Randomized, Double-Blind Comparison of Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF), Each Coformulated With Elvitegravir, Cobicistat, and Emtricitabine (E/C/F) for Initial HIV-1 Treatment: Week 144 Results

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Abstract: In 2 double-blind phase 3 trials, 1733 antiretroviral-naive adults were randomized to tenofovir alafenamide (TAF) or tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir/cobicistat/emtricitabine (E/C/F). At 144 weeks, TAF was superior to TDF in virologic efficacy, with 84.2% vs 80.0% having HIV-1 RNA <50 copies/mL (difference 4.2%; 95% confidence interval: 0.6% to 7.8%). TAF had less impact than TDF on bone mineral density and renal biomarkers. No participants on TAF had renal-related discontinuations vs 12 on TDF ($P < 0.001$), with no cases of proximal tubulopathy for TAF vs 4 for TDF. There were greater increases in lipids with TAF vs TDF, with no difference in the total cholesterol to high-density lipoprotein ratio. For initial HIV therapy, E/C/F/TAF is superior to E/C/F/TDF in efficacy and bone and renal safety.

Key Words: tenofovir alafenamide, integrase inhibitor, randomized controlled trial, HIV, bone mineral density, renal safety

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INTRODUCTION

Use of tenofovir disoproxil fumarate (TDF)-based regimens is highly effective but may be associated with renal and bone toxicity, attributed to high circulating plasma levels of tenofovir (TFV).[1–5] By contrast, use of tenofovir alafenamide (TAF)-based regimens has less impact on measures of renal and bone safety, attributed to significantly lower plasma TFV levels while increasing delivery of intracellular TFV-diphosphate, the active moiety of both compounds.[6]

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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. J.R.A. enrolled participants, analyzed data and independently interpreted the results, and edited and approved the manuscript. M.T., P.E.S., B.H., C.M.D., D.A.W., E.D.J., and A.E.C. enrolled participants, reviewed and interpreted analyses of data, and edited the draft manuscript. A.P., A.C., M.D., and S.M.C. designed the study. S.G. and H.W. performed the data analyses, which were reviewed and interpreted by C.C., A.C., M.D., and S.M.C. The first draft was written by J.R.A. and S.M.C. 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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In treatment-naive individuals and those switching from TDF-containing regimens, the single-tablet coformulation of elvitegravir/cobicistat/emtricitabine/TAF (E/C/F/TAF) demonstrated high efficacy and significantly reduced effects on estimated glomerular filtration rate (eGFR), proteinuria, albuminuria, and bone mineral density (BMD) compared with TDF-containing regimens.[6–9] Treatment-naive participants in 2 large randomized, international, double-blind, placebo-controlled trials (GS-US-292-0104 and GS-US-292-0111, ClinicalTrials.gov numbers NCT01780506 and NCT01797445) who received TAF had significantly less bone demineralization in the lumbar spine and total hip and significantly lower rates of total proteinuria, albuminuria, and proximal tubular proteinuria at weeks 48 and 96 compared with those on TDF.[6,7]

Given these efficacy and safety data, E/C/F/TAF has become a recommended initial regimen in the HIV treatment guidelines for the United States (U.S.) and Europe.[10–16] However, the durability of virologic response and the persistence of the favorable effects of TAF compared with TDF on renal and bone safety parameters are of long-term interest because HIV-infected patients who initiate TAF-containing regimens could anticipate receiving lifelong therapy. We present efficacy and safety data from these trials through 144 weeks of blinded treatment.

METHODS

Study Design and Participants

Details on design, inclusion criteria, and methodology of the trials have been previously reported.[6] Briefly, antiretroviral treatment–naive adults were randomized 1:1 to once-daily TAF 10 mg vs TDF 300 mg, both coformulated with elvitegravir 150 mg, cobicistat 150 mg, and emtricitabine 200 mg (E/C/F). The studies were approved by the U.S. Food and Drug Administration (FDA) and institutional review boards at all sites.

