ORIGINAL ARTICLE

Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV

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ABSTRACT

BACKGROUND

Durable suppression of replication of the human immunodeficiency virus (HIV) depends on the use of potent, well-tolerated antiretroviral regimens to which patients can easily adhere.

METHODS

We conducted an open-label, noninferiority study involving 517 patients with HIV infection who had not previously received antiretroviral therapy and who were randomly assigned to receive either a regimen of tenofovir disoproxil fumarate (DF), emtricitabine, and efavirenz once daily (tenofovir–emtricitabine group) or a regimen of fixed-dose zidovudine and lamivudine twice daily plus efavirenz once daily (zidovudine–lamivudine group). The primary end point was the proportion of patients without baseline resistance to efavirenz in whom the HIV RNA level was less than 400 copies per milliliter at week 48 of the study.

RESULTS

Through week 48, significantly more patients in the tenofovir–emtricitabine group reached and maintained the primary end point of less than 400 copies of HIV RNA per milliliter than did those in the zidovudine–lamivudine group (84 percent vs. 73 percent, respectively; 95 percent confidence interval for the difference, 4 to 19 percent; P=0.002). This difference excludes the inferiority of the tenofovir DF, emtricitabine, and efavirenz regimen, indicating a significantly greater response with this regimen. Significant differences were also seen in the proportion of patients with HIV RNA levels of less than 50 copies per milliliter (80 percent in the tenofovir–emtricitabine group vs. 70 percent in the zidovudine–lamivudine group; 95 percent confidence interval for the difference, 2 to 17 percent; P=0.02) and in increases in CD4 cell counts (190 vs. 158 cells per cubic millimeter, respectively; 95 percent confidence interval for the difference, 9 to 55; P=0.002). More patients in the zidovudine–lamivudine group than in the tenofovir–emtricitabine group had adverse events resulting in discontinuation of the study drugs (9 percent vs. 4 percent, respectively; P=0.02). In none of the patients did the K65R mutation develop.

CONCLUSIONS

Through week 48, the combination of tenofovir DF and emtricitabine plus efavirenz fulfilled the criteria for noninferiority to a fixed dose of zidovudine and lamivudine plus efavirenz and proved superior in terms of virologic suppression, CD4 response, and adverse events resulting in discontinuation of the study drugs. (ClinicalTrials.gov number, NCT00112047.)

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Highly active antiretroviral therapy has fundamentally altered the course of human immunodeficiency virus (HIV) infection by making it possible to suppress the plasma viral load below the limit of detection and to increase the number of CD4 cells.[1] The cornerstone of durable suppression of HIV replication is maintenance of a potent and tolerable regimen to which the patient can adhere. Adherence is necessary to prevent the emergence and replication of drug-resistant strains of the virus.[2]

Current guidelines for the management of HIV infection recommend the use of zidovudine or tenofovir disoproxil fumarate (DF) with lamivudine or emtricitabine as preferred nucleoside reverse-transcriptase inhibitors (NRTIs) along with the nonnucleoside reverse-transcriptase inhibitor (NNRTI) efavirenz.[3] Our study compared the efficacy and tolerability of two regimens, efavirenz plus a fixed dose of zidovudine and lamivudine or efavirenz plus tenofovir DF and emtricitabine.

METHODS

STUDY DESIGN

We conducted a prospective, randomized, multicenter noninferiority study comparing the regimens of tenofovir DF, emtricitabine, and efavirenz and a fixed dose of zidovudine and lamivudine plus efavirenz at sites in France, Germany, Italy, Spain, the United Kingdom, and the United States. An institutional review board or an ethics committee at each site approved the study protocol and the informed-consent form. Each participant gave written informed consent.

Adult patients (defined as persons 18 years of age or older) were considered for inclusion in this open-label study if they had never received antiretroviral treatment and had plasma HIV RNA levels greater than 10,000 copies per milliliter. Patients had to meet the following criteria: estimated glomerular filtration rate (GFR) (measured according to the Cockcroft–Gault method[4]) no lower than 50 milliliters per minute (0.84 milliliter per second); aminotransferase levels, no more than three times the upper limit of the normal range (alanine aminotransferase: 6 to 43 U per liter in men; 6 to 34 U per liter in women; aspartate aminotransferase: 11 to 36 U per liter in men; 9 to 34 U per liter in women); total bilirubin level, no more than 1.5 mg per deciliter (25.65 μmol per liter); absolute neutrophil count, no lower than 1000 per cubic millimeter; hemoglobin, no lower than 8.0 g per deciliter; platelet count, no lower than 50,000 per cubic millimeter; serum amylase level, no more than 1.5 times the upper limit of the normal range (28 to 100 U per liter for patients 18 to 50 years of age; 28 to 120 U per liter for patients 50 to 60 years of age; 28 to 150 U per liter for patients 60 to 70 years of age); and serum phosphorus level, no lower than 2.2 mg per deciliter (0.71 mmol per liter). No minimum CD4 cell count was required.

Patients were excluded if a new condition defining the acquired immunodeficiency syndrome had been diagnosed within 30 days before entry into the study (except on the basis of CD4 criteria), if they were receiving ongoing therapy with nephrotoxic drugs (e.g., aminoglycoside antibiotics, amphotericin B, cidofovir, cisplatin, foscarnet, and intravenous pentamidine) or agents that interact with efavirenz (e.g., astemizole, terfenadine, dihydroergotamine, ergotamine, midazolam, triazolam, cisapride, rifampin, ergonovine, and methylergonovine), if they were pregnant or lactating, if they had a history of clinically significant renal or bone disease or malignant disease other than Kaposi's sarcoma or basal-cell carcinoma, or if they had a life expectancy of less than one year. All patients were required to use an effective method of contraception while receiving the study treatment and for 30 days after completion of the study regimen. The trial was extended from 48 to 144 weeks.

