Virological, Immunological, and Clinical Impact of Switching from Protease Inhibitors to Nevirapine or to Efavirenz in Patients with Human Immunodeficiency Virus Infection and Long-Lasting Viral Suppression

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Seventy-seven subjects infected with human immunodeficiency virus were randomized to switch from protease inhibitor (PI) therapy to nevirapine therapy (group A; n = 26) or to efavirenz therapy (group B; n = 25) or to continue PI therapy (group C; n = 26). At month 12, viral suppression had been maintained in 96% of patients in group A, 92% of patients in group B, and 92% of patients in group C. A significant increase in the CD4+ level was observed in all 3 groups. In group A, lipid profiles improved, whereas levels of γ-glutamyltransferase and alanine aminotransferase significantly increased; 1 subject interrupted treatment because of hepatotoxicity. In group B, an increase in γ-glutamyltransferase levels was also observed, and 3 patients interrupted treatment because of central nervous system symptoms. Two patients in group C withdrew therapy. Quality of life significantly improved for groups A and B. In patients receiving effective PI-based therapy, the replacement of the PI with either nevirapine or efavirenz is safe and virologically effective.

Clinical studies have demonstrated that, for antiretroviral-naive patients infected with HIV, antiretroviral regimens that include nonnucleoside reverse transcriptase inhibitors (NNRTIs) and 2 nucleoside reverse transcriptase inhibitors (NRTIs) are at least as potent as protease inhibitor (PI)–based regimens [1–5]. To reduce the toxicity and the complexity of the antiretroviral regimens and to improve long-term adherence, simpler and better-tolerated therapy with PI-sparing regimens that contain either nevirapine or efavirenz (NNRTIs) is being used [6–12]. Preliminary studies support the role of NNRTIs in therapy simplification strategies for patients who receive PI-containing regimens [6, 7], but most of these studies have been uncontrolled and relatively short. In addition, clinical trials directly comparing nevirapine-containing and efavirenz-containing regimens have not been done.

The aim of our study was to assess, at 1-year follow-up, the potency, tolerability, and toxicity of therapy with nevirapine or efavirenz as a replacement for PI-based therapy, as compared with continued PI therapy, in HIV-infected adults who had been receiving PI-containing regimens and who had long-term viral suppression.
METHODS

Study design and patients. We designed a prospective, randomized, open-label, 3-arm trial. Subjects who had been receiving a PI-containing regimen and who had long-lasting plasma HIV-1 RNA suppression were randomly assigned to have the PI replaced with nevirapine (group A) or with efavirenz (group B) or to continue to receive their previous PI-containing regimen (group C).

All eligible subjects were HIV-infected adults who had been receiving a PI-containing triple-drug regimen for at least 12 months, had a CD4 cell count of >300 cells/mm³, and had had a plasma HIV-1 RNA levels of <80 copies/mL for >9 months at the start of the study. Individuals who had received NRTIs at any time or drugs to reduce lipid levels during the 6 months previous to study entry were not eligible. All subjects enrolled gave written informed consent.

Patients assigned to group A received nevirapine (200 mg every 12 h, started in escalating doses) and patients in group B received efavirenz (600 mg every 24 h at dinner time). In all cases, patients continued to receive the same NRTIs during the study that they had received before the study. Subjects randomized to group C continued to receive the PI-containing regimen they had been receiving.

Aims. The main objectives of this study were to compare the efficacy of 3 regimens—1 PI-containing regimen and 2 PI-sparing regimens that included nevirapine or efavirenz—in maintaining the suppression of plasma HIV-1 RNA levels and allowing the progressive immunological improvement of patients. Secondary objectives were to assess the impact of PI-sparing regimens on metabolic profile, other adverse events, and quality of life. In addition, we aimed to evaluate the variations in body shape in patients who had lipodystrophy at baseline after they began receiving nevirapine or efavirenz instead of a PI, in comparison with patients who continued to receive PIs.

