Significant Efficacy and Long Term Safety Difference with TAF-based STR in Naïve Adults

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Poster P074

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Introduction

- Two randomized, controlled, double-blinded, multinational Phase 3 trials (Studies 104 [NCT01780506] and 111 [NCT01797445]) compared the NRTIs tenofovir alafenamide (TAF) and tenofovir disoproxil fumarate (TDF), each in single-tablet regimens coformulated with elvitegravir (E)/cobicistat (C)/emtricitabine (F)
- At Weeks 48 (primary endpoint) and 96, E/C/F/TAF had noninferior efficacy (HIV-1 RNA <50 copies/mL) to E/C/F/TDF, and less impact on bone and renal safety[1,2]
- We now present long-term (144-wk) efficacy, safety, and tolerability of treatment with E/C/F/TAF vs E/C/F/TDF in treatment-naïve participants with HIV-1 from these trials
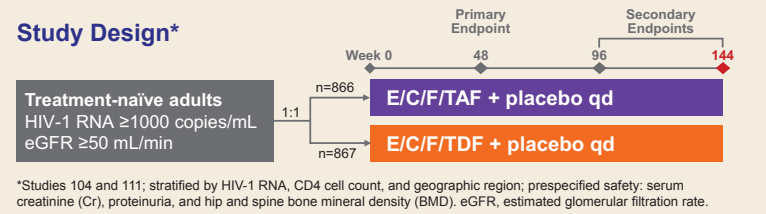
Prodrug Pharmacology: TAF vs TDF[1,3]
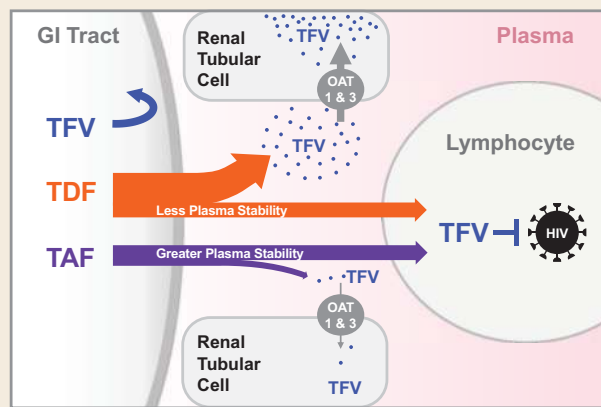
*TAF 25 mg results in 80–90% lower TFV plasma levels than TDF 300 mg. GI, gastrointestinal; OAT, organic anion transporter; TFV, tenofovir.

Methods

Study Design*

*Studies 104 and 111; stratified by HIV-1 RNA, CD4 cell count, and geographic region; prespecified safety: serum creatinine (Cr), proteinuria, and hip and spine bone mineral density (BMD). eGFR, estimated glomerular filtration rate.

Results

Baseline Characteristics and Past Medical History

		E/C/F/TAF n=866	E/C/F/TDF n=867
Median age, yrs (range)		33 (18–74)	35 (18–76)
Female, %		15	15
Race and ethnicity, %	Black or African heritage	26	25
	Asian	11	10
	Hispanic or Latino	19	19
Median CD4 count, cells/µL		404	406
CD4 <50 cells/µL, %		3	3
HIV-1 RNA >100,000 copies/mL, %		23	22
Median eGFR$_{CG}$, mL/min		117	114
Medical history, %	Diabetes mellitus	3	5
	Hypertension	14	17
	Cardiovascular disease	1	3
	Hyperlipidemia	11	12

CG, Cockcroft-Gault.

### Virologic Outcome at Weeks 48, 96, and 144*[1,2]

HIV-1 RNA <50 Copies/mL
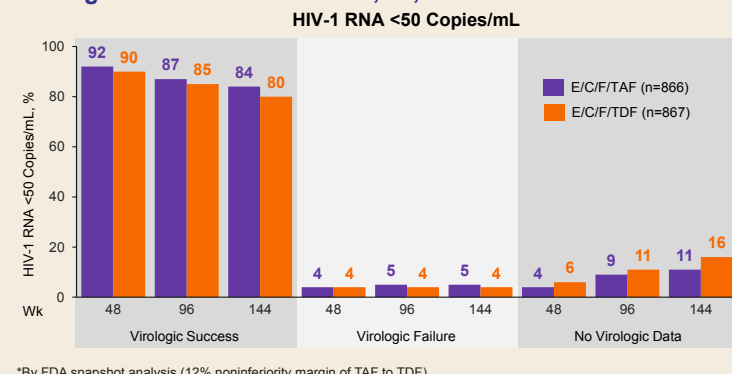
*By FDA snapshot analysis (12% noninferiority margin of TAF to TDF).

