

Efficacy and Safety of Tenofovir DF vs Stavudine in Combination Therapy in Antiretroviral-Naive Patients

A 3-Year Randomized Trial

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HIGHLY ACTIVE ANTIRETROVIRAL therapy has transformed human immunodeficiency virus (HIV) infection into a chronic manageable disease.¹⁻³ However, although many regimens lower plasma viral load to below the limit of detection in most patients, maintaining a durable response remains challenging because of adverse effects, long-term toxicity, and complex dosing schedules, all of which can lead to non-adherence, virologic failure, and drug resistance.⁴⁻⁶

Adverse effects and metabolic toxicity associated with protease inhibitor use have resulted in increasing use of regimens containing nonnucleoside reverse transcriptase inhibitors (NNRTIs) for initial therapy. However, some nucleoside analogue reverse transcriptase inhibitors (NRTIs) have also been

Context Tenofovir disoproxil fumarate (DF) is a once-daily nucleotide analogue reverse transcriptase inhibitor.

Objective To evaluate the efficacy and safety of tenofovir DF compared with stavudine in antiretroviral-naive patients.

Design, Setting, and Participants A prospective, randomized, double-blind study conducted at 81 centers in the United States, South America, and Europe from June 9, 2000, to January 30, 2004. A total of 753 patients infected with HIV who were antiretroviral naive were screened and 602 patients entered the study.

Intervention Patients were randomized to receive either tenofovir DF (n=299) or stavudine (n=303), with placebo, in combination with lamivudine and efavirenz.

Main Outcome Measure Proportion of patients with HIV RNA levels of less than 400 copies/mL at week 48.

Results In the primary intent-to-treat analysis in which patients with missing data or who added or switched antiretroviral medications before week 48 were considered as failures, the proportion of patients with HIV RNA of less than 400 copies/mL at week 48 was 239 (80%) of 299 in patients receiving tenofovir DF and 253 (84%) of 301 in patients receiving stavudine (95% confidence interval, -10.4% to 1.5%), exceeding the predefined -10% limit for equivalence. However, equivalence was demonstrated in the secondary analyses (HIV RNA <50 copies/mL) at week 48 and through 144 weeks. Virologic failure was associated most frequently with efavirenz and lamivudine resistance. Through 144 weeks, the K65R mutation emerged in 8 and 2 patients in the tenofovir DF and stavudine groups, respectively ($P=.06$). A more favorable mean change from baseline in fasting lipid profile was noted in the tenofovir DF group at week 144: for triglyceride levels (+1 mg/dL for tenofovir DF [n=170] vs +134 mg/dL for stavudine [n=162], $P<.001$), total cholesterol (+30 mg/dL [n=170] vs +58 mg/dL [n=162], $P<.001$), direct low-density lipoprotein cholesterol (+14 mg/dL [n=169] vs +26 mg/dL [n=161], $P<.001$), and high-density lipoprotein cholesterol (+9 mg/dL [n=168] vs +6 mg/dL [n=154], $P=.003$). Investigator-reported lipodystrophy was less common in the tenofovir DF group compared with the stavudine group (9 [3%] of 299 vs 58 [19%] of 301, $P<.001$). The number of bone fractures and the renal safety profile were similar between the 2 groups.

Conclusions Through 144 weeks, the combination of tenofovir DF, lamivudine, and efavirenz was highly effective and comparable with stavudine, lamivudine, and efavirenz in antiretroviral-naive patients. However, tenofovir DF appeared to be associated with better lipid profiles and less lipodystrophy.

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associated with long-term toxicity, including lipoatrophy, lactic acidosis, and peripheral neuropathy.⁷ It has been proposed that these toxicities are caused by NRTI-induced damage to mitochondrial DNA.⁸

Tenofovir disoproxil fumarate (tenofovir DF) is the first nucleotide analogue reverse transcriptase inhibitor approved for the treatment of HIV infection.⁹ It has a long intracellular half-life and is formulated as a single 300-mg tablet that is taken once daily.^{10,11} In vitro, tenofovir DF is a weak inhibitor of mitochondrial DNA polymerase gamma and appears not to affect the mitochondrial DNA content in multiple cell types.¹² In a viral dynamics study of tenofovir DF monotherapy, antiretroviral-naive patients experienced a 1.6 log₁₀ median decrease in HIV RNA over 3 weeks.¹³ The potency of tenofovir DF has been demonstrated in treatment-experienced patients.^{14,15} In placebo-controlled trials with treatment-experienced patients, the 24-week toxicity profile was similar to that of placebo, and in longer-term studies no significant toxicities have emerged after 96 weeks of follow-up.¹⁶ The K65R mutation is selected by tenofovir DF in vitro and has been reported in treatment-naive and treatment-experienced patients.^{17,18} Preliminary 96-week interim data on the efficacy and safety of tenofovir DF have been reported,¹⁹ as has its efficacy in the setting of coinfection with HIV-1 and hepatitis B virus.²⁰ In antiretroviral-naive patients, the combination of tenofovir DF with lamivudine and efavirenz has been classified as a preferred regimen in the Department of Health and Human Services treatment guidelines.²¹

To evaluate the safety and efficacy of tenofovir DF treatment in antiretroviral-naive patients, we conducted a randomized, double-blind trial comparing tenofovir DF with stavudine, both given in combination with lamivudine and efavirenz.

METHODS

Study Population and Design

This study was conducted at 81 centers in South America, Europe, and the United States. Eligible adult patients

were treatment-naive (no prior treatment with any NNRTI or protease inhibitor, ≤ 4 weeks of prior treatment with NRTIs) and had plasma HIV RNA levels greater than 5000 copies/mL. These eligibility criteria were similar to those of another HIV clinical trial performed at that time.²² Patients were required to have adequate hematologic (absolute neutrophil count $\geq 1000/\mu\text{L}$, platelets $\geq 50 \times 10^3/\mu\text{L}$, hemoglobin ≥ 8.0 g/dL), hepatic (transaminases $\leq 3 \times$ upper limit of normal), and renal function (serum creatinine < 1.5 mg/dL [$< 132.6 \mu\text{mol/L}$] and calculated creatinine clearance [Cockcroft-Gault formula] ≥ 60 mL/min [≥ 1.00 mL/s]). There was no minimum CD4 cell count for study entry. There were no requirements for normal lipid profiles at entry into the study. Each participant provided written informed consent. An institutional review board or ethics committee reviewed and approved the study protocol and informed consent form for each study center.

