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

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Background: Abacavir/lamivudine and tenofovir/emtricitabine fixed-dose combinations are commonly used first-line antiretroviral therapies, yet few studies have comprehensively compared their safety profiles.

Methods: Forty-eight–week data are presented from this multicenter, randomized, open-label study comparing the safety profiles of abacavir/lamivudine and tenofovir/emtricitabine, both administered with efavirenz, in *HLA-B*5701*-negative HIV-1–infected adults.

Results: Three hundred eighty-five subjects were enrolled in the study. The overall rate of withdrawal was high (28%). Changes in estimated glomerular filtration rate from baseline were similar between arms [difference 0.953 $mL \cdot min^{-1} \cdot 1.73\ m^{-2}$ (95% confidence interval: −1.445 to 3.351), $P = 0.435$]. Urinary excretion of retinol-binding protein and β-2 microglobulin increased significantly more in the tenofovir/emtricitabine arm (+50%; +24%) compared with the abacavir/lamivudine arm (no change; −47%) ($P < 0.0001$). A lower proportion achieved viral load <50 copies per milliliter in the abacavir/lamivudine arm (114 of 192, 59%) compared with the tenofovir/emtricitabine arm (137 of 193, 71%) [difference 11.6% (95% confidence interval: 2.2 to 21.1)]. The overall virological failure rate was low. The adverse event rate was similar between arms (except drug hypersensitivity, reported more in the abacavir/lamivudine arm).

Conclusions: The study showed no difference in estimated glomerular filtration rate between the arms, however, increases in markers of tubular dysfunction were observed in the tenofovir/emtricitabine arm, the long-term consequence of which is unclear. A significant difference in efficacy favoring tenofovir/emtricitabine was observed.

Key Words: abacavir/lamivudine, cardiovascular, efficacy, tenofovir/emtricitabine, HIV-1, renal

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INTRODUCTION

Treatment guidelines recommend a range of antiretroviral therapy (ART) combinations for initial use in treatment-naive, HIV-1–infected patients.[1,2] The fixed-dose combinations of abacavir sulfate 600 mg/lamivudine 300 mg (Kivexa/Epzicom) and tenofovir disoproxyl fumarate 300 mg/emtricitabine 200 mg (Truvada) have facilitated once-daily dosing,

combining 2 nucleoside(tide) reverse transcriptase inhibitors in 1 tablet. Their relative long-term safety profiles are of particular importance because treatment is currently life long.

Preclinical studies with tenofovir identified renal and bone toxicities as potential issues with this agent, however, the incidence of nephrotoxicity in the pivotal clinical studies, which excluded subjects with low estimated glomerular filtration rate (eGFR), was relatively low.[3,4] Subsequently, case reports have described serious renal toxicity, including acute renal failure requiring dialysis, progressive decline in renal function, proximal renal tubular dysfunction, and Fanconi syndrome.[5–7] Further studies have suggested older age, more advanced HIV-1 infection, lower body mass, impaired renal function, and co-administration of protease inhibitors or additional nephrotoxic drugs as possible risk factors for tenofovir-associated nephrotoxicity.[6–9] Renal or bone abnormalities have not been identified in preclinical or clinical studies with abacavir or lamivudine.[10]

Abacavir is associated with an immunologically mediated hypersensitivity reaction (HSR) in approximately 5%–8% of patients during the first 6 weeks of treatment which may be fatal if abacavir is not discontinued or if it is discontinued and subsequently reinitiated.[11,12] Screening for the major histocompatability complex class I allele, *HLA*B-5701* and subsequent avoidance of abacavir use in patients with this allele eliminated immunologically confirmed HSRs and significantly reduced the incidence of clinically suspected HSRs.[13]

Recently abacavir has been reported to be associated with an increased risk of myocardial infarction (MI)[14] and raised high-sensitive C-reactive protein (hs-CRP) and interleukin-6 (IL-6).[15] However, data from different studies are inconsistent, with the possible association of increased MI risk being reduced when traditional risk factors, including renal disease and intravenous drug use, are taken into account.[16–20] In comparative studies with tenofovir/emtricitabine, abacavir/lamivudine has shown greater increases in total cholesterol (TC), low-density lipoprotein cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides, but the HDL/TC ratio improved in both arms in ART-naive patients.[21] Similarly, lipid levels were not reduced as much with abacavir/lamivudine compared with tenofovir/emtricitabine after a switch of therapy.[22,23] The data related to abacavir and MI remain inconclusive.

