# Tenofovir Alafenamide Vs. Tenofovir Disoproxil Fumarate in Single Tablet Regimens for Initial HIV-1 Therapy: A Randomized Phase 2 Study

*Paul E. Sax, MD,* Andrew Zolopa, MD,† Indira Brar, MD,‡ Richard Elion, MD,§ Roberto Ortiz, MD,‖ Frank Post, MD, PhD, FCP (SA),¶ Hui Wang, PhD,# Christian Callebaut, PhD,# Hal Martin, MD, MPH,# Marshall W. Fordyce, MD,# and Scott McCallister, MD#*

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023

**Objectives:** To evaluate the safety and efficacy of the novel tenofovir prodrug, tenofovir alafenamide (TAF), as part of a single-tablet regimen (STR) for the initial treatment of HIV-1 infection.

**Design:** Phase 2, randomized, double-blind, double-dummy, multicenter, active-controlled study.

**Methods:** Antiretroviral naive adults with HIV-1 RNA ≥5000 copies per milliliter and a CD4 count ≥50 cells per microliter were randomized 2:1 to receive an STR of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide (E/C/F/TAF) or elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate (E/C/F/TDF), plus placebo for 48 weeks.

**Results:** Patients on both E/C/F/TAF (n = 112) and E/C/F/TDF (n = 58) had high rates of virologic suppression (<50 HIV copies per milliliter) at week 24 (86.6%; 89.7%) and at week 48 (88.4%; 87.9%), and had similar improvements in CD4 at week 48 (177; 204), respectively. Both treatments were well tolerated, and most adverse events were self-limiting and of mild to moderate severity. Compared with patients on E/C/F/TDF, patients on E/C/F/TAF had smaller reductions in estimated creatinine clearance (−5.5 vs. −10.1 mL/min, $P = 0.041$), significantly less renal tubular proteinuria, and smaller changes in bone mineral density for hip (−0.62% vs. −2.39%, $P < 0.001$) and spine (−1.00% vs. −3.37%, $P < 0.001$). Patients on E/C/F/TAF had higher increases in total cholesterol, low-density lipoprotein, and high-density lipoprotein, but the total cholesterol/high-density lipoprotein ratio was unchanged for both.

**Conclusions:** Treatment-naive patients given the STR that contained either TAF or TDF achieved a high rate of virologic success. Compared with those receiving TDF, patients on E/C/F/TAF experienced significantly smaller changes in estimated creatinine clearance, renal tubular proteinuria, and bone mineral density.

**Key Words:** tenofovir alafenamide, GS-7340, elvitegravir, stribild, clinical trials

(*J Acquir Immune Defic Syndr* 2014;67:52–58)

Received for publication January 24, 2014; accepted May 5, 2014.

From the *Division of Infectious Diseases, Brigham and Women's Hospital and Harvard Medical School, Boston, MA; †Division of Infectious Diseases, Stanford University, Atherton, CA; ‡Infectious Diseases Division, Henry Ford Hospital, Detroit, Detroit, MI; §Department of Internal Medicine, George Washington University Hospital, Washington, DC; ‖Orlando Immunology Center, Orlando, FL; ¶Centre for Global Health, Kings College London, Weston Education Centre, London, United Kingdom; and #Gilead Sciences, Foster City, CA.

Supported by Gilead Sciences, Foster City, CA.

P.E.S., A.Z., I.B., R.E., and R.O. enrolled patients and reviewed and interpreted analyses of data. S.M., M.W.F., C.C., and H.W. designed the study. Data collection was overseen by H.W., C.C., H.M., M.W.F., and S.M. H.W. analyzed data, which were reviewed and interpreted by C.C., H.M., M.F., and S.M. The first draft of this report was written by P.E.S., H.M., M.F., and S.M. The draft report was edited by P.E.S., A.Z., I.B., R.E., and R.O.

P.E.S.: Consultant or Scientific Advisory Board member: Abbott, BMS, Gilead, GSK, Merck, Janssen; Grant support for research: BMS, Gilead, GSK. A.Z.: Funding: Gilead. I.B.: Speakers Bureau: Gilead, Funding: Gilead, Merck, Viiv, Stock: Gilead. R.E.: Advisory Panels: Gilead, BMS, Jannsen, ViiV, Speakers Bureaus: Gilead, BMS, Jannsen, ViiV, Merck, Research Grants: Gilead, AbbVie, BMS, ViiV. R.O.: Speaker's bureaus: Gilead, BMS, Funding: Gilead. H.W., C.C., H.M., M.W.F., S.M. are Employees of Gilead Sciences.

Abstract presented by Dr Paul Sax, during 53rd Annual ICAAC Conference, September 10–13, 2013, Denver, CO.

Correspondence to: Hal Martin, MD, MPH, Gilead Sciences, 333 Lakeside Drive, Foster City, CA 94404 (e-mail: hal.martin@gilead.com).

Copyright © 2014 by Lippincott Williams & Wilkins

## INTRODUCTION

Currently available antiretroviral regimens have led to marked declines in the morbidity and mortality of patients living with HIV-1[1–3] and decreased risk of HIV-1 transmission.[4–6] This success has shifted clinical attention toward antiretroviral drug regimens that optimize tolerability, long-term safety, and durable efficacy. Morbidity and mortality are increasingly driven by non-AIDS associated comorbidities, which are observed earlier than in age-matched controls, despite durable suppression with the best available antiretroviral therapy (ART).[1,2,7–10] Current guidelines recommend that patients begin ART earlier and stay on it continuously,[11] so the contribution of specific antiretroviral agents to long-term morbidity and mortality is increasingly important. In regimens of comparable efficacy, pill burden, dose frequency, safety, and tolerability are significant factors affecting maximal adherence over the long term.[12–14] Single-tablet regimens (STRs) represent a simple and convenient way for patients to maximize adherence and to control their HIV for many years.

