PrEP Initiative / Iniciativa PrEx

Sponsored by

NIH/NIAID/DAIDS

with co-funding by the

Bill & Melinda Gates Foundation

and drug donated by

Gilead Sciences

iPrEx: Global Prevention Initiative

Enrolled	**2,499**
HIV Test Visits	**39,613**
False Positives	**7**
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**

650,000
Case Report
Forms
through
May 1, 2010

22 stories
217 feet

Coit Tower, 180 feet, San Francisco

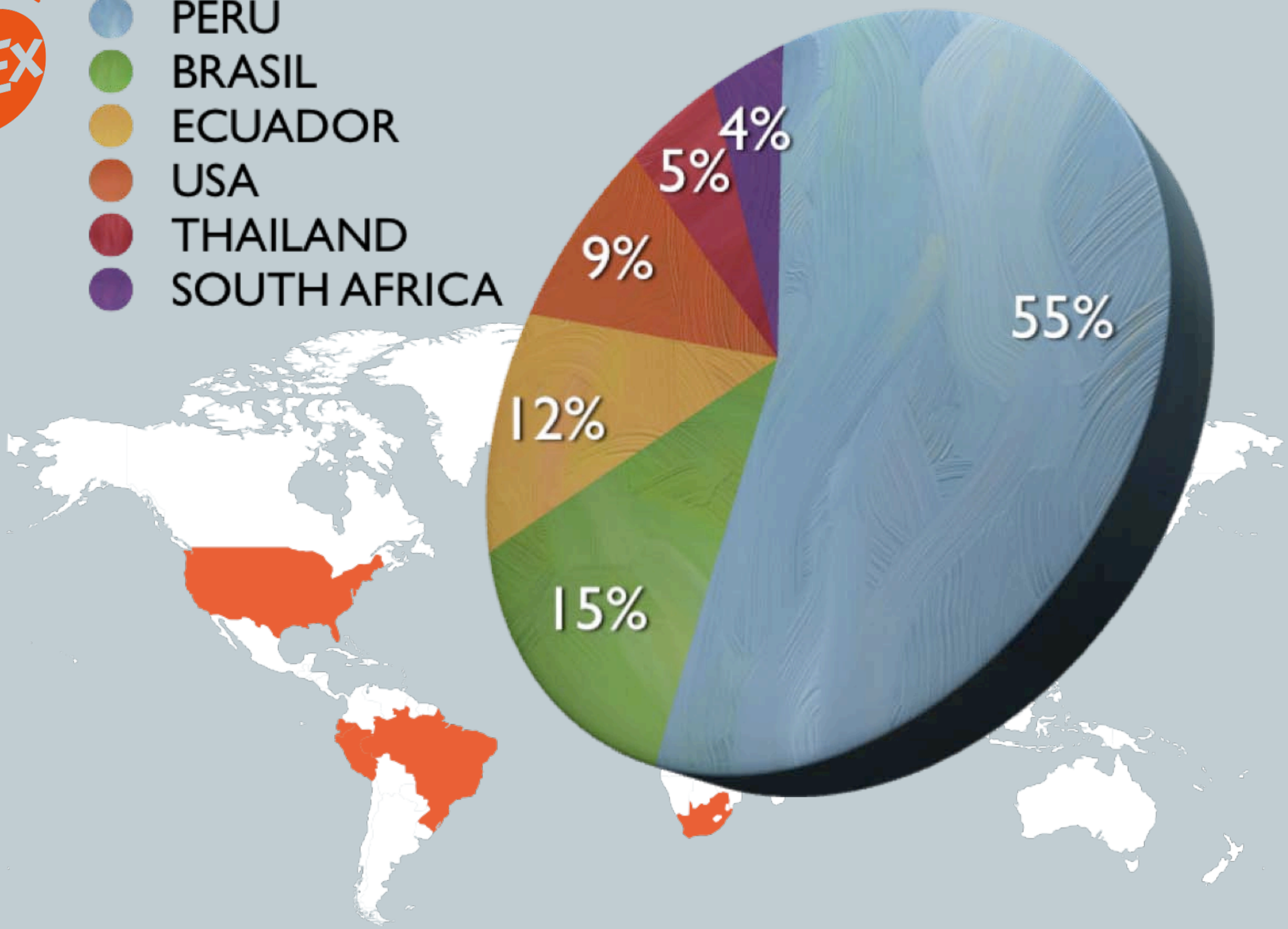
Fully enrolled as of December 2009

Sites	11
Participants	2.499

Participants	2499

GLOBAL PrEX

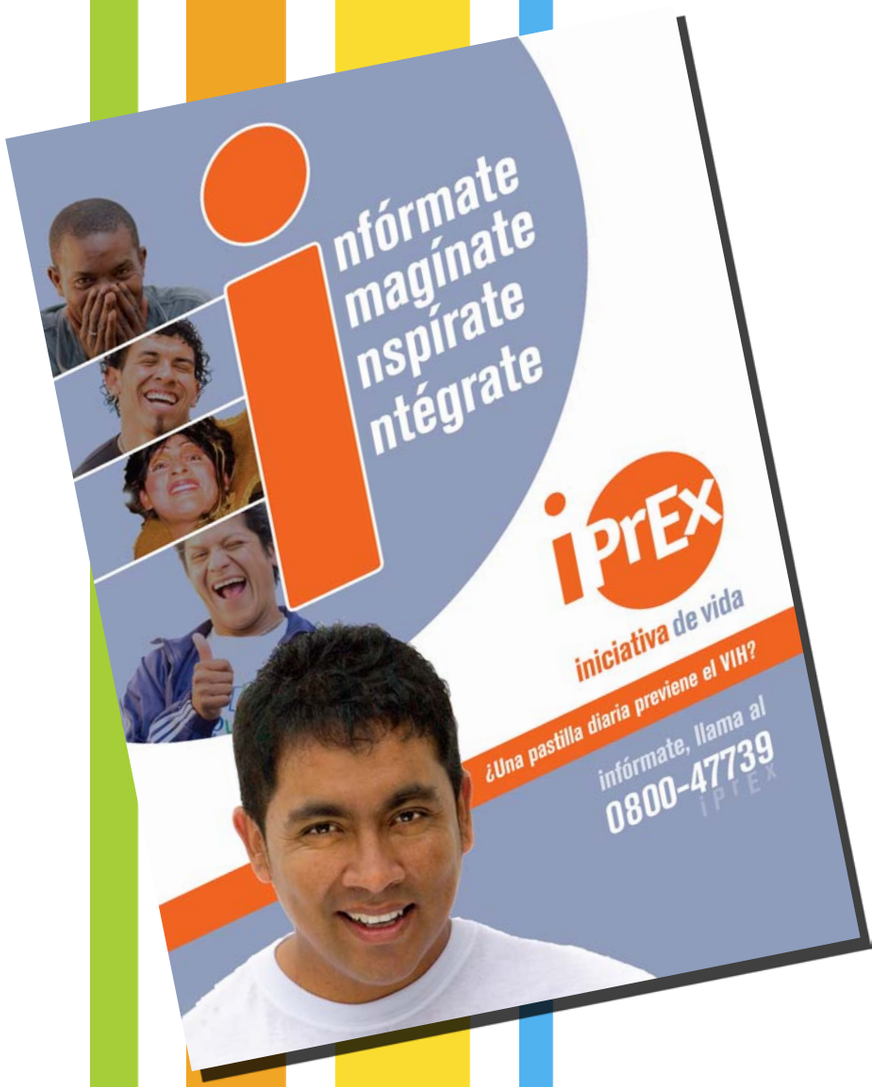
- PERU
- BRASIL
- ECUADOR
- USA
- THAILAND
- SOUTH AFRICA



- **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**



The iPrEx Study

- **High Risk 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
- Pre- and Post-test counseling
- Condoms (15 or more)
- STI testing if any symptoms, monthly
- STI screening for all every 24 weeks
- Partner treatment
- PEP if recently exposed
- HBV vaccine

The primary efficacy and safety analysis is based on visits between June 2007 and May 1st 2010

CONSORT DIAGRAM

4,905 Screened

4,905 Screened

1,564 (32%) Ineligible

410 HIV Positive
405 Lab Ineligible
247 Low HIV Risk
502 Other Reasons

842 Eligible, Not Enrolled

2,499 Randomized

1,251 (50%)
Randomized to FTC/TDF

1,248 (50%)
Randomized to Placebo

25 No Follow Up HIV Test

23 No Follow Up HIV Test

1,226 (98%)
Followed

1,225 (98%)
Followed

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FTC/TDF

1,226 (98%) Followed

Quarterly Visit Attendance

W12	1,075/1,194	90%
W24	984/1,116	88%
W36	882/1,019	87%
W48	759/880	86%
W60	642/719	89%
W72	516/582	89%
W84	415/646	89%
W96	343/384	89%
W108	258/283	91%
W120	147/157	94%
W132	70/75	93%
W144	6/8	75%

