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Comparison of the effectiveness of initial combined antiretroviral therapy with nelfinavir or efavirenz at a university-based outpatient service in Brazil

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Abstract

Since there are some concerns about the effectiveness of highly active antiretroviral therapy in developing countries, we compared the initial combination antiretroviral therapy with zidovudine and lamivudine plus either nelfinavir or efavirenz at a university-based outpatient service in Brazil. This was a retrospective comparative cohort study carried out in a tertiary level hospital. A total of 194 patients receiving either nelfinavir or efavirenz were identified through our electronic database search, but only 126 patients met the inclusion criteria. Patients were included if they were older than 18 years old, naive for antiretroviral therapy, and had at least 1 follow-up visit after starting the antiretroviral regimen. Fifty-one of the included patients were receiving a nelfinavir-based regimen and 75 an efavirenz-based regimen as outpatients. Antiretroviral therapy was prescribed to all patients according to current guidelines. By intention-to-treat (missing/switch = failure), after a 12-month period, 65% of the patients in the efavirenz group reached a viral load <400 copies/mL compared to 41% of the patients in the nelfinavir group (P = 0.01). The mean CD4 cell count increase after a 12-month period was also greater in the efavirenz group (195 x 10^6 cells/L) than in the nelfinavir group (119 x 10^6 cells/L; P = 0.002). The efavirenz-based regimen was superior compared to the nelfinavir-based regimen. The low response rate in the nelfinavir group might be partially explained by the difficulty of using a regimen requiring a higher patient compliance (12 *vs* 3 pills a day) in a developing country.

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Introduction

Highly active antiretroviral therapy (HAART) has changed the course of the AIDS epidemic worldwide. With the issue of law No. 9313/96, Brazil has provided free antiretroviral drugs to all AIDS patients, resulting in a substantial decrease in the incidence of AIDS-related deaths and hospitalizations (1).

Despite the initial enthusiasm for HAART based on protease inhibitors (PI), the high adherence requirements (2,3), the low rates of durable virologic responses in unselected clinical cohorts (4), the high incidence of adverse effects (5,6), the frequent development of antiretroviral resistance (7,8), in addition to the high treatment cost have brought some doubts about which HAART regimen should be considered the best first-line choice for AIDS patients (9). Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor with a high potency and since its approval in 1998 it has become an appealing alternative to PI use in the initial regimen. In clinical trials, EFV has shown superior antiretroviral efficacy compared with PI in naive patients (in comparison to indinavir and nelfinavir (NFV)) and in dual nucleoside-experienced patients (in comparison to NFV) (10-12). However, the effectiveness of therapy outside a clinical trial setting may differ substantially from the efficacy documented in clinical trials (4). Many factors may influence the effectiveness of these agents outside clinical trials, especially in developing countries, where educational problems and economic restrictions are huge obstacles to treatment compliance (13). Despite the considerable number of studies addressing this issue in Africa, there are only few studies addressing it in Latin America (13,14).

For this reason, in the setting of a university-based HIV clinic in Brazil, we performed a retrospective comparative cohort study evaluating the virologic and immunologic effectiveness of initial combination therapy with zidovudine (AZT) and lamivudine (3TC) plus either NFV or EFV, these being considered the first-line treatment regimens during the period evaluated by this study (15).

Patients and Methods

This retrospective cohort study was conducted in a university-based HIV clinic in the city of Ribeirão Preto, SP, Brazil. This clinic is responsible for the care of 1400 HIV-infected patients, who are seen regularly at 1- to 3-month intervals depending on their clinical status. It is worth noting that the State of São Paulo contains most of the AIDS patients in Brazil (16).

Patients were included in the study if they were older than 18 years, naive for antiretroviral therapy, if they received treatment with either EFV- or NFV-based HAART in combination with AZT + 3TC, and had at least 1 follow-up visit after starting this antiretroviral regimen. Patients were identified through electronic databases that record the antiretroviral distribution. Once a patient was identified, his medical records were reviewed. The recorded data retrieved were: sex, age, baseline CD4 cell count, and HIV-1 viral load (the closest measurement before starting HAART), CD4 cell counts and HIV viral load measurements up to 12 months, adverse effects, death, and discontinuation. If HAART was changed or discontinued, the date and reason for the change were recorded. CD4 cell counts were measured by flow cytometry. Most of the HIV-1 RNA viral load measurements were made using the Versant HIV-1 RNA 3.0 Assay (limit of detection of 50 copies/mL).

The primary end point evaluated in the present study was the percentage of patients with an HIV-1 viral load <400 copies/mL at month 12. We chose HIV-1 viral load <400 copies/mL as our primary outcome because this level of viral suppression was the limit

for the assay available during the first year of the study, and it has been associated with significantly reduced rates of HIV-1 disease progression in several large cohort studies (16). Secondary end points included mean HIV-1 viral load (log copies/mL) reduction at month 12, mean CD4 cell count increase at month 12, and frequency of adverse effects. The adverse effects were evaluated taking into account their identification recorded on the charts by the patient's physician.

An intention-to-treat analysis was performed considering drop-outs and changes of treatment regimens as failures. All data were stored in the database and analyzed with the Epi-Info, version 3.3.2, and Graphpad Instat softwares. The percentage of patients with an HIV-1 viral load <400 copies/mL at month 12 and the incidence of adverse effects were compared using the Yates-corrected test for categorical variables. Mean HIV-1 viral load reduction and mean CD4 cell count increase at month 12 were compared using the unpaired *t*-test for continuous variables.

Results

A total of 194 patients receiving HAART regimens containing either NFV or EFV were identified with our database search from January 2002 to December 2003, but only 126 patients met the inclusion criteria. The main reason why some of patients enrolled were not included in the study was the previous use of antiretroviral therapy, with 32 of them receiving EFV-based HAART and 25 receiving NFV-based HAART. Fifty-one of the patients included in the analysis received NFV-based HAART and 75 received EFV-based HAART.

The basal characteristics of the cohort including both therapy groups are shown in Table 1. Patients in the two groups did not differ significantly in terms of sex, race or age. Both groups presented closely similar mean baseline HIV-1 viral loads (NFV 5.3 *vs* EFV 4.9), but the difference was statistically significant. Regarding baseline immunologic characteristics, the NFV group presented a significantly lower mean baseline CD4 cell count compared to the EFV group (76.7 *vs* 158.6, respectively).

Virologic and immunologic responses

In an intention-to-treat (missing/switch = failure) analysis, after a 12-month period, a higher percentage of patients receiving EFV-based HAART (65%) reached a viral load below the detectable level compared to patients receiving NFV-based HAART (41%; P = 0.01). Figure 1 also shows that the difference in the percentage of patients with an HIV viral load <400 copies/mL between the two groups increased during the period. The percentage of patients without a follow-

Table 1. Basal characteristics of the antiretroviral-naive patients at the beginning of therapy.

Characteristics	Efavirenz (N = 75)	Nelfinavir (N = 51)
Female gender	33.3%	27.4%
African-American	21.3%	25.4%
Age	37.7 (16-74)	35.9 (19-66)
CD4 cell count (x 10^6 cells/L)	158.6 (6-550)	76.7 (7-385)*
HIV viral load (log copies/mL)	4.9 (2.2-6.6)	5.3 (4-7.1)*

Data are reported as percent or median and interquartile range in parentheses.
*P < 0.05 compared to efavirenz treatment (Yates-corrected test).

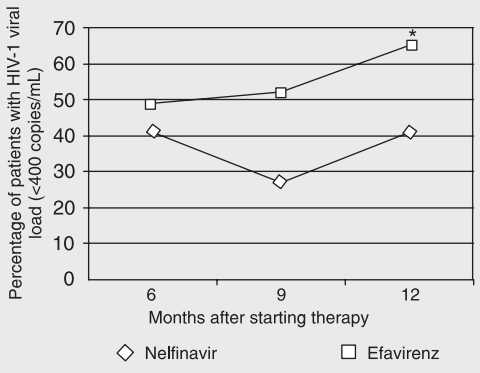

Figure 1. Percentage of patients with viral load <400 copies/mL according to regimen type. P < 0.01 at month 12 comparing efavirenz and nelfinavir (Yates-corrected test for categorical variables).

up HIV-1 viral load measurement at the end of the study period in the NFV group (23%) was not significantly different from the EFV group (21%).

The mean reduction of HIV-1 viral load in the 12-month period was greater in the EFV group (-4.2 log copies/mL) than in the NFV group (-3.2 log copies/mL; P = 0.02). As illustrated in Figure 2, during the 12-month period, the EFV group presented a steady-mean reduction of HIV-1 viral load, whereas the NFV group presented a variation of the mean reduction of HIV-1 viral load during the period.

The mean CD4 cell count increase at month 12 was higher in the EFV group (195 x 10^6 cells/L) than in the NFV group (119 x 10^6 cells/L; P = 0.002), reflecting a close relationship between the immunologic response and the virologic response obtained.

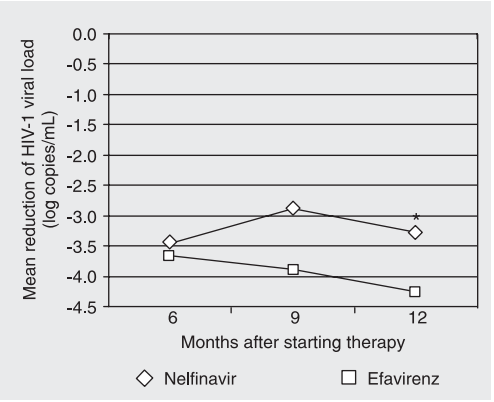

Figure 2. Mean reduction of HIV-1 viral load (log copies/mL) according to regimen type. P = 0.02 comparing efavirenz to nelfinavir by the unpaired *t*-test for continuous variables.

Table 2. Adverse effects observed in both groups of the antiretroviral regimens.

	Efavirenz (N = 75)	Nelfinavir (N = 51)
Adverse effect	36 (48%)	24 (47%)
Interruption	8 (10%)	6 (12%)
Anxiety	3 (4%)	1 (2%)
Dizziness	13 (17%)	2 (4%)*
Headache	2 (2%)	6 (12%)
Insomnia	6 (8%)	1 (2%)
Diarrhea	16 (21%)	15 (30%)
Nausea	10 (13%)	9 (17%)
Dyspnea	0 (0%)	1 (2%)
Fatigue	4 (5%)	2 (4%)
Peripheral neurological symptoms	7 (9%)	1 (2%)
Lipodystrophy	0 (0%)	0 (0%)
Anemia	2 (2%)	7 (14%)*
Elevated aminotransferases	5 (6%)	5 (10%)
Dyslipidemia	4 (5%)	3 (6%)

Data are reported as number with percent in parentheses.
*P < 0.05 compared to efavirenz treatment (Yates-corrected test).

Adverse effects

Table 2 shows the most frequently observed adverse effects in the two treatment groups. Notice that the frequency of any adverse effect was similar for the two treatment groups (EFV 48% *vs* NFV 47%, P = 0.93), as also was the frequency of treatment interruption because of toxicity (EFV 10% *vs* NFV 12%, P = 0.83). However, when the adverse effects were analyzed separately, the two treatment groups were significantly different regarding dizziness and anemia. A higher percentage of patients presented dizziness in the EFV group than in the NFV group (17 *vs* 4%, respectively, P = 0.04), and, regarding laboratory abnormalities, the NFV group presented a significantly higher percentage of anemia than the EFV group (14 *vs* 2%, respectively, P = 0.04).

Discussion

During recent years, a large number of antiretroviral clinical trials have been published, showing promising results. As previously mentioned, cohort studies provide important and timely information regarding current clinical dilemmas, and are important complements to clinical trials. Some investigators have also expressed concerns regarding antiretroviral effectiveness in developing countries, because of the lack of health information and infrastructure (13). To investigate this hypothesis, we performed this retrospective comparative cohort study evaluating the virologic and immunologic effectiveness of initial combination therapy with AZT and 3TC plus either NFV or EFV in the setting of a university-based HIV clinic in Brazil. To our knowledge, this is the first

publication that has analyzed the comparative effectiveness of these two HAART regimens for the treatment of Latin American patients.

By intention-to-treat (missing/switch = failure) analysis, after a 12-month period of HAART, the percentage of patients achieving viral suppression was approximately 15% higher among patients receiving EFV-based regimens than among those receiving NFV-based HAART, with the difference being statistically significant. The mean CD4 cell count increase was also significantly higher in the EFV group than in the NFV group (195 x 10^6 *vs* 119 x 10^6 cells/L, respectively). It is reasonable to think that the better results achieved by the patients in the EFV group were related to the higher potency and/or more convenient use of this regimen. However, the difference in the baseline CD4 cell count might have also contributed to the different responses observed in the two groups. It is worth noting that in this study the frequency of dizziness in patients receiving EFV was almost two times higher than that reported by Staszewski et al. (10). A higher frequency of anemia was observed in the NFV group. In our opinion, this higher frequency could be a side-effect of AZT, a false-positive result due to either a multiple subgroup analysis or to the sample size of our study, or may even be related to the worse baseline immunologic status of the patients in the NFV group and to other characteristics not controlled in the study such as drugs (e.g., pyrimethamine) and opportunistic diseases (e.g., disseminated *Mycobacterium avium* complex disease) (17,18).

Concerning antiretroviral effectiveness, the percentage of patients with an HIV-1 viral load <400 copies/mL at month 12 in the group of patients receiving EFV-based HAART was similar to those reported in other studies (10,19,20). However, a recently published systematic overview whose primary goal was the comparison of the effectiveness of a three-drug combination antiretroviral therapy in treatment-naive HIV-infected persons showed a higher effectiveness (73%) on the non-nucleoside reverse transcriptase inhibitors than that observed in our study (65%) (21). On the other hand, when comparing the data obtained at 12 months, the percentage of patients with undetectable viral load in the group receiving NFV-based HAART was lower than those reported by Walmsley et al. (22) and by others (23). This fact may be explained by the limitations that a regimen with a high adherence requirement like NFV-based HAART has in a developing country setting and outside clinical trials.

Our study has several limitations, most of them commonly observed in retrospective cohort studies. First, the present results reflect the experience of a single-university-based clinic with a limited number of patients and may not be applicable to other settings. Second, patients were not randomized to the treatments received, with the possibility of confounding by indication. It is possible that NFV-HAART was preferred for patients with a lower CD4 cell count and higher HIV-1 viral load, especially because PI-HAART had been used for a longer time. On the other hand, it is also possible that EFV-HAART was preferred for patients for whom adherence was considered to be a potential problem. In our study the distribution of patients between the two treatment groups was not controlled for factors known to be associated with a poor response such as history of injecting drug use, low-baseline CD4 cell count and high-baseline HIV-1 viral load (19). Third, the study did not measure the durability of viral suppression among patients who achieved viral suppression. Fourth, because of temporal differences in the availability of antiretroviral agents, EFV was most used at the end of the study period, and we cannot rule out the possibility that a greater experience with HAART among clinicians or greater emphasis on adherence would explain part of the association be-

tween EFV and viral suppression.

The results of our study suggest that EFV-based HAART has superior effectiveness compared to NFV-based HAART for the treatment of naive HIV-infected patients with a response rate similar to those reported in other studies. However, in our study NFV-based HAART showed a lower response rate than reported in previous studies, which may have been caused by the difficulties of using a regimen with a higher adherence requirement (12 *vs* 3 pills a day) in a specific population such as the one attended in our clinic, characterized by a large number of intravenous drug users. The lower efficacy of NFV-based HAART compared to other regimens containing either other PIs or EFV has been reported in other studies, and these findings are probably related to the fact that NFV has been considered to present the lowest potency in its drug class. Since this study was not randomized and baseline characteristics were not controlled, we cannot completely rule out residual bias, which should always be considered when interpreting the results of observational studies (24). These limitations should be overcome in future studies and long-term follow-up should also determine the durability of viral suppression, the rate of adverse metabolic effects and the economic impact of these antiretroviral regimens.

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