Once-Daily Combination Therapy with Emtricitabine, Didanosine, and Efavirenz in Human Immunodeficiency Virus–Infected Patients

Jean-Michel Molina,1 Françoise Ferchal,1 Corinne Rancinan,2 François Raffi,3 Willy Rozenbaum,4 Daniel Sereni,2 Philippe Morlat,4 Valérie Journot,5 Jean-Marie Decazes,3 and Geneviève Chêne6 for the Montana (Agence Nationale de Recherches sur le SIDA 091) Study Group

The safety and efficacy of a once-daily regimen that combines emtricitabine, didanosine, and efavirenz was studied among 40 previously untreated human immunodeficiency virus (HIV)–infected patients. The median plasma HIV RNA level was 4.77 log_{10} copies/mL at baseline and decreased by a median of 3.5 log_{10} copies/mL at 24 weeks, with 98% and 93% of patients achieving plasma HIV RNA levels <400 and <50 copies/mL, respectively. The median CD4 cell count was 373 cells/μL at baseline and increased by a median of 159 cells/μL at week 24. The most common treatment-related adverse events were mild to moderate central nervous system symptoms (73% of patients), diarrhea (33%), rashes (10%), and biochemical abnormalities. Adverse reactions led to permanent drug discontinuation in only 1 patient. The once-daily combination therapy of emtricitabine, didanosine, and efavirenz was safe and demonstrated strong antiviral and immunologic effects that lasted for the 24-week period of the study.

The advent of highly active antiretroviral therapy (HAART) has raised new hopes in the management of human immunodeficiency virus (HIV) infection [1–3]. However, a number of concerns have emerged recently, because the need for long-term suppression of viral replication for years or decades seems inevitable. Issues such as the numbers of pills to be taken, the frequency of dosing, drug interactions, adherence to the drug regimen, and long-term adverse events have become increasingly important [4–5]. In an effort to optimize treatment adherence and patients’ quality of life, the availability of a simple, once-a-day HAART regimen is being investigated.

Two antiviral medications are currently available as once-a-day drugs—efavirenz, a nonnucleoside reverse transcriptase in-
Eligible patients were assigned to receive the following combination of drugs orally, once daily at bedtime (7 pills per day): emtricitabine (200 mg daily), didanosine (400 mg daily for patients who weighed ≥60 kg and 250 mg daily for patients who weighed <60 kg), and efavirenz (600 mg daily).

Monitoring. Participants were followed with a clinical assessment and routine laboratory monitoring every 2 weeks until week 4 and then every 4 weeks up to week 24. Plasma HIV-1 RNA concentrations were determined at a central laboratory at baseline and at every visit thereafter with an ultrasensitive polymerase chain reaction assay (Ultrasensitive Amplicor HIV-1 Monitor 1.5; Roche Molecular Systems, Branchburg, NJ), with a lower limit of quantification of 20 copies/mL.

During follow-up, adverse events were graded in severity from 1 to 4, in accordance with the grading scheme used in the Agence Nationale de Recherches sur le SIDA trials. Adherence with study medications was assessed on the basis of patient-reported missed doses. Failure to take any dose of ≥1 medications for a total of ≥28 consecutive or nonconsecutive days during the 24-week trial period was defined as nonadherence in this study.

Assessment of outcomes. The primary outcome measure was the antiretroviral effect, as measured by the proportion of patients who had plasma HIV-1 RNA levels <400 copies/mL from week 12 to week 24. Other outcomes included the mean change in CD4 cell counts and plasma HIV-1 RNA levels between baseline and week 24, the proportion of patients who had plasma HIV-1 RNA levels <50 copies/mL during the study (although the limit of sensitivity of the ultrasensitive assay we used was 20 copies/mL), this threshold of 50 copies/mL was chosen because it is becoming the standard in clinical trials), the assessment of adherence, and the occurrence of severe or serious adverse events (all grade 3 or 4 adverse events).

Statistical analysis. Virologic success was defined in this trial as a plasma HIV-1 RNA level that remained below 400 copies/mL from week 12 to week 24 of the study. The sample size (n = 40), was calculated in order to take into account the fact that, if the lower bound of the confidence interval (CI) of the proportion of virologic success was <70%, the treatment strategy should be abandoned (with an overall type I error of 5% and a 1-sided test, Fleming’s single-stage procedure).

For the purpose of mean change calculations, HIV-1 RNA values reported as <20 copies/mL were considered equivalent to 20 copies/mL, and HIV-1 RNA values underwent log_{10} transformation before analysis.

Results

Recruitment and characteristics of the patients. There were 44 patients screened between 8 February 1999 and 6 April 1999. Four patients were not enrolled in the study because of major violations of inclusion criteria (n = 3) or withdrawal of consent (n = 1). None of these 4 patients started study treatment. Forty patients were included in the final analysis; 93% were at Centers for Disease Control and Prevention disease stage A. The baseline characteristics of the study patients are shown in table 1.

