A Pill a Day To Keep HIV Away

Robert M Grant,

Jan 6, 2011

Maurice Cook (EM Designs Group, Inc.)

The HIV Pandemic

- 2.6 Million New HIV Infections in 2009
  - –41% in Young People (ages 15-24)
  - –One New Infection...
    - Every 12 Seconds in the World
    - Every 9 Minutes in the United States
    - Every Day in San Francisco
- 1.2 Million Started Therapy in 2009
  - –2 New Infections For Everyone Starting Therapy

World Health Organization

UNAIDS

HIV Prevention For Sexual Transmission With Efficacy Demonstrated in RCT

Intervention	Population	Exposed Mucosa
Male Circumcision	Heterosexual Men	Penile
Enhanced STI Care	Heterosexual Men and Women	Penile and Vaginal
ALVAC/AIDSVAX	General Population	Mixed
TDF 1% Vaginal Gel	Heterosexual Women	Vaginal

Grosskurth 2000, Auvert 2005, Gray 2007, Bailey 2007, Rerks-Ngarm 2009, Abdool Karim 2010.

HIV Prevention Methods
With Demonstrated Efficacy in MSM

None

MSM Have 19.3 Higher Odds of HIV Infection

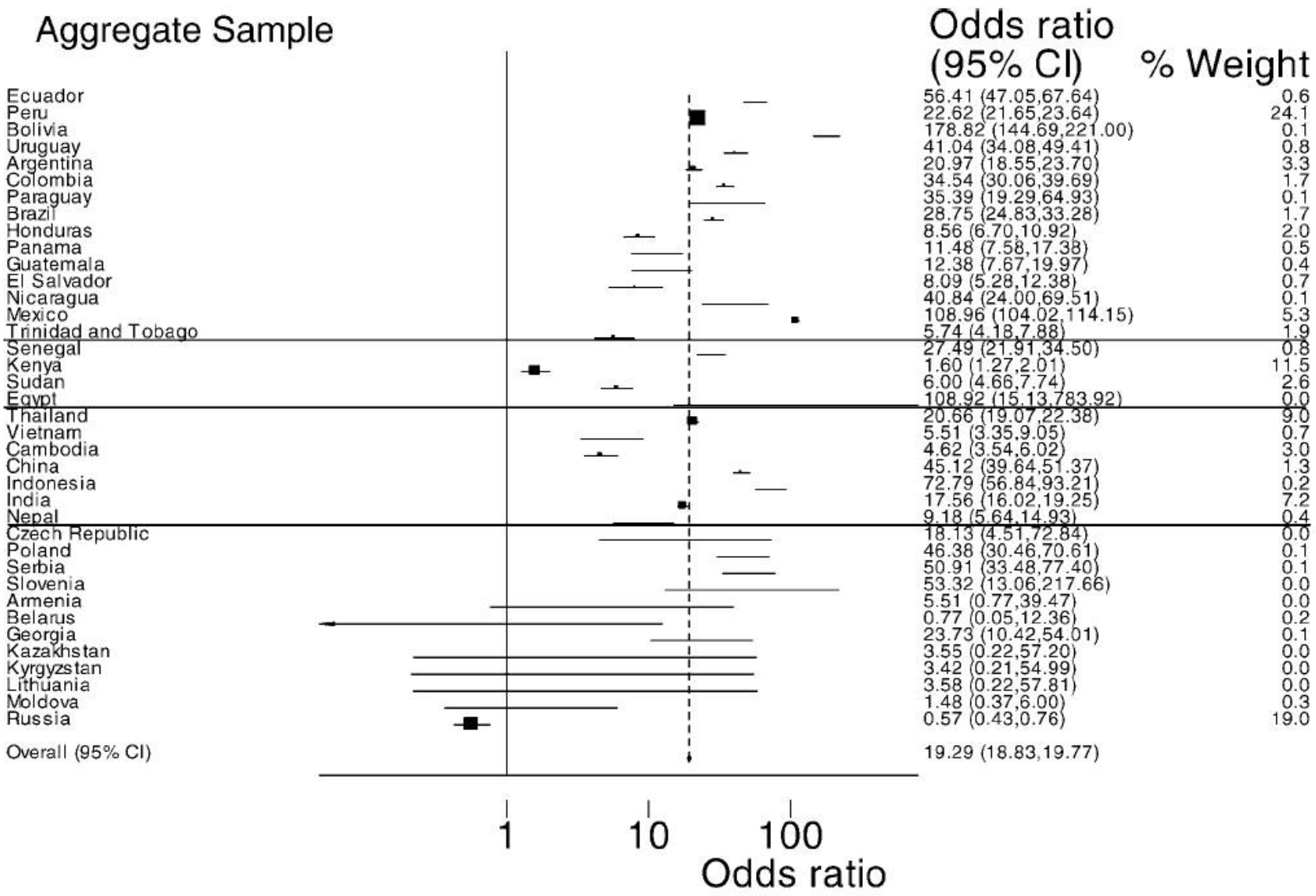


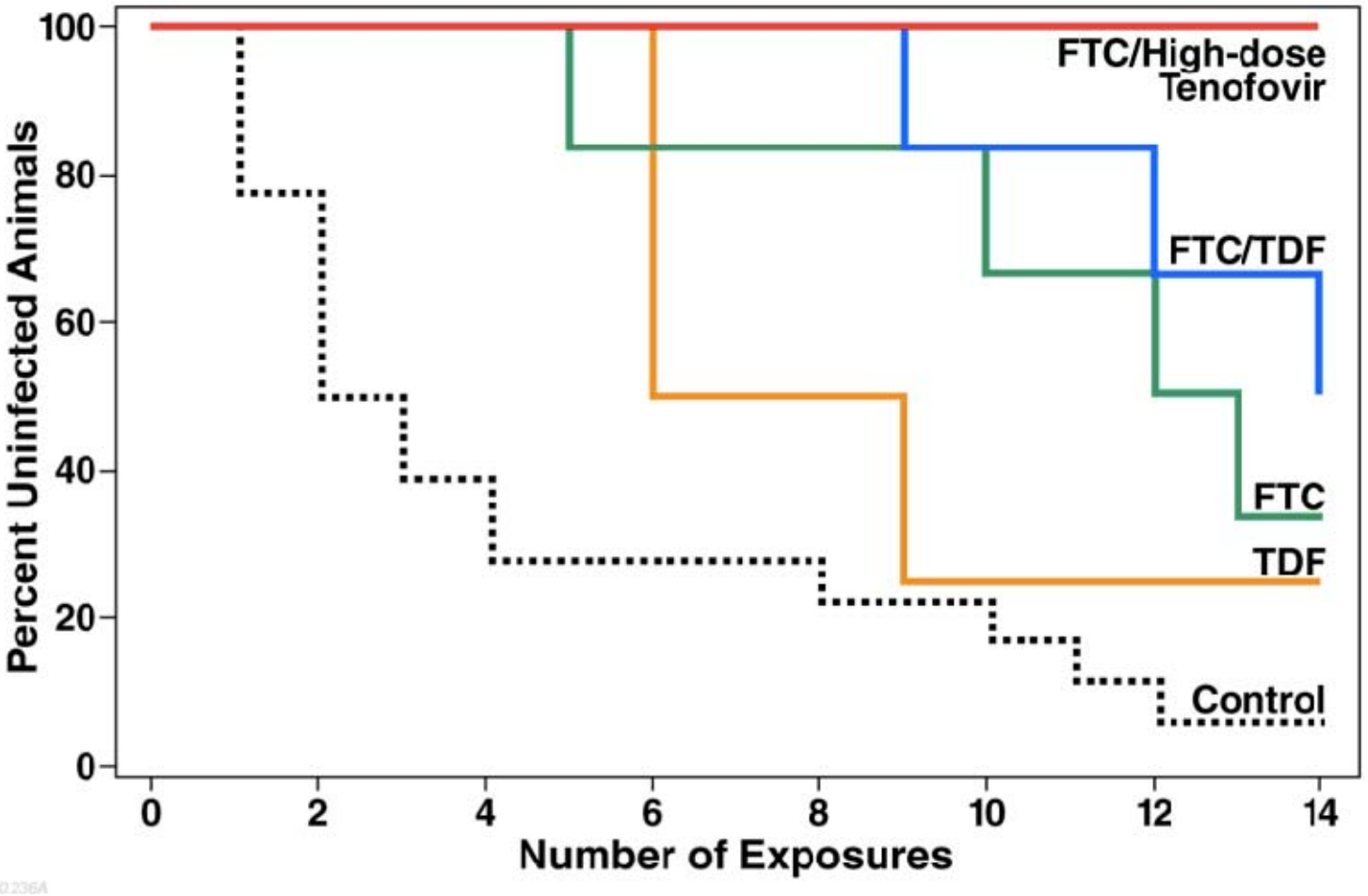
Figure 2. Forest Plot Showing Meta-Analysis of Risk of HIV Infection among MSM Compared with Adults of Reproductive Age in Low- and Middle-Income Countries, 2000–2006

Baral S, Plos Med 2007

Why
Tenofovir
and/or
Emtricitabine?

