Phase 3 Randomized, Controlled DISCOVER Study of Daily F/TAF or F/TDF for HIV Pre-exposure Prophylaxis: Week 96 Results

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Introduction

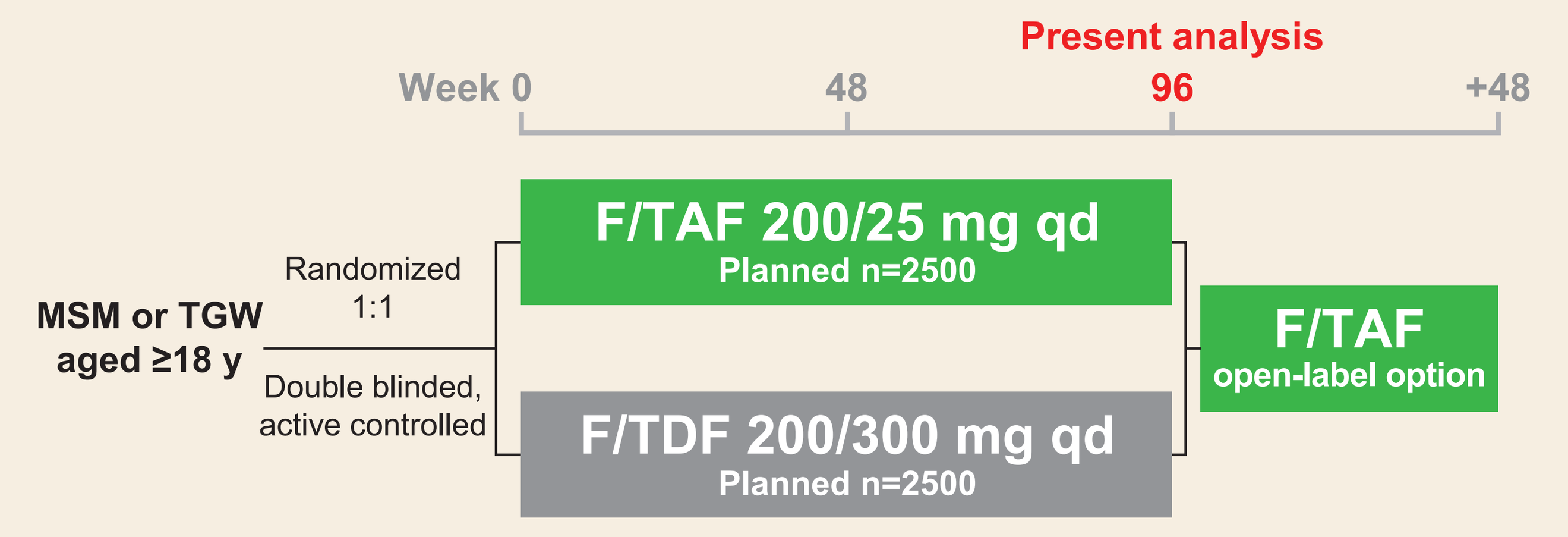
- Emtricitabine/tenofovir alafenamide (F/TAF) was recently approved in the United States for HIV pre-exposure prophylaxis (PrEP)[1]
- The DISCOVER study (ClinicalTrials.gov NCT02842086) was a Phase 3, randomized, controlled trial that evaluated the efficacy and safety of F/TAF for PrEP among cis-men who have sex with men (MSM) and transgender women (TGW) at high risk of HIV infection
- Interim data analysis was conducted when 100% of participants completed Week 48 and 50% completed Week 96, and demonstrated that[2]:
  - F/TAF was noninferior to emtricitabine/tenofovir disoproxil fumarate (F/TDF) in preventing HIV infection
  - Both drugs were well tolerated, with low rates of adverse event (AE)–related discontinuations
  - F/TAF had significantly better bone and renal safety outcomes vs F/TDF
- Here we present longer term results conducted after all participants completed the Week 96 visit

Objectives

- To assess the long-term (96-wk) efficacy and safety of HIV PrEP with F/TAF vs F/TDF in MSM and TGW

