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

A Randomized Trial

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Context Emtricitabine is a new, once-daily nucleoside reverse transcriptase inhibitor (NRTI) with potent activity against human immunodeficiency virus (HIV).

Objective To assess the efficacy and safety of emtricitabine as compared with stavudine when used with a background regimen of didanosine and efavirenz.

Design, Setting, and Patients Randomized, double-blind, double-dummy study conducted at 101 research clinics in North America, Latin America, and Europe. The first patient was enrolled on August 21, 2000; no investigator or patient was unblinded until the last patient randomized completed the week 48 visit on October 24, 2002. Analyses were based on data collected in a double-blind setting with a median follow-up of 60 weeks. Patients were 571 antiretroviral-naive, HIV-1–infected adults aged 18 years or older with viral load levels greater than or equal to 5000 copies/mL.

Interventions Receipt of either 200 mg of emtricitabine once daily (plus stavudine placebo twice daily) (n=286) or stavudine at standard doses twice daily (plus emtricitabine placebo once daily) (n=285) plus open-label didanosine and efavirenz, once daily.

Main Outcome Measure Persistent virological response, defined as achieving and maintaining viral load at or below the limit of assay quantification (≤400 or 50 copies/mL).

Results At the interim analysis on June 14, 2002, when the last patient randomized completed 24 weeks of double-blind treatment (median follow-up time of 42 weeks), patients in the emtricitabine group had a higher probability of a persistent virological response ≤50 copies/mL vs the stavudine group (85% vs 76%, P=.005). This was associated with a higher mean CD4 cell count change from baseline for the emtricitabine group (156 cells/µL vs 119 cells/µL, P=.01 [of note, there was no statistical difference at 48 weeks (P=.15), although a sensitivity analysis, using an intent-to-treat population with the last CD4 cell count observation carried forward to week 48 showed a difference (P=.02)].) The independent data and safety monitoring board recommended offering open-label emtricitabine based on the interim analysis. The probability of persistent virological response ≤50 copies/mL through week 60 was 76% for the emtricitabine group and 54% for the stavudine group (P<.001). The probability of virological failure through week 60 was 4% in the emtricitabine group and 12% in the stavudine group (P<.001). Patients in the stavudine group had a greater probability of an adverse event that led to study drug discontinuation through week 60 than did those in the emtricitabine group (15% vs 7%, P=.005).

Conclusion Once-daily emtricitabine appeared to demonstrate greater virological efficacy, durability of response, and tolerability compared with twice-daily stavudine when used with once-daily didanosine and efavirenz.
increase the likelihood of treatment success. A novel synthetic cytidine nucleoside analogue, emtricitabine, has potent in vitro activity against HIV. Following administration of a 200-mg once-daily dose, the long plasma half-life (10 hours) of emtricitabine results in maintenance of steady state concentrations above the concentration necessary to produce 90% inhibition of HIV-1 replication for more than 80 hours. The intracellular half-life of the active moiety, emtricitabine-triphosphate, is approximately 39 hours, lending further support for the use of once-daily dosing. In vitro, emtricitabine is one of the most potent nucleoside agents. In vivo, emtricitabine produced a median 1.92 log10 copies/mL reduction in viral load when given as monotherapy to 8 HIV-1–infected patients for 2 weeks, a result comparable with that obtained with the most potent protease inhibitors or fusion inhibitors.

On the basis of encouraging results from Study ANRS 091 showing 93% of patients with viral load less than or equal to 50 copies/mL at week 24, a larger phase 3 trial (FTC-301A) was designed using the same regimen. Didanosine and efavirenz were selected as components because they could be given once daily, thus making this combination the only entirely once-daily HAART option available at the time the study was initiated. In addition, this regimen had the advantage of not containing a thymidine analogue (eg, zidovudine or stavudine), thus avoiding the emergence of thymidine analogue mutations, which can result in resistance to most nucleoside analogues if multiple mutations accumulate. Stavudine, an approved thymidine analogue, was selected as the comparator nucleoside reverse transcriptase inhibitor. Stavudine was the most-prescribed drug in its class at the time the study was initiated, and the combination of stavudine plus didanosine was a popular choice for the dual nucleoside component of a HAART regimen; these 2 drugs in combination are no longer recommended for initial therapy.

The objective of the FTC-301A study was to investigate the efficacy and safety of a simple, compact, non–thymidine analogue, once-daily regimen as first-line treatment for antiretroviral drug–naive HIV-1–infected patients.

METHODS

Patients

Patients were at least 18 years old, had more than 5000 copies/mL of plasma HIV-1 RNA (based on screening viral load, not baseline measurement), were antiretroviral-naive (no prior treatment with antiretroviral drugs for more than 3 days), and had a Karnofsky score of more than 80. Patients were excluded if they had severe hepatic, hematologic, or pancreatic abnormalities at screening. The institutional review board or independent ethics committee at each site approved the study, and all patients provided written informed consent.