Enrollment, visit schedule, and data collected. The inclusion period was April—August 1999. All patients had follow-up visits at baseline and every 3 months thereafter. Data collected included plasma HIV-1 RNA levels, CD4 and CD8 cell counts, and routine biochemical and hematology plasma values, as well as anthropometric measurements and a report of clinical events (e.g., adverse events or changes in fat distribution). At each visit, treatment adherence and quality of life were also assessed by a group of psychologists. Quality of life was measured with use of a 5-point scale adapted from the MOS (medical outcomes study)—HIV questionnaire [13]: a score of 1 indicated a quality of life much worse than, 5 indicated a quality of life much better than, and 3 indicated a quality of life equal to that at the last visit. A score 3 was used as the baseline reference value. Adherence was reported by the patient and calculated according to the following formula: (number of pills taken/number of pills prescribed) × 100. Appropriate adherence was defined as the consumption of ≥95% of the medication prescribed [14].

For the subgroup of subjects who had lipodystrophy, dual-energy x-ray absorptiometry (DEXA) was performed, and body-region and whole-body photographs were taken at baseline and every 6 months. Plasma HIV-1 RNA levels were determined by use of a nucleic acid sequence–based amplification assay (Organon Teknika), which has a detection limit of 80 HIV-1 RNA copies/mL. Lymphocyte CD4 and CD8 cell counts were determined by means of flow cytometry. Treatment failure was defined as HIV RNA plasma levels of >80 copies/mL at 2 consecutive determinations.

Abnormal total cholesterol and triglyceride values were defined as those >200 mg/dL. Abnormal aspartate aminotransferase (AST), alanine aminotransferase (ALT), and γ-glutamyltranspeptidase (GGT) levels were defined as values >35 U/L, >43 U/L, and >85 U/L, respectively. Acute hepatitis was defined as an AST, ALT, or GGT level that increased by 5-fold from its highest value at baseline.

Statistical analysis. Analysis of data was performed according to the intention-to-treat approach. Differences between months 3, 6, 9, and 12 and baseline values were calculated for biochemical, anthropometric, immunological, and virological parameters. The statistical significance of the longitudinal changes in these parameters in each group was assessed with use of Student’s t-test and the Wilcoxon test for pairwise data and general linear models. Comparisons between the 3 study groups were done with use of analysis of variance and Kruskall-Wallis and Mann-Whitney U tests. In further analysis, and in order to evaluate the effect of treatment on some analytical parameters, patients were divided into groups according to whether they had normal or altered baseline cholesterol and triglyceride values. The proportion of patients with altered cholesterol and triglyceride values were compared between groups by means of the χ² or Fisher’s exact test for proportions, as appropriate.

RESULTS

Baseline characteristics of the patients. A total of 77 HIV-infected patients were included in the study. Twenty-six patients were assigned to group A, 25 to group B, and 26 to group C. Baseline characteristics of participants were well balanced between groups at the time they entered the study (table 1). Results were considered to be significant at P ≤ .05.