Patients were stratified according to baseline CD4 cell count (<200 vs. ≥200 cells per cubic millimeter) but not according to site or country, and patients were randomly assigned centrally by an interactive voice-response system in a one-to-one ratio to receive either a once-daily regimen of efavirenz (600 mg; Sustiva, Bristol-Myers Squibb) plus tenofovir DF (300 mg; Viread, Gilead Sciences) and emtricitabine (200 mg; Emtriva, Gilead Sciences) as separate components (to be taken without regard to meals and preferably at bedtime) or to a regimen of efavirenz (600 mg) once daily and a fixed dose of zidovudine (300 mg) and lamivudine (150 mg; Combivir, GlaxoSmithKline) twice daily, in an open-label manner. Nevirapine (200 mg; Viramune, Boehringer Ingelheim) twice daily could be substituted for efavirenz in the presence of intolerable central nervous system side effects.

Clinical examinations and laboratory analyses were conducted at the screening visit, before the baseline visit, at the baseline visit (when administration of the study drugs was initiated), at weeks 2, 4, and 8, and then every 8 weeks through the 48 weeks of the study or, for patients who discontinued participation in the study early, at 30 days after discontinuation. Adherence was assessed on the basis of pill counts at each visit by study coordinators or nurses at each site. A physical examination (including evaluation for hyperpigmentation) was performed at each visit. Other assessments included CD4 cell counts, measurement of plasma HIV RNA levels (Amplicor HIV-1 Monitor Test, version 1.5, Roche Diagnostics), hematology and plasma chemistry profiles, urinalysis, and a fasting lipid panel. The protocol was amended before week 48, at which point lipodystrophy assessments by whole-body dual-energy x-ray absorptiometry were performed in a subgroup of 100 patients. These scans were read centrally by radiologists who were unaware of the treatment assignments.

The clinical data were gathered by Charles River Laboratories. The study was designed by and the data were analyzed at Gilead Sciences. All authors had full access to the data and vouch for the accuracy and completeness of the data and the analyses. The manuscript was written by all the authors, each of whom contributed to the drafts and revisions and all of whom approved the final manuscript.

EFFICACY ANALYSIS

The primary objective was to assess the noninferiority of the regimen of tenofovir DF, emtricitabine, and efavirenz to the regimen of zidovudine, lamivudine, and efavirenz as measured by HIV RNA levels of less than 400 copies per milliliter through week 48, defined according to the algorithm of the Food and Drug Administration (FDA) for the time to loss of virologic response, which requires confirmation (two consecutive values) of response or of no response (missing data or early termination of participation in the study was considered to be failure).[5] The 487 eligible patients without baseline resistance to efavirenz who underwent randomization and received treatment were the predefined population for the primary end-point analysis. The secondary objective was to assess the noninferiority of tenofovir DF, emtricitabine, and efavirenz to zidovudine, lamivudine, and efavirenz as assessed by HIV RNA levels of less than 50 copies per milliliter and changes in the CD4 cell count.

SAFETY ANALYSIS

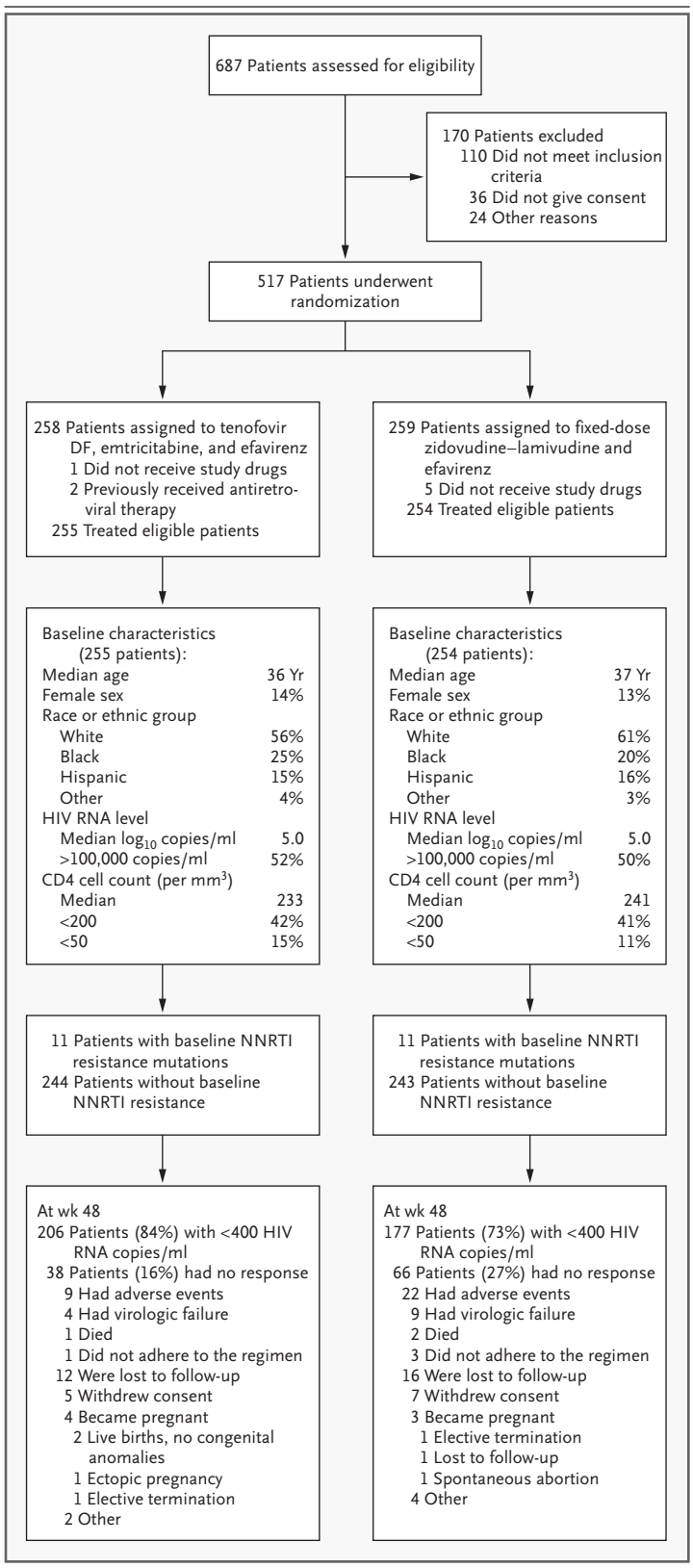
All patients who received at least one dose of the study medications were included in the primary safety analysis, which evaluated events that occurred from the initiation of the assigned study regimen to 30 days after discontinuation of the regimen. The severity of adverse events and laboratory abnormalities was graded according to a modified Common Toxicity Criteria of the National Institutes of Allergy and Infectious Diseases.[6]