This study compared the long-term safety profiles of abacavir/lamivudine with tenofovir/emtricitabine when utilized with efavirenz. Renal function was assessed by calculation of eGFR and creatinine clearance, quantification of urinary total protein and β_2-microglobulin (β_2M), and in supplemetary analyses, urinary albumin, retinol-binding protein (RBP), and N-acetyl-β-D-glucosaminidase (NAG). β_2M and RBP are low molecular weight proteins that are relatively freely filtered by the glomerulus and almost completely removed from the ultrafiltrate by the proximal tubules; their increased presence in the urine usually indicates defective proximal tubular uptake and/or transport, whereas NAG is a proximal tubule lysosomal enzyme and its presence in the urine suggests proximal tubular damage.[24] These markers were selected to assess differences in renal tubular function as significant tubular injury may occur in the absence of changes in eGFR or marked increases in total urinary protein excretion.[25] In addition, although eGFR is a fairly sensitive marker of changes in renal function in patients with eGFR <60 mL per minute, it performs less well in those with normal renal function. In addition to renal safety, efficacy, cardiovascular, and other safety analyses from the primary 48-week timepoint are reported here.

METHODS

Study Design

This multicenter, randomized, open-label study was conducted in 76 centers across 13 European countries. Eligible ART-naive, *HLA-B*5701*-negative, HIV-1–infected adult subjects were randomized to abacavir/lamivudine or tenofovir/emtricitabine administered with efavirenz for 96 weeks. Randomization was conducted centrally, stratified by screening eGFR [calculated by Modified Diet in Renal Disease (MDRD) equation], black or nonblack race, and body mass index (BMI). An interactive voice response system with allocation ratio of 1:1 and block size of 4 was used. Efavirenz was selected as the third agent because it is recommended by guidelines and, at the study design stage, was thought to have no impact on renal or bone endpoints. Subjects unable to tolerate efavirenz-related central nervous system side effects were allowed to switch to nevirapine.

Study Population

Eligible subjects were antiretroviral-naive (no previous therapy with any nonnucleoside reverse transcriptase inhibitor and ≤14 days of prior therapy with any other antiretroviral), *HLA-B*5701*-negative adults (≥18 years of age) with a plasma HIV-1 RNA ≥1000 copies per milliliter at screening.

Subjects with an estimated creatinine clearance <50 mL per minute (Cockcroft-Gault method) during the screening period were excluded. Similarly, subjects with an active, AIDS-defining illness at baseline were excluded. Hepatitis B surface antigen and hepatitic C antibody were assessed at screening; subjects positive for hepatitis B were excluded. All subjects were assessed for transmitted resistance to the antiretrovirals in the study using the Virco TYPE HIV-1 assay. Subjects with evidence of resistance at screening or prior documented evidence of genotypic and/or phenotypic resistance were excluded.

Study Procedures

Clinical and laboratory assessments were conducted at the week 4 and week 12 clinic visits and thereafter at visits every 12 weeks. Serum, plasma, and urine samples were collected at each 12-week visit and stored for exploratory analyses or resistance testing in the event of virologic failure. A follow-up visit was conducted 2–4 weeks after the completion of treatment for any subject with an ongoing adverse event (AE).

Safety Assessments

The primary endpoint for the study was the change from baseline in eGFR (MDRD), at week 48. Secondary safety endpoints included change from baseline in eGFR (Cockcroft-Gault), proportion of subjects with decline from baseline in eGFR, and proportion of subjects with National Kidney Foundation chronic kidney disease. β_2M was assayed from

urine samples during the study, whereas albumin, RBP, and NAG were assayed from stored urine samples. AEs (including abacavir hypersensitivity) and clinical laboratory evaluations (including fasting lipid profile) were summarized.

After reports of an association between abacavir and increased risk of MI,[14,15] an exploratory analysis of hs-CRP, IL-6, and adiponectin was performed on stored serum samples.

Definitions of Renal Toxicities

Subjects who experienced either progression to an eGFR (MDRD) of <60 mL·min^{-1}·1.73 m^{-2} or progression to an eGFR (Cockcroft-Gault) of <50 mL/min, confirmed at consecutive visits, were considered to have a decline in renal function. Subjects who experienced a confirmed rise in serum creatinine of ≥ 0.5 mg/dL from baseline and serum phosphate <2.0 mg/dL or one of these 2 elements plus 2 of glycosuria (≥ 250 mg/dL) in a nondiabetic, low serum potassium (<3 mEq/L) and low serum bicarbonate (<19 mEq/L) [adapted from Smith et al[21]] were considered to have proximal renal tubule dysfunction.