Study Design

The study was a randomized, double-blind, double-dummy (patients received blinded randomized active study drug plus placebo for the comparator), multicenter trial designed to compare the efficacy and safety of emtricitabine to stavudine in HIV-1–infected patients with a background regimen of didanosine and efavirenz. Randomization was stratified based on plasma HIV-1 RNA levels less than or equal to or greater than 100 000 copies/mL at screening, as well as on geographic region (North America, Latin America, and Europe). Efficacy evaluations included measurements of viral load, CD4 cell counts, and genotypic resistance. Safety evaluations included adverse events, laboratory evaluations, and physical examinations.

Assessment and Monitoring

The patients were evaluated at baseline, week 2, and then every 4 weeks through week 48 and every 12 weeks thereafter until the last patient randomized completed week 48. At each visit the following procedures were performed: an interim medical history, assessment for adverse events, hematologic and chemistry evaluation, and determination of HIV-1 RNA level and CD4 cell count. Furthermore, a fasting lipid profile (levels of total cholesterol, low- and high-density lipoprotein cholesterol, and triglycerides) was obtained at baseline, every 12 weeks, and at the last study visit. Lipodystrophy was spontaneously reported as an adverse event and no pre-defined criteria were used; however, body measurements including weight, abdominal girth, and waist, hip, and chest circumferences were recorded at 12-week intervals. Data using a self-assessment questionnaire were collected but are not yet available and will be addressed in future analyses.

Plasma HIV-1 RNA levels were measured using the standard (limit of quantification of 400 copies/mL) and ultrasensitive (limit of quantification of 50 copies/mL) reverse transcriptase polymerase chain reaction (PCR) assay AmpliPlex HIV-1 Monitor tests (Roche Molecular Systems, Branchburg, NJ) versions 1.0 and 1.5, in accordance with methods delineated in the inserts for the commercial kits. Screening viral load was measured using both the standard version 1.0 and version 1.5 assays. If a patient satisfied the inclusion criteria for screening viral load and the difference in values between version assays was greater than or equal to 0.7 log10 copies/mL, the patient was followed up throughout the study using the version 1.5 assay for determination of the viral load. The ultrasensitive assay was used at all time points except screening and baseline.

Adverse events and laboratory abnormalities were evaluated using the Division of AIDS table for grading severity of adult adverse experiences. All patients were to receive blinded study medications until the last patient randomized completed week 48. Patient adherence to the blinded medications was assessed by returned-pill count at each study visit. An independent data and safety monitoring board (DSMB) was responsible for ensuring the accurate and complete review of safety data in a blinded manner throughout the study.

Treatment Regimens

Patients were centrally assigned to receive blinded study medication according to a computer-generated random-
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ization in a 1:1 ratio and received either emtricitabine 200 mg once daily plus stavudine-placebo twice daily or emtricitabine-placebo once daily plus stavudine 40 mg twice daily (patients weighing <60 kg received 30 mg). Commercially purchased stavudine capsules (Zerit; Bristol-Myers Squibb, Princeton, NJ) were overencapsulated to look identical to stavudine placebo capsules in order to preserve the blinding. A bioequivalence study comparing the overencapsulated stavudine with commercial stavudine was performed and showed bioequivalence. All patients also received open-label enteric-coated didanosine 400 mg (Videx EC; Bristol-Myers Squibb) (patients weighing <60 kg received 250 mg) and efavirenz 600 mg (Sustiva; Bristol-Myers Squibb; and Stocrin; Merck and Co, West Point, Pa), both prescribed as a once-daily dose. Efavirenz could be substituted with nelfinavir (Viracept; Agouron, La Jolla, Calif) at a dose of 1250 mg twice daily if the patient experienced intolerance (ie, rash, central nervous system symptoms) to efavirenz. Of note, our primary end point involved regimen termination, so there was no follow-up after permanent discontinuation of the randomized double-blind study treatment; thus, analysis of subsequent HAART regimens was not possible. The patient, the investigator, and the sponsor were blinded to randomized treatment assignment.

Study End Points
Persistent virological response, defined as achieving and maintaining plasma HIV-1 RNA levels at or below the limit of assay quantification (calculated through weeks 24, 48, and 60 [the latter was the median duration of double-blind follow-up when the last patient randomized completed week 48]), was used as the primary efficacy end point. This end point followed the US Food and Drug Administration (FDA) time to loss of virologic response (TLOVR) algorithm, which considered a patient as a nonresponder at the earliest time point of the following events: death (all reasons), permanent discontinuation of study drug, loss to follow-up, having 2 consecutive viral load values above the limit of assay quantification after having achieved the limit of assay quantification (loss of response), or never achieving suppression of viral load at the lower limit of assay quantification (lack of response). Patients who never achieved confirmed viral loads below the limit of assay quantification before any of the above events were considered nonresponders at study day 1. All visits with an observed viral load while receiving blinded study medications, including off-schedule visits and visits after week 48, were used in the algorithm. Viral load was not interpolated for visits or time points with missing data. No data were collected on patients after termination of study drug, and missing data at isolated time points were censored from all analyses. In this manner, all patients were classified as either responders or nonresponders. Patients who substituted nelfinavir for efavirenz were not considered nonresponders. For the TLOVR analysis, patients missing data as a result of discontinuation of the regimen were considered nonresponders at the time of discontinuation, and any single missing value for patients continuing in the study was ignored. Persistent virological response was analyzed separately using each of the viral load assay thresholds, ie, 50 copies/mL and 400 copies/mL.