RESISTANCE ANALYSIS

HIV type 1 genotyping was performed on blood samples obtained at baseline in batches for all patients. Genotypic and phenotypic resistance analyses were also performed for patients who met the following criteria: they continued to receive the assigned study drugs and had no less than 400 copies per milliliter of HIV RNA as measured on at least two consecutive visits after achieving levels no more than 400 copies per milliliter on at least one occasion (viral rebound); they continued the assigned study drugs and had HIV RNA levels no lower than 400 copies per milliliter at week 48; or they discontinued the assigned study drugs before week 48 and had HIV RNA levels no lower than 400 copies per milliliter on their last visit (before discontinuing the study drugs).

STATISTICAL ANALYSIS

The regimen of tenofovir DF, emtricitabine, and efavirenz was to be considered not inferior to the regimen of zidovudine, lamivudine, and efavirenz if the lower bound of the 95 percent confidence interval for the difference between the two groups, those receiving tenofovir DF, emtricitabine, and efavirenz (the tenofovir–emtricitabine group) minus those receiving zidovudine, lamivudine, and efavirenz (the zidovudine–lamivudine group) for the primary end point (in the proportion of patients with an HIV RNA level of less than 400 copies per milliliter) was no lower than –13 percent. Assuming a response rate of 70 percent at week 48 for the zidovudine, lamivudine, and efavirenz regimen and a one-sided type I error of 2.5 percent, the planned sample size of 500 patients provided the study with 85 percent power to dem-



onstrate the noninferiority of the tenofovir DF, emtricitabine, and efavirenz regimen. Substitution of nevirapine for efavirenz was not classified as treatment failure. The two treatment groups were compared with use of the Cochran–Mantel–Haenszel test for categorical data and by the Wilcoxon rank-sum test for continuous data. Analyses of CD4 data and safety laboratory data included patients who received the assigned regimens. All statistical analyses were performed with the use of SAS software, version 8.2 (SAS Institute), at Gilead Sciences. Two interim analyses (submitted to health regulatory authorities) at weeks 16 and 24 were performed by Gilead Sciences. There were no stopping rules. All reported P values are two-sided and were not adjusted for multiple testing.

RESULTS

During the recruitment period from July 2003 to January 2004, 517 patients at 67 sites were randomly assigned to receive efavirenz and either tenofovir DF and emtricitabine or a fixed dose of zidovudine and lamivudine. All visits for the 48-week study were completed by December 2004. The disposition and baseline characteristics of the two treatment groups are shown in Figure 1. Eight patients were excluded from the intention-to-treat population, two because they had previously received antiretroviral treatment and six because they never received the assigned study medication. The median number of patients per site was 12 (range, 1 to 38). In 19 patients (10 assigned to the tenofovir–emtricitabine group and 9 assigned to the zidovudine–lamivudine group), nevirapine was substituted for efavirenz because of treatment-related side effects of efavirenz.

During the trial, 22 patients (11 in each of the two groups) were found to have HIV mutations associated with resistance to efavirenz (K103N in 17 patients) at entry into the study. For this reason, data on two populations of eligible, treated patients randomly assigned to treatment were analyzed statistically — 509 patients with or with-

Figure 1. Characteristics of Patients at Baseline and at Week 48.

Race or ethnic group was determined by the investigators. HIV denotes human immunodeficiency virus, and NNRTI nonnucleoside reverse-transcriptase inhibitor.

out baseline NNRTI resistance and 487 patients without baseline NNRTI resistance.