Randomization, Interventions, and Monitoring

Patients were centrally randomized in a 1:1 ratio to receive either 300 mg/d of tenofovir DF (Gilead Sciences, Foster City, Calif) or 40 mg twice daily (or 30 mg twice daily if weight < 60 kg) of stavudine (Bristol-Myers Squibb, Princeton, NJ) plus corresponding placebo, in combination with 150 mg twice daily of lamivudine (GlaxoSmithKline, Research Triangle Park, NC) and 600 mg/d of efavirenz (Bristol-Myers Squibb). A 200-mg dose twice daily of nevirapine (Boehringer Ingelheim, Ridgefield, Conn) could be substituted for efavirenz in the event of intolerable efavirenz-associated neuropsychiatric toxicity. Patients were stratified according to screening viral load levels ($<$ or $\geq 100\,000$ copies/mL) and CD4 cell count ($<$ or ≥ 200 cells/ μL). Interactive Clinical Technologies Inc (Yardley, Penn) developed and maintained an interactive voice response system (IVRS), which centralized patient randomization and blinded kit numbers for drug dispensation. This system con-

sisted of a CD4 cell count and HIV RNA stratified randomization scheme prepared by Interactive Clinical Technologies to program the IVRS. Using a touch-tone telephone, the investigators dialed into the IVRS and through a system of voice prompts entered the patient's study number, date of birth, weight, CD4 cell count, and HIV RNA level at screening. The IVRS then assigned blinded study drug bottles for each patient.

Clinical and laboratory evaluations were performed at screening, prebaseline, baseline, week 2, week 4, every 4 weeks through week 48, and every 8 weeks through week 144. Evaluations included review of adverse events and concomitant medications, complete or symptom-directed physical examination, weight, hematology and chemistry profile, plasma lactate (at US sites only), urinalysis, calculated creatinine clearance, CD4 cell count, plasma HIV-1 RNA, bone densitometry, serum and urine bone biochemical markers, peripheral blood mononuclear cell sampling, and study drug accountability. At each study visit, patients were asked to bring previously dispensed study drug bottles to receive the next supply of study drug. Patients were queried regarding study drug adherence, drug interruptions, and extra tablets. Pill count data were not available for this analysis. At screening, prebaseline, and baseline, the standard Roche Amplicor HIV-1 Monitor viral load assay (version 1.0 and version 1.5 [depending on the study site], Indianapolis, Ind) was used (lower limit of quantification, 400 copies/mL). For all subsequent visits, the Roche Amplicor HIV-1 Monitor Ultrasensitive assay (version 1.0 or 1.5; lower limit of quantification, 50 copies/mL) was used. Patients who exhibited neuropathy were assessed according to the Division of AIDS definition of HIV-related neuropathy.²³ Bone densitometry data were collected on all patients at baseline and every 24 weeks thereafter. The prebaseline visit was scheduled 5 days before the baseline visit. At the prebaseline visit, the patients underwent a bone densitometry scan. A technically satisfactory bone densitometry measurement was re-

quired for a patient to proceed to the baseline visit. Lipodystrophy and lactic acidosis were clinically assessed as adverse events by investigators and were not based on predefined assessment scales. Lipodystrophy assessments were performed in a subset of patients receiving whole body dual-energy x-ray absorptiometry (DXA) scans at weeks 96 (n=262) and 144 (n=232). Not all sites were able to participate in the whole body substudy because the DXA scanning machines at some sites lacked the software to measure total body fat by subregion. A proxy for adherence was calculated for each patient who received study medication, the intent-to-treat (ITT) group (299 in the tenofovir DF group and 301 in the stavudine group). Antiretroviral drug administration was recorded on a separate case report form (independent of nonantiretroviral medications), on which dosing information was explicitly documented for start dates, stop dates, and total daily dose of each antiretroviral drug. These data were used to determine both total time of interruptions while the patient was receiving the study regimen and the total time on randomized study regimen (defined as time from the first to the last date of study regimen). Thus, the proxy of adherence was calculated as (total time on randomized study regimen – total time of interruptions)/(total time on randomized study regimen).

An independent data monitoring committee reviewed the progress and safety profile of the study approximately every 6 months from the beginning of the study. The committee was unblinded to summary data by treatment group; there were no requests by the committee for unblinding by individual participant.

Objectives

The primary objective of this study was to assess the equivalence of tenofovir DF vs stavudine in combination with lamivudine and efavirenz for the treatment of patients infected with HIV who were antiretroviral naive as determined by the proportion of patients in

each regimen with plasma HIV RNA levels of less than 400 copies/mL. The secondary objectives of this study were to assess efficacy as measured by change in CD4 cell count and proportion of patients with HIV RNA levels of less than 50 copies/mL, and to compare the safety and tolerability of the 2 treatment regimens.

End Points

The primary efficacy end point was the proportion of patients with HIV RNA levels of less than 400 copies/mL at week 48. Patients with missing HIV RNA data and patients who added or switched antiretroviral medications were analyzed as having HIV RNA levels of more than 400 copies/mL. The secondary efficacy end points were the proportion of patients with HIV RNA levels of less than 50 copies/mL and the change in CD4 cell count from baseline at weeks 48, 96, and 144. Patients who discontinued blinded study medications were encouraged to remain in the study while off study medications. Safety was assessed by the frequency and severity of adverse events and clinical laboratory abnormalities.

Sample Size

The planned sample of 600 patients (300 per group) gave the study 80% power to establish equivalence between the 2 study groups. The calculations assumed a response rate of 75%²⁴ in each treatment group.