Duration of follow-up and study treatment. The duration of study treatment was 24 weeks. One patient (3%) discontinued the study treatment prematurely because of an adverse event at week 14 (gastrointestinal disturbance attributed to didanosine), resumed therapy at week 20, with a combination of stavudine, emtricitabine, and efavirenz, and continued to the end of follow-up (patient A). Another patient was nonadherent and stopped therapy for weeks 6–12 (patient B). These 2 patients remained off therapy for 123 and 40 days, respectively.

Changes in plasma HIV-1 RNA levels. Over the 24-week period of the study, plasma HIV-1 RNA levels declined sharply, with a median (interquartile range) decrease at the end of study of 3.5 (3.1–3.7) log_{10} copies/mL (data not shown).

The proportions of patients who had plasma HIV-1 RNA levels <400 copies/mL are shown in figure 1. At week 12, 39 (98%) of 40 patients had levels <400 copies/mL, and this proportion was sustained at 24 weeks. All but 1 patient (patient A) achieved a plasma HIV-RNA level <400 copies/mL at week 24. Plasma HIV-RNA was 1080 copies/mL at week 24 for patient A.

In this trial, the estimated rate of virological success (i.e., maintaining a virus load <400 copies/mL from week 12 to week 24) was 95% (38 of 40 patients) with a lower limit of the 1-sided 95% CI of 85%. Therefore, only 2 patients (5%) experienced a virologic failure under the combination therapy we tested. For patient B, however, virus load at week 24 was <20 copies/mL.

The antiviral efficacy of this combination regimen is further emphasized by the proportion of patients whose HIV-1 RNA levels decreased to <50 copies/mL (figure 1). This percentage increased steadily over time and reached 93% (37 of 40 patients) at week 24 (95% CI, 80–98).

Changes in CD4 cell counts. The median CD4 cell count (interquartile range) increase at the end of the 24-week period of the study was 159 (58–251) cells/µL (data not shown).

Progression of HIV disease. No patient experienced AIDS-defining events or died during the study period. One patient experienced zoster and 2 recurrent episodes of oral candidiasis.

Adverse events. The study treatment was generally well tolerated during the 24-week period of the study. Only 1 patient (3%) discontinued study treatment at week 14, because of gastrointestinal intolerance attributed to didanosine.

Table 1. Baseline characteristics of the patient population under study (n = 40).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No.</th>
</tr>
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<tbody>
<tr>
<td>Male sex</td>
<td>35  (88)</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>33 ± 6</td>
</tr>
<tr>
<td>HIV risk factors</td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>28 (69)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>10 (25)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (3)</td>
</tr>
<tr>
<td>HIV-1 RNA levels (ultrasensitive assay)</td>
<td></td>
</tr>
<tr>
<td>Median, log_{10} copies/mL</td>
<td>4.77</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4.52–4.96</td>
</tr>
<tr>
<td>CD4 count, cells/µL</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>373</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>272–484</td>
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NOTE. Data are no. (%), except where noted. HIV, human immunodeficiency virus.
A total of 6 patients developed serious adverse events during the 24-week period of the study. One patient had concomitant grade 4 creatine phosphokinase elevation (90 times ULN) and grade 3 transaminase elevation (7 times ULN) at week 4 without clinical symptoms. This event was attributed to intense exercising and cleared spontaneously at week 8 without treatment interruption. Two patients were hospitalized; 1 underwent surgical repair for a lumbar herniated disc, and another underwent incision and drainage of a forearm abscess. One patient became pregnant at week 4. She voluntarily terminated her pregnancy and stopped therapy for only 2 days. Grade 3 hypertriglyceridemia was reported in 2 other patients who both had grade 1 hypertriglyceridemia at baseline. Blood samples were drawn from patients who had not fasted, however, and these events, which were not confirmed at subsequent visits, did not warrant an earlier return of the patients.

Most adverse events in this trial were mild to moderate. Central nervous system (CNS) complaints were the most frequently identified adverse events in 29 patients (73%) and occurred during the first days of therapy. These symptoms—sleep disturbances with insomnia and abnormal dreaming, depression and mood changes, dizziness, and asthenia—lasted for a median duration of 28, 35, 4, and 34 days, respectively. Eleven patients (28%) experienced headaches, and 4 patients (10%) experienced a maculopapular rash that cleared without treatment interruption in all patients. Diarrhea was reported by 13 patients (33%), and 6 patients complained of abdominal pain.

Twelve grade 2 biological adverse events were reported, mainly hypertriglyceridemia (4 patients), creatine phosphokinase elevations (3 patients), hyperamylasemia (2 patients), neutropenia and elevations of cholesterol, and gamma glutamyl transferase (1 patient each).

