Virologic and Immunologic Response to Regimens Containing Nevirapine or Efavirenz in Combination with 2 Nucleoside Analogues in the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) Study

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This nonrandomized study compared the virologic and immunologic responses to potent regimens containing either efavirenz or nevirapine after considering potential systematic differences between patients receiving these drugs. Virologic failure was defined as the first of 2 consecutive measurements of virus load >500 human immunodeficiency virus RNA copies/mL. Of the 694 patients included in the analysis, 460 (66.3%) started nevirapine and 234 (33.7%) started efavirenz. The adjusted relative hazard of virologic failure for patients who started nevirapine, compared with those who started efavirenz, was 2.08 (95% confidence interval, 1.37–3.15; $P = .0006$). In addition, patients receiving efavirenz tended to recover 5 CD4 cells/μL more per quarter ($P = .05$). Although comparisons of drug efficacy in nonrandomized studies should be viewed with caution, no results from randomized controlled comparisons of these drugs are thought to be available. The findings of this study are in agreement with those of other observational studies.

Ideally, responses to antiretroviral drugs (regimens) should not be compared by use of observational studies. However, if persons receiving the drug regimens of interest are very comparable and results from clinical trials regarding that particular comparison are not yet available, analyses of nonrandomized studies may be useful [1]. Even if we cannot exclude possible bias in different observational studies across Europe, often when a result is reproducible across a variety of different studies, it cannot simply be explained as bias introduced by nonrandomization [2–5]. Thus, it is important to repeat controversial comparisons in different settings, possibly by use of standardized statistical methods.

For one such comparison (i.e., the outcome of triple drug regimens containing the nonnucleoside reverse-transcriptase inhibitors [NNRTIs] nevirapine vs. efavirenz plus 2 nucleoside analogue reverse-transcriptase inhibitors [NRTIs]), only preliminary results from clinical trials are available [6, 7]. This comparison also has been the focus of analysis in 3 other nonrandomized cohort studies [8–10]. Nevirapine and efavirenz are the only 2 NNRTIs licensed in Europe and were approved by the US Food and Drug Administration in 1996 and 1998, respectively. US and UK guidelines recommend the use of these drugs in both antiretroviral-naive and pretreated patients, and they are as widely used in clinical practice as protease inhibitor (PI)–containing highly active antiretroviral therapy (HAART) regimens [11–13]. Such combinations are often preferred to PI-containing regimens because they are potent against viral replication, easier to take, and more tolerable.

Three clinical trials showed that NNRTIs in combination with 2 NRTIs are virologically equivalent or superior to similar combinations containing a PI in antiretroviral-naive patients [14–16]. Specific comparisons between nevirapine and efavirenz have been made, in addition to the aforementioned clinical trials (results have only been presented at meetings [6, 7]), in 3 observational studies [8–10]. There are also 2 other larger ongoing clinical trials (FIRST and 2NN). Analysis of the observational studies showed different virologic (and clinical) outcomes for

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persons who used the different regimens. This could reflect a difference in efficacy, but bias is impossible to rule out.

In the present study, we evaluated the virologic and immunologic response to HAART regimens that included 2 NRTIs and nevirapine (or efavirenz) in both antiretroviral-naive and pretreated patients enrolled in a large observational study in Italy. We also compared the rates of discontinuations of these drugs over the follow-up period. We hope that our findings contribute to the discussion regarding the efficacy of these drugs in clinical practice while we await results of randomized studies.

Patients and Methods

We studied patients enrolled in a large observational study in 67 Italian infectious disease wards from which patients were recruited from 1997 to 1999, when they were still antiretroviral naive. In 2000, enrollment was restarted to include antiretroviral-naive patients who had more recent access to the same clinics. Details of the study design and data collection have been reported elsewhere [17].

