Simplification Therapy with Once-Daily Emtricitabine, Didanosine, and Efavirenz in HIV-1–Infected Adults with Viral Suppression Receiving a Protease Inhibitor–Based Regimen: A Randomized Trial

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Background. We assessed a once-daily combination to simplify therapy in patients infected with human immunodeficiency virus type 1 (HIV-1).

Methods. A total of 355 adults with plasma HIV-1 RNA levels <400 copies/mL were randomly assigned to either switch to once-daily emtricitabine, didanosine, and efavirenz (n = 178) or maintain their protease inhibitor (PI)–based regimens (n = 177). The primary end point was sustained suppression of plasma HIV-1 RNA levels to <400 copies/mL.

Results. At week 48, the proportion of patients meeting the end point was 87.6% in the PI group and 90.5% in the once-daily group, with a treatment difference of 2.9% (upper bound of the 1-tailed 95% confidence interval, 2.6%). The proportion of patients with HIV-1 RNA levels <50 copies/mL was higher in the once-daily group (87%) than in the PI group (79%) (P < .05). Resistance mutations to efavirenz and emtricitabine were detected in all patients in the once-daily group who experienced virologic failure while receiving study medication. The proportion of patients discontinuing study medication because of adverse events was similar between the once-daily group (9%) and the PI group (10%) (P = .8).

Conclusions. Substituting a convenient once-daily combination of emtricitabine, didanosine, and efavirenz for a PI-based regimen was well tolerated and associated with sustained virologic suppression.

HIV-1 infection is now a chronic manageable disease that requires life-long therapy [1–4]. However, the substantial benefits conferred by antiretroviral therapy require a high rate of adherence to treatment regimens, which were initially protease inhibitor (PI) based [4–5]. These regimens are often complex, and failure of antiretroviral therapy is often due to poor adherence [6–10]. Also, antiretroviral therapy, including PI-based regimens, has been associated with morphologic changes and metabolic abnormalities that could further decrease adherence and that are potentially atherogenic [11–13].

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The investigators participating in the ALIZE study are listed after the text.
Thus, strategies of simplifying antiretroviral therapy should increase adherence and the likelihood of treatment success. Reducing the pill burden by replacing the PI with a nonnucleoside reverse-transcriptase inhibitor (NNRTI) has become an increasingly popular strategy [14–18]. In an effort to further optimize the convenience of antiretroviral therapy, we have assessed a once-daily regimen combining emtricitabine, didanosine, and efavirenz. The results of a previous pilot study are encouraging [19]. To confirm these observations, we designed a large, randomized, comparative trial in which patients successfully treated with a PI-based regimen were switched to this once-daily combination.

PATIENTS, MATERIALS, AND METHODS

Patients. Eligible patients were HIV-1–infected adults who were receiving antiretroviral therapy consisting of at least 1 PI plus 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and who had a CD4 cell count ≥100 cells/mm³, were naive to NNRTIs, and had plasma HIV-1 RNA levels <400 copies/mL for at least 6 months. Exclusion criteria were pregnancy, prior treatment with NNRTIs, prior virologic failure of the PI-based regimen, and a history of peripheral neuropathy or pancreatitis. Additional exclusion criteria were a hemoglobin level <10 g/dL, a neutrophil count <1000 cells/mm³, a platelet count <50,000 platelets/mm³, serum amylase or creatinine levels ≥2 times the upper limit of normal, and total bilirubin level or hepatic aminotransferase levels ≥3 times the upper limit of normal. Suboptimal antiretroviral therapy with NRTIs alone, before starting PI-based therapy, was not an exclusion criterion, provided that the patients had not received didanosine monotherapy and were receiving lamivudine at baseline.

Study design. The study was a multicenter, randomized, open-label, comparative 48-week trial performed at 58 centers in France. The protocol was approved by the Paris Saint-Louis ethics committee. All patients gave written, informed consent. Randomization was performed by a centralized procedure and was stratified on the basis of center and on previous exposure to suboptimal therapy with NRTIs.