Efficacy Assessments

Secondary efficacy endpoints conducted at weeks 24 and 48 included the proportion of subjects with HIV-1 RNA <50 copies per milliliter, the proportion of subjects with HIV-1 RNA <400 copies per milliliter, absolute values and change from baseline in HIV-1 RNA and CD4$^+$ cell count, CD4$^+$ and CD8$^+$ lymphocyte counts, and HIV-1–associated conditions.

Virologic failure was defined in the protocol as failure to achieve a 1-log reduction in HIV-1 RNA by week 4, or a confirmed rebound to ≥ 400 copies per milliliter after confirmed reduction to <400 copies per milliliter by week 24, or confirmed HIV-1 RNA ≥ 400 copies per milliliter after week 24. In the event of virologic failure, both the baseline and virologic failure timepoints were assessed using the Virco TYPE HIV-1 assay for genotypic evaluation.

Statistical Analyses

The primary analysis of interest was conducted at week 48, with a final analysis planned at week 96. For sample size calculation, a 10 mL·min^{-1}·1.73 m^{-2} difference in change from baseline in eGFR (MDRD) was considered clinically relevant. Assuming a SD of 30 mL·min^{-1}·1.73 m^{-2} and a 2-sided 5% level of significance, a total of 380 subjects (190 per treatment arm) would be needed to provide 90% power to detect a 10 mL per minute difference between arms.

The intent-to-treat exposed (ITT-E) Population, comprising all randomized subjects who received at least 1 dose of study medication, was used for assessing primary and secondary safety objectives and efficacy. The primary analysis was conducted using a repeated measures mixed model for change from baseline in MDRD, adjusted for baseline eGFR, BMI, and race. The impact of age, gender, baseline viral load, baseline CD4 cell count, concurrent diabetes, hypertension, hepatitis C or B, country, HIV risk factor, use of prohibited medication, Centers for Disease Control and Prevention class, and Framingham cardiovascular risk were assessed for model inclusion using a stepwise covariate selection method. The model also included interactions for treatment by visit and baseline value by visit. Interactions between treatment and other covariates included in the models were also investigated. Supportive analyses using Cockcroft-Gault equation and using a Per Protocol Population were similarly conducted.

The efficacy analyses were based on the proportion who achieved HIV-1 RNA less than the predefined threshold at 48 weeks (intent-to-treat exposed, using the time to loss of virologic response algorithm). Responders were subjects with confirmed viral load less than the threshold, on 2 consecutive occasions, who had not yet met any nonresponder criterion. Nonresponders were subjects who never achieved confirmed HIV-1 RNA less than the threshold, prematurely discontinued study or study drug for any reason, had confirmed rebound greater than or equal to the threshold, or had an unconfirmed HIV-1 RNA greater than or equal to the threshold on their final study visit.

RESULTS

Study Population

Between July 2007 and December 2007, 392 subjects were randomized and 385 subjects received treatment with either abacavir/lamivudine or tenofovir/emtricitabine (Fig. 1). At the week 48 data cut-off, 107 subjects (28%) had withdrawn prematurely, 63 subjects (33%) receiving abacavir/lamivudine, and 44 subjects (23%) receiving tenofovir/emtricitabine. Baseline demographics were similar across the treatment arms (Table 1).

Primary Endpoint

At week 48, the adjusted mean change from baseline in eGFR by MDRD was +0.22 mL·min^{-1}·1.73 m^{-2} and +1.18 mL·min^{-1}·1.73 m^{-2} for the abacavir/lamivudine and tenofovir/emtricitabine arms, respectively. The adjusted mean difference between arms was 0.953 mL·min^{-1}·1.73 m^{-2} [95% confidence interval (CI): -1.445 to 3.351, $P = 0.435$] (Fig. 2). Similarly, no difference was observed between treatment arms using the Cockcroft Gault method or the Per Protocol Population.

Baseline eGFR had a significant effect on the change from baseline in eGFR by both MDRD and Cockcroft-Gault. Subjects with a baseline eGFR <90 mL per minute experienced a greater mean change in eGFR (improvement) at week 48 compared with subjects who had a baseline eGFR ≥ 90 mL per minute ($P < 0.05$). There was no evidence that baseline BMI or baseline CD4$^+$ cell count had a significant effect on change from baseline in eGFR.