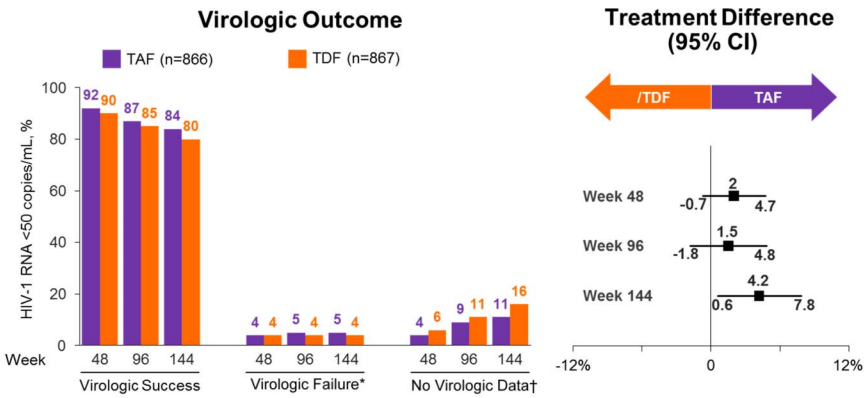
Statistical Analysis

Pooled analyses of week 144 data from both studies were prespecified in the protocols and analysis plans. Efficacy was assessed by examining the proportion in each group with plasma HIV-1 RNA <50 copies/mL at week 144 (U.S. FDA–defined snapshot algorithm).[17] A 12% margin and 2-sided 95% confidence interval (CI) (unadjusted alpha level) were used to establish noninferiority; once established, the same CI was prespecified for use to evaluate superiority. An identical approach was applied using a plasma HIV-1 RNA threshold of <20 copies/mL. Adverse events (AEs) were coded with the Medical Dictionary for Regulatory Activities (version 19.0). The Fisher exact test was used to compare differences for AEs and Wilcoxon rank-sum test to compare differences for continuous laboratory test results (SAS; version 9.2). A post hoc evaluation of proximal renal tubulopathy was performed using the following confirmed criteria: rise in serum creatinine ≥0.4 mg/dL, dipstick proteinuria ≥2 grade-level increase from baseline in urine protein, normoglycemic glycosuria, and a 1 grade-level change in serum hypophosphatemia.

RESULTS

A total of 1733 adults received at least 1 dose of study drug: 866 TAF and 867 TDF. Baseline characteristics were similar between groups (Table S1 http://links.lww.com/QAI/A986), with similar rates of retention through week 144 (TAF 85% vs TDF 82%).

At 144 weeks, 84.2% of participants receiving TAF and 80.0% receiving TDF had HIV-1 RNA <50 copies/mL (U.S. FDA–defined snapshot algorithm) using the full analysis set (difference 4.2%; 95% CI: 0.6% to 7.8%) (Fig. 1). Treatment discontinuation (primarily due to AEs or withdrawal of consent, among other reasons not related to efficacy) contributed to the lower percentage of virologic success with TDF. Analyses comparing rates of virologic suppression between treatments within prespecified subgroups favored TAF over TDF at week 144 for those with baseline HIV-1 RNA ≤100,000 copies/mL, those with baseline CD4 count ≥200 cells/μL, women, adults ≥50 years of age, nonblack participants, and those with an adherence rate of ≥95% (Figure S1 http://links.lww.com/QAI/A986). At 144 weeks, 81.1% on TAF and 75.8% on TDF had HIV-1 RNA <20 copies/mL (U.S. FDA–defined snapshot algorithm) (difference 5.4%;