Methods

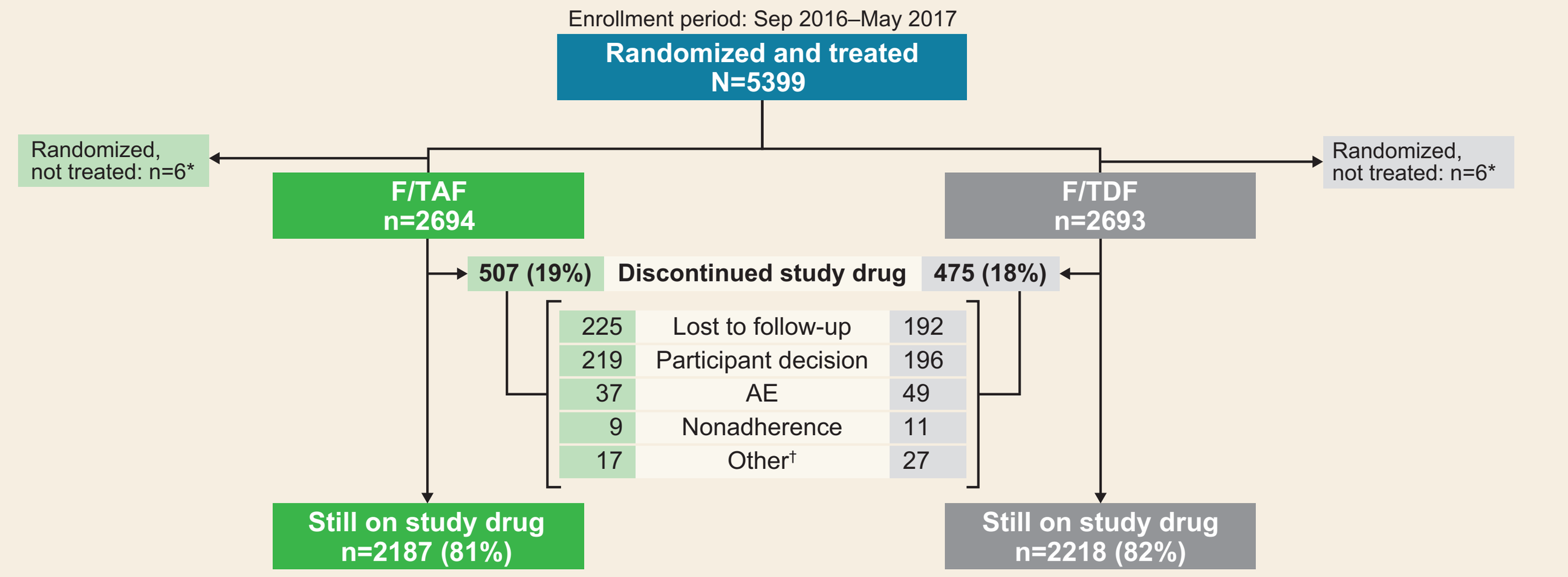
Study Design



- Eligibility: high sexual risk of HIV
  - 2+ episodes of condomless anal sex in past 12 wk **or** rectal gonorrhea/chlamydia or syphilis in past 24 wk
  - HIV and hepatitis B virus negative, and estimated glomerular filtration rate by Cockcroft-Gault ($eGFR_{CG}$) ≥60 mL/min
  - Prior use of PrEP allowed
- Study conducted in Europe and North America in cities/sites with high HIV incidence
- Assessments:
  - Safety: AEs, AE-related discontinuations, bone mineral density (BMD), and renal biomarkers
  - Adherence: self-report, pill counts, drug levels, and dried blood spots
  - HIV lab testing: rapid HIV testing on site and central lab
  - HIV risk behavior: confidential computer-aided self-interview questionnaire, sexually transmitted infection (STI) assessment at every visit (gonococcus/chlamydia trachomatis [GC/CT]: rectum, urethra, and oropharynx [nucleic acid amplification test], and syphilis testing)
- Primary efficacy endpoint analysis:
  - HIV incidence rate (events/100 person-years [PY]): $\frac{\text{No. of HIV infections}}{\text{PY exposure}} \times (100)$
  - Incidence rate ratio (IRR): $\frac{\text{HIV incidence rate: F/TAF arm}}{\text{HIV incidence rate: F/TDF arm}}$
  - Noninferiority (NI) margin: 1.62; preserves 50% of F/TDF effect vs placebo in 3 prior randomized controlled trials in MSM
  - F/TAF NI to F/TDF established if upper bound of IRR 95% confidence interval (CI) was <1.62
  - Interim data analysis analysis was conducted when 100% completed Week 48 and 50% completed Week 96