Statistical Methods

For the primary efficacy end point, we compared the 2 groups using a 2-sided 95% confidence interval (CI) for the stratum weighted difference (stratified on baseline HIV RNA and CD4 cell count) in treatment group response rates (tenofovir DF-containing group – stavudine-containing group). We used an ITT analysis in which patients missing HIV RNA data and patients who added or switched antiretroviral medications were analyzed as having HIV RNA levels of more than 400 copies/mL (ITT, missing=failure [M=F], antiretroviral

switch=failure [Switch=F]). In this conventional analysis,²⁵ all patients with missing data or who discontinued study regimen but remained on-study taking another regimen were considered as failures. Substitution of nevirapine for efavirenz was not considered to be an addition or switch of an antiretroviral medication.

With the exception of replacement of efavirenz by nevirapine for central nervous system toxicity or rash, patients had to stop the study regimen before taking any other antiretroviral drugs. Because this was a blinded study, this included any use of open-label tenofovir DF or stavudine. Thus, patients who discontinued the study regimen included those who added or switched to new antiretroviral drugs (Switch=F) or who dropped out of the study (M=F). Patients were followed up in the study after permanent discontinuation of the study regimen, and dropouts refer to patients who discontinued the study, which was the most common reason for missing data. A pure M=F analysis would ignore addition of or switch to new antiretroviral drugs, considering only those patients who dropped out as failures. In such an analysis, a patient who discontinued the assigned study regimen and had a viral load of less than 400 copies/mL at week 144 while on a new antiretroviral regimen would not be classified as a failure, which could result in a bias toward the assumption that the 2 treatment groups were equally efficacious when in fact they were not. In contrast, the Switch=F analysis considers those patients who discontinued the study regimen as failures, which better reflects the effect of the treatment under investigation.

The tenofovir DF-containing group was considered equivalent to the stavudine-containing group if the lower confidence bound for the difference between groups in the proportion with HIV RNA levels of less than 400 copies/mL was more than –10%. Antiretroviral treatment-naïve studies using 3 drug regimens often use –10% to –13% as the lower bound of the equivalence criteria. A lower limit of –10% consti-

tutes a more stringent and conservative equivalence criterion because a treatment difference of this magnitude is a small fraction of the additional benefit provided by the third drug in the regimen. There was no upper bound for the predefined CIs because the study was designed as a noninferiority trial (ie, equivalence) and the lower bound of the 2-sided 95% CI for the difference of the primary end point (the tenofovir DF group – stavudine group) was compared with –10% to determine noninferiority of tenofovir DF relative to stavudine.

The secondary analyses of efficacy included the CD4 cell count change from baseline, mean change in HIV RNA from baseline, and the proportion of patients with HIV RNA levels of less than 50 copies/mL using both the ITT, M=F, antiretroviral Switch=F, and ITT, M=F analyses. The ITT, M=F was used in addition to ITT, antiretroviral Switch=F as a secondary end point to provide sensitivity analysis to further assess the ro-

bustness of the results. In addition, the ITT, M=F analysis is often used in other trials involving antiretroviral-naive patients. For calculating the mean change from baseline in HIV RNA and CD4 cell count, the ITT population with all available data was used. (Because patients were followed up in the study after permanent discontinuation of the study regimen, all available data collected after study regimen discontinuation were included [ITT, missing = excluded] in the analyses regarding changes from baseline in viral load and CD4 cell count). Forty-nine copies/mL was used for samples with viral load below the limit of quantification (<50 copies/mL).

For the safety analyses, treatment-emergent adverse events and laboratory toxicities were summarized for the 2 treatment groups by incidence and grade, and changes in laboratory measurements from baseline were summarized by visit. Unless otherwise specified, the 2 treatment groups were compared using the Fisher exact test for

categorical data and Wilcoxon rank sum test for continuous data. All statistical analyses were performed using SAS version 8.2 (SAS Institute Inc, Cary, NC). $P < .05$ was considered statistically significant. Independent statistical review was also obtained.

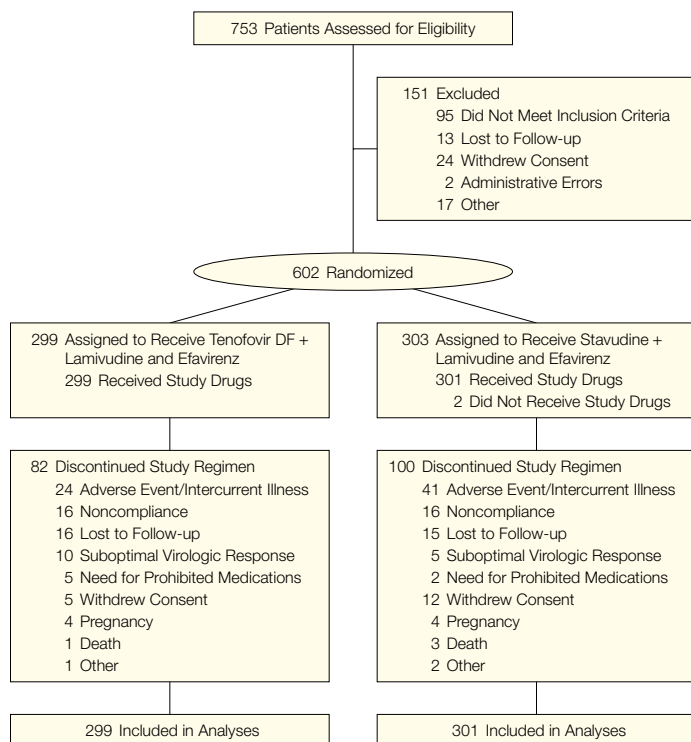
Resistance Analyses

Plasma for resistance analysis was stored at prebaseline, baseline, and every other study visit thereafter until week 144. Patients meeting the following virologic failure criteria were analyzed for development of resistance: patients who had HIV RNA levels of at least 400 copies/mL on at least 2 consecutive visits after achieving HIV RNA levels of less than 400 copies/mL; patients who had HIV RNA levels of at least 400 copies/mL at week 48, 96, or 144; and patients who discontinued study before week 144 and had HIV RNA levels of at least 400 copies/mL at discontinuation and had at least 1 post-baseline sample stored for analysis. The sample analyzed corresponded to the last available on-study sample. Genotypic analyses (Virtual Phenotype²⁶; Virco, Mechelen, Belgium) included the first 400 amino acids of the reverse transcriptase coding sequence and phenotypic analyses (PhenoSense HIV²⁷; Virologic, South San Francisco, Calif) included susceptibility to tenofovir and all other licensed NRTIs and NNRTIs. All resistance assays were performed and analyzed in a blinded fashion.