Monkey Studies at CDC

Repeated Rectal SHIV Exposure



Subbarao ‘06; Garcia-Lerma ’08;
See also, Tsai ‘95; Van Rompay ‘99 ‘00 ‘01 ‘04;

OPEN ACCESS Freely available online

PLOS CLINICAL TRIALS

Tenofovir Disoproxil Fumarate for Prevention of HIV Infection in Women: A Phase 2, Double-Blind, Randomized, Placebo-Controlled Trial

Leigh Peterson[1*], Doug Taylor[1], Ronald Roddy[2], Ghiorghis Belai[1], Pamela Phillips[1], Kavita Nanda[1], Robert Grant[3,4], Edith Essie Kekawo Clarke[5], Anderson Sama Doh[6], Renee Ridzon[7], Howard S. Jaffe[8], Willard Cates[1]

2007

- Daily oral TDF vs Placebo
- 936 Women, 428 person years
- No Excess Adverse Events
  - Including in 23 with HBsAg+
- A trend toward efficacy
  - 8 seroconversions (2 TDF: 6 Placebo; P=0.34)
  - 2 seroconversions after 1 and 2 months of TDF

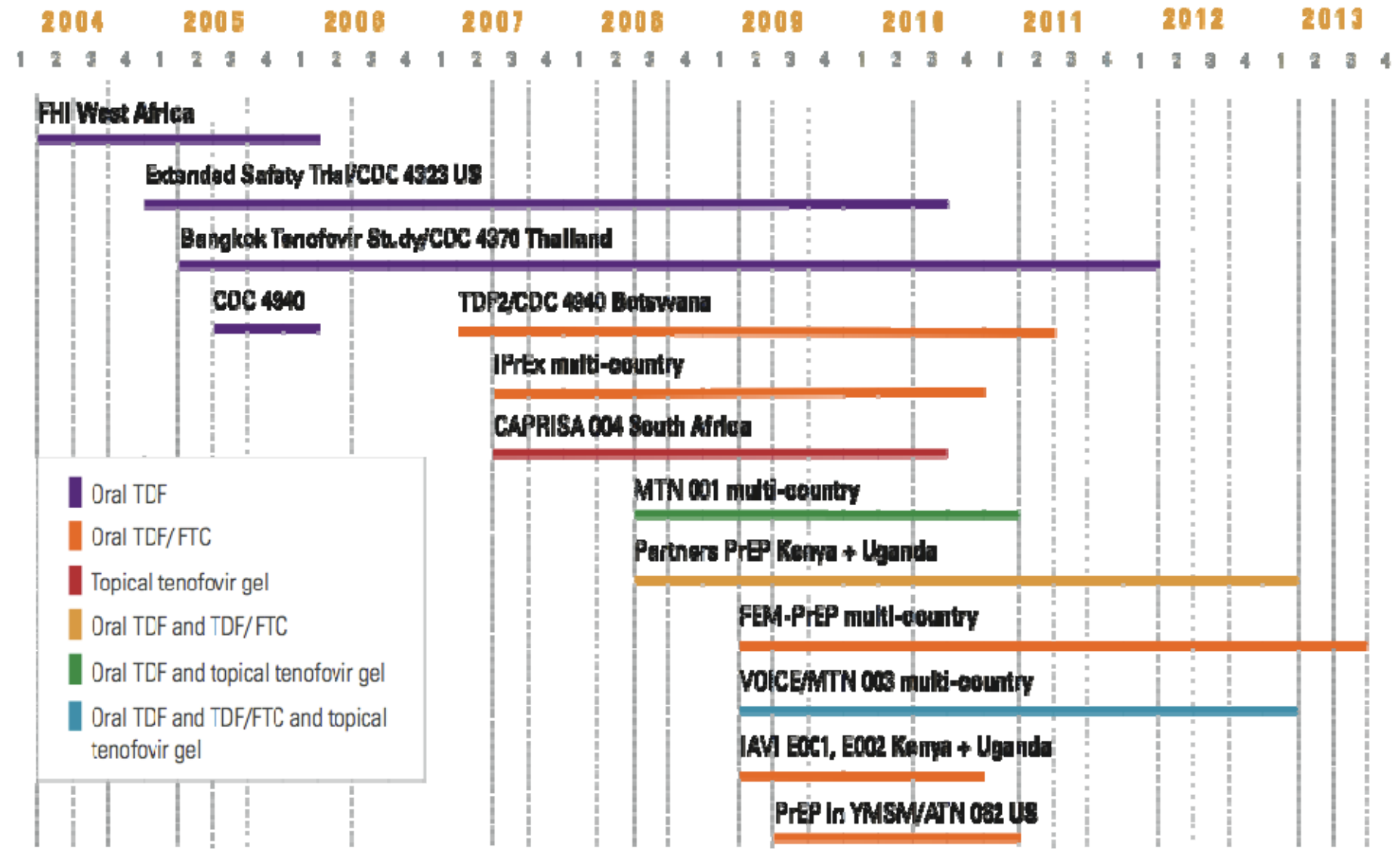
CDC US MSM Study

	TDF	Placebo
• 400 MSM in United States		
• Cr Increase > 0.5mg/dL	1.1%	3.2%
• Grade 3 or 5 hypophos	0%	2.6%
• Any Grade 3 or 4 AE	10%	9.0%
• 5% loss of BMD	8%	3%*
• HIV infections	0	3
– +3 in deferred arm		

Grohskopf et al, Vienna 2010

*P=0.21

PrEP Trials Timeline*



AVAC

November 2010

* The trial end-dates listed in this table are estimates. Due to the nature of clinical trials the actual dates may change. AVAC will continue to monitor trial progress and will update the timeline accordingly. To view or download an updated timeline visit www.avac.org/prep.

PrEP Initiative / Iniciativa PrEx

Sponsored by

NIH/NIAID/DAIDS

with co-funding by the

Bill & Melinda Gates Foundation

and drug donated by

Gilead Sciences

New England Journal of Medicine, online Nov 23, 2010

iPrEx: Global Prevention Initiative

Enrolled	**2,499**
HIV Test and Counseling Visits	**39,613**
Baseline Partners (median, 12 wks)	**7**
Follow-up Partners (median, 12 wks)	**2**
Syphilis Cases Dx and Rx	**1,019**
Condoms distributed	**585,000**
HBV vaccine doses given	**4,533**

New England Journal of Medicine, online Nov 23, 2010

650,000
Case Report Forms
through
May 1, 2010

22 stories
217 feet

Coit Tower, 180 feet, San Francisco

New England Journal of Medicine, online Nov 23, 2010

- **MSM Bear a Major Burden**
  - Throughout the Americas
  - In Parts of Asia
  - Burden in Africa Is Increasingly Appreciated
- **Efficacy Could Be Different**
  - Possibly Different Penetration of Virus and Drug into Rectal Tissue
- **iPrEx is The Only Efficacy Study of PREP in MSM**

New England Journal of Medicine, online Nov 23, 2010

Fully enrolled as of December 2009

Sites	11
Participants	2,499

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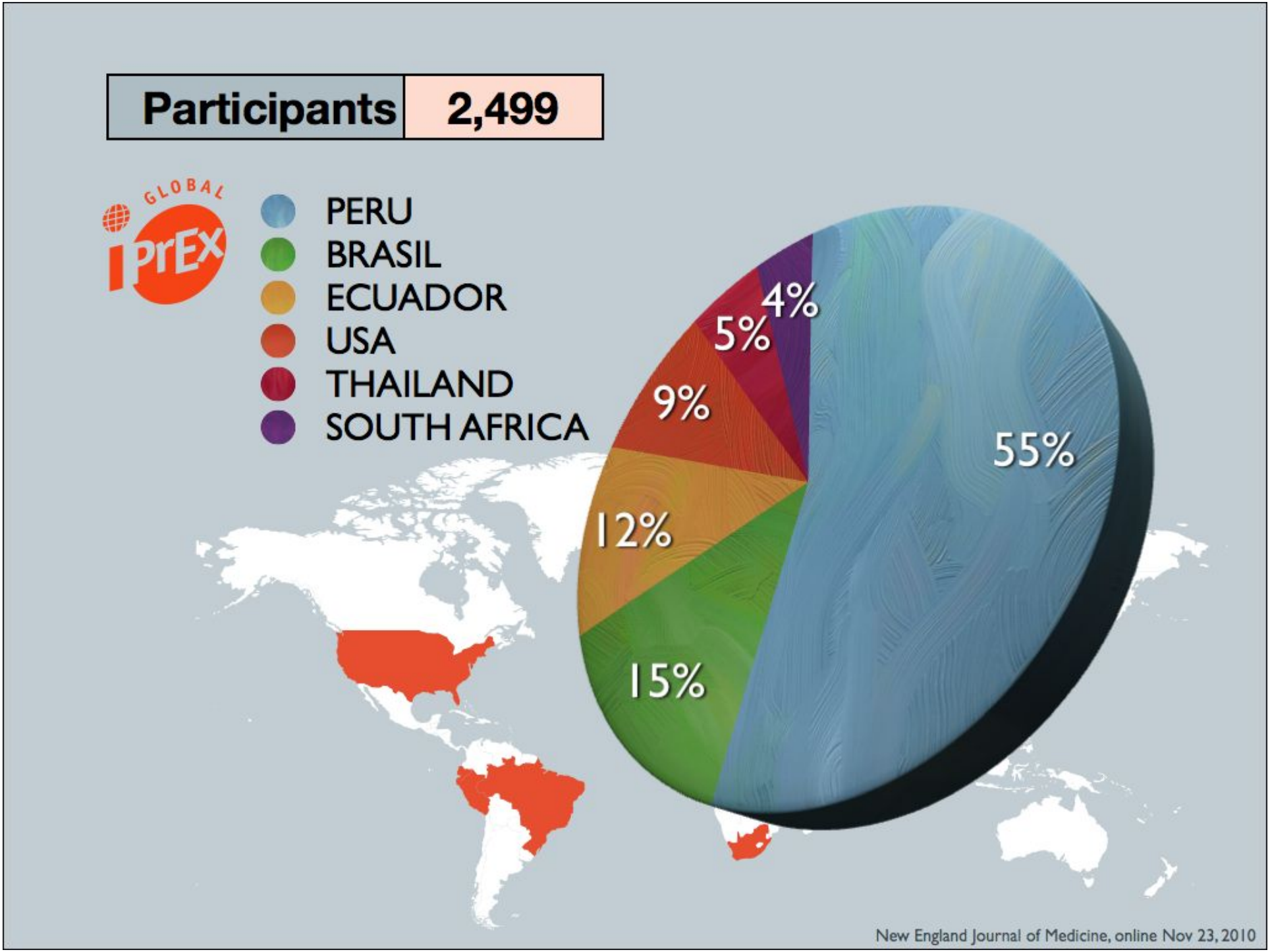
Participants	2,499