Results

Participant Disposition Through Week 96


Enrollment period: Sep 2016–May 2017
Randomized and treated
N=5399
Randomized, not treated: n=6*
F/TAF
n=2694
F/TDF
n=2693
Randomized, not treated: n=6*
507 (19%)
Discontinued study drug
475 (18%)
225
Lost to follow-up
192
219
Participant decision
196
37
AE
49
9
Nonadherence
11
17
Other†
27
Still on study drug
n=2187 (81%)
Still on study drug
n=2218 (82%)

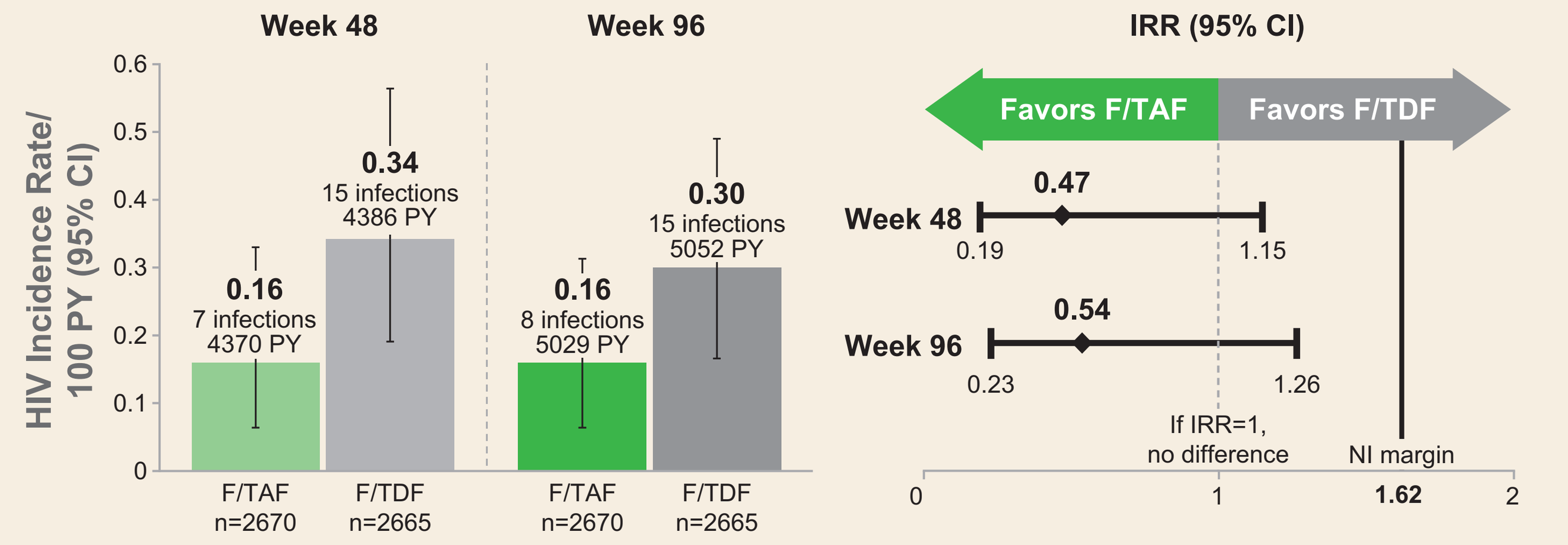
*Includes protocol violation (n=1), withdrew consent (n=8), HIV-1 infection (n=2), and investigator's discretion (n=1); †Includes protocol violation (n=3), investigator's discretion (n=11), HIV infection (n=10), and death (n=3).