- At Week 144, E/C/F/TAF was superior to E/C/F/TDF in efficacy difference at both <50 copies/mL (4.2% [95% CI 0.6%, 7.8%; p=0.02]) and <20 copies/mL (5.4% [95% CI 1.5%, 9.2%; p=0.01])

Resistance

- By 144 wk, virologic failure with resistance occurred in 24 participants: 12 (1.4%) on TAF vs 12 (1.4%) on TDF
- Genotypic resistance data: NRTI and EVG resistance (n=8) and NRTI resistance only (n=4) in the TAF group; NRTI and EVG resistance (n=7), NRTI resistance only (n=4), and EVG resistance only (n=1) in the TDF group

Treatment Difference in Virologic Outcome at Week 144 by Prespecified Subgroups
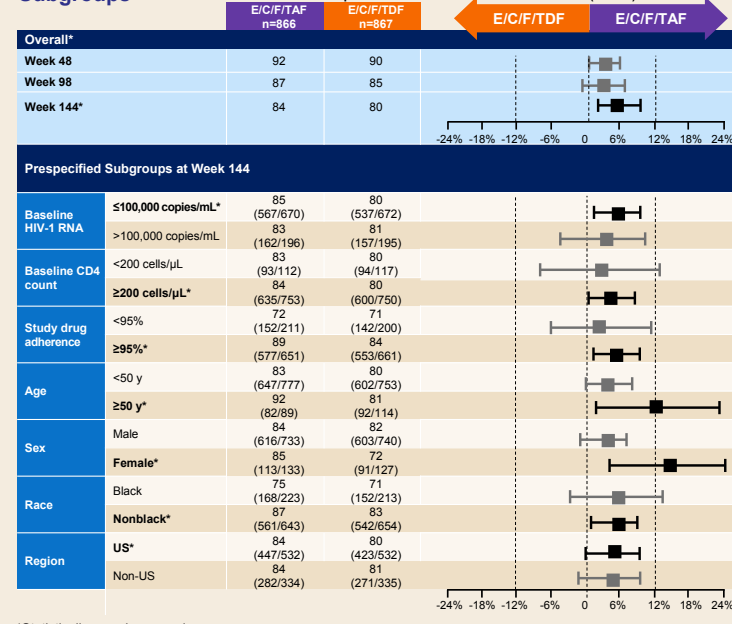
*Statistically superior. c, copies.

Results (Cont'd)

Renal Adverse Events Leading to Discontinuation

Renal AE D/C, n*	E/C/F/TAF n=866	E/C/F/TDF n=867	p-value[†]
Total	**0**	**12**	**<0.001**
Proximal renal tubulopathy[‡]	0	4	
Increased Cr/decreased eGFR	0	3	
Renal Failure	0	2	
Nephropathy	0	1	
Proteinureia	0	1	
Bladder spasm	0	1	

*Adverse events (AEs) coded as renal and urinary disorders (MedDRA 19.0); [†]Calculated using Fisher's exact test; [‡]Renal tubular disorder, Fanconi syndrome/glycosuria.

