Longer Term Safety of Tenofovir Alafenamide in Renal Impairment

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Poster #

Introduction

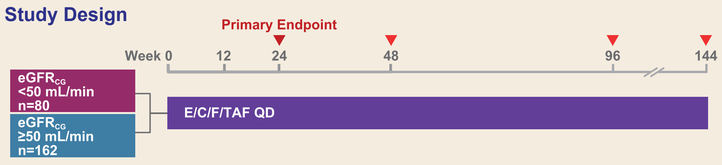
- Tenofovir disoproxil fumarate (TDF) has been associated with clinically significant renal and bone toxicity[1-3]
- Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir (TFV) that results in 91% lower plasma TFV levels than TDF 300 mg
- TAF, administered as part of a single-tablet, once daily regimen of elvitegravir, cobicistat, emtricitabine (FTC), and TAF (E/C/F/TAF), had no effect on renal tubular function (quantified proteinuria)[4]
- Switching to E/C/F/TAF in HIV-1–infected patients with a creatinine clearance (estimated glomerular filtration rate by Cockcroft-Gault equation [$eGFR_{CG}$]) of 30–69 mL/min was shown to be effective and safe through 48 weeks[5]

Objectives

- To evaluate the 2-year (96-week) safety and efficacy of a single-tablet, once-daily regimen of E/C/F/TAF in HIV-1–infected patients with mild–moderate renal impairment

Methods

Study Design



QD, once daily.

- Phase 3, 144-week, multicenter, open-label study (Study 112; NCT01818596)
- Virologically suppressed adults with stable $eGFR_{CG}$ (30–69 mL/min) switched from TDF- or non-TDF–containing regimens to open-label E/C/F/TAF
- Week-96 efficacy and safety data are described, including tests of renal function and bone mineral density (BMD)

Key Inclusion Criteria

- CD4 cell count ≥50 cells/µL
- No chronic hepatitis B or C virus infection
- HIV-1–suppressed patients: HIV-1 RNA <50 copies/mL for ≥6 months

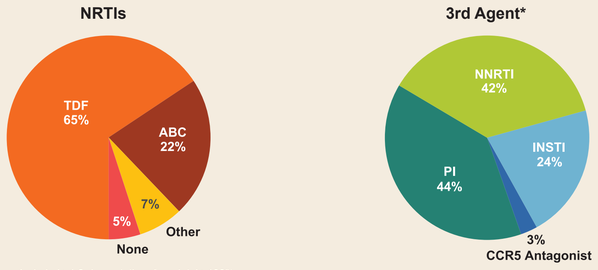
Results

Baseline Characteristics

	Baseline eGFR <50 mL/min n=80	Baseline eGFR ≥50 mL/min n=162
Median age, y (range)	59 (31–82)	58 (24–76)
Age ≥65 y, n (%)	25 (31)	38 (23)
Female, n (%)	21 (26)	29 (18)
Black or African descent, %	18	19
HIV-1 RNA <50 copies/mL, %	98	98
Median CD4 count, cells/µL	622	635
Pre-switch TDF, %	58	69
TDF dose adjusted	37	-
Hypertension, %	50	34
Diabetes, %	15	13
Median $eGFR_{CG}$, mL/min	43	60
Median $eGFR_{CKD\text{-}EPI,sCr}$, mL/min/1.73 m²*	45	58
Median $eGFR_{CKD\text{-}EPI,cysC}$, mL/min/1.73 m²†	57	77
Dipstick proteinuria, %	44	27
1+	29	20
2-3+	15	7
Significant proteinuria (UPCR >200 mg/g), %	56	35
Significant albuminuria (UACR ≥30 mg/g), %	64	42