2 Infected at Enrollment

1,224 Followed for Seroconversion

GLOBAL PrEP

PLACEBO

1,225 (98%) Followed

Quarterly Visit Attendance

W12	1,098/1,203	92%
W24	989/1,130	88%
W36	901/1,025	88%
W48	783/886	88%
W60	624/706	88%
W72	517/572	90%
W84	397/460	86%
W96	331/378	88%
W108	252/275	92%
W120	136/150	91%
W132	62/66	94%
W144	4/5	80%

8 Infected at Enrollment

1,217 Followed for Seroconversion

2 Infected at Enrollment	8 Infected at Enrollment
1,224 Followed for Seroconversion	1,217 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%

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%

FTC/TDF

PLACEBO

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Baseline Characteristics of the Participants, According to Study Group

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)

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/African American	117 (9)	97 (8)
White	223 (18)	208 (17)
Mixed/Other	849 (68)	878 (70)
Asian	62 (5)	65 (5)
Hispanic/Latino - no. (%) P=0.72	900 (72)	906 (73)

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)

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)

Baseline Characteristics of the Participants, According to Study Group

Characteristic		FTC/TDF	PLACEBO
Sexual Risk Factors at screening		**(n=1,251)**	**(n=1,248)**
Numbers of Partners last 12 weeks-mean (SD)	**P=0.51**	18 (35)	18 (43)
Unprotected Receptive Anal Intercourse last 12 weeks - no. (%)	**P=0.37**	732 (59)	753 (60)
Unprotected Anal Intercourse with HIV+/ Unknown Status Partner last 6 months - no. (%)	**P=0.34**	992 (79)	1,009 (81)
Involved in Transactional Sex last 6 months - no. (%)	**P=0.84**	517 (41)	510 (41)
Known HIV+ Partner last 6 months - no. (%)	**P=0.22**	23 (2)	32 (3)
History of STI last 6 months - no. (%)	**P=0.36**	327 (26)	307 (25)

Baseline Characteristics of the Participants, According to Study Group

Characteristic		FTC/TDF	PLACEBO
Sexually Transmitted Infections diagnosed at screening		**(n=1,251)**	**(n=1,248)**
Syphilis Seroreactivity (confirmed) - no. (%)	**P=0.95**	164/1,240 (13)	162/1,239 (13)
Serum Herpes Simplex Virus Type 2 Infection - no. (%)	**P=0.24**	458/1,241 (37)	430/1,243 (35)
Urine Leukocyte Esterase positive - no. (%)	**P=1.0**	23 (2)	22 (2)

Baseline Characteristics of the Participants, According to Study Group

Characteristic	FTC/TDF	PLACEBO
Hepatitis B (HBV) Status - no (%) P=0.11	**(n=1,251)**	**(n=1,248)**
Susceptible (anti-HBs neg.anti-HBc neg. HBsAg neg)	827 (66)	803 (64)
Immune due to natural infection (anti-HBs pos, anti HBc pos)	247 (20)	222 (18)
Immune due to prior vaccination (anti-HBs pos, anti HBc neg)	149 (12)	190 (15)
Current Hepatitis B infection (HBsAg pos)	7 (1)	6 (0)

Perceived Group Assignment At Week 12

By Randomized Group

Perceived Drug Assignment	Placebo	FTC/TDF	Overall
Strongly Truvada	131 (11%)	154 (13%)	285 (12%)
Somewhat Truvada	144 (12%)	124 (11%)	268 (11%)
Don’t Know	719 (61%)	710 (61%)	1429 (61%)
Somewhat Placebo	86 (7%)	79 (7%)	165 (7%)
Strongly Placebo	29 (3%)	29 (3%)	58 (3%)
Decline to State	72 (6%)	74 (6%)	146 (6%)
Total	**1,181 (100%)**	**1,170 (100%)**	**2,351 (100%)**

Perceived group assignment was recorded on a computer assisted structured interview at the week 12 visit. The majority of participants responded that the did not know their randomization group. The responses were evenly distributed by group (P=0.60 by Fisher exact test) indicating the integrity of the blinding

Perceived Group Assignment At Week 12 By Randomized Group

HIV Testing

39,613 visits with HIV testing

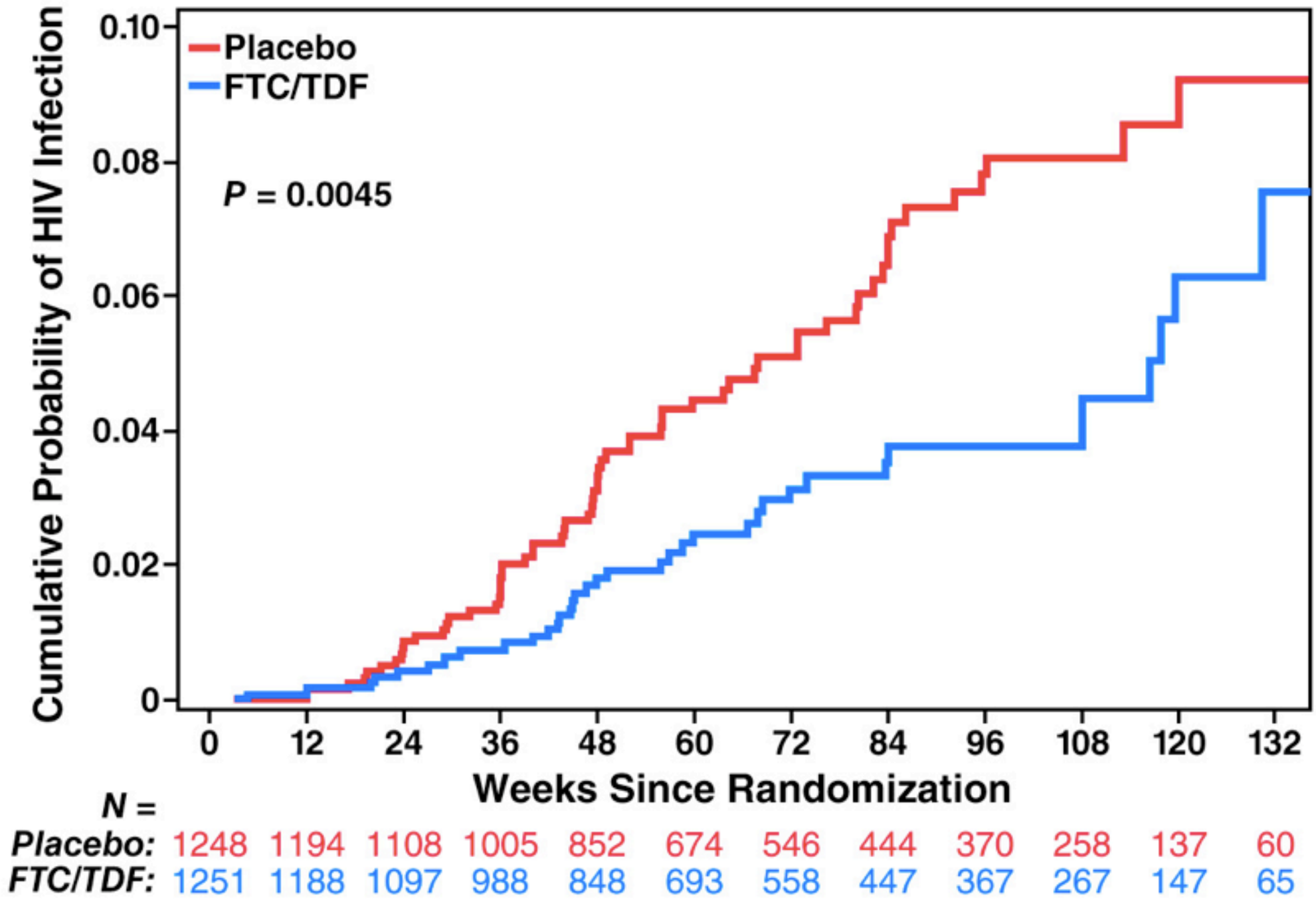
7 false positive tests in 3 people

HIV Infections

110 in total (100 incident, 10 at baseline)