Current Department of Health and Human Services guidelines recommend tenofovir disoproxil fumarate (TDF) as a preferred component of the nucleotide reverse-



Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023

transcriptase inhibitor (NRTI) backbone for HIV-1–positive treatment-naive patients.[11] Despite a favorable safety and tolerability profile, TDF has been associated with nephrotoxicity,[15,16] requires dose adjustment as creatinine clearance falls <50 mL/min,[17] and has been shown to result in a greater decline in bone mineral density (BMD) relative to some other NRTIs.[18,19]

Tenofovir (TFV) is a nucleotide analog HIV-1 reverse transcriptase inhibitor. TDF, the first-generation prodrug of TFV, undergoes rapid metabolism in the plasma after oral administration.[20] TFV is then distributed intracellularly, where it is phosphorylated to the active moiety TFV diphosphate (TFV-DP). TFV alafenamide (TAF, formerly GS-7340) is a next-generation oral prodrug of TFV that may offer improved safety and efficacy. Relative to TDF, TAF is more stable in plasma and is predominantly metabolized intracellularly to TFV by cathepsin A.[20–22] This intracellular drug metabolism results in higher intracellular levels of the active metabolite TFV-DP and lower plasma levels of TFV, relative to TDF.[20,21]

Both nonhuman primate studies and human clinical studies have shown a relationship between plasma TFV levels and renal toxicity.[23–25] Because TFV (but not TAF) actively enters renal tubular cells via organic anion transporters 1 and 3, the reduced TFV levels that occur with TAF may be clinically manifest as reduced nephrotoxicity.[26,27] The higher intracellular TFV-DP levels may result in improved antiviral potency. In a 10-day monotherapy study in HIV-1–positive patients, those who received 25 mg of TAF had an approximately 0.5 $\log_{10}$ greater decline in plasma HIV-1 RNA than did patients who received the standard 300-mg dose of TDF.[28] In vitro, higher intracellular TFV-DP levels enable TAF to retain activity against viruses that have reduced susceptibility to TDF,[29] suggesting the potential use of TAF in a broader range of patients.

Because cobicistat increases the bioavailability of TAF by approximately 2.2-fold via the inhibition of P-glycoprotein intestinal secretion, the 10-mg dose of TAF delivered by the E/C/F/TAF STR is equivalent to the 25-mg dose of TAF.[28,30,31] To confirm the antiviral activity and safety profile of TAF compared with that of TDF, we conducted a randomized, double-blind Phase 2 clinical trial of 2 STRs—elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and TAF 10 mg (E/C/F/TAF) compared with elvitegravir 150 mg, cobicistat 150 mg, emtricitabine 200 mg, and TDF 300 mg (E/C/F/TDF), licensed as Stribild (Gilead Sciences, Foster City, CA). The primary objective of this study, GS-292-0102, was to evaluate the efficacy and safety of TAF relative to TDF, both as part of an elvitegravir-based STR in treatment-naive patients at 24 weeks, with a particular focus on virologic, renal, and bone endpoints. Here, we report the efficacy and safety data from this study through 48 weeks.

## METHODS

### Study Design

Study 292-0102 is an ongoing randomized, double-blind, double dummy, active controlled, Phase 2 study being conducted in the United States that was approved by the US Food and Drug Administration and by institutional review boards at all sites. HIV-positive treatment-naive adults were considered eligible if they were ≥18 years of age with a plasma HIV-1 RNA ≥5000 copies per milliliter, a $CD4^+$ cell count >50 cells per microliter, an HIV-1 genotype showing sensitivity to TFV and emtricitabine (FTC), and an estimated glomerular filtration rate (eGFR; Cockcroft–Gault) of ≥70 mL/min. Patients were excluded if they were hepatitis B or C coinfected, had a new AIDS-defining condition within 30 days of screening, or were pregnant. The study was conducted from December 2011 through April 2013 (week 48 endpoint) and is posted on clinicaltrials.gov (NCT01497899).

Eligible participants were randomized centrally by a third party interactive voice/web response system, stratified by screening HIV-1 RNA (≤ or >,100,000 copies per milliliter), in a 2:1 fashion to receive treatment with either E/C/F/TAF or E/C/F/TDF administered once daily with food; all patients also received matching placebo tablets.

Randomized patients were seen at screening, baseline, and at weeks 2, 4, 8, 12, 16, and then every 8 weeks through week 48. Laboratory analyses (hematology, serum chemistries, $CD4^+$ cell count, and urinalysis; Covance Laboratories, Indianapolis, IN), HIV-1 RNA (TaqMan 2.0; Roche Diagnostics, Indianapolis, IN), and physical examinations were performed at all visits. HIV-1 genotype (reverse transcriptase and protease) was tested at screening (GenoSure MG, Monogram Biosciences, South San Francisco, CA). Any patient with confirmed virologic failure (2 consecutive viral load samples >50 copies/mL) and an HIV RNA >400 copies/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).

Trough pharmacokinetic (PK) samples were collected at weeks 8, 24, and 48 visits, and population PK samples were collected at weeks 2, 4, 12, 16, 24, and 40. An intensive PK substudy was performed on a subset of patients at week 4 or 8 and included peripheral blood mononuclear cell (PBMC) sampling for intracellular TFV-DP levels.