Secondary Renal Endpoints

No differences were observed between treatment arms in the proportion of subjects with a decline from baseline in eGFR of ≥ 10 mL per minute, >20 mL per minute, 10%, or 20% when estimated by either MDRD or Cockcroft-Gault or the proportion of subjects with renal failure using the National Kidney Foundation chronic kidney disease stage categories.

Although no subjects met the protocol-defined decline in renal function or proximal renal tubule dysfunction criteria, there were differences between arms for 2 biomarkers of

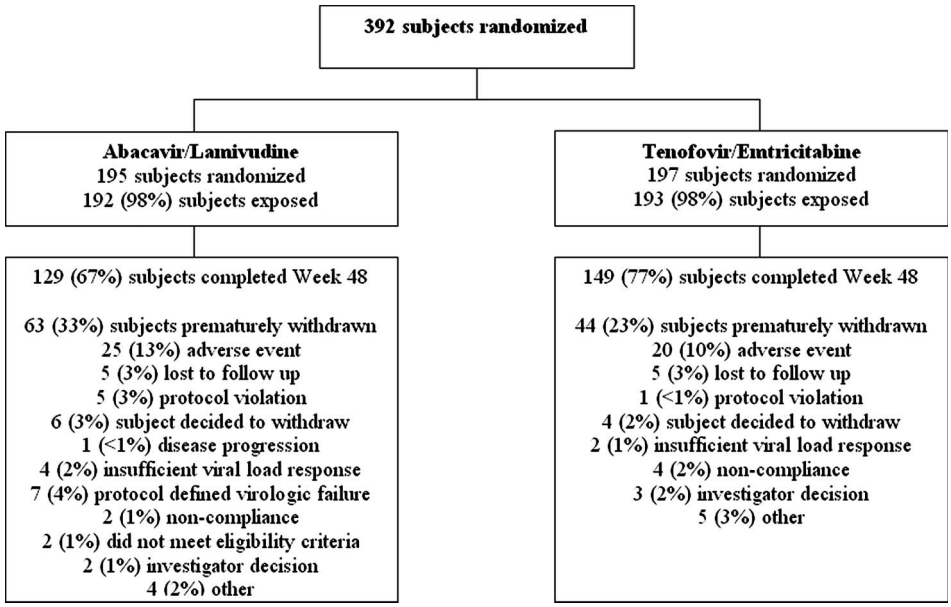

FIGURE 1. Summary of subject disposition.

tubular renal function, RBP, and β_2M (Table 2). A significantly higher percentage change from baseline in RBP/creatinine ratio and β2M/creatinine ratio was observed in the tenofovir/emtricitabine arm (+50%; +24%) compared with the abacavir/lamivudine arm (no change; −47%) at week 48. The observed changes in tubular biomarkers occurred within the first 24 weeks were sustained through to week 48, and the difference between the 2 treatment arms in the change from baseline at both week 24 and week 48 was statistically significant ($P < 0.0001$).

Secondary Efficacy Endpoints

In the time to loss of virologic response analysis at week 48, a greater proportion of subjects receiving tenofovir/emtricitabine (148 of 193, 77%) compared with abacavir/lamivudine (129 of 192, 67%) achieved HIV-1 RNA <400

TABLE 1. Demographic and Baseline Characteristics (ITT-E Population)

	ABC/3TC FDC QD (n = 192)	TDF/FTC FDC QD (n = 193)	Total (n = 385)
Age (years), median (range)	38.0 (19–70)	36.0 (18–66)	37.0 (18–70)
Sex: male, n (%)	159 (83)	154 (80)	313 (81)
Race: black, n (%)	26 (14)	30 (16)	56 (15)
Weight (kg), median (range)	71.0 (46.0–175.0)	73.0 (33.0–107.0)	72.0 (33.0–175.0)
Family history of premature cardiac heart disease, n (%)	23 (12)	18 (9)	41 (11)
Current smoker, n (%)	69 (36)	74 (38)	143 (37)
Current hypertension, n (%)	10 (5)	7 (4)	17 (4)
Hepatitis C reactive, n (%)	16 (8)	18 (9)	34 (9)
Screen eGFR ($mL \cdot min^{-1} \cdot 1.73\ m^{-2}$), n (%)			
<90	62 (32)	63 (33)	125 (32)
≥90	130 (68)	130 (67)	260 (68)
Baseline body mass index (kg/m^2), n (%)			
<25	127 (66)	130 (67)	257 (67)
≥25	64 (33)	63 (33)	127 (33)
Missing	1 (<1)	0	1 (<1)
Baseline $CD4^+$ cell count, median $CD4^+$ (range), $cells/mm^3$	240 (10–610)	230 (10–600)	240 (10–610)
Baseline HIV-1 RNA, median plasma HIV-1 RNA (range), log_{10}copies/mL	5.01 (2.88–6.78)	5.12 (3.31–6.75)	5.06 (2.88–6.78)
CDC category C (AIDS), n (%)	10 (5)	18 (9)	28 (7)
10-year coronary heart disease risk (using Framingham risk score), median (range)	2.97 (0.00–36.24) 188*	2.90 (0.00–35.28) 189*	2.904 (0.00–36.24) 377

*Total sample size.