- 0 case of proximal renal tubulopathy in E/C/F/TAF arm vs 4 in E/C/F/TDF arm
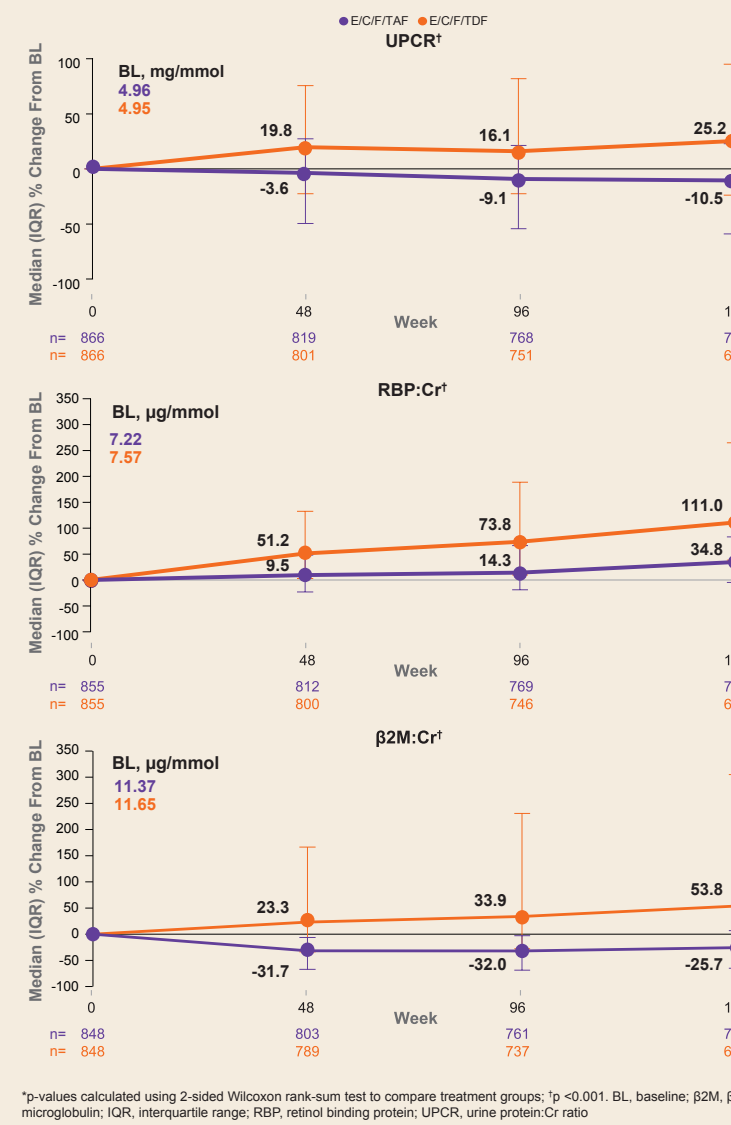 – 2 additional cases in E/C/F/TDF arm since Week 96

Week 144 Safety Summary*

	Participants, n (%)		E/C/F/TAF n=866	E/C/F/TDF n=867	p-value[†]
Safety Summary	Any AE		817 (94.3)	933 (96.1)	–
	Grade 3 or 4 AE		140 (16.2)	137 (15.8)	–
	Serious AE		121 (14.0)	124 (14.3)	–
	Death		4 (0.5)[†]	5 (0.6)[‡]	–
	AE-related D/C	Week 48	8 (0.9)	13 (1.5)	0.38
		Week 96	10 (1.2)	20 (2.3)	0.10
		Week 144	11 (1.3)	29 (3.3)	0.01
AEs in ≥10% of Participants	Diarrhea		203 (23.4)	212 (24.5)	–
	Upper respiratoryt tract infection		176 (20.3)	170 (19.6)	–
	Headache		166 (19.2)	135 (15.6)	–
	Nausea		150 (17.3)	167 (19.3)	–
	Nasopharyngitis		125 (14.4)	123 (14.2)	–
	Cough		117 (13.5)	102 (14.2)	–
	Fatigue		101 (11.7)	97 (11.2)	–
	Arthralgia		104 (12.0)	82 (8.9)	–
	Back pain		104 (12.00	104 (12.0)	–
	Insomnia		94 (10.9)	68 (7.8)	–
	Syphilis		86 (9.9)	97 (11.2)	–
	Osteopenia		69 (8.0)	87 (10.0)	–

*Safety analysis set included all participants who received ≥1 dose; [†]Calculated using Fisher's exact test test to compare treatment groups; [‡]Stroke (n=2), alcohol intoxication (n=1), suicide (n=1); [†]Alcohol and drug intoxication (n=1), myocardial infarction (n=2), cardiac arrest (n=1), unknown (n=1). D/C, discontinuation.