Dual energy x-ray absorptiometry (DEXA) was used to measure BMD only at the hip and lumbar spine before study drug administration at baseline and every 24 weeks. These were read centrally by BioClinica (Newtown, PA), with investigators and patients blinded to the results. Patients were scanned with the same machine throughout the study, and phantom scans were used for quality assurance across sites. Blood and urine for selected bone and renal biomarkers were collected and analyzed at baseline and weeks 24 and 48.

### Statistical Methods

The primary objective was to determine the efficacy of a regimen containing E/C/F/TAF vs. E/C/F/TDF in HIV-1 treatment-naive adults at week 24 (primary endpoint) and week 48 (secondary endpoint) according to US Food and Drug Administration snapshot analysis (the proportion of patients with HIV-1 RNA <50 copies per milliliter).[32] The sample size of 150 patients (100 in the E/C/F/TAF arm) was chosen to estimate the response rate of HIV-1 RNA <50

© 2014 Lippincott Williams & Wilkins


Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023

copies per milliliter at week 24 and to have 76% power to detect a 1.5% (standard deviation of 3.2%) difference in hip BMD in the E/C/F/TAF arm relative to the E/C/F/TDF treatment group. The safety and tolerability of the 2 treatment arms through 48 weeks of treatment were assessed as secondary endpoints.

An individual patient was considered a treatment success if he or she had HIV-1 RNA <50 copies per milliliter at week 24 without virologic failure (confirmed >50 copies per milliliter in week 24 window). These criteria were also used for the week 48 secondary analysis. Safety analyses included available data from all participants who consented to participate, and who received at least 1 dose of study medication; patients who discontinued were followed up for 30 days after drug discontinuation. Demographic and baseline characteristics were summarized using standard descriptive methods.

## RESULTS

Of 233 patients screened, 171 were randomized, and 170 received at least 1 dose of study drug (E/C/F/TAF, n = 112, E/C/F/TDF, n = 58). Baseline characteristics are outlined in Table 1. Patients were primarily male, and approximately 30% were black or African American; most had no prior AIDS-defining condition. The median viral load at baseline was 4.6 $\log_{10}$ copies per milliliter, and the median $CD4^+$ cell count was 391 cells per microliter. Overall, 21% had baseline HIV-1 RNA >100,000 copies per milliliter, and 15% had a baseline CD4 count <200 cells per microliter (E/C/F/TAF, 12.5%; E/C/F/TDF, 18.9%). The median eGFR at baseline was 114 mL/min. Through week 48, 4 patients in the E/C/F/TAF arm and 0 in the E/C/F/TDF arm discontinued due to adverse events; 3 of the discontinuations due to unrelated illness (coxsackie infection, dual cytomegalovirus/*Mycobacterium avium* infection on day 13, acute promyelocytic leukemia) and 1 due to flushing that was considered drug related.

At week 24, virologic success was attained in 87.5% of those on the E/C/F/TAF arm and 89.7% for those receiving E/C/F/TDF [weighted difference −3.7%, 95% confidence interval −14.4 to 7.0, $P$ = 0.48]. At week 48, there was virologic success in 88.4% (99/112) of patients who received E/C/F/TAF and 87.9% (51/58) who received E/C/F/TDF (weighted difference −1.0%, 95% confidence interval −12.1 to 10.0, $P$ = 0.84). An analysis of virologic response using different virologic endpoints (missing = failure) demonstrated that 79% of patients in the E/C/F/TAF arm had HIV-1 RNA <20 copies per milliliter compared with 74% on E/C/F/TDF ($P$ = 0.56), whereas no RNA signal was detectable in 59% of those on E/C/F/TDF vs. 53% on E/C/F/TDF. Median adherence to study treatment was equivalent in the 2 treatment arms (98%). Two patients in the E/C/F/TDF arm and none in the E/C/F/TAF arm discontinued their treatment due to the loss of efficacy. The mean $CD4^+$ cell count increase from baseline was 177 cells per microliter in the E/C/FTAF arm vs. 204 cells per microliter in the E/C/F/TDF arm ($P$ = 0.41).

Six patients, 3 in each treatment arm (3/112 = 2.7% for E/C/F/TAF, 3/58 = 5.2% for E/C/F/TDF), met the criteria for virologic resistance testing. No resistance was detected in the E/C/F/TAF arm.

Resistance was detected in 2 patients in the E/C/F/TDF arm: 1 developed NRTI resistance with M184V and K70E and 1 developed both NRTI and Integrase Strand Transfer Inhibitor (INSTI) resistance with M184V and E92Q.

In patients in the intensive PK substudy (n = 26), plasma TFV exposure was 91% lower for patients taking E/C/F/TAF than for patients taking E/C/F/TDF, as measured by $AUC_{tau}$. Conversely, intracellular TFV-DP levels in PBMCs were 5.3-fold higher for patients in the E/C/F/TAF arm.

The 48-week safety profile of E/C/F/TAF was generally similar to that of E/C/F/TDF, with 94.6% (106) vs. 94.8% (55) patients reporting any treatment-emergent adverse event, and 9.8% (11) vs. 5.2% (3) reporting a grade 3 or 4 adverse event. The most common treatment-emergent adverse events were nausea and diarrhea, where nausea was reported in 21% on E/C/F/TAF and 12% of those on E/C/F/TDF. Of the 23 patients reporting nausea in the E/C/F/TAF treatment arm, 18 of these were grade 1, and 5 were grade 2, 15 resolved within 2 weeks, and none led to treatment discontinuation. A total of 7% in each arm reported vomiting. Diarrhea was reported in 16% in each treatment arm. No patient in either arm discontinued treatment due to any of these gastrointestinal events. Adverse events reported in at least 5% of participants in either arm are shown in Table 2.