For this analysis, we focused on 694 patients who started exactly 2 NRTIs and nevirapine (or efavirenz), who were NNRTI naive at the start of this therapy, and for whom virus load and CD4 cell count data were available for the 24 weeks prior to treatment initiation. We compared baseline characteristics of patients receiving nevirapine and efavirenz by using the χ^2 test (for categorical variables) and the Wilcoxon 2-sample test (normal approximation, with continuity correction of 0.5). The frequency of discontinuation of nevirapine and efavirenz was calculated by reason for stopping therapy and was compared by the χ^2 test. The time to discontinuation of these drugs was estimated and compared by Kaplan-Meier analysis and log-rank test.

We defined virologic failure separately according to whether the virus load was ≤ 500 or > 500 human immunodeficiency virus (HIV) RNA copies/mL at the time of start of therapy with an NNRTI (time zero [t_0] of the analysis). If the virus load was ≤ 500 HIV RNA copies/mL, failure was defined at the time of the first of 2 consecutive virus load measurements > 500 HIV RNA copies/mL (time of first loss of virus suppression). If, instead, virus load was > 500 HIV RNA copies/mL, we defined failure at the time of the first of 2 consecutive virus load measurements > 500 HIV RNA copies/mL after 6 months of therapy (virus rebound or failure to suppress by 6 months). Follow-up of patients who did not reach the end point was censored at the time of the last virus load measurement. Patients who had a virus load > 500 HIV RNA copies/mL at t_0 but whose virus load was last measured before week 24 were excluded from the analysis. This end point was chosen to try to repeat the analysis done in the EuroSIDA study by use of a standardized definition [8]. The only difference was that patient follow-up was censored at the date of the last virus load measurement available rather than at the date of the penultimate virus load measurement.

The incidence of virologic failure was calculated as the number of events per person-year of follow-up, and confidence intervals (CIs) were calculated by use of normal approximation. Akin to the survival analysis, for patients with an initial virus load ≤ 500 HIV RNA copies/mL, person-years were calculated from the date of start of HAART to the date of treatment failure (or the last date of virus load measurement). For patients whose initial virus load was > 500 HIV RNA copies/mL, person-years were calculated starting 6 months after the date of therapy initiation and ending at the date of treatment failure (or the date of the last virus load measurement).

We used a multivariate proportional hazards Cox regression model to compare the time to virologic failure in patients receiving the nevirapine- or efavirenz-containing HAART. The choice of the factors included in the multivariate analysis was made a priori by considering the factors with a largely unbalanced distribution between the 2 groups plus several other potential confounders (i.e., factors known to be associated with the virologic response). The model was stratified by calendar time of initiation of therapy. Proportionality assumption was evaluated by use of graphical methods proposed by Hess [18] and by a statistical test based on the distribution of Schoenfeld residuals [19].

Immunologic response was compared by fitting a mixed linear model with fixed effects for nevirapine and efavirenz, time since the initiation of therapy, and the interaction between these 2 factors. Thus, both the mean CD4 cell count before therapy and the slope of change over follow-up in the nevirapine and efavirenz group could be compared by Fisher's F test. Pretherapy CD4 cell count was also fitted as a covariate to control for the fact that the 2 groups started with different pretherapy CD4 cell counts.

Given the importance of ruling out any possible bias or residual confounding, several sensitivity analyses were conducted. In the Cox regression, therapeutic failure was also defined as virologic failure (as defined above) or discontinuation of nevirapine or efavirenz, whichever occurred first (discontinuation = failure analysis). Alternatively, follow-up of patients who discontinued nevirapine or efavirenz was censored at the time of ending treatment (discontinuation = censored).

Because the use of nevirapine and efavirenz was unbalanced in the different infectious disease wards that recruited patients for the Italian Cohort Naive Antiretrovirals (I.Co.N.A.) study, we also used a proportional hazard model stratified by clinical center (with calendar year included as an additional covariate).

Results

Patients. Of the 694 patients included in the analysis, 460 (171 antiretroviral naive and 289 pretreated) started 2 NRTIs and nevirapine and 234 (94 antiretroviral naive and 140 pretreated) started 2 NRTIs and efavirenz. Thus, in total, the analysis was conducted on 265 (171 + 94) antiretroviral-naive and 429 (289 + 140) pretreated patients. Table 1 and table 2 show the characteristics of naive and pretreated patients at the time of start of therapy by nevirapine or efavirenz treatment.

