Nevirapine or Lamivudine plus Stavudine and Indinavir: Examples of 2-Class versus 3-Class Regimens for the Treatment of Human Immunodeficiency Virus Type 1

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We compared use of a 3-class regimen (nevirapine [Nvp], stavudine [d4T], and indinavir [Idv; 1000 mg 3 times daily]) with use of a 2-class regimen (lamivudine [3TC], d4T, and Idv [800 mg 3 times daily]) for 145 patients infected with human immunodeficiency virus type 1 (HIV-1). At week 72, the plasma HIV-1 RNA level was undetectable in 52% of Nvp recipients versus 79% of 3TC recipients ($P < .001$). Idv trough levels were 81 ng/mL in the Nvp group and 99 ng/mL in the 3TC group ($P = .012$). In the Nvp group, 42.5% of patients discontinued the study regimen; in the 3TC group, 22.5% of patients discontinued therapy ($P = .013$). The rate of resistance to nonnucleoside analogue reverse-transcriptase inhibitors among patients in the Nvp group with virological failure was not different from the rate of resistance to 3TC among patients in the 3TC group with virological failure. These results do not support the use of a 3-class regimen that includes Nvp for patients with no or limited exposure to nucleoside analogues.

The current goal of treatment of HIV-1 infection is prolonged suppression of viral replication with minimal toxicity. First-line therapy for HIV-1 infection usually includes a combination of 2 nucleoside reverse-transcriptase inhibitors (NRTIs) and either a protease inhibitor (PI) or a nonnucleoside reverse-transcriptase inhibitor (NNRTI) [1, 2]. However, it has been reported that as many as 40% of patients who receive such potent regimens experience virological failure at 18 months after initiation of therapy [3], and the toxic effects of therapy often lead to treatment interruption. The objective of a “3-class” therapy that includes 1 drug from each class (NRTI/NNRTI/PI) is to act on protease and on reverse transcriptase with 2 different mechanisms, with the expected consequence of providing more-potent antiretroviral activity. To date, such a 3-class therapy has not been evaluated in a randomized trial involving PI- and NNRTI-naive patients. Therefore, we conducted a 72-week randomized, controlled study to compare the efficacy and tolerance of 2 triple-drug therapies consisting of indinavir (Idv) and stavudine (d4T) plus either nevirapine (Nvp), for 3-class therapy,
lamivudine (3TC), for 2-class therapy. These latter 2 drugs were selected for their similar profile in terms of antiretroviral potency [4, 5] and the genetic barrier to virological resistance [6, 7].

**PATIENTS AND METHODS**

**Study design and patients.** The present study was a prospective, multicenter trial in which, during the course of 72 weeks, the combination of Nvp plus d4T and Idv (given to patients known as “the Nvp group”) was compared with that of 3TC plus d4T and Idv (given to patients known as “the 3TC group”) in HIV-1–infected patients who were antiretroviral naïve or who previously had received treatment with zidovudine, didanosine, or zalcitabine. Patients were >18 years of age and had a CD4 cell count \( \geq 100 \times 10^3/\text{L} \), a plasma HIV-1 RNA level \( \geq 5000 \text{ copies/mL} \), a Karnofsky score >70%, acceptable laboratory values, and no prior exposure to d4T, 3TC, or any NNRTI or PI.

Patients were randomly assigned to receive either 1 of the 2 following open-label treatment regimens given orally for 72 weeks: Nvp (200 mg given daily for 14 days, escalating to 200 mg given twice daily thereafter), d4T (40 mg given twice daily), and Idv (800 mg given 3 times daily on an empty stomach); or 3TC (150 mg given twice daily), d4T (40 mg given twice daily), and Idv (800 mg given 3 times daily on an empty stomach). For patients weighing <60 kg, d4T was administered in a dosage of 30 mg given twice daily. The higher dose of Idv administered to the Nvp group was used to balance the increased metabolism of Idv in the presence of Nvp [8–10]. Randomization was stratified according to prior exposure to antiretroviral treatment.