All postbaseline grade 3 or 4 laboratory abnormalities are shown in Table 3. Grade 3 or 4 low-density lipoprotein (LDL) cholesterol elevations were more common in the E/C/F/TAF than in the E/C/F/TDF arm (9% vs. 3%). Fasting metabolic assessments showed that the median increase in LDL cholesterol was 17 mg/dL for E/C/F/TAF vs. 11 mg/dL for E/C/F/TDF ($P$ = 0.11). There were statistically significant differences between groups in the median changes in total cholesterol (30 vs. 17 mg/dL, $P$ = 0.007) and high-density lipoprotein (HDL) cholesterol (7 vs. 3 mg/dL, $P$ = 0.023), whereas total cholesterol/HDL cholesterol ratio remained unchanged (median increase 0.2 vs. 0.1, $P$ = 0.34). However, categorical analysis at week 48 by National Cholesterol Education Program Adult Treatment Panel III[33] classification showed no differences between the 2 treatment arms for total cholesterol ($P$ = 0.54) or for LDL cholesterol

**TABLE 1.** Baseline Characteristics

| Characteristic | E/C/F/TAF (n = 112) | E/C/F/TDF (n = 58) |
|---|---|---|
| Age (yrs), median | 34 | 38 |
| Male (%) | 96 | 98 |
| Race (%) | | |
| White | 67 | 69 |
| Black/African descent | 30 | 28 |
| Hispanic/Latino | 22 | 19 |
| Asymptomatic HIV infection (%) | 88 | 91 |
| HIV-1 RNA ($\log_{10}$ copies/mL), median | 4.55 | 4.58 |
| >100,000 copies/mL | 17% | 28% |
| CD4 cell count (cells/mm$^3$), median | 385 | 397 |
| ≤ 200 cells/mm$^3$ | 13% | 19% |
| Estimated GFR, median, (Cockcroft–Gault), mL/min | 115 | 113 |


© 2014 Lippincott Williams & Wilkins

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023

**TABLE 2.** Adverse Events

| Adverse Event (Any Grade) Occurring in At Least 5% of Patients, % (n) | E/C/F/TAF (n = 112) | E/C/F/TDF (n = 58) |
|---|---|---|
| Nausea | 21% (23) | 12% (7) |
| Diarrhea | 16% (18) | 16% (9) |
| Upper respiratory tract infection | 15% (17) | 21% (12) |
| Fatigue | 14% (16) | 9% (5) |
| Headache | 10% (11) | 14% (8) |
| Cough | 10% (11) | 10% (6) |
| Pharyngitis | 8% (9) | 3% (2) |
| Rash | 8% (9) | 5% (3) |
| Vomiting | 7% (8) | 7% (4) |
| Influenza | 7% (8) | 0 |
| Bronchitis | 6% (7) | 5% (3) |
| Nasopharyngitis | 6% (7) | 3% (2) |
| Depression | 6% (7) | 3% (2) |
| Conjunctivitis | 6% (7) | 0 |
| Anogenital warts | 5% (6) | 5% (3) |
| Abnormal dreams | 5% (6) | 2% (1) |
| Flatulence | 5% (6) | 3% (2) |
| Insomnia | 4% (4) | 7% (4) |
| Sinusitis | 4% (5) | 5% (3) |
| Seasonal allergies | 3% (3) | 5% (3) |
| Back pain | 3% (3) | 10% (6) |
| Paresthesia | 3% (3) | 7% (4) |
| Neck pain | 3% (3) | 5% (3) |
| Syphilis | 3% (3) | 5% (3) |
| Anxiety | 2% (2) | 9% (5) |
| Pain in extremities | 1% (1) | 5% (3) |
| Skin papilloma | 0 | 5% (3) |

($P = 0.37$), and there were no differences in change in triglycerides or serum glucose between treatment arms.

There was a rise in serum creatinine and consequent decline in creatinine clearance in both arms. Compared with baseline, the median change in serum creatinine at week 48 was 0.07 mg/dL for E/C/F/TAF vs. 0.10 mg/dL for E/C/F/TDF ($P = 0.077$), and the median change in eGFR by Cockcroft–Gault was −5.5 mL/min for E/C/F/TAF vs. −10.1 mL/min for E/C/F/TDF ($P = 0.041$). The median changes in serum creatinine generally occurred by week 4 for both treatment arms and then stabilized for the duration of the study.

There were no clinically defined cases of proximal renal tubulopathy in either arm, and there were no treatment discontinuations due to laboratory or clinical renal events. Less proteinuria (urine protein/creatinine ratio) and albuminuria (urine albumin/creatinine ratio) were observed with E/C/F/TAF, but the differences were not statistically significant (Fig. 1). Renal tubular proteinuria [urine retinol-binding protein (RBP)/creatinine ratio and urine β-2 microglobulin/creatinine ratio] was significantly lower in patients who received E/C/F/TAF (Fig. 1).