Adverse events and treatment discontinuation. Ten (12.9%) of 77 patients were lost to follow-up: 1 subject in group A and 2 in group C did not continue scheduled visits, and the remaining 7 subjects (2 in group A, 3 in group B, and 2 in group C) discontinued treatment because of adverse events. Side effects described in group A included nevirapine-associated
Table 1. Baseline characteristics of HIV-infected patients who were receiving a protease inhibitor (PI)–containing regimen and replaced the PI with nevirapine (group A) or efavirenz (group B) or continued to receive the PI (group C).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>A (n = 26)</th>
<th>B (n = 25)</th>
<th>C (n = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration previous to study entry with virus load of &lt;80 copies/mL, months</td>
<td>31.7 ± 7</td>
<td>29.0 ± 9</td>
<td>29.2 ± 8</td>
</tr>
<tr>
<td>Duration previous to study entry receiving antiretroviral therapy, weeks</td>
<td>67.1</td>
<td>63.3</td>
<td>64.2</td>
</tr>
<tr>
<td>Antiretroviral therapy at baseline, % of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavudine, lamivudine, and a PI</td>
<td>60</td>
<td>57</td>
<td>63</td>
</tr>
<tr>
<td>Zidovudine, lamivudine, and a PI</td>
<td>31</td>
<td>36</td>
<td>33</td>
</tr>
<tr>
<td>Zidovudine, didanosine, and a PI</td>
<td>9</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Received HAART as first antiretroviral regimen, % of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4⁺ T-cell counts, cells/mm³</td>
<td>641 ± 285</td>
<td>595 ± 303</td>
<td>660 ± 277</td>
</tr>
<tr>
<td>Nadir CD4⁺</td>
<td>221 ± 267</td>
<td>275 ± 351</td>
<td>241 ± 330</td>
</tr>
<tr>
<td>CD8⁺</td>
<td>1361 ± 667</td>
<td>1112 ± 575</td>
<td>1207 ± 527</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td>223 ± 49</td>
<td>227 ± 48</td>
<td>207 ± 36</td>
</tr>
<tr>
<td>Triglyceride level, mg/dL</td>
<td>203 ± 96</td>
<td>178 ± 101</td>
<td>231 ± 134</td>
</tr>
<tr>
<td>Lipodystrophy, no. (%) of patients</td>
<td>20 (76.9)</td>
<td>19 (76.0)</td>
<td>19 (72.9)</td>
</tr>
<tr>
<td>GGT level, U/L</td>
<td>43 ± 53</td>
<td>41 ± 51</td>
<td>57 ± 90</td>
</tr>
<tr>
<td>AST level, U/L</td>
<td>44 ± 67</td>
<td>33 ± 20</td>
<td>32 ± 18</td>
</tr>
<tr>
<td>ALT level, U/L</td>
<td>48 ± 68</td>
<td>41 ± 29</td>
<td>39 ± 26</td>
</tr>
<tr>
<td>Hepatitis C coinfection, % of patients</td>
<td>42</td>
<td>40</td>
<td>38</td>
</tr>
</tbody>
</table>

**NOTE.** Data are mean ± SD unless otherwise indicated. ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; HAART, highly active antiretroviral therapy.

rash, in 2 patients, and acute nevirapine-related acute hepatitis, in 5 patients; however, only 2 patients had to interrupt nevirapine treatment, one due to a rash and another due to hepatotoxicity.

A significant increase in GGT levels was observed in groups A and B (P < .02 for both groups and all time points, compared with baseline values), but not in group C. In group A, there was a 3-fold increase in mean GGT levels at 3 months, which persisted during 12 months of follow-up (table 2). Conversely, mean GGT values progressive increased in group B, achieving a level 2-fold above the upper limits of normal at month 9. In addition, only in group A, there was a significant but transient increase in mean ALT levels at month 3 of follow-up (1.5-fold greater than the upper limit of normal; P < .028 for comparison with baseline values), which had returned to baseline values by month 12. All cases of acute hepatitis were observed in patients who were also coinfected with hepatitis C virus. In addition, 18% of patients without coinfection experienced hepatotoxicity; however, none of these patients had aminotransferase levels that increased to >2-fold greater than their baseline values, and increases were always transient; none of these patients had to interrupt treatment for this reason.

Efavirenz-induced rash was observed in 1 patient whose condition showed improvement with systemic steroid therapy. Nine cases of CNS symptoms (sleep disturbances, dizziness, vivid dreams, and/or irritability) were also reported in group B. For 6 of these patients, these adverse events were considered to be grade II, according to World Health Organization (WHO) criteria; 3 individuals had to discontinue efavirenz because of the severity (grade III) or the prolonged duration of CNS symptoms.

Adverse events seen in group C included 3 cases of nelfinavir-associated diarrhea (defined as >3 stools per day), but only 1 of these patients had to interrupt treatment. Another patient had to interrupt treatment because indinavir-related nephrolithiasis developed.

Virological and immunological outcome and treatment failure. Overall, 93% of participants maintained HIV-1 RNA levels of <80 copies/mL through 12 months of follow-up: 96% of patients in group A, 92% in group B, and 92% in group C. Only 5 patients (1 patient in group A, 2 in group B, and 2 in group C) experienced treatment failure during the follow-up period (3 patients at month 6, 1 in group B at month 9, and 1 in group C at month 12). Poor adherence was confirmed in
2 of these patients (1 in group A and 1 in group C). All patients who experienced virological failure had been treated with sequential suboptimal NRTI-based regimens prior to starting HAART.

