Once-Daily versus Twice-Daily Lamivudine, in Combination with Zidovudine and Efavirenz, for the Treatment of Antiretroviral-Naive Adults with HIV Infection: A Randomized Equivalence Trial

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A randomized, double-blind, double-dummy controlled, multicenter trial was conducted that involved 554 antiretroviral-naive human immunodeficiency virus–infected adults (plasma HIV type 1 [HIV-1] RNA level, ⩾400 copies/mL; $CD4^+$ cell count, >100 cells/mm^3) and compared a 300-mg once-daily (q.d.) regimen of lamivudine (3TC) versus a 150-mg twice-daily (b.i.d.) regimen of 3TC, combined with zidovudine (300 mg b.i.d.) and efavirenz (600 mg q.d.), during a 48-week period. Treatments were considered equivalent if the 95% confidence interval (CI) for the difference in proportions of patients achieving an HIV-1 RNA level of <400 copies/mL was within the bound of −12% to 12%. At week 48 of the study, an intent-to-treat analysis in which patients with missing data were considered to have experienced treatment failure showed that the 3TC q.d. and 3TC b.i.d. regimens were equivalent (HIV-1 RNA level <400 copies/mL, 178 [64%] of 278 vs. 174 [63%] of 276; treatment difference, 1% [95% CI, −7.1% to 8.9%]; HIV-1 RNA level <50 copies/mL, 165 [59%] of 278 vs. 168 [61%] of 276; treatment difference, 1.7% [95% CI, −9.7% to 6.6%]). Median increase above baseline in $CD4^+$ cell count was similar (q.d. group, +144 cells/mm^3; b.i.d. group, +146 cells/mm^3), and the incidences of adverse events, disease progression, and HIV-associated conditions were comparable.

The goal of implementing HAART is maximal suppression of plasma HIV-1 RNA levels to reduce HIV replication and the risk of developing drug resistance [1, 2]. However, attainment of this goal is only possible if patients consistently adhere to their antiretroviral dosing schedules [3–5]. Because adherence to therapy appears to increase as the complexity of the regimen decreases, much attention in HIV therapeutics has been directed at finding potent and well-tolerated HAART regimens that are simple and convenient for patients to adhere to [6, 7].

Once-daily administration of antiretroviral drugs facilitates adherence because such a regimen is easy to remember and minimally disruptive to the lifestyles of patients [8, 9]. The nucleoside reverse transcriptase inhibitor (NRTI) lamivudine (3TC)—which, during the past decade, has demonstrated considerable value when administered twice-daily as a key component of many combination regimens [10]—has a plasma and intracellular pharmacokinetic profile that appears appropriate for successful once-daily dosing [11–13]. 3TC is metabolized intracellularly by phosphorylation to an active triphosphate form (3TC-triphosphate) that has a long intracellular half-life of 15–19 h [11, 12]. Ad-

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ministration of 3TC at either 300 mg q.d. or 150 mg b.i.d. has been shown to result in similar 24-h area under the plasma concentration-versus-time curves (AUCs) for 3TC and has been shown to result in similar 24-h intracellular AUCs and steady-state maximum intracellular concentrations (C_{max}) for 3TC-triphosphate [12].

In view of these pharmacokinetic findings and data from 2 small pilot clinical trials that examined once-daily 3TC regimens [14, 15], a large-scale, double-blind, international study was designed to compare once-daily and twice-daily dosing of 3TC, combined with zidovudine and efavirenz, with respect to antiviral equivalence and safety.

METHODS

Study participants. Male and nonpregnant female outpatients were eligible for study enrollment if they were ⩾18 years of age; had HIV infection, as documented by HIV-1 antibody ELISA and confirmed by Western blot test; were treatment naive (i.e., had received <7 days of any prior antiretroviral medication); and had a plasma HIV-1 RNA level of ⩾400 copies/mL and a $CD4^+$ cell count of >100 cells/mm^3 at least once within the 21 days before initiation of the study.

Study design. This 48-week trial was a randomized, double-blind, double-dummy, controlled, multicenter trial that was conducted at 67 centers in the United States, Canada, Argentina, and Brazil. After screening, patients were stratified according to their HIV-1 RNA level at screening (⩽100,000 copies/mL vs. >100,000 copies/mL; figure 1) and were then randomized 1:1 to receive either 3TC at 300 mg q.d. (with 3TC b.i.d. placebo) or 3TC at 150 mg b.i.d. (with 3TC q.d. placebo), in combination with zidovudine (300 mg b.i.d.) and efavirenz (600 mg q.d.). 3TC was administered as single 150-mg and 300-mg tablets of Epivir (GlaxoSmithKline), zidovudine was administered as single 300-mg tablets of Retrovir (GlaxoSmithKline), and efavirenz was administered as three 200-mg tablets of Sustiva or Stocrin (Dupont).