ABC/3TC FDC QD abacavir/lamivudine fixed dose combination daily; CDC Centers for Disease Control and Prevention; ITT-E population, intent-to-treat exposed population; TDF/FTC FDC QD tenofovir/emtricitabine fixed dose combination daily.

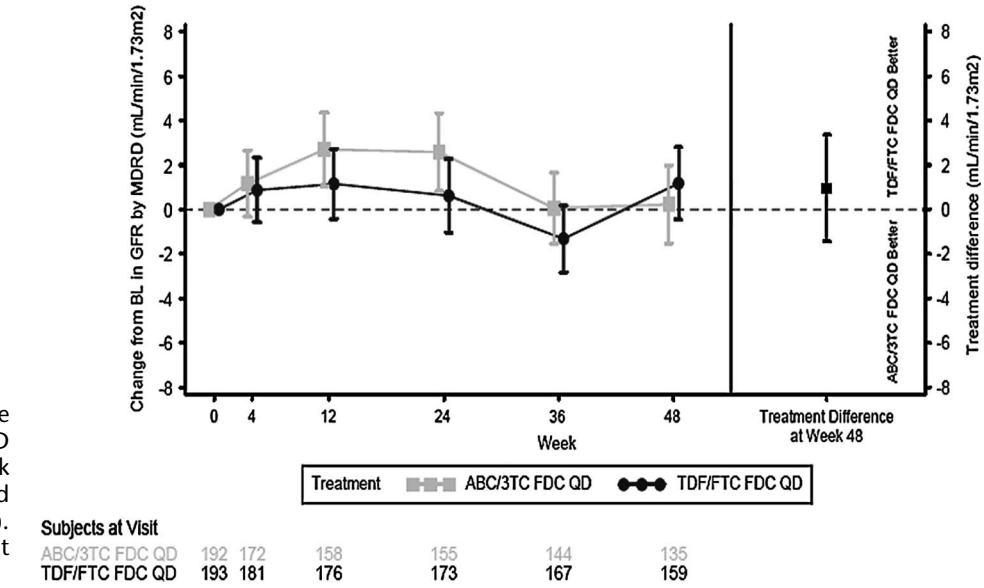

FIGURE 2. Adjusted mean change from baseline in eGFR by MDRD (mL·min^{-1}·1.73 m^{-2}) at week 48—repeated measures mixed model analysis (ITT-E Population). ITT-E population, intent-to-treat exposed population.

copies per milliliter (difference 9.5%, 95% CI: 0.6 to 18.4). Similarly, a greater proportion of subjects receiving tenofovir/emtricitabine (137 of 193, 71%) compared with abacavir/lamivudine (114 of 192, 59%) achieved HIV-1 RNA <50 copies milliliter (difference 11.6%, 95% CI: 2.2 to 21.1). The difference between the treatment arms was driven by investigator reported lack of efficacy and early withdrawals (occurring before virologic suppression), specifically from AEs, such as abacavir HSR (Fig. 3). Administrative discontinuations (eg, lost to follow-up, protocol violation, subject decision) in the study were unusually high and higher in the abacavir/lamivudine arm. Despite *HLA B*5701* testing, differences in the rate of withdrawals due to AEs between the arms was driven by drug hypersensitivity events (6% in the abacavir/lamivudine arm versus <1% in the tenofovir/emtricitabine arm). No difference between the arms was observed in discontinuation after suppression, and a high response rate in the observed analysis indicated that subjects who achieved suppression and remained in the study continued to respond to treatment.

Treatment response was reduced in subjects with baseline viral load ≥100,000 copies per milliliter in both treatment arms. Differences between arms were observed in the proportion of subjects achieving viral load <50 copies per milliliter at week 48 in subjects with baseline viral load <100,000 copies per milliliter, and ≥100,000 copies per milliliter. In the low viral load subgroup, 64% (61 of 95) versus 75% (62 of 83) of subjects achieved suppression in the abacavir/lamivudine and tenofovir/emtricitabine arms, respectively. In the high viral load subgroup, corresponding responses were 55% (53 of 97) versus 68% (75 of 110).