Patients were randomly assigned, at a ratio of 1:1, to either switch to a once-daily combination of emtricitabine, didanosine, and efavirenz (once-daily group) or maintain their PI-based antiretroviral regimens (PI group). Emtricitabine was provided as 1 200-mg capsule, didanosine as either 1 400-mg capsule, or efavirenz as 3 200-mg capsules. Patients were instructed to take all 5 pills together at least 2 h after dinner. The whole regimen, as randomized, was called “study medication.”

Study monitoring. Patients were assessed at baseline, week 4, week 8, and every 8 weeks thereafter. At each visit, clinical data were collected through medical history and physical examination, and blood specimens were obtained. Routine analyses were performed at each site throughout the study period and included a complete blood count, CD4 cell count, measurement of plasma HIV-1 RNA level (Chiron and Roche assays were used in the present study, but a patient had to be tested by the same assay throughout the study), and tests of liver, kidney, muscle, and pancreatic function. Furthermore, at baseline and every 8 weeks thereafter, glucose, triglyceride, total cholesterol, and low- and high-density lipoprotein cholesterol (HDL-C) levels were measured after an overnight fast. Safety was assessed through the reporting of adverse events and abnormal laboratory measurements. The severity of adverse events was assessed by use of the Agence Nationale de Recherches sur le SIDA (ANRS) toxicity grading scale (available at: http://www.isped.u-bordeaux2.fr/RECHERCHE/GETSI/grilles_gravite/FR-GETSI-ANRS-099-grille-ANRS.htm). Only events judged to be definitely, probably, possibly, or likely related to study medication (adverse reactions) were analyzed. Only events not related to study medications were excluded.

For patients who discontinued study medication because of adverse events, physicians were asked to substitute, if possible, nevirapine for efavirenz in the once-daily group (with the recommendation of prescribing the full dose of 400 mg/day after a 2-week period of 200 mg/day) and to use another PI in the PI group, to maintain the treatment strategy in both groups. When a plasma HIV-1 RNA level ≥400 copies/mL was measured in a patient at a center (local measurement), a second plasma sample was obtained within 15–30 days and was sent to the central laboratory of virology for confirmation of virologic failure (confirmatory measurement). For patients who experienced virologic failure while receiving study medication, a genotypic resistance test was performed in accordance with the consensus method of the ANRS resistance group [20]. HIV-1 mutations associated with drug resistance were defined according to the International AIDS Society–USA drug resistance mutations group definition [21]. For patients with resistance-associated mutations at the time of virologic failure, proviral DNA obtained from peripheral blood mononuclear cells at baseline was amplified, to detect archived preexisting mutations. Results of genotypic resistance tests were available to investigators, to allow them to make informed decisions to modify therapy.

At the end of the study, plasma samples collected at each visit at the different centers were centralized, to retest plasma HIV-1 RNA levels by use of the Amplicor HIV-1 Monitor 1.5 ultrasensitive assay (Roche Molecular Systems), which has a lower limit of quantification of 50 copies/mL. At baseline and at weeks 24 and 48, patients were also assessed for morphologic changes related to body-fat abnormalities, by their physicians, who used
a specific questionnaire. Patients were categorized as having lipodystrophy, lipohypertrophy, or both, the severity of which was graded as mild, moderate, or severe, as described elsewhere [22]. Adherence to study medication was assessed at baseline and every 4 weeks, by patient self-reporting by use of questionnaires about the number of pills not taken during the 4 days before each visit [23]. Full adherence during the study period was defined as 100% of the pills taken during the 4 days before all visits, calculated by use of available questionnaires only.

