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Switching to Tenofovir Alafenamide, Coformulated With Elvitegravir, Cobicistat, and Emtricitabine, in HIV-Infected Adults With Renal Impairment: 96-Week Results From a Single-Arm, Multicenter, Open-Label Phase 3 Study

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Abstract: Tenofovir disoproxil fumarate is associated with renal and bone toxicity. In a single-arm, open-label study of 242 virologically suppressed, HIV-infected participants with creatinine clearance 30–69 mL/min who switched to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide, participants had stable creatinine clearance, significant and durable improvements in proteinuria, albuminuria, and tubular proteinuria ($P < 0.001$), and significant increases in hip and spine bone mineral density through 96 weeks ($P < 0.001$). Eighty-eight percent maintained HIV-1 RNA <50 c/mL at week 96. These longer-term results support the use of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide in HIV-infected individuals with mild-moderately impaired renal function.

Key Words: tenofovir alafenamide, emtricitabine, chronic kidney disease, bone mineral density, HIV

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All authors were involved in the development of the primary manuscript, interpretation of data, have read and approved the final version, and have met the criteria for authorship as established by the ICMJE. F.A.P. enrolled participants, analyzed data, and independently interpreted the results, and edited and approved the manuscript. P.T., A.C., L.C., and W.S. enrolled participants, reviewed, and interpreted analyses of data, and edited the draft manuscript. M.E.A. and M.W.F. designed the study. S.J. performed the data analyses, which were reviewed and interpreted by A.C., M.D., and M. W.F. The first draft was written by F.A.P. and M.W.F. All authors contributed to edits of the final report. Gilead Sciences (Sponsor) had a role in deciding whether or not the results would be published.

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INTRODUCTION

Chronic kidney disease (CKD) is a common and important comorbidity in HIV-infected individuals with prevalence expected to rise as this population ages.[1–4] Antiretroviral treatment options for those with CKD are limited, because the use of tenofovir disoproxil fumarate (TDF) can be nephrotoxic[5] and the use of abacavir (ABC) has been associated with increased cardiovascular risk in large observational studies.[6] For individuals who cannot take either TDF or ABC, alternative nucleos(t)ide-sparing regimens have been suggested in treatment guidelines[7]; however, this approach is hampered because of concerns of reduced virologic activity of these combinations.

Several years after its approval, renal and bone toxicity seen with TDF was noted to be associated with high circulating plasma levels of tenofovir (TFV).[8–11] TFV alafenamide (TAF) is a novel TFV prodrug that is associated with 91% lower plasma TFV levels compared with TDF.[12] Although the exact mechanism through which the lower plasma TFV levels leads to reduced nephrotoxicity is not established, it may be due to lower drug levels inside proximal renal tubular cells.[13,14]

Compared with TDF-containing regimens, the single-tablet coformulation of elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) has demonstrated high efficacy and improved renal and

bone safety in phase 3 clinical trials of HIV-infected, treatment-naive, or virologically suppressed participants, with a significantly reduced effect of TAF compared with TDF on estimated glomerular filtration rate (eGFR), total and tubular proteinuria, albuminuria, and bone mineral density (BMD).[12,15,16] E/C/F/TAF has been approved by the United States Food and Drug Administration, European Medicines Agency, and other health authorities in multiple regions for treatment of naive and stably suppressed patients age 12 and older and is one of the recommended initial regimens in HIV treatment guidelines in the United States and Europe.[7,17–20] Importantly, E/C/F/TAF can be administered without dose adjustment to individuals with creatinine clearance (CrCl) down to 30 mL/min.

We conducted a single-arm, open-label phase 3 clinical trial to assess the long-term safety of E/C/F/TAF in adults with mild to moderate renal impairment with a protocol-specified focus on renal and bone safety (ClinicalTrials.gov number NCT01818596). In this study, we present safety and efficacy data collected from participants in this trial through 2 years of treatment.

