year ⁵	5,059
Percent of eligible people using PrEP in the past year	31%

1. SF City Clinic 2014 survey x HIV negative MSM population of 50,000;
2. SF NHBS self report of STI among MSM with 0 ncAI in 2014 x HIV negative MSM population of 50,000;
3. SF NHBS MSM reporting female partners in 2014 x HIV positive MSM population of 14638.
4. IDU and ncRAI in est. 923 HIV negative trans women in SF, adapted from Wilson *BMCID* 2014 14:430.
5. SF NHBS 2014, data on file.

Fenway Health: PrEP Experience



- 85.5% of initiators still on PrEP; Longest: 3.8 years
- 79.7% White; 8% Black; 12.3% Latino
- 95.1% identified as gay
- 158 zip codes
- “Gayborhood” <10%
- Private Ins: 80.7%; Medicare: 9%; Medicaid: 8.7%
- 25.9% who d/c’ed PrEP, initiated again
- More than 30 prescribers

Factors Associated with PrEP Use among US MSM

Multivariable Model, Manhunt Survey, 1/14

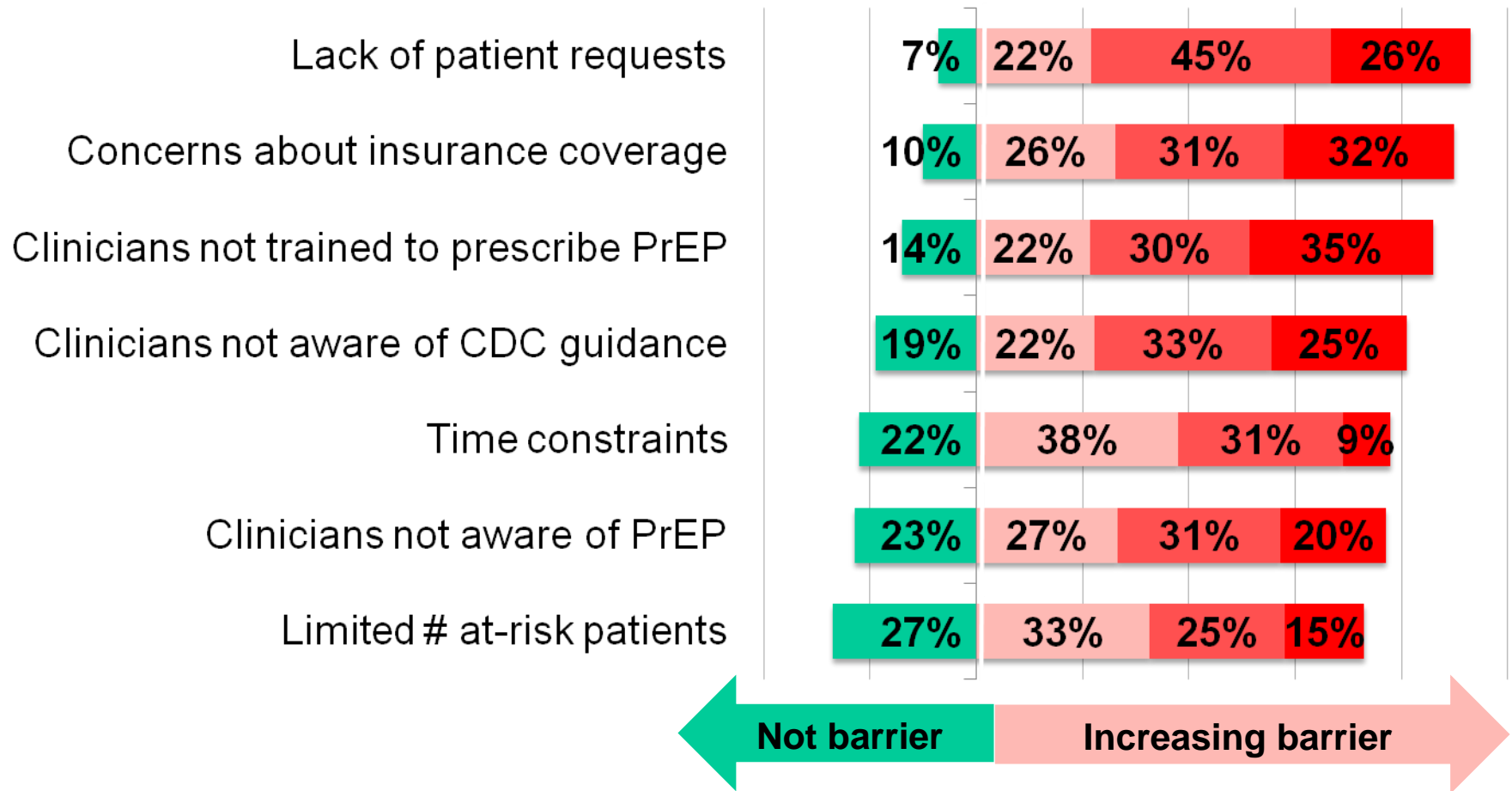
(under review)