Demographics and Baseline Characteristics*

		F/TAF n=2694	F/TDF n=2693
Demographics	Median age, y (range)	34 (18–76)	34 (18–72)
	Race, %		
	White	84	84
	Black*	9	9
	Asian	4	5
	Hispanic or Latinx, %	24	25
	Proportion TGW, %	2	1
HIV Risk Factors, %	≥2 condomless anal sex (receptive) in past 12 wk	62	60
	Rectal gonorrhea in past 24 wk	10	10
	Rectal chlamydia in past 24 wk	13	12
	Syphilis in past 24 wk	9	10
	Recreational drug use in past 12 wk	67	67
	Binge drinking†	23	22
	Taking F/TDF for PrEP at baseline	17	16

*Includes mixed black race; †≥6 drinks on ≥1 occasion at least monthly.

Primary Endpoint Analysis: HIV Incidence


Week 48
Week 96
IRR (95% CI)
HIV Incidence Rate/100 PY (95% CI)
0.34
15 infections
4386 PY
0.16
7 infections
4370 PY
0.30
15 infections
5052 PY
0.16
8 infections
5029 PY
F/TAF n=2670
F/TDF n=2665
F/TAF n=2670
F/TDF n=2665
Favors F/TAF
Favors F/TDF
Week 48
0.47
0.19
1.15
Week 96
0.54
0.23
1.26
If IRR=1, no difference
NI margin
0
1
1.62
2

- Primary analysis: 22 HIV infections in 8756 PY of follow-up
- Week-96 analysis: 23 HIV infections in 10,081 PY of follow-up
- F/TAF was NI to F/TDF for HIV prevention as the upper bound of IRR 95% CI was <1.62

Overall Safety Summary

	F/TAF n=2694	F/TDF n=2693
Any AE, %	93	93
Study drug-related AE	21	24
Grade ≥2 AE, %	49	47
Grade ≥3 AE, %	7	6
Serious AE, %	7	6
Study drug related	0.1	0.2
AE leading to discontinuation, %	1	2
Death, n*	1	2

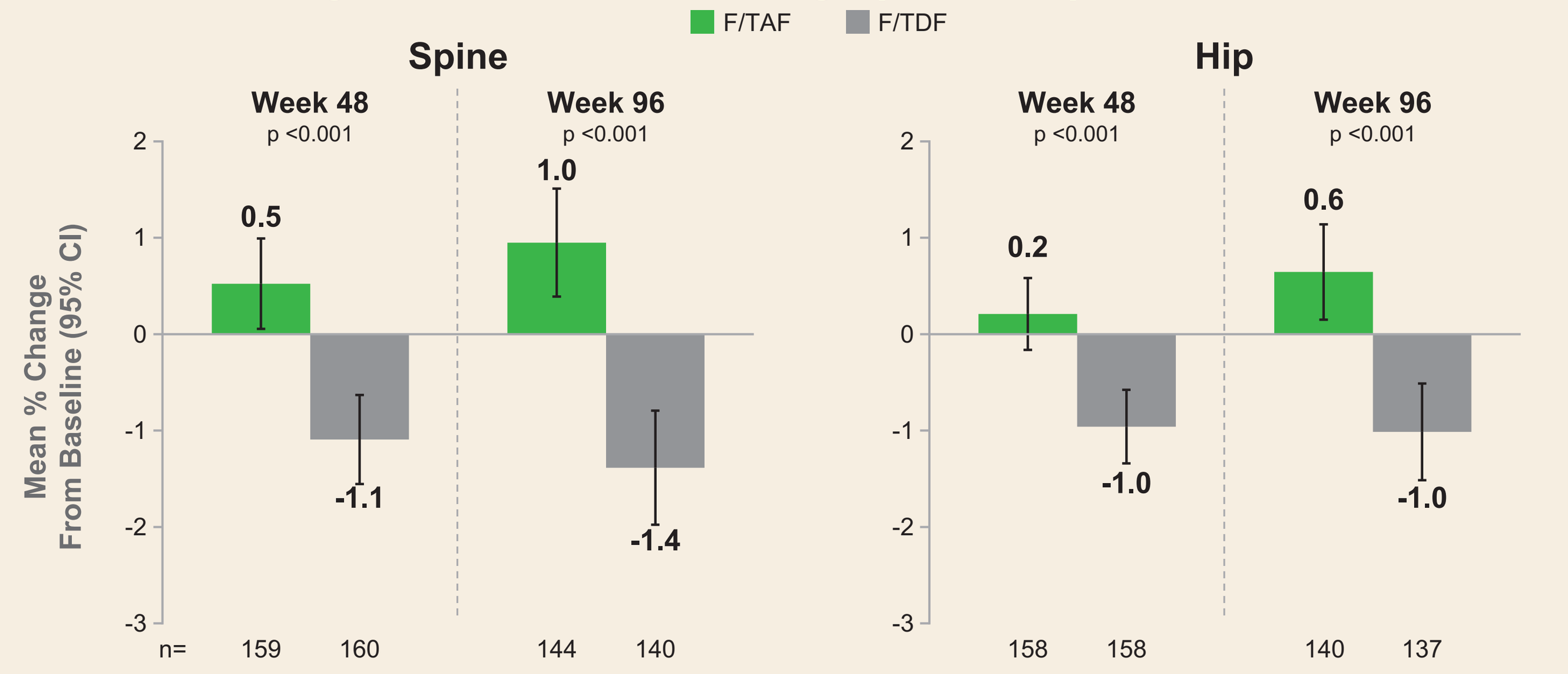
*Reasons: traffic accident, metastatic squamous cell carcinoma, and unknown.