**Study end points and definitions.** The primary efficacy end point was the proportion of patients with sustained viral suppression from weeks 0 to 48, defined as the nonoccurrence of virologic failure from weeks 0 to 48. Virologic failure was defined for the primary efficacy end point as the occurrence of 2 consecutive measurements of plasma HIV-1 RNA levels $\geq 400$ copies/mL. The date of virologic failure was defined as the date of the first measurement $\geq 400$ copies/mL. Secondary end points included the time to virologic failure; the proportion of patients with sustained viral suppression (determined by use of a threshold of 50 copies/mL and defined as the nonoccurrence of virologic failure from weeks 0 to 48—i.e., 2 consecutive measurements of plasma HIV-1 RNA levels $\geq 50$ copies/mL); changes in CD4 cell counts; clinical progression to AIDS (defined as the occurrence of any new clinical event included in category C of the 1993 classification of the Centers for Disease Control and Prevention [24]); the proportion of patients with moderate (grade 2) to severe (grade 4) clinical adverse reactions and laboratory abnormalities, with body-fat abnormalities, who discontinued study medication (defined as a change of at least 1 drug in the whole randomized antiretroviral regimen), and who were fully adherent to study medication; and changes in plasma glucose and lipids levels.

**Statistical analysis.** The sample size was calculated on the basis of the primary virologic end point, to show noninferiority of the once-daily group, compared with the PI group. For this purpose, we assumed that the upper bound of the 1-tailed 95% confidence interval (UBCI) of the difference between the groups (PI group minus once-daily group) was $\leq 15\%$. On the basis of an expected virologic suppression rate of 75% in the PI group, 175 patients/group were required for this noninferiority assessment, with a 1-sided $\alpha$ level of 0.05 and a statistical power of 80%.

The primary efficacy end point was analyzed on an intention-to-treat basis, including all randomized patients, and all patients for whom plasma viral load data were missing were considered to have experienced treatment failure, (i.e., >400 copies/mL). Patients who discontinued study medication and switched antiretroviral therapy continued to be followed until the end of the study so that any subsequent virologic failure contributed to this analysis. To confirm the primary analysis, an analysis of sensitivity to missing data was performed by use of the worst-case methodology, in which all patients for whom plasma viral load data were missing were considered to have experienced treatment failure, in the once-daily group, but not in the PI group. The primary efficacy end point was also analyzed on a receiving-study-medications basis (including all randomized patients continuing study medication and censoring those who discontinued study medication, were lost to follow-up, or withdrew from the study), and patients for whom plasma viral load data were missing were considered to have experienced treatment failure.

Probability of virologic failure and probability of treatment-limiting adverse reactions were estimated by use of the Kaplan-Meier method, and comparison between the groups was performed by use of a log rank test. Comparison of the proportion of patients with lipodystrophy in each group was performed by use of a logistic regression test, with adjustment on week-0 proportions. Otherwise, proportions of patients with adverse reactions at week 48 were compared by use of the $\chi^2$ test, and median changes in plasma lipid levels at week 48 were compared by use of the Kruskal-Wallis test. Two-sided $p$ values are reported for each comparison. Statistical analyses were performed by use of SAS software (version 8.2; SAS Institute).

**RESULTS**

**Study population.** Between May 2000 and April 2001, 389 patients underwent screening procedures, and 355 were found to be eligible for randomization into the study (figure 1). The baseline characteristics of the patients were well balanced between the groups (table 1). Overall, 77% of the patients in the PI group and 85% of the patients in the once-daily group completed 48 weeks of therapy receiving their randomized study medication ($P = .10$) (figure 1). Adverse events were the most common reason for early discontinuation of study medication.

**Study end points.** In the intention-to-treat analysis, in which patients for whom plasma viral load data were missing were considered to have experienced treatment failure, the proportion of patients with sustained virologic suppression was 87.6% in the PI group and 90.5% in the once-daily group. The treatment difference was $-2.9\%$, with a UBCI of 2.6% (i.e., below the predefined noninferiority threshold of 15%). Therefore, the noninferiority of the once-daily group, compared with the PI group, was demonstrated. The Kaplan-Meier estimates of the probability of follow-up without virologic failure (defined as the occurrence of 2 consecutive measurements of plasma HIV-1 RNA levels $\geq 400$ copies/mL) were similar between the 2 groups ($P = .50$, log rank test) (figure 2A).

