Baseline HIV-1 RNA Level and CD4 Cell Count Predict Time to Loss of Virologic Response to Nelfinavir, but Not Lopinavir/Ritonavir, in Antiretroviral Therapy–Naive Patients

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Baseline CD4 cell counts and human immunodeficiency virus (HIV)–1 RNA levels have been shown to predict immunologic and virologic responses in HIV-infected patients receiving antiretroviral therapy. In our randomized, double-blind, comparative trial, 653 antiretroviral therapy–naïve patients received lopinavir/ritonavir or nelfinavir, plus stavudine and lamivudine, for up to 96 weeks. The risk of loss of virologic response was significantly higher for nelfinavir-treated patients than for lopinavir/ritonavir-treated patients (Cox model hazard ratio, 2.2; 95% confidence interval, 1.7–3.0; P < .001). For nelfinavir-treated patients, but not for lopinavir/ritonavir-treated patients, higher baseline HIV-1 RNA levels and lower baseline CD4 cell counts were associated with a higher risk of loss of virologic response.

Protease inhibitor–based combination antiretroviral therapy has been associated with dramatic improvements in HIV-associated morbidity and mortality [1]. In several studies, higher baseline HIV-1 RNA levels and/or lower baseline CD4 cell counts [2–4] have been associated with a reduced probability of the achievement or durability of virus suppression during treatment with a protease inhibitor–based regimen.

Lopinavir, a novel peptidomimetic protease inhibitor with potent in vitro activity against HIV, is coformulated with low-dose ritonavir, a cytochrome p450 3A4 enzyme inhibitor, to enhance its pharmacokinetic profile. Lopinavir/ritonavir-based regimens have demonstrated antiviral activity in antiretroviral therapy–naïve and protease inhibitor–experienced patients [5, 6], and, in a phase 2 study of a lopinavir/ritonavir-based regimen in antiretroviral therapy–naïve patients, virologic response through 4 years of treatment was not decreased among patients with lower CD4 cell counts or higher HIV-1 RNA levels at baseline [7].

In a randomized, double-blind clinical trial conducted in antiretroviral therapy–naïve patients, a lopinavir/ritonavir-based regimen demonstrated virologic response superior to that of a nelfinavir-based regimen, through 48 weeks of treatment [8]. Our objective was to assess, in that study, the effect of baseline HIV-1 RNA levels and CD4 cell counts on virologic response for up to 96 weeks.

**Patients, materials, and methods.** Antiretroviral therapy–naïve patients were enrolled in a randomized, double-blind phase 3 clinical trial comparing lopinavir/ritonavir to nelfinavir. Details of study design and results through 48 weeks have been reported elsewhere [8]. Patients were enrolled at 93 centers in 13 countries in North and South America, Europe, Africa, and Australia. The study was approved by the institutional review board or ethics committee at each center, and all patients provided written, informed consent. Patients had plasma HIV-1 RNA levels >400 copies/mL with no CD4 cell count restriction. Patients were randomized 1:1 to either lopinavir/ritonavir plus nelfinavir placebo or nelfinavir plus lopinavir/ritonavir placebo. All patients received lamivudine and stavudine. After the last active patient completed 60 weeks of treatment, patients and investigators were unblinded to treatment assignment, and, after the last active patient completed 72 weeks of treatment, the study was stopped.

Patients were evaluated at baseline, every 4 weeks through week 24, every 8 weeks through week 48, and every 12 weeks thereafter. HIV-1 RNA levels and CD4 cell counts were determined at a central laboratory. HIV-1 RNA levels were determined at every visit by use of version 1.0 or version 1.5 (South America only) of the Amplicor HIV-1 Monitor assay (Roche Diagnostics), with a limit of quantitation of 400 copies/mL.
The primary end point was the time to loss of virologic response through week 96. Loss of virologic response was defined by 2 consecutive HIV-1 RNA rebound levels $>400$ copies/mL following any HIV-1 RNA level $<400$ copies/mL or by a single HIV-1 RNA rebound level $>400$ copies/mL followed by study discontinuation. Patients who never achieved HIV-1 RNA levels $<400$ copies/mL were considered to have a loss of virologic response on day 0. Patients who discontinued or completed the study without demonstrating a loss of virologic response were censored as of their final virus load measurement while receiving randomized treatment.

All statistical tests were 2-tailed and based on a 0.05 level of significance, unless otherwise indicated. No adjustments for multiple comparisons were made. For each patient, adherence was measured as the ratio of the number of capsules consumed compared with the number of capsules expected to be consumed.