Two major imbalances were clearly noticeable in both antiretroviral-naive and pretreated patients. First, antiretroviral-naive patients who received efavirenz were, in general, at a more advanced stage of HIV disease, with lower CD4 cell counts and higher virus loads, and a larger percentage were previously diagnosed with AIDS (table 1). Second, consistent with the time of introduction of these drugs in clinical practice in Italy, more patients received efavirenz in more recent years (table 1 and table 2). In patients starting HAART with an NNRTI for the

Table 1. Characteristics of 265 antiretroviral-naive patients at the start of therapy with nevirapine or efavirenz.

Characteristic	Nevirapine ($n = 171$)	Efavirenz ($n = 94$)	P
Female sex	60 (35.1)	27 (28.7)	.29[a]
Source of HIV exposure			.78[a]
IDU	12 (7.1)	4 (4.3)	
Prior IDU	55 (32.2)	28 (29.8)	
Homosexual	29 (17.0)	19 (20.2)	
Heterosexual	69 (40.4)	41 (43.6)	
Other	6 (3.5)	2 (2.1)	
Previous AIDS	5 (2.9)	19 (20.2)	.001[a]
Year treatment started			.001[a]
1997	1 (0.6)	0	
1998	70 (40.9)	1 (1.1)	
1999	58 (33.9)	19 (20.2)	
2000	41 (24.0)	72 (76.6)	
2001	1 (0.6)	2 (2.1)	
HCV positive ($n = 221$)	62 (43.1)	32 (41.6)	.83[a]
Age, median years (range)	35 (18–65)	35 (20–70)	.17[b]
CD4 cell count, median cells/μL (range)	423 (28–1487)	307 (19–1368)	.0001[b]
Virus load, median $\log_{10}$ HIV RNA copies/mL (range)	4.56 (3.08–6.08)	4.70 (3.20–6.36)	.04[b]
NRTI started			
Zidovudine	131 (76.6)	51 (54.3)	.001[a]
Stavudine	39 (22.8)	39 (41.4)	.001[a]
Lamivudine	125 (73.1)	74 (78.7)	.31[a]
Didanosine	44 (25.7)	24 (25.5)	.97[a]
Zalcitabine	3 (1.8)	0	.20[a]

NOTE. Data are no. (%) of patients, except where noted. HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; NRTI, nucleoside reverse-transcriptase inhibitor.

[a] χ^2 test.

[b] Wilcoxon 2-sample test.

first time, zidovudine was more frequently used with nevirapine and stavudine with efavirenz (table 1). Again, this could be related to patient treatment practices in more recent years.

Among pretreated patients, those given efavirenz had prior experience with a larger number of drugs (mean prior NRTIs, 2.3 for nevirapine vs. 2.4 for efavirenz; mean prior PIs, 0.9 vs. 1.3). Also, the duration of receiving antiretroviral treatment was longer in patients who received efavirenz than in those given nevirapine, possibly because changes to efavirenz may have been more common in recent times, when treatment regimens were not modified as quickly as in the past (table 2). Of note, the population of pretreated patients had a set of patients who switched to an NNRTI and had a virus load of >500 HIV RNA copies/mL (221 switches due to failure) and a group of patients whose virus load was stable at $\leqslant 500$ HIV RNA copies/mL at the time of switch (208 switches likely to be due to intolerance, toxicity, or therapy simplification; table 2).

Frequency of drug interruption and reason. Over a median clinical follow-up of 46 weeks (interquartile range, 23–79 weeks), frequency of discontinuation was higher in patients receiving nevirapine, regardless of the reason for stopping (table 3). In addition, a larger difference in the rate of discontinuation was observed during the first 12–16 weeks, possibly because of interruptions due to hypersensitivity reactions to nevirapine (table 3 and figure 1), whereas the probability of stopping nevirapine or efavirenz was similar after the first 24 weeks of therapy ($P = .003$, log-rank; figure 1).