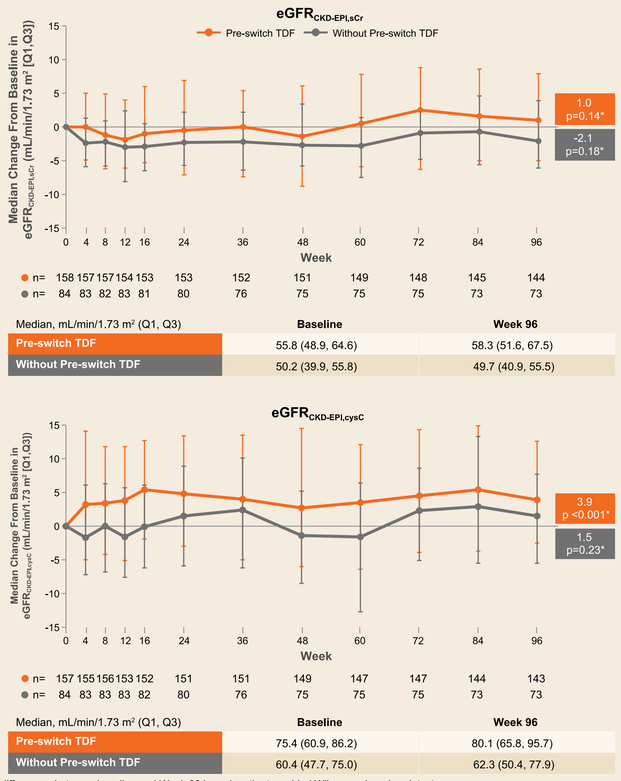
*Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation using serum creatinine (sCr; adjusted for age, sex, and race); †CKD-EPI equation using cystatin C (cysC; adjusted for age and sex). UACR, urine albumin:Cr; UPCR, urine protein:Cr.

Antiretroviral Treatment Prior to Switching to E/C/F/TAF



*Some regimens included >1 3rd agent; therefore, total >100%.
ABC, abacavir; CCR5, C-C chemokine receptor type 5; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

Estimated GFR: Changes Over Time



Median, mL/min/1.73 m² (Q1, Q3)	Baseline	Week 96
Pre-switch TDF	55.8 (48.9, 64.6)	58.3 (51.6, 67.5)
Without Pre-switch TDF	50.2 (39.9, 55.8)	49.7 (40.9, 55.5)

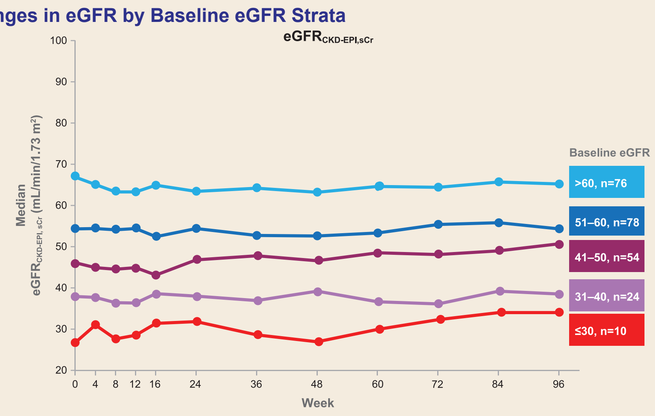
Median, mL/min/1.73 m² (Q1, Q3)	Baseline	Week 96
Pre-switch TDF	75.4 (60.9, 86.2)	80.1 (65.8, 95.7)
Without Pre-switch TDF	60.4 (47.7, 75.0)	62.3 (50.4, 77.9)

*P-values for differences between baseline and Week 96 based on the two-sided Wilcoxon signed-rank test.

- Median (Q1,Q3) changes from baseline with pre-switch TDF use:
  - $eGFR_{CKD\text{-}EPI,sCr}$: 1.0 (-5.0, 7.9) mL/min/1.73 m²
  - $eGFR_{CKD\text{-}EPI,cysC}$: 3.9 (-2.5, 12.6) mL/min/1.73 m²

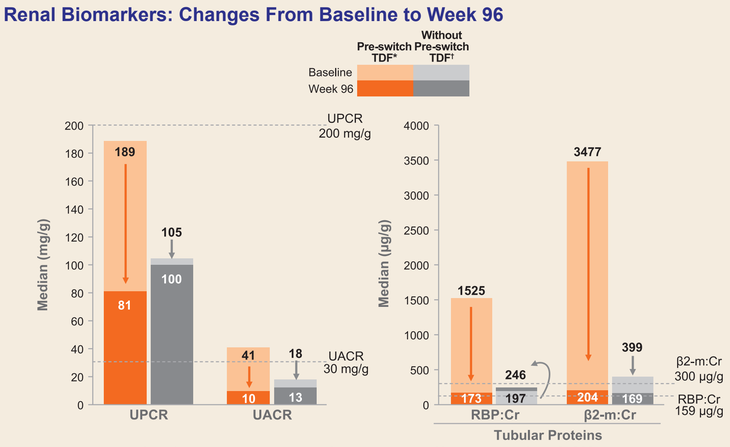
Results (continued)