The Cox proportional hazards model was used to assess the association of the time to loss of virologic response with treatment group, baseline HIV-1 RNA level, baseline CD4 cell count, race, sex, age, weight, adherence, and time since diagnosis. Treatment group, race (white/non-Hispanic vs. all others), sex, and adherence (above vs. below the median adherence level) were analyzed as categorical variables; other covariates were analyzed as quantitative variables. Interactions between treatment group and covariates considered to be statistically significant were evaluated by use of a likelihood ratio test, to assess the appropriateness of pooling data from both treatment groups for analysis; $P < .25$ was used to determine whether treatment groups should be analyzed separately [9].

Univariate analyses were conducted in each treatment group separately. Multivariable proportional hazards models were conducted within each treatment group by use of a forward stepwise selection procedure, with entry and exit $P$ values of .15. In each treatment group, Kaplan-Meier estimates of the time to loss of virologic response were computed within strata of baseline CD4 cell counts and baseline HIV-1 RNA levels, to illustrate the effects of these variables on the time to loss of virologic response. Analyses were conducted by use of the SAS System (release 6.12; SAS Institute).

**Results.** Patients treated with lopinavir/ritonavir ($n = 326$) or nelfinavir ($n = 327$) were enrolled between 30 March 1999 and 30 September 1999 and were included in the analysis. No significant differences between treatment groups were observed for any baseline characteristics. Patients were primarily men (80%) and white (57%), and the overall mean (median) baseline HIV-1 RNA level and CD4 cell count were $4.90$ ($4.99$) log$_{10}$ copies/mL and 259 (232) cells/mm$^3$, respectively.

Overall, 77% of patients (80% receiving lopinavir/ritonavir and 74% receiving nelfinavir) completed at least 60 weeks of treatment. The median durations of blinded treatment were 84 weeks (lopinavir/ritonavir) and 81 weeks (nelfinavir), with median durations of overall treatment of 92 weeks (lopinavir/ritonavir) and 87 weeks (nelfinavir) and the maximum duration of treatment of 114 weeks in each group. Premature discontinuations after unblinding were infrequent, occurring in only 2% (lopinavir/ritonavir) and 5% (nelfinavir) of enrolled patients. Discontinuations due to study drug–related adverse events were uncommon, occurring in 6% of patients in each treatment group through the end of the study. Pill count–based adherence was similar between treatment groups, with mean (median) overall adherence levels of 92% (95%) for lopinavir/ritonavir-treated patients and 93% (96%) for nelfinavir-treated patients.

A total of 189 patients met the criteria for loss of virologic response (63 receiving lopinavir/ritonavir and 126 receiving nelfinavir), including 61 who never achieved HIV-1 RNA levels $<400$ copies/mL (22 receiving lopinavir/ritonavir and 39 receiving nelfinavir) and 128 with confirmed viral rebound after suppression to $<400$ copies/mL (41 receiving lopinavir/ritonavir and 87 receiving nelfinavir). Of these 189 patients, only 2 demonstrated loss of virologic response after unblinding. Of the 128 patients with viral rebound, 107 had at least 1 follow-up HIV-1 RNA value without a change in regimen, and resuppression of HIV-1 RNA level to $<400$ copies/mL was more common in lopinavir/ritonavir-treated (22/32; 69%) than in nelfinavir-treated (17/75; 23%) patients ($P < .001$, Fisher’s exact test); for 3 lopinavir/ritonavir-treated patients, virus resuppression occurred after unblinding.

Treatment with nelfinavir ($P < .001$), higher baseline HIV-1 RNA level ($P < .001$), lower baseline CD4 cell count ($P < .001$), adherence below the median ($P < .001$), lower weight ($P < .05$), younger age ($P < .05$), and longer time since diagnosis ($P < .05$) were each significantly associated with shorter time to loss of virologic response, whereas race and sex were not. Time to virologic response, through week 96. HR, Cox proportional hazards model hazard ratio; CI, confidence interval.

![Figure 1](https://academic.oup.com/jid/article-abstract/190/2/280/987334)
loss of virologic response by treatment group is shown in figure 1, on the basis of Kaplan-Meier analysis.

Although the interactions of treatment group with weight, age, and time since diagnosis were not notable (P > .25 for each), those of treatment group with baseline HIV-1 RNA level (P = .08) and CD4 cell count (P = .07) indicated that these variables have differing effects and, therefore, that the treatment groups should not be pooled for analysis. In each treatment group, lower adherence was associated with loss of virologic response. For nelfinavir-treated patients, the hazard ratio (HR) was 2.5 for adherence below versus above the median (95% confidence interval [CI], 1.7–3.6; P < .001), and, for lopinavir/ritonavir-treated patients, the HR was 2.4 (95% CI, 1.3–4.4; P = .003). For nelfinavir-treated patients, baseline HIV-1 RNA level (P < .001) and baseline CD4 cell count (P < .001) were statistically significantly associated with virologic response, whereas, for lopinavir/rito-
navir-treated patients, neither variable was associated with loss of virologic response ($P > .05$ for each). The Kaplan-Meier analysis of the time to loss of virologic response within each treatment group is shown by baseline HIV-1 RNA level and CD4 cell count in figure 2. Results were confirmed by multivariable stepwise analysis. The final model for the nelfinavir-treated group included adherence, baseline HIV-1 RNA level, baseline CD4 cell count, and age, whereas the final model for the lopinavir/ritonavir-treated group included adherence, weight, and time since diagnosis, but not HIV-1 RNA level or CD4 cell count.