**Enrollment, laboratory monitoring, and clinical follow-up.** Clinical assessment, determination of plasma HIV-1 RNA level and CD4 cell count, and routine laboratory monitoring were performed before patients entered the study, at the time of entry, at weeks 4 and 8 of the study, and every 8 weeks thereafter up to week 72. At all scheduled visits, AIDS-defining and adverse events were recorded, and a blood specimen was processed. Samples were stored at \(-80^\circ \text{C}\) and were subsequently assayed in batches at a central laboratory for determination of the level of plasma HIV-1 RNA and viral resistance.

Virological failure was defined as a reduction in plasma HIV-1 RNA level of \( <1 \log_{10} \text{ copies/mL} \) (from the baseline level) after 16 weeks or virological rebound (defined by a detectable plasma HIV-1 RNA level in patients with a previously undetectable HIV-1 RNA level or an increase in plasma HIV-1 RNA level \( >0.5 \log_{10} \text{ copies/mL from the nadir} \)). Research was performed in accordance with the Helsinki Declaration of 1975, as revised in 1983, and was approved by the Saint-Antoine Hospital Ethics Board (Paris, France) and the institutional review board of the French National Agency for AIDS Research. Written and oral informed consent was obtained from all patients.

**Virological methods.** The plasma HIV-1 RNA level was measured using the Amplicor HIV-1 Monitor Cobas 1.5 test (Roche Diagnostics Systems) with the ultrasensitive specimen preparation ultradirect assay, which has a lower limit of quantification of 20 copies/mL, according to the manufacturer’s protocol [11].

Retrospective genotypic testing was performed on plasma samples obtained at baseline from patients who had previously received an NRTI. For patients with virological failure, genotypic testing was performed at baseline, at the time of virological failure, and at week 72 of the study. Retrospective phenotypic testing was restricted to patients with virological failure. Resistance-associated mutations in protease and reverse-transcriptase (RT) genes were identified on plasma viral RNA by use of the TruGene HIV-1 kit (Visible Genetics). The interpretation of resistance genotypes was determined according to the consensus algorithm from the French National Agency for AIDS Research (Agence Nationale de Recherche sur le SIDA [ANRS]) [2]. Phenotypic testing of plasma virus was done using a single-cycle recombinant virus assay (Phenoscript; Viralliance) [12, 13]. Phenotypic values were grouped into 1 of 3 resistance categories: susceptible (defined by a \(<4\)-fold increase in IC\(_{50}\) or IC\(_{90}\)), intermediately susceptible (hereafter known as “intermediate”; defined by a 4–10-fold increase in IC\(_{50}\) or IC\(_{90}\)), or resistant (defined by a >10-fold increase in IC\(_{50}\) or IC\(_{90}\)), compared with a wild-type strain. Both intermediate and resistant viruses were considered to be phenotypically resistant. Isolates were considered to be resistant if either a genotypic or phenotypic resistance was demonstrated.

**Determination of plasma drug levels.** Plasma concentrations of Idv and Nvp were assessed after 8 and 24 weeks of therapy by measuring the trough plasma levels of both Idv and Nvp and the peak level of Idv. The interval between the most recent drug ingestion and sampling for the trough Idv level was recorded. Morning doses of treatment were taken immediately thereafter, and sampling for the peak Idv level was done 1 h later. Plasma underwent blinded analysis for Idv and Nvp plasma concentrations by use of a validated high-performance liquid chromatography assay with UV detection [14]. The limit of assay quantification was 5 ng/mL for Idv and 0.05 mg/L for Nvp.

**Adherence.** The adherence score was defined as the difference between the number of pills dispensed and the number of pills returned, divided by the number of pills prescribed during the assessment interval.

**Assessment of outcomes.** The primary end point for activity was the change in the plasma HIV-1 RNA level from baseline to week 72, at which time the ultrasensitive PCR assay
was used. The primary end point for toxicity was the frequency of adverse events, which were defined as events with a severity grade of 3 or 4 (according to the ANRS grading system) or events leading to discontinuation of therapy.

Secondary evaluation assessed the following: the proportion of patients with plasma HIV-1 RNA levels of <200 copies/mL and <20 copies/mL at weeks 16 and 72, the change in the CD4 cell count measured at baseline and again at week 72, development of an HIV-1–related AIDS-defining event [15], time to discontinuation of therapy, plasma drug concentrations, resistance outcome by genotypic and phenotypic analysis, and adherence to therapy. Time to adverse events was also compared between the 2 groups.