- AEs leading to D/C in the E/C/F/TAF group primarily happened early, whereas in the E/C/F/TDF group, AEs leading to D/C continued to accumulate, with a significant difference in total number of AEs at Week 144
- Most AEs occurred within first 4 wk of treatment initiation

Renal Parameters at Week 144*

*p-values calculated using 2-sided Wilcoxon rank-sum test to compare treatment groups; [†]p <0.001. BL, baseline; β2M, β2 microglobulin; IQR, interquartile range; RBP, retinol binding protein; UPCR, urine protein:Cr ratio

- At Week 144, median change from baseline in eGFR$_{CG}$ was significantly lower with E/C/F/TAF vs E/C/F/TDF (1.6 vs 7.7 mL/min; p<0.001)

Week 144 Grade 3 or 4 Laboratory Abnormalities

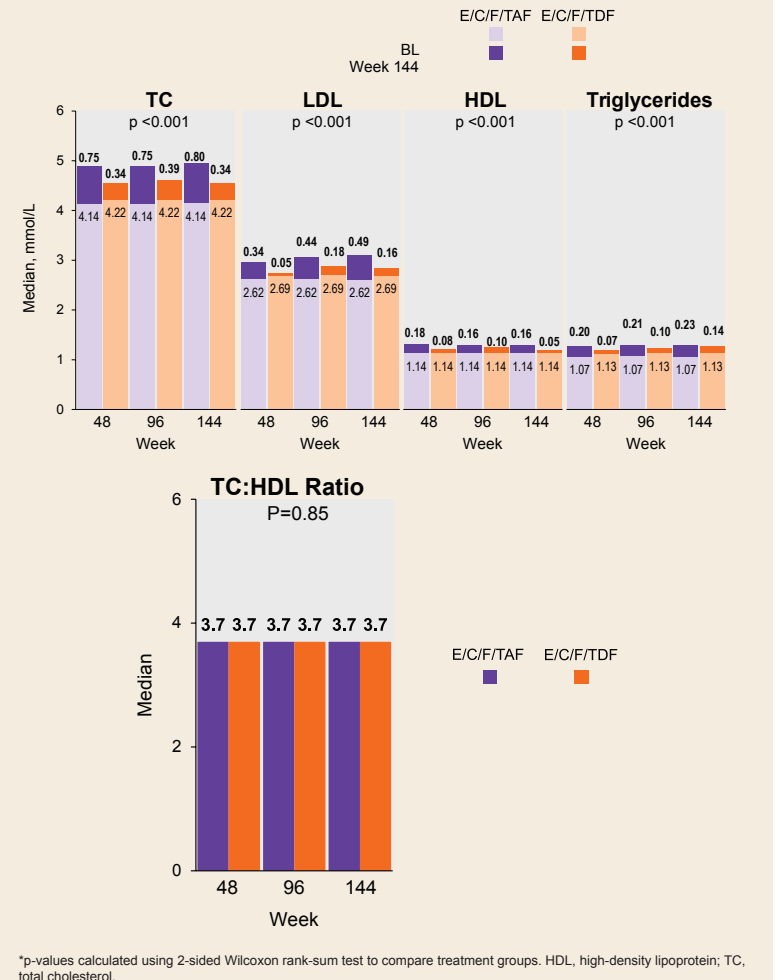| Partiipants, n (%)	E/C/F/TAF n=862	E/C/F/TDF n=865*
Any Grade 3 or 4 lab abnormalities[†]	**284 (32.9)**	**266 (30.7)**
Creatine kinase elevation	99 (11.5)	87 (10.1)
LDL elevation (fasting)	92/839 (11.0)	40/834 (4.8)
Lipase[‡]	6/127 (5)	13/154 (8)
Hypercholesterolemia (fasting)	34/839 (4.7)	23/835 (2.8)
AST	29 (3.4)	32 (4.0)
Amylase	22 (2.6)	43 (5.0)
Hematuria (quantitative)	25 (2.9)	26 (3.0)
Neutropenia	16 (1.9)	26 (3.0)

[†]Denominator for percentage is number of participants in safety analysis set with ≥1 postbaseline lab value (for each test); [‡]Occurring in ≥3% of participants in either group; [‡]Lipase test was only performed for participants with serum amylase >1.5x upper limit of normal. AST, aspartate aminotransferase; LDL, low-density lipoprotein.