To further assess the robustness of this result, missing virologic data were assessed by use of the worst-case methodology in the once-daily group, but not in the PI group. In this analysis, the difference between the groups was 1.6%, with a UBCI of 6.6%, which is still $<15\%$ (data not shown).
Once-Daily Antiretroviral Therapy for HIV-1 Infection

Figure 1. Profile of patient enrollment and discontinuation of study medication through week 48. Among the 37 patients who discontinued study medication in the protease inhibitor (PI) group, 27 maintained the same treatment strategy and used another PI-based regimen (*). Similarly, among the 24 patients who discontinued study medication in the once-daily group, 13 maintained the same treatment strategy and switched from efavirenz to nevirapine once daily. One patient with a history of toxoplasma encephalitis died at week 4 from generalized convulsions (**). Seven patients in the PI group and 1 in the once-daily group continued to take study medication up to week 48 despite virologic failure (***)

In the receiving-study-medication analysis, in which patients for whom plasma viral load data were missing considered to have experienced treatment failure, the proportion of patients with sustained virologic suppression was 93.1% in the PI group and 96.0% in the once-daily group. The treatment difference was −2.8%, with a UBCI of 1.2%, which is below the predefined noninferiority threshold of 15%. The Kaplan-Meier estimates of the probability of follow-up without virologic failure were again similar between the 2 groups (P = .27, log rank test) (figure 2B).

In an intention-to-treat analysis by strata, we found that patients who had received prior suboptimal antiretroviral therapy with mono- or dual-NRTIs alone were not at a higher risk for virologic failure (10% vs. 11%; P = .58, log rank test) (data not shown). In an assessment of secondary virologic end points in an intention-to-treat analysis restricted to measures of plasma HIV-1 RNA centralized at the end of study, in which patients for whom plasma viral load data were missing were considered to have experienced treatment failure, the Kaplan-Meier estimates of the probability of follow-up without virologic failure (defined here as the occurrence of 2 consecutive measurements of plasma HIV-1 RNA levels ≥50 copies/mL) were higher in the once-daily group (87%) than in the PI group (79%) (P < .05, log rank test) (figure 3).

There were no significant differences between the groups in median CD4 cell counts over time. At week 48, the median increases from baseline were 15 and 16 CD4 cells/mm³ in the PI and once-daily groups, respectively (P = .68, Kruskal-Wallis test). No patient experienced progression to AIDS during the study, and only 1 patient, who had a history of toxoplasma encephalitis and was randomized to the PI group, died from generalized convulsions. During the course of the study, among the 14 patients who experienced virologic failure while receiving study medication, 13 (5 in the once-daily group and 8 in the PI group) had an amount of plasma HIV-1 RNA that could be amplified to perform a genotypic resistance test.

Among the 5 genotypes available in the once-daily group, mutations associated with resistance to efavirenz were detected in all samples, at position K103N in 4 and at L100I in 2, none of which was present at baseline in proviral DNA. Furthermore, all genotypes also showed the M184V mutation associated with resistance to emtricitabine. One sample carried the L74V mutation associated with resistance to didanosine. Among the 8 genotypes available in the PI group, however, only 3 had major mutations associated with resistance to PIs, at positions D30N in 1, at M46L in 2, and at V82T and L90M in 1. In 1 patient, these mutations (V82T, M46L, and L90M) were seen in proviral DNA at baseline. The M184V mutation was detected in 5 samples.