- Respective median weight changes with F/TAF and F/TDF were +1.0 and 0.0 kg at Week 48 ($p < 0.001$), and +1.7 and +0.5 kg at Week 96 ($p < 0.001$)

Common Adverse Events (≥10%)

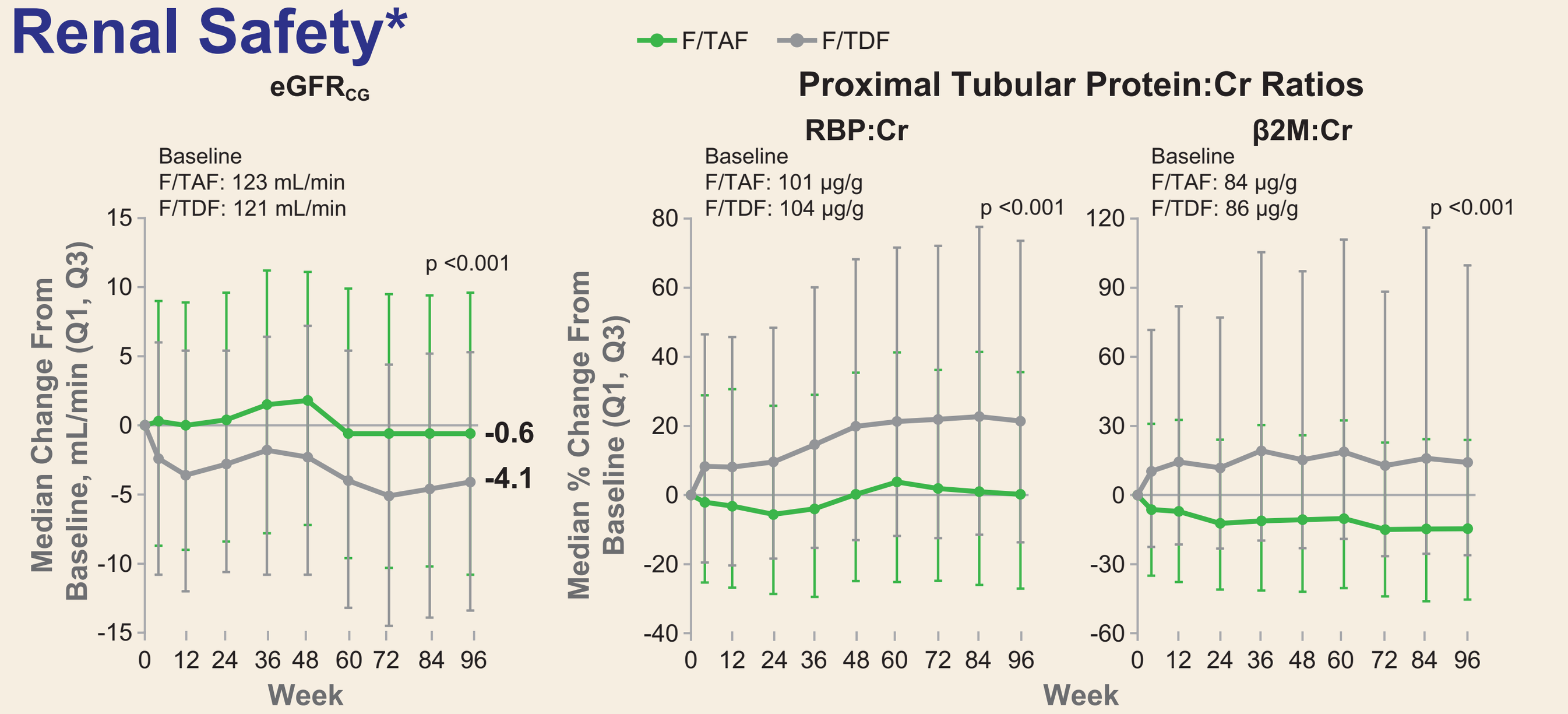
Participants, %	F/TAF n=2694	F/TDF n=2693
Rectal chlamydia	30	30
Oropharyngeal gonorrhea	31	30
Rectal gonorrhea	28	28
Exposure to communicable disease	19	18
Diarrhea	17	16
Nasopharyngitis	14	14
Syphilis	14	13
Upper respiratory tract infection	14	12
Urethral chlamydia	12	11