Proportionality assumption. The Cox model is appropriate only under the assumption that the hazard of virologic failure in the nevirapine group divided for the hazard of failure in the efavirenz group remains constant over time. Therefore, it is crucial to evaluate the validity of this assumption. The plotted lines of minus the natural logarithm (l_n) of minus l_n of survival time for the nevirapine and efavirenz group versus the l_n of the analysis time were reasonably parallel, and the Kaplan-Meier observed survival curves overlapped with the Cox predicted curves. Although useful, these graphical methods are somehow subjective; however, the statistical tests based on Schoenfeld residual were also not significant ($P = .28$, global test; $P = .19$, specific nevirapine-efavirenz covariate test). Similarly, the covariate indicating the previous history of antiretroviral treatment did not appear to violate the proportionality assumption ($P = .64$, Schoenfeld residual).

Virologic response. Over a median follow-up of 66 weeks (range, 3–201 weeks), 179 patients (25.8%) experienced virologic failure by our definition (confirmed virus load >500 HIV

Table 2. Characteristics of 429 pretreated patients at the start of therapy with nevirapine or efavirenz.

Characteristic	Nevirapine ($n = 289$)	Efavirenz ($n = 140$)	P
Female sex	91 (31.5)	39 (27.9)	.44
HIV exposure			.69
IDU	25 (8.7)	12 (8.6)	
Former IDU	83 (28.7)	43 (30.7)	
Homosexual	61 (21.1)	36 (25.7)	
Heterosexual	104 (36.0)	41 (29.3)	
Other	16 (5.5)	8 (5.7)	
Previous AIDS	33 (11.4)	26 (18.6)	.04
Year of treatment initiation			.001
1998	71 (24.6)	3 (2.1)	
1999	130 (45.0)	35 (25.0)	
2000	72 (24.9)	93 (66.4)	
2001	16 (5.5)	9 (6.4)	
HCV positive ($n = 372$)	111 (45.3)	59 (46.5)	.83
Virus load $\leq$500 HIV RNA copies/mL	125 (43.3)	83 (59.3)	.002
Age, median years (range)	35 (19–65)	35 (23–57)	.70
CD4 cell count, median cells/μL (range)	504 (13–1210)	558 (3–1414)	.09
Virus load, median $\log_{10}$ HIV RNA copies/mL (range)	3.08 (1.30–6.37)	2.50 (1.61–5.97)	.01
Months receiving antiretroviral therapy, median (range)	16 (1–44)	27 (2–47)	.0001
NRTI started			
Zidovudine	168 (58.1)	77 (55.0)	.54
Stavudine	120 (41.5)	60 (42.9)	.79
Lamivudine	229 (79.2)	115 (82.1)	.48
Didanosine	55 (19.0)	21 (15.0)	.31
Zalcitabine	6 (2.1)	2 (1.4)	.64
Abacavir	4 (1.4)	7 (5.0)	.03
No. of prior NRTIs			.07
0	3 (1.0)	0	
1 or 2	223 (77.2)	97 (69.3)	
3–5	63 (21.8)	43 (30.7)	
No. of prior protease inhibitors			.001
0	90 (31.1)	14 (15.2)	
1 or 2	189 (65.4)	115 (82.1)	
3 or 4	10 (3.5)	11 (7.9)	
No. of new drugs			.55
0	162 (56.1)	85 (60.7)	
1	71 (24.6)	28 (20.0)	
2 or 3	56 (19.40	27 (19.3)	

NOTE. Data are no. (%) of patients, except where noted. HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDU, injection drug use; NRTI, nucleoside reverse-transcriptase inhibitor.

RNA copies/mL). Total virologic follow-up was 548 person-years, so the incidence rate of virologic failure in the whole population was 179 events over 548 person-years (i.e., 0.33 events/person-year; 95% CI, 0.28–0.38 events/person-year). In pretreated patients, the rate was 127 events over 336 person-years (i.e., 0.38 events/person-year; 95% CI, 0.32–0.45 events/person-year).