RESULTS

A total of 602 participants were enrolled between June 9, 2000, and January 13, 2001. Two patients never received study drugs. The last enrolled patient completed all visits for the double-blind 144-week study on January 30, 2004. Participant flow is shown in FIGURE 1. Baseline demographic and laboratory characteristics were comparable between the 2 groups (TABLE 1). Through 144 weeks, the study regimen permanent discontinuation rate was 82 (27%) of 299 in the tenofovir DF group and 100 (33%) of 301 in the stavudine group (Figure 1). Overall,

Figure 1. Study Flow of Participants



DF indicates disoproxil fumarate.

there were 5 (2%) of 299 and 6 (2%) of 301 deaths in tenofovir DF and stavudine groups, respectively. Reported causes of death were pneumonia, respiratory failure, hepatic failure, sepsis, and Kaposi sarcoma; no death was assessed by the investigator as study drug-related.

Efficacy

The primary end point was the proportion achieving an HIV RNA level of less than 400 copies/mL at week 48 using an ITT, M=F, antiretroviral Switch=F analysis. In the tenofovir DF group, 80% of patients met this end point compared with 84% of patients in the stavudine group (95% CI for the difference, -10.4% to 1.5%) (TABLE 2 and FIGURE 2). Equivalence was predefined as a stratum weighted 95% CI with a lower limit of -10%. Although equivalence was not achieved for the primary end point at week 48, it was demonstrated using the more stringent secondary analysis, the proportion with HIV RNA level of less than 50 copies/mL (ITT, M=F, antiretroviral Switch=F) at week 48. Equivalence was also demonstrated in secondary analyses using the ITT, M=F, antiretroviral Switch=F for both HIV RNA levels of less than 400 copies/mL and less than 50 copies/mL at weeks 96 and 144, respectively. In the ITT, M=F analyses, equivalence between the 2 regimens was demonstrated for the proportion of patients achieving HIV RNA levels of less than 400 copies/mL and less than 50 copies/mL at weeks 48, 96, and 144 (Table 2).

Excluding patients with missing data and those who switched to nevirapine, 24 (8%) in the tenofovir DF group and 12 (4%) in the stavudine group added or switched an antiretroviral agent through week 48 ($P=.04$). Included in this group were 4 patients from the tenofovir DF group and 1 from the stavudine group who added zidovudine due to pregnancy and had HIV RNA levels of less than 50 copies/mL prior to pregnancy detection. In addition, 3 patients in the tenofovir DF group and none in the stavudine group had baseline resistance to efavirenz

Table 1. Baseline and Laboratory Characteristics of Patients*

Characteristics	Tenofovir DF + Lamivudine and Efavirenz (n = 299)	Stavudine + Lamivudine and Efavirenz (n = 301)
Age, mean (absolute range), y	36 (19-61)	36 (18-64)
Sex, No. (%)		
Male	220 (74)	225 (75)
Female	79 (26)	76 (25)
Race, No. (%)		
White	191 (64)	193 (64)
Black	64 (21)	53 (18)
Other†	23 (8)	32 (11)
Hispanic	21 (7)	23 (8)
Weight, mean (SD), kg	71.8 (13.8)	72.1 (14.4)
HIV-1 RNA, mean (SD), log ₁₀ copies/mL	4.91 (0.64)	4.91 (0.61)
Mean HIV-1 RNA, copies/mL	81 300	81 300
≥100 000 copies/mL, No. (%)	138 (46)	129 (43)
CD4 cell count, mean (SD)	276 (201)	283 (200)
<200 cells/μL, No. (%)	118 (39)	113 (38)
<50 cells/μL, No. (%)	51 (17)	43 (14)

Abbreviations: DF, disoproxil fumarate; HIV, human immunodeficiency virus.

*One patient in the stavudine group was missing data on weight.

†Includes Asian, Native American, and mixed races.

Table 2. Proportion of Patients With HIV RNA Levels of <400 and <50 Copies/mL at Weeks 48, 96, and 144*

HIV RNA Levels	No./Total (%)		Weighted Difference, 95% Confidence Interval†
	Tenofovir DF + Lamivudine and Efavirenz (n = 299)	Stavudine + Lamivudine and Efavirenz (n = 301)	
Week 48			
ITT, M = F, antiretroviral Switch = F analysis			
<400 copies/mL	239/299 (79.9)	253/301 (84.1)	−10.4 to 1.5
<50 copies/mL	228/299 (76.3)	240/301 (79.7)	−9.8 to 3.0
ITT, M = F			
<400 copies/mL	259/299 (86.6)	262/301 (87.0)	−6.0 to 4.6
<50 copies/mL	244/299 (81.6)	244/301 (81.1)	−5.6 to 6.4
Week 96			
ITT, M = F, antiretroviral Switch = F analysis			
<400 copies/mL	226/299 (75.6)	214/301 (71.1)	−2.7 to 11.3
<50 copies/mL	217/299 (72.6)	204/301 (67.8)	−2.4 to 12.0
ITT, M = F			
<400 copies/mL	244/299 (81.6)	235/301 (78.1)	−2.7 to 10.0
<50 copies/mL	232/299 (77.6)	222/301 (73.8)	−2.6 to 10.9
Week 144			
ITT, M = F, antiretroviral Switch = F analysis			
<400 copies/mL	211/299 (70.6)	193/301 (64.1)	−0.8 to 14.0
<50 copies/mL	203/299 (67.9)	188/301 (62.5)	−1.8 to 13.3
ITT, M = F			
<400 copies/mL	228/299 (76.3)	217/301 (72.1)	−2.6 to 11.3
<50 copies/mL	219/299 (73.2)	209/301 (69.4)	−2.9 to 11.4

Abbreviations: DF, disoproxil fumarate; HIV, human immunodeficiency virus; ITT, intent-to-treat; M = F, missing = failures; Switch = F, switch = failures.