RESPONSE TO TREATMENT

At week 48, 206 of the 244 patients (84 percent) in the tenofovir–emtricitabine group and 177 of the 243 patients in the zidovudine–lamivudine group (73 percent) reached and maintained HIV RNA levels of less than 400 copies per milliliter, which was the primary end point (Fig. 2). The 95 percent confidence interval for the difference between the two groups was 4 to 19 percent (P=0.002), which excludes the inferiority of the tenofovir DF, emtricitabine, and efavirenz regimen. The confidence interval for the difference also excludes zero, indicating a significantly greater response with the tenofovir DF, emtricitabine, and efavirenz regimen. At week 48, 194 of 244 patients (80 percent) in the tenofovir–emtricitabine group and 171 of 243 patients in the zidovudine–lamivudine group (70 percent) reached and maintained HIV RNA levels of less than 50 copies per milliliter. The 95 percent confidence interval for the difference between the two groups was 2 to 17 percent (P=0.02), which excludes the inferiority of the tenofovir DF, emtricitabine, and efavirenz regimen and indicates a significantly greater response with this regimen. Similar statistically significant differences were observed in the intention-to-treat population (509 patients) on the basis of HIV RNA levels of less than 400 copies per milliliter (81 percent in the tenofovir–emtricitabine group vs. 70 percent in the zidovudine–lamivudine group; 95 percent confidence interval for the difference, 3 to 18 percent; P=0.005) or HIV RNA levels of less than 50 copies per milliliter (77 percent vs. 68 percent, respectively; 95 percent confidence interval for the difference, 1 to 16 percent; P=0.03).

At week 48, the patients treated with the tenofovir DF, emtricitabine, and efavirenz regimen had significantly greater increases from baseline in absolute CD4 cell counts (mean increase, 190 vs. 158 cells per cubic millimeter; 95 percent confidence interval for the difference, 9 to 55; P=0.002) and in median percentages of CD4 lymphocytes (CD4 percentage) (11 percent in the tenofovir–emtricitabine group vs. 10 percent in the zidovudine–lamivudine group, P=0.02). On the basis of pill counts, the mean adherence to treatment

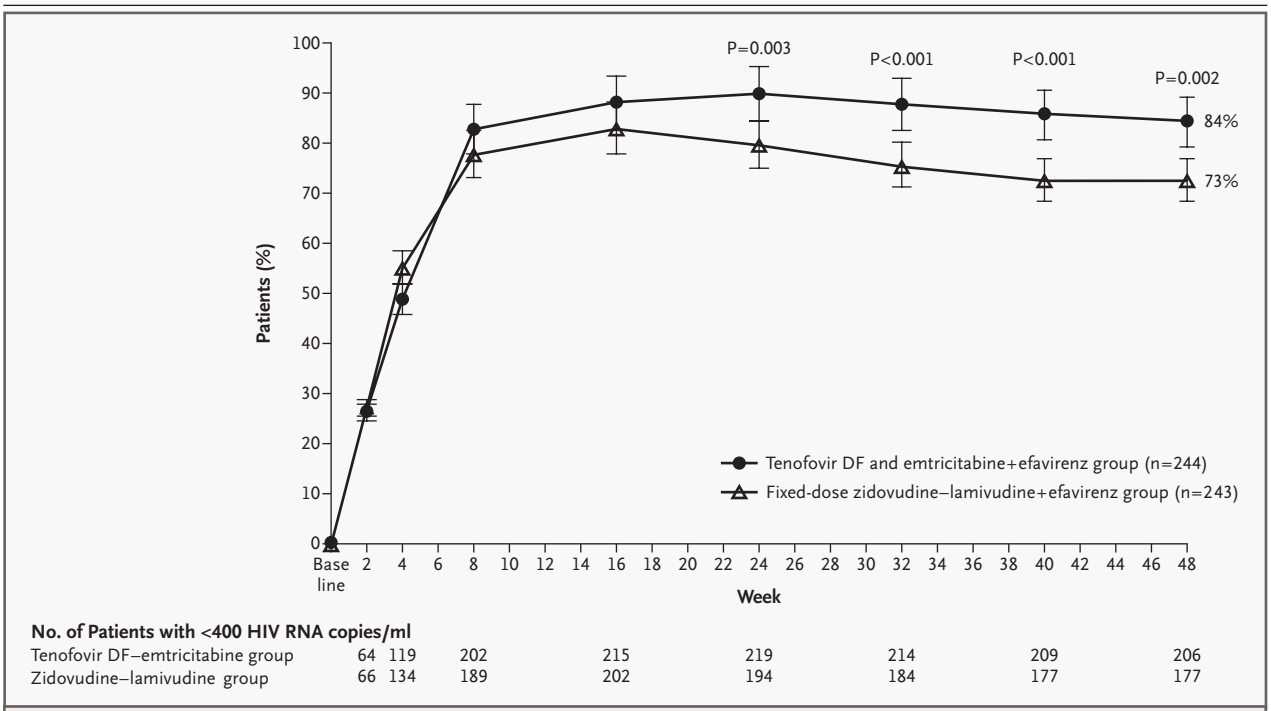


Figure 2. Proportion of Patients with HIV RNA Levels below 400 Copies per Milliliter.

HIV RNA responses were defined according to the Food and Drug Administration's algorithm for the time to loss of viral response. P values are for the comparison between the two treatment groups.

was greater among patients receiving the tenofovir DF, emtricitabine, and efavirenz regimen (90 percent) than among those receiving the zidovudine, lamivudine, and efavirenz regimen (87 percent, P=0.04).

GENOTYPIC ANALYSIS

Genotypic data were collected on 35 patients who met the criteria for resistance analyses. Overall, there were no significant differences between the two groups (Table 1). Of mutations resulting from exposure to reverse-transcriptase inhibitors, M184V/I, which can be selected by either lamivudine or emtricitabine, was detected in two patients in the tenofovir–emtricitabine group, as compared with seven patients in the zidovudine–lamivudine group. K65R, which can be selected by tenofovir DF, was not detected in the 34 patients for whom genotypic data were available (12 patients in the tenofovir–emtricitabine group and 22 patients in the zidovudine–lamivudine group).