In the multivariate analysis, which was done with the entire study population, patients receiving nevirapine had twice the risk of virologic failure than those receiving efavirenz after adjusting for the potential confounders shown in table 4. Other strong predictors of virologic failure were having received antiretroviral therapy prior to the start of NNRTI and having a high virus load at the start of NNRTI (table 4). In pretreated patients, who never achieved virus suppression $\leq$500 HIV RNA copies/mL, the number of prior NRTIs and longer exposure to antiretroviral treatment were significantly associated with increased risk of virologic failure (table 5). The difference in efficacy between nevirapine and efavirenz along with 2 NRTIs in pretreated patients was similar among those with a virus load $\leq$500 or $>$500 HIV RNA copies/mL at t_0 ($P = .23$, test for interaction).

Sensitivity analyses. The adjusted relative hazard (RH) of virologic failure for patients receiving nevirapine (vs. those receiving efavirenz) for the whole study population, after stratifying for infectious disease ward, was 1.84 (95% CI, 1.13–2.99; $P = .01$). When we defined all nevirapine and efavirenz interruptions (regardless of the reason for stopping) as therapy fail-

Table 3. Reasons for discontinuing nevirapine or efavirenz in the follow-up period (all patients).

Treatment status	Nevirapine ($n = 460$)	Efavirenz ($n = 234$)
Receiving treatment[a]	281 (61.1)	186 (79.5)
Not receiving treatment, reason for stopping		
Therapy failure	31 (6.7)	5 (2.1)
Virologic	26 (5.7)	3 (1.3)
Immunologic	2 (0.4)	1 (0.4)
Resistance	3 (0.7)	1 (0.4)
Clinical toxicity	84 (18.3)	23 (9.8)
Gastrointestinal	12 (2.6)	1 (0.4)
Hypersensitivity	56 (12.2)	5 (2.1)
Central nervous system disorders	1 (0.2)	12 (5.1)
Side effects or symptoms	6 (1.7)	4 (1.3)
Lipodystrophy	3 (0.7)	0
Other	6 (1.3)	1 (0.4)
Laboratory toxicity	17 (3.7)	4 (1.7)
Hematologic	3 (0.7)	1 (0.4)
Liver function tests	9 (2.0)	1 (0.4)
Other	5 (1.1)	2 (0.9)
Patient related	47 (10.2)	16 (6.8)
Poor adherence	7 (1.5)	2 (0.9)
Patient's decision	36 (7.8)	12 (5.1)
Therapy simplification	4 (0.9)	2 (0.9)

NOTE. Data are no. (%) of patients.
[a] $P = .001$, nevirapine vs. efavirenz.

ures, the adjusted RH for treatment failure was 1.81 (95% CI, 1.35–2.42; $P = .0001$). After stratifying for clinical center in this same model, the adjusted RH was 2.16 (95% CI, 1.50–3.11; $P = .0001$). Finally, when we censored patient follow-up time at the date of nevirapine or efavirenz discontinuation, the adjusted RH of virologic failure was 2.87 (95% CI, 1.62–5.07; $P = .0003$) in the main analysis and 3.51 (95% CI, 1.69–7.30; $P = .0008$) after stratification by clinical center.

Immunologic response. Estimates of the differences in the CD4 cell intercept and slope between the nevirapine and efavirenz groups are shown in figure 2. In agreement with table 1, patients receiving efavirenz had, on average, fewer CD4 cells at the time of therapy initiation (31 cells/μL lower; $P = .08$, from the model estimation). However, after adjusting for this initial difference, there was a tendency in patients receiving efavirenz for a faster increase of CD4 cells (5 cells/μL more than the nevirapine group for every 3 months of therapy; $P = .05$; figure 2).