*For week 48, there were missing data for 27 patients in the tenofovir DF group and 28 in the stavudine group. For week 96, there were missing data for 46 patients in the tenofovir DF group and 48 in the stavudine group. For week 144, there were missing data for 57 patients in the tenofovir DF group and 64 in the stavudine group.

†The confidence interval is based on a stratum weighted difference between the 2 treatment groups. Equivalence was predefined if the lower confidence bound was greater than -10%.

leading to treatment failure and a switch in therapy.

Through 144 weeks, data on subsequent antiretrovirals used following study regimen discontinuation were available for 41 (50%) of 82 patients in the tenofovir DF group and 46 (46%) of 100 in the stavudine group. The antiretroviral agents used (tenofovir DF vs stavudine groups) included zidovudine (16 vs 19), stavudine (14 vs 8), tenofovir DF (9 vs 15), abacavir (3 vs 6), didanosine (5 vs 4), and emtricitabine (1 vs 0). Tenofovir DF or stavudine were also used as a subsequent drug in patients who were originally randomized to those treatment groups since investigators were blinded to treatment assignment or patients may have discontinued due to non-tenofovir DF or non-stavudine-related toxicities such as efavirenz intolerance. Most patients continued on NNRTIs (22 tenofovir DF vs 25 stavudine) with fewer patients starting protease inhibitors (12 tenofovir DF vs 8 stavudine). The number of patients switching from efavirenz to nevirapine for efavirenz-associated neuropsychiatric toxicity was similar in both groups through week 144: 21 (7%) of

299 patients in the tenofovir DF group vs 26 (9%) of 301 patients in the stavudine group. There were 57 (19%) of 299 patients and 64 (21%) of 301 patients in the tenofovir DF and stavudine groups, respectively, with no viral load values at week 144. All but 3 of these patients also discontinued the study regimen prior to week 144. They were treated as failures or excluded in the ITT analysis.

In an ITT (missing = excluded [see Statistical Methods]) analysis, patients in both groups demonstrated a similar mean HIV RNA decrease from baseline ($3.1 \log_{10}$ copies/mL) at weeks 48 and 144. Through week 144, patients in the tenofovir DF and stavudine groups achieved a mean CD4 cell count increase of 263 and 283 cells/ μ L, respectively.

The calculated adherence rate using the rough estimate for adherence via the proxy approach based on the duration on study regimen was 98% for both the tenofovir DF and the stavudine group.

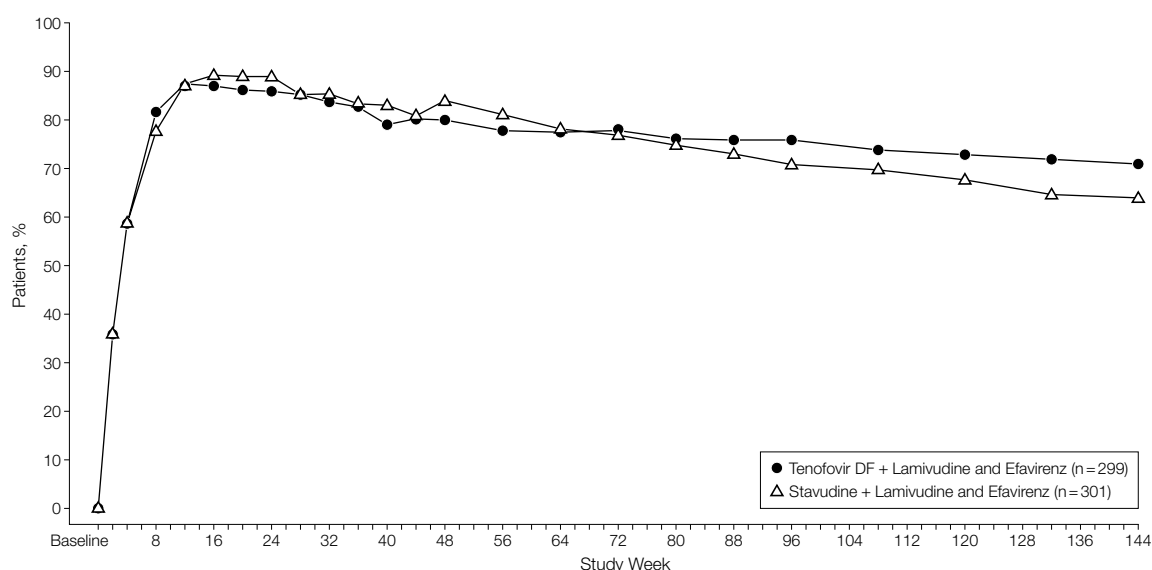
Resistance Analyses

Similar proportions of patients met the failure criteria for resistance analysis

through week 144: 47 (16%) of 299 patients in the tenofovir DF group and 49 (16%) of 301 patients in the stavudine group ($P = .91$). Baseline resistance will be addressed in separate analyses. Post-baseline and baseline genotypic data were obtained for all patients with virologic failure. Mutations conferring resistance to efavirenz and lamivudine were observed most frequently (TABLE 3).

The K65R mutation in HIV-1 reverse transcriptase can be selected by tenofovir DF and other NRTIs, and confers reduced antiviral activity to tenofovir, abacavir, didanosine, and lamivudine.²⁸⁻³² K65R mutants retain activity to thymidine analogues (zidovudine and stavudine).^{31,33-35} In this study, the K65R mutation occurred in 8 patients (7 prior to week 48, 1 from weeks 48-96, and none after week 96) administered tenofovir DF and 2 patients administered stavudine ($P = .06$). The K65R mutation was always accompanied by resistance to efavirenz or efavirenz plus lamivudine. Among patients in the tenofovir DF group who developed the K65R mutation, the median baseline HIV RNA level and CD4

Figure 2. Percentage of Patients With HIV RNA Levels of Less Than 400 Copies/mL Using Intent-to-Treat Analysis



HIV indicates human immunodeficiency virus; DF, disoproxil fumarate. Because the analysis represented in this Figure is intent-to-treat, the number of participants did not vary at each time point (Missing = Failure, Switch = Failure).