Study monitoring. To evaluate efficacy, an assessment of HIV-1 RNA levels, $CD4^+$ cell counts, and HIV-associated conditions was made at screening and at baseline (14–21 days after screening), and at week 2, week 4, and every 4 weeks through week 48 of the study. Plasma HIV-1 RNA levels were measured in blood samples obtained during study visits using both the Roche Amplicor PCR Standard 1.0 assay (lower limit of quantitation [LLOQ], 400 copies/mL; Roche Diagnostics) and the Roche PCR assay Amplicor HIV Monitor UltraSensitive, version 1.0 (LLOQ, 50 copies/mL; Roche Diagnostics). $CD4^+$ cell counts were measured by flow cytometry.

To evaluate safety, a medical history was obtained, a physical examination was performed, and a Centers for Disease Control and Prevention (CDC; Atlanta, GA) classification was established at screening and baseline; an assessment of adverse events, serum chemistry testing, and hematological testing was performed at screening, baseline, week 2, week 4, and every 4 weeks through week 48 of the study. Adverse events were evaluated using the Division of AIDS table for grading the severity of adult adverse experiences [16].

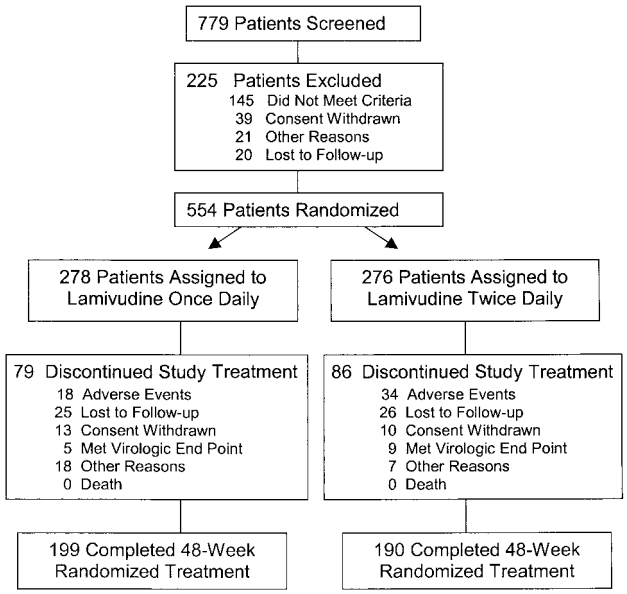

Figure 1. Profile of patient enrollment and discontinuation of therapy through 48 weeks of treatment.

Efficacy assessments. The primary efficacy end point was proportion of patients achieving an HIV-1 RNA level of <400 copies/mL at week 48 of the study. Secondary end points were the proportion of patients with HIV-1 RNA levels of <50 copies/mL, an increase in $CD4^+$ cell count of ⩾50 cell/mm^3, or disease progression or death at week 48 of the study; changes from baseline values for HIV-1 RNA level and $CD4^+$ cell count; and HIV-1 RNA average area under the curve minus baseline (AAUCMB). Patients were defined as having experienced virologic failure if they had an HIV-1 RNA level of ⩾400 copies/mL at week 24 of the study; time to rebound in the virus load was defined as the time between initiation of therapy and 2 consecutive HIV-1 RNA levels of ⩾400 copies/mL.

Resistance analysis. Genotypic analyses of plasma samples obtained from patients who experienced virologic failure were performed at baseline, week 8, week 24, week 48, and/or at treatment discontinuation. The sequence of the HIV-1 *pol* coding region was determined using the ViroSeq HIV-1 Genotyping System Kit (PE Biosystems) and the ABI 3700 DNA sequencer (ABI), according to the manufacturer's protocols. For analysis of samples with HIV-1 RNA levels of <2000 copies/mL, the protocol was altered to include an additional nested PCR reaction.

Phenotypic susceptibility to a standard panel of antiretroviral

drugs, including zidovudine, 3TC, and efavirenz, was analyzed using the Phenosense HIV recombinant virus assay (Virologic).