**Discussion.** In the present analysis, the superior virologic response of lopinavir/ritonavir, compared with that of nelfinavir, in antiretroviral therapy–naive patients, previously reported through 48 weeks [8], was maintained for up to 96 weeks of treatment. The significant effect of baseline HIV-1 RNA level and CD4 cell count on virologic response to a nelfinavir-containing regimen is consistent with previous reports of similar effects with highly active antiretroviral therapy, including protease inhibitor–based, nonnucleoside reverse-transcriptase inhibitor–based, and triple nucleoside reverse-transcriptase inhibitor regimens [2–4, 10, 11]. In contrast, the absence of a significant effect of baseline HIV-1 RNA level and CD4 cell count on response to a lopinavir/ritonavir-containing regimen in the present study is consistent with results from a phase 2 study of a lopinavir/ritonavir-based regimen in antiretroviral therapy–naive patients who were followed for up to 4 years [7].

The risk of loss of virologic response was >2-fold higher for nelfinavir-treated patients than for lopinavir/ritonavir-treated patients. In addition, the implications of detectable virus load during therapy with nelfinavir were potentially more serious, in that the greater rates of primary protease inhibitor resistance (0% for lopinavir/ritonavir vs. 45% for nelfinavir) and reverse-transcriptase inhibitor resistance (37% vs. 82%) observed in this study [12] may limit the effectiveness of subsequent treatment options. Among lopinavir/ritonavir-treated patients, the high degree of virus suppression and the absence of protease inhibitor resistance suggest that the events of loss of virologic response were due to temporary nonadherence or other factors resulting in low drug exposures.

The regimens in the present study demonstrated comparable tolerability and adherence; thus, the differences observed may be attributable to other factors, such as pharmacologic characteristics. Nelfinavir provides mean trough drug levels only 3–4-fold greater than the IC$_{50}$ for wild-type HIV [13, 14], whereas lopinavir/ritonavir provides trough concentrations ~75-fold greater than the IC$_{50}$ [5]. This margin potentially provides a more forgiving pharmacokinetic profile and a high genetic barrier to resistance, facilitating control of viral replication by a lopinavir/ritonavir-based regimen, even in the presence of high baseline HIV-1 RNA levels and low baseline CD4 cell counts.

There are potential limitations to this analysis. The use of version 1.0 of the HIV-1 Monitor assay instead of version 1.5 may have modestly overestimated the absolute rates of virus suppression, although such an effect would be unlikely to change any conclusions. With a longer duration of follow-up, baseline HIV-1 RNA levels and CD4 cell counts might demonstrate a significant effect on response to lopinavir/ritonavir, as evidenced by a trend toward lowered response in lopinavir/ritonavir-treated patients with baseline CD4 cell counts <50 cells/mm$^3$. Although this result suggests the possibility of lowered response to lopinavir/ritonavir in antiretroviral therapy–naive patients with very advanced HIV disease, its context is difficult to determine, since clinical trials of other antiretroviral therapies often exclude patients with very low CD4 cell counts. In recently reported studies of efavirenz, indinavir, and atazanavir, entry criteria excluded patients with CD4 cell counts <50 or <75 cells/mm$^3$ [15, 16]; thus, the efficacy of these agents in patients with low CD4 cell counts may not be well understood. It is unknown whether other ritonavir-boosted protease inhibitor regimens will ultimately demonstrate a similarly robust virologic response in patients with higher HIV-1 RNA levels or lower CD4 cell counts. In a recent study of ritonavir-boosted fosamprenavir, similar response rates at 48 weeks were observed among patients with HIV-1 RNA levels > or <100,000 copies/mL [17], although the importance of this result is unclear, since, in the overall analysis, the ritonavir-boosted fosamprenavir regimen did not show virologic response superior to that of a nelfinavir-based regimen.

The results of the present study confirm the prognostic value of baseline CD4 cell counts and plasma HIV-1 RNA levels in predicting virologic response among patients treated with a nelfinavir-based regimen. In contrast, our results demonstrate that lopinavir/ritonavir-based treatment did not lead to significantly decreased virologic response in patients with lower baseline CD4 cell counts and higher baseline HIV-1 RNA levels. Our findings are consistent with the concept that the predictive value of CD4 cell count and HIV-1 RNA level is dependent on the potency of the regimen used, and these results continue to suggest an important role for lopinavir/ritonavir as the initial protease inhibitor–based treatment for HIV infection.

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**References**