Secondary end points included virological failure, change from baseline in absolute CD4 cell count, genotypic resistance, clinical disease progression, treatment-limiting adverse events, and treatment-emergent grade 3 or 4 laboratory abnormalities. The analysis of change from baseline in CD4 cell count used observed data; thus, missing data were ignored. Since withdrawal due to virological failure in a group with lesser response to therapy could artificially improve the observed CD4 cell response (survivor effect), a sensitivity analysis was performed using an intent-to-treat analysis with the last CD4 cell count observation carried forward to week 48. Virological failure was defined as lack or loss of response as classified by the TLOVR algorithm, using the 400 copies/mL limit of assay quantification. If the time of virological failure was immediately preceded by a single missing scheduled visit or multiple consecutive missing scheduled visits, then the time of virological failure was determined to be the first time of such missing visits. In the analysis of time to virological failure, patients who met an alternative end point (such as drop-out for adverse events, death, or loss to follow-up) as defined by the FDA TLOVR algorithm were censored from the analysis at the time of discontinuation (ie, they were ignored); similarly, in the analysis of treatment-limiting adverse events, only patients who were classified as having experienced tolerability failure by the TLOVR algorithm were counted as end points in the analysis of time to tolerability failure. Thus, the time to virological failure essentially provides a measure of efficacy independent of discontinuations due to tolerability issues or loss to follow-up, and the time to tolerability failure provides a measure of the safety independent of the efficacy of the drugs. Clinical disease progression was defined as a development of a new clinical event included in category C of the 1993 classification of the US Centers for Disease Control and Prevention, or death due to any cause. A treatment-limiting adverse event was defined as an adverse event resulting in the permanent discontinuation of blinded study medication.

Genotypic Analysis
Genotypic analysis was performed on plasma samples (baseline and time of failure) from patients who experienced virological failure (defined previously, ie, viral load >400 copies/mL). HIV-1 RNA extracted from plasma served as the template for amplification of the protease and reverse transcriptase genes. Viral RNA was extracted, reverse transcribed, and the complementary DNA amplified by nested polymerase chain reaction. The prepared PCR product was used as the template in a fluorescence-based cycle sequencing reaction. Dideoxy sequencing was performed using the ABI 377 sequencing system us-
ing labeled dye terminators following standard techniques.19-21 Analysis of the sequence fragments was performed with the Sequencher DNA sequencing program (Gene Codes Corp Inc, Ann Arbor, Mich), and the resulting HIV amino acid sequence was compared with a consensus reference (NL4-3) to determine amino acid changes. HIV-1 reverse transcriptase mutations associated with drug resistance were defined according to the Resistance Collaborative Group definition.22 Resistance to efavirenz was defined as the presence of mutations at positions A98, L100, K101, K103, V106, V108, Y181, Y188, G190, or P225. Resistance to didanosine was defined as the presence of mutations at positions K65 or L74. Thymidine analogue mutations were defined as amino acid changes at positions M41, D67, K70, L210, T215, or K219. Resistance to emtricitabine was defined as mutations at amino acid position M184.

Statistical Analysis
The primary population for analysis was all randomized patients who received at least 1 dose of blinded study drug (intent-to-treat). The planned sample size of 250 patients per group provided 80% power to detect an absolute difference of 12.5% in the proportion of patients with plasma HIV-1 RNA levels less than or equal to 50 copies/mL using a 2-sided significance level of .05, based on the predicted response rate of 50% in the stavudine control group. The probabilities of persistent virological response, of virological failure, and of developing a treatment-limiting adverse event were analyzed using Kaplan-Meier methods. Treatment-group comparisons (ie, emtricitabine-stavudine) of the overall probability curves were made using a log-rank test, and cross-sectional probability comparisons were made based on the difference in binomial proportions. Patients who did not achieve viral load suppression below 400 copies/mL by week 12 (confirmed at week 16) were considered to have virological failure at study day 1. Patient disposition, change from baseline in absolute CD4 cell count, incidence of adverse events, laboratory abnormalities, changes from baseline in body measurements, changes from baseline in lipid profile, and viral resistance were summarized and compared between groups (ie, emtricitabine-stavudine) using a stratum-adjusted (randomization strata) analysis based on the difference in binomial proportions for categorical variables and the difference in means for continuous variables. Incidence of adverse events, laboratory abnormalities, changes in body measurements, changes in lipid profile, and viral resistance were calculated using all double-blind data available at the time the last patient randomized completed the week 48 visit. Analysis of change from baseline results used all available double-blind data without imputation of missing data. To confirm the robustness of the viral load findings, a sensitivity analysis was performed using an as-treated analysis. In the as-treated analysis, only data from patients continuing their randomized treatment at week 48 were considered for analysis. Patients who permanently discontinued study drug, were lost to follow-up, or were missing data on viral load were censored. Also, a sensitivity analysis using an intent-to-treat analysis with the last CD4 cell count observation carried forward to week 48 was performed. The homogeneity of treatment group results for participants classified as persistent virological responders was assessed across geographic region strata using a Breslow-Day test. The data were gathered at study centers by site investigators and study coordinators and then forwarded to Parexel International Inc for database preparation. Gilead Sciences performed all statistical analyses using SAS software version 8.0 (SAS Institute Inc, Cary, NC). A 2-sided significance test using an \( \alpha \) of .05 was used to declare statistical differences between treatment groups. Independent statistical review was also obtained (see “Independent Statistical Review” section at the end of this article).