Safety and tolerability. There was a trend toward a higher overall incidence of patients who experienced grade 2–4 adverse reactions in the once-daily group (85 patients [48%]) than in the PI group (67 patients [38%]) (P = .06, χ² test) (data not shown). This difference was mainly observed during the first 4 weeks of the study and was related to the rapid emergence of neurosensory adverse reactions (mainly abnormal dreams, dizziness, and headaches) in the once-daily group. These adverse reactions were the main reason for discontinuation of study medication in this group (12 patients [7%]). More patients in the once-daily group (12 vs. 3 in the PI group) also experienced increases in liver aminotransferase levels, but only 2 discontinued study medication. However, the incidence of all grade 4 adverse reactions was similar in the PI group (8 patients [5%]) and in the once-daily group (10 patients [6%]) (P =
Table 1. Baseline characteristics of the patients.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>PI (n = 177)</th>
<th>Once daily (n = 178)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median (interquartile range), years</td>
<td>41 (35–51)</td>
<td>41 (36–47)</td>
</tr>
<tr>
<td>Male, no. (%)</td>
<td>154 (87)</td>
<td>152 (85)</td>
</tr>
<tr>
<td>Route of HIV-1 infection, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male homosexual sex</td>
<td>99 (56)</td>
<td>87 (48)</td>
</tr>
<tr>
<td>Heterosexual sex</td>
<td>46 (26)</td>
<td>60 (34)</td>
</tr>
<tr>
<td>Injection drug use</td>
<td>11 (6)</td>
<td>17 (10)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>21 (12)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>AIDS, no. (%)</td>
<td>45 (25)</td>
<td>50 (28)</td>
</tr>
<tr>
<td>CD4 cell count, median (interquartile range), cells/mm³</td>
<td>547 (396–740)</td>
<td>509 (375–756)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA level &lt;50 copies/mL,a no. (%)</td>
<td>152 (89)</td>
<td>158 (92)</td>
</tr>
<tr>
<td>PI, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Indinavir</td>
<td>87 (49)</td>
<td>66 (37)</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>65 (37)</td>
<td>68 (38)</td>
</tr>
<tr>
<td>Ritonavir</td>
<td>8 (5)</td>
<td>11 (6)</td>
</tr>
<tr>
<td>Combinations with low-dose ritonavir</td>
<td>13 (7)</td>
<td>27 (15)</td>
</tr>
<tr>
<td>Other</td>
<td>4 (2)</td>
<td>6 (3)</td>
</tr>
<tr>
<td>NRTIs, no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zidovudine plus lamivudine</td>
<td>76 (43)</td>
<td>74 (42)</td>
</tr>
<tr>
<td>Stavudine plus lamivudine</td>
<td>77 (44)</td>
<td>81 (46)</td>
</tr>
<tr>
<td>Stavudine plus didanosine</td>
<td>16 (9)</td>
<td>14 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>8 (5)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Duration of HAART, median (interquartile range), months</td>
<td>34 (26–45)</td>
<td>36 (25–47)</td>
</tr>
<tr>
<td>Prior suboptimal therapy with NRTIs, no. (%)</td>
<td>79 (45)</td>
<td>83 (47)</td>
</tr>
<tr>
<td>Metabolic values,b median (interquartile range), mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>90 (83–101)</td>
<td>88 (79–95)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>221 (199–251)</td>
<td>216 (191–243)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (38–54)</td>
<td>45 (38–56)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>149 (97–228)</td>
<td>137 (89–218)</td>
</tr>
<tr>
<td>Lipodystrophy (all grades), no. (%)</td>
<td>68 (38)</td>
<td>53 (30)</td>
</tr>
<tr>
<td>Lipohypertrophy</td>
<td>81 (46)</td>
<td>76 (43)</td>
</tr>
<tr>
<td>Lipoatrophy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete adherence to the current regimen,c no. (%)</td>
<td>124 (89)</td>
<td>120 (92)</td>
</tr>
</tbody>
</table>

**NOTE.** HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein cholesterol; NRTIs, nucleoside reverse-transcriptase inhibitors.

a Data available for 171 patients in the protease inhibitor (PI) group and 172 in the once-daily group.

b Measured after an overnight fast.

c Only 140 questionnaires were available from the PI group and 131 from the once-daily group.

Furthermore, the number of patients in each group who discontinued study medication because of adverse events was similar (17 patients [10%] in the PI group vs. 16 patients [9%] in the once-daily group) ($P = .8$, $\chi^2$ test). The main reasons for discontinuation of study medication in the PI group were gastrointestinal adverse reactions ($n = 5$), lipoatrophy ($n = 3$), and neuropsychiatric ($n = 3$), renal ($n = 2$), or musculoskeletal adverse reactions ($n = 2$).