Changes in BMD, expressed as the median percent change from baseline, are shown in Figure 2. There was significantly less change in the E/C/F/TAF arm in BMD as measured by using DEXA at both the hip (−0.62% vs. −2.39%, $P < 0.001$) and lumbar spine (−1.00% vs. −3.37%, $P < 0.001$) at week 48, which were also significant at week 24. In the E/C/F/TAF arm, 32% of the patients had no decrease seen in hip BMD vs. 7% in the E/C/F/TDF arm ($P < 0.001$), and no decrease at the lumbar spine was seen in 37% of the patients who received E/C/F/TAF vs. 11% who received E/C/F/TDF ($P < 0.001$). Conversely, a change in BMD >3% from baseline at the hip was observed 11.5% vs. 40.0% and at the lumbar spine in 24.8% vs. 55.3% (E/C/F/TAF vs. E/C/F/TDF, respectively, $P < 0.001$ for both). At weeks 24 and 48, markers of bone turnover were lower in patients on E/C/F/TAF than on E/C/F/TDF. At week 48, procollagen type 1 N-terminal propeptide, a marker of bone formation, increased 9% from baseline for E/C/F/TAF vs. 69% for E/C/F/TDF ($P < 0.001$), whereas C-terminal telopeptide (CTx), a marker of bone resorption, increased 19% from baseline for E/C/F/TAF vs. 78% for E/C/F/TDF ($P < 0.001$). There were no fragility fractures in either arm of the study.

**TABLE 3.** Grade 3 or 4 Laboratory Abnormalities

| Maximum Toxicity Grade Postbaseline % (n) | E/C/F/TAF (n = 112) | E/C/F/TDF (n = 58) |
|---|---|---|
| Any grade 3 or grade 4 abnormality | 25% (28) | 17% (10) |
| LDL | 9% (10) | 3% (2) |
| Creatine phosphokinase | 6% (7) | 3% (2) |
| Neutropenia | 5% (6) | 2% (1) |
| Amylase | 3% (3) | 3% (2) |
| Urine RBC | 2% (2) | 0 |
| Total cholesterol | 2% (2) | 0 |
| ALT | 1% (1) | 2% (1) |
| AST | 1% (1) | 0 |
| GGT | 1% (1) | 2% (1) |
| White blood cells | 1% (1) | 0 |
| Hypophosphatemia | 1% (1) | 0 |
| Urine protein | 1% (1) | 0 |
| Glucose | 1% (1) | 2% (1) |
| Triglycerides | 1% (1) | 2%(1) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma glutamyl transpeptidase; RBC, red blood cells.

## DISCUSSION

TDF is a preferred NRTI in the initial therapy based on its favorable efficacy and safety data in randomized clinical trials and widespread use in clinical practice.[11] However, TDF may be associated with renal toxicity,[15,16] and comparative studies demonstrate that TDF treatment is linked to a greater loss in bone density as compared with other NRTI options.[18,34] Given the prolonged survival of patients with HIV with effective therapy, and the need for indefinite treatment, there is a need for an NRTI option that provides antiviral activity comparable with TDF with an improved safety profile.

In this Phase 2, randomized clinical trial, HIV-positive treatment-naive adults received STRs of E/C/F/TAF or E/C/F/TDF. Both E/C/F/TAF and E/C/F/TDF demonstrated high and comparable rates of virologic suppression, with expected rises in the $CD4^+$ cell count through 48 weeks of therapy. Both regimens were well tolerated, with few discontinuations due to adverse events. Although nausea occurred more

© 2014 Lippincott Williams & Wilkins


Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023

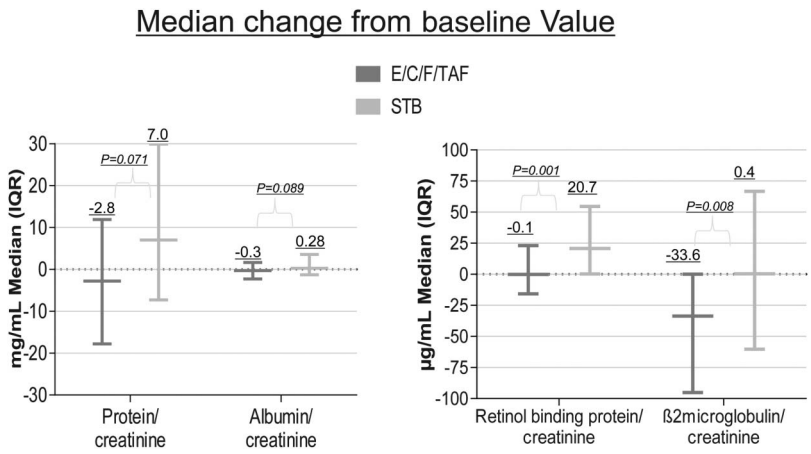
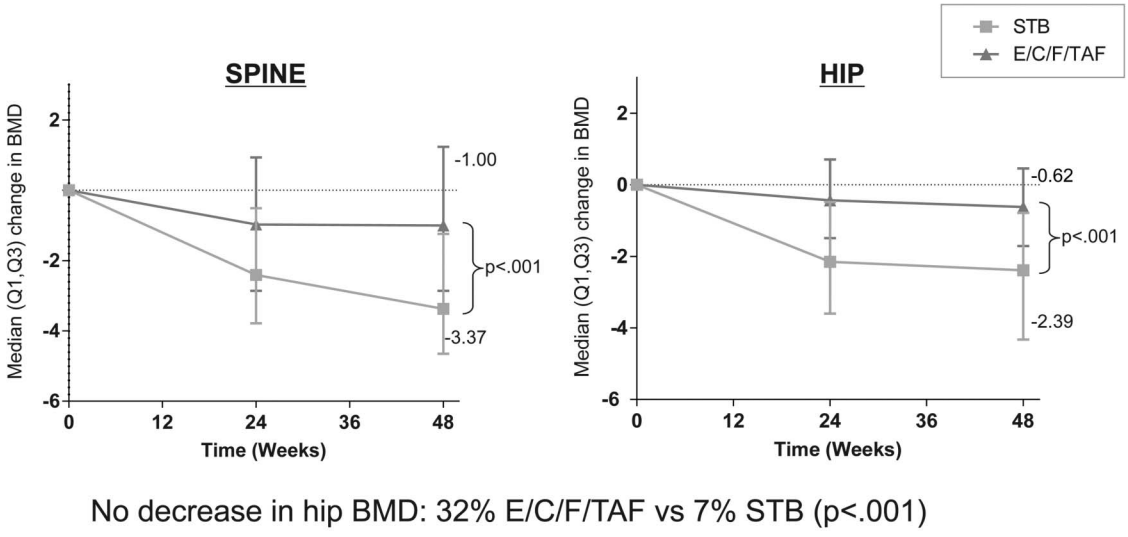