Statistical analysis. A total of 275 patients per study arm were deemed necessary to demonstrate equivalence between treatment groups with 80% power at $\alpha = 0.05$, assuming an equivalence interval of 12% and identical 60% success rates (HIV-1 RNA levels of <400 copies/mL at week 48) in each arm. The efficacy analyses were conducted in the intent-to-treat (ITT) population, defined as all patients who were randomized into the study, regardless of what treatment was actually received and regardless of the eventual outcome of study participation. An ITT analysis was used in which patients with values that were missing for any reason—including as a result of treatment changes or premature discontinuation of randomized treatment—were considered to have experienced treatment failure (ITT missing-equals-failure analysis). Only data from patients continuing randomized treatment were considered for analysis. An as-treated analysis was also performed, which only included data obtained during the period in which the patients received the study drug. The safety analysis was conducted on a subset of the ITT population that consisted only of patients who were exposed to the study drug.

To assess noninferiority, the point estimate and the 95% CIs were calculated around the difference in proportions of patients achieving HIV-1 RNA levels of <400 copies/mL. The 2 treatments were considered equivalent if the 95% CI for the difference in proportions of patients achieving virologic suppression was within the bound of −12% to 12% [17]. The 95% CIs were constructed with and without adjusting for screening plasma HIV-1 RNA strata. Adjusted 95% CIs used Mantel-Haenszel weights.

RESULTS

Baseline characteristics. Five hundred fifty-four adult patients were enrolled in the study from 21 September 1999 through 1 August 2001; 278 were randomized to the 3TC q.d. regimen, and 276 were randomized to the 3TC b.i.d. regimen. The 3TC q.d. and 3TC b.i.d. treatment arms were similar with respect to demographic characteristics, baseline median plasma HIV-1 RNA levels (4.64 $\log_{10}$ copies/mL vs. 4.69 $\log_{10}$ copies/mL), and baseline median $CD4^+$ cell counts (340 cells/mm^3 vs. 386 cells/mm^3) (table 1). The study population mostly comprised male subjects (79%) and was ethnically diverse: 50% of the patients were white, 27% were black, and 19% were Hispanic. Most (81%) of the patients had HIV infections that were designated as CDC class A.

Seventy-two percent of the patients randomized to the 3TC q.d. arm and 69% of the patients randomized to the 3TC b.i.d. arm completed all 48 weeks of treatment (figure 1). The reasons for premature discontinuation were generally similar between treatment arms, with the exception of adverse events, which occurred more often in the 3TC b.i.d. arm. Kaplan-Meier estimates of the time to treatment discontinuation were not significantly different between the 2 treatment arms (figure 2).

Plasma HIV-1 RNA levels. After initiation of treatment, reduction in HIV-1 RNA levels was equally rapid in both treatment groups, with a median 1.91 $\log_{10}$ copies/mL decrease from baseline having occurred by week 4. At week 48, the median decrease in HIV-1 RNA level from baseline was 2.06 $\log_{10}$ copies/mL and 2.04 $\log_{10}$ copies/mL in the 3TC q.d. and 3TC b.i.d. arms, respectively. The proportions of patients with HIV-1 RNA levels of <400 copies/mL at week 48 were equivalent in the 3TC q.d. and 3TC b.i.d. arms according to the ITT missing-equals-failure analysis (64% vs. 63%) and the as-treated analysis (97% for both arms) (figure 3*A*). The proportions of patients who achieved HIV-1 RNA levels of <50-copies/mL at week 48 in the 3TC q.d. and 3TC b.i.d. arms were also determined to be equivalent according to the ITT missing-equals-failure analysis (59% vs. 61%) and the as-treated analysis (90% vs. 95%) (figure 3*B*).

Analysis by virus load stratum. At week 48, in the stratum of patients who had HIV-1 RNA levels of ⩽100,000 copies/mL at screening, equivalent proportions of patients in the 3TC q.d. and 3TC b.i.d. arms achieved HIV-1 RNA levels of <400 copies/mL (ITT missing-equals-failure analysis, 62% vs. 67%; as-treated analysis, 97% vs. 98%; figure 4*A*) and of <50 copies/mL (ITT missing-equals-failure analysis, 59% vs. 66%; as-treated analysis, 92% vs. 97%; figure 4*B*).

In the stratum of patients who had HIV-1 RNA levels of >100,000 copies/mL at screening, the proportion of patients who achieved plasma HIV-1 RNA levels of <400 copies/mL at week 48 was higher in the 3TC q.d. arm than in the 3TC b.i.d. arm, according to the ITT missing-equals-failure analysis (68% vs. 53%). This finding possibly reflects the fact that there were more patients who discontinued therapy as a result of adverse events in the 3TC b.i.d. arm than in the 3TC q.d. arm (16% vs. 3%). In the same stratum of patients, the proportion of who achieved plasma HIV-1 RNA levels of <400 copies/mL at week 48 was similar in both arms of the study, according to the as-treated analysis (96% vs. 93%). Despite these differences, both analyses confirmed the equivalence of the regimens. Using the Ultrasensitive assay, results obtained for patients who had HIV-1 RNA levels of >100,000 copies/mL at screening also showed equivalence of the 3TC q.d. and 3TC b.i.d. regimens, with similar proportions of patients achieving HIV-1 RNA levels of <50 copies/mL at week 48 (ITT missing-equals-failure analysis, 59% vs. 48%; as-treated analysis, 85% vs. 88%).