During the study, there were no significant differences between the groups in the median change from baseline in plasma total cholesterol and triglyceride levels (figure 4). However, at week 48, there was a significant increase from baseline in median plasma HDL-C levels in the once-daily group (+7.8 mg/dL), compared with that in the PI group (+0.4 mg/dL) ($P < .0001$, Kruskall-Wallis test) (figure 4). Also, at week 48, the proportion of patients with plasma HDL-C levels >60 mg/dL was significantly higher in the once-daily group (63 patients [39%]) than in the PI group (28 patients [17%]) ($P < .0001$, $\chi^2$ test) (data not shown). The proportion of patients with abnormal plasma glucose levels was not significantly different between the groups (data not shown).

Overall, the proportion of patients with lipohypertrophy remained unchanged in both groups. In contrast, the proportion of patients with lipoatrophy increased from 46% at baseline to 60% at week 48 in the PI group but remained unchanged in the once-daily group (43% at baseline and 42% at week 48) ($P < .0001$, adjusted $\chi^2$ test).

Finally, using patient self-reporting of adherence to the study...
medication during the 4 days before the visit to the physician, we observed that the proportion of patients with full adherence to study medication through week 48 was significantly higher in the once-daily group (137/168 patients [82%]) than in the PI group (108/171 patients [63%]) ($P = .0002$, $\chi^2$ test).

### DISCUSSION

The present study has shown that, in HIV-1–infected patients with suppression of viral replication receiving a PI-based regimen, a switch to a simple once-daily combination of emtricitabine and lamivudine was associated with an increased likelihood of full adherence to study medication and virologic success.
citabine, didanosine, and efavirenz was successful in maintaining durable control of plasma HIV-1 RNA through week 48. In the intention-to-treat analysis, 87.6% of patients in the PI group and 90.5% of patients in the once-daily group maintained a viral load <400 copies/mL through week 48. Moreover, in a secondary analysis, a higher proportion of patients in the once-daily group than in the PI group maintained a viral load <50 copies/mL (87% vs. 79%, respectively) (P < .05). The switch to once-daily therapy was not, however, associated with better outcomes in either CD4 cell counts or disease progression. The once-daily regimen represented only 5 pills/day. The same regimen can be administered today with only 3 pills/day by use of the new formulation of efavirenz, and it has been proven to be efficacious in a large randomized trial in antiretroviral-naive patients [25].

Emtricitabine is a novel cytidine NRTI that is a fluorinated derivative of lamivudine, which explains why the same mutation at position M184V will confer a high level of resistance to both lamivudine and emtricitabine [26]. Emtricitabine has a long plasma half-life (10 h) and an intracellular half-life of the triphosphate active moiety of >39 h [27]. Efavirenz and didenoxyadenosine-triphosphate, the active moiety of didanosine, also have long plasma and intracellular half-lives (20 and 50 h, respectively), making them very suitable drugs for a once-daily regimen [28].

One concern regarding once-daily antiretroviral therapy has been the virologic impact of missing a scheduled dose. The hazard associated with missing a dose of medication is probably more closely associated with the relationship between dosing interval and drug half-life, and missing a dose of a medication with a short half-life administered twice-daily may have greater consequences than missing a dose of a once-daily combination of drugs with very long half-lives, such as those used in the once-daily regimen assessed in the present study.

Another potential concern of this once-daily regimen is the selection for resistance mutations in patients experiencing virologic failure. Indeed, the genetic barrier to resistance is lower among patients receiving an NNRTI than among patients receiving a PI. Similar to previous studies, in the present study, patients who experienced virologic failure while receiving therapy with efavirenz were infected with viruses with mutations associated with cross-resistance to all available NNRTIs [14, 16]. This

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Figure 4. Median change in plasma total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglyceride levels (milligrams per deciliter), measured after an overnight fast, from baseline to week 48. There were no significant differences in total cholesterol (A) and triglyceride (C) levels between the groups. The median change from baseline to week 48 in HDL-C levels (B) was significantly higher in the once-daily group (dashed line) than in the protease inhibitor (PI) group (bold line) (P < .0001, Kruskall-Wallis test).
finding has to be taken into account when selecting such a regimen for patients. Also, all patients with virologic failure were infected with viruses with the M184V mutation, which confers high levels of resistance to both lamivudine and emtricitabine. Therefore, although the risk of failure was low in the once-daily group, patients who experienced treatment failure while receiving study medication developed resistance mutations to almost all drugs in the combination. In the PI group, however, the selection of resistance mutations was less frequent.

