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ORIGINAL RESEARCH

# A comparison of the long-term durability of nevirapine, efavirenz and lopinavir in routine clinical practice in Europe: a EuroSIDA study

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**Objectives**

The durability of combination antiretroviral therapy (cART) regimens can be measured as time to discontinuation because of toxicity or treatment failure, development of clinical disease or serious long-term adverse events. The aim of this analysis was to compare the durability of nevirapine, efavirenz and lopinavir regimens based on these measures.

**Methods**

Patients starting a nevirapine, efavirenz or lopinavir-based cART regimen for the first time after 1 January 2000 were included in the analysis. Follow-up started $\geq 3$ months after initiation of treatment if viral load was $<500$ HIV-1 RNA copies/mL. Durability was measured as discontinuation rate or development/worsening of clinical markers.

**Results**

A total of 603 patients (21%) started nevirapine-based cART, 1465 (51%) efavirenz, and 818 (28%) lopinavir. After adjustment there was no significant difference in the risk of discontinuation for any reason between the groups on nevirapine and efavirenz ($P = 0.43$) or lopinavir ($P = 0.13$). Compared with the nevirapine group, those on efavirenz had a 48% ($P = 0.0002$) and those on lopinavir a 63% ($P < 0.0001$) lower risk of discontinuation because of treatment failure and a 31% ($P = 0.01$) and 66% ($P < .0001$) higher risk, respectively, of discontinuation because of toxicities or patient/physician choice. There were no significant differences in the incidence of non-AIDS-related events, worsening anaemia, severe weight loss, increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels or increased total cholesterol. Compared with patients on nevirapine, those on lopinavir had an 80% higher incidence of high-density lipoprotein (HDL) cholesterol decreasing below 0.9 mmol/L ($P = 0.003$), but there was no significant difference in this variable between those on nevirapine and those on efavirenz ($P = 0.39$).

**Conclusions**

The long-term durability of nevirapine-based cART, based on risk of all-cause discontinuation and development of long-term adverse events, was comparable to that of efavirenz or lopinavir, in patients in routine clinical practice across Europe who initially tolerated and virologically responded to their regimen.

**Keywords:** antiviral therapy, durability, long-term adverse events

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*See Appendix S1.

## Introduction

Choosing an antiretroviral treatment regimen for patients requires consideration of a number of factors, including comorbidities, likely adherence, convenience, adverse events and the potential for drug interactions with other

treatments [1]. Adverse effects have been reported with all antiretrovirals and are one of the most common reasons for discontinuation of treatment [2–4]. Some adverse events, such as gastrointestinal problems and hypersensitivity, occur rapidly, within the first few months of starting treatment, while other adverse events, such as cardiovascular disease and pancreatitis, can take much longer to develop [5–7]. Such long-term adverse events can influence the durability of a regimen.

Combination antiretroviral therapy (cART) regimens most often include a nonnucleoside reverse transcriptase inhibitor, such as efavirenz or nevirapine, or a ritonavir-boosted protease inhibitor, such as lopinavir [8,9]. cART regimens with durability as well as virological efficacy are required in order to achieve long-term virological suppression and to maintain CD4 cell counts at a level that significantly reduces the risk of morbidity and mortality. Many cohort studies have compared the short-term and long-term efficacies of different cART regimens [10–14], but less is known about the durability of different regimens, particularly in patients who have started a cART regimen more recently. If a regimen is virologically effective, durability can then be measured as the time to discontinuation of the regimen because of treatment failure or toxicity, or the rate at which changes occur in potential markers of toxicity, such as liver transaminases and cholesterol.

The aim of the study was therefore to compare the long-term durability of nevirapine-based cART regimens with those of efavirenz- or lopinavir-based cART regimens based on the time to discontinuation and the development of any serious clinical adverse events once virological suppression had been achieved and after at least 3 months on the drug to exclude discontinuations because of early-onset potentially treatment-limiting toxicities that each of the three drugs may cause.

## Methods

### Patients

The EuroSIDA study is a prospective, observational pan-European study of 16 599 HIV-1-infected patients from across Europe, Israel and Argentina. The study has been described in detail previously [15]. In brief, patients were enrolled into eight cohorts from May 1994. At each follow-up visit, details on all CD4 cell counts and HIV RNA measurements since the last follow-up visit are recorded as well as the date of starting or stopping any antiretroviral drug, the use of any prophylaxis against opportunistic infections, the date and type of development of any AIDS-defining illnesses, non-AIDS-defining illness or opportunistic infections, and death. Data are collected from the centres through follow-up forms at 6-monthly intervals and the database updated accordingly. The follow-up forms contain information on all data accrued on individual patients seen as required at the clinical centre in the previous 6 months. This analysis includes follow-up data to a median date of May 2009.