All 3 study arms showed a significant increase in the mean lymphocyte CD4 cell count (an increase of 115 ± 193 cells/mm³ in group A [P = .02] and increase of 106 ± 125 cells/mm³ in group B [P = .001], and increase of 67 ± 177 cells/mm³ in group C [P = .04]) and a significant decline in mean CD8 cell counts (figure 1; table 2). At the month 12 of follow-up, no statistically significant differences were found between groups with respect to the increase in the mean CD4 cell counts or the decrease in the mean CD8 cell count.

**Metabolic abnormalities.** A statistically significant decrease in mean total cholesterol values was observed in nevirapine-including arm at month 3 of follow-up, which persisted until month 12 (at each time point; table 2). Such decrease in mean total cholesterol values was due to the significant decrease in low-density lipoprotein cholesterol levels in group A (P < .001 at each time point; table 2). This decrease was not seen in groups B and C (P value not significant). The improvement in total cholesterol levels from baseline values was due to the significant decrease in low-density lipoprotein cholesterol levels in group A (P < .03). In the remaining groups, the mean low-density lipoprotein cholesterol level did not change significantly (P value not significant). Levels of high-density lipoprotein cholesterol did not vary in any study arm (P value not significant; figure 2).

In addition, triglyceride levels decreased significantly in group A at month 3 and thereafter (P < .01 for all time points; table 2). Conversely, mean triglyceride values did not decrease in the remaining study arms. Indeed, at month 9, mean triglyceride levels in group B exceeded normal values, although the increase did not achieve statistical significance (figure 2).

During follow-up, only 4 of 77 patients initiated treatment with drugs that decrease lipid levels (1 patient in group A, 1 in group B, and 2 in group C). All 4 patients did so because they had a total cholesterol level of >250 mg/dL and/or a triglyceride levels of >500 mg/dL. No significant differences were found in glucose metabolism in any group (data not shown).

**Body-shape changes.** Fifty-six patients (20 in group A, 17 in group B, and 19 in group C), all of whom had lipodystrophy at baseline, were examined by use of DEXA. No patients who had lipodystrophy at the beginning of the study demonstrated any significant improvement in (or any significant worsening of) fat redistribution during the follow-up. DEXA findings and anthropometric measurements confirmed the lack of changes in body-shape abnormalities in any study arm during follow-up (data not shown).

**Psychological impact.** Adherence was notably high during the follow-up in all study groups (mean adherence score [±SD], 99.6 ± 0.7 in group A; 98.7 ± 1.2 in group B; and 99.1 ± 1.3 in group C). Quality of life scores increased in groups A and B during follow-up (P < .001). In group A, the mean quality of life scores (±SDs) were as follows: at month 3, 3.5 ± 0.6; at month 6, 3.7 ± 0.9; at month 9, 4.2 ± 0.5; and at month 12, 4.4 ± 0.3 (P < .001). In group B, the mean quality of life scores (±SDs) were as follows: at month 3, 3.7 ± 0.8; at month 6, 3.9 ± 0.7; at month 9, 4.4 ± 0.8; and at month 12, 4.7 ± 1.2 (P < .001). Patients in group C did not report any variations in their quality of life. The reasons for improvement most commonly reported in groups A and B were the simplicity of the regimen and the lack of adverse events.

**DISCUSSION**

This randomized open-label trial shows that, through 1 year of follow-up, an antiretroviral regimen in which a PI is replaced with either nevirapine or efavirenz has antiviral activity that is similar to that for prior PI-based regimens in HIV-infected patients with long-lasting viral suppression. For the great majority of our patients, full HIV-1 RNA suppression was maintained, and there was a significant increase in the CD4 count.