As would be expected in a population of patients successfully treated for >6 months, the incidence of adverse reactions was greater in the group of patients who switched to the once-daily regimen. However, during the 48-week follow-up, the incidence of grade 4 adverse reactions and the incidence of discontinuation of study medication were similar between the 2 groups. The difference in tolerance between the groups was seen essentially during the first 4 weeks of treatment and was mainly related to a higher incidence of neurosensorial adverse reactions in the once-daily group. We also observed a trend toward more-frequent increases in liver aminotransferase levels in the once-daily group. These increases in aminotransferase levels could be associated with any of the 3 drugs in the combination. Recent studies comparing emtricitabine to either lamivudine or stavudine found no significant difference in the incidence of increases in liver enzyme levels between these drugs [29, 25].

Interestingly, a significant increase in HDL-C levels, measured after an overnight fast, was seen in the once-daily group. Increases in HDL-C levels have already been reported among subjects receiving efavirenz-containing regimens but were usually not significant [14, 15, 17, 30]. In the present study, 39% of patients in the once-daily group, but only 17% of patients in the PI group, had an HDL-C level >60 mg/dL at week 48, a level associated with protection against cardiovascular risk [31]. Since antiretroviral therapy could be associated with a higher risk of cardiovascular disease, this benefit could be of interest [13, 32].

Also, although no significant change in the incidence of lipohypertrophy was seen in any group during the 48 weeks of the study, an increase in the incidence of lipoatrophy was observed in the PI group. No such increase was observed in the once-daily group. Although the potential benefit of a lower incidence of lipoatrophy in the once-daily group was difficult to ascertain, because we lacked objective measures of lipodystrophy and because of the open-label design of the study, it could be related to the switch to nonthymidine NRTIs. Indeed, almost all patients in the PI group were receiving either zidovudine or stavudine, and previous reports have suggested that thymidine analogues, particularly stavudine, play a role in the development of lipoatrophy [22, 33–35]. The benefit, if any, of the switch to once-daily therapy appears, however, to be limited, but our data suggest that the progression to lipoatrophy could be reduced by this switch.

In the present study, an enhanced rate of adherence was observed in patients assigned to the once-daily regimen. It is interesting to see that, in a population of already-adherent patients, the switch to a simplified once-daily regimen was associated with a further increase in adherence. This enhanced rate of adherence, along with the potency of the combination, is likely to explain, at least in part, the virologic success obtained with the once-daily regimen in the present study. Since adherence is a major factor contributing to the long-term success of antiretroviral therapy, such once-daily regimens could become very attractive [4, 7, 10].

In conclusion, we have demonstrated the safety and efficacy of a once-daily regimen combining emtricitabine, didanosine, and efavirenz in HIV-1–infected patients with suppressed viral replication receiving a PI-based regimen. This regimen offers the advantage of simplicity and low pill burden and, therefore, represents a new and attractive therapeutic option for HIV-1–infected patients.

**ALIZE STUDY TEAM**

The members of ALIZE study team were as follows: J.-M. Molina (trial chair); G. Chêne, C. Rancinan, and F. Collin (trial coordinator and monitors); V. Journot (trial statistician); F. Ferchal, L. Morand-Joubert, P. Palmer, and A. Charrois (trial virologists); J.-M. Molina, G. Chêne, V. Journot, C. Rancinan, I. Madelaine, P. Morlat, W. Rozenbaum, D. Sereni, J.-L. Vilde, F. Ferchal, L. Morand-Joubert, I. Poizot-Martin, E. Rosenthal, F. Raffi, and J. Reynes (scientific committee); and M. Seligmann, V. Calvez, D. Costagliola, P.-M. Girard, and B. Hoen (data safety and monitoring board).


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