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The iPrEx Study

- **MSM**
- **Randomized 1:1 Daily Oral PREP**
- **FTC/TDF vs Placebo**
- **Followed on Drug for:**
  - HIV seroconversion
  - Adverse Events (especially renal & liver)
  - Metabolic Effects (Bone, Fat, Lipids)
  - HBV Flares among HBsAg+
  - Risk Behavior & STIs
  - Adherence
  - If infected
    - *Drug Resistance*
    - *Viral load*
    - *Immune responses & CD4 Count*

Comprehensive Prevention Services Given to All

- HIV testing monthly
- Risk reduction counseling
- Condoms (15 or more)
- STI testing if any symptoms, monthly
- STI screening for all every 24 weeks
- Partner STI treatment
- PEP if requested and meet local criteria
- HBV vaccine

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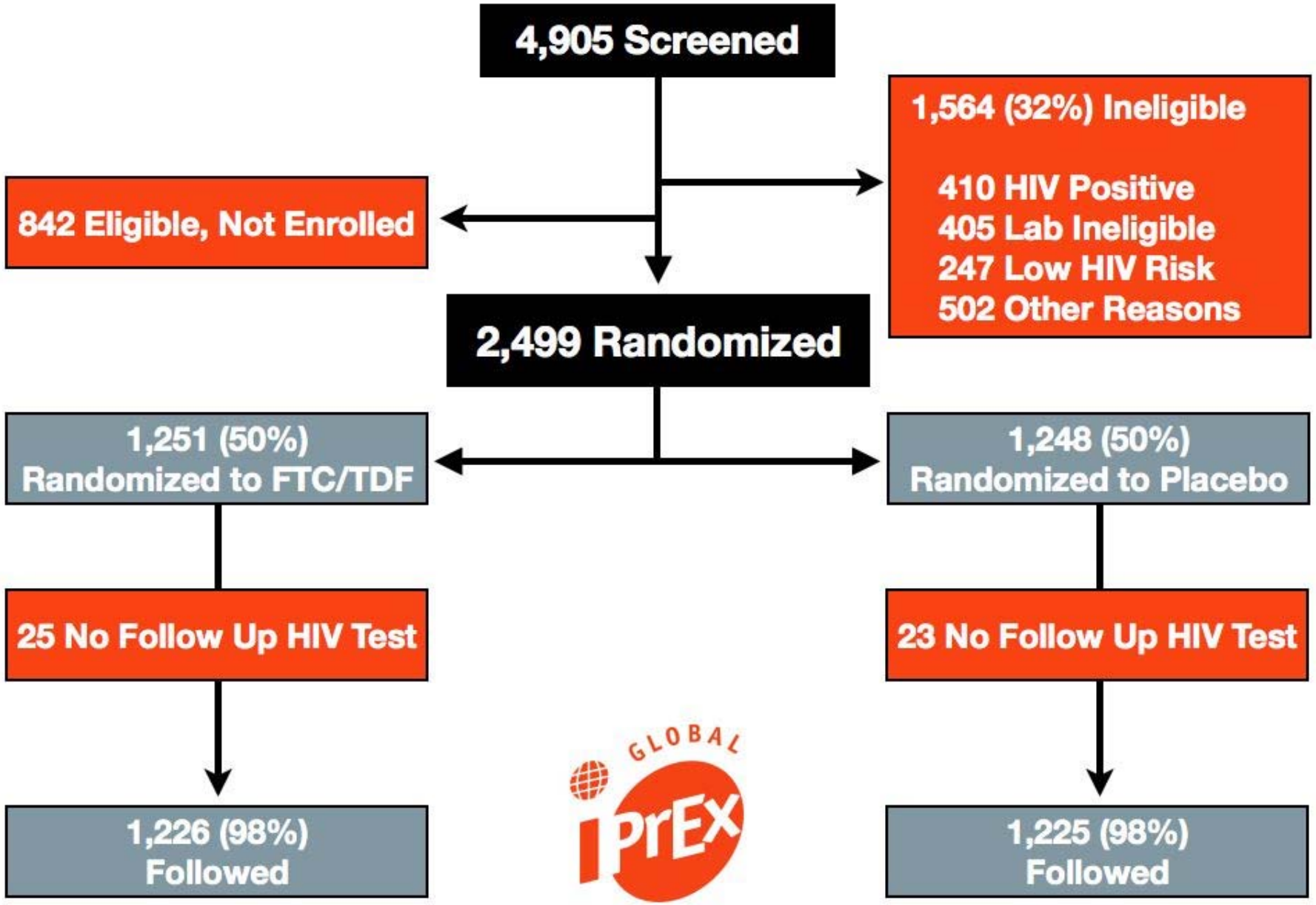

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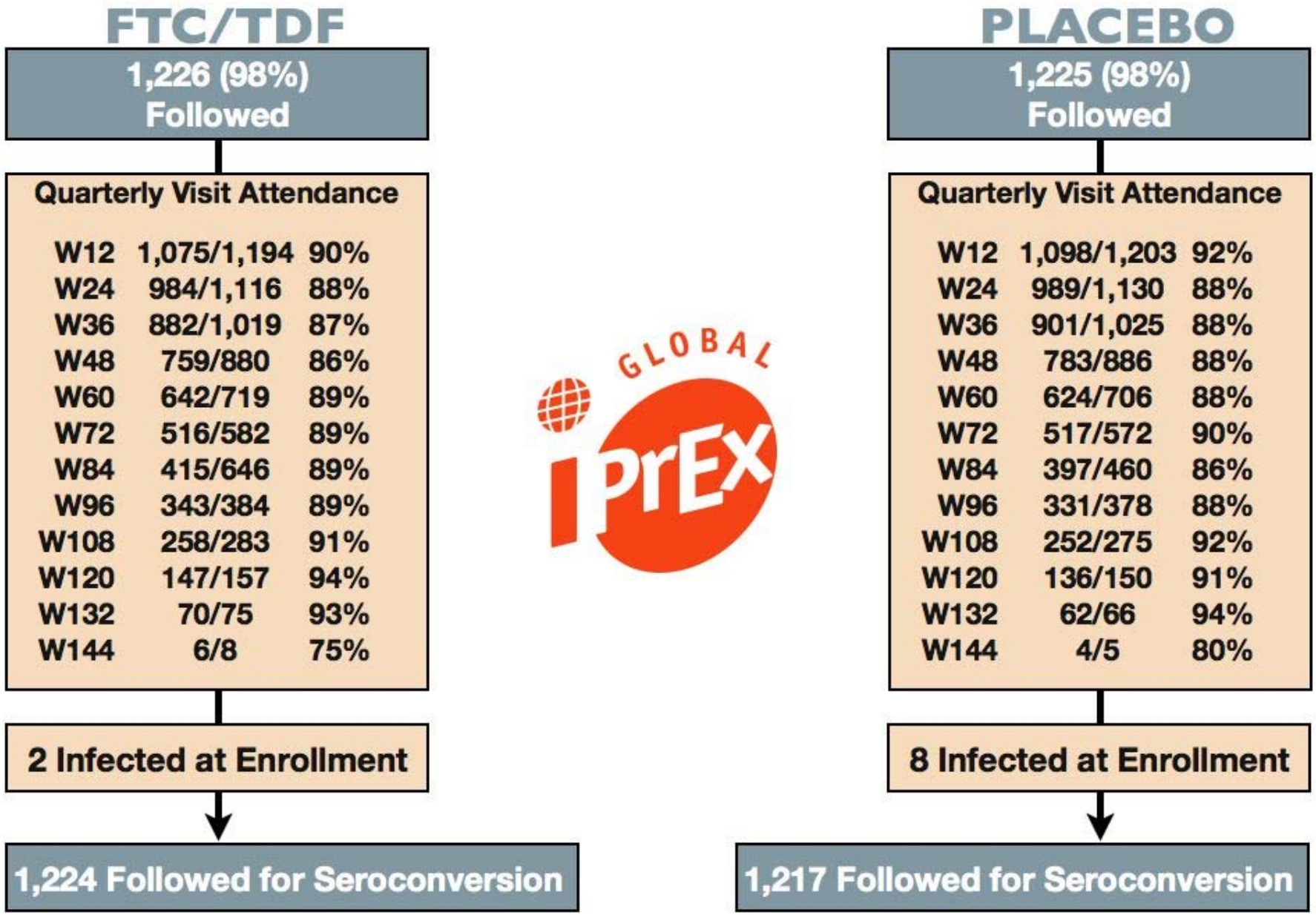

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2 Infected at Enrollment

1,224 Followed for Seroconversion

Off Study During Follow -Up	199	16%
- Unable to contact	87	7%
- Participant relocated	51	4%
- Refused further participation	41	3%
- Investigator decision	11	1%
- Death	1	0%
- Other reasons	8	1%

FTC/TDF

8 Infected at Enrollment

1,217 Followed for Seroconversion

Off Study During Follow -Up	182	15%
- Unable to contact	55	4%
- Participant relocated	59	5%
- Refused further participation	46	4%
- Investigator decision	5	0%
- Death	4	0%
- Other reasons	13	1%

PLACEBO

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Baseline Characteristics of the Participants, According to Study Group