Patients starting nevirapine, efavirenz or lopinavir together with exactly two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) after 1 January 2000 were included in the analysis. Baseline was defined as either the date of first virological suppression (defined as a single viral load $<500$ HIV-1 RNA copies/mL) or 3 months after starting treatment, whichever occurred later. Patients were excluded if they did not have a CD4 cell count or viral load measured in the 6 months prior to starting the new regimen or if they did not have any prospective follow-up. Treatment-experienced patients were included provided that they had not previously been exposed to any of the regimens of interest.

Ethical approval for each participating centre is sought according to local regulations.

### Statistical methods

Durability was measured as the rate of discontinuation of nevirapine, efavirenz or lopinavir, development of any serious non-AIDS-related adverse events, or worsening of other clinical or laboratory markers. The reasons for discontinuation were compared among the three regimens and the incidence of overall discontinuation calculated. Time to discontinuation was determined using Kaplan–Meier methodology. Consistent with previous work [4,16] in addition to discontinuation for any reason, analyses considered separately discontinuation because of toxicities or patient/physician choice and discontinuation because of treatment failure. Reasons given for discontinuation were taken from patients' notes and reported on standardized EuroSIDA follow-up forms (see forms at www.cphiv.dk). One reason for discontinuation per antiretroviral was collected. Discontinuation because of reported treatment failure included virological, immunological and clinical failure. Cox proportional hazards models, stratified by centre, were used to compare the risk of discontinuation among the three regimens. Patients were followed until discontinuation of the main drug or their last recorded visit in EuroSIDA. Sensitivity analysis investigated discontinuation of any drug in the regimen and the durability of the three regimens in a subgroup of patients who were treatment naïve.

The development of any serious non-AIDS clinical events or changes in clinical markers was compared among the three treatment groups using Poisson regression. Diagnosis of a non-AIDS clinical event was defined as

the development of a non-AIDS-defining malignancy, pancreatitis, end-stage renal disease, grade III or IV hepatic encephalopathy, myocardial infarction, stroke or other cardiovascular disease. Changes in major clinical or laboratory markers were defined as developing or worsening anaemia, losing $>10\%$ of body weight at baseline, an increase in total cholesterol to $>6.2$ mmol/L or a decrease in high-density lipoprotein (HDL) cholesterol to $<0.9$ mmol/L, and an increase in aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels to $>2$ times the upper limit of normal (ULN). Anaemia was defined as a haemoglobin level $\leq 12$ or $\leq 14$ mg/dL for women and men, respectively [17]. Patients could develop anaemia or, for those with anaemia, worsening anaemia was defined as a haemoglobin level $\leq 8$ mg/dL. For the liver function tests, 40 IU/L was taken as the ULN (for both ALT and AST) [18].

Patients were followed until they experienced an event or to the date of their last measurement for each clinical or laboratory marker in EuroSIDA. It should be noted that not all patients in all groups had information on these markers available for all analyses; therefore, the number of patients included in each analysis differed according to the availability of data. Patients with the event at baseline were excluded from analyses.

Any factor that was significant at the 10% level in univariate analyses ($P<0.1$) was included in multivariate analyses. In multivariate analyses, statistical significance was attained if $P<0.05$. All analyses were performed using SAS 9.1 (SAS Institute, Cary, NC, USA).

## Results

### Patient characteristics

A total of 6634 patients started a nevirapine- (1600; 24%), efavirenz- (3109; 47%) or lopinavir- (1925; 29%) based cART regimen after 1 January 2000. A total of 1750 patients (26%) were excluded from the analysis because they had no CD4 cell count or viral load measurement prior to starting treatment: 410 (26%) on nevirapine, 888 (29%) on efavirenz, and 452 (23%) on lopinavir. A total of 1039 patients (21%) were excluded because of previous exposure to any of the three drugs: 339 on nevirapine (28%), 297 on efavirenz (13%) and 403 on lopinavir (27%). Nine hundred and fifty-nine patients (25%) did not achieve suppression, had stopped treatment within the first 3 months or did not have sufficient follow-up and were therefore excluded: 248 (29%) on nevirapine, 459 (24%) on efavirenz, and 252 (24%) on lopinavir. Thus, a total of 2886 patients were included in the analysis; 603 of these patients (21%) were on a nevirapine-based cART regimen, 1465 (51%) on an efavirenz-based cART regimen, and 818 (28%) on a lopinavir-based cART regimen. Patients excluded from the analysis had similar characteristics to those included, but were more likely to have previous cART exposure (64% *vs.* 57%, respectively; $P<0.0001$) and to have a prior AIDS diagnosis (32% *vs.* 26%, respectively; $P<0.0001$).