RESULTS
Patients were recruited from 101 research clinics in 9 countries in North America (Canada, Puerto Rico, United States), Latin America (Argentina, Brazil, Chile, Mexico), and Europe (France, Germany, United Kingdom). Of the 820 patients who underwent screening procedures, 580 patients were eligible and randomized between August 21, 2000, and November 22, 2001, and the last patient randomized completed 48 weeks of treatment on October 24, 2002. The baseline characteristics were similar between the 2 treatment groups (TABLE 1). Approximately 40% of patients enrolled had screening HIV-1 RNA levels greater than 100,000 copies/mL. Nine patients never received study drug because they did not return for the baseline visit; the remaining 571 were included in the intent-to-treat analysis. Eighty-one percent of the emtricitabine-treated patients and 68% of the stavudine-treated patients completed 48 weeks of randomized, blinded therapy, corresponding to discontinuation rates of 19% and 32%, respectively (FIGURE 1). The median duration of double-blind follow-up was 60 weeks.

A protocol-planned interim analysis was conducted using all data available after the last patient randomized completed week 24 and was provided to the DSMB while maintaining the study blinding. The median duration of double-blind follow-up was 42 weeks at the time of this analysis. Based on review of the interim analysis, the DSMB recommended on July 19, 2002, that the double-blind comparative phase be terminated and all patients in the group demonstrating lesser response to therapy be allowed access to the group demonstrating greater response. Unblinding was permitted at the group level only and in no case at the individual patient level. As a result of the DSMB recommendation, and after consultation with the FDA, all patients were given the option to continue receiving blinded therapy or to switch to open-label emtricitabine (without information regarding their original randomized regimen) until the last randomized patient completed week 48. The option to receive open-label emtricitabine without knowledge of original treatment assignment preserved the double
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blinding of the trial. The investigator and patient were informed of the original treatment assignment after the last patient randomized completed the week 48 visit and the database was locked. A total of 4 patients (<1%) completed the week 48 visit after switching to open-label emtricitabine. All double-blind data collected as of October 24, 2002, are the subject of this report. The 4 patients who opted to receive open-label emtricitabine did so at their week 44, week 46 (n = 2), and week 47 visits; thus, they were considered completers of blinded week 48, since their last visit while receiving blinded study medication occurred in the time window for week 48 (day 322-day 350). Three of the 4 patients were randomized to emtricitabine and 1 was randomized to stavudine; all 4 patients were responders at week 48.

Following the recommendation of the DSMB and discussions with the FDA, the protocol was amended on July 23, 2002, to offer the emtricitabine-containing regimen to all patients in the study with the same schedule of assessments as the original protocol. The amended protocol was submitted by each investigator to their ethics committee or institutional review board for approval prior to initiating the amended protocol. The amendment approval process began in the middle of August with the last approval obtained in October 2002. By that time, many individuals had reached the week 48 visit (the median duration of double-blind follow-up was 60 weeks at the time the last randomized patient completed the week 48 visit, and data collection for the study ended on October 24, 2002).

Efficacy
At week 24 there was a statistically significant greater probability of persistent virological response in the emtricitabine treatment group vs the stavudine treatment group using both the 50 and 400 copies/mL HIV-1 RNA thresholds (FIGURE 2A). Probability of persistent virological response less than or equal to 50 copies/mL was 85% for the emtricitabine group vs 76% for the stavudine group (Figure 2A) (P = .005). Probability of persistent virological response less than or equal to 400 copies/mL was 88% for the emtricitabine group vs 81% for the stavudine group (Figure 2B) (P = .03). The findings were associated with a higher mean CD4 cell count change from baseline of 156 cells/µL for