Characteristic	FTC/TDF	PLACEBO
Age - no. (%) P=0.04	**(n=1,251)**	**(n=1,248)**
18-24	591 (47)	662 (53)
25-29	274 (22)	241 (19)
30-39	249 (20)	224 (18)
≥40	137 (11)	121 (10)

New England Journal of Medicine, online Nov 23, 2010

Baseline Characteristics of the Participants, According to Study Group

Characteristic	FTC/TDF	PLACEBO
Education Level - no. (%) P=0.26	**(n=1,251)**	**(n=1,248)**
Less than Secondary	279 (22)	244 (20)
Complete Secondary	430 (34)	453 (36)
Post-Secondary	525 (42)	539 (43)
No Answer / Missing	17 (1)	12 (1)

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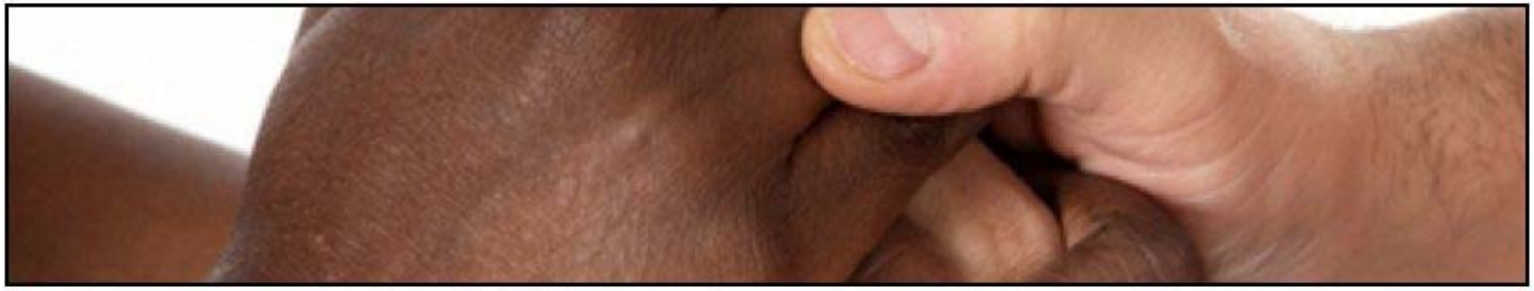
Baseline Characteristics of the Participants, According to Study Group



Characteristic	FTC/TDF	PLACEBO
Race/Ethnicity - no. (%) P=0.40	(n=1,251)	(n=1,248)
Black	117 (9)	97 (8)
White	223 (18)	208 (17)
Mixed/Other	849 (68)	878 (70)
Asian	62 (5)	65 (5)
Hispanic/Latino (any race)	900 (72)	906 (73)

iPrEx

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Baseline Characteristics of the Participants, According to Study Group

Characteristic	FTC/TDF	PLACEBO
Number of Alcoholic Drinks (on Days when Alcohol Consumed - no. (%) P=0.40	(n=1,251)	(n=1,248)
0 (in the past month)	206 (16)	184 (15)
1-4 per day	348 (28)	345 (28)
≥ 5 per day	666 (53)	687 (55)
Refused/Missing/Don't Know	31 (2)	32 (3)

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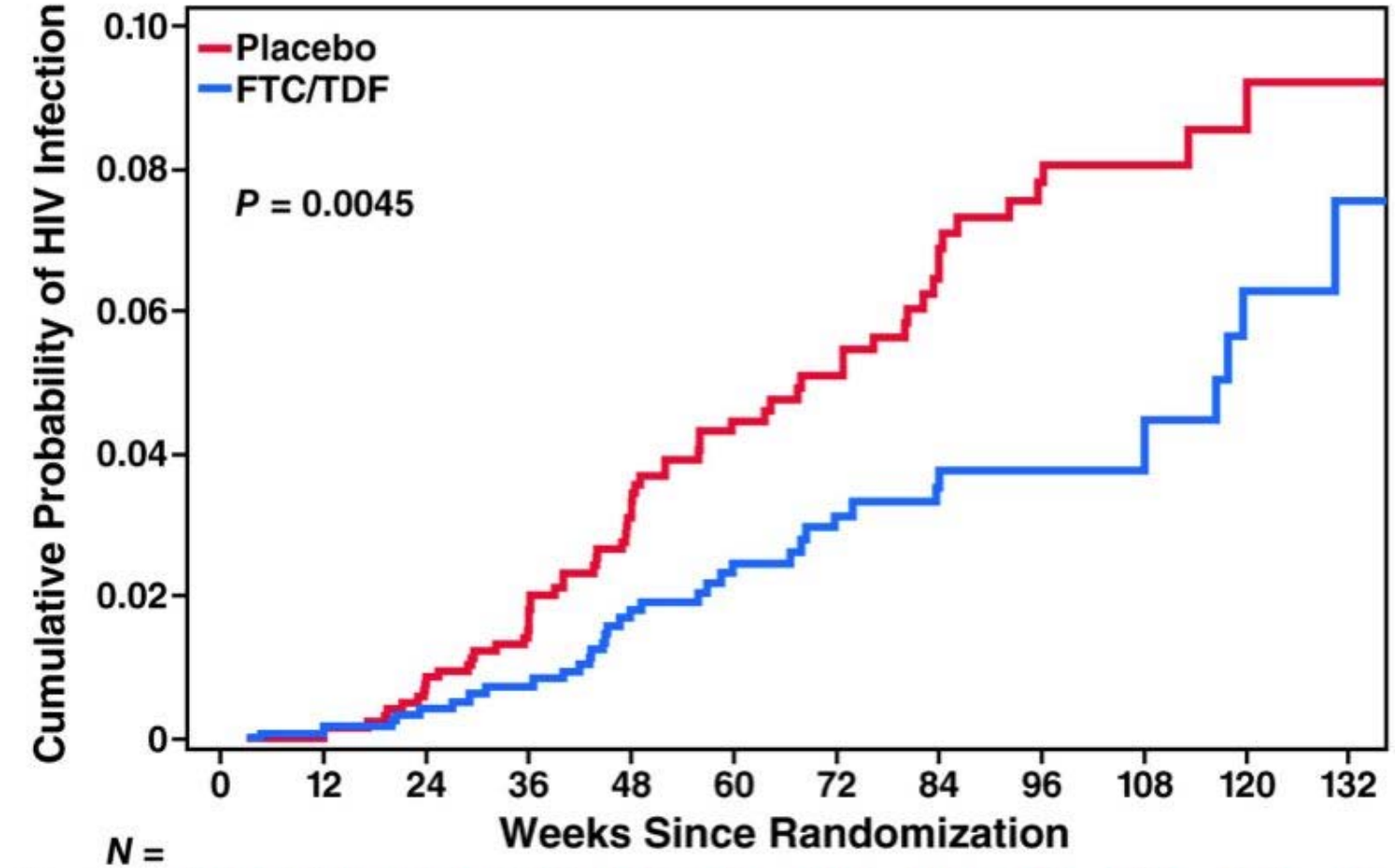
HIV Infections

110 in total (100 incident, 10 at baseline)

At least on specimen with undetectable RNA for all incident seroconverters

Efficacy (MITT) 44% (15-63%)
Infection Numbers: 64 – 36 = 28 averted



N =												
Placebo:	1248	1194	1108	1005	852	674	546	444	370	258	137	60
FTC/TDF:	1251	1188	1097	988	848	693	558	447	367	267	147	65

10.200B2

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Summary
Efficacy of Oral FTC/TDF PrEP

	Efficacy	95% CI	P Value
Intention to Treat	47%	22-64	P=0.001
Modified Intention to Treat	44%	15-63	P=0.005
As Treated (50%)	50%	18-70	P=0.006
As Treated (90%)	73%	41-88	P<0.0006
Unprotected RAI at Baseline	58%	32-74	P<0.0006