METHODS

Study Design and Participants

The design and inclusion criteria of the trial have been previously described.[21] Briefly, we enrolled HIV-1–infected, virologically suppressed adults (aged ≥18 years) with stable, mild to moderate renal impairment (CrCl 30–69 mL/min). We excluded individuals with positive hepatitis B surface antigen or hepatitis C antibody. Eligible participants received co-formulated elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and TAF 10 mg (E/C/F/TAF) once daily. Postbaseline study visits occurred at weeks 1, 2, 4, 8, 12, 16, and 24, after which participants continued treatment with visits every 12 weeks until week 144. Laboratory tests included hematological analysis, serum chemistry tests, fasting lipid parameters, $CD4^+$ cell counts, measures of renal function {CrCl and eGFR [calculated using the Cockcroft–Gault formula, the CKD Epidemiology Collaboration (CKD-EPI) serum cystatin C method adjusted for age and sex, and the CKD-EPI serum creatinine method], urine protein to creatinine ratio, urine albumin to creatinine ratio, tubular proteinuria [retinol binding protein to creatinine ratio, β2-microglobulin to creatinine ratio, fractional excretion of uric acid, and fractional excretion of phosphate] [Covance Laboratories, Indianapolis, IN]}, and measurement of HIV RNA concentration (Roche TaqMan 2.0; Roche Diagnostics, Rotkreuz, Switzerland). Participants with confirmed virologic failure (2 consecutive viral load samples ≥50 c/mL) and an HIV RNA >400 c/mL at week 8 or later had the second, confirmatory sample sent for resistance analysis by GeneSeq Integrase, PhenoSense GT, and PhenoSense Integrase (Monogram Biosciences, South San Francisco, CA). Dual energy x-ray absorptiometry of the hip and lumbar spine was conducted at baseline and weeks 24, 48, 72, 96, 120, and 144 [analyzed centrally by BioClinica (Newton, PA)].

The study was performed in accordance with the Declaration of Helsinki and approved by central or site-specific review boards or ethics committees. Each participant gave written informed consent.

Statistical Analyses

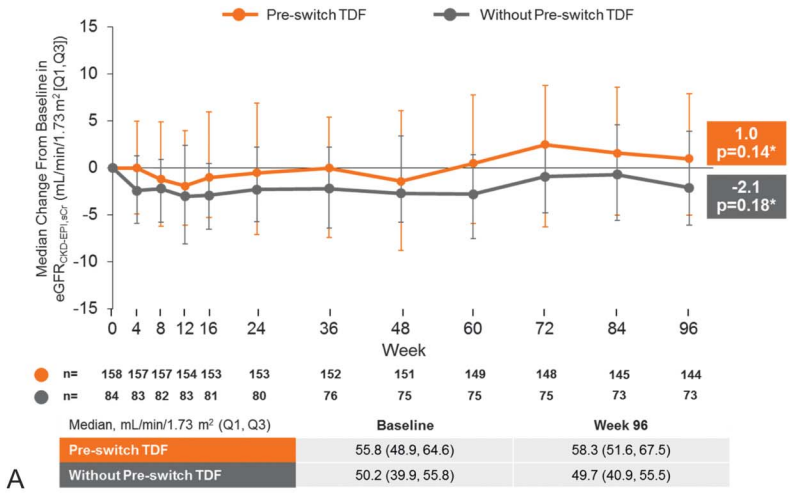
The primary endpoint of the study was change from baseline in CrCl [$eGFR_{CG}$ (Cockcroft–Gault), $eGFR_{CKD\text{-}EPI,\ cysC}$ (CKD-EPI, using serum cystatin C), and $eGFR_{CKD\text{-}EPI,\ creatinine}$ (CKD-EPI, using serum creatinine)]. Secondary endpoints included renal, bone, and metabolic endpoints. Changes from baseline were summarized by visit using descriptive statistics, and median change from baseline was analyzed by 2-sided Wilcoxon signed-rank test. Subgroup analyses were conducted for all endpoints for participants taking a TDF-containing regimen before switch and for participants with baseline CrCl <50 mL/min. Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 18.1).