Characteristic	Multivariable OR (95% CI)
College graduate or above (vs. less than college education)	5.33 (1.25 to 22.7)
Ever diagnosed with an STI	2.74 (1.36 to 5.52)
Used PEP	16.0 (8.24 to 31.2)
Comfortable talking with provider about MSM sex	4.19 (1.51 to 11.6)

MSM in states that were more LGBT supportive were more likely to use PrEP, be out to their providers, and less likely to engage in condomless sex (Oldenburg et al, AIDS, in press, 2015)

New England providers perceived numerous barriers to prescribing PrEP

(Krakower, PLOS ONE, in press 2015)



Beth Israel Deaconess
Medical Center



A teaching hospital of
Harvard Medical School



Numbers represent percentage for each response category: not a barrier, minor barrier, moderate barrier, major barrier. Bars total to 100%

Purview paradox: contradictory beliefs about who should prescribe PrEP

(Krakower D, AIDS and Behavior, 2014; Smith D, JAIDS, 2014)

HIV providers:

PrEP best
prescribed

By PCP

**Primary care
providers:**

PrEP meds are too
complicated

HIRI-MSM Risk Index*			
1	How old are you today (yrs)?	<18 years	score 0
		18–28 years	score 8
		29–40 years	score 5
		41–48 years	score 2
		≥49 years	score 0
2	How many men have you had sex with in the last 6 months?	>10 male partners	score 7
		6–10 male partners	score 4
		0–5 male partners	score 0
3	In the last 6 months, how many times did you have receptive anal sex (you were the bottom) with a man?	1 or more times	score 10
		0 times	score 0
4	How many of your male sex partners were HIV positive?	>1 positive partner	score 8
		1 positive partner	score 4
		<1 positive partner	score 0
5	In the last 6 months, how many times did you have insertive anal sex (you were the top) with a man who was HIV positive?	5 or more times	score 6
		0 times	score 0
6	In the last 6 months, have you used methamphetamines such as crystal or speed?	Yes	score 5
		No	score 0
7	In the last 6 months, have you used poppers (amyl nitrate)?	Yes	score 3
		No	score 0
Add down entries in right column to calculate total score			Total score†

Conclusions

- Oral PrEP works, if used
- Adherence is the 1⁰ issue to ensure success
- Behavioral interventions may ↑ adherence
- New technologies to measure adherence are being developed
- New technologies to enhance adherence are also being developed
- New delivery systems for PrEP may obviate some challenges for PrEP (e.g. quarterly injections)
- Providers need to be engaged
- PrEP is a work in progress