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Emtricitabine Plus Didanosine and Efavirenz (n = 286)</th>
<th>Stavudine Plus Didanosine and Efavirenz (n = 285)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td>47 (16.4)</td>
<td>39 (13.7)</td>
</tr>
<tr>
<td>Male</td>
<td>239 (83.6)</td>
<td>246 (86.3)</td>
</tr>
<tr>
<td>Ethnic origin, No. (%)</td>
<td>136 (47.6)</td>
<td>159 (55.8)</td>
</tr>
<tr>
<td>White</td>
<td>150 (52.4)</td>
<td>126 (44.2)</td>
</tr>
<tr>
<td>Male</td>
<td>3 (1.0)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Black</td>
<td>52 (18.2)</td>
<td>40 (14.0)</td>
</tr>
<tr>
<td>Male</td>
<td>77 (26.9)</td>
<td>70 (24.6)</td>
</tr>
<tr>
<td>Other</td>
<td>18 (6.3)</td>
<td>14 (4.9)</td>
</tr>
<tr>
<td>Age, mean (SD) [range], y</td>
<td>35.8 (9.3) [18-67]</td>
<td>36.5 (9.6) [18-69]</td>
</tr>
<tr>
<td>Region of enrollment, No. (%)</td>
<td>131 (45.8)</td>
<td>128 (44.9)</td>
</tr>
<tr>
<td>North America</td>
<td>93 (32.5)</td>
<td>96 (33.7)</td>
</tr>
<tr>
<td>Latin America</td>
<td>62 (21.7)</td>
<td>61 (21.4)</td>
</tr>
<tr>
<td>Baseline log_{10} plasma HIV-1 RNA, mean (SD) [range], copies/mL†</td>
<td>4.8 (0.67) [2.6-7.0]</td>
<td>4.8 (0.67) [2.6-6.5]</td>
</tr>
<tr>
<td>Baseline CD4 cell count, mean (SD) [range], cells/µL</td>
<td>312 (203) [5-1156]</td>
<td>324 (203) [6-1317]</td>
</tr>
<tr>
<td>History of CDC class C events, No. (%)</td>
<td>7 (2.4)</td>
<td>9 (3.2)</td>
</tr>
</tbody>
</table>

Abbreviations: CDC, Centers for Disease Control and Prevention; HIV-1, human immunodeficiency virus type 1.

*There is no statistically significant difference between groups in baseline characteristics for any parameter. Twenty-nine patients (5%) were missing baseline measurements of viral load. All patients had measurements of viral load at screening. Fifteen patients (3%) were missing baseline CD4 cell counts. Nine patients (5%) were missing baseline measurements of viral load. All patients had measurements of viral load at screening. Fifteen patients (3%) were missing baseline CD4 cell counts.

†Baseline plasma HIV-1 RNA <2.6 log_{10} copies/mL in 3 patients randomized to emtricitabine and 2 randomized to stavudine (patients were enrolled on the basis of viral load measured at screening and not at baseline).

Figure 1. Flow of Patients Through the FTC-301A Study
The percentages presented in the curves include those patients who have not yet reached the lower limit of assay detection, as well as those who have achieved it and are maintaining it, until the point of failure. If patients did not achieve the lower limit of assay detection by week 12 (confirmed at week 16) and did not discontinue therapy for some other reason, they were classified as nonresponders having virological failure at day 1, accounting for the curves dropping to approximately 80%-90% at day 1. If they never achieved the lower limit of assay detection and discontinued therapy for some other reason, they were classified as nonresponders at the time of discontinuation. If they achieved the lower limit of assay detection and had a confirmed loss of suppression, they were classified as nonresponders having virological failure at the time that the first of 2 values was greater than the limit of assay detection. If patients achieved the lower limit of assay detection and maintained it without discontinuation of therapy, they were considered persistent responders.

HIV-1 indicates human immunodeficiency virus type 1.

Figure 2. Kaplan-Meier Analysis of Persistent Virological Response (Achieving and Maintaining Plasma HIV-1 RNA ≤50 copies/mL and ≤400 copies/mL) Through Week 60

At week 48 the probability of persistent virological response less than or equal to 50 copies/mL was 78% for the emtricitabine group vs 59% for the stavudine group (Figure 2A) (P<.001). For patients entering the study with viral load less than or equal to 100000 copies/mL, the response rate was 79% in the emtricitabine group vs 65% in the stavudine group (P=.005). In patients with baseline viral load greater than 100000 copies/mL, the response rate was 80% in the emtricitabine group vs 61% in the stavudine group (P<.001).

In a sensitivity analysis using the as-treated population (patients completing 48 weeks of double-blind treatment), results for the proportion of patients having a viral load less than or equal to 50 copies/mL at week 48 were 91% for the emtricitabine group vs 84% for the stavudine group (P=.004).

For patients completing week 48 of study, absolute CD4 cell counts increased in both treatment groups, with a mean increase from baseline of 168 cells/µL and 134 cells/µL, respectively, in the emtricitabine and stavudine treatment groups (P=.15). Thirty-one patients (9 in the emtricitabine group and 22 in the stavudine group) completing week 24 were missing data on viral load, and 19 patients (9 in the emtricitabine group and 10 in the stavudine group) completing week 24 were missing CD4 cell counts.

At week 48 the probability of persistent virological response less than or equal to 50 copies/mL was 81% for the emtricitabine group vs 68% for the stavudine group (Figure 2B) (P<.001). For patients entering the study with viral load less than or equal to 100000 copies/mL, the response rate was 82% in the emtricitabine group vs 73% in the stavudine group (P=.05). In patients with baseline viral load greater than 100000 copies/mL, the response rate was 80% in the emtricitabine group vs 61% in the stavudine group (P<.001).