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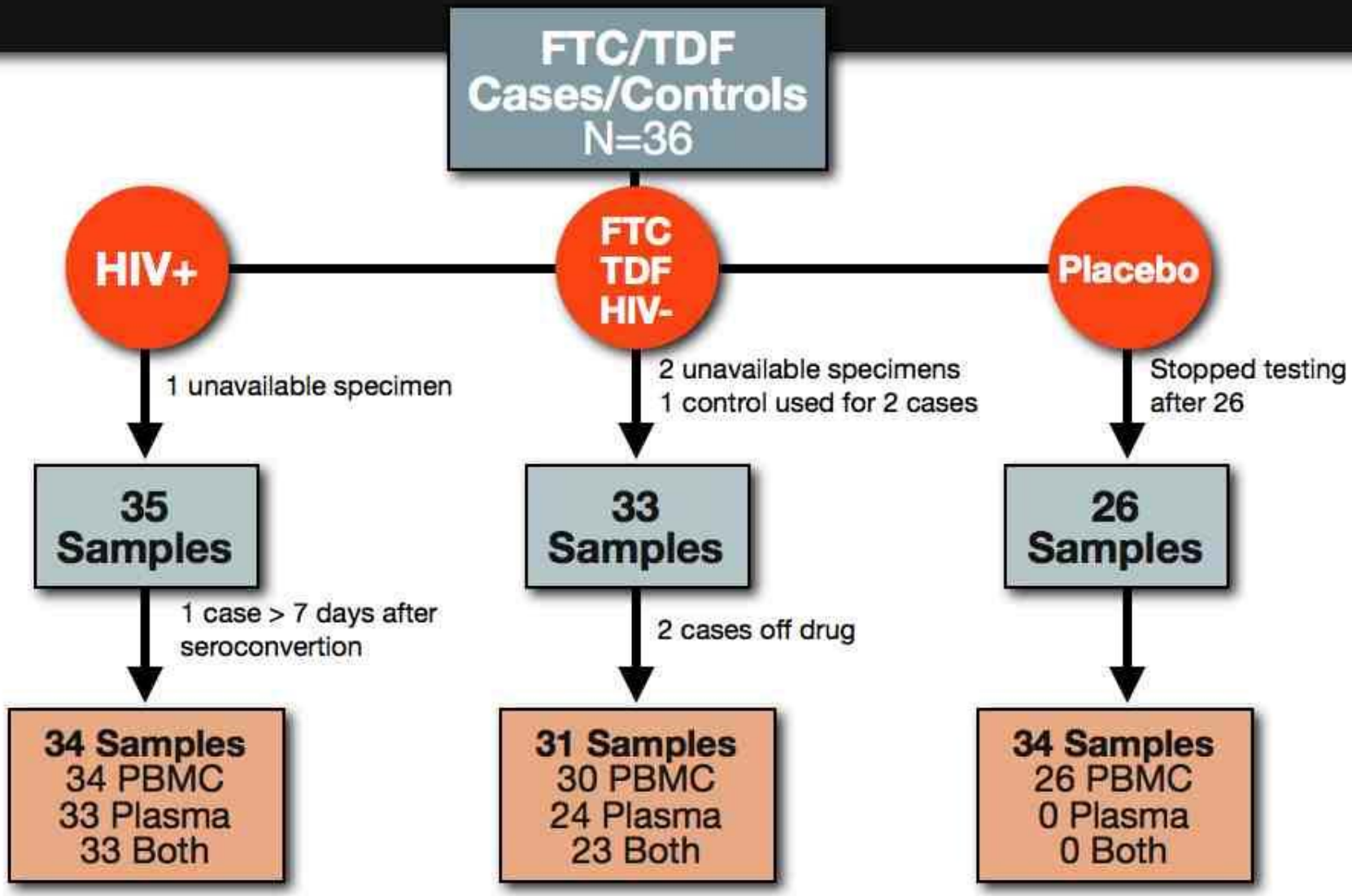
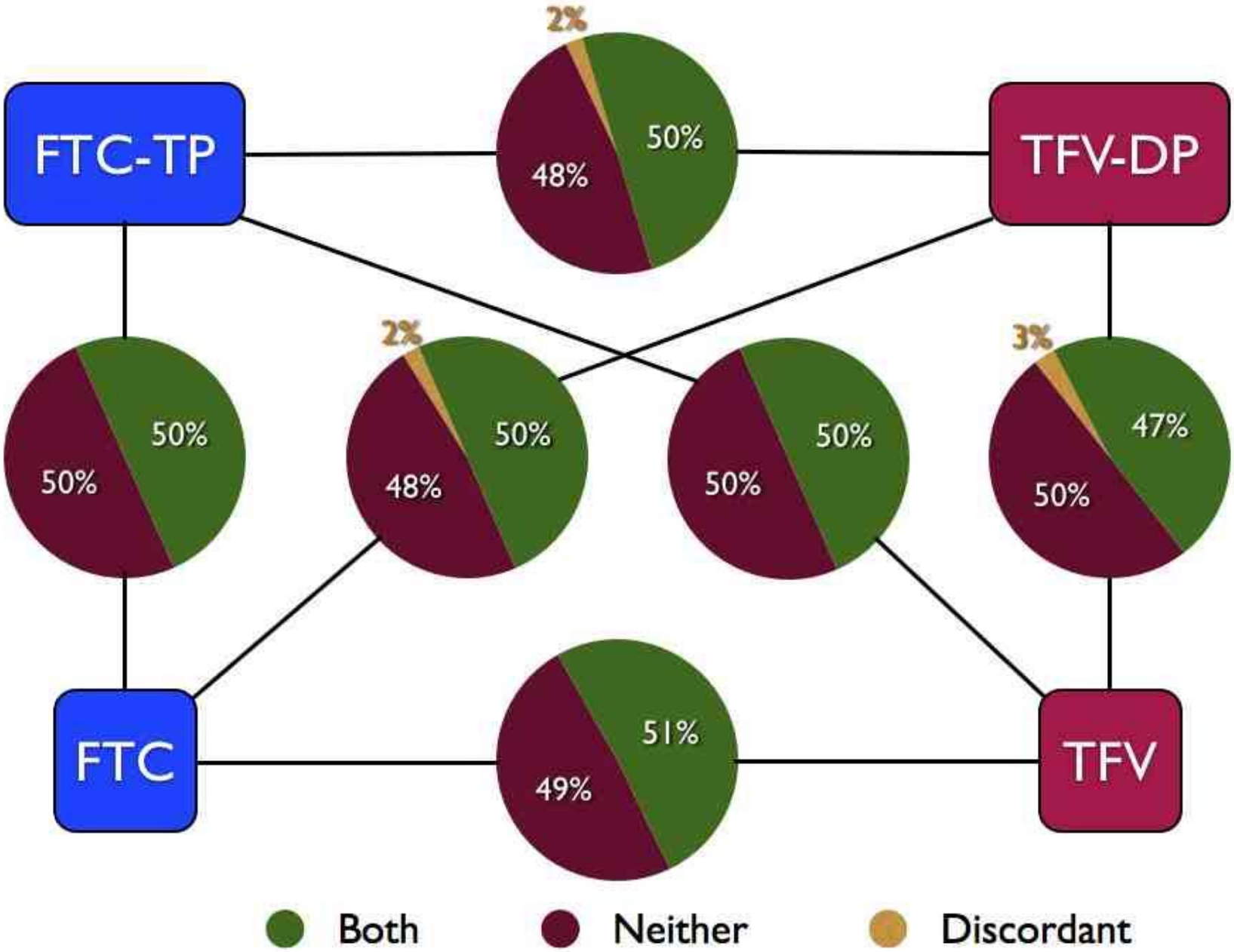
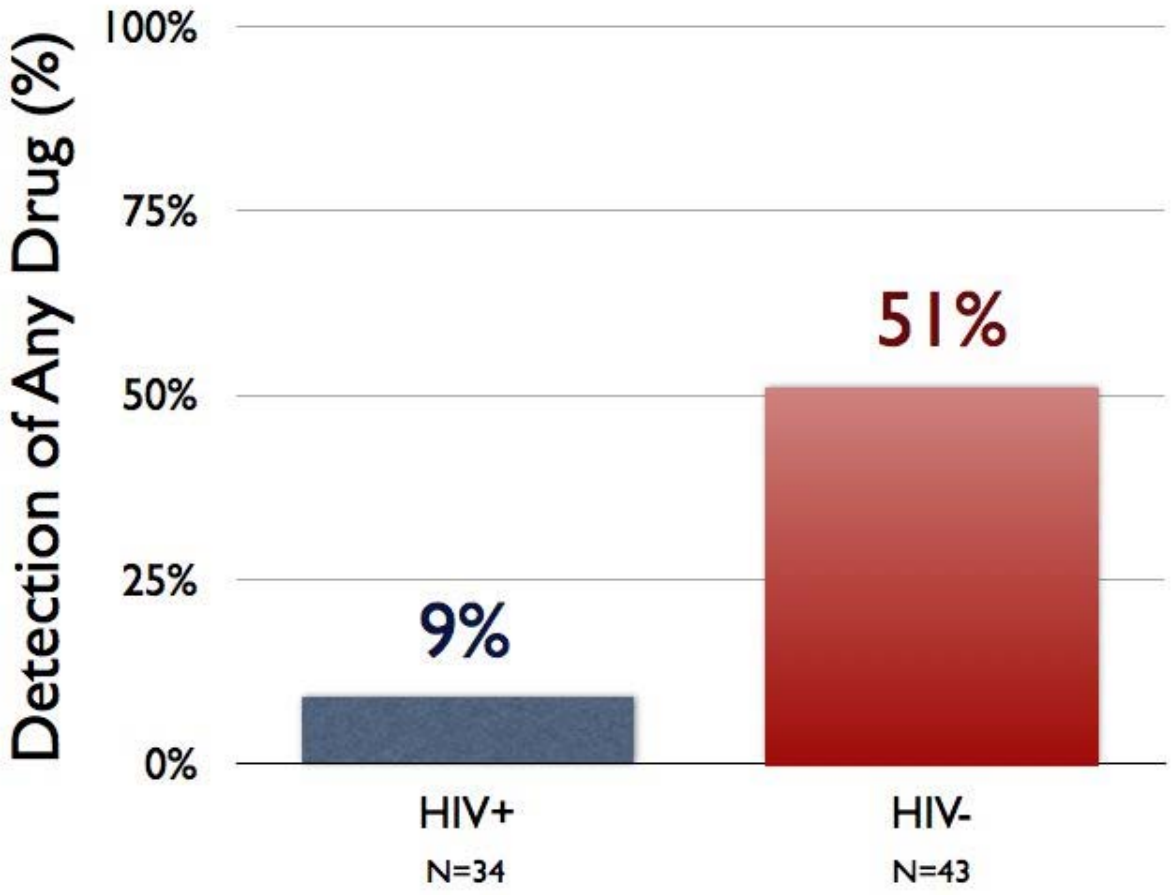
Sampling for Case Control Study