Reasons for virologic failure and no virologic data at Week 144	TAF (N = 866)	TDF (N = 867)
*HIV-1 RNA ≥50 c/mL	40 (4.6%)	34 (3.9%)
HIV-1 RNA ≥50 c/mL in Week 144 Window	10 (1.2%)	9 (1.0%)
Discontinued Study Drug Due to Lack of Efficacy	7 (0.8%)	8 (0.9%)
Discontinued Study Drug Due to Other Reasons and Last Available HIV-1 RNA ≥50 c/mL	21 (2.4%)	15 (1.7%)
Added New ARV	2 (0.2%)	2 (0.2%)
†No Virologic Data in Week 144 Window	97 (11.2%)	139 (16.0%)
Discontinued Study Drug Due to AE/Death	13 (1.5%)	29 (3.3%)
Discontinued Study Drug Due to Other Reasons[¥] and Last Available HIV-1 RNA <50 c/mL	79 (9.1%)	99 (11.4%)
Missing Data During Window but on Study Drug	5 (0.6%)	11 (1.3%)

FIGURE 1. Virologic outcomes at weeks 48, 96, and 144.

95% CI: 1.5% to 9.2%). CD4 cell counts increased in both groups, with mean (SD) changes from baseline of 326 (215.3) cells/μL for TAF and 305 (204.5) cells/μL for TDF ($P = 0.062$) at week 144.

By 144 weeks, virologic failure with resistance occurred in 24 participants: 12 (1.4%) on TAF vs 12 (1.4%) on TDF. Genotypic resistance data: nucleoside reverse-transcriptase inhibitor (NRTI) and Elvitegravir (EVG) resistance (n = 8), NRTI resistance only (n = 4) in the TAF group; NRTI and EVG resistance (n = 7), NRTI resistance only (n = 4), EVG resistance only (n = 1) in the TDF group. Two participants on TAF and 4 on TDF had newly detected genotypic resistance between weeks 96 and 144. In those with genotypic resistance, there was no statistical difference in median baseline viral load between TAF and TDF (252,200 vs 115,500 HIV-1 RNA copies/mL; $P = 0.270$).

Both regimens continued to be well tolerated through week 144, with similar rates of drug-related AEs with TAF (44.1%) and TDF (48.9%). The most common drug-related AEs in both groups were nausea (TAF 10.5%, TDF 13.3%), diarrhea (TAF 7.3%, TDF 8.9%), and headache (TAF 6.1%, TDF 5.4%). AEs leading to study drug discontinuation occurred in 11 participants (1.3%) on TAF vs 29 (3.3%) on TDF (Table S2 http://links.lww.com/QAI/A986). AEs leading to drug discontinuation in the TAF group occurred predominantly within the first 48 weeks, whereas those in the TDF group continued at a similar frequency through 144 weeks [cumulative events in TAF vs TDF at 48, 96, and 144 weeks: n = 8 vs n = 13 ($P = 0.380$); 10 vs 20 ($P = 0.096$); and 11 vs 29 ($P = 0.006$)]. Incidence of serious AEs was low and similar between groups (TAF 14.0%, TDF 14.3%). Serious AEs considered drug related by the investigator occurred in 5 participants (0.6%) on TAF (abdominal pain, staphylococcal skin infection, rotator cuff syndrome, erythematous rash, and hypovolemic shock) and 6 participants (0.7%) on TDF (spontaneous abortion, immune reconstitution inflammatory syndrome, acute pancreatitis, cholelithiasis, acute coronary syndrome, and drug interaction). Incidence of grade 3 or 4 laboratory abnormalities was similar between groups (TAF 32.9% vs TDF 30.8%); the most common was elevated creatine kinase (TAF 11.5% vs TDF 10.1%).