cell count were 246 000 copies/mL and 24 cells/ μ L, respectively. In addition, the K65R mutation was associated with a mean 1.3-fold decrease in susceptibility to tenofovir DF ($n=8$; range, 0.9-fold to 2.2-fold) without significant changes in susceptibility to zidovudine or stavudine. Reductions in susceptibility were observed for didanosine, abacavir, and lamivudine in vitro but only when the K65R mutation was present together with the lamivudine-associated M184V mutation (5 of 8 patients). One sample was reported as mixture of K65R/K (mutant and wild-type) along with M184V and had a fold-change of 0.9 fold (lowest of the group). Two samples exceeded the 1.4-fold cut-off for tenofovir in the PhenoSense assay (1.9- and 2.2-fold, one with M184V and one without). Overall, the M184V mutation appeared to be frequently responsible for improving the susceptibility to tenofovir in the presence of K65R, consistent with larger database analyses.³³ Among the 8 patients who had developed the K65R mutation in the tenofovir DF group, 5 achieved an HIV RNA level of less than 50 copies/mL on their investigator-chosen second regimen with a median follow-up of 155 weeks, 2 patients were without follow-up, and 1 was nonadherent. The second-line regimens chosen for each patient were unique but all included a protease inhibitor and 1 to 2 other NRTIs. Two continued tenofovir DF in the subsequent regimen; both achieved complete virologic suppression.

Safety

The overall incidence of grade 3 and 4 laboratory abnormalities and clinical adverse events was similar (TABLE 4). However, being in a tenofovir DF vs stavudine group was associated with a significantly lower mean increase from baseline in fasting triglycerides (+1 mg/dL [+0.01 mmol/L] [$n=170$] vs +134 mg/dL [+1.51 mmol/L] [$n=162$], $P<.001$), total cholesterol (+30 mg/dL [+0.78 mmol/L] [$n=170$] vs +58 mg/dL [+1.50 mmol/L] [$n=162$], $P<.001$), and directly measured low-density lipoprotein cholesterol (+14 mg/dL [+0.36

mmol/L] [$n=169$] vs +26 mg/dL [+0.67 mmol/L] [$n=161$], $P<.001$), and higher increase in high-density lipoprotein cholesterol (+9 mg/dL [+0.23 mmol/L] [$n=168$] vs +6 mg/dL [+0.16 mmol/L]

[$n=154$], $P=.003$). There were no significant differences between groups in fasting lipid profile at baseline. Investigators were allowed to prescribe lipid-lowering agents (consisting of a statin

Table 3. NRTI-Associated and NNRTI-Associated Resistance Mutations at Virologic Failure Through Week 144*

	No. of Mutations		P Value†
	Tenofovir DF + Lamivudine and Efavirenz (n = 299)	Stavudine + Lamivudine and Efavirenz (n = 301)	
Virologic failures	47‡	49	.91
Any EFV resistance mutation§	26‡	24	.77
Alone	7	6	.79
+ M184V/I	10	12	.83
+ K65R	3	1	.37
+ K65R + M184V/I	5	1	.12
+ Other NRTI resistance	1	4	.37
Any M184V/I mutation	18	17	.86
M184V/I alone	3	2	.86
Any K65R mutation	8	2	.06
K65R alone	0	0	>.99
Wild-type or as baseline	18	23	.52

Abbreviations: DF, disoproxil fumarate; EFV, efavirenz; NRTI, nucleoside analogue reverse transcriptase inhibitors; NNRTI, nonnucleoside reverse transcriptase inhibitors.

*No data were missing for these analyses. Any mutation is meant to specify all mutations of that type whether or not they occurred in conjunction with other mutations.

†Fisher exact test.

‡Three patients (all in tenofovir DF group) had more than a 4-fold EFV resistance at baseline (K103N/S, V106I+V179D, V108I+V179E) and developed additional EFV resistance.

§K103N, V106M, Y188C/L, or G190A/S/E/Q (K103N in 38 of 50 mutations; >50-fold EFV resistance with other mutations).

||Other NRTI resistance mutations are M41L, A62V, D67N/G, T69D/N/A, K70R/E, L74V/I, V75M/T/L, F77L, Y115F, F116Y, Q151M, L210W, T215Y/F, or K219 Q/E/N/R in reverse transcriptase.

Table 4. Grade 3 to 4 Adverse Events and Laboratory Abnormalities Through Week 144*

	No./Total (%)	
	Tenofovir DF + Lamivudine and Efavirenz (n = 299)	Stavudine + Lamivudine and Efavirenz (n = 301)
Patients with adverse events†	81/299 (27)	76/301 (25)
Rash	7/299 (2)	6/301 (2)
Bacterial infection	7/299 (2)	3/301 (1)
Depression	6/299 (2)	4/301 (1)
Pneumonia	5/299 (2)	6/301 (2)
Fever	5/299 (2)	2/301 (<1)
Patients with laboratory abnormalities‡	107/296 (36)	125/296 (42)
Creatine kinase	35/296 (12)	36/296 (12)
Amylase	27/296 (9)	23/296 (8)
Hematuria	19/296 (6)	22/296 (7)
Aspartate transaminase	15/296 (5)	20/296 (7)
Alanine transaminase	13/296 (4)	15/296 (5)
Neutrophils	10/296 (3)	2/296 (<1)
Triglycerides§	8/296 (3)	40/296 (14)