At least one specimen with undetectable RNA for all incident seroconverters

Efficacy (MITT) 43.8% (15.4-62.6%)
Infection Numbers: 64 – 36 = 28 averted



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MITT Results

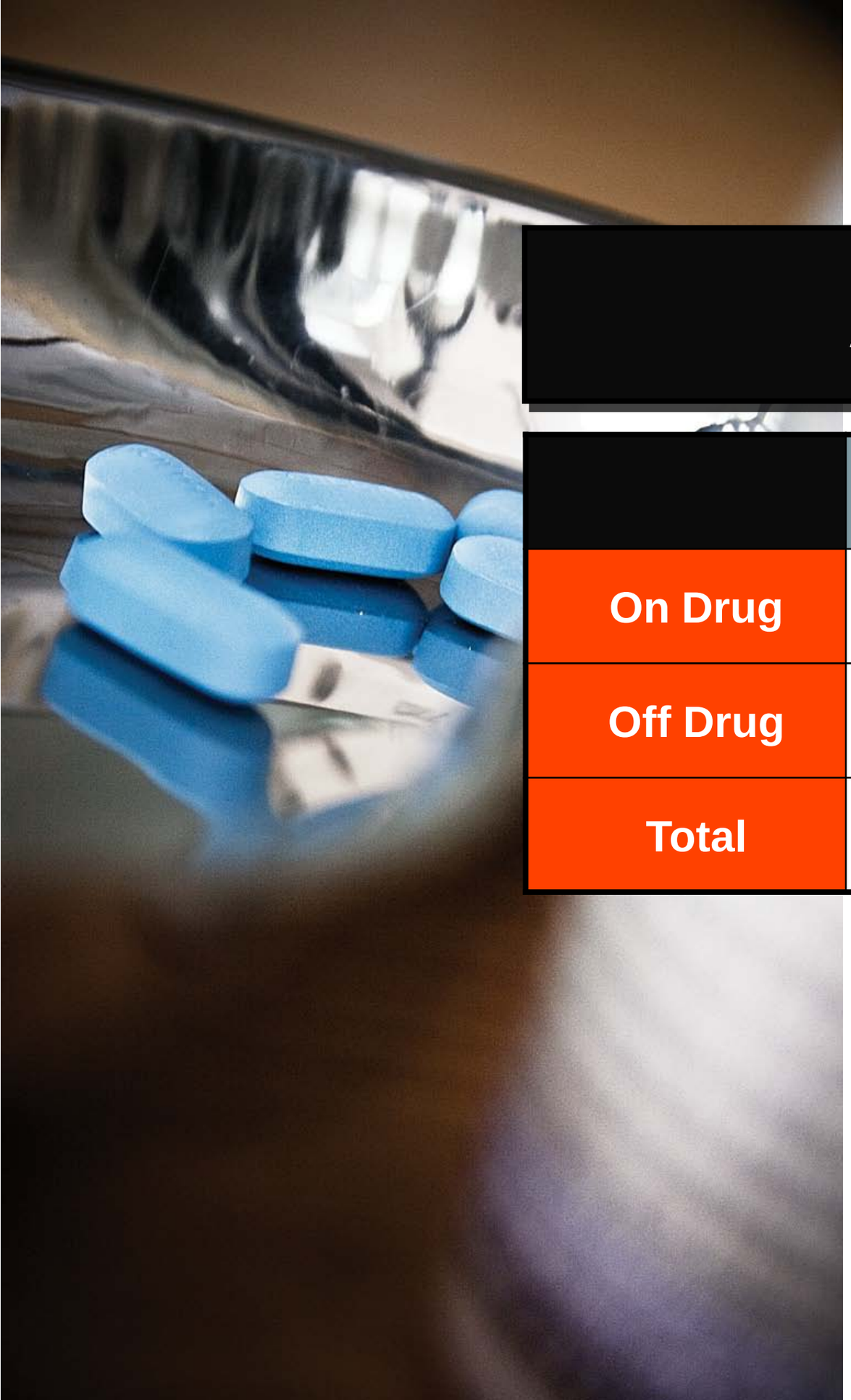
- P-value for any efficacy, **p=0.005**
(two-sided, logrank)

- P-value for 30% efficacy, **p=0.15**
(one-sided, logrank, stratified by site)

- No clear evidence of waning efficacy, **p=0.44**
for non-proportional hazards

As Treated Analysis

- Entirely pre-specified
- All visits analyzed
  - Classified as “on” or “off” treatment
- Intersects 3 streams of pill taking
  - Self report, pill counts, dispensation
- Conservative Assumptions
  - Pills in unreturned bottles taken
  - Late visits ok if enough pills
  - >50% pill use considered on treatment



As Treated Analysis

	Placebo	FTC/TDF	Overall
On Drug	47	23	70
Off Drug	17	13	30
Total	64	36	100

Efficacy = 50%

95% CI 18% to 70%

P=0.006

Summary
Efficacy of Oral FTC/TDF PrEP

	Efficacy	95% CI	P-Value
Intention to Treat	**47%**	**22-64**	**0.001**
Modified Intention to Treat	**44%**	**15-63**	**0.005**
As Treated (50%)	**50%**	**18-70**	**0.006**

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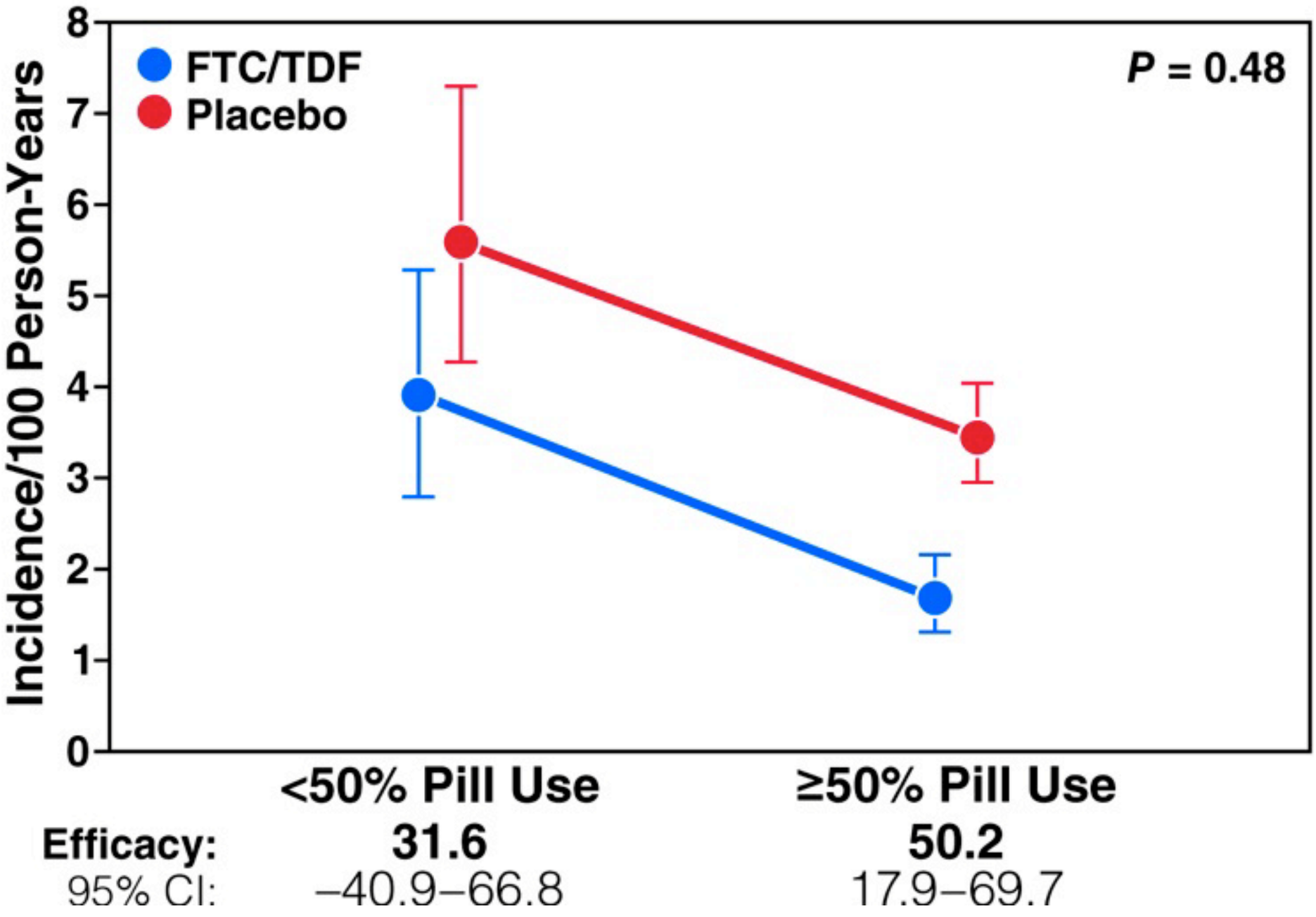
Subgroup Analysis