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or equal to 400 copies/mL was 80% in the emtricitabine group vs 69% in the stavudine group (P=.02). In patients with baseline viral load greater than 100 000 copies/mL, the response rate was 78% in the emtricitabine group vs 56% in the stavudine group (P<.001). The probability of virological failure was 4% in the emtricitabine group vs 12% in the stavudine group (P<.001) (FIGURE 3). The difference in the probability of virological failure between the emtricitabine and stavudine treatment groups was larger in the patients with screening plasma viral load greater than 100 000 copies/mL. For patients entering the study with a viral load less than or equal to 100 000 copies/mL, there was a 4% excess probability of virological failure in the stavudine group vs the emtricitabine group (7% vs 3%, respectively, P=.08). The difference between groups increased to 12% in favor of emtricitabine for patients with baseline viral load greater than 100 000 copies/mL (7% vs 19% for emtricitabine vs stavudine, P=.01). Of the 278 patients reaching week 60, 12 (7 in the emtricitabine group and 5 in the stavudine group) were missing data on viral load.

Overall, the proportion of patients with progression of clinical disease was 1.7% (5/286) in the emtricitabine group vs 3.5% (10/285) in the stavudine group (P=.19). These events included Kaposi sarcoma (1 patient in the emtricitabine group, 2 in the stavudine group), esophageal candidiasis (1 emtricitabine, 1 stavudine), wasting syndrome (0 emtricitabine, 4 stavudine), diarrhea due to Cryptosporidium (1 stavudine) or Isospora belli (1 emtricitabine), and several events occurring in single patients only. These were Mycobacterium tuberculosis and herpes simplex virus infection in the emtricitabine group and Pneumocystis pneumonia with herpes simplex proctitis in the stavudine group. Two patients receiving double-blind study medication died. Both of these patients were in the stavudine group. One patient died on study day 324 subsequent to surgical operations for cholelithiasis, wound infection, and dehiscence, which were considered unrelated to all study medications. One patient death (on study day 419) was due to metabolic acidosis secondary to pneumonia and lactic acidosis.

Adherence

There was no statistically significant difference between groups in adherence to prescribed blinded study medication as measured by returned-pill count. Overall, the majority of patients (62%) returned less than 10% of their prescribed blinded study drug (64% emtricitabine vs 60% stavudine), with 72% of patients (75% emtricitabine vs 70% stavudine) returning less than 20% of prescribed blinded study drug (P=.31 for the difference between groups). Twenty-two patients replaced efavirenz with nelfinavir due to intolerance (5 [1.7%] in the emtricitabine group vs 17 [6%] in the stavudine group). The majority of replacements of efavirenz with nelfinavir (n=12) occurred within the first 4 weeks of initiating therapy.

Viral Resistance

Genotypic resistance analysis was performed on 48 of the 50 patients with virological failure (13 in the emtricitabine group and 35 of the 37 patients with failure in the stavudine group). In patients with virological failure, resistance mutations were observed at baseline in 38% (5/13) of the patients in the emtricitabine group and 34% (12/35) of the patients in the stavudine group, with mutations associated with nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance being most prevalent. Phenotypic analysis of baseline isolates that contained the K103N mutation confirmed resistance to efavirenz.

Virological failure with at least 1 new genotypic mutation developed in a greater proportion of patients in the stavudine group (11%) vs the emtricitabine group (4%) (P=.005). Virological failure with wild-type virus was observed in 1 of 286 patients (0.3%) in the emtricitabine group vs 4 of 285 patients (1.4%) in the stavudine group. Eight patients in the emtricitabine group and 22 patients in the stavudine group developed a new genotypic mutation at position K103N at the time of virological failure and had acquired resistance to efavirenz (TABLE 2). In the 13 patients who experienced virological failure in the emtricitabine group, 11 patients developed an NNRTI-associated mutation. Five of these 11 patients developed the M184V/I mutation in addition to an NNRTI mutation and 1 developed a mutation at position K65N (possibly associated with didanosine) in addition to an NNRTI mutation. In the 35 patients who experienced virological failure in the stavudine group, 31 developed an NNRTI-associated mutation. Seven of these 31 patients developed a thymidine analogue mutation (associated with stavudine) in addition to an NNRTI mutation and 3 developed the L74V didanosine-associated mutation in addition to an NNRTI mutation.

Adverse Events

Treatment-emergent adverse events observed with a significant difference between groups were diarrhea, nausea, lactic acidosis, lipodystrophy, abnormal dreams (nightmares, extremely vivid dreams), neuropathy, paresthesia, skin discoloration, and increased cough (TABLE 3). With the exception of cough and skin discoloration, fewer adverse events were noted in the emtricitabine group vs the stavudine group. Pancreatitis (n=4 [1%]) and symptomatic hyperlactatemia/lactic acidosis (n=7 [2%]), were observed only in the stavudine group. Lipodystrophy was re-
ported by the investigator in 1 patient (0.4%) in the emtricitabine group and 17 patients (6%) in the stavudine group (Table 3). Skin discoloration was observed in 10 patients (3%) (grade 1, n=9; grade 2, n=1) in the emtricitabine group and 1 patient (grade 1) in the stavudine group. Skin discoloration was manifested by hyperpigmentation on the palms and/or soles that was generally mild and asymptomatic, though the mechanism and clinical significance remain unknown. The number of patients who experienced a serious adverse event was not statistically different between the 2 treatment groups, with an overall incidence of 8% (24/286) in the emtricitabine group and 14% (39/285) in the stavudine group (P=.13).