Changes in eGFR by Baseline eGFR Strata



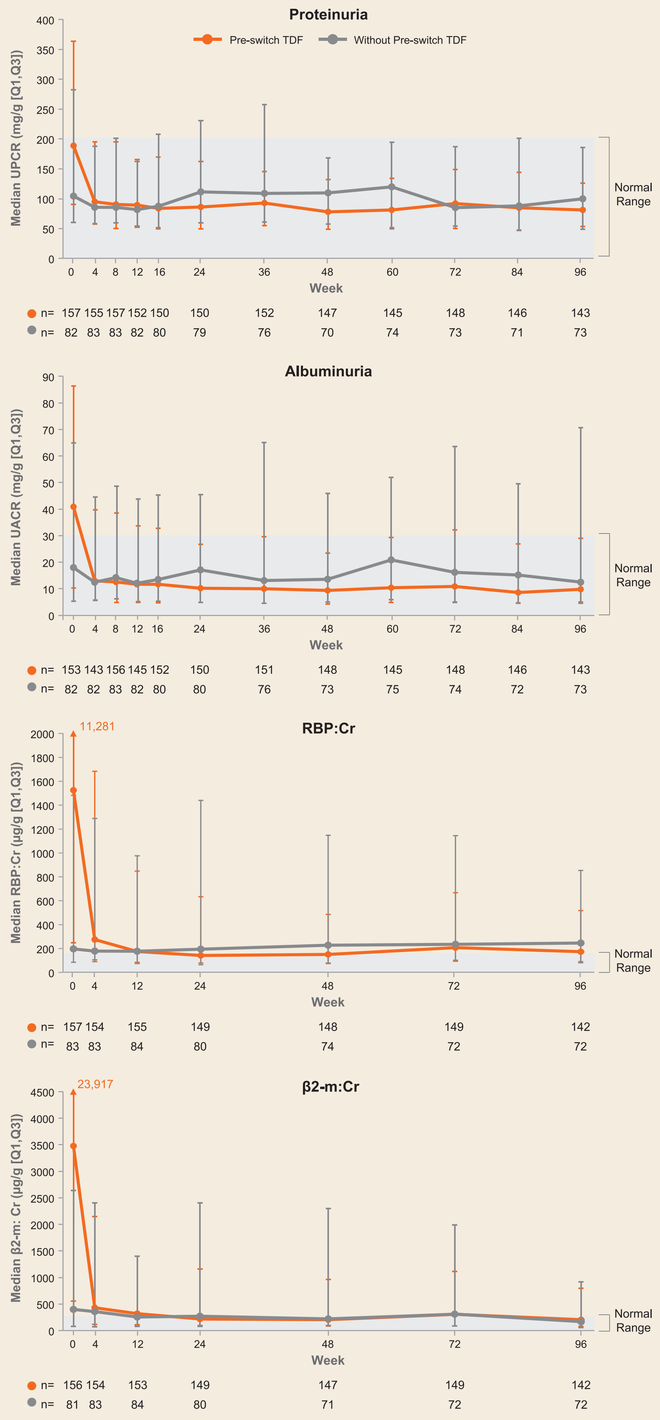
One patient was excluded due to missing cysC data at baseline.

Renal Biomarkers: Changes From Baseline to Week 96



*All changes statistically significant; †all changes not statistically significant with exception of β2-microglobulin (β2-m):Cr. RBP, retinol-binding protein.

Renal Biomarkers: Changes Over Time



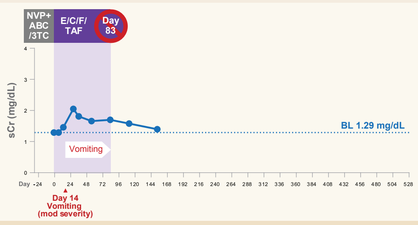
Discontinuations Due to Renal Adverse Events

1

52-year-old white female with history of right nephrectomy and uncontrolled hypertension at baseline, managed with valsartan and ramipril, experienced vomiting, dehydration, and pre-renal azotemia (BUN:Cr >20)

Declining eGFR prompted study drug discontinuation

No evidence of tubulopathy

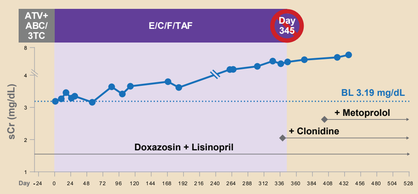


2

51-year-old white male with poorly controlled hypertension prompting escalation in antihypertensive therapy