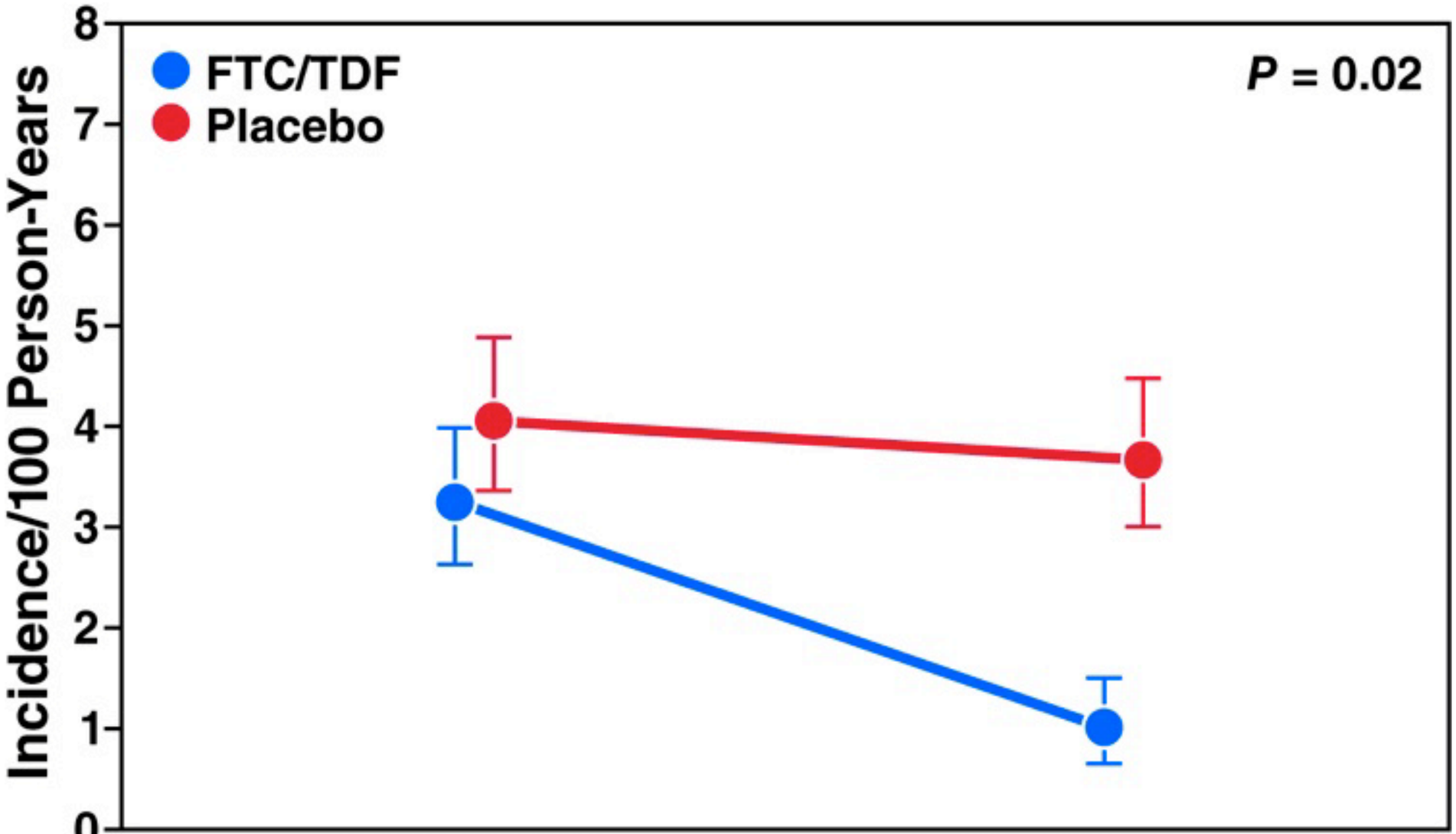
HIV Incidence by 50% Pill Use and Group

Bars Are SE of the Incidence Estimate



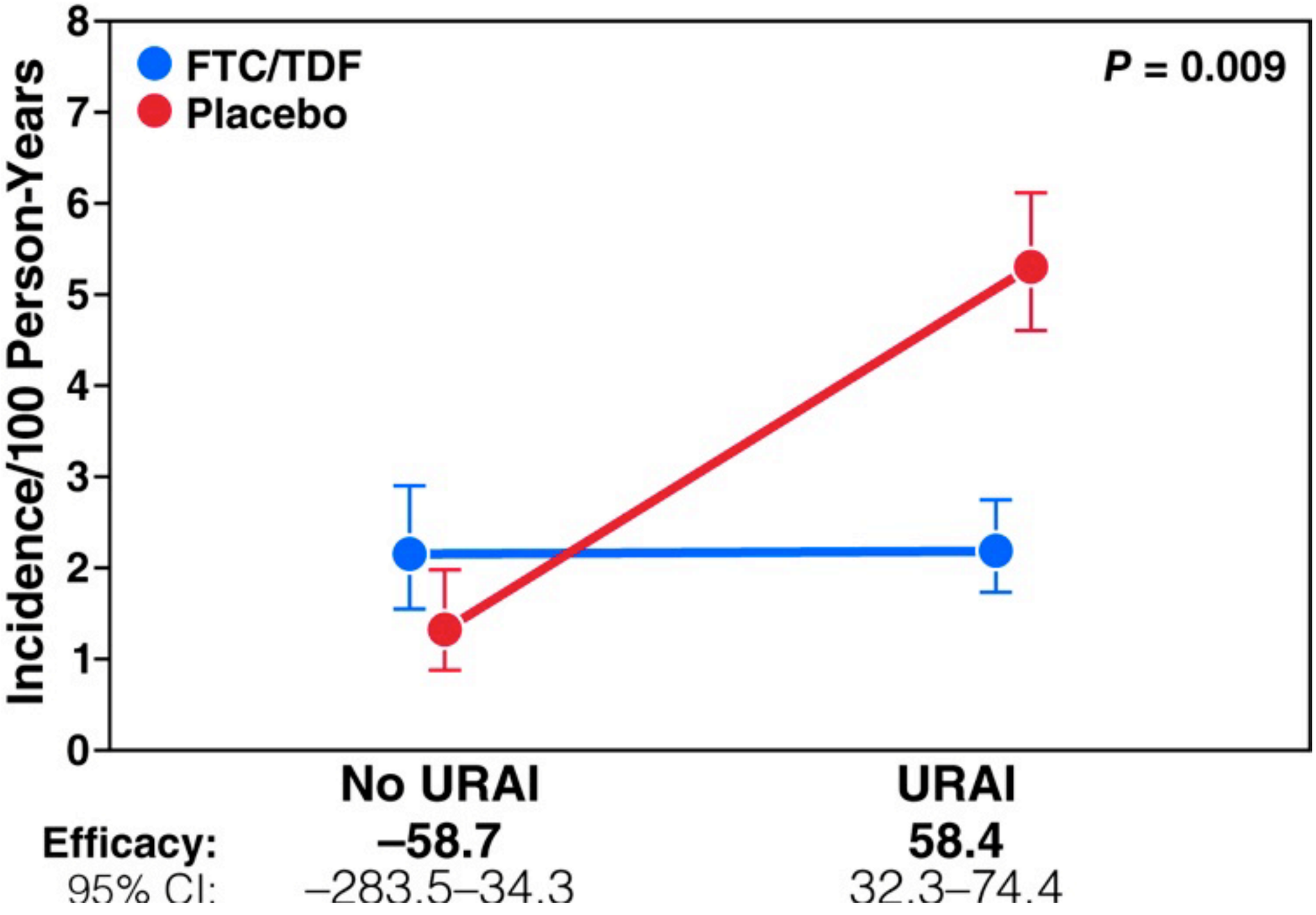
HIV Incidence by 90% Pill Use and Group

Bars Are SE of the Incidence Estimate



HIV Incidence by URAI and Group

Bars Are SE of the Incidence Estimate



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<0.001**
Unprotected RAI at Baseline	**58%**	**32-74**	**P<0.001**