**Statistical methods.** A sample size of 60 patients per group was calculated to ensure 80% power to detect a difference of ≥0.5 log₁₀ in the reduction of the plasma HIV-1 RNA level from baseline to week 72 across the 2 groups, assuming a SD of 0.9 log₁₀ in the HIV-1 RNA level variation between week 72 and week 0 across the study population and an 8% rate of discontinuation of assigned treatments. During the course of the study, the sample size was subsequently increased to 72 patients per group to restore 80% power with a revised therapy discontinuation rate of 16%.

The Wilcoxon 2-sample test was used to test for no difference in continuous variables by categorical variables. Fisher’s exact test was used to test the association between categorical variables. The mean of the 2 plasma concentrations determined at weeks 8 and 24 was used to compare treatment groups with respect to both peak and trough plasma levels of Idv and trough levels of Nvp. The time to permanent discontinuation of the study medication was estimated using the Kaplan-Meier method and was compared using the log-rank test.

Analyses were performed on an intent-to-treat basis. For primary analysis of antiretroviral activity, involving the change in the plasma HIV-1 RNA level from baseline to week 72, we analyzed the reduction in the plasma HIV-1 RNA level by use of both crude and censored methods. For the crude method, all HIV-1 RNA levels <20 copies/mL were recorded as 20 copies/mL. The censored method acknowledges that HIV-1 RNA levels <20 copies/mL cannot be precisely determined. Therefore, estimates of the median reduction in the HIV-1 RNA level were also obtained using the Kaplan-Meier method, which accommodates censored observations [16].

In the secondary analysis of proportions of patients with HIV-1 RNA levels of <200 copies/mL or <20 copies/mL at

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**Table 1. Clinical and demographic characteristics of and biological findings for the 144 study patients at baseline, by treatment group.**

<table>
<thead>
<tr>
<th>Characteristic or finding</th>
<th>d4T-Idv-Nvp (n = 73)</th>
<th>d4T-Idv-3TC (n = 71)</th>
<th>All patients (n = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male sex</td>
<td>54 (74)</td>
<td>58 (82)</td>
<td>112 (78)</td>
</tr>
<tr>
<td>Age, mean years ± SD</td>
<td>37 ± 9</td>
<td>36 ± 8</td>
<td>36 ± 8</td>
</tr>
<tr>
<td>HIV-1 risk factor⁵</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>29 (40)</td>
<td>47 (66)</td>
<td>76 (53)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>33 (41)</td>
<td>14 (20)</td>
<td>47 (33)</td>
</tr>
<tr>
<td>IDU</td>
<td>5 (7)</td>
<td>8 (11)</td>
<td>13 (9)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>8 (11)</td>
<td>2 (3)</td>
<td>10 (7)</td>
</tr>
<tr>
<td>CDC disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>46 (63)</td>
<td>54 (76)</td>
<td>100 (69)</td>
</tr>
<tr>
<td>B</td>
<td>21 (29)</td>
<td>17 (24)</td>
<td>38 (26)</td>
</tr>
<tr>
<td>C</td>
<td>2 (3)</td>
<td>4 (6)</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Prior NRTI therapy⁶</td>
<td>15 (21)</td>
<td>15 (21)</td>
<td>30 (21)</td>
</tr>
<tr>
<td>Plasma HIV-1 RNA level, log₁₀ copies/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>4.75 ± 0.6</td>
<td>4.77 ± 0.6</td>
<td>4.76 ± 0.6</td>
</tr>
<tr>
<td>Median (range)</td>
<td>4.81 (4.34–5.27)</td>
<td>4.86 (4.35–5.21)</td>
<td>4.84 (4.35–5.22)</td>
</tr>
<tr>
<td>CD4 count, ×10⁶ cells/mL</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>371 ± 189</td>
<td>388 ± 157</td>
<td>380 ± 174</td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (%) of patients, unless indicated otherwise. 3TC, lamivudine; d4T, stavudine; CDC, Centers for Disease Control and Prevention; IDU, injection drug use; Idv, indinavir; NRTI, nucleoside reverse-transcriptase inhibitor; Nvp, nevirapine.