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**Table 2.** Immunological, lipidic, and hepatic biochemical parameters at month 12 of follow-up for HIV-infected patients who replaced a protease inhibitor (PI) with nevirapine (group A) or efavirenz (group B) or continued to receive the PI (group C).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean value ± SD, by group</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4⁺ cells/mm³</td>
<td>A  756 ± 285</td>
</tr>
<tr>
<td>CD8⁺ cells/mm³</td>
<td>A  1150 ± 500</td>
</tr>
<tr>
<td>Total cholesterol level, mg/dL</td>
<td>A  199 ± 38</td>
</tr>
<tr>
<td>Triglyceride level, mg/dL</td>
<td>A  160 ± 94</td>
</tr>
<tr>
<td>GGT level, U/L</td>
<td>A  135 ± 133</td>
</tr>
<tr>
<td>AST level, U/L</td>
<td>A  52 ± 72</td>
</tr>
<tr>
<td>ALT level, U/L</td>
<td>A  75 ± 128</td>
</tr>
</tbody>
</table>

**NOTE.** ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase.
Figure 1. Changes in mean CD4 and CD8 cell counts, compared with baseline values. All 3 study arms showed a significant increase in lymphocyte CD4 cell counts (group A, \(P < .001\); group B, \(P = .001\); group C, \(P = .02\)) and a significant decrease in lymphocyte CD8 cell counts (group A, \(P < .001\); group B, \(P = .001\); group C, \(P = .02\)), but there were no significant differences between groups at month 12 of follow-up.

and a significant decrease in the CD8 count. These favorable responses were seen in all 3 study arms. The prolonged suppression of plasma HIV-1 RNA levels prior to the start of the study might explain the low incidence of virological failure seen in our cohort, in spite of the fact that 75% of patients had received non-suppressive therapy (i.e., dual-NRTI therapy) before HAART and in spite of the intrinsically low genetic barrier of NNRTIs. It is possible, however, that patients receiving NNRTIs may eventually harbor drug-resistant virus variants despite prolonged viral suppression [15]. Thus, with longer follow-up, the rate of virological failure might eventually increase among patients who have previously received sequential non-suppressive therapies. According to current knowledge, probably the safest strategy is to replace the PI only for those patients with prolonged undetectable HIV-1 RNA levels who have previously exclusively received drug combinations considered as HAART; however, this last recommendation should be specifically evaluated in further studies.

Abnormalities in lipid levels and distribution associated with PI-including regimens are well documented [16]. It has been proposed that replacement of the PI with another agent may help to reduce these abnormalities [6, 8, 9]. Such improvement may have an influence in reducing the risk of cardiovascular effects [17] and the need for drugs that decrease lipid levels and the associated risk of drug-drug interactions. With respect to the effect of the switch to nevirapine on the lipid profile, Tebas et al. [9] have reported results similar to ours with 6 months of follow-up. Our group also obtained similar results in a randomized comparative study; in patients who switched to a PI-sparing regimen that contained nevirapine, cholesterol and triglyceride levels showed significant improvement [6].

However, data about the effect of efavirenz on the lipid profile are somewhat more discordant. Although some studies [12, 18] have found no improvements in lipid profile after switching from a PI to efavirenz, others [19] have reported partial improvement in the mean triglyceride level, although not in the total and high-density lipoprotein cholesterol levels and the glucose level. In the present study, patients who switched to efavirenz did not show significant variations in their metabolic profile.

The effect of replacement of a PI with an NNRTI on anti-retroviral-induced fat redistribution is also controversial. Although a few studies have observed some improvements in lipodystrophy [8, 10, 11], the majority of have not detected significant changes after the switch to a PI-sparing regimen [6, 9, 12]. In our trial, no patient who had lipodystrophy at the start of the trial showed improvement in the condition after receiving a PI-sparing regimen for 12 months. Our results were supported by the findings of DEXA scans and by anthropometric measurements. Some reasons that could explain these divergent data include the following: (a) the diversity of clinical manifestations and the lack of a consensus on how to define the syndrome leads to heterogeneity in the different groups studied; (b) previous trials had small samples and short follow-up, and (c) NRTIs probably contributed independently to the pathogenesis of the syndrome, augmenting the well-established causative role of PIs [20]. The contribution of NRTIs to the pathogenesis of lipodystrophy may have influenced the degree of reversion in body-shape changes in our cohort, because the prior NRTI combination was not changed for patients in our study [21, 22].