Participants receiving TAF had significantly smaller declines in total hip and lumbar spine BMD than those receiving TDF through week 144 (% change from baseline at week 144: hip: TAF −0.75%, TDF −3.36%; spine: TAF −0.92%, TDF −2.95%) ($P < 0.001$) (Fig. 2A). More participants on TAF recovered from osteopenia or osteoporosis at either the hip (TAF n = 14 vs TDF n = 10) or spine (TAF n = 24 vs TDF n = 10) by week 144 ($P < 0.001$ for difference in distribution of clinical BMD status). Fractures were rare, reported for 6 participants (0.7%) on TAF and 16 (1.8%) on TDF ($P = 0.051$); all fractures were due to trauma and unrelated to study drug. No discontinuations due to BMD decreases occurred with TAF. Between weeks 48 and 144, 6 men discontinued TDF because of a >5% decrease in BMD (ages ranged from 20 to 50 years). At all time points, median percent changes from baseline in serum parathyroid hormone (PTH) were lower with TAF than TDF (week 144: TAF 47.3%, TDF 71.8%; $P < 0.001$) (Fig. 2A). Median values for each group remained within the normal range. Fewer participants on TAF compared with TDF initiated calcium, vitamin D, or other nutritional supplements during the study (16.2% vs 20.7%, $P = 0.018$).

Median change from baseline in creatinine clearance (CrCl; eGFR by Cockcroft Gault) was significantly lower with TAF (−1.6 mL/min) than TDF (–7.7 mL/min) at week 144 ($P < 0.001$) (Fig. 2B). At week 144, significantly fewer participants on TAF (17.6%) had a clinically meaningful decrease of ≥25% from baseline in CrCl compared with TDF (33.4%) ($P < 0.001$). A quantitative marker of proteinuria (urine protein to creatinine ratio) and specific markers of proximal tubular proteinuria (retinol-binding protein/Cr and β-2-microglobulin/Cr) increased from baseline with TDF, whereas decreases or smaller increases were observed with TAF ($P < 0.001$) (Figs. 2B, C). Fewer participants on TAF developed clinically significant proteinuria (urine protein to creatinine ratio >200 mg/g) (n = 22 vs 40, $P = 0.016$ for difference in distribution of changes above and below 200 mg/g).

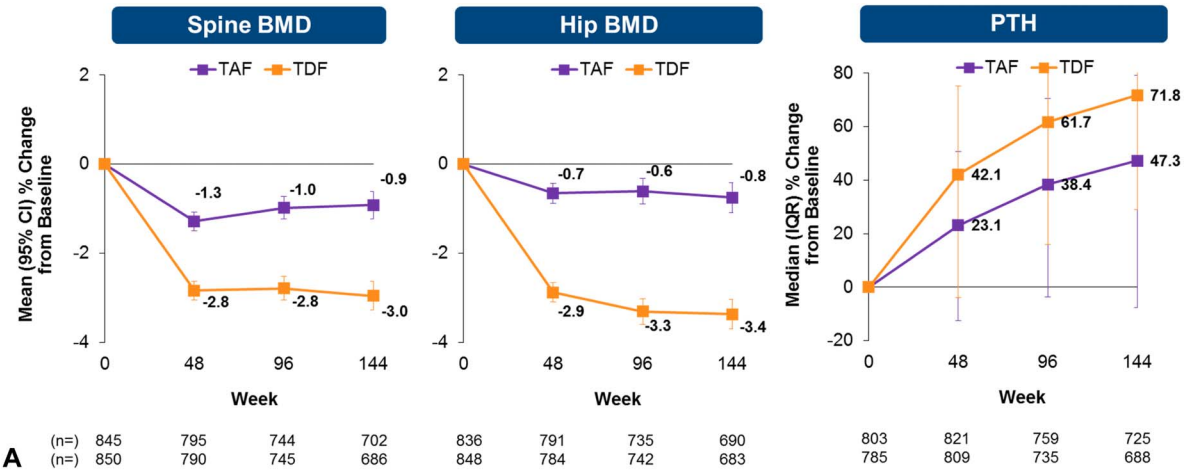
No study drug discontinuations due to renal events occurred with TAF, whereas 12 participants discontinued TDF because of renal-related AEs ($P < 0.001$) (Table S2 http://links.lww.com/QAI/A986): 4 before week 48, 2 between weeks 48 and 96, and 6 after week 96. No cases of proximal tubulopathy occurred in the TAF group, whereas 4 participants receiving TDF had investigator-reported tubulopathy. Seven participants on TDF met laboratory criteria for proximal renal tubulopathy (Tables S3 and S4 http://links.lww.com/QAI/A986), including 4 of the 12 discontinued participants.