There were no significant differences in the frequency of viral rebound (confirmed by HIV RNA levels of >400 copies per milliliter) between the two groups (3 percent [7 of 244 patients] in the zidovudine–lamivudine group and 1 percent [2 of 243 patients] in the tenofovir–emtricitabine group, P=0.11). In eight of the nine patients who had viral rebound, resistance mutations developed (two patients in the tenofovir–emtricitabine group [one with a wild-type mutation, the other with an efavirenz-resistance mutation] and seven patients in the zidovudine–lamivudine group [all seven had an efavirenz-resistance mutation, five had M184V/I, and one had a thymidine analogue mutation]).

Table 1. Genotypic Analysis through 48 Weeks of Treatment.*

Variable	Tenofovir–Emtricitabine Group (N=244)	Zidovudine–Lamivudine Group (N=243)
No. of patients in genotypic analysis	12	23†
Genotype		
Wild-type	3	5
Any resistance mutation	9	17
K65R	0	0
Any M184V/I	2	7
Any efavirenz resistance mutation‡	9	16
Efavirenz resistance mutation plus M184V	2	6
Any thymidine analogue resistance mutation	0	1

* Twenty-two patients with baseline NNRTI resistance were excluded from the analysis.
† Genotyping of one patient in the zidovudine–lamivudine group failed for technical reasons.
‡ Of mutations resulting from exposure to the nonnucleoside reverse-transcriptase inhibitor efavirenz, the K103N mutation developed in 21 of 25 patients; others that developed include K101E, K103E, V108I/M, V179D, Y188H, G190A/S/E, P225H, and M230L.

SAFETY AND TOLERABILITY

The safety analysis is based on 511 patients who received any study medications (Fig. 1). Adverse events (severity grades 2 through 4 according to the modified Common Toxicity Criteria) occurred in 163 of 257 patients (63 percent) in the tenofovir–emtricitabine group and in 161 of 254 patients (63 percent) in the zidovudine–lamivudine group (Table 2). Laboratory abnormalities (grades 2 through 4) arose in 142 of 254 patients (56 percent) in the tenofovir–emtricitabine group and 142 of 251 patients (57 percent) in the zidovudine–lamivudine group (Table 2).

Significantly more patients in the zidovudine–lamivudine group had adverse events that resulted in discontinuation of study medications (P=0.02) (Fig. 1 and Table 3). The most common cause of discontinuation of the zidovudine, lamivudine, and efavirenz regimen was marked anemia (14 patients vs. 0 in the tenofovir–emtricitabine group; P<0.001). Among these 14 patients, the median hemoglobin level at baseline was 13.8 g per deciliter (range, 10.8 to 16.0), which dropped to a nadir of 6.9 g per deciliter (range, 3.7 to 9.3) before discontinuation of the zidovudine, lamivudine, and efavirenz regimen. Seven patients received erythropoietin before discontinuation and seven patients received transfusions. Of these 14 patients, 1 was black and 13 were male; the mean CD4 count at baseline was 95 cells per cubic millimeter (range, 4 to 294). There were no obvious coexisting medical conditions or non-antiretroviral medications that might have contributed to their anemia.

We closely followed markers of renal function. Renal safety was similar in the two groups over the 48 weeks of the study, and no patient discontinued study drugs because of renal events. There were changes in the two groups in the median GFR, as measured by the Cockcroft–Gault method[4] or the modification of diet in renal disease[7] equations, from baseline to week 48 (Cockcroft–

Gault method: change in GFR in the tenofovir–emtricitabine group, –1 ml per minute [–0.02 ml per second]; and in the zidovudine–lamivudine group, +6 ml per minute [0.1 ml per second]; modification of diet in renal disease equations: change in the two groups, less than –1 ml per minute per 1.73 m^2). There were no confirmed abnormalities graded for severity in serum levels of creatinine or phosphorus in the tenofovir–emtricitabine group, but toxic levels were found in three patients (1 percent) in the zidovudine–lamivudine group. There were no cases of Fanconi's syndrome.

Hyperpigmentation was confirmed or could not be ruled out in seven patients in the tenofovir–emtricitabine group and four in the zidovudine–lamivudine group (P=0.54). All cases were mild except that in one patient in the zidovudine–lamivudine group. No patient discontinued the study drugs because of hyperpigmentation.

Patients in the tenofovir–emtricitabine group had a lower mean increase from baseline in fasting total cholesterol levels (21 mg per deciliter [0.54 mmol per liter]) than did those in the zidovudine–lamivudine group (35 mg per deciliter [0.91 mmol per liter]; P<0.001) and fasting low-density lipoprotein cholesterol levels (13 mg per deciliter [0.34 mmol per liter] vs. 20 mg per deciliter [0.52 mmol per liter]; P=0.01). The increase from baseline in fasting high-density lipoprotein levels was significantly higher in the zidovudine–lamivudine group (9 mg per deciliter [0.23 mmol per liter]) than in the tenofovir–emtricitabine group (6 mg per deciliter [0.16 mmol per liter], P=0.004). The increase from baseline in mean fasting triglyceride levels was not significantly different in the two groups (3 mg per deciliter [0.03 mmol per liter] in the tenofovir–emtricitabine group vs. 31 mg per deciliter [0.35 mmol per liter] in the zidovudine–lamivudine group, P=0.38).