Drug Detection is Highly Concordant



Drug Detection by HIV Status in the FTC/TDF Group



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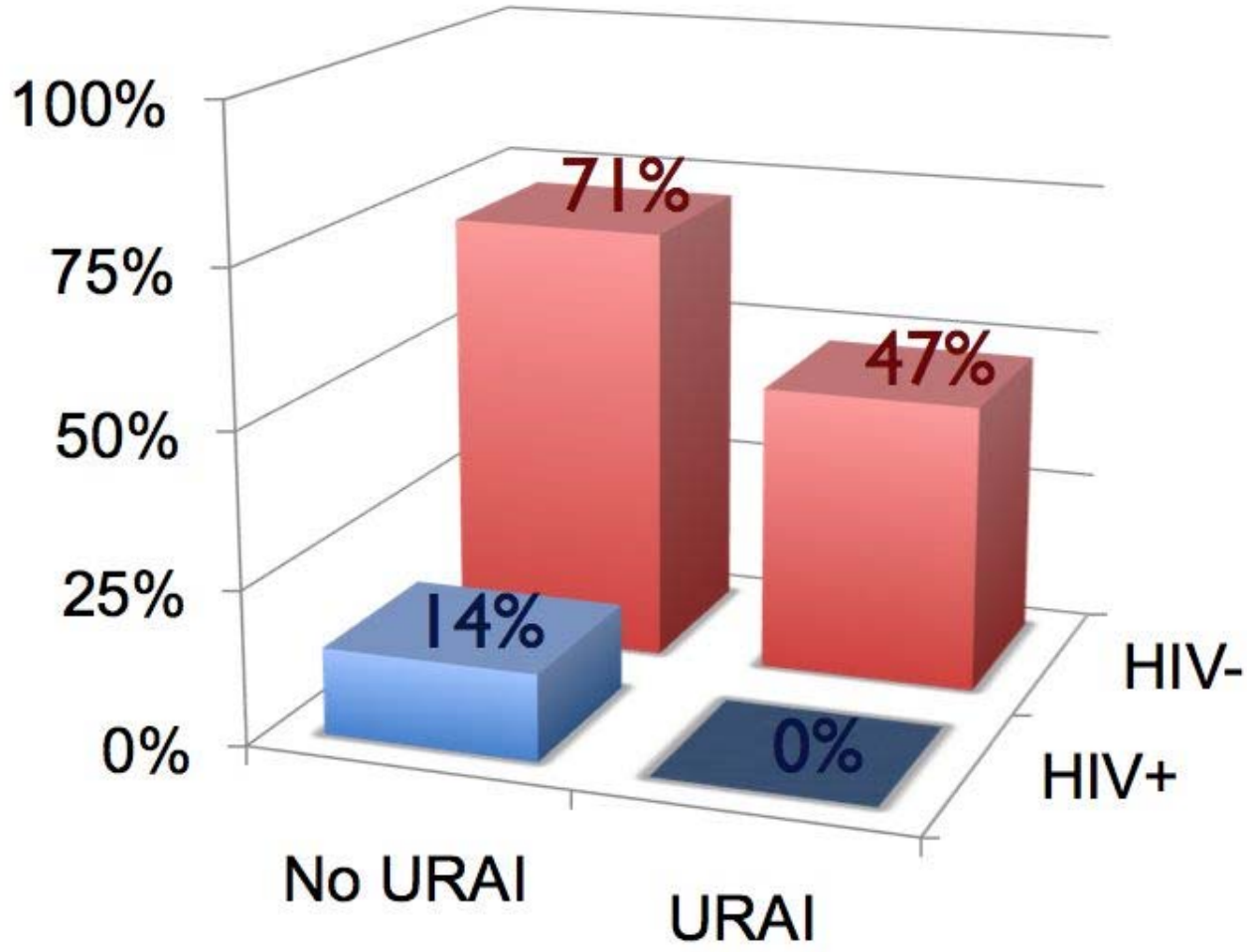
Drug Detection by HIV Status

by Unprotected Receptive Anal Intercourse (URAI)



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Drug Level And Decreased HIV Risk Ratio

- Case-control study is nested in a larger cohort
  - Matched for time on study and place
  - Conditional logistic regression used

- Strong Correlate of Protection
  - Odds ratio 12.9, P<0.001
  - **92%** reduction in HIV risk (95% CI 40-99%)

- If adjusted for URAI
  - **95%** reduction in HIV risk (95% CI 70-99%)

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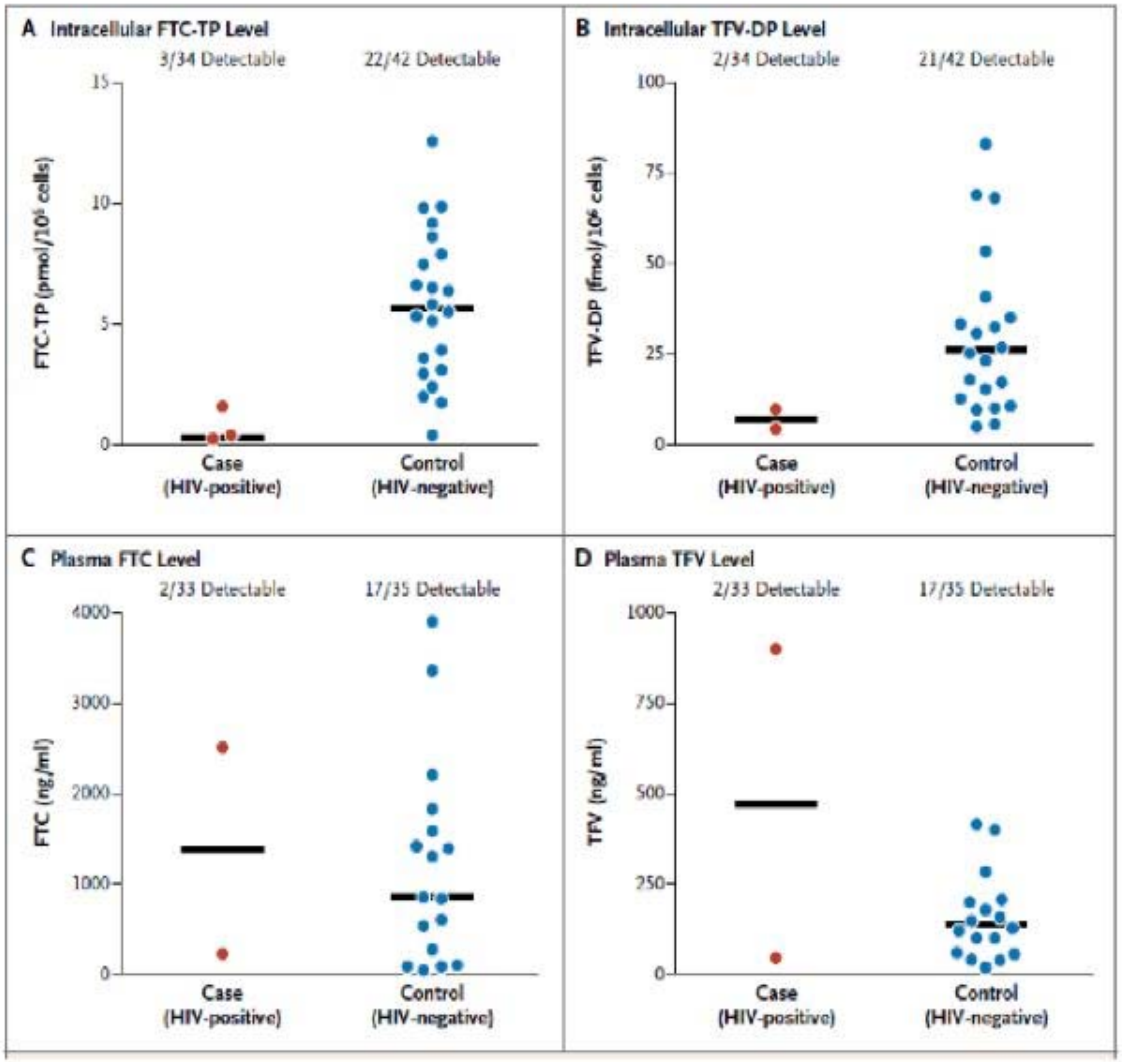
Drug Levels



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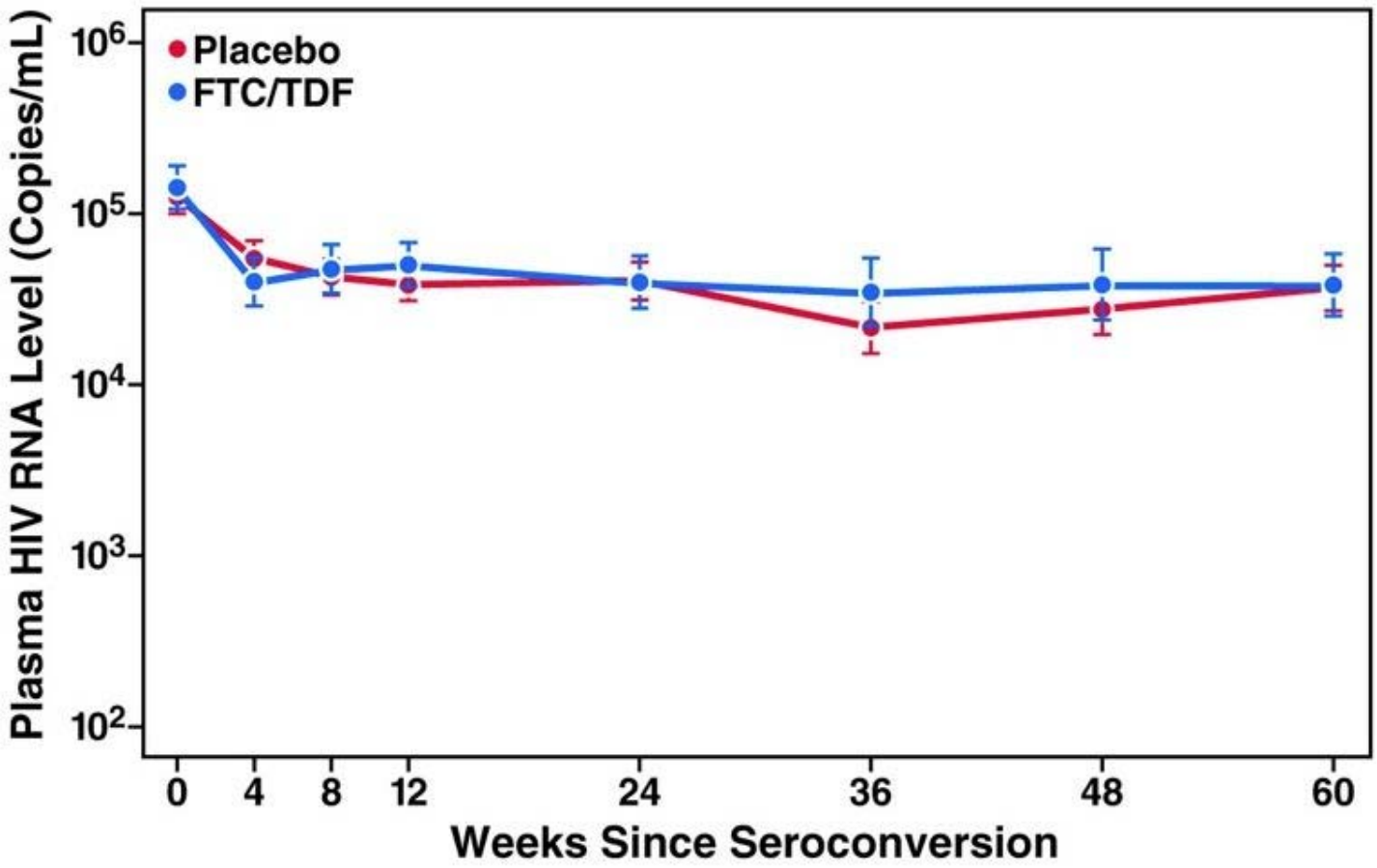
Plasma HIV Level