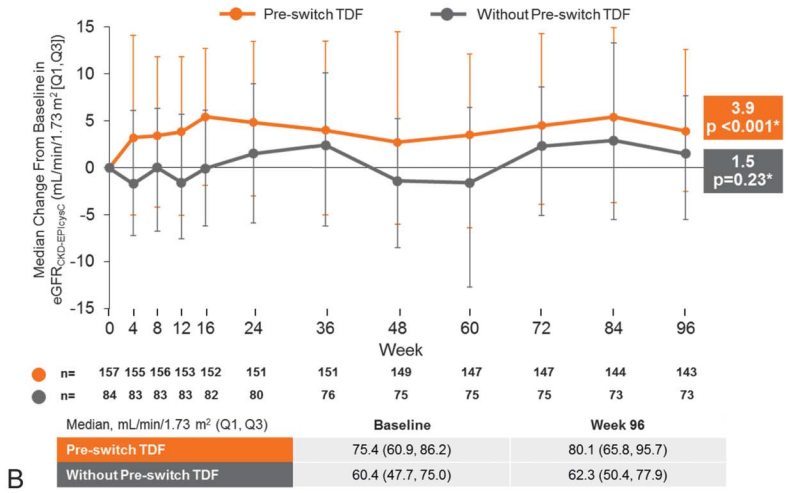
RESULTS

We enrolled 242 participants with stable CrCl 30–69 mL/min [including 80 (33%) participants with baseline CrCl <50 mL/min] and switched them from their baseline antiretroviral treatment regimens to E/C/F/TAF. Median age at baseline was 58 years, with 26% ≥65 years. Median CrCl at baseline was 56 mL/min; 42% of participants had significant proteinuria (urine protein to creatinine ratio ≥ 200 mg/g), 49% had significant albuminuria (urine albumin to creatinine ratio ≥ 30 mg/g), 39% had hypertension, and 14% were diabetic. Antiretroviral regimens before switch included TDF (65%), ABC (22%), and nucleos(t)ide-free regimens (5%). Participants were exposed to study drug for a median of 108 weeks.

Through 96 weeks, there was no decrease in median eGFR (Fig. 1A, B, $eGFR_{CG}$ not shown). Results were similar for participants whether they switched from a TDF- or non–TDF-based regimen, or whether baseline CrCl was <50 or ≥50 mL/min (data not shown). Changes from baseline in eGFR for participants stratified by baseline eGFR are shown in Figure 1C.

In our study, a large number of participants had evidence of subclinical tubulopathy at baseline. We observed significant improvements in total proteinuria, albuminuria, and tubular proteinuria (urine retinol–binding protein/creatinine ratio and β2-microglobulin/creatinine ratio) in participants switching to E/C/F/TAF from a TDF-containing regimen, whereas renal function in participants switching from non-TDF regimens generally did not significantly change (Fig. 2). Changes occurred by week 1 after switch and remained stable through 96 weeks. Two participants had a history of Fanconi syndrome before enrollment. Both successfully remained on E/C/F/TAF for more than 2 years and neither experienced recurrent Fanconi syndrome. Our study included 80 participants with baseline CrCl <50 mL/min, who were slightly older and more likely to have hypertension than the whole group. These participants had no significant changes in $eGFR_{CG}$ ($P = 0.05$) or $eGFR_{CKD\text{-}EPI,\ creatinine}$ ($P = 0.54$) but did have significant increases in $eGFR_{CKD\text{-}EPI,\ cysC}$ ($P < 0.001$) and significant improvements in renal tubular function from baseline to week 96. In addition, across the entire study population, we observed significant improvements in fractional excretion of uric acid





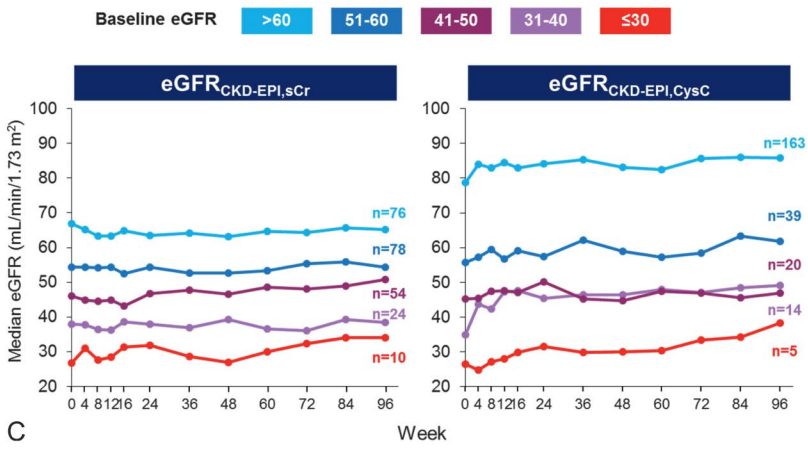


FIGURE 1. A, $eGFR_{CKD\text{-}EPI,\ sCr}$: changes over time no significant change from baseline in $eGFR_{CKD\text{-}EPI,\ sCr}$ was observed through 96 weeks. **P*-values for differences between baseline and week 96 based on the 2-sided Wilcoxon signed-rank test. B, $eGFR_{CKD\text{-}EPI,\ cysC}$: changes over time. A significant improvement in $eGFR_{CKD\text{-}EPI,\ cysC}$ was observed in patients whose preswitch regimen contained TDF. **P*-values for differences between baseline and week 96 based on the 2-sided Wilcoxon signed-rank test. C, Changes in eGFR by baseline eGFR strata.