Patients in the two groups entered the trial with the same mean weight (76 kg [168 lb]). Through week 48, patients in the tenofovir–emtricitabine group had an increase from baseline in mean

Table 2. Adverse Events (Grades 2 through 4) and Laboratory Abnormalities (Grades 2 through 4) through 48 Weeks.*

Variable	Tenofovir–Emtricitabine Group	Zidovudine–Lamivudine Group
	no./total no. of patients (%)	
Adverse event	163/257 (63)	161/254 (63)
Dizziness	21/257 (8)	18/254 (7)
Nausea	20/257 (8)	15/254 (6)
Diarrhea	17/257 (7)	10/254 (4)
Fatigue	18/257 (7)	14/254 (6)
Depression	11/257 (4)	17/254 (7)
Headache	13/257 (5)	10/254 (4)
Rash	12/257 (5)	10/254 (4)
Insomnia	11/257 (4)	13/254 (5)
Anemia	1/257 (<1)	13/254 (5)
Laboratory abnormality†	142/254 (56)	142/251 (57)
Amylase (≥132 U/liter)	44/254 (17)	32/251 (13)
Triglycerides (≥400 mg/dl)	34/254 (13)	34/251 (14)
Creatine phosphokinase (men, ≥499 U/liter; women, ≥424 U/liter)	31/254 (12)	38/251 (15)
Neutrophils (<1000/mm^3)	18/254 (7)	35/251 (14)
Hematuria (>10 RBC/HPF)	22/254 (9)	15/251 (6)
Alanine aminotransferase (men, ≥109 U/liter; women, ≥86 U/liter)	20/254 (8)	18/251 (7)
Aspartate aminotransferase (men, ≥91 U/liter; women, ≥86 U/liter)	18/254 (7)	18/251 (7)

* Values are for events that occurred in not less than 5 percent of patients in either of the two treatment groups. To convert the value for triglycerides to millimoles per liter, multiply by 0.0113. RBC denotes red cell, and HPF high-power field.
† The numbers are actual levels.

Table 3. Adverse Events Resulting in Discontinuation in the Safety Population through 48 Weeks.*

Event	Tenofovir–Emtricitabine Group (N=257)	Zidovudine–Lamivudine Group (N=254)
	number (percent)	
Any adverse event	10 (4)	23 (9)
Anemia	0	14 (6)
Nausea	1 (<1)	4 (2)
Fatigue	0	3 (1)
Vomiting	0	2 (1)
Rash (NNRTI-associated)	2 (1)	0
Neutropenia	0	2 (1)

* Values are for events that occurred in two or more patients in either of the two treatment groups. NNRTI denotes nonnucleoside reverse-transcriptase inhibitor.

weight of 2.1 kg (4.6 lb), as compared with 1.1 kg (2.4 lb) among those in the zidovudine–lamivudine group (P=0.14). At week 48, as measured by dual-energy x-ray absorptiometry, total limb fat was significantly less in a subgroup of 49 patients in the zidovudine–lamivudine group who underwent scanning than in a subgroup of 51 patients in the tenofovir–emtricitabine group (mean, 6.9 kg [15.2 lb] vs. 8.9 kg [19.6 lb]; P=0.03).

DISCUSSION

In this large, randomized trial, the tenofovir DF, emtricitabine, and efavirenz regimen fulfilled the criteria for noninferiority to the zidovudine, lamivudine, and efavirenz regimen. The results also indicate significantly greater responses to the tenofovir DF, emtricitabine, and efavirenz regimen (as defined by the FDA's algorithm for the time to loss of viral response) as compared with the well-established regimen of zidovudine, lamivudine, and efavirenz.[8,9] The regimens also differed in their effect on immune reconstitution: in the tenofovir–emtricitabine group, there was a significantly greater increase in the total CD4 cell counts and the CD4 percentages.

The data collected over the 48 weeks of the study indicate greater tolerability of the tenofovir DF and emtricitabine backbone and the potential for clinically significant anemia associated with zidovudine. These results are not surprising, because the efficacy, tolerability, and toxicity profiles of these drugs are consistent with profiles observed in other studies.[8-11] Renal adverse events have been reported with antiretroviral regimens containing tenofovir DF.[12-16] However, the overall renal safety profile in the group receiving tenofovir DF in our study was favorable, as has been reported in other long-term studies of this agent.[10,17]

In a subgroup of patients who underwent dual-energy x-ray absorptiometry, those in the tenofovir–emtricitabine group had significantly more limb fat at week 48 than those in zidovudine–lamivudine group. Declines in limb fat have not been seen in patients receiving initial long-term antiretroviral therapy with a tenofovir DF, lamivudine, and efavirenz regimen.[10,17] Fat loss in patients receiving a regimen containing zidovudine has been previously reported.[18,19] Lipoatrophy has also been associated in multiple studies with the use of stavudine, another thymidine analogue.[20-22] Although some studies have reported improvement in lipoatrophy with the substitution of other NRTIs for thymidine analogues, the increase in limb fat was <1 kg (2.2 lb) after 48 weeks.[23-25] Thus, avoiding therapy with antiretroviral agents that are associated with lipoatrophy may be preferable to changing therapy in response to lipoatrophy. We do not yet know whether data from this study at 96 and 144 weeks will show significant differences in long-term toxic effects, specifically lipoatrophy and hyperlipidemia, as was seen in Study 903 (a three-year, double-blind comparison between an antiretroviral regimen consisting of stavudine, lamivudine, and efavirenz with a tenofovir DF, lamivudine, and efavirenz regimen).[10] A preliminary analysis of a subgroup of 255 patients in our study population who have completed 96 weeks of therapy suggests that the differences in limb fat seen at 48 weeks persist, with further loss of limb fat as measured by dual-energy x-ray absorptiometry in the zidovudine–lamivudine group.