**Laboratory Abnormalities**

At least 1 treatment-emergent grade 3 or 4 laboratory abnormality occurred in 96 patients (34%) in the emtricitabine group and 108 patients (38%) in the stavudine group. Among all grade 3 or 4 abnormalities, elevation in levels of serum amylase was statistically higher in the stavudine group (10% [27/285]) vs the emtricitabine group (5% [13/286]) (P=.02). There was a low incidence of grade 3 or 4 laboratory abnormalities across all other parameters, which was balanced between treatment groups as follows: creatine kinase level (12% emtricitabine; 11% stavudine), alanine aminotransferase level (5% emtricitabine; 6% stavudine), aspartate aminotransferase level (6% emtricitabine; 9% stavudine), hypertriglyceridemia (9% emtricitabine; 6% stavudine), neutropenia (5% emtricitabine, 7% stavudine), glucose abnormalities (2% emtricitabine; 3% stavudine), lipase level (1% emtricitabine; 2% stavudine), and thrombocytopenia (0% emtricitabine; 1% stavudine). All other grade 3 or 4 laboratory abnormalities occurred in 2 or fewer patients in either group.

**Treatment-Limiting Adverse Events**

The probability of developing a treatment-limiting adverse event through week 60 was statistically greater in the stavudine group (15%) vs the emtricitabine group and 17 patients (6%) in the stavudine group (Table 3). Skin discoloration was observed in 10 patients (3%) (grade 1, n=9; grade 2, n=1) in the emtricitabine group and 1 patient (grade 1) in the stavudine group. Skin discoloration was manifested by hyperpigmentation on the palms and/or soles that was generally mild and asymptomatic, though the mechanism and clinical significance remain unknown. The number of patients who experienced a serious adverse event was not statistically different between the 2 treatment groups, with an overall incidence of 8% (24/286) in the emtricitabine group and 14% (39/285) in the stavudine group (P=.13).

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Anthropometric Measurements and Lipid Profile Changes

Increase in weight from baseline occurred in both treatment groups at 12, 24, and 36 weeks of therapy. Beyond week 36, the patients in the emtricitabine group continued to gain weight, with a mean (SD) increase in body weight through week 60 of 1.5 (5.38) kg, while the patients in the stavudine group progressively lost weight, with a mean decrease in body weight through week 60 of 1.6 (5.22) kg. The stratum-adjusted mean difference between treatment groups at week 60 was statistically significant (−2.9 [10.1] kg, *P* < .001) (Table 4).

The mean (SD) change in levels of fasting serum total triglycerides increased from baseline through week 60 in both treatment groups but was numerically greater in patients receiving stavudine (53.1 [132.4] mg/dL vs 80.1 [115.5] mg/dL [0.6 [1.5] mmol/L vs 0.9 [1.3] mmol/L] for emtricitabine vs stavudine) (Table 4). At week 60, the mean change from baseline for levels of fasting total cholesterol and low-density lipoprotein cholesterol increased in both treatment groups (Table 4).

COMMENT

In this study, the emtricitabine regimen (emtricitabine, didanosine, and efavirenz) appeared to demonstrate greater efficacy compared with the stavudine regimen (stavudine, didanosine, and efavirenz) for all primary and secondary end points. All patients were offered early access to the emtricitabine-containing regimen. The probability of persistent virological response with plasma HIV-1 RNA levels less than or equal to 50 copies/mL through week 48 was significantly greater in patients receiving emtricitabine performance, it may be useful to compare the proportion of patients with viral load less than or equal to 50 copies/mL observed in the stavudine, didanosine, and efavirenz group in our study at 24 weeks (76%) with week 24 findings involving stavudine plus didanosine and efavirenz in Study DMP-044 (65%). The week 48 response rates (50 copies/mL) in the emtricitabine group herein was 79% for patients entering the study with viral load less than or equal to 100 000 copies/mL, while it was 76% in patients with baseline viral load greater than 100 000 copies/mL. These response rates compare favorably with the approximately 65% response rates at 48 weeks observed in study DMP006 for both low and high baseline viral loads for the efavirenz plus zidovudine and lamivudine group.