⁵ Some patients reported multiple HIV-1 risk factors.

⁶ Prior therapy with zidovudine, didanosine, or zalcitabine.
weeks 16 and 72, respectively, missing plasma HIV-1 RNA measurements were handled in the following way: the missing HIV-1 RNA value at any point was considered a failure (>20 copies/mL or >200 copies/mL), with the exception of missing values at week 16, for which the preceding and subsequent measurements indicated treatment success (<20 copies/mL or <200 copies/mL) and, therefore, the missing value was considered to denote treatment success. All P values reported are 2-sided.

RESULTS

Characteristics at baseline and disposition of patients. A total of 145 patients were recruited from 37 centers and randomized between November 1997 and August 1998. One patient was excluded from analysis because he did not start receiving the study treatment. Characteristics of the patients are detailed in table 1.

Permanent withdrawal was observed in 47 patients (33%) (figure 1). Reasons for discontinuation of study treatment are shown in table 2. Discontinuation of the study treatment for any reason was seen among a larger proportion of patients in the Nvp group, compared with those in the 3TC group (42.5% and 22.5%, respectively; P = .013, by Fisher’s exact test). The time to discontinuation of the randomized treatment was also shorter in the Nvp group than in the 3TC group (P = .005, by log-rank test) (figure 1).

Evaluation of activity. At week 72, the percentage of patients with a plasma HIV-1 RNA level below the limit of detection was higher in the 3TC group than in the Nvp group,

Table 2. Findings of patient follow-up, by treatment group.

<table>
<thead>
<tr>
<th>Finding</th>
<th>d4T-Idv-Nvp (n = 73)</th>
<th>d4T-Idv-3TC (n = 72)</th>
<th>All patients (n = 145)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failed to receive study medication</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>5 (7)</td>
<td>1</td>
<td>6 (4)</td>
</tr>
<tr>
<td>Discontinued study drug</td>
<td>31 (42.5)</td>
<td>16 (22.2)</td>
<td>47 (32)</td>
</tr>
<tr>
<td>Reason for discontinuation of study drug</td>
<td>2 (3)</td>
<td>0</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>20 (27)</td>
<td>14 (19)</td>
<td>34 (23)</td>
</tr>
<tr>
<td>Serious adverse event</td>
<td>14 (19)</td>
<td>4 (6)</td>
<td>18 (12.4)</td>
</tr>
<tr>
<td>Virological failure</td>
<td>3 (4)</td>
<td>0</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Patient request</td>
<td>6 (8)</td>
<td>2 (3)</td>
<td>8 (6)</td>
</tr>
</tbody>
</table>

NOTE. Data are no. or no. (%) of patients; 3TC, lamivudine; d4T, stavudine; Idv, indinavir; Nvp, nevirapine.
When either the standard assay (plasma HIV-1 RNA level <200 copies/mL in 86% vs. 63%; \( P = .002 \)) or the ultrasensitive RNA assay (plasma HIV-1 RNA level <20 copies/mL in 79% vs. 52%; \( P < .001 \)) was used (figure 2). By use of the crude method, the median change in the plasma level of HIV-1 RNA (limit of detection, 20 copies/mL) from baseline to week 72, which was censored in 79 and 52 of the patients in the 3TC and Nvp groups, respectively, was not statistically different between the 3TC and the Nvp groups (\(-3.3 \log_{10}\) vs. \(-3.15 \log_{10}\) copies/mL, respectively; \( P = .40 \); figure 3). However, the median reduction in the plasma HIV-1 RNA level at week 72, according to the censored method, was greater in the 3TC group than in the Nvp group (more than \(-5.13 \log_{10}\) vs. \(-4.16 \log_{10}\) copies/mL, respectively; \( P = .03 \)).