Our data also support the recommendation that patients be followed closely in order to control the development of other adverse events after the switch from PIs to NNRTIs. Monthly monitoring of the liver function of patients who begin to receive mainly nevirapine is suggested. It is interesting that patients treated with efavirenz also had increased GGT levels, although this increase was less than in patients treated with nevirapine, and no patients in group B needed to interrupt treatment for this reason. In the present study, all subjects in whom hepatic enzyme levels increased >5-fold above the normal values after the switch were coinfected with hepatitis C virus. Other studies
Figure 2. Changes in mean total cholesterol and triglyceride levels, compared with baseline values. A significant decrease in total cholesterol values was observed in group A ($P < .001$). Such a decrease was not seen in groups B and C ($P$ value not significant). Triglyceride levels decreased significantly in group A ($P < .001$) but did not decrease in the remaining study arms. Indeed, at month 9, triglyceride levels were elevated to abnormal values in group B patients, although they did not achieve statistical significance.

have already suggested that the risk of HAART-induced hepatotoxicity is higher in subjects coinfected with HIV and hepatitis C virus, who demonstrate an increase in hepatitis C virus viremia and liver enzymes, probably because of destruction of hepatocytes by cytotoxic T cells associated with the immune recovery [23]. Therefore, according to our results, it seems wise to monitor liver function more frequently in patients who start NNRTIs—mainly nevirapine—especially in HCV-coinfected patients. We would advise performing this follow-up at monthly intervals, at least during the first 3 months of therapy.

CNS symptoms are the most frequent efavirenz-induced adverse events; they appear within the first weeks of treatment in ~50% of patients who start this drug [1, 24]. Although the symptoms are usually mild, 2%–15% of subjects have to interrupt therapy because of moderate-to-severe or prolonged symptoms [, 19]. In the present study, ~36% of individuals treated with efavirenz demonstrated some neurological symptoms. Therefore, before an efavirenz-containing regimen is initiated, a patient should be carefully assessed for efavirenz-induced adverse events and should be closely monitored. Adequate information about these symptoms may prevent the need to interrupt therapy suddenly.

Patients who switched from a PI-containing to a PI-sparing regimen reported a significant improvement in their quality of life, and patients who continued with the PI regimen did not. This improvement was due to the simplicity of the new regimen and the reduction of adverse events that limited their activities. Nevertheless, results about quality of life should be interpreted with caution, because people who enroll in such trials may be especially motivated to stop PI therapy, which would cause an overestimate of quality-of-life improvements in groups who switch from PI to NNRTI therapy. However, our results are consistent with and strongly supported by other studies [6, 25]. Today, subjects who have received multiple antiretrovirals and have prolonged viral suppression frequently ask for a therapeutic switch to improve the tolerability of their regimen and/or their quality of life. Therefore, simpler treatment strategies should be considered in experienced patients to assure long-term adherence to therapy [26].

Because of the small sample size of this study, we cannot definitively conclude that virological response was equivalent for the group that received nevirapine and the group that received efavirenz ($β$ error rate, 89.9%, where $α = 0.05$; $n = 77$). Accordingly, we can only affirm that we did not find significant differences between these arms. Our results, however, are clear, plausible, and consistent with clinical practice, and, therefore, they should be revisited in further studies with larger cohort samples.

In conclusion, the replacement of a PI by either nevirapine or by efavirenz for patients receiving a successful PI-containing regimen was as safe and as virologically effective as maintaining the PI-containing therapy. Patients who switched from a PI to nevirapine achieved a better metabolic profile; however, no significant improvement was seen in lipodystrophy-related body shape changes during 12 months of follow-up. In addition, NNRTI-containing regimens improved patients’ quality of life. After replacing a PI with nevirapine or efavirenz, close monitoring is warranted to control nevirapine-induced hepatotoxicity (mainly in HCV-coinfected patients) and efavirenz-related CNS toxicity.

References


3. Murphy RL, Katlama C, Johnson V, et al. The ATLANTIC study: a randomized open-label trial comparing two protease inhibitors-sparing antiretroviral strategies versus a standard PI-containing regimen. 48-