The results with regard to resistance were unexpected. The lack of emergence of the K65R mutation in the tenofovir–emtricitabine group is in contrast to the results of Study 903, in which 7 of 299 patients had K65R mutations at 48 weeks.[10,26] In addition, the M184V mutation occurred in only two patients in the tenofovir–emtricitabine group, as compared with seven in the zidovudine–lamivudine group. Whether these differences can be explained by the greater potency or the longer half-life of emtricitabine, as compared with lamivudine, is unclear. Approxi-

mately 5 percent of the patients in our international, multicenter study who had not previously received antiretroviral therapy had NNRTI resistance at baseline. Consistent with published international guidelines, these data provide support for baseline resistance testing before the initiation of antiretroviral therapy.[27]

Tenofovir DF and emtricitabine were administered once daily as separate agents in this trial, but a fixed-dose combination of emtricitabine and tenofovir DF that may further improve adherence is now available.

This study, involving HIV-infected patients who had not previously received antiretroviral therapy, directly compared the efficacy and safety at 48 weeks of two antiretroviral regimens that are now classified as "preferred" in the treatment guidelines of the Department of Health and Human Services.[3] The superior outcome in the tenofovir–emtricitabine group in the study provides further support for the use of this regimen in patients who have not previously received antiretroviral therapy. These findings have important implications for the choice of an initial nucleoside-analogue backbone in the treatment of such patients.

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APPENDIX

In addition to the authors, other participants in the Study 934 Group were the following: A. Diamond AIDS Research Center, New York City — M. Markowitz; AIDS Healthcare Foundation, Los Angeles — H. Khanlou; Albany Medical College, Albany, N.Y. — G. Drusano, R. Liporace; Beth Israel Deaconess Medical Center, Boston — M. Albrecht; Boston University Medical Center, Boston — P. Skolnik; Brighton and Sussex University Hospitals, Brighton, United Kingdom — M. Fisher; Capital Medical Associates, Washington, D.C. — B. Rashbaum; Centre Hospitalier Universitaire de Nice-L'Archet, Nice, France — P. Dellamonica; Community Research Initiative of New England, Springfield, Mass. — A.B. Morris; CORE Center, Chicago — D.E. Barker; Drexel University College of Medicine, Philadelphia — D.F. Alvarez; Dupont Circle Physicians Group, Washington, D.C. — D. Ward; Emory University and Grady Infectious Disease Program, Atlanta — J.L. Lennox; Ft. Lauderdale, Fla. — G. Richmond; Hampton Roads Medical Specialists, Hampton, Va. — S.L. Green; Henry Ford Hospital, Detroit — I. Brar; Hôpital Gui-de-Chauliac, Montpellier, France — J. Reynes; Hôpital Purpan, Toulouse, France — P. Massip; Hôpital Tenon, Paris — W. Rozenbaum; Hospital de la Santa Creu i Sant Pau, Barcelona — P. Domingo; Hospital St. Raffaele University, Milan — A. Lazzarin; Hospital Vall d'Hebron, Barcelona — E. Ribera; Infectious Disease of Indiana, Indianapolis — J. Fraiz; Infectious Disease Research Institute, Tampa, Fla. — B.G. Yangco; Infectious Disease Specialists of Atlanta, Decatur, Ga. — R.H. Dretler; Infectious Diseases Associates of Houston, Houston — T.C. Samo; Infectious Diseases Associates, Sarasota, Fla. — V. Vega; IPM Study Center, Hamburg, Germany — L. Weitner; Jemsek Clinic, Huntersville, N.C. — J.G. Jemsek; Johann Wolfang Goethe-Universität, Frankfurt, Germany — S. Staszewski; Kaiser Permanente Medical Group, Sacramento, Calif. — J. Flamm; Kaiser Permanente Medical Group, San Francisco — S. Follansbee; Living Hope Clinical Foundation, Long Beach, Calif. — S. Schneider; Louisiana State University Health Sciences Center HIV Outpatient Clinic Clinical Research, New Orleans — R. Clark; Massachusetts General Hospital, Boston — K. Zachary; Montrose Clinic, Houston — S. Schrader; N.C. Bellos, Dallas; North Broward Hospital District, Ft. Lauderdale, Fla. — M. Sension; North Texas Center for AIDS and Clinical Research, Dallas — J.D. Brand; NorthStar Medical Center, Chicago — D.S. Berger; Ohio State University, Columbus — M.F. Para; Ospedale Amedo di Savoia, Torino, Italy — G. Di Perri; Pacific Horizon Medical Group, San Francisco — L. Thornton; Pacific Oaks Medical Group, Beverly Hills, Calif. — P.R. Wolfe; Phoenix Body Positive, Phoenix, Ariz. — R.A. Myers; Puerto Rico Network in Clinical Research on AIDS, San Juan — L. Santiago; Rose Medical Center, Denver — B. Young; Royal Free Hospital, London — M.A. Johnson; San Juan Veterans Affairs Hospital, San Juan, Puerto Rico — C.R. Rivera-Vázquez, S. Saavedra; South Florida Clinical Research, Atlantis, Fla. — L.M. Bush; St. Joseph's Comprehensive Research Institute, Tampa, Fla. — D. Norris; St. Thomas' Hospital, London — A. de Ruiter; Steinhart Medical Associates and Mercy Hospital, Miami — C. Steinhart; Therapeutic Concepts, Houston — J.C. Gathe; Tower ID [Infectious Disease] Medical Associates, Los Angeles — R. Stryker; Treasure Coast Infectious Disease Consultants, Vero Beach, Fla. — G. Pierone; University of California, San Diego — S. Letendre; University of North Carolina at Chapel Hill, Chapel Hill — D.A. Wohl; University of Southern California Keck School of Medicine, Los Angeles — K.E. Squires, R. Larsen; University of Texas Health Science Center at Houston, Houston — B.J. Barnett; Veterans Affairs Medical Center Washington, D.C. — A.M. Labriola; Wake Forest University School of Medicine, Winston-Salem, N.C. — S. Pegram; Gilead Sciences, Foster City, Calif. — S.-S. Chen, S.-M. Chuang, B. Doherty, V. Ho, H.S. Jaffe, S. Liaw, V. Marchesin, N.A. Margot, G. Mattiuzzo, M.D. Miller, J.F. Rooney, J. Sayre, S. Wong, M. Wulfsohn.