Subgroup analysis of the percentages of patients with a plasma HIV-1 RNA level <20 copies/mL at week 72, according to baseline plasma HIV-1 RNA level (<100,000 copies/mL or \( \geq 100,000 \) copies/mL), baseline CD4 cell count (<200 \( \times 10^5 \) cells/L or \( \geq 200 \times 10^5 \) cells/L), and receipt/nonreceipt of prior antiretroviral therapy, is shown in figure 4. Rates of undetectable virus load were higher in all 3TC subgroups than in corresponding Nvp subgroups of patients. The difference reached statistical significance the 3 largest subgroups evaluated: patients with plasma HIV-1 RNA levels <100,000 copies/mL, those with baseline CD4 cell counts \( \geq 200 \times 10^5 \) cells/L, and those with no prior receipt of NRTI therapy.

At week 72, a total of 97 patients were still following the regimen assigned at randomization (55 patients in the 3TC group and 42 patients in the Nvp group). The percentages of these patients who had plasma HIV-1 RNA levels <200 copies/mL or 20 copies/mL at week 72 were 93% and 85.5%, respectively, in the 3TC group and 78.5% and 62%, respectively, in the Nvp group. At week 72, the median change in the CD4 cell count was +242 \( \times 10^5 \) cells/L in the 3TC group and +198 \( \times 10^5 \) cells/L in the Nvp group (\( P = .08 \); figure 3).

No deaths occurred during the study period. Three new AIDS-defining events occurred in the 3TC group and 1 occurred in the Nvp group.

**Evaluation of tolerance.** Sixty-six patients (46%) had an adverse event with a severity grade of \( \geq 3 \) or discontinued their treatment because of toxicity (28 patients in the 3TC group and 38 in the Nvp group) (\( P = .14 \)). The time to occurrence of this end point was shorter in the Nvp group than in the 3TC group (\( P = .029 \), by log-rank test). Twenty-nine severe adverse events were reported among 21 patients in the 3TC group, and 52 severe adverse events were reported among 32 patients in the Nvp group (\( P = .09 \); table 3).

A total of 15 patients (10%) experienced a rash, 14 (19%) in the Nvp group and 1 (1.4%) in the 3TC group. Eleven patients with rash in the Nvp group subsequently had their treatment permanently withdrawn. Thirty cases of nephrolithiasis were reported in 20 patients (6 patients in the Nvp group and 14 patients in the 3TC group) (\( P = .05 \)). Concentrations of Idv in these 2 groups of patients are presented in the “Determination of plasma drug levels” subsection that appears below.

**Resistance analysis.** Genotypic testing was performed using plasma samples obtained at baseline from 28 patients who had previously received an NRTI. Amplification of the RT gene was not available for 2 patients. Eighteen patients (64%) had

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**Figure 2.** Percentage of patients with plasma HIV-1 RNA levels <200 copies/mL (solid line) and <20 copies/mL (dotted line). Results were analyzed by intent-to-treat analysis. Missing data denote virological failure, unless previous and subsequent values are <20 copies/mL or <200 copies/mL. 3TC, lamivudine; d4T, stavudine; Idv, indinavir; Nvp, nevirapine.
mutations conferring NRTI resistance, with no statistical difference between the 2 treatment groups evident (47% in the Nvp group and 77% in the 3TC group; \( P = .14 \)). No resistance to 3TC, NNRTI, or PI was detected. During follow-up, 36 patients experienced \( \geq 1 \) occurrence of a plasma HIV-1 RNA level >1000 copies/mL: 23 patients (32%) in the Nvp group and 13 patients (18%) in the 3TC group. Findings of resistance analysis were available for 32 of these 36 patients (22 in the Nvp group and 10 in the 3TC group). The rate of occurrence of resistance to NNRTI among patients in the Nvp group with virological failure (11 of 22) was not different from the rate of resistance to 3TC among patients in the 3TC group with treatment failure (6 of 10). During the study period, none of the naive patients developed resistance to d4T, and only 1 patient in each group developed resistance to PI.

**Determination of plasma drug levels.** The effect of Nvp on plasma concentrations of Idv is shown in figure 5. Median peak plasma levels of Idv were not different between the 2 groups. Median trough plasma levels of Idv, measured with a median self-reported delay of 10 h after the last Idv intake, were significantly lower in the Nvp group than in the 3TC group (81 ng/mL and 99 ng/mL, respectively; \( P = .04 \)). Median trough plasma levels of Idv were higher in patients with plasma HIV-1 RNA levels <20 copies/mL at week 72 than in patients with plasma HIV-1 RNA levels \( \geq 20 \) copies/mL (97 and 71 ng/mL, respectively; \( P = .012 \)) and in patients who developed nephrolithiasis than in patients who did not (126 and 84 ng/mL, respectively; \( P = .02 \)).