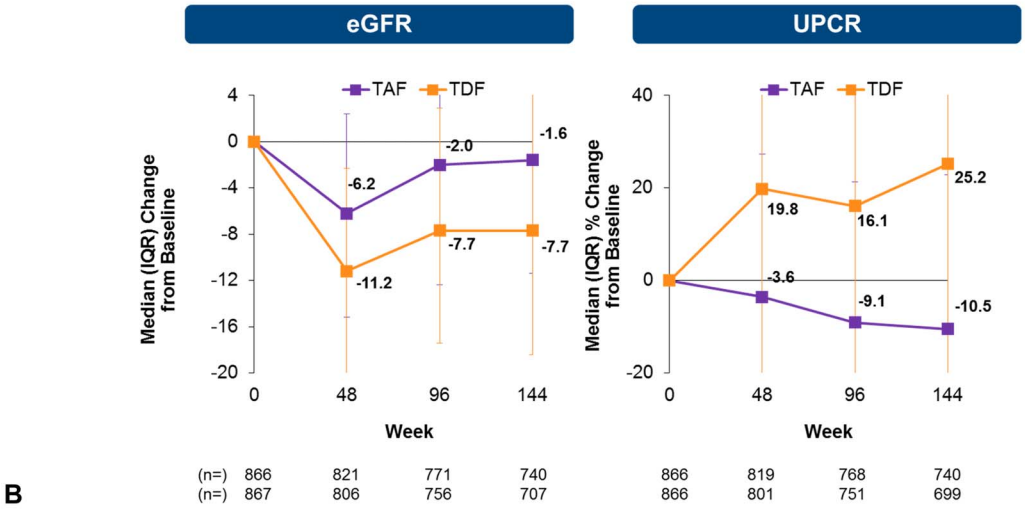
There were greater median increases in total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein, and triglycerides in the TAF group compared with the TDF group ($P < 0.001$), whereas there were no differences in the median TC to HDL ratio between groups ($P > 0.72$ for weeks 48, 96, and 144) (Fig. 3). There were no differences between TAF and TDF in cardiovascular or cerebrovascular events: 24 participants (2.8%) vs 33 (3.8%) ($P = 0.28$), serious cardiovascular or cerebrovascular events: 5 (0.6%) vs 6 (0.7%) ($P = 1.00$), or use of lipid-modifying agents: 48 (5.5%) vs 50 (5.8%) ($P = 0.92$).

DISCUSSION

After 144 weeks of treatment, a TAF-based single-tablet regimen maintained a high rate of virologic suppression in treatment-naive participants (84%) and met prespecified criteria for both noninferiority and superiority to a TDF-based similar combination, using a priori cutoffs of HIV-1 RNA <50 and <20 copies/mL. Concordant with this durable high level of suppression was the rare emergence of antiretroviral resistance (1.4%).

During this extended period of study, both study regimens continued to be well tolerated. As we have previously reported, the majority of the most common AEs occurred within the first 4 weeks of treatment initiation.[18] Of note, not only did fewer participants on TAF discontinue