**FIGURE 1.** Urine tubular proteins: median change from the baseline value.

frequently in the E/C/F/TAF than in the E/C/F/TDF arm, the nausea reported was all grade 1 and grade 2 in severity, did not lead to drug discontinuation in any patient, and was comparable with the rate of nausea in the phase 3 studies of E/C/F/TDF.[35,36]

Because the 2 treatment regimens in this study differed only in whether patients received TAF or TDF, the study offered an opportunity to compare the pharmacokinetics, renal, and bone effects of the 2 prodrugs. Plasma concentrations of TFV were substantially (91%) lower with E/C/F/TAF than with E/C/F/TDF, and the TAF regimen delivered 5.3 times the intracellular, physiologically active metabolite, TFV-DP, to PBMCs, which could translate into less end-organ toxicity and/or improved virologic control. Although the effect of these differences did not translate into an observed significant difference in antiviral activity between the 2 regimens, the study had not been powered to demonstrate differences in virologic endpoints, and this is being further explored in the E/C/F/TAF Phase 3 program. In addition, no genotypic resistance emerged in the E/C/F/TAF group for the 3 patients with virologic failure and who met criteria for resistance analysis.

There were significant differences between the E/C/F/TAF and E/C/F/TDF treatment groups in specified renal, bone, and lipid endpoints. Early small increases in creatinine were seen in both arms, which were expected to be due to the known nonpathologic inhibitory effect of cobicistat on tubular creatinine secretion.[37] However, after week 2, patients on TAF had a lower magnitude increase in serum creatinine than did patients on TDF despite receiving the same other components of combination ART. The mechanism for this




| W48 Median Value of Bone Biomarkers as % of Baseline: E/C/F/TAF vs. STB | |
|---|---|
| Procollagen Type 1 N-terminal propeptide (P1NP): | 109% vs 169% (p<0.001) |
| C-terminal telopeptide (CTx): | 119% vs. 178% (p<0.001) |

**FIGURE 2.** Percent change in the spine and hip BMD as determined using DEXA.

 © 2014 Lippincott Williams & Wilkins

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023

difference is currently unknown but potentially may be related to the 91% lower plasma TFV exposure observed when TFV is delivered as TAF compared with TDF, because higher plasma TFV levels have been associated with an increased risk of renal impairment in other studies.[24,25] TFV in plasma is actively transported into the proximal renal tubular cell via organic anion transporter (OAT) 1 and OAT 3, but TAF is not a substrate for these transporters.[27] Thus, the intracellular concentration of TFV within proximal tubules is lower in patients treated with TAF compared with those treated with TDF, and decreased cytotoxicity of TAF in isolated human renal cells was recently demonstrated.[27]

The effect of TAF vs. TDF on proximal renal function was assessed using standard clinical measures of proteinuria and albuminuria, and markers of proximal renal tubular cell dysfunction, RBP, and β-2 microglobulin. These low molecular weight proteins are freely filtered at the glomerulus, and hence are almost entirely removed from the ultrafiltrate and catabolized in the proximal renal tubules.[38,39] The presence of these proteins in increased amounts in the urine may indicate subclinical renal tubular cell dysfunction.[38,39] In this study, urinary RBP/creatinine and β-2 microglobulin/creatinine ratios were significantly lower in the E/C/F/TAF arm, which suggests that TAF has a lesser effect than TDF on the proximal renal tubular cell. Whether this translates into long-term clinical benefit in renal function must be explored in larger studies with a longer follow-up. Nonetheless, these data are encouraging, as they demonstrate that TAF has a reduced effect on serum creatinine and is associated with reduced tubular proteinuria, both of which are important clinical markers of chronic kidney disease.

Patients with HIV have a lower BMD than age-matched HIV-uninfected controls, and they also experience higher fracture rates.[10,19] In addition, several studies have shown that TDF-containing regimens lead to a greater decline in bone density than in the case of comparator drugs.[18,34] In this study, patients who received E/C/F/TAF had smaller decreases in BMD through 48 weeks than those receiving E/C/F/TDF. It is noteworthy that the magnitude of BMD change that was observed for patients on the E/C/F/TAF arm was the lowest magnitude BMD change reported to date for treatment-naive study patients receiving NRTIs who had bone density assessed with bone DEXA scans. For example, the ASSERT study compared patients treated with TDF/FTC vs. ABC/3TC, each combined with efavirenz, and found a loss of BMD in both groups after the initiation of ART. However, there was a statistically greater loss of BMD at the hip and spine in patients treated with TDF/FTC than in those given ABC/3TC.[18] Although cross-study comparisons should only be made cautiously, the STR E/C/F/TAF demonstrated less loss of BMD than seen with ABC/3TC + EFV demonstrated in the ASSERT study (hip: −0.62% vs. −1.9%; spine: −1.0% vs. −1.6% for E/C/F/TAF and ABC/3TC + EFV, respectively). The DEXA results in this study were supported by changes in markers of bone turnover, with significantly less change in markers of bone formation (procollagen type 1 N-terminal propeptide) and bone resorption (CTX) among patients on E/C/F/TAF compared with those on E/C/F/TDF.