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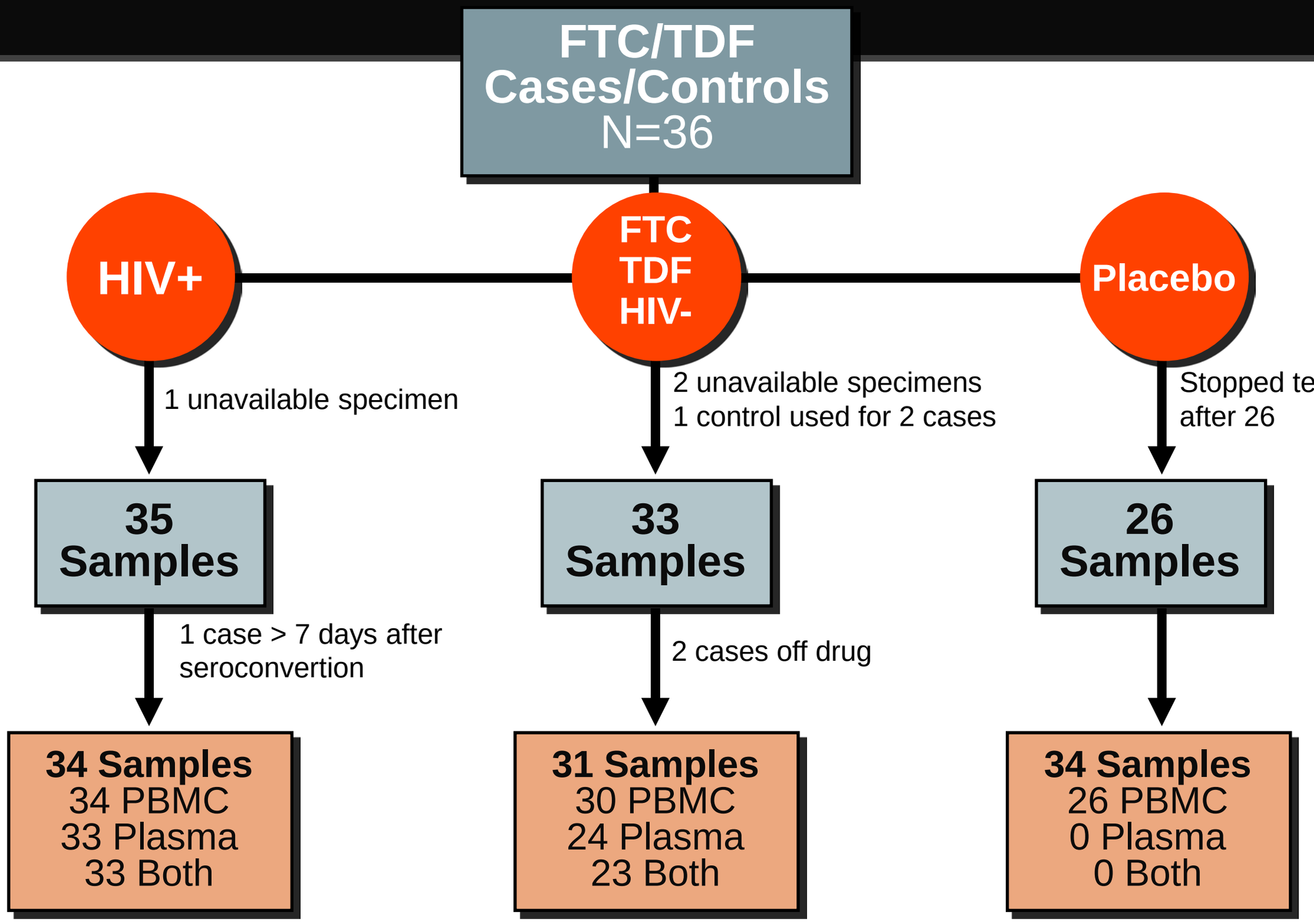
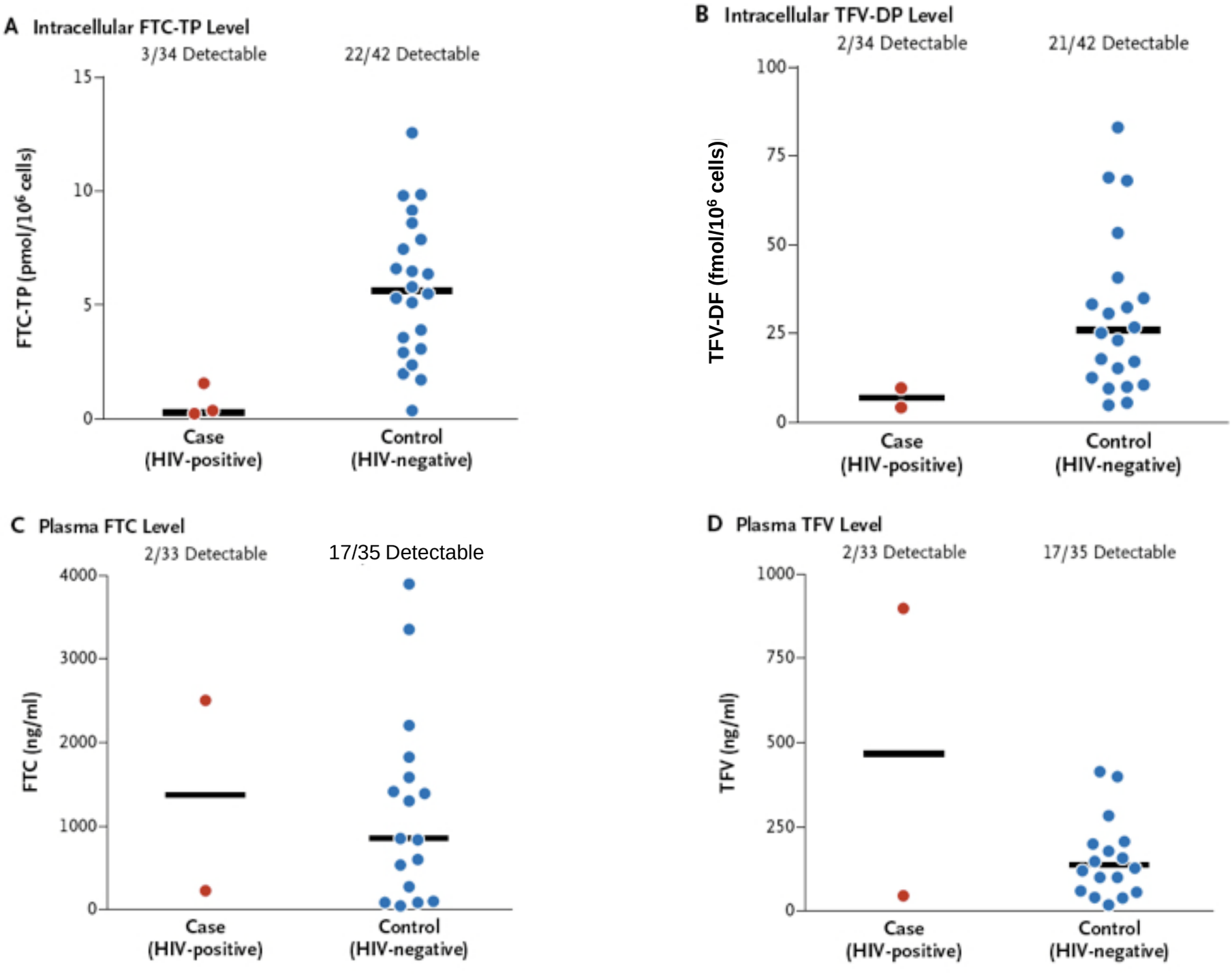
Sampling for Case Control Study



Drug Levels


A Intracellular FTC-TP Level
3/34 Detectable
22/42 Detectable
FTC-TP (pmol/10^6 cells)
15
10
5
0
Case (HIV-positive)
Control (HIV-negative)
B Intracellular TFV-DP Level
2/34 Detectable
21/42 Detectable
TFV-DF (fmol/10^6 cells)
100
75
50
25
0
Case (HIV-positive)
Control (HIV-negative)
C Plasma FTC Level
2/33 Detectable
17/35 Detectable
FTC (ng/ml)
4000
3000
2000
1000
0
Case (HIV-positive)
Control (HIV-negative)
D Plasma TFV Level
2/33 Detectable
17/35 Detectable
TFV (ng/ml)
1000
750
500
250
0
Case (HIV-positive)
Control (HIV-negative)