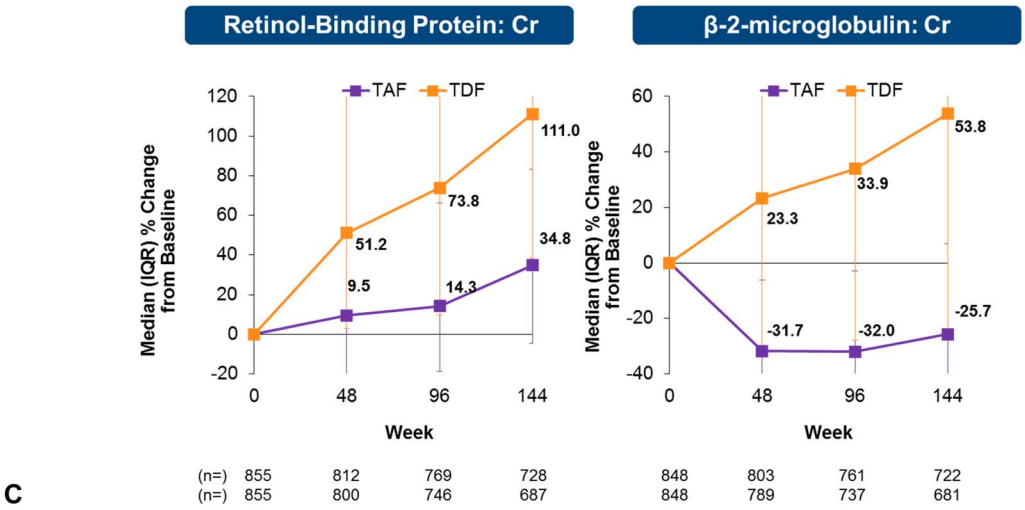


FIGURE 2. Key safety endpoints. A, Measures of bone safety: BMD and PTH; (B) Measures of renal safety: eGFR and proteinuria; (C) measures of renal safety: tubular proteinuria. $P < 0.001$ for all parameters at all time points. IQR, interquartile range.

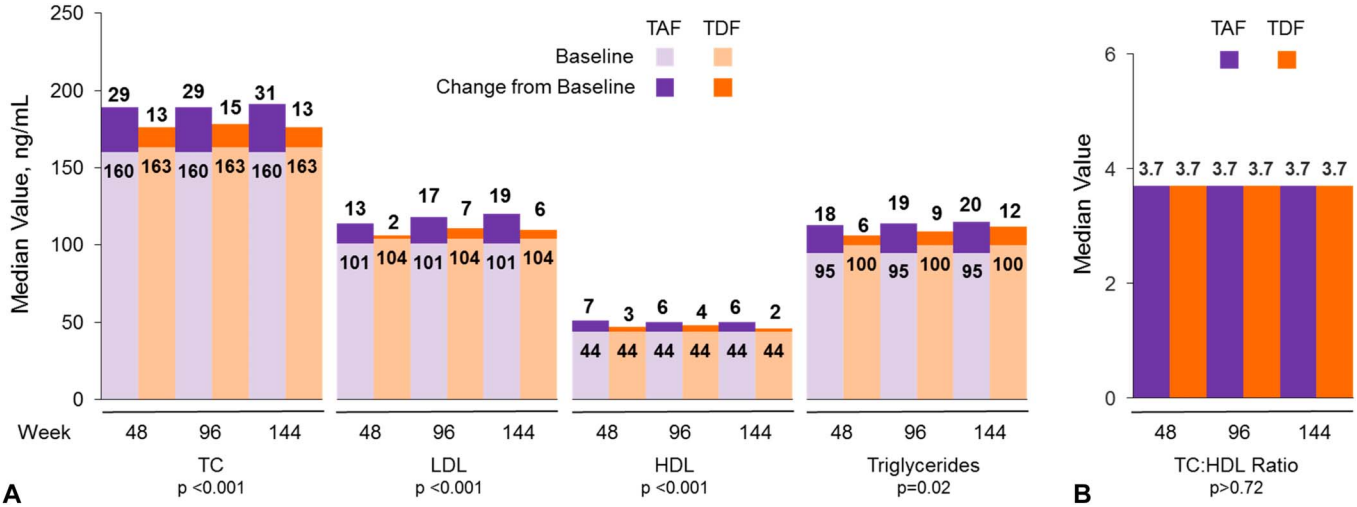


FIGURE 3. Fasting lipid parameters. A, Baseline lipid levels are shown in the lighter color. Increases from baseline are shown in the darker color at each time point. B, Median TC:HDL ratio is shown at each time point.

because of AEs, these AEs leading to discontinuation happened early in the TAF group, whereas those on TDF continued to experience AEs leading to discontinuation steadily through week 144.