Protocol-defined virologic failures were rare in both treatment arms. Through week 48, 2% (8 of 385) subjects met the criteria for virologic failure (6 abacavir/lamivudine, 2 tenofovir/emtricitabine). Two patients, in the abacavir/lamivudine arm, subsequently achieved a viral load <400 copies per milliliter although continuing to receive abacavir/lamivudine and efavirenz. The On Treatment Resistance Population comprised all subjects who fulfilled the definition of

TABLE 2. Summary of Renal Biomarkers—Week 24 and Week 48

Renal Biomarker	Baseline, Median (IQR)* ABC/3TC FDC QD	Baseline, Median (IQR)* TDF/FTC FDC QD	Visit	Percentage of Baseline† ABC/3TC FDC QD	Percentage of Baseline† TDF/FTC FDC QD	Ratio of Changes From Baseline (95% CI)	*P*
Albumin (mg/mmol)‡	0.798 (0.501–1.540)	0.750 (0.477–1.556)	Week 24	90%	86%	0.96 (0.78 to 1.17)	0.6650
			Week 48	87%	94%	1.08 (0.90 to 1.29)	0.4237
β_2M (mg/mmol)‡	0.013 (0.005–0.024)	0.015 (0.009–0.030)	Week 24	72%	124%	1.72 (1.32 to 2.24)	<0.0001
			Week 48	53%	124%	2.33 (1.71 to 3.19)	<0.0001
RBP (μg/mmol)‡	12.26 (8.86–18.57)	12.57 (8.49–16.73)	Week 24	108%	151%	1.40 (1.21 to 1.63)	<0.0001
			Week 48	100%	150%	1.50 (1.28 to 1.76)	<0.0001
NAG (μmol/h/mmol)‡	34.39 (21.87–60.99)	34.87 (21.63–47.57)	Week 24	85%	92%	1.09 (0.95 to 1.24)	0.2344
			Week 48	87%	92%	1.05 (0.91 to 1.22)	0.5084

*Baseline sample size varied for each arm and analyte (n = 146–177) based on collection and availability of stored samples and weeks 24 and 48 sample size further declined (n = 100–142) due to withdrawals and missing samples.

†Percentage change from baseline in geometric mean, for example, percentages greater than 100 represent an increase from baseline, and less than 100 represent a decrease.

‡Expressed as a ratio with creatinine.

ABC/3TC FDC QD, abacavir/lamivudine fixed-dose combination daily plus efavirenz; TDF/FTC FDC QD, tenofovir/emtricitabine fixed-dose combination daily plus efavirenz.

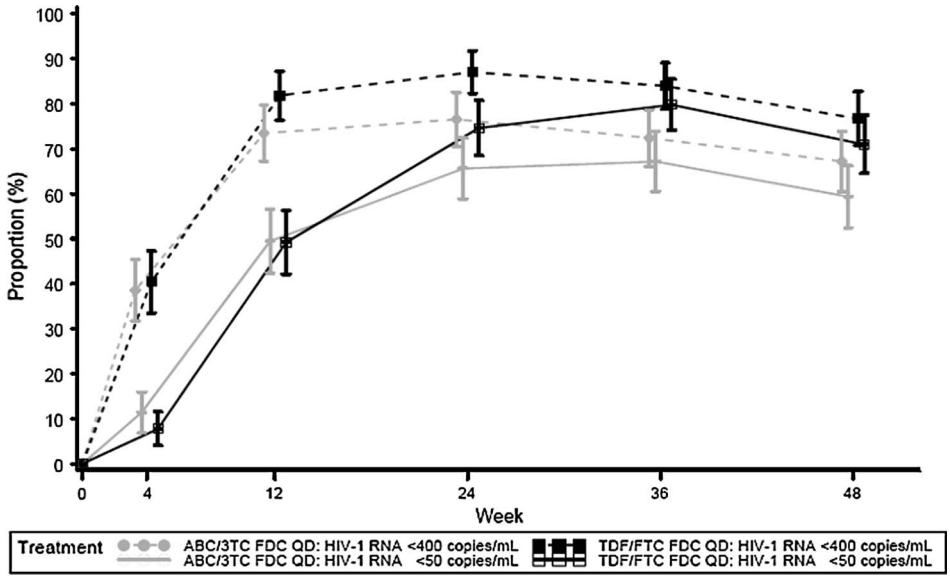

FIGURE 3. Proportion of subjects with HIV-1 RNA <400 copies per milliliter and <50 copies per milliliter by visit—TLOVR analysis. TLOVR, time to loss of virologic response.