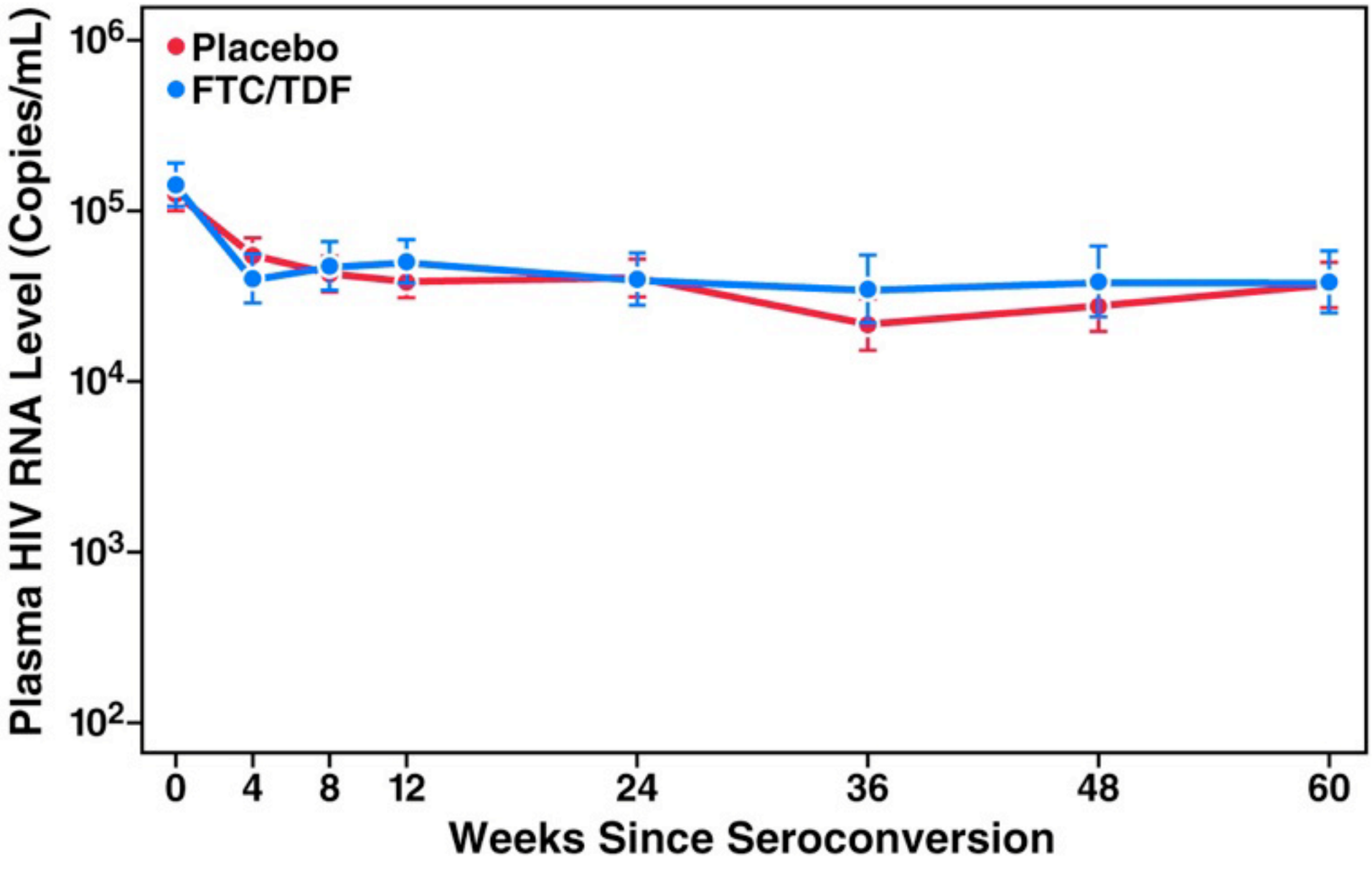
Drug Level And Decreased Risk Ratio

- Robust because case-control study is nested in a larger cohort

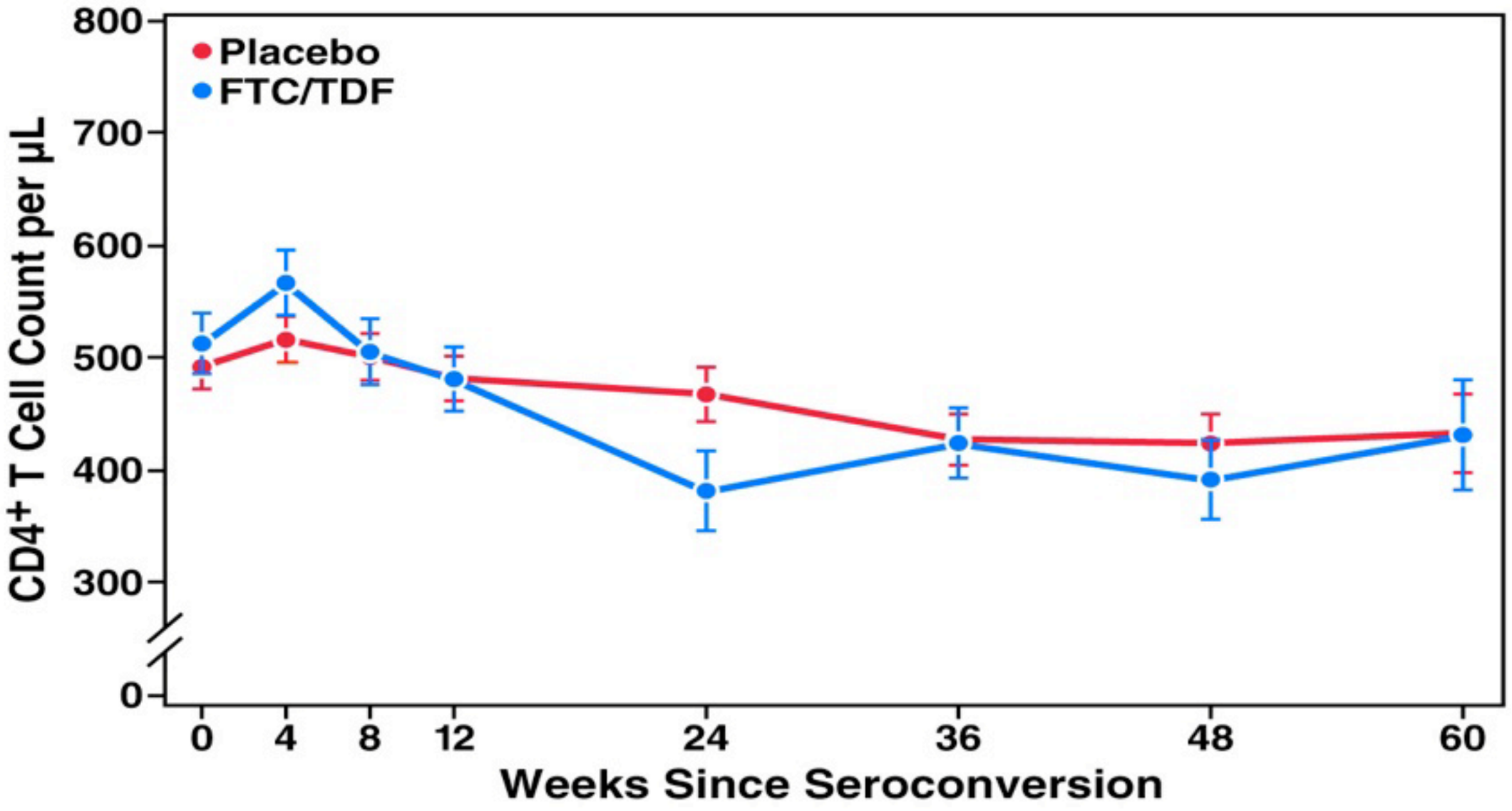
- Strong Correlate of Protection
  - Odds Ratio 12.9, P<0.001
  - **92%** reduction in risk (95% CI 40-99%)

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

Plasma HIV Level



CD4+ T cell count



Drug Resistance Cases

Case	Study Arm	Study Visit	Plasma HIV RNA Level (copies/ml)	Rapid Antibody Tests	Reverse Transcriptase Nutations Conferring Resistance	FTC Resistance Phenotype (Fold Change FTC IC50)	Timing Resistance
1	Placebo	Enrollment	417	Non-reactive	M184V, T215Y,and K103N	Not done	Primary
		W4	111.961	Reactive	M184V, T215Y,and K103N	>300	
2	FTC/TDF	Enrollment**	10,000,000	Non-reactive	Wild Type	Not done	Secondary
		W4	3,109*	Reactive	M184V	>300	
3	FTC/TDF	Enrollment***	48	Non-reactive	Assay Failed	Not done	Indeterminate
		W4	<400*	Reactive	M184I	>300	

*Tested at week 8 after enrollment
** Symptomatic at enrollment, with fever, runny nose, and sinus tenderness, diagnosed as “sinusitis”
*** Returned for interim visit 7 days after enrollment with sore throat

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%)

Safety

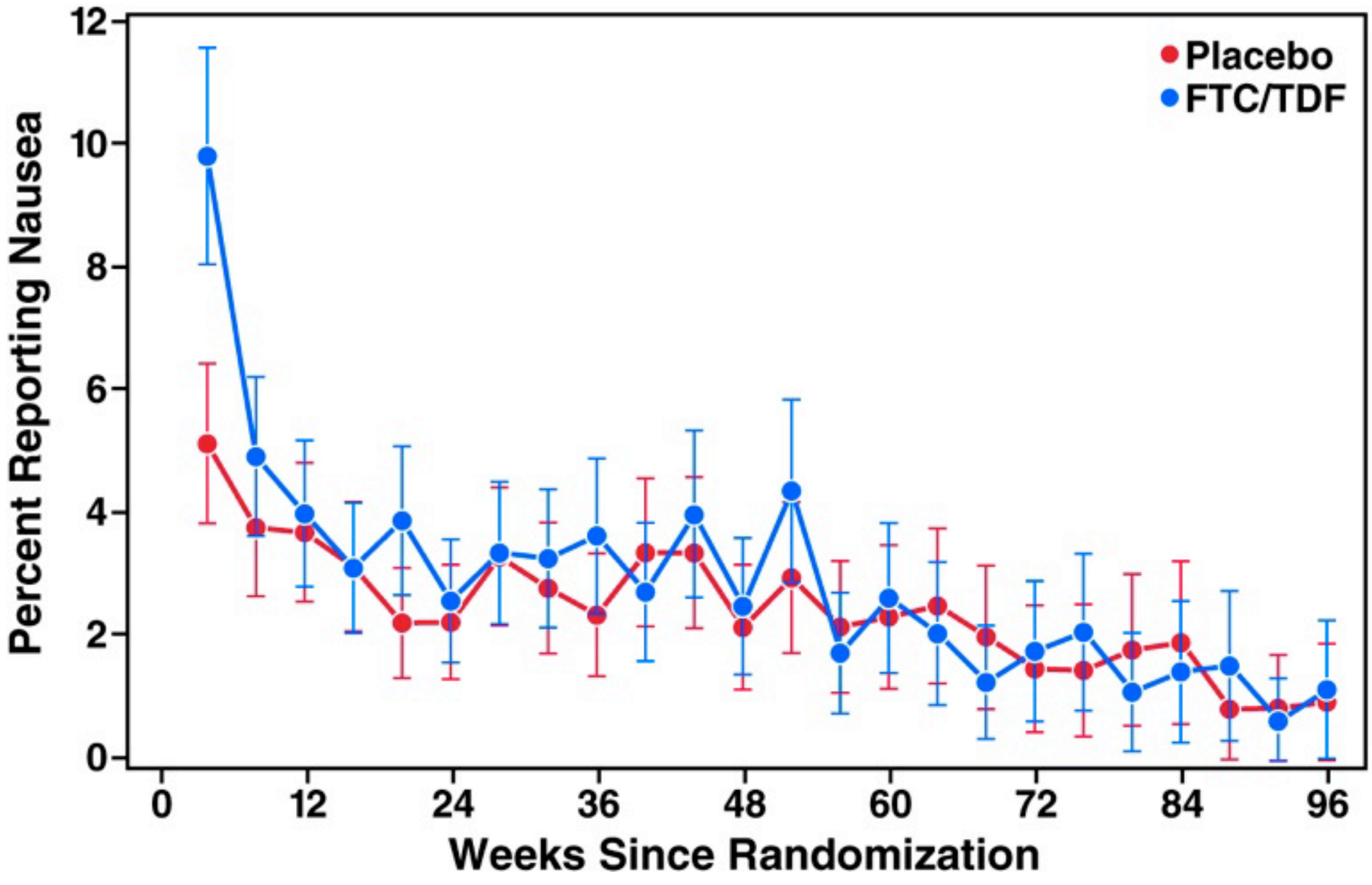
Adverse events

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
Depression	43 (3%)	46	62 (5%)	63	p=0.07
Nausea	20 (2%)	22	9 (<1%)	10	p=0.04
Weight Decreased	27 (2%)	34	14 (1%)	19	p=0.04
Diarrhea	46 (4%)	49	56 (4%)	61	p=0.36
Bone Fracture	15 (1%)	16	11 (<1%)	12	p=0.41