The Kaplan-Meier plot of time to failure of treatment was similar between treatment arms (figure 5). Within the final time interval of the study (weeks 40–48), 67% of patients in the 3TC q.d. arm (95% CI, 0.61–0.73) and 65% of patients in the 3TC b.i.d. arm (95% CI, 0.60– 0.71) had plasma HIV-1 RNA

Table 1. Baseline characteristics of patients participating in a study comparing once-daily and twice-daily regimens of lamivudine (3TC), by treatment group.

Characteristic	3TC q.d. (n = 278)	3TC b.i.d. (n = 276)
Sex		
Male	227 (82)	210 (76)
Female	51 (18)	66 (24)
Age, median years (range)	35 (19–74)	35 (18–72)
Race		
White	136 (49)	142 (51)
Black	83 (30)	68 (25)
Hispanic or Latino	50 (18)	57 (21)
Other	9 (3)	9 (3)
CDC disease stage		
A[a]	226 (81)	221 (80)
B[b]	40 (14)	46 (17)
C[c]	12 (4)	9 (3)
HIV type 1 RNA level		
No. of patients, copies/mL		
⩽100,000	202	196
>100,000	76	80
Median, $\log_{10}$ copies/mL	4.64	4.69
$CD4^+$ cell count, median cells/mm^3 (range)	340 (69–945)	386 (80–1089)
Premature discontinuation of treatment	79 (28)	86 (31)
Primary reason for premature discontinuation of treatment		
Adverse event	18 (6)	34 (12)
Protocol-defined virologic failure	5 (2)	9 (3)
Insufficient virus load response	4 (1)	1 (<1)
Clinical progression of disease	1 (<1)	0
Protocol violation	8 (3)	4 (1)
Consent withdrawn/lost to follow-up	38 (14)	36 (12)
Other[d]	5 (2)	2 (1)

NOTE. Data are no. (%) of patients, unless otherwise indicated. Both regimens also included efavirenz (600 mg q.d.) and zidovudine (300 mg b.i.d.). CDC, Centers for Disease Control and Prevention.

[a] Mildly symptomatic.
[b] Moderately symptomatic.
[c] Severely symptomatic.
[d] Includes patients who, on the basis of the applied time-windows, missed the week-48 assessments.

levels of <400 copies/mL with no disease progression to class C, indicating no difference between the 2 treatment regimens with respect to the time to failure of treatment.

$CD4^+$ cell counts. At baseline, the median $CD4^+$ cell counts were 340 cells/mm^3 and 386 cells/mm^3 in the 3TC q.d. and 3TC b.i.d. arms, respectively. At week 48, the proportions of patients who had $CD4^+$ cell count increases of >50 cells/mm^3 were equivalent (3TC q.d. group, 236 [89%] of 278 patients; 3TC b.i.d. group, 239 [89%] of 276 patients), as were median increases above baseline in absolute $CD4^+$ cell counts (3TC q.d. group, +144 cells/mm^3; 3TC b.i.d. group, +146 cells/mm^3).

Progression of disease. Incidences of HIV-associated conditions were comparable between treatment arms, with 16 (6%) of the patients in the 3TC q.d. treatment arm and 23 (8%) of the patients in the 3TC b.i.d. treatment arm reporting ⩾1 HIV-associated condition during the study. The majority of patients in both 3TC treatment arms did not experience progression of HIV disease during the study, and the proportions of patients who did not experience disease progression were similar between the 2 treatment groups (3TC q.d. group, 273 [98%] of 278 patients; 3TC b.i.d. group, 268 [97%] of 276 patients).