Antiretrovirals alone are not sufficient

Interventions to Increase Testing

Test

HIV Negative

HIV Positive

Risk Assessment
PrEP, Adherence
Counseling

Positive
Prevention

Linkage
To Care

Address concomitant concerns:
depression, substance use, relationship
dynamics

Enroll in Care

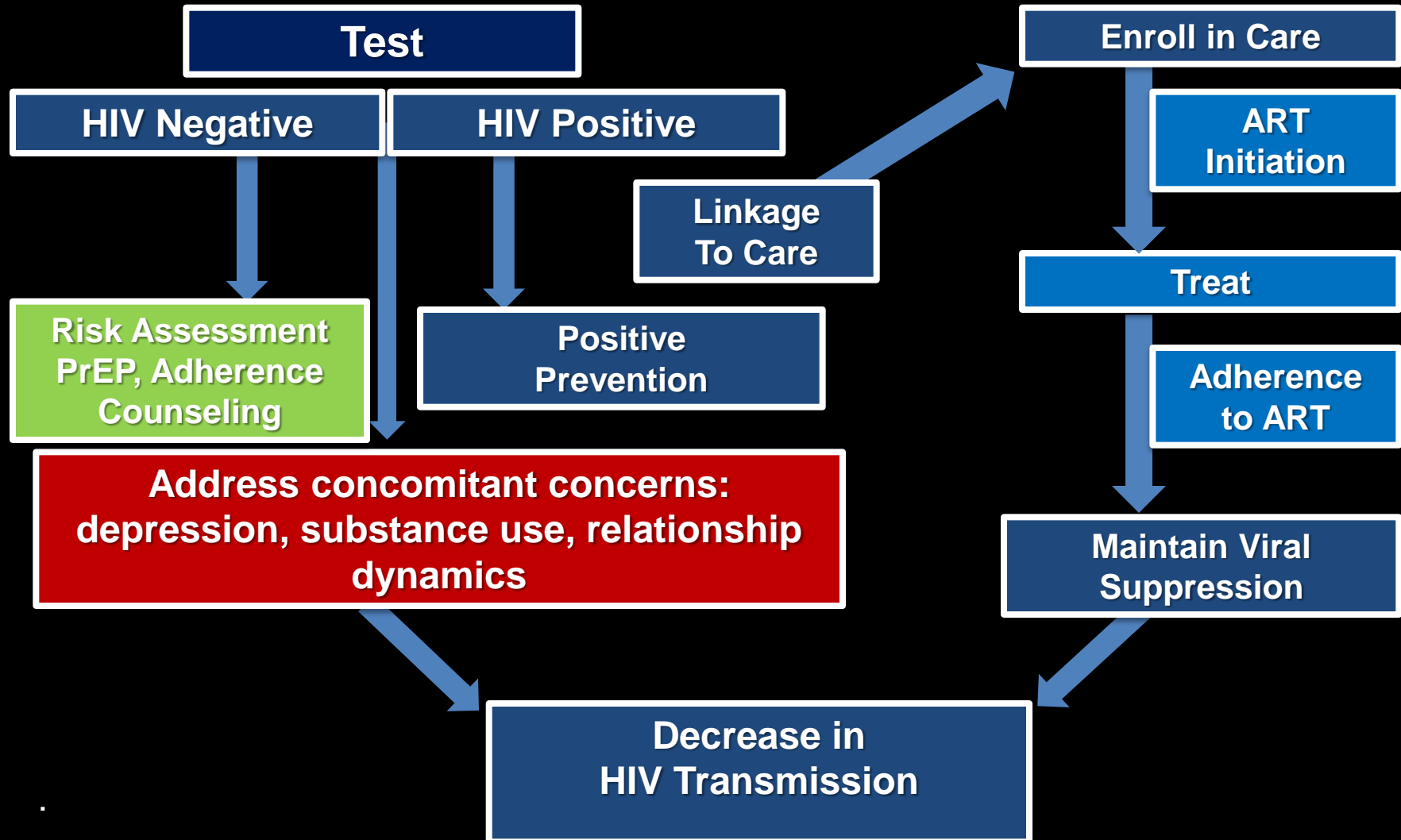
ART
Initiation

Treat

Adherence
to ART

Maintain Viral
Suppression

Decrease in
HIV Transmission



Salim and Quarraisha Abdool Karim

Rivet Amico

Peter Anderson

Susan Buchbinder

Marcy Gelman

David Glidden

Sarit Golub

Robert Grant

Craig Hendrix

Jessica Haberer

Sybil Hosek

Doug Krakower

Raphy Landovitz

Albert Liu

Sheena McCormack

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Ian McGowan

Jean-Michel Molina

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