REFERENCES

1. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. N Engl J Med 1998;338:853-60.

2. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance. Clin Infect Dis 2003;37:1112-8.

3. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Washington, D.C.: Department of Health and Human

Services, December 23, 2005. (Accessed December 23, 2005, at http://AIDSinfo.nih.gov.)
4. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31-41.
5. U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Guidance for industry: antiretroviral drugs using plasma HIV RNA measurements — clinical considerations for accelerated and traditional approval. Washington, D.C.: Department of Health and Human Services, October 2002. (Accessed December 23, 2005, at http://www.fda.gov/cder/guidance.)
6. Regulatory Compliance Center. Division of AIDS (DAIDS) table of grading severity of adult adverse experiences. Bethesda, Md.: National Institute of Allergy and Infectious Diseases, August 1992. (Accessed December 23, 2005, at http://rcc.tech-res-intl.com/tox_tables.htm.)
7. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Ann Intern Med 1999;130:461-70.
8. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med 1999;341:1865-73.
9. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. N Engl J Med 2003;349:2293-303.
10. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs. stavudine in combination therapy in antiretroviral naïve patients: a 3-year randomized trial. JAMA 2004;292:191-201.
11. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV infected adults. Clin Infect Dis 2004;39:1038-46.
12. Verhelst D, Monge M, Meynard JL, et al. Fanconi syndrome and renal failure induced by tenofovir: a first case report. Am J Kidney Dis 2002;40:1331-3.
13. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis 2003;36:1070-3.
14. Creput C, Gonzalez-Canali G, Hill G, Piketty C, Kazatchkine M, Nochy D. Renal lesions in HIV-1-positive patient treated with tenofovir. AIDS 2003;17:935-7.
15. Rollot F, Nazal EM, Chauvelot-Moachon L, et al. Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: the role of lopinavir-ritonavir-didanosine. Clin Infect Dis 2003;37:e174-e176.
16. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis 2005;40:1194-8.
17. Cassetti I, Madruga JVR, Suleiman JMAH, Zhong L, Enejosa J, Cheng AK. Tenofovir DF in combination with lamivudine and efavirenz in antiretroviral naive patients: a 4 year follow-up. In: Program and abstracts of the 3rd IAS [International AIDS Society] Conference on HIV Pathogenesis and Treatment, Rio de Janeiro, Brazil, July 24–27, 2005.
18. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS 2000;14:1309-16.
19. Bogner JR, Vielhauer V, Beckman RA, et al. Stavudine versus zidovudine and the development of lipodystrophy. J Acquir Immune Defic Syndr 2001;27:237-44.
20. Dube MP, Parker RA, Tebas P, et al. Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides. AIDS 2005;19:1807-18.
21. Saint-Marc T, Partisani M, Poizot-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. AIDS 2000;14:37-49.
22. Heath KV, Hogg RS, Singer J, Chan KJ, O'Shaughnessy MV, Montaner JS. Antiretroviral treatment patterns and incident HIV-associated morphologic and lipid abnormalities in a population-based cohort. J Acquir Immune Defic Syndr 2002;30:440-7.
23. McComsey GA, Ward DJ, Hessenthaler SM, et al. Improvement in lipoatrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. Clin Infect Dis 2004;38:263-70.
24. Martin A, Smith DE, Carr A, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. AIDS 2004;18:1029-36.
25. Moyle G, Sabin C, Cartledge J, et al. A 48 week, randomized, open-label comparative study of tenofovir DF vs. abacavir as substitutes for a thymidine analog in persons with lipoatrophy and sustained virologic suppression of HAART. In: Program and abstracts of the 12th Conference on Retroviruses and Opportunistic Infections, Boston, February 22–25, 2005. abstract.
26. Miller MD, Margot NA, McColl DJ, Tran S, Coakley DF, Cheng AK. Genotypic and phenotypic characterization of virologic failure through 48 weeks among patients taking tenofovir DF or stavudine in combination with lamivudine and efavirenz. Presented at the 6th International Congress on Drug Therapy in HIV Infection, Glasgow, United Kingdom, November 17–21, 2002.
27. Hirsch MS, Brun-Vezinet F, Clotet B, et al. Antiretroviral drug resistance testing in adults infected with human immunodeficiency virus type 1: 2003 recommendations of an International AIDS Society-USA Panel. Clin Infect Dis 2003;37:113-28.

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