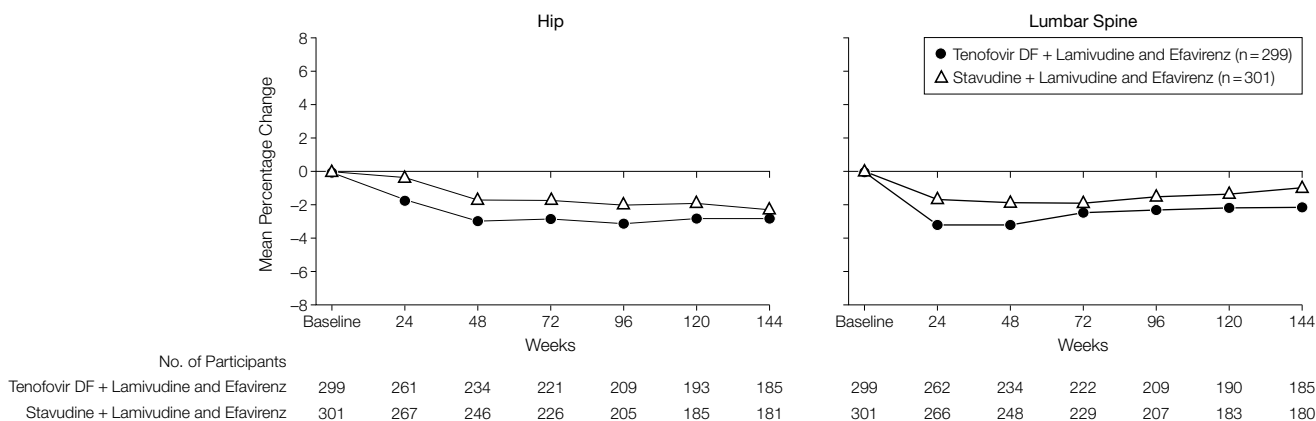
Abbreviation: DF, disoproxil fumarate.

*There were no missing data for the clinical adverse event analyses. For the laboratory abnormality analyses, data were missing for 3 patients in the tenofovir DF group and 5 in the stavudine group.

†Grade 3 to 4 adverse events reported if greater than or equal to 2% in either group.

‡Grade 3 to 4 laboratory abnormalities reported if greater than or equal to 3% in either group.

§ $P<.001$, Fisher exact test.

Figure 3. Mean Percentage Change in Hip and Lumbar Spine Bone Mineral Density From Baseline to Week 144

DF indicates disoproxil fumarate. The range of variability (SD) of percentage change in lumbar spine and hip bone mineral density was from 2.5% to 5.2%.

and/or a fibrate derivative) based on clinical judgment during the course of the study. A Kaplan-Meier analysis of time to use of first lipid-lowering agent (patients on lipid-lowering agents at baseline were excluded) showed that through 144 weeks, 38 of 301 patients (16%; 95% CI, 11.3%-20.7%) receiving stavudine initiated a lipid-lowering agent compared with 11 of 294 patients (5%; 95% CI, 2.0%-7.4%) receiving tenofovir DF ($P < .001$).

Toxicities that have been attributed to mitochondrial toxicity (peripheral neuropathy, lipodystrophy, and lactic acidosis) were reported in 100 patients, 83 (28%) of 301 in the stavudine group and 17 (6%) of 299 in the tenofovir DF group ($P < .001$). Neuropathy was observed in 31 (10%) of 301 and 9 (3%) of 299 patients in the stavudine and tenofovir DF groups, respectively ($P < .001$). Investigator-defined lipodystrophy was reported more often in patients receiving stavudine vs tenofovir DF (58 [19%] of 301 vs 9 [3%] of 299, respectively; $P < .001$). Using whole body DXA, significantly less total limb fat was observed in the stavudine group at week 96 (7.9 kg tenofovir DF [$n = 128$] vs 5.0 kg stavudine [$n = 134$], $P < .001$) and week 144 (8.6 kg tenofovir DF [$n = 115$] vs 4.5 kg stavudine [$n = 117$], $P < .001$). Investigator-defined lactic acidosis occurred in 3 patients, all of whom were in the stavudine group.

Patients in both treatment groups gained approximately 1.5 kg to 2.0 kg during the first 24 weeks. Thereafter, patients in the stavudine group progressively lost weight and essentially returned to baseline by week 144 (mean gain, 0.6 kg), whereas the patients in the tenofovir DF group had stable weight gain through week 144 (mean gain, 2.9 kg). The differences at weeks 48, 96, and 144 were statistically significant ($P = .04$, $P = .001$, and $P = .001$, respectively).

At week 144, a greater mean percentage decrease from baseline in bone mineral density was observed at the lumbar spine in the tenofovir DF group (-2.2% tenofovir DF vs -1.0% stavudine, $P = .001$) but similar changes were observed at the hip (-2.8% tenofovir DF vs -2.4% stavudine, $P = .06$). Notably, these decreases occurred through weeks 24 to 48 and stabilized through week 144 (FIGURE 3). Sixteen patients (11 in the stavudine group and 5 in the tenofovir DF group) developed bone fractures through 144 weeks. Nearly all fractures were related to trauma, except for a vertebral compression fracture for 1 patient in the stavudine group.

Through 144 weeks, the renal safety profile was similar between the 2 groups (TABLE 5). Two patients in each group developed a creatinine level of more than 2.0 mg/dL ($> 176.8 \mu\text{mol/L}$), while hypophosphatemia ($< 2.0 \text{ mg/dL}$

$< 176.8 \mu\text{mol/L}$) was observed in 10 patients receiving tenofovir DF and 8 patients receiving stavudine. The incidence of proteinuria and/or glycosuria was similar between the two groups. No patient developed Fanconi syndrome or discontinued from study due to tenofovir DF-related renal abnormalities. The renal safety profile associated with these drugs is addressed in more detail in other analyses.³⁶

A total of 20 patients (11 of 299 in the tenofovir DF group and 9 of 301 in the stavudine group, $P = .40$) reported 21 category C AIDS-defining conditions (based on the Centers for Disease Control and Prevention 1993 revised guidelines³⁷) at least 30 days after the first dose of study drugs. These category C conditions were disseminated *Mycobacterium avium* complex, tuberculosis, cytomegalovirus retinitis, *Pneumocystis jirovecii* pneumonia, progressive multifocal leukoencephalopathy, cryptococcosis, cryptosporidiosis, toxoplasmosis, Kaposi sarcoma, esophageal candidiasis, chronic herpes simplex, and recurrent pneumonia.