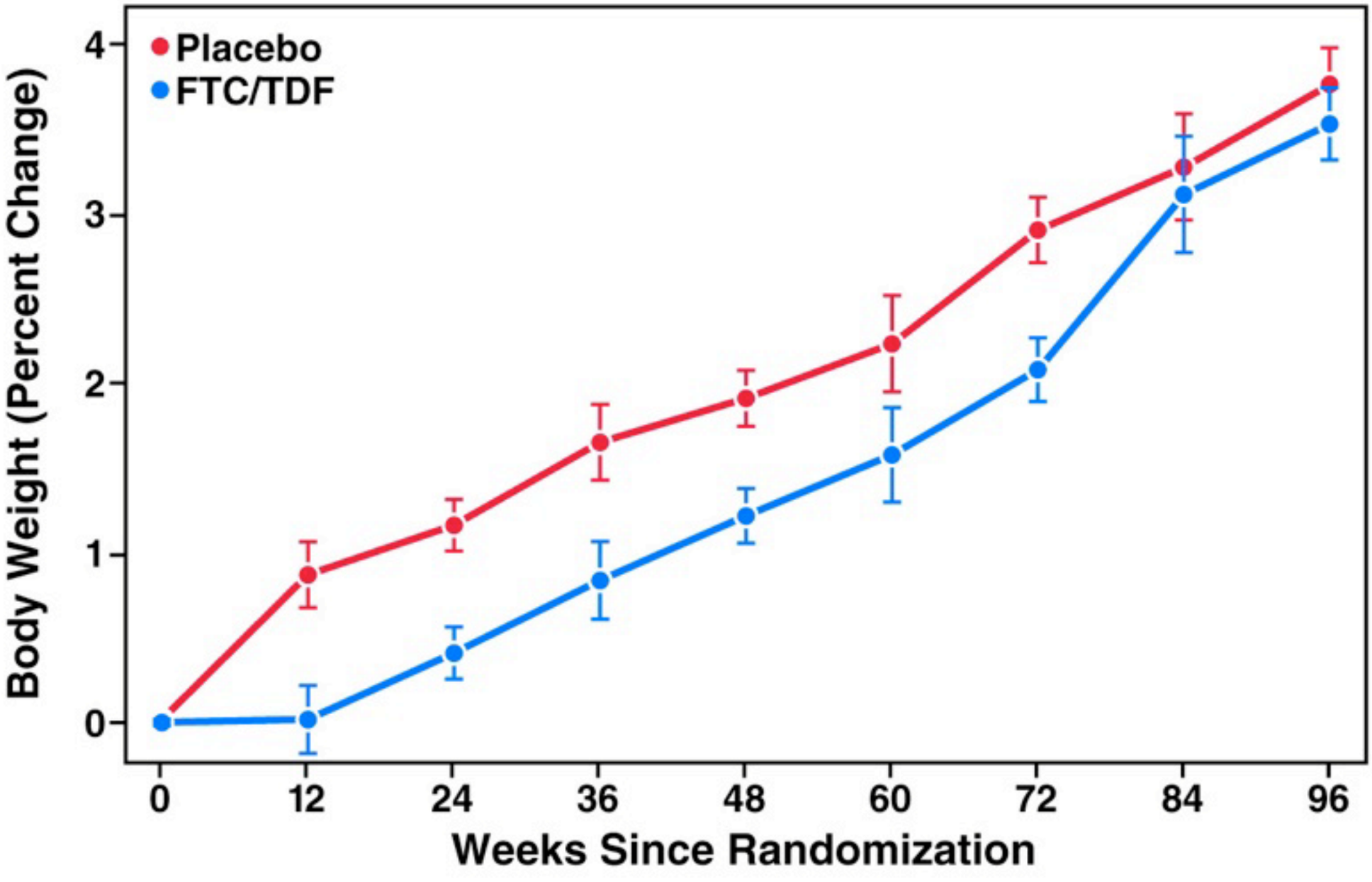
Adverse events

Adverse Event	TDF/FTC		Placebo		P value
	n (%)	Events	n (%)	Events	
Grade 3	110 (9%)	197	117 (9%)	225	p=065
Grade 4	41 (3%)	51	47 (4%)	60	p=0.57
Grade 3 or Grade 4	151 (12%)	248	164 (13%)	285	p=0.51
Death	1 (<1%)	1	4 (<1%)	4	p=0.18
Drug Stopped (Perm.)	25 (2%)	26	27 (2%)	33	p=0.82
Drug Stopped (All)	79 (6%)	99	72 (6%)	92	p=0.54
Serious AE	60 (5%)	76	67 (5%)	87	p=0.57
All AE	867 (69%)	2.630	877 (70%)	2,611	p=0.50