**Adherence.** The median adherence score was 100% (range, 40%–100%), with no difference noted between the 2 groups (\( P = .36 \)). The percentage of patients with an adherence score \( \geq 95\% \) was higher among patients with a plasma HIV-1 RNA level <20 copies/mL at week 72 than among patients with a plasma HIV-1 RNA level \( \geq 20 \) copies/mL (76% and 24%, respectively; \( P = .012 \)).

**DISCUSSION**

Conventional therapy for HIV-1 infection usually combines \( \geq 3 \) drugs from 2 different classes (2 NRTIs and an NNRTI or a PI) or from the same class (3 NRTIs). Whether a combination of 3 drugs from 3 different classes (3-class therapy) would result in a higher level of antiviral activity than would a combination of 3 drugs from 2 different classes (2-class therapy) remains unknown. We compared 2 triple-drug regimens that both incorporated an NRTI (d4T) and a PI (Idv) and that differed only with regard to the third drug used: either an NNRTI (Nvp) for the 3-class therapy or an NRTI (3TC) for the 2-class therapy. Nvp and 3TC were selected because, although they represent different classes of drugs, they do not differ with regard to 2 important virological characteristics: the level of intrinsic in vivo activity [4, 5] and a low genetic barrier to virological resistance [6, 7]. Therefore, the main difference between these 2 regimens was the number of different classes of drugs used.

In the present study, which involved HIV-1–infected patients, all of whom were PI and NNRTI naive and 79% of whom were treatment naive, both the 3-class and the 2-class triple therapies demonstrated potent and sustained antiretroviral activity. The high proportion of patients (79%) who, when analyzed on an intention-to-treat basis, had an undetectable plasma HIV-1 RNA level (<20 copies/mL) after receiving therapy with the 2-class therapy for 72 weeks reflects both the high level of antiviral activity and the excellent adherence observed.
activity of this regimen and the low rate of loss to follow-up and treatment discontinuation. The 3-class therapy did not demonstrate the expected increased antiretroviral activity when compared with the 2-class therapy in any of the analyses performed. Although the median change in the plasma virus load from baseline to 72 weeks was not significantly different between the 2 groups in the crude analysis, it differed in the censored analysis, and, consistently, the percentage of patients with plasma HIV-1 RNA levels below the limit of quantification at 72 weeks was higher with the 2-class therapy than with the 3-class therapy (86% and 63%, respectively, with a cutoff of 200 copies/mL [P < .002], and 79% and 52%, respectively, with a cutoff of 20 copies/mL [P < .001]). In every subgroup analysis of efficacy outcome based on baseline plasma HIV-RNA level, baseline CD4 cell count, and receipt or nonreceipt of prior therapy with an NRTI, the 2-class therapy was more active than was the 3-class therapy. The difference reached statistical significance in the 3 subgroups with the largest number of patients: patients with baseline levels of plasma HIV-1 RNA < 100,000 copies/mL, patients with baseline CD4 cell counts ≥ 200 cells/mm³, and patients with no prior receipt of antiretroviral therapy.

One study has shown that, in patients who had extensive prior treatment with an NRTI, suppression of HIV-1 RNA below the limit of detection occurred in a significantly greater proportion of patients receiving nelfinavir and efavirenz in addition to 2 NRTIs, at least 1 of which they had not previously received, than in patients receiving either nelfinavir or efavirenz in addition to 2 NRTI [18]. However, in that study, as in others, the higher level of antiretroviral activity of 3-class combinations could reflect the number of combined drugs (≥ 4), which was higher than that in conventional regimens [19–21].

The rate of treatment discontinuation was higher in the Nvp group than in the 3TC group (42.5% and 22.5%, respectively; P = .13), and was largely the result of rashes and hepatotoxicity. Rash occurred with a frequency of 19% in the Nvp group and

d4T, stavudine; Idv, indinavir; Nvp, nevirapine.