Moreover, TAF continued to demonstrate significantly less impact on measures of bone and renal safety than TDF. Through 144 weeks of treatment with TAF, clinical bone and renal AEs in the TAF group were rare. No participants on TAF discontinued study drug because of bone loss, compared with 6 participants on TDF. Significant differences between TAF and TDF in mean changes from baseline in total hip and lumbar spine BMD observed at week 48 persisted through week 144. Significant differences between groups in median percent changes from baseline in PTH were noted early and through 144 weeks, and the median levels of PTH continued to increase for both groups. However, the median PTH levels stayed within the normal range. The relationship between the observed changes in BMD and PTH is unknown.

Markers of renal function also continued to be more favorable with TAF compared with TDF. A small and rapid decline in CrCl is expected with administration of cobicistat, which is known to interfere with tubular secretion of creatinine, thereby leading to an increase in serum creatinine and decrease in eGFR without an effect on actual GFR.[19] In this study, an expected decline in CrCl was observed in both groups but was more pronounced with TDF, as demonstrated by a significant difference favoring TAF in percentage of participants who had a CrCl decline of ≥25%,[20] a change most likely due to the impact of cobicistat on renal transporters of creatinine.[19] No participants in the TAF group discontinued because of renal AEs compared with 12 in the TDF group, a statistically significant difference reflecting the lack of TFV-associated nephrotoxicity with TAF.

Proximal renal tubular dysfunction, or tubulopathy, is a rare toxicity associated with TDF and was reported by investigators in 4 participants receiving this agent. With no standardized diagnostic criteria for tubulopathy, an assessment of measures of proximal renal tubular dysfunction was applied to all participants. Tubulopathy was not identified in any participant on TAF. Seven cases identified in the TDF group included 4 of the 12 participants who discontinued treatment because of renal-related AEs. Notably, 1 TDF-taking participant reported to have acquired Fanconi syndrome did not meet the validation criteria. Taken together, these longer-term safety data support the hypothesis that circulating levels of TFV are responsible for bone and renal toxicity with TDF, and markedly reduced TFV levels delivered by TAF minimize such exposure.

Treatment with TDF has consistently been associated with lower lipids compared with other regimens in treatment-naive or virologically suppressed individuals.[21,22] This TDF lipid effect is believed to be associated with plasma levels of TFV.[21,23,24] In this study, participants receiving TAF had greater increases in TC, HDL, low-density lipoprotein, and triglycerides, likely related to significant reductions in plasma TFV concentrations. Changes in fasting lipid levels are most accurately reported not as an adverse effect of TAF but rather as an effect of an absence of high plasma TFV concentrations. Importantly in this study, no treatment differences were observed in the TC:HDL ratios between groups, which is included in cardiovascular risk predictors in the general population such as the Framingham risk and American College of Cardiology/American Heart Association (ACC/AHA) risk calculators[25] and associated with the risk for cardiovascular disease in HIV-infected individuals.[26] We have previously reported that there is no difference between the TAF vs TDF groups in atherosclerotic cardiovascular disease estimated cardiovascular risk, eligibility for statins, or the incidence of cardiovascular AEs.[27]

Overall, in these large, international, randomized trials following 3 years of treatment, 84% of those assigned to TAF remained virologically suppressed. TAF was superior to TDF in virologic efficacy and produced significantly more favorable changes in multiple markers of renal and bone health. Despite the increases in lipids in the TAF group, there were no differences between groups in TC:HDL ratio, a predictor

of cardiovascular risk. 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.

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