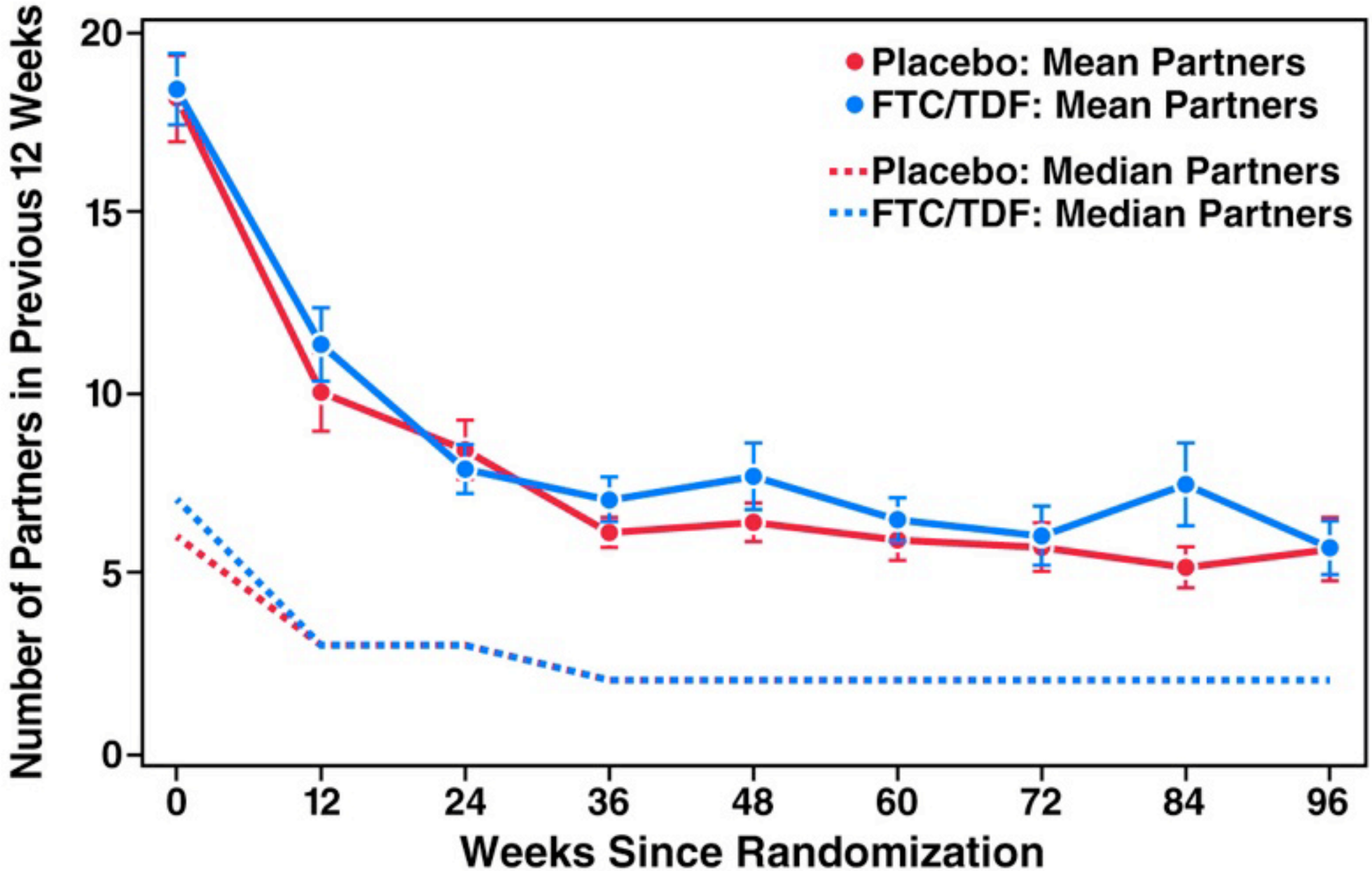
Nausea on History



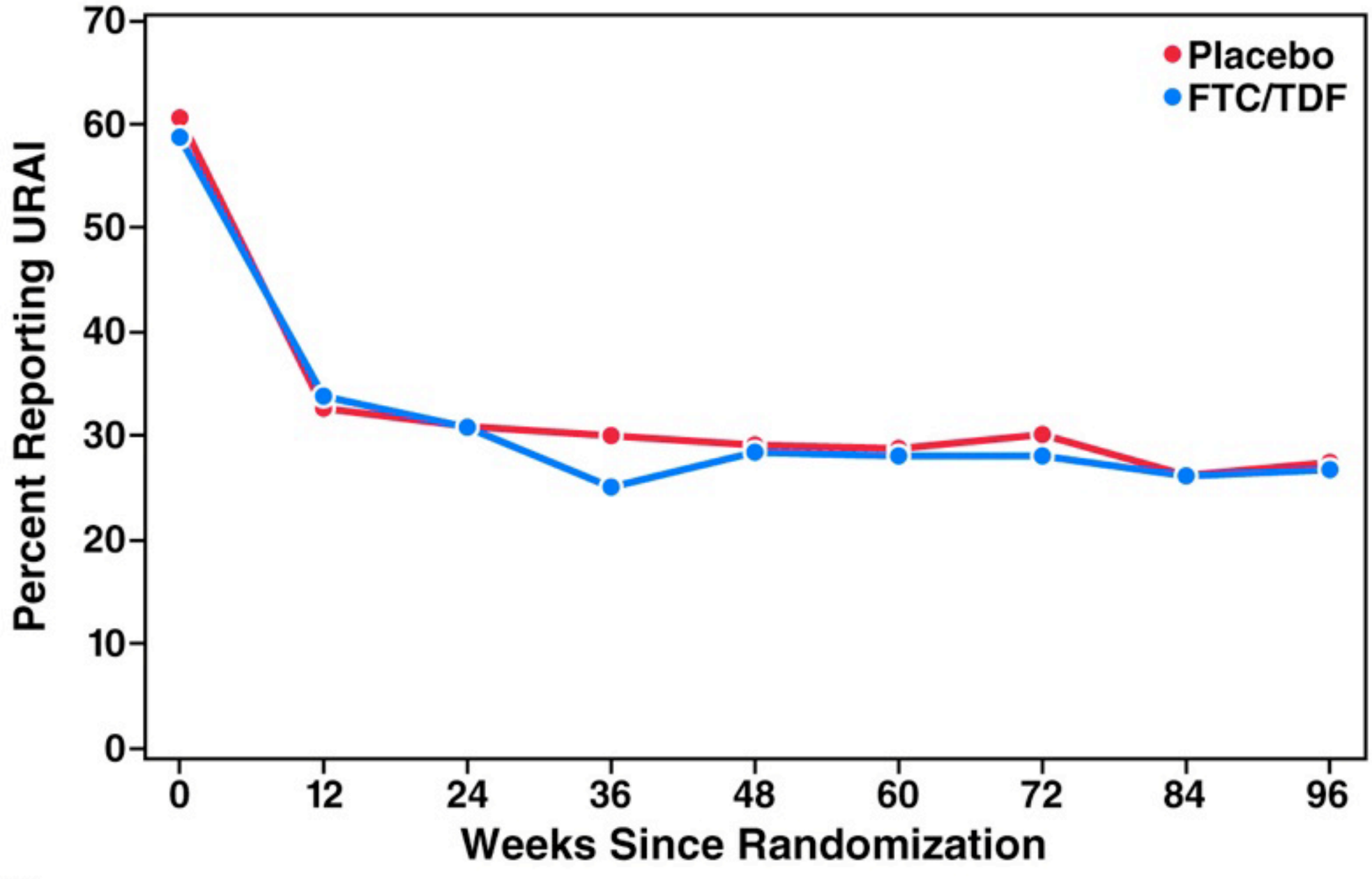
Weight Gain


Placebo
FTC/TDF
Body Weight (Percent Change)
4
3
2
1
0
0
12
24
36
48
60
72
84
96
Weeks Since Randomization

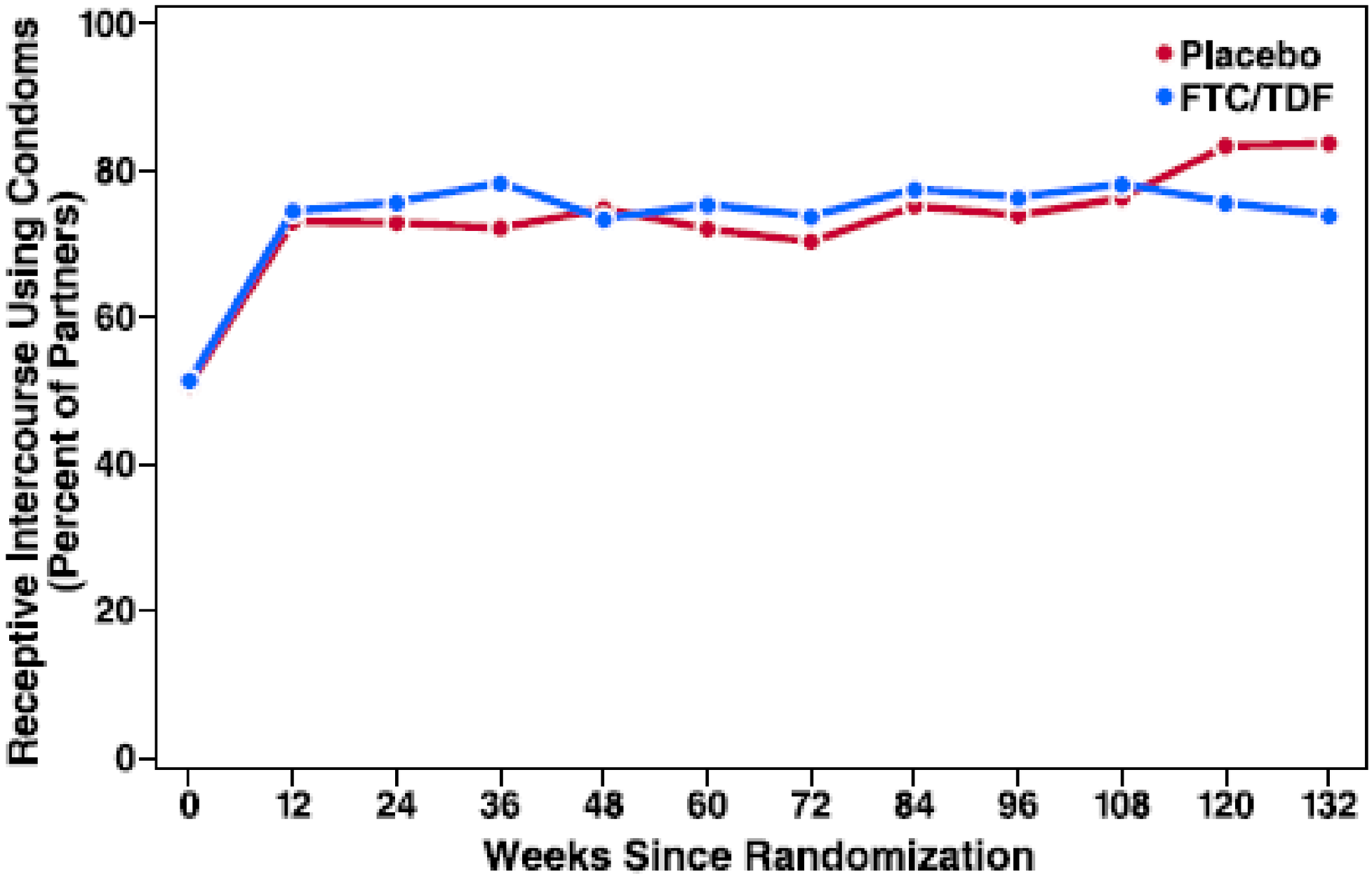
Sexual Partners



High Risk Sexual Partnerships



Condom Use with High Risk Sex



Conclusions

Conclusions

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.

Proposed Open Label Extensión

Sponsored by
NIH/NIAID/DAIDS

with drug donated by
Gilead Sciences

Premise

Risk compensation and adherence are significant determinants of PREP effects

Information about PrEP safety and efficacy could affect behavior

“Next Step” Counseling For PrEP Pill Taking

- Separation of roles
  - –Monitoring
  - –Promotion
- Monitoring is Neutral
- Promotion focus
  - –On Barriers and facilitators
  - –Blind to actual reported use


GLOBAL
PrEX

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