NOTE. Data are no. of serious adverse events/no of. patients evaluated. 3TC, lamivudine; APL, alkaline phosphatase level; d4T, stavudine; Idv, indinavir; Nvp, nevirapine.

* One patient had DRESS (drug rash with eosinophilia and systemic symptoms) [17].
led to the discontinuation of Nvp therapy for 15% of patients, not restricted to patients with severe rashes. This incidence of Nvp discontinuation is high, according to others’ reports [22–25]. The fear of severe toxicity and the large number of treatment options now available to HIV-1–infected individuals may have contributed to the relatively high rates of Nvp discontinuation in this study. The difference in the rate of treatment discontinuation between the Nvp and the 3TC groups could explain, in part, the higher rate of virological failure in the Nvp group, because more patients in the Nvp group than in the 3TC group had to alter their current therapy. However, on-treatment analysis for antiretroviral activity did not show that 3-class therapy was more active than was 2-class therapy.

Drug exposure is an important determinant of virological outcome, particularly with PIs, and attention has focused on the predictive value of trough plasma concentrations [26, 27]. In the present study, the dosage of Idv was increased from 800 mg to 1000 mg 3 times daily in the Nvp group, to compensate for an Nvp-Idv pharmacokinetic interaction that is known to result in a decrease of plasma levels of Idv [8–10]. Despite this increase in the Idv dosage, a median trough plasma level of Idv was observed that was significantly lower in the Nvp group than in the 3TC group, and nephrolithiasis was also reported 2 times more frequently in the 3TC group (14 patients) than in the Nvp group (6 patients) (P = .05). The frequency of nephrolithiasis is known to positively correlate with the plasma concentration of Idv [28]. Both the higher trough plasma levels of Idv and the higher incidence of nephrolithiasis among patients who received 3TC argue for a higher exposure to Idv in this group than in the Nvp group. Previous studies have reported that low levels of Idv increase the risk of treatment failure as a result of suboptimal exposure [26, 27, 29]. Therefore, the possibility that a lower exposure to Idv among patients receiving Nvp might have contributed to the lower antiviral activity of the 3-class therapy, compared with the 2-class therapy, cannot be ruled out. However, it should be noted that, in the present study, the median trough level of Idv in patients who received Nvp (81 mg/mL at 10 h after dosing) falls in the range of values recommended as optimal [27]. An antiretroviral adherence score of <95% is associated with virological failure [30, 31]. In the present study, although the daily pill burden differed between the 2 groups, there was no difference with respect to compliance with therapy, and 63% of the patients were considered compliant (defined by an adherence score of >95%). Therefore, differences in antiviral activity between 3-class and 2-class therapies are not explained by differences in adherence to treatment.

The present study shows that, among patients experiencing virological failure, mutations linked to NNRTI or 3TC resistance were detected in 50% of the patients in the Nvp group.
and in 60% of the patients in the 3TC group. These results are probably best explained by the similarly low genetic barrier of these 2 drugs. On the other hand, only 2 patients developed resistance to Idv, and none of the treatment-naive patients developed resistance to d4T during the 72 weeks of the study. It is well known that 3TC- and NNRTI-resistant variants emerge rapidly in the presence of viral replication, as opposed to Idv resistance [32]. In the Trile`ge trial [33] and the AIDS Clinical Trials Group 343 study [34], almost all escaping viruses carried no mutation in the protease gene, although the 3TC-associated mutation M184V was very common. Data from these studies are in agreement with our findings.

The triple-drug 3-class therapy that combined Nvp with d4T and Idv did not demonstrate higher antiviral activity or a better resistance pattern in case of virological failure than did 2-class therapy that combined 3TC with d4T and Idv for use in this population of patients who were previously untreated or who had limited experience with nucleoside analogues. In addition, regimen termination, especially because of toxicity, was more frequent with the 3-class regimen than with the 2-class regimen. Furthermore, in the 3-class treatment arm, viral rebound was often associated with resistance to Nvp, precluding the use of any other NNRTI because of the large degree of cross-resistance between compounds of this class. Therefore, our findings do not support the use of 3-class therapy that combines Nvp with d4T and Idv in treatment-naive HIV-1–infected patients.

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