[median (Q1, Q3) change from baseline to week 96, −1.4% (−4.1%, 0.2%); $P < 0.001$], whereas there were no significant changes in fractional excretion of phosphate [median (Q1, Q3) change from baseline to week 96, 0.2% (−5.2%, 5.3%), $P = 0.98$] or serum phosphorus [median (Q1, Q3) change from baseline to week 96, −0.1 (−0.4, 0.3) mg/dL; $P = 0.071$].

Overall, median hip and spine BMD significantly increased (+1.78% and +2.08%, respectively) from baseline

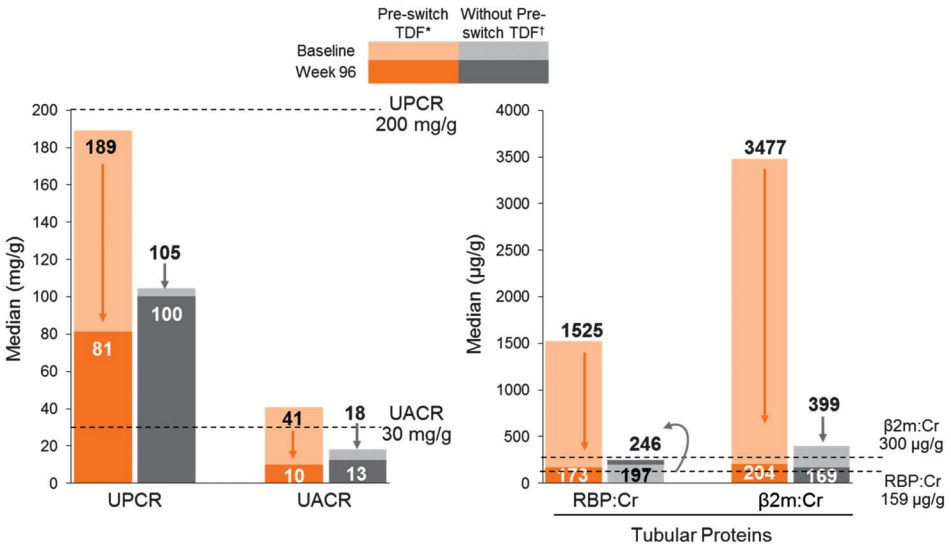


FIGURE 2. Renal biomarkers: changes from baseline to week 96. *All changes statistically significant; †all changes not statistically significant with exception of β2m:Cr. β2m, β2-microglobulin; RBP, retinol-binding protein. Normal range is ≤200 mg/g for urine protein to creatinine ratio and <30 mg/g for urine albumin to creatinine ratio.[25] β2m:Cr >300 µg/g and/or RBP:Cr >159 µg/g are consistent with proximal tubular dysfunction.[5,26]

to week 96. Improvements in median BMD occurred in participants on a TDF-containing regimen at baseline [hip: +2.22% ($P < 0.001$); spine: +2.83% ($P < 0.001$)]. For participants on non–TDF-containing regimen at baseline, median BMD also improved after switch to E/C/F/TAF [hip: +1.08% ($P = 0.04$); spine: +0.59% ($P = 0.09$)]. There were 5 fractures, all related to mechanical trauma and considered by the investigator to be unrelated to study drug.

Fasting lipid levels decreased in participants who used non–TDF-containing regimens before switching to E/C/F/TAF, whereas lipid levels increased slightly in those using TDF-containing regimens at baseline. However, there was no difference observed in the total:high-density lipoprotein cholesterol ratio between those receiving either TDF- or non–TDF-regimens at baseline because the lipid changes associated with the switch were concordant for both the total cholesterol and the high-density lipoprotein cholesterol fraction.