Resistance analysis. The incidence of virologic failure was

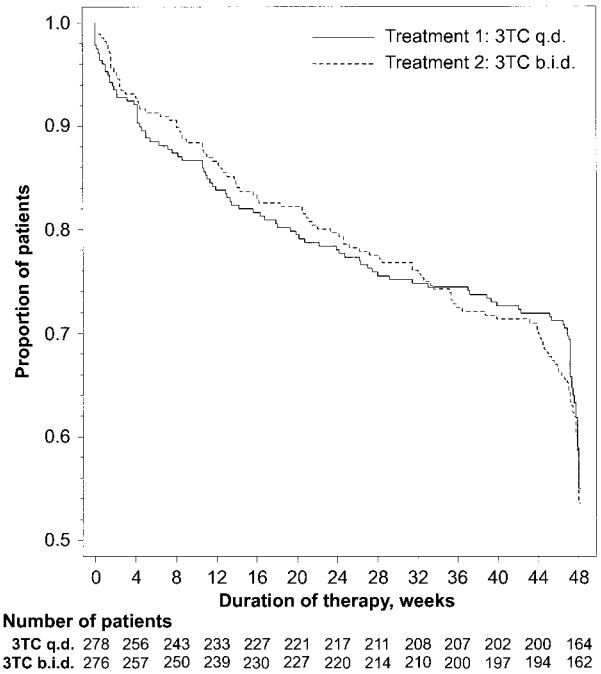

Figure 2. Kaplan-Meier estimates of time to discontinuation of treatment, according to an intent-to-treat, missing-equals-failure analysis. $P = .7577$, by log rank test stratified by baseline HIV-1 RNA level; $P = .7871$, by unstratified log rank test. 3TC, lamivudine.

low (53 [10%] of 545 patients experienced virologic failure by week 48) and was similar between the 2 treatment arms. Twenty-eight (53%) of the 53 patients who experienced virologic failure were in the 3TC q.d. arm, and 25 (47%) were in the 3TC b.i.d. arm. Fourteen (32%) of 44 patients who had genotyping performed after baseline had virus that developed 3TC mutations while they were receiving treatment. Eight of these patients were in the 3TC q.d. arm, and 6 patients were in the 3TC b.i.d. arm. There was no statistical difference between the 2 treatment groups with respect to the development of 3TC genotypic drug resistance ($P = .747$). Six of 14 patients (4 in the 3TC q.d. group and 2 in the 3TC b.i.d. group) had evidence of resistance to $\geq$1 drug in the study at baseline, as determined by genotype and/or phenotype. Of the 14 patients with virus that developed 3TC genotypic drug resistance, 8 had virus with drug-resistance phenotypes on treatment, as well. In each of the latter 8 patients, phenotypic determinations confirmed the genotypic result. Virus isolated from 3 additional patients (2 in the 3TC q.d. group and 1 in the 3TC b.i.d. group) was found to be resistant to 3TC according to phenotype only, with no corresponding drug-resistant genotype.

Adverse events. The 3TC q.d. and 3TC b.i.d. regimens were generally well tolerated, with no differences between the 2 regimens in type or incidence of drug-related adverse events or grade 3/4 laboratory abnormalities (as defined by the World Health Organization) and with no deaths (table 2). More patients in the 3TC b.i.d. treatment arm prematurely discontinued use of the study drug due to adverse events (34 [13%] of 276 vs. 19 [7%] of 278), primarily nausea (4% vs. 2%) and dizziness (3% vs. <1%).