Discussion

Here, we describe the use of nevirapine and efavirenz in combination with 2 NRTIs in patients enrolled in a large observational study in Italy. This study was prompted by analysis results of similar cohort studies [8, 9]. These drugs were used in first-line HAART regimens and for pretreated patients. Typically, pretreated patients had received both NRTI and PI drugs; patients receiving efavirenz had previously received slightly more drugs. In addition, efavirenz was given to patients with, on average, more advanced HIV disease, and the use of this drug was increased in recent years.

The incidence of confirmed virologic failure, as defined by the first of 2 consecutive virus load measurments of >500 HIV RNA copies/mL, was fairly high overall (0.33 events/person-year) and slightly higher in pretreated patients (0.38 events/person-year). These rates are lower than those in the EuroSIDA cohort (~0.48 events/person-year) [8]. The most likely explanation for this finding is that patients in the I.Co.N.A. study were much less drug experienced when starting an NNRTI than were the EuroSIDA patients. Indeed, all patients in the I.Co.N.A. study were antiretroviral naive at the time of enrollment (1997–1999) and most received HAART as their first regimen. The frequency of virus load measurements was similar in the 2 cohorts and should not have caused the difference in virologic failure rate.

We compared the frequency of discontinuation of nevirapine and efavirenz when given with 2 NRTIs. Nevirapine was discontinued more frequently than efavirenz, regardless of the reason for stopping, and this difference was more extreme during the first 12–16 weeks of therapy. Most nevirapine discontinuations were due to hypersensitivity to the drug, whereas a high percentage of patients interrupted efavirenz because of neurologic symptoms.

Patients who received nevirapine also seemed to have a worse virologic response than those receiving efavirenz. This held true consistently among antiretroviral-naive or pretreated patients of the cohort and among pretreated patients who had virus loads >500 HIV RNA copies/mL at the start of NNRTI therapy or stable virus loads ≤500 HIV RNA copies/mL. We cannot rule out the possibility that patients who received efavirenz were those thought by doctors to be less prone to neurologic side effects. Since patients prone to neurologic problems also have

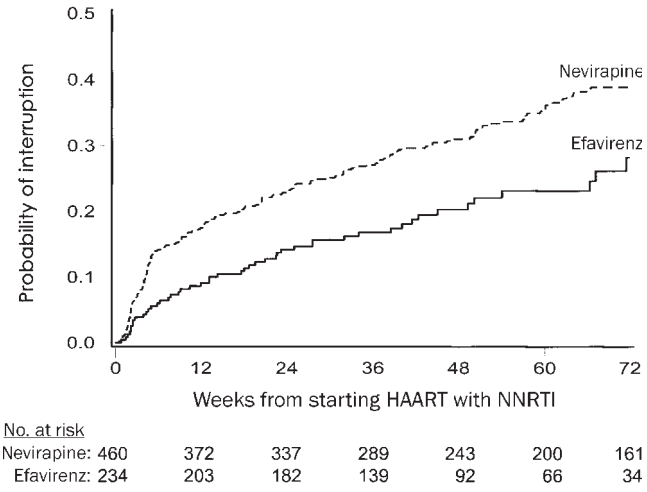

Figure 1. Kaplan-Meier estimates of time to drug discontinuation by patients in nonnucleoside reverse-transcriptase inhibitor (NNRTI) treatment group, by NNRTI received (nevirapine or efavirenz). HAART, highly active antiretroviral therapy.

Table 4. Relative hazards (RHs) of virologic failure by fitting a proportional hazards model (all patients).