The most common adverse events were upper respiratory tract infection (14%), diarrhea (13%), and arthralgia (12%). The rate of adverse events and grades were similar in participants with baseline CrCl <50 vs ≥50 mL/min. Adverse events leading to study drug discontinuation occurred in 5% of participants (n = 12). Five participants (2.1%) discontinued study drug by Investigator discretion for decreased CrCl and $eGFR_{CKD\text{-}EPI,\ cystatin\ C}$. None of these participants, nor any other study participant, had laboratory evidence of proximal renal tubulopathy or Fanconi syndrome.

At week 96, 214 participants (88%) maintained HIV-1 RNA <50 c/mL, 23 (10%) did not have virologic data available at that point, and 5 (2%) were considered to have virologic failure. Of these 5, 2 discontinued because of lack of efficacy and 3 remain on study drug. Drug resistance emerged in 3 participants (1.2%); 1 with probable reinfection who achieved resuppression with continued E/C/F/TAF treatment, 1 with persistent low-level viremia and a resistance mutation profile identical to his historical genotype, and 1 with resistance to nucleos(t)ide reverse transcriptase inhibitors and integrase strand transfer inhibitors, as well as to nonstudy drugs but no historical genotype for comparison. The median (interquartile range) increase from baseline in CD4 cell counts at week 96 (observed data) was +22 (−66, +98) cells per microliter.

DISCUSSION

After 2 years of treatment, HIV-infected individuals with preexisting mild to moderate renal impairment due to multiple comorbidities who switched to E/C/F/TAF from TDF- or non–TDF-containing regimens had stable eGFR. No increase in eGFR was expected, because participants had multiple comorbidities contributing to their stable CKD at study entry. However, proteinuria, albuminuria, proximal renal tubular function, and BMD significantly improved after the switching from TDF-containing regimens. E/C/F/TAF was well tolerated, and discontinuations for adverse events were uncommon. This prospective, single-arm study suggests that E/C/F/TAF does not adversely affect renal function or BMD, supporting its use in HIV-infected individuals with mild to moderate renal impairment.

Our study was conducted in a population at increased risk of TFV-associated tubulopathy. Reassuringly, no participants developed proximal tubulopathy while receiving TAF. Consistent with the natural history of CKD, few participants (2%) experienced eGFR decline that resulted in study drug discontinuation. Nonetheless, our study provides further evidence that TAF has minimal effect on renal tubular function, as those who received non-TDF regimens at baseline did not experience increases in proteinuria, whereas those receiving TDF at baseline achieved reductions in proteinuria, with normalization of urinary protein concentrations in most of the participants.

Improvements in BMD were seen through week 96 in those who switched to E/C/F/TAF from a TDF-based regimen, and smaller increases in BMD were observed after switch from a non–TDF-based baseline regimen. These data support the favorable BMD profile of E/C/F/TAF relative to other antiretroviral regimens, particularly those containing TDF. Treatment with TDF has consistently been associated with lower lipids compared with other regimens in treatment-

naive or virologically suppressed individuals.[22,23] This TDF lipid effect is thought to be associated with the plasma level of TFV.[22,24] In this study, participants switching from TDF-containing regimens showed increases in total, high, and low-density lipoprotein cholesterol and triglycerides, likely related to the significant reductions in plasma TFV concentrations. Therefore, the changes in fasting lipid levels should be interpreted not an adverse effect of TAF but rather an absence of an effect of high plasma TFV concentrations.

Strengths of this study include the size of the study population (more than 200 participants), which included a substantial number of individuals with moderately impaired renal function, older age, and significant comorbidities. Rigorous evaluation of renal and bone function were used to carefully assess TFV's off-target effects. One limitation of the study is the single-arm, noncomparative study design. However, our results are consistent with those of 2 international phase 3 clinical trials comprising over 1700 participants who support the favorable renal and bone safety of TAF as compared with TDF over 2 years, in a randomized, double-blind design.[12]

In conclusion, participants with preexisting mild to moderate renal impairment who switched to E/C/F/TAF had no changes in eGFR, whereas proteinuria, proximal renal tubular function, and BMD significantly improved over 2 years. Of particular note, participants with CrCl <50 mL/min who currently require dose adjustment for both TDF and emtricitabine had changes in eGFR and tubular function similar to participants with CrCl ≥ 50 mL/min through 96 weeks after switching to once daily E/C/F/TAF without dose adjustment. Our data support the use of single-tablet E/C/F/TAF in HIV-infected individuals with mild and moderate renal impairment without dose adjustment. Studies in those with more severe renal impairment are underway.

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