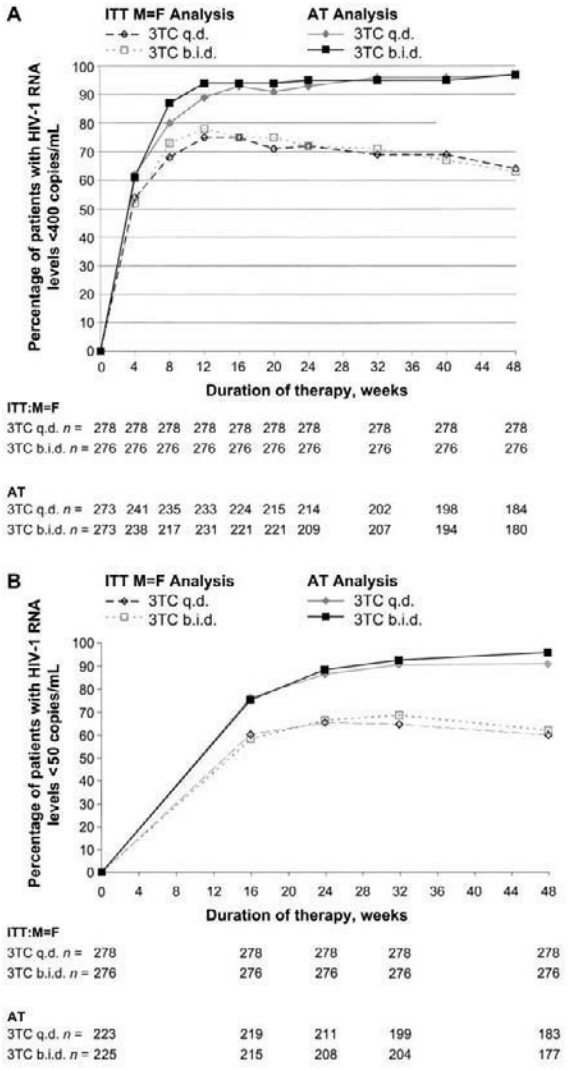

Figure 3. *A,* The percentage of patients in the lamivudine (3TC) q.d. and 3TC b.i.d. arms who achieved HIV-1 RNA levels of <400 copies/mL at week 48. According to an intent-to-treat, missing-equals-failure (ITT M=F) analysis, data are as follows: 178 (64%) of 278 patients vs. 174 (63%) of 276 patients; treatment difference, 1; 95% CI, −7.1 to 8.9. According to an as-treated (AT) analysis, data are as follows: 178 (97%) of 184 patients vs. 174 (97%) of 180 patients; treatment difference, 0.1; 95% CI, −3.6 to 3.7. *B,* The percentage of patients in the 3TC q.d. and 3TC b.i.d. arms who achieved HIV-1 RNA levels of <50 copies/mL at week 48. According to an ITT M=F analysis, data are as follows: 165 (59%) of 278 patients vs. 168 (61%) of 276 patients; treatment difference, −1.5; 95% CI, −9.7 to 6.6. According to an AT analysis, data are as follows: 165 (90%) of 183 patients vs. 168 (95%) of 177 patients; treatment difference, −4.8; 95% CI, −10.1 to 0.6.

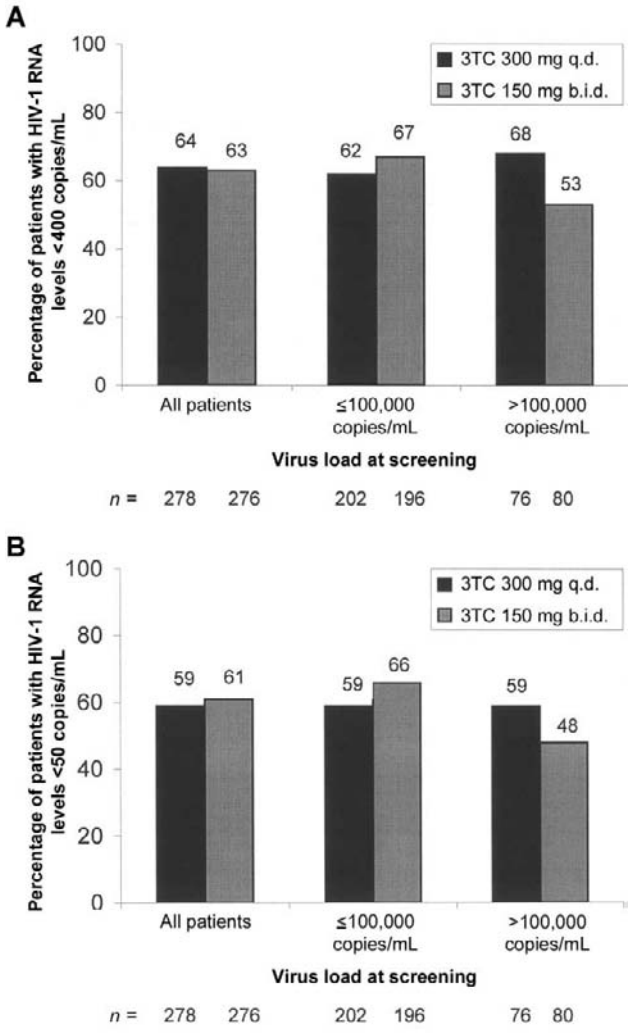

Figure 4. Percentage of patients with HIV-1 RNA levels of <400 copies/mL *(A)* and <50 copies/mL *(B)* after 48 weeks of therapy with either lamivudine (3TC) 300 mg q.d. or 3TC 150 mg b.i.d., by virus load at screening. Data was determined by an intent-to-treat, missing-equals-failure analysis.

DISCUSSION

The results of this study show that a 300-mg once-daily regimen of 3TC, administered with efavirenz (600 mg q.d.) and zidovudine (300 mg b.i.d.), produces virologic suppression equivalent in magnitude and durability to that seen with the standard 3TC regimen of 150 mg b.i.d. plus efavirenz and zidovudine. Equivalent virologic efficacy and increases in $CD4^+$ cell count were expected in view of a study by Yuen et al. [12] that showed that equivalent 3TC steady-state plasma concentrations and intracellular 3TC-triphosphate concentrations were produced after treatment with 3TC 300 mg q.d. and 150 mg b.i.d. regimens. In addition to receiving the same concurrent antiretroviral drugs at a fixed dose (zidovudine 300 mg b.i.d. and efavirenz 600 mg q.d.), patients in the 3TC q.d. and 3TC b.i.d. arms in our study were well matched with respect to sex, baseline virus load, and baseline $CD4^+$ cell counts. Therefore, if any differences in efficacy or safety had existed, diversity in patient characteristics and in disease severity would not have been contributory.