There were significantly greater increases in total and HDL cholesterol in the E/C/F/TAF than in the E/C/F/TDF study arm. By contrast, the total cholesterol/HDL ratio, triglycerides, and glucose were not significantly different, and there were no differences in National Cholesterol Education Program risk classification. The likely cause of these differences may relate to the previously reported lipid-lowering effect of TFV,[40,41] and the markedly lower plasma concentrations of TFV in the E/C/F/TAF compared with that in the E/C/F/TDF arm.

## CONCLUSIONS

Treatment-naive patients given either TAF or TDF as part of an STR containing emtricitabine, cobicistat, and elvitegravir achieved a high rate of virologic suppression, with comparably low rates of adverse events and adverse event-related drug discontinuation in both arms. Nausea was more common in those receiving E/C/F/TAF than in those receiving E/C/F/TDF in this study, though it was mild and did not lead to study drug discontinuation. Pharmacokinetic data demonstrated that TAF delivers the parent drug TFV into PBMCs, where the active, phosphorylated metabolite, TFV-DP, achieves a concentration 5- to 7-fold higher than TDF, with 91% lower plasma TFV levels. The E/C/F/TAF-treatment group had a significantly higher eGFR and significantly less tubular proteinuria than E/C/F/TDF; further, changes in BMD significantly favored E/C/F/TAF. These promising results await confirmation in fully powered Phase 3 randomized controlled clinical trials comparing TAF with TDF, which are underway.

## REFERENCES


1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med.* 1998;338:853–860.
2. Mocroft A, Vella S, Benfield TL, et al. Changing patterns of mortality across Europe in patients infected with HIV-1. EuroSIDA Study Group. *Lancet*. 1998;352:1725–1730.
3. Kitahata MM, Gange SJ, Abraham AG, et al. Effect of early versus deferred antiretroviral therapy for HIV on survival. *N Engl J Med.* 2009;360:1815–1826.
4. Cohen MS, Chen YQ, McCauley M, et al. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med.* 2011;365:493–505.
5. Mayer K, Gazzard B, Zuniga JM, et al. Controlling the HIV epidemic with antiretrovirals: IAPAC consensus statement on treatment as prevention and preexposure prophylaxis. *J Int Assoc Provid AIDS Care.* 2013;12:208–216.
6. Wood E, Milloy MJ, Montaner JS. HIV treatment as prevention among injection drug users. *Curr Opin HIV AIDS.* 2012;7:151–156.
7. Capeau J. Premature aging, premature age-related comorbidities in HIV-infected patients: facts and hypotheses. *Clin Infect Dis.* 2011;53:1127–1129.
8. Centers for Disease Research. *HIV/AIDS Surveillance Report, 2005*. 17th ed. Atlanta; 2007:1–54.
9. Guaraldi G, Zona S, Menozzi M, et al. Cost of noninfectious comorbidities in patients with HIV. *Clinicoecon Outcomes Res.* 2013;5:481–488.
10. Guaraldi G, Orlando G, Zona S, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis.* 2011;53:1120–1126.
11. US Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretrovira agents in HIV-1 infected adults and adolescents. Available at: http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. 2013. Accessed October 15, 2013.


© 2014 Lippincott Williams & Wilkins


Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.

Downloaded from http://journals.lww.com/jaids by BhDMf5ePHKav1zEoum1tQfN4a+kJLhEZgbsIHo4XMi0hCywCX1AWnYQp/IlQrHD3i3D0OdRyi7TvSFl4Cf3VC4/OAVpDDa8KKGKV0Ymy+78= on 08/01/2023