Table 1 compares the characteristics of the patients in each group at the time of starting their new regimen. A lower proportion of patients starting nevirapine were treatment naïve: 28%, compared with 38% of patients starting efavirenz and 38% of patients starting lopinavir. Patients on nevirapine had a higher median CD4 count [359 cells/μL; interquartile range (IQR) 230–583 cells/μL] and a lower median viral load (2.70 $\log_{10}$ copies/mL; IQR 1.70–4.56 $\log_{10}$ copies/mL) compared with those on efavirenz [median CD4 count 323 cells/μL (IQR 190–535 cells/μL) and median viral load 3.59 $\log_{10}$ copies/mL (IQR 1.70–4.95 $\log_{10}$ copies/mL)] and lopinavir [median CD4 count 252 cells/μL (IQR 131–439 cells/μL) and median viral load 4.05 $\log_{10}$ copies/mL (IQR 2.07–5.14 $\log_{10}$ copies/mL)]. The median follow-up time was 2.6 years (IQR 1.1–4.8 years). The majority of patients in the three treatment groups were on an NRTI backbone of zidovudine (ZDV) and lamivudine (3TC): 46%, 46% and 48% on nevirapine, efavirenz and lopinavir, respectively. Twenty-four per cent, 18% and 14%, respectively, were on stavudine (d4T) and lamivudine; this was the second most common NRTI backbone for those on nevirapine and efavirenz. For patients on lopinavir, the second most common NRTI backbone was tenofovir with one other NRTI.

## Discontinuation of treatment

### Discontinuation of treatment (all-cause)

A total of 1417 patients (49%) discontinued nevirapine, efavirenz or lopinavir while under follow-up. Of these, 299 (50%) discontinued nevirapine, 748 (51%) discontinued efavirenz and 370 (45%) discontinued lopinavir for any reason while under follow-up. Figure 1 shows the Kaplan–Meier estimation of the probability of all-cause discontinuation of the regimen. At 24 months after starting the regimen, 30.4% [95% confidence interval (CI) 26.6–34.2%] were estimated to have discontinued nevirapine, compared with 28.1% (95% CI 25.7–30.5%) for efavirenz and 31.7% (95% CI 28.4–35.2%) for lopinavir. The corresponding figures at 48 months were 47.2% (95% CI 42.9–51.5%), 44.3% (95% CI 41.5–47.1%) and 51.2% (95% CI 47.1–55.3%), respectively ($P=0.02$). In a multivariate Cox proportional hazards model (Fig. 2), stratified by centre, compared with patients starting nevirapine there was no significant difference in the risk of discontinuation of efavirenz [hazard ratio (HR) 1.06; 95% CI 0.91–1.23; $P=0.43$] or lopinavir (HR 1.14; 95% CI 0.96–1.36; $P=0.13$).