Previous studies of HAART with once-daily 3TC in treatment-naive patients have reported HIV-1 RNA levels of <400 copies/mL in 80%–100% of patients after up to 48 weeks of therapy, although the populations evaluated were generally small (10–40 patients) [14, 15, 18–26]. The 3TC b.i.d. regimen evaluated in the present study was previously compared with a regimen of abacavir (300 mg b.i.d.)/zidovudine (300 mg b.i.d.)/efavirenz (600 mg q.d.) in 654 treatment-naive patients with baseline median HIV-1 RNA levels of 4.79 $\log_{10}$ copies/mL [26]. At 48 weeks, the 3TC b.i.d. regimen had virologic efficacy comparable to that observed in the present study, and it was noninferior to the abacavir/zidovudine/efavirenz regimen (median HIV-1 RNA level, ≤50 copies/mL; virologic efficacy, 69% vs. 70% [according to an ITT analysis of subjects exposed to the study drug]) [26].

Our study showed that, compared with the 3TC b.i.d. regimen, the 3TC q.d. regimen produced virologic suppression that was as potent and durable in patients with high screening virus loads of >100,000 copies/mL as it was in patients with

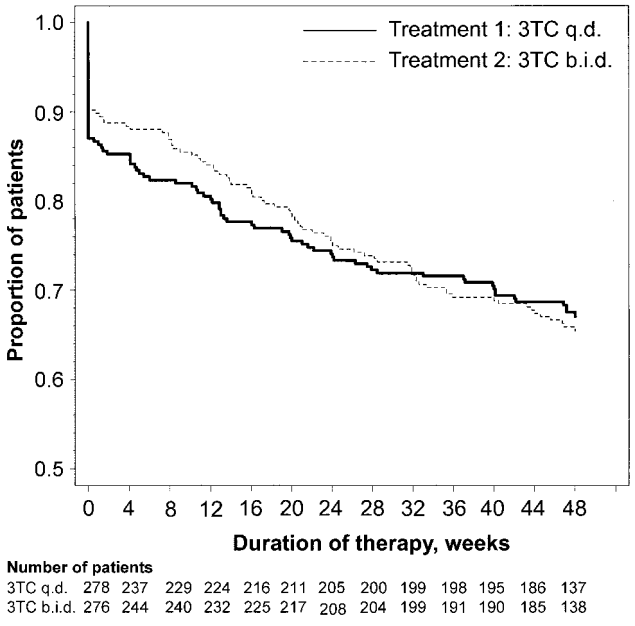

Figure 5. Kaplan-Meier estimates of time to treatment failure (with use of an intent-to-treat, missing-equals-failure analysis). The durability of the plasma HIV type 1 RNA response was evaluated as time to treatment failure, where event-time was calculated by averaging the time of the visit when the event was observed and the time of the prior visit. The distribution of time-to-event was estimated using Kaplan-Meier product-limit estimates and is presented graphically. The null hypothesis of no treatment effect was evaluated using the log-rank test. 3TC, lamivudine.

Table 2. Drug-related adverse events and laboratory abnormalities among patients participating in a study comparing once-daily and twice-daily regimens of lamivudine (3TC).

Event or abnormality	No. (%) of patients, by treatment group	
	3TC q.d. (n = 272)	3TC b.i.d. (n = 273)
Adverse event reported in ⩾10% of patients in either arm[a]		
Nausea	84 (31)	96 (35)
Dizziness	76 (28)	90 (33)
Dreams	69 (25)	62 (23)
Fatigue	61 (22)	56 (21)
Headaches	48 (18)	38 (14)
Rashes	38 (14)	37 (14)
Sleep disorders	38 (14)	32 (12)
Mood disorders	30 (11)	21 (8)
Vomiting	18 (7)	28 (10)
Diarrhea	26 (10)	18 (7)
Grade 3/4 laboratory abnormalities[b]		
Neutrophil count	15 (6)	17 (6)
Hemoglobin level	2 (<1)	2 (<1)
Platelet count	0	1 (<1)
WBC count	2 (<1)	1 (<1)
Aspartate aminotransaminase level	4 (2)	10 (4)
Alanine aminotransaminase level	9 (3)	14 (5)
Alkaline phosphatase level	0	1 (<1)
Total serum bilirubin level	0	1 (<1)
Amylase level	8 (3)	4 (2)
Hypertriglyceridemia	11 (4)	8 (3)
Hyperglycemia	1 (<1)	4 (2)
Hypercholesterolemia	2 (<1)	0
Hyperkalemia	0	1 (<1)

NOTE. Both regimens also included efavirenz (600 mg q.d.) and zidovudine (300 mg b.i.d.).