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Drug Resistance

Genotypic Resistance	HIV Status at Enrollment			
	Infected		Uninfected	
	Placebo N=8	FTC/TDF N=2	Placebo N=64	FTC/TDF N=36
65R	0 (0%)	0 (0%)	0 (0%)	0 (0%)
70E	0 (0%)	0 (0%)	0 (0%)	0 (0%)
184I	0 (0%)	1 (50%)	0 (0%)	0 (0%)
184V	1 (13%)	1 (50%)	0 (0%)	0 (0%)
TDF Resistance	0 (0%)	0 (0%)	0 (0%)	0 (0%)
FTC Resistance	1 (13%)	2 (100%)	0 (0%)	0 (0%)

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Adverse events

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Grade 3 or Grade 4	151 (12%)	248	164 (13%)	285	p=0.51
Serious AE	60 (5%)	76	67 (5%)	87	p=0.57
Death	1 (<1%)	1*	4 (<1%)	4	p=0.18

*Motorcycle accident

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Adverse events

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Creatinine Elevated	25 (2%)	28	14 (1%)	15	p=0.08
Headache	56 (4%)	66	41 (3%)	55	p=0.10
Nausea	20 (2%)	22	9 (<1%)	10	p=0.04
Weight Decreased	27 (2%)	34	14 (1%)	19	p=0.04

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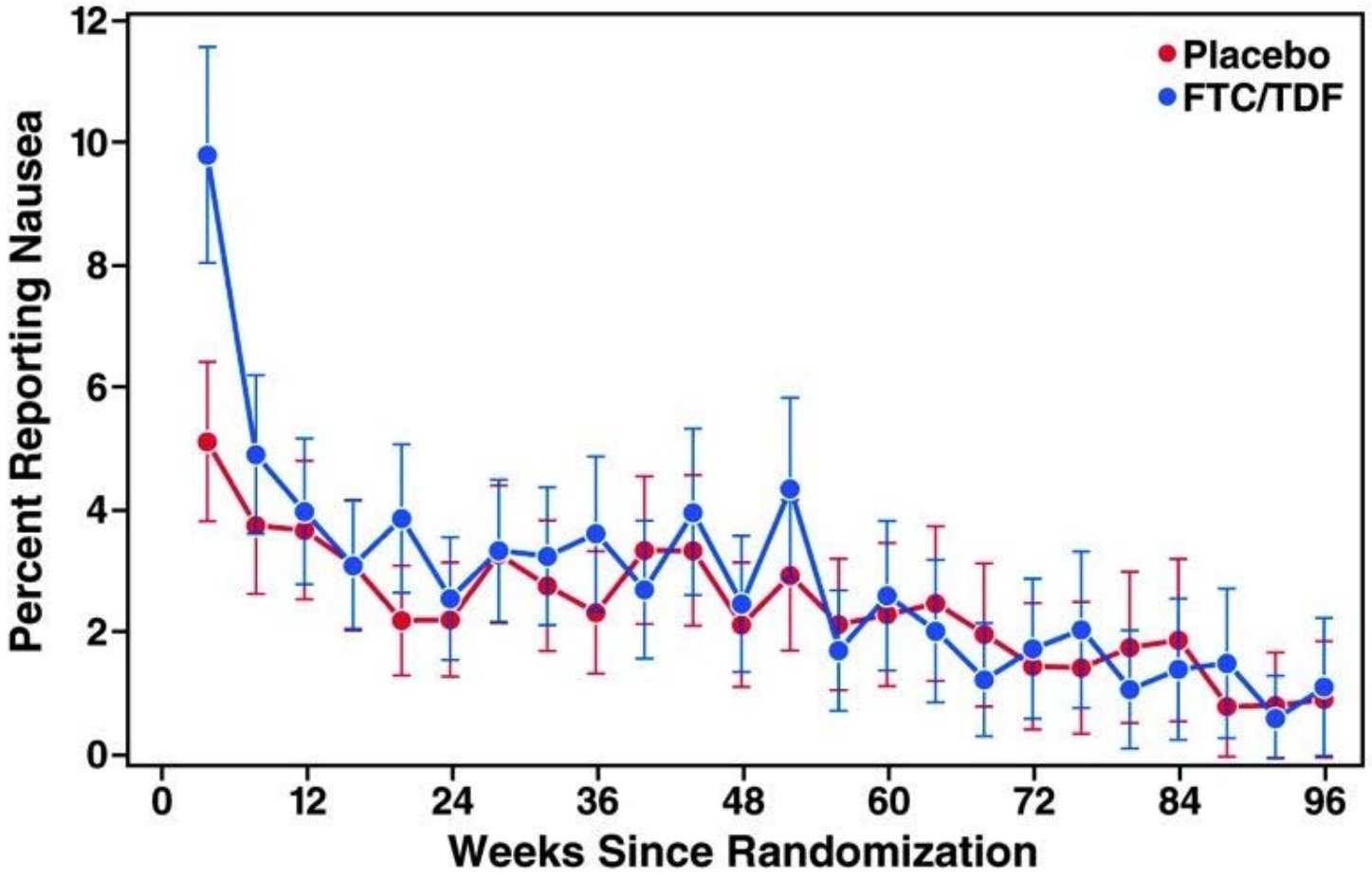
Nausea on History



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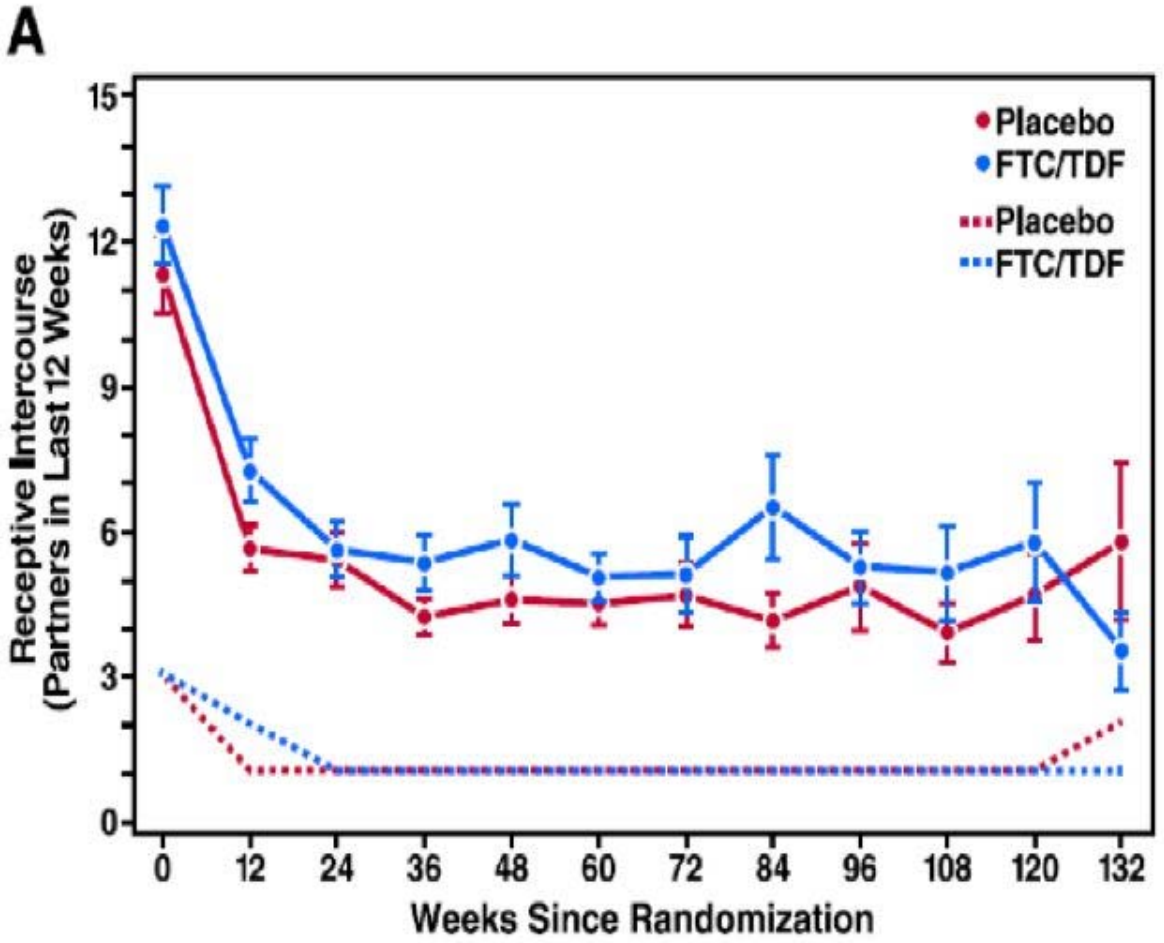
Sexual Partners