Declining eGFR prompted study drug discontinuation

No evidence of tubulopathy

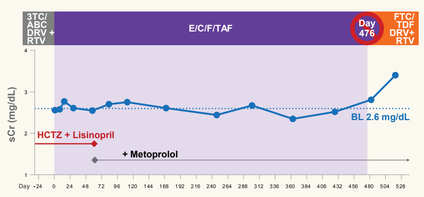


3

41-year-old black male with uncontrolled hypertension

Declining eGFR and worsening total proteinuria prompted study drug discontinuation

No evidence of tubulopathy

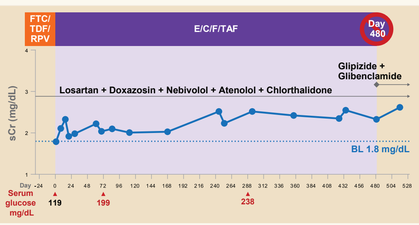


4

54-year-old white male with poorly controlled hypertension and new-onset diabetes

Declining eGFR prompted study drug discontinuation

No evidence of tubulopathy

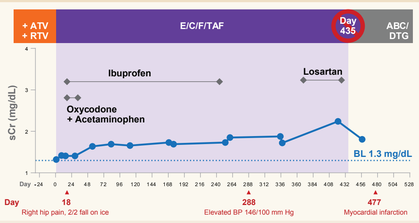


5

68-year-old white male with well-controlled hypertension and diabetes

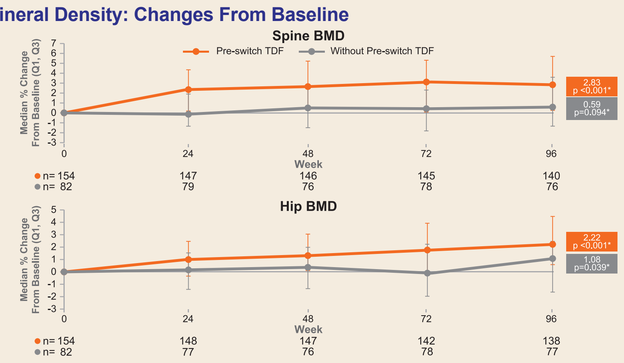
Declining eGFR prompted study drug discontinuation

No evidence of tubulopathy



3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BL, baseline; BUN, blood urea nitrogen; DRV, darunavir; DTG, dolutegravir; FTC, emtricitabine; HCTZ, hydrochlorothiazide; mod, moderate; NVP, nevirapine; RPV, rilpivirine; RTV, ritonavir; sCr, serum creatinine.

Bone Mineral Density: Changes From Baseline



*P-values for differences between baseline and Week 96 based on the two-sided Wilcoxon signed-rank test.

Virologic Outcomes at Week 96

- 88% of patients (214/242) maintained HIV-1 viral load <50 copies/mL at Week 96
- In 10% (23/242), virologic data were not available
  - 13 patients discontinued due to adverse events (AEs)
  - 10 discontinued for other reasons (lost to follow-up, noncompliance, protocol violation) and last available HIV-1 RNA <50 copies/mL
- 2% (5/242) had virologic failure
  - HIV-1 RNA ≥50 copies/mL at Week 96 (n=2), discontinued due to lack of efficacy (n=2), took additional antiretroviral medications (n=1)

Safety Summary

- Upper respiratory tract infection (14%), diarrhea (13%), and arthralgia (12%) were the most common AEs
- AEs, grades, and frequencies were similar in patients with baseline eGFR < vs ≥50 mL/min
- 12 patients (5%) discontinued study drug for AEs
  - 7 with non-renal AEs
    - Diarrhea, malignant lung neoplasm, choking, dry mouth/fatigue/pruritis, joint swelling, sleep disorder, bladder transitional cell carcinoma
  - 5 (2%) for decreased eGFR
    - 3 patients experienced renal disease progression (2 of these had poorly controlled hypertension)
- No study participants developed tubulopathy or Fanconi syndrome
- Two patients with a medical history of TDF-associated Fanconi syndrome remain on treatment with E/C/F/TAF with stable GFR, and significant reductions in total and tubular proteinuria

Conclusions

- This is the first study of a single-tablet antiretroviral regimen in patients with eGFR of 30–69 mL/min
- At Week 96, switching to E/C/F/TAF maintained viral suppression, and was associated with stable eGFR, reductions in proteinuria, and improvements in proximal renal tubular function, and hip and spine BMD
- These data support the safety and efficacy of once-daily E/C/F/TAF in HIV+ patients with eGFR of 30–69 mL/min without dose adjustment

References

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