**Discussion**

Maximal antiviral suppression, as demonstrated by the decrease in plasma HIV-1 RNA to levels below the limit of quantification of the most sensitive assays, is predictive of sustained antiviral efficacy [14]. The utility of HAART depends on both the antiviral potency of the combination and the adherence of patients. The once-daily combination of emtricitabine, didanosine, and efavirenz in this study met these criteria. At 24 weeks, a very high proportion of patients (93%) achieved <50 copies/mL HIV-RNA, with almost all patients (98%) reaching <400 copies/mL. The 2 patients who did not achieve virological success were also the 2 patients who discontinued therapy for >28 days during the study.

This short-term sustained response in plasma HIV-RNA concentration with this convenient once-a-day regimen compares at least as favorably with the results obtained at 24 weeks with other triple regimens in patients with similar baseline virus loads [3, 7].

The study regimen was generally well tolerated, with only 1 patient discontinuing the study treatment because of adverse events. No patient was lost to follow-up. Six patients exposed to the emtricitabine, didanosine, and efavirenz combination experienced serious adverse events, but only 2 of them (both hypertriglyceridemia) were possibly related to the study medi-
cations. CNS complaints were reported by more than two-thirds of the patients in this study, a proportion that seems higher than the one reported previously with efavirenz [7]. Such CNS events have not been reported so far with FTC, with headaches only being reported by 10% of patients. It could be that the high incidence of CNS symptoms in this study is due to a better reporting of these events, which are now well known with efavirenz. Alternatively, FTC could have had a potentiation effect on efavirenz. However, most of these events were mild to moderate, disappeared without treatment interruption, and did not lead to treatment discontinuation in any patient. Mild diarrhea also was reported commonly during the trial, and a few maculopapular rashes occurred that cleared without discontinuing treatment. Creatine phosphokinase elevations and hypertriglyceridemia were the most significant biochemical abnormalities reported during the trial, but their relation to study medications was difficult to ascertain.

In summary, we suggest that a once-daily combination of emtricitabine, didanosine, and efavirenz could be a safe and effective alternative to protease inhibitor–containing regimens in antiretroviral-naïve patients. Obviously, these encouraging preliminary results need to be confirmed, with longer follow-up times, in a comparative-trial setting.

Montana Study Group Members

The following institutions and investigators participated in the Agence Nationale de Recherches sur le SIDA 091 study: J. Modai, J.-M. Decazes, J. M. Molina, I. Madeleine, M. N. Sombardier, M. Martinie, D. Sérény, C. Lascoux-Combes, G. Bayol-Honnet, and J. Krulik (Hôpital Saint-Louis, Paris); A. M. Simonpoli, C. Chandemerle, M. Bloch, C. Michon, and Ph. Vinceneux (Hôpital Louis-Mourier, Colombes); J. F. Delfraissy, C. Goujard, C. Rousseau, and M. T. Rannou (Hôpital de Bicêtre, Le Kremlin Bicêtre); P. Galanaud, F. Boue, and C. Colson (Hôpital A. Bécère, Clamart); W. Rozenbaum, P. M. Girard, T. H. Nguyen, and N. Adda (Hôpital Rothschild, Paris); A. G. Saimot, J. P. Coulaud, R. Landman, S. Masson, and S. Matheron (Hôpital Bichat–Claude Bernard, Paris); B. Hoen, Y. Bourczane, and J. M. Estavonian (Hôpital Saint-Jacques, Besançon); J. Beylot, P. Morlat, D. Lacoste, and M. Bonarek (Hôpital Saint-André, Bordeaux); C. Trepo, L. Cotte, V. Guerpel, P. Mialhilhes, and C. Carre (Hôtel Dieu, Lyon); F. Raffi, B. Bonnet, C. Alavena, J. L. Esnault, M. F. Charonnat, and M. Sicot (Hôtel Dieu, Nantes); and P. Canton, T. May, C. Burty, and C. Rabaud (Hôpital Brabois, Nancy).

Acknowledgments

We thank J. Dormont and P. Yéni for helpful discussions and support during this trial. We thank F. Rousseau and J. Delechanty from Triangle Pharmaceuticals, who provided emtricitabine for this trial. We thank D. Chiche, T. Greuters, and S. Schnittman from Bristol-Myers Squibb, who provided didanosine. We thank B. Baconnet and D. Manion from Dupont-Pharmaceuticals, who provided efavirenz. We are grateful to J. Modai and R. Salamon for their continual support during the study. We thank V. Calvez, D. Costagliola, B. Hoen, and C. Michon, who are members of the data and safety monitoring board of the study. We thank T. Debord, A. Maillard, S. Pérusat, A. Chibois, and G. Sagardoy for their contribution to the trial.

References