Bone Safety: BMD Substudy (n=375)*



*p-values from analysis of variance model with baseline F/TDF for PrEP and treatment as fixed effects.

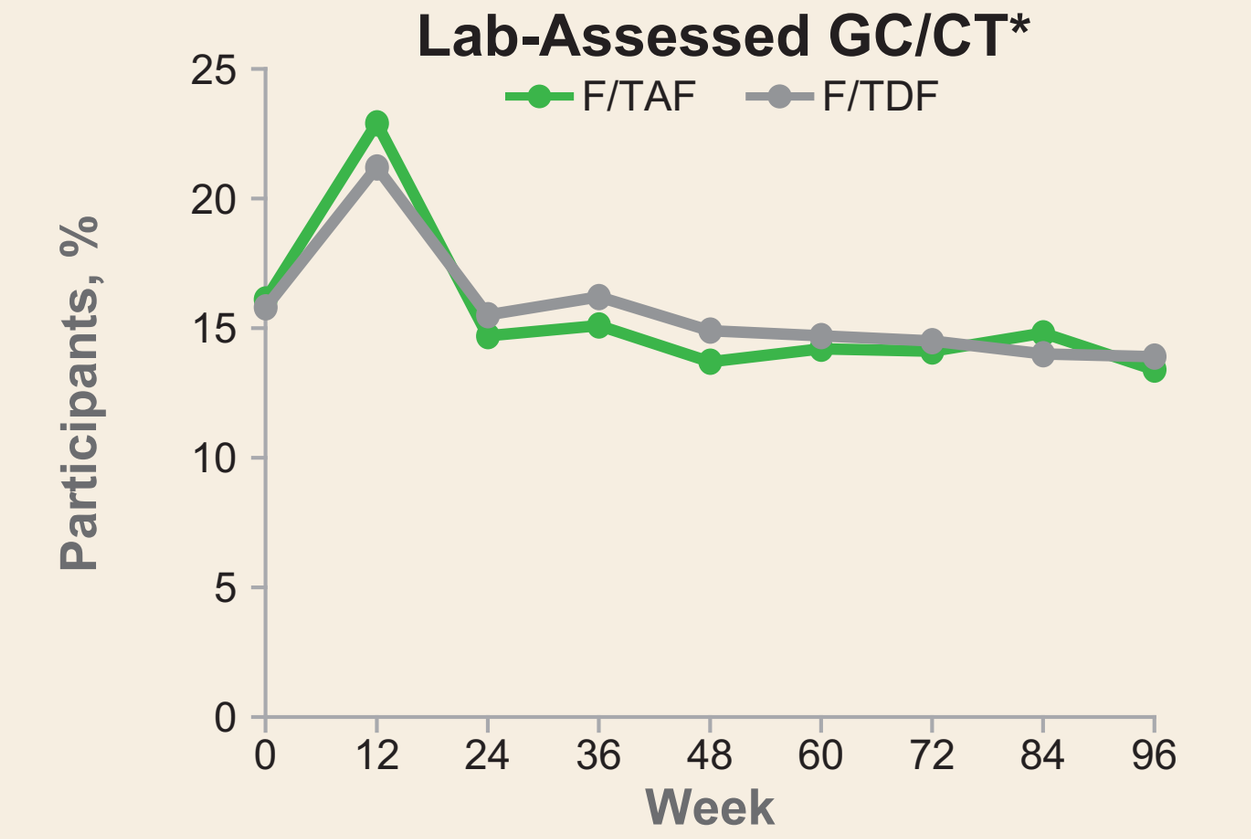
Renal Safety*


F/TAF
F/TDF
eGFRCG
Baseline
F/TAF: 123 mL/min
F/TDF: 121 mL/min
p <0.001
-0.6
-4.1
Median Change From Baseline, mL/min (Q1, Q3)
Proximal Tubular Protein:Cr Ratios
RBP:Cr
Baseline
F/TAF: 101 μg/g
F/TDF: 104 μg/g
p <0.001
β2M:Cr
Baseline
F/TAF: 84 μg/g
F/TDF: 86 μg/g
p <0.001
Median % Change From Baseline (Q1, Q3)
Week

*p-values from Van Elteren test stratified by baseline F/TDF for PrEP to compare 2 treatment groups. β2M, β2-microglobulin; Cr, creatinine; Q, quartile; RBP, retinol-binding protein.

- Renal discontinuations: F/TAF, n=2; F/TDF, n=6
- Fanconi syndrome: F/TAF, n=0; F/TDF, n=1

Sexually Transmitted Infections



Lab-Assessed GC/CT Incidence

	F/TAF n (incidence: n/100 PY)	F/TDF n (incidence: n/100 PY)
Gonorrhea (any site)	2269 (45)	2171 (43)
Rectal	1048 (21)	993 (20)
Chlamydia (any site)	2041 (41)	2025 (40)
Rectal	1343 (27)	1374 (27)
Syphilis	499 (10)	471 (9)

*Results from STI testing at Weeks 4 and 12 were combined.

- Incidence rate of gonorrhea, chlamydia, or syphilis while on study (based on AE reporting): F/TAF=142.7/100 PY and F/TDF=136.9/100 PY

Conclusions

- F/TAF was noninferior to F/TDF in preventing HIV infection through 96 wk: IRR 0.54 (95% CI 0.23, 1.26)
- Both drugs were well tolerated, with low rates of non-STI AE-related discontinuations and no new safety signals detected
- As demonstrated by the incidence of on-study STIs, participants had consistently high rates of sexual risk behavior, with no risk compensation
- Longer term data showed that the significantly better bone and renal safety outcomes with F/TAF vs F/TDF observed at Week 48 persisted though Week 96
- Weight changes were similar to those noted in the Phase 3 iPrEX trial[3]
- F/TAF is an effective option for PrEP in cis-MSM and TGW at risk for HIV infection, and has safer renal and bone outcomes than F/TDF

References: **1.** Descovy [package insert]. Foster City, CA: Gilead Sciences, Inc., 10/2019; **2.** Hare CB, et al. CROI 2019, abstr 104; **3.** Glidden DV, et al. Clin Infect Dis 2018;67:411-9.

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