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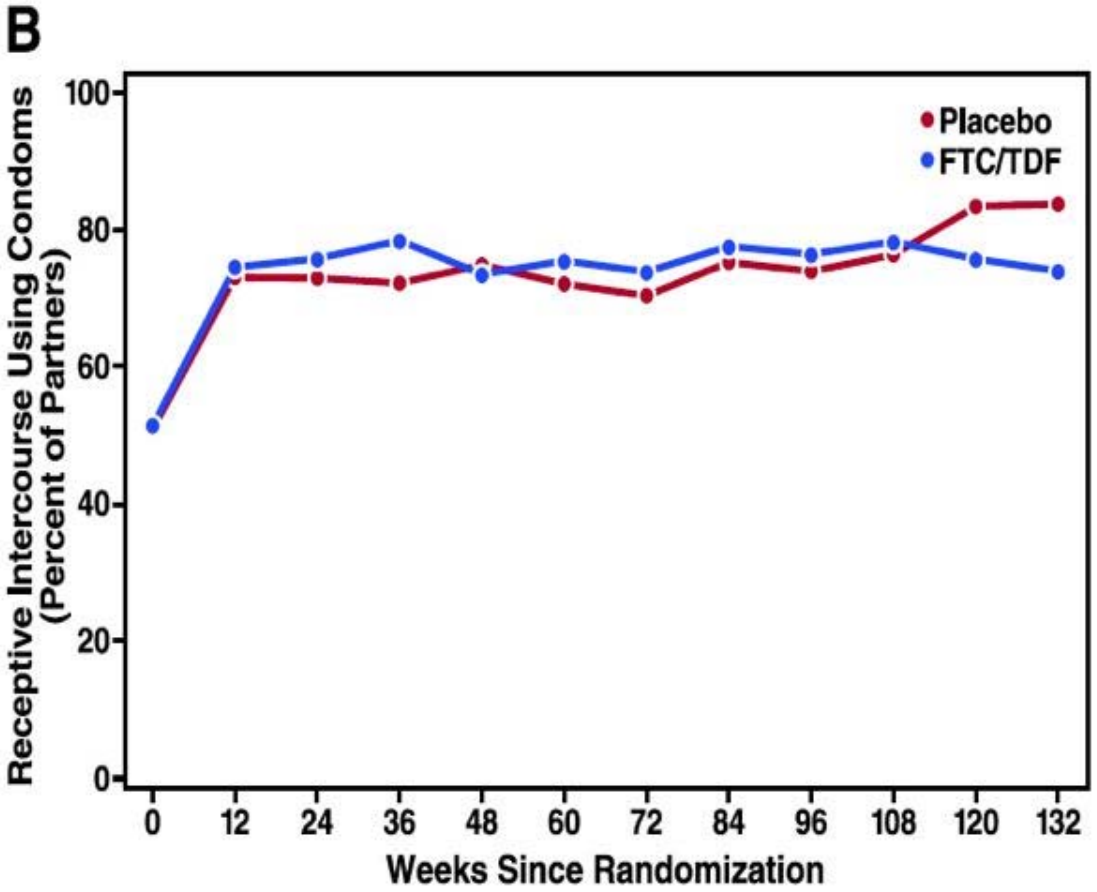
Condom Use with High Risk Sex



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Conclusions: Efficacy

Oral FTC/TDF PrEP provided additional protection against the acquisition of HIV infection among MSM receiving a comprehensive package of prevention services.

Detectable drug in blood strongly correlated with the prophylactic effect.

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Conclusions: Safety

There was no moderate or severe toxicity.

Nausea and unintentional weight loss were more common in the first few weeks of FTC/TDF use, occurring in less than 1 in 10.

FTC resistance occurred when FTC/TDF was started in people who were already HIV infected.

FTC and TDF resistance did not occur among those infected after PrEP started.

New England Journal of Medicine, online Nov 23, 2010

Open Label Extension

Sponsored by
NIH/NIAID/DAIDS

with drug donated by
Gilead Sciences

Premise

Sexual and pill taking behavior are significant determinants of PrEP effects in practice

Information about PrEP safety and efficacy could affect behavior

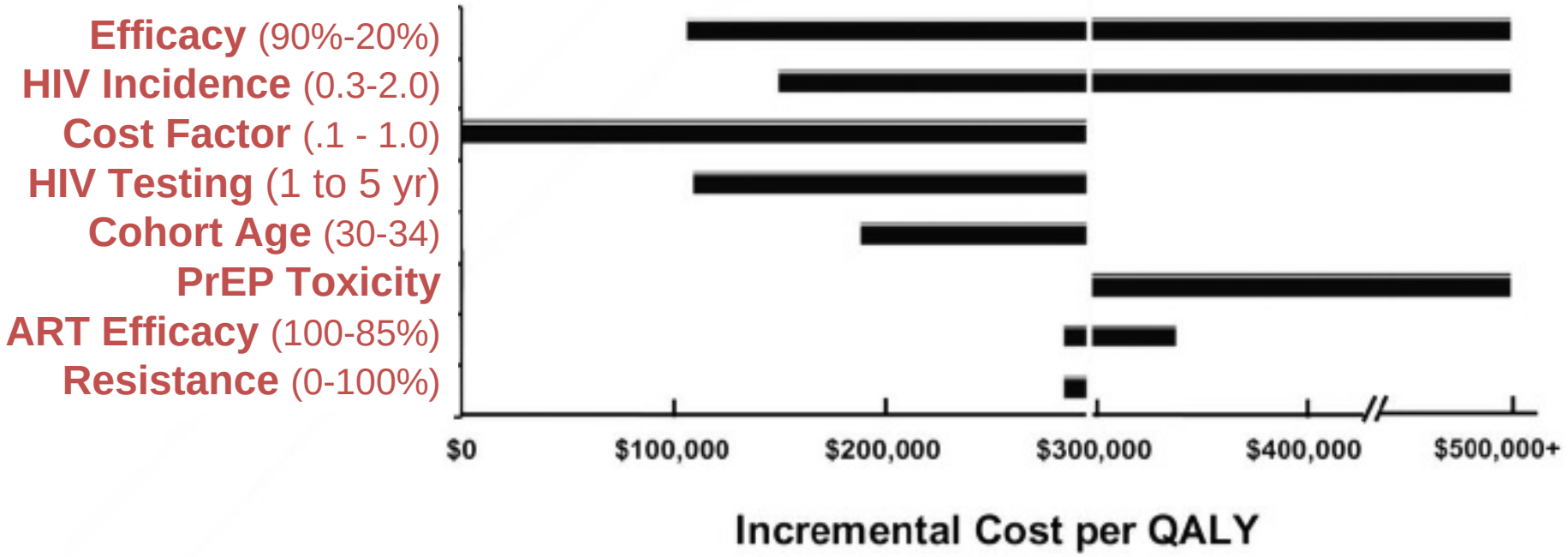
Next Steps

- Open Label Extension of iPrEx
- Demonstration Projects to Evaluate
  - feasibility in VCT and STI centers
  - feasibility of every 12 week visits
  - Impact on testing behavior
  - Impact on treatment linkages
  - Impact on stigma

HIV Preexposure Prophylaxis in the United States: Impact on Lifetime Infection Risk, Clinical Outcomes, and Cost-Effectiveness

A. David Paltiel,[1] Kenneth A. Freedberg,[2,3,4,5,7,8,9] Callie A. Scott,[3] Bruce R. Schackman,[12] Elena Losina,[8,9,10] Bingxia Wang,[3] George R. Seage III,[6] Caroline E. Sloan,[3] Paul E. Sax,[4,5,11] and Rochelle P. Walensky[2,3,4,5,11]

806 • CID 2009:48 (15 March) • HIV/AIDS

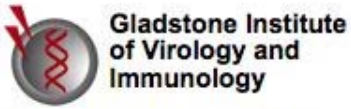


Factors Favoring Cost Effective Implementation

- Activity in young MSM
- No Serious Toxicity
- Lab Monitoring Minimal
  - Creatinine every 12 weeks
  - HIV testing (frequency to be determined)
- High-level protection among those who took tablets enough to achieve drug levels
- Synergies with behavioral approaches

Factors not Favoring Cost Effectiveness

- High Prices in Some Settings
- Efficacy 47% on ITT Basis
  - Approximately half continued to receive pills but did not take enough to obtain a drug level
  - Unclear whether this will occur in the absence of a placebo and visit incentives
- Daily dosing
  - Non-daily may be non-inferior



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Peter Anderson
Lane Bushman

Brian Postle

Howard Jaffe Jim Rooney

Stephen Becker

National Institute
of Allergy and
Infectious Diseases

David Burns

Grace Chow
Ana Martinez

The iPrEx Study: Safety, Efficacy, Behavior, and Biology


GLOBAL
IPrEX