protocol-defined virologic failure and had paired baseline and virologic failure genotypic data for analysis. Three subjects (all receiving abacavir/lamivudine) developed efavirenz-associated mutations (K103N, V106M, and G190A/G) and 1 of these subjects also developed K65R, D67N mutations. Three weeks before the week 36 virologic failure time point, this subject started the prohibited medication St Johns Wort, which is contraindicated with efavirenz; it potentially decreases efavirenz levels, leading to increased viral load and possible resistance to efavirenz or cross-resistance to other anti-HIV drugs.

Median $CD4^+$ cell count increases were observed in both treatment arms through week 48 (abacavir/lamivudine; n = 136, +150 cells/mm^3 and tenofovir/emtricitabine; n = 156, +150 cells/mm^3). Eight subjects (abacavir/lamivudine 3 of 192, 2%; tenofovir/emtricitabine 5 of 193, 3%) experienced HIV-1 disease progression to Centers for Disease Control and Prevention Class C or death.

Secondary Safety Endpoints

A total of 87% of subjects reported at least 1 AE during the study with dizziness, nasopharyngitis, and diarrhea being the most frequent. The proportion of drug-related (investigator opinion) AEs was similar between the treatment arms (abacavir/lamivudine 51% (98 of 192); tenofovir/emtricitabine 47% (91 of 193)]. Drug hypersensitivity, including abacavir HSR, was more commonly observed in the abacavir/lamivudine arm [abacavir/lamivudine 6% (12 of 192); tenofovir/emtricitabine <1% (1 of 193)]. The proportion of drug-related grade 2–4 AEs was numerically higher in the abacavir/lamivudine arm (29%) than the tenofovir/emtricitabine arm (20%); dizziness, abnormal dreams, and drug hypersensitivity were the most common AEs and occurred in both arms.

Six cases of clinically suspected abacavir HSRs were reported in this population of *HLA-B*5701*-negative subjects (3%). The mean exposure to abacavir/lamivudine was 11.7 days, and all subjects reported a rash. Two subjects reported fever (1 of whom also reported respiratory and constitutional symptoms), 2 subjects reported constitutional symptoms, gastrointestinal or respiratory events, and 2 subjects reported just rash. All subjects diagnosed with a clinically suspected HSR fully recovered from the event. There were no reports of abacavir rechallenge or death in these patients.

A total of nine subjects (abacavir/lamivudine 3%, 5 of 192; tenofovir/emtricitabine 2%, 4 of 193) reported a cardiac AE by week 48. This included 1 subject in the tenofovir/emtricitabine arm who experienced a MI and 1 subject in the abacavir/lamivudine arm who was reported with an intracardiac thrombus. This subject had suffered a MI before participating in the trial.

Greater increases from baseline were observed in the abacavir/lamivudine arm compared with the tenofovir/emtricitabine arm in median TC (1.36 mg/dL versus 0.66 mg/dL), triglycerides (0.23 mg/dL versus 0.05 mg/dL), low-density lipoprotein cholesterol (0.81 mg/dL versus 0.39 mg/dL) and HDL-cholesterol (0.38 mg/dL versus 0.28 mg/dL). However, the mean TC/HDL cholesterol ratio reduced in both treatment arms (−0.599 versus −0.934).

In an exploratory analysis of inflammation markers, minor changes were seen in hs-CRP and IL-6 levels, with no significant differences observed between the treatment arms. A rise in adiponectin from baseline to week 48 was observed in both the abacavir/lamivudine arm (30% increase) and tenofovir/emtricitabine arm (20% increase); the difference between the arms was statistically significant (ratio of the mean ratios = 0.9, (95% CI: 0.9 to 1.0, $P = 0.0187$).