[a] Forty-five patients (8%) experienced a serious adverse event; these events were considered to be attributable to the study drug by the investigator for 8 patients In the 3TC q.d. group, these adverse events were anemia (in 1 patient) and abdominal pain, nausea, and vomiting (in 1 patient); in the 3TC b.i.d. group, these adverse events were rash (in 3 patients), hypotension (in 1 patient), acidosis (in 1 patient), and hepatitis (in 1 patient).

[b] As defined by the World Health Organization.

screening virus loads of ⩽100,000 copies/mL. The virologic findings of our study indicated that the 3TC q.d./zidovudine/efavirenz regimen, like the 3TC b.i.d./zidovudine/efavirenz regimen, may be an important treatment option for patients in whom treatment is initiated at high virus loads. The 3TC q.d. regimen has the added benefit of a smaller pill burden. Because of its simplicity, the 3TC q.d. regimen would be expected to be valuable in treating patients with a history of nonadherence to medications. This is important because ⩾95% adherence to antiretroviral regimens is needed to ensure maximal virologic suppression [4].

The equivalence in virologic efficacy between the 3TC q.d. and 3TC b.i.d. regimens that was demonstrated in this study was supported by genotypic and phenotypic findings. These results suggest that, through 48 weeks of therapy, the use of once-daily dosing does not increase the incidence or the time to emergence of the M184V mutation or resistance to other study drugs in the regimen. Although steady-state trough concentrations of intracellular 3TC-triphosphate after 7 days of treatment with a 300-mg once-daily regimen of 3TC were previously shown to be 18%–24% lower than after 7 days of treatment with a 150-mg twice-daily regimen of 3TC, these trough concentrations nevertheless remain in the range associated with optimal virologic suppression [12]. A detailed analysis of the genotypic and phenotypic findings of this study has confirmed that there were no differences in drug resistance in general or in NRTI mutations in particular between the 3TC q.d. and 3TC b.i.d. regimens [27].

The safety profile of 3TC administered as a 300-mg single dose did not differ from the safety profile observed with the standard 3TC 150 mg b.i.d. regimen. Treatment with 3TC, 300 mg q.d., is known to produce maximum 3TC plasma concentrations at steady state that are 66% higher than those after treatment with 3TC, 150 mg b.i.d. [12]. However, plasma levels this high were not shown to affect the type or incidence of adverse events during 7 days of administration in a pharmacokinetic study [12]. Moreover, the 3TC expanded access trial (protocol NUCA3004), which involved 24,229 patients, showed that monotherapy with 3TC, 300 mg b.i.d. (twice the standard daily dose), administered for an average of 230 days, did not result in a greater incidence of adverse events or laboratory abnormalities than did lamivudine, 150 mg b.i.d., given as monotherapy (GlaxoSmithKline, unpublished data). It is unclear why the 3TC b.i.d. regimen was associated with more incidents of nausea than was the 3TC q.d. regimen in the present study.

Although our study had many strengths (e.g., double-blind design; large, diverse population; and long duration), it did have a few limitations. Ideally, for once-daily regimens to optimally facilitate adherence, all components should be given once per day [28]. In our study, 2 of the components of the 3TC q.d. regimen, zidovudine and 3TC placebo, were administered twice per day. Although zidovudine has been evaluated when administered as a 600-mg once-daily regimen and has been shown not to be significantly different from the standard 300-mg twice-daily regimen with respect to safety, genotypic changes, and pharmacodynamic effects [29], zidovudine intracellular trough levels produced by the once-daily regimen are lower and are periodically subtherapeutic; therefore, once-daily use is not supported (GlaxoSmithKline, unpublished data). This study did not evaluate adherence, which is often given as a key reason for considering a once-daily regimen. However, because of the double-blind design of this study, an equivalent pill count had to be administered in both arms. Thus, had

adherence data from the once-daily arm been generated, such data would not have been representative of or meaningful to the setting of actual clinical practice, in which the pill burden of the once-daily regimen administered is lower.

In conclusion, the results of this study indicate that, during 48 weeks of therapy, 3TC q.d. and 3TC b.i.d., in combination with zidovudine and efavirenz, demonstrated equivalent, sustained virologic suppression and similar immunological response and safety profiles in antiretroviral-naive patients with HIV infection.

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