In addition to superior efficacy, the patients in the emtricitabine group appeared to tolerate their regimen better over time than did patients in the stavudine group. This difference in tolerability was apparent as the duration of

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Table 4. Body Measurement and Lipid Profile Changes From Baseline at Week 48 and Week 60

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Week 48</th>
<th>Week 60</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Emtricitabine Plus Didanosine and Efavirenz</td>
<td>Stavudine Plus Didanosine and Efavirenz</td>
</tr>
<tr>
<td></td>
<td>No.</td>
<td>Mean (SD)</td>
</tr>
<tr>
<td>Body measurements</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>229</td>
<td>1.5 (6.01)</td>
</tr>
<tr>
<td>Body mass index†</td>
<td>227</td>
<td>0.5 (1.99)</td>
</tr>
<tr>
<td>Abdominal girth, cm</td>
<td>222</td>
<td>1.2 (6.01)</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>219</td>
<td>0.8 (7.44)</td>
</tr>
<tr>
<td>Hip circumference, cm</td>
<td>223</td>
<td>0.3 (5.9)</td>
</tr>
<tr>
<td>Chest circumference, cm</td>
<td>223</td>
<td>0.7 (5.04)</td>
</tr>
<tr>
<td>Fasting blood lipid levels, mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>141</td>
<td>27.2 (124.48)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>141</td>
<td>12 (11.65)</td>
</tr>
<tr>
<td>LDL-C</td>
<td>141</td>
<td>26.1 (30.13)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>141</td>
<td>44.3 (33.1)</td>
</tr>
<tr>
<td>HDL-C &gt; 60 mg/dL, No./total (%)</td>
<td>39/186 (21)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Abbreviations: HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NA, not applicable.

SI conversion factors: To convert mg/dL of triglycerides to mmol/L, multiply by 0.0113; mg/dL of HDL-C, LDL-C, and total cholesterol to mmol/L, multiply by 0.0259.

*Statistically significant (P < .05) based on stratum-adjusted difference in treatment groups.

†Calculated as weight in kilograms divided by the square of height in meters.
therapy increased beyond 24 weeks, indicative of cumulative toxicity over time of the stavudine-containing regimen. Complications commonly believed to be associated with mitochondrial dysfunction, such as peripheral neuropathy and lipodystrophy, were more frequent among the recipients of the stavudine regimen. The relative risk of peripheral neuropathy was 2.7-fold higher among patients in the stavudine group than in the emtricitabine group (95% CI, 1.7–4.4). Reports of lipodystrophy were significantly greater in patients treated with the stavudine regimen. Although lipodystrophy was spontaneously reported as an adverse event with no predefined criteria, these results are consistent with a recent analysis of anthropomorphic measurements from this study. 27 Eighteen percent of the emtricitabine group vs 6% of the stavudine group had a fasting high-density lipoprotein cholesterol level greater than or equal to 60 mg/dL (1.6 mmol/L) at week 60 (P = .004), which is a level associated with protection against cardiovascular risk. 28

Since virological failure and development of treatment-limiting adverse events were both more frequent among patients receiving stavudine, it can be hypothesized that virological failure was a consequence, in many individuals, of differences both in the potency between emtricitabine and stavudine as well as in the frequency of stavudine interruptions secondary to drug-related adverse effects, as demonstrated in previous studies. 29,30 T he efficacy difference between treatment groups was larger in patients with high viral load (>100,000 copies/mL) at study entry in favor of emtricitabine, 31 suggesting that drug potency played a larger role in the comparative efficacy than did interruptions of stavudine treatment. Results from the ACTG 384 study demonstrated the lesser performance of stavudine plus didanosine vs zidovudine plus lamivudine in combination with efavirenz, but not with neflavinavir. 32 The ACTG 384 study also showed that the time to develop severe drug toxicities or dose-modifying events was shorter in the regimens containing stavudine plus didanosine vs zidovudine plus lamivudine but did not address which component of the stavudine plus didanosine regimen was responsible for the more-rapid toxicity. Simpler, better-tolerated regimens with prolonged plasma and intracellular half-lives, such as those used in more-contemporary clinical trials, 23,33 are rapidly emerging as desirable initial therapy for HIV.

The results of this study establish that this entirely once-daily, well-tolerated regimen produces a high level of virological control through a median follow-up of 60 weeks (76% probability of persistent suppression to less than 50 copies/mL), with a low incidence of virological failure with new genotypic mutations at time of failure (4%).

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Deceased.

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Study concept and design: Barry, Quinn, Rousseau. Acquisition of data: Saag, Cahn, Raffi, Wolff, Pearce, Molina, Shaw, Borroto-Esoda, Quinn, Rousseau. Analysis and interpretation of data: Saag, Molina, Powderly, Shaw, Mondou, Hinkle, Borroto-Esoda, Quinn, Rousseau. Drafting of the manuscript: Saag, Shaw, Mondou, Borroto-Esoda, Hinkle, Quinn, Rousseau. Critical revision of the manuscript for important intellectual content: Saag, Cahn, Raffi, Wolff, Pearce, Molina, Powderly, Shaw, Mondou, Hinkle, Quinn, Rousseau. Statistical analysis: Hinkle, Quinn. Obtained funding: Barry, Quinn.

Administrative, technical, or material support: Shaw, Mondou, Borroto-Esoda.

Study supervision: Saag, Cahn, Raffi, Pearce, Shaw, Mondou, Rousseau.

Patient enrollment: Saag, Cahn, Raffi, Wolff, Pearce, Molina.

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EMTRICITABINE VS STAVUDINE IN HIV-1-INFECTED PATIENTS