DISCUSSION

This study evaluated 2 once-daily regimens, abacavir/lamivudine and tenofovir/emtricitabine, both with efavirenz, with a particular focus on renal toxicity. Our results confirm the findings of other trials in a low-risk patient population, showing that both tenofovir and abacavir have minimal effects on creatinine-based estimations of renal function.[21,26] Data from randomized and cohort studies suggest that subjects with

impaired renal function or proteinuria frequently experience improvements in eGFR after highly active ART initiation,[27,28] and eGFR can remain stable for up to 7 years.[29,30] However, other studies have suggested that HIV-infected patients treated with ART continue to lose kidney function over time.[31] Nonetheless, an overall initial beneficial effect of ART on kidney function is supported by the SMART study, in which discontinuation of ART was associated with the development of severe renal events and worsening renal function.[32,33]

The primary objective of demonstrating a clinically significant difference in eGFR between treatment arms was not met, and no patients met decline in renal function or proximal renal tubular dysfuntion criteria. Of note, an increase of renal tubular proteinuria was observed in the tenofovir/emtricitabine arm, suggesting altered proximal tubular function. Recent studies have reported high rates of subclinical proximal tubulopathy in HIV-1–infected subjects (6%–50% depending on ART regimen and proximal tubulopathy criteria used) and/or altered renal phosphate handling, with more severe abnormalities seen in subjects receiving tenofovir.[20,24,34] The risk of tenofovir-associated tubulopathy has been shown to increase with age and lower body mass and in the presence of specific polymorphisms in the genes encoding drug transporters.[35] The observed loss of tubular proteins in this study was milder than seen with Fanconi-like syndromes,[25,36] not associated with serum hypophosphatemia, and the long-term clinical significance of low-grade tubular proteinuria remains unknown. Interestingly, urinary NAG excretion in our study was similar between the 2 treatment arms, suggesting that the increased tubular proteinuria in the tenofovir/emtricitabine arm was more likely the result of altered tubular function rather than tubular injury.[27,37]

In this study, a higher proportion of subjects in the tenofovir/emtricitabine arm achieved undetectable levels of viremia. Of note, our study was confounded by an unexpectedly high withdrawal rate in both arms, nearly 30% of the population, not consistent with other studies.[4,21] The majority of these withdrawals were attributed to early AEs or administrative reasons. However, more difficult to ascertain is the impact of conducting this open-label study during a time of increased concern and uncertainty of the safety and potency of abacavir.[14,38]

When the study was designed, there was no reason to suspect that there might be a difference in efficacy between the 2 treatment arms and, as such, efficacy was not the primary endpoint but was included as a secondary endpoint. Subsequently, 2 additional data sets with a similar nucleoside backbone randomization, the AIDS Clinical Trials Group A5202, and Head-to-head Epzicom and Truvada (HEAT) studies have been reported and results of our study should be interpreted alongside them.[21,38] Both of these studies were designed with efficacy as the primary endpoint and robustly powered accordingly. A5202 and HEAT were both double-blind, placebo-controlled, randomized studies of abacavir/lamivudine versus tenofovir/emtricitabine, In A5202, after a Data and Safety Monitoring Board review, subjects in the high viral load cohort were unblinded due to a shorter time to virologic failure in subjects in this subgroup receiving abacavir/lamivudine. In HEAT, final 96-week results demonstrated non-inferiority of the 2 arms. Differences in study design, populations, concomitant antiretrovirals, and success/failure definitions have been proposed to explain some of the inconsistencies between study results such as these.[39,40]

Safety results were broadly consistent with available data for both regimens. A higher proportion of subjects reported AEs in the abacavir/lamivudine arm, although examination of individual AEs did not identify new signals of note. Despite recruiting only *HLA*B-5701*-negative subjects to this study, 6 subjects were diagnosed with a clinically suspected abacavir HSR. An assessment of the symptoms of abacavir HSRs reported in the PREDICT-1 study indicated that subjects with immunologically confirmed abacavir HSRs were more likely to develop symptoms from at least 3 categories of organ and involving fever.[41] Not all of the cases of abacavir HSR reported in this study had these symptoms.

Recently, data from the D:A:D observational cohort have raised questions regarding a cardiovascular signal in subjects receiving abacavir.[14] This signal was not apparent in the present study with a low incidence of cardiac AEs in both arms; 1 MI was reported in the tenofovir/emtricitabine arm. Although greater increases in cholesterol levels were seen in the abacavir/lamivudine arm, the TC:HDL cholesterol ratio, believed to be the strongest predictor of Coronary Heart Disease,[42] improved similarly in both arms. As exploratory analyses, stored plasma samples were analyzed for markers of inflammation.[43,44] Our analyses did not provide evidence to suggest an evolving inflammatory or cardiovascular process in subjects receiving abacavir or tenofovir.

In summary, no difference in eGFR were observed between the arms, although increases in markers of tubular dysfunction were observed in the tenofovir/emtricitabine arm. The long-term clinical significance of these results are unclear, and ASSERT continues through to 96 weeks to study this further.

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