COMMENT

This is to our knowledge the first large 3-year, randomized, double-blind trial of antiretroviral therapy in treatment-naïve patients. The primary end point (ITT, M=F, antiretroviral Switch=F) analysis accounts for not only missing patient data but also antiretroviral

changes due to adverse effects, tolerability, or regimen potency. The primary end point was the achievement of an HIV RNA level of less than 400 copies/mL at week 48. By this analysis, the 95% CI slightly exceeded (by 0.4%) the lower predefined limit of -10%, narrowly missing the criteria for equivalence. However, equivalence was suggested in the secondary analyses using the more stringent measure of HIV RNA level of less than 50 copies/mL at week 48. Equivalence was also demonstrated at weeks 96 and 144. It is notable that the -10% lower predefined limit is more stringent than the -12% that has been reported in a similar randomized, double-blind antiretroviral-naive trial.²⁵

The high proportion of patients achieving HIV RNA level below limit of quantification through 144 weeks in both regimens is presumed to be due to a combination of the potency of the drugs used and the tolerability and simplicity of the regimens. Because the 2 regimens were so effective, treatment failure was uncommon. The development of the K65R mutation was less common than resistance to efavirenz or lamivudine. This mutation appears to be the only pathway to tenofovir resistance among treatment-naive patients, analogous to observations in treatment-experienced patients.^{17,18} The K65R mutation was observed in 8 patients (1 patient after week 48) failing therapy in the tenofovir DF group through 144 weeks, which represents less than 3% of the total number of patients treated or 17% of those experiencing virologic failure in the tenofovir DF group. All viral isolates expressing the K65R mutation retained susceptibility to zidovudine and stavudine, and possibly to abacavir, didanosine, and tenofovir. As a single mutation, K65R was not associated with a sufficient decrease in susceptibility to result in phenotypic resistance. However, when combined with M184V, the fold-change in susceptibility typically exceeded the assay cutoffs for abacavir and didanosine. These findings are consistent with recent published data

Table 5. Renal Parameters and Calculated Creatinine Clearance Through Week 144*

Renal Parameters	No./Total (%)	
	Tenofovir DF + Lamivudine and Efavirenz	Stavudine + Lamivudine and Efavirenz
Serum creatinine, >2.0 mg/dL	2/296 (<1)	2/296 (<1)
Serum phosphorus, <2.0 mg/dL	10/296 (3)	8/296 (3)
Proteinuria, >30 mg/dL	54/293 (18)	69/294 (23)
Glucosuria, ≥250 mg/dL	8/293 (3)	9/294 (3)

Calculated Creatinine Clearance, mL/min†	Mean (SD)	
	Tenofovir DF + Lamivudine and Efavirenz (n = 292)	Stavudine + Lamivudine and Efavirenz (n = 296)
Baseline	122 (29.1)	125 (33.1)
Mean change from baseline	+2 (21.3)	+7 (26.0)

Abbreviation: DF, disoproxil fumarate.
 SI conversion factors: To convert creatinine clearance to mL/s, multiply by 0.0167; serum creatinine to μmol/L, multiply by 88.4; serum phosphorus to mmol/L, multiply by 0.323.
 *There were no missing data for the clinical adverse event analyses. For the laboratory abnormality analyses, data were missing for 3 patients in the tenofovir DF group and 5 in the stavudine group.
 †Using Cockcroft-Gault equation.

using this assay.³³ Of the 8 patients who developed the K65R mutation, 5 achieved virologic success with subsequent second-line regimens (consisting of 2 unique NRTIs plus protease inhibitor) after a median follow-up of 155 weeks, demonstrating that second-line regimens can be effectively constructed after virologic failure with K65R and other regimen-associated mutations.

This trial demonstrated significantly more favorable lipid profiles in the tenofovir DF group and more patients required the addition of lipid-lowering agents in the stavudine group. The difference in lipid profiles between stavudine and tenofovir DF had not previously been well defined in a large double-blind study. Improvements in lipid abnormalities in patients switching from stavudine to tenofovir DF have recently been reported.³⁸

The overall incidence of adverse events attributed to mitochondrial toxicity was significantly more among patients receiving stavudine. Significantly less total limb fat and a greater incidence of lipodystrophy were observed in the stavudine group. In the absence of effective treatments for fat loss,^{39,40} avoiding antiretrovirals associated with fat loss may be the best practice. Finally, patients in the tenofovir DF group continued to gain weight

through 144 weeks, in contrast with the patients in the stavudine group who lost weight from week 24 to week 144. This initial weight gain through week 24 may arise from the initiation of antiretroviral therapy but the subsequent weight decline through 144 weeks may be a consequence of loss of peripheral limb fat.

Although decreased bone mineral density and nephrotoxicity have been observed in experiments with monkeys receiving high doses of subcutaneous tenofovir, in this 3-year trial decreases in bone mineral density were small and largely nonprogressive but significantly greater in the tenofovir DF group at the lumbar spine but not at the hip. There have been case reports of renal toxicity in patients with antiretroviral regimens containing tenofovir DF.⁴¹⁻⁴³ However, through 3 years in this study in patients with normal renal function at baseline, the renal safety profile was similar between the tenofovir DF and stavudine groups.

Although lamivudine and stavudine were administered twice daily in this study, lamivudine is now approved for once-a-day administration. A stavudine extended-release tablet has been approved for once-a-day administration but is not currently available. Once-daily regimens are likely to be easier to adhere to and also allow for directly ob-

served therapy in selected settings. Directly observed therapy has been shown to improve outcomes when used in the treatment of HIV infection.⁴⁴

These data support the use of tenofovir DF as a component of initial therapy for HIV infection. They also provide further support for the use of efavirenz-based regimens in this patient population. Although both tenofovir DF and stavudine performed equally well with respect to antiviral potency, the 3-year results indicate that tenofovir DF was associated with less toxicity than stavudine.

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Author Contributions: Dr Gallant had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition of data: Gallant, Staszewski, Pozniak, DeJesus, Suleiman, Miller, Coakley.

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Independent Statistical Review: Steven Grambow, PhD, Assistant Research Professor, Department of Biostatistics and Bioinformatics, Duke University Medical Center, was given full access to all of the data and was provided SAS statistical output by Gilead Sciences. Dr Grambow verified the accuracy of the primary results of the article and reviewed the appropriateness of the analytical approach for the primary efficacy measures and select secondary outcomes, and was compensated by Gilead Sciences for this statistical review.

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