**Table 1** Characteristics at time of starting regimen

| | Nevirapine | | Efavirenz | | Lopinavir | | *P*-value |
|---|---|---|---|---|---|---|---|
| | *n* | % | *n* | % | *n* | % | $\chi^2$ |
| *n* | 603 | 20.8 | 1465 | 50.7 | 818 | 28.3 | |
| Gender | | | | | | | |
| Male | 423 | 70.2 | 1102 | 75.2 | 597 | 73.0 | 0.05 |
| Female | 180 | 29.8 | 363 | 24.8 | 221 | 27.0 | |
| HIV exposure group | | | | | | | |
| Homosexual | 241 | 40.0 | 596 | 40.7 | 331 | 40.5 | 0.004 |
| IDU | 113 | 18.7 | 280 | 19.1 | 200 | 24.5 | |
| Heterosexual | 213 | 35.3 | 494 | 33.7 | 224 | 27.4 | |
| Other | 36 | 6.0 | 95 | 6.5 | 63 | 7.7 | |
| Ethnic origin | | | | | | | |
| White | 550 | 91.2 | 1309 | 89.4 | 727 | 88.9 | 0.31 |
| Other | 53 | 8.8 | 156 | 10.6 | 91 | 11.1 | |
| Region of Europe | | | | | | | |
| South/Argentina | 255 | 42.3 | 501 | 34.2 | 178 | 21.8 | <0.0001 |
| West Central | 128 | 21.2 | 228 | 15.6 | 127 | 15.5 | |
| North | 99 | 16.4 | 392 | 26.8 | 221 | 27.0 | |
| East | 121 | 20.1 | 344 | 23.5 | 292 | 35.7 | |
| Prior AIDS | | | | | | | |
| Yes | 146 | 24.2 | 369 | 25.2 | 239 | 29.2 | 0.05 |
| Hepatitis B status | | | | | | | |
| Negative | 417 | 69.2 | 1047 | 71.5 | 597 | 73.0 | 0.01 |
| Positive | 28 | 4.6 | 58 | 4.0 | 53 | 6.5 | |
| Unknown | 158 | 26.2 | 360 | 24.6 | 168 | 20.5 | |
| Hepatitis C status | | | | | | | |
| Negative | 320 | 53.1 | 804 | 54.9 | 431 | 52.7 | <0.0001 |
| Positive | 106 | 17.6 | 272 | 18.6 | 210 | 25.7 | |
| Unknown | 177 | 29.3 | 389 | 26.5 | 177 | 21.6 | |
| Prior ARV treatment | | | | | | | |
| Naïve | 166 | 27.5 | 561 | 38.3 | 309 | 37.8 | <0.0001 |
| ART | 57 | 9.5 | 93 | 6.3 | 38 | 4.6 | |
| cART | 380 | 63.0 | 811 | 55.4 | 471 | 57.6 | |
| NRTI backbone | | | | | | | |
| ZDV and 3TC | 275 | 45.6 | 677 | 46.2 | 396 | 48.4 | <0.0001 |
| ddI and d4T | 47 | 7.8 | 117 | 8.0 | 55 | 6.7 | |
| d4T and 3TC | 142 | 23.6 | 259 | 17.7 | 110 | 13.5 | |
| Tenofovir + one other | 46 | 7.6 | 144 | 9.8 | 127 | 15.5 | |
| Abacavir + one other | 47 | 7.8 | 147 | 10.0 | 59 | 7.2 | |
| Other | 46 | 7.6 | 121 | 8.3 | 71 | 8.7 | |

| | Median | IQR | Median | IQR | Median | IQR | Kruskal–Wallis |
|---|---|---|---|---|---|---|---|
| Age (years) | 40 | 34–47 | 40 | 34–46 | 40 | 33–46 | 0.74 |
| CD4 count at starting (cells/μL) | 359 | 230–583 | 323 | 190–535 | 252 | 131–439 | <0.0001 |
| Nadir CD4 count (cells/μL) | 190 | 98–287 | 170 | 70–258 | 114 | 48–210 | <0.0001 |
| Viral load at starting ($\log_{10}$ copies/mL) | 2.70 | 1.70–4.56 | 3.59 | 1.70–4.95 | 4.05 | 2.07–5.14 | <0.0001 |
| Date started regimen (month/year) | 10/01 | 9/00–10/03 | 10/02 | 4/01–10/04 | 03/04 | 7/02–3/06 | <0.0001 |
| Time to baseline* (days) | 91 | 91–131 | 91 | 91–144 | 91 | 91–153 | 0.26 |

ART, antiretroviral therapy; ARV, antiretroviral; 3TC, lamivudine; cART, combination antiretroviral therapy; d4T, stavudine; ddI, didanosine; IDU, injecting drug use; IQR, interquartile range; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; ZDV, zidovudine.
*Baseline was defined as either the time of virological suppression (defined as a single viral load <500 copies/mL), or 3 months after starting treatment, whichever occurred later.

## Discontinuation of regimens for specific reasons

Figures 3(a) and (b) show the Kaplan–Meier estimation of the probability of discontinuation for specific reasons. Seventy-four patients (12%) discontinuing nevirapine, 101 patients (7%) discontinuing efavirenz and 33 patients (4%) discontinuing lopinavir did so because of reported treatment failure (virological, immunological or clinical). One hundred and fifty-five patients (75%) discontinuing because of reported treatment failure (i.e. on patient follow-up forms) had a viral load >500 copies/mL measured in the 6 months prior to discontinuation. After

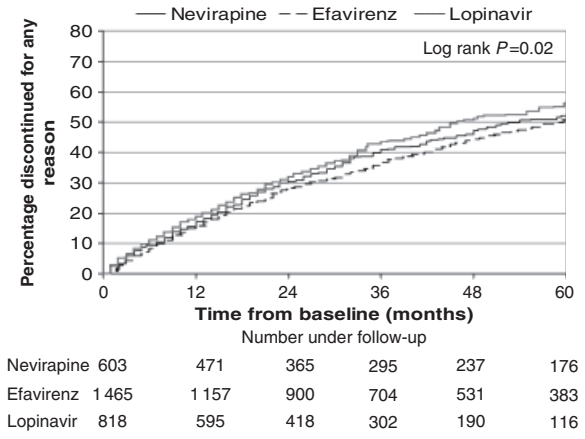


**Fig. 1** Kaplan–Meier risk of discontinuation for any reason.

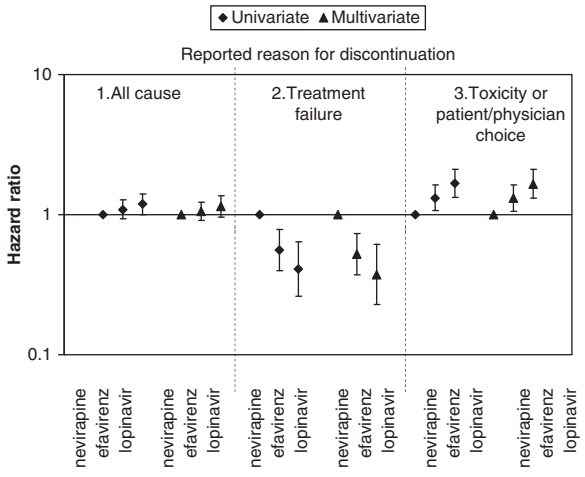


**Fig. 2** Cox proportional hazards models to investigate the risk of discontinuation across the three treatment regimens and the reasons reported for discontinuation. *Adjusted for gender, hepatitis C status, age, nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, CD4 cell count nadir and viral load at starting regimen. †Adjusted for HIV exposure group, prior antiretroviral treatment, NRTI backbone, viral load at starting regimen and date of starting regimen. ‡Adjusted for gender, HIV exposure group, hepatitis C status, age, CD4 cell count nadir and viral load at starting regimen.

adjustment, compared with patients starting nevirapine, patients starting efavirenz had a 48% lower risk of discontinuation because of treatment failure (HR 0.52; 95% CI 0.37–0.73; $P = 0.0002$) and those starting lopinavir had a 63% lower risk of discontinuation because of treatment failure (HR 0.37; 95% CI 0.23–0.61; $P < 0.0001$) (Fig. 2).

One hundred and thirty-nine patients (23%) discontinuing nevirapine, 436 patients (30%) discontinuing efavirenz and 247 patients (30%) discontinuing lopinavir did so because of reported toxicity or patient/physician choice. The most commonly recorded toxicity for discontinuing nevirapine (20%) was associated with the gastrointestinal (GI) tract, liver or pancreas; this was also the case for lopinavir (21%). Only 6% of patients discontinued efavirenz because of toxicities associated with the GI tract, liver or pancreas; the most common reported toxicities for efavirenz were associated with the central nervous system (26%). After adjustment, patients on efavirenz had a 31% higher risk (HR 1.31; 95% CI 1.06–1.62; $P = 0.01$) of discontinuation because of toxicities or patient/physician choice and patients on lopinavir had a 66% higher risk (HR 1.66; 95% CI 1.31–2.10; $P < 0.0001$) of discontinuing because of toxicity or patient/physician choice, compared with those on nevirapine (Fig. 2).

## Development or worsening of clinical and laboratory markers

Table 2 provides the numbers of patients included in these different analyses. In general, patients with clinical markers recorded and included in the analysis were more likely to have been on antiretroviral therapy (ART) prior to starting their current regimen, and to have higher CD4 cell counts and lower viral loads at the time of starting the regimen, and were less likely to be from Eastern Europe. For example, of 1489 patients with weight measured within 1 year prior to baseline, 251 patients (17%) lost $> 10\%$ of their body weight at baseline while under follow-up: 50 on nevirapine, 134 on efavirenz and 67 on lopinavir. Table 2 shows the results of the adjusted analysis looking at the development or worsening of clinical and laboratory markers over time. After adjustment, patients on lopinavir had almost double the rate of HDL cholesterol falling below 0.9 mmol/L compared with patients on nevirapine [adjusted incidence rate ratio (IRR) 1.80; 95% CI 1.22–2.66; $P = 0.003$], while there was no significant difference between patients on efavirenz and those on nevirapine in the rate of HDL cholesterol falling below 0.9 mmol/L (IRR 1.16; 95% CI 0.82–1.65; $P = 0.39$). After adjustment, there was no significant difference in the rate of worsening of any of the other clinical markers among the three treatment regimens.

### Sensitivity analyses

The sensitivity analysis looking at discontinuation of any drug included in the regimen (rather than nevirapine, efavirenz or lopinavir specifically) found after adjustment, in Cox proportional hazards models, that there was no significant difference in rates of discontinuation for any reason for patients on efavirenz (HR 0.91; 95% CI 0.81–1.03; $P = 0.15$) or patients on lopinavir (HR 0.93;