12. Chesney MA. Factors affecting adherence to antiretroviral therapy. *Clin Infect Dis.* 2000;30(suppl 2):S171–S176.
13. Aldir I, Horta A, Serrado M. Single-tablet regimens in HIV: does it really make a difference? *Curr Med Res Opin.* 2014;30:89–97.
14. Sterrantino G, Santoro L, Bartolozzi D, et al. Self-reported adherence supports patient preference for the single tablet regimen (STR) in the current cART era. *Patient Prefer Adherence.* 2012;6:427–433.
15. Hall AM, Hendry BM, Nitsch D, et al. Tenofovir-associated kidney toxicity in HIV-infected patients: a review of the evidence. *Am J Kidney Dis.* 2011;57:773–780.
16. Post FA, Moyle GJ, Stellbrink HJ, et al. Randomized comparison of renal effects, efficacy, and safety with once-daily abacavir/lamivudine versus tenofovir/emtricitabine, administered with efavirenz, in antiretroviral-naive, HIV-1-infected adults: 48-week results from the ASSERT study. *J Acquir Immune Defic Syndr.* 2010;55:49–57.
17. *VIREAD (Tenofovir Disoproxil Fumarate) Tablets and Powder. US Prescribing Information*. Foster City, CA: CGSI; 2012.
18. Stellbrink HJ, Orkin C, Arribas JR, et al. Comparison of changes in bone density and turnover with abacavir–lamivudine versus tenofovir–emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis.* 2010;51:963–972.
19. Schafer JJ, Manlangit K, Squires KE. Bone health and human immunodeficiency virus infection. *Pharmacotherapy*. 2013;33:665–682.
20. Lee WA, He GX, Eisenberg E, et al. Selective intracellular activation of a novel prodrug of the human immunodeficiency virus reverse transcriptase inhibitor tenofovir leads to preferential distribution and accumulation in lymphatic tissue. *Antimicrob Agents Chemother.* 2005;49:1898–1906.
21. Birkus G, Kutty N, He GX, et al. Activation of 9-[(*R*)-2-[[(*S*)-[[(*S*)-1-(isopropoxycarbonyl)ethyl]amino] phenoxyphosphinyl]-methoxy]propyl] adenine (GS-7340) and other tenofovir phosphonoamidate prodrugs by human proteases. *Mol Pharmacol.* 2008;74:92–100.
22. Birkus G, Wang R, Liu X, et al. Cathepsin A is the major hydrolase catalyzing the intracellular hydrolysis of the antiretroviral nucleotide phosphonoamidate prodrugs GS-7340 and GS-9131. *Antimicrob Agents Chemother.* 2007;51:543–550.
23. Van Rompay KK, Durand-Gasselin L, Brignolo LL, et al. Chronic administration of tenofovir to rhesus macaques from infancy through adulthood and pregnancy: summary of pharmacokinetics and biological and virological effects. *Antimicrob Agents Chemother.* 2008;52:3144–3160.
24. Poizot-Martin I, Solas C, Allemand J, et al. Renal impairment in patients receiving a tenofovir–cART regimen: impact of tenofovir trough concentration. *J Acquir Immune Defic Syndr.* 2013;62:375–380.
25. Rodriguez-Novoa S, Labarga P, D'Avolio A, et al. Impairment in kidney tubular function in patients receiving tenofovir is associated with higher tenofovir plasma concentrations. *AIDS.* 2010;24:1064–1066.
26. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. *Antimicrob Agents Chemother.* 2006;50:3297–3304.
27. Bam RA, Yant SR, Cihlar T. Tenofovir alafenamide is not a substrate for renal organic anion transporters (OATs) and does not exhibit OAT-dependent cytotoxicity. *Antivir Ther.* 2014; ePub ahead of print, April 4, 2014, 10.3851/IMP2770.
28. Ruane PJ, DeJesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr.* 2013;63:449–455.
29. Margot N, Liu Y, Babusis D, Miller MD, et al. Antiviral activity of tenofovir alafenamide (TAF) against major NRTI-resistant viruses: improvement over TDF/TFV is driven by higher TFV-DP loading in target cells. Paper presented at: International Workshop on HIV & Hepatitis Virus Drug Resistance and Curative Strategies. Toronto, Canada: 2013.
30. Lepist EI, Phan TK, Roy A, et al. Cobicistat boosts the intestinal absorption of transport substrates, including HIV protease inhibitors and GS-7340, in vitro. *Antimicrob Agents Chemother.* 2012;56: 5409–5413.
31. Ramanathan SWX, Custodio J, Wang H, et al. Pharmacokinetics of a novel EVG/COBI/TFC/GS-7340 single tablet regimen. Paper presented at: 13th International Workshop on Clinical Pharmacology of HIV Therapy. Barcelona, Spain: 2012.
32. Smith FH, Soon T, Zhou G, et al. A meta-analysis to assess the FDA DAVP's TLOVR algorithm in HIV submissions. *Drug Inf J.* 2011;45: 291–300.
33. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the third report of The National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult treatment panel III). *JAMA*. 2001;285:2486–2497.
34. McComsey GA, Kitch D, Daar ES, et al. Bone mineral density and fractures in antiretroviral-naive persons randomized to receive abacavir–lamivudine or tenofovir disoproxil fumarate–emtricitabine along with efavirenz or atazanavir–ritonavir: Aids Clinical Trials Group A5224s, a substudy of ACTG A5202. *J Infect Dis.* 2011;203:1791–1801.
35. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet.* 2012;379: 2429–2438.
36. Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet.* 2012;379:2439–2448.
37. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. *J Acquir Immune Defic Syndr.* 2012;61:32–40.
38. Hall AM, Edwards SG, Lapsley M, et al. Subclinical tubular injury in HIV-infected individuals on antiretroviral therapy: a cross-sectional analysis. *Am J Kidney Dis.* 2009;54:1034–1042.
39. Post FA, Wyatt CM, Mocroft A. Biomarkers of impaired renal function. *Curr Opin HIV AIDS.* 2010;5:524–530.
40. Behrens G, Maserati R, Rieger A, et al. Switching to tenofovir/emtricitabine from abacavir/lamivudine in HIV-infected adults with raised cholesterol: effect on lipid profiles. *Antivir Ther.* 2012;17:1011–1020.
41. Tungsiripat M, Kitch D, Glesby MJ, et al. A pilot study to determine the impact on dyslipidemia of adding tenofovir to stable background antiretroviral therapy: ACTG 5206. *AIDS.* 2010;24:1781–1784.


 © 2014 Lippincott Williams & Wilkins

Cipla v. Gilead IPR2025-00033 Petitioner Exhibit 1025

Copyright © Lippincott Williams & Wilkins. Unauthorized reproduction of this article is prohibited.