Median Change in Spine and Hip BMD through Week 144

Spine

Hip
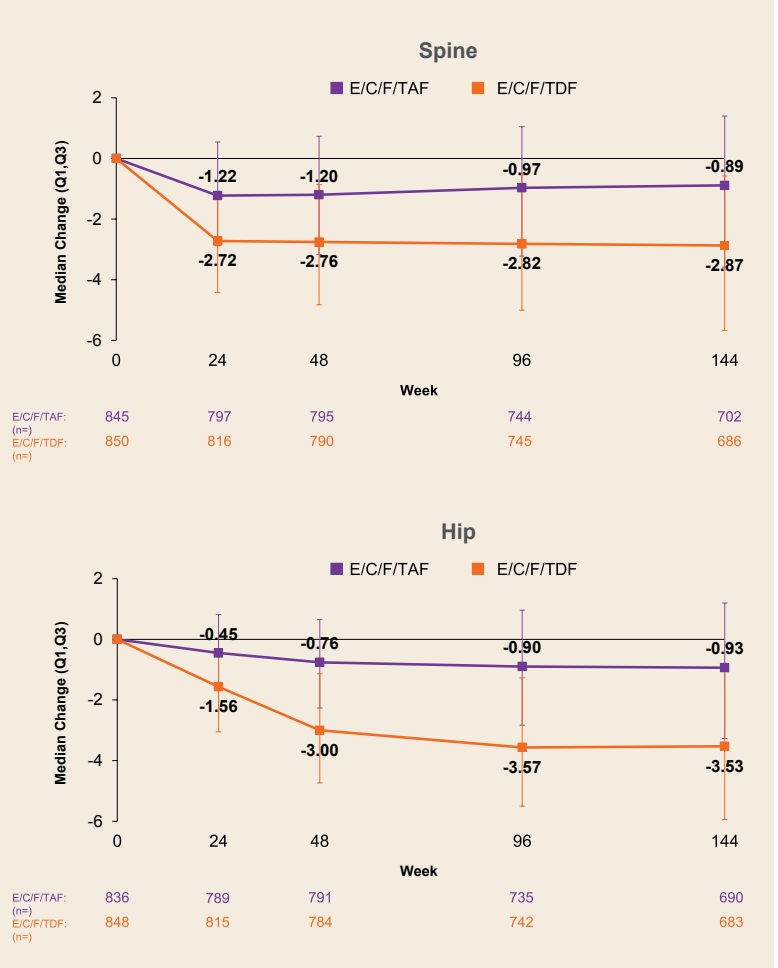
- % initiating meds during study to increase BMD: TAF 16% vs. TDF 21%; p=0.018

Fasting Lipids Through Week 144*

TC:HDL Ratio

*p-values calculated using 2-sided Wilcoxon rank-sum test to compare treatment groups. HDL, high-density lipoprotein; TC, total cholesterol.

- Participants on E/C/F/TAF had greater increases in TC, LDL, and HDL than those on E/C/F/TDF, with no difference in rate of initiation of lipid-modifying agents (E/C/F/TAF: 5.5% [n=48]; E/C/F/TDF: 5.8% [n=50])

Conclusions

- At Week 144, E/C/F/TAF was superior to E/C/F/TDF in virologic efficacy
  – HIV RNA <50 copies/mL: 84% vs 80%
  – HIV RNA <20 copies/mL: 76% vs 76%
- Emergence of resistance was rare
- E/C/F/TAF had significantly less impact than E/C/F/TDF on renal biomarkers
  – 0 vs 12 renal AEs; 0 vs 4 cases of proximal tubulopathy
- E/C/F/TAF had significantly less impact than E/C/F/TDF on BMD
  – 0 vs 6 D/C for bone loss
- These longer-term data support the use of E/C/F/TAF as a safe, well-tolerated, and durable regimen for initial and ongoing HIV-1 treatment

References

1. Sax P, et al. Lancet 2015;385:2606–15.
2. Wohl D et al. J Acquir Immune Defic Syndr 2016;72:58–64.
3. Sax P, et al. J Acquir Immune Defic Syndr 2014;67:52–8.

Acknowledgments