	Crude analysis		Adjusted analysis	
Covariate	RH (95% CI)	*P*	RH (95% CI)	*P*
HIV exposure				
Heterosexual contact	1.00		1.00	
Active IDU	1.79 (1.10–2.90)	.02	1.42 (0.87–2.31)	.17
Previous AIDS	0.88 (0.53–1.45)	.61	0.87 (0.51–1.49)	.62
CD4 cell count 100 cells/μL higher	0.99 (0.94–1.04)	.71	1.02 (0.96–1.08)	.53
Virus load $\log_{10}$ HIV RNA copies/mL higher	1.14 (1.01–1.29)	.03	1.38 (1.19–1.59)	.0001
Antiretroviral naive	0.52 (0.37–0.71)	.0001	0.36 (0.25–0.52)	.0001
NRTI started				
Zidovudine sparing	1.00		1.00	
Zidovudine	0.92 (0.69–1.25)	.60	1.67 (0.43–6.57)	.46
Stavudine sparing	1.00		1.00	
Stavudine	1.15 (0.85–1.55)	.36	1.72 (0.44–6.77)	.44
NNRTI started				
Efavirenz	1.00		1.00	
Nevirapine	2.21 (1.46–3.36)	.0002	2.06 (1.36–3.12)	.0007

NOTE. CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug use; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor.

poorer compliance rates [20–23], failing to control for adherence may have introduced bias. However, the results held true in the population of patients with stable pretherapy virus loads of ⩽500 HIV RNA copies/mL, and the frequency of drug interruption because of therapy failure was 3 times higher for nevirapine. Of note, in another prospective, multicenter, nonrandomized study of patients who switched from a PI- to an NNRTI-containing regimen when virus load had been ⩽200 HIV RNA copies/mL during the previous 12 months, 93% (as treated, 78% intent-to-treat [ITT]) of patients receiving efavirenz and 87% (75% ITT) of those receiving nevirapine maintained virus loads of ⩽50 HIV RNA copies/mL by week 24 [24].

Possibly as a consequence of the inferior virologic outcome in those who started the nevirapine-containing regimen, we also found that CD4 cell counts of patients receiving efavirenz by week 60 of therapy were similar to those of patients receiving nevirapine, despite the fact that patients receiving efavirenz started, on average, with fewer CD4 cells. These data seem to suggest

Table 5. Relative hazards (RHs) of virologic failure shown by fitting a proportional hazards model by treatment history.

	Antiretroviral-naive patients		Pretreated patients	
Covariate	Adjusted RH (95% CI)	*P*	Adjusted RH (95% CI)	*P*
HIV exposure				
Heterosexual contact	1.00		1.00	
Active IDU	1.27 (0.47–3.44)	.63	1.36 (0.76–2.44)	.30
Previous AIDS	0.61 (0.14–2.73)	.52	1.00 (0.56–1.78)	.99
CD4 cell count 100 cells/μL higher	0.99 (0.88–1.12)	.91	1.04 (0.97–1.12)	.29
Virus load $\log_{10}$ HIV RNA copies/mL higher	1.32 (0.85–2.03)	.22	1.40 (1.17–1.67)	.0002
NRTI started				
Zidovudine sparing	1.00		1.00	
Zidovudine	1.01 (0.13–7.94)	.99	2.95 (0.70–12.41)	.14
Stavudine sparing	1.00		1.00	
Stavudine	1.14 (0.14–9.10)	.91	2.50 (0.59–10.61)	.21
Previous virus load ⩽500 HIV RNA copies/mL	NA	NA	0.61 (0.39–0.96)	.03
Duration of antiretroviral therapy 1 month longer	NA	NA	1.03 (1.01–1.06)	.009
No. of previous NRTIs (1 additional)	NA	NA	1.48 (1.13–1.94)	.004
No. of previous PI (1 additional)	NA	NA	0.91 (0.72–1.15)	.45
No. of new drugs (1 additional)	NA	NA	1.04 (0.81–1.33)	.79
NNRTI started				
Efavirenz	1.00		1.00	
Nevirapine	2.15 (0.90–5.13)	.08	2.42 (1.43–4.07)	.0009

NOTE. CI, confidence interval; HIV, human immunodeficiency virus; IDU, injection drug use; NA, not applicable; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

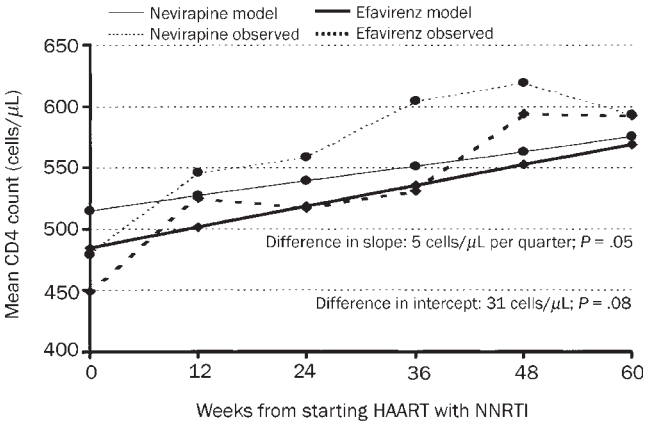

Figure 2. Mean CD4 cell count increase, by nonnucleoside reverse-transcriptase inhibitor (NNRTI) started. Solid lines are estimated increase from fitting a mixed linear model (*thick line,* efavirenz; *thin line,* nevirapine). Dotted lines are 3-monthly observed mean values (*thick line,* efavirenz; *thin line,* nevirapine). HAART, highly active antiretroviral therapy.

that the patients given efavirenz recovered more CD4 cells over follow-up (~5 cells/μL every 3 months) than those receiving nevirapine. However, this finding was only marginally significant.

The most important limitation of this study is undoubtedly the lack of randomization. However, we believe that this is the fourth cohort study showing a better virologic response to efavirenz than to nevirapine when used in HAART [8–10]. In the past, for drug comparisons when no results were available from randomized trials, results from a variety of different cohort studies were consistent, disfavoring the hard-gel formulation of the PI saquinavir, compared with other drugs of the same class [2–4]. Because the bioavailability of this drug was markedly inferior to that of the other PIs, a new formulation was introduced in the market [5, 25].

In addition, bias due to nonrandomization is less likely to be corrected by multivariate analyses such as those used in this study when there is a large imbalance of potential confounders between the compared groups [1]. The large number of imbalances in our cohort was limited, and we tried to control for these factors and for other factors known to be associated with the virologic response. One such factor was HIV disease stage. A more advanced stage of HIV disease, which was more frequent in patients receiving efavirenz, is a major potential confounder as it is likely associated with the probability of virologic failure. Indeed, it may affect the virologic response in different directions, because patients with more-advanced disease tend to be more adherent than the average patient [8] but also may be less likely to tolerate antiretroviral therapy. Our findings showed a tendency for patients with a previous AIDS diagnosis to have a lower risk of virologic failure. Similarly, HIV management has improved in recent years, and it was imperative to make sure that observed favorable responses to efavirenz did not simply reflect the fact that clinicians are now more experienced in treating HIV infection. Furthermore, by stratifying for infectious disease wards, we attempted to control for center-specific preferences for one drug, again with similar results. Obviously, we cannot rule out the presence of residual confounding due to unknown factors associated with both the virologic response and the frequency of NNRTI use or other confounders not measured in this study.

It was reassuring that results were similar when we performed other sensitivity analyses. The main comparison of virologic response was done by an ITT principle that ignored any therapy modification. Because nevirapine was discontinued more frequently than efavirenz, it was conceivable that a smaller difference in virologic response would be observed if we compared only patients who continued to receive the allocated treatment. However, this difference, in favor of the group using efavirenz, was even larger when patients were censored at the date of drug discontinuation. In addition, results were similar when drug interruptions were considered along with virologic failures as therapy failures.

In summary, we believe that this study is the fourth observational study to show a superior virologic response to an efavirenz-containing HAART regimen as opposed to a nevirapine-containing HAART regimen. One study showed a difference mainly in pretreated patients and the other 2 in antiretroviral-naive patients. Our study confirms the findings in both settings. We also found that this difference does not depend only on how frequently the drugs are discontinued and that it may also determine a tendency for more-rapid restoration of CD4 cells in efavirenz-containing regimens. We are aware of 2 small and 2 larger ongoing randomized trials; however, no results from these studies are available. While awaiting additional study results, it remains important to compare the largest possible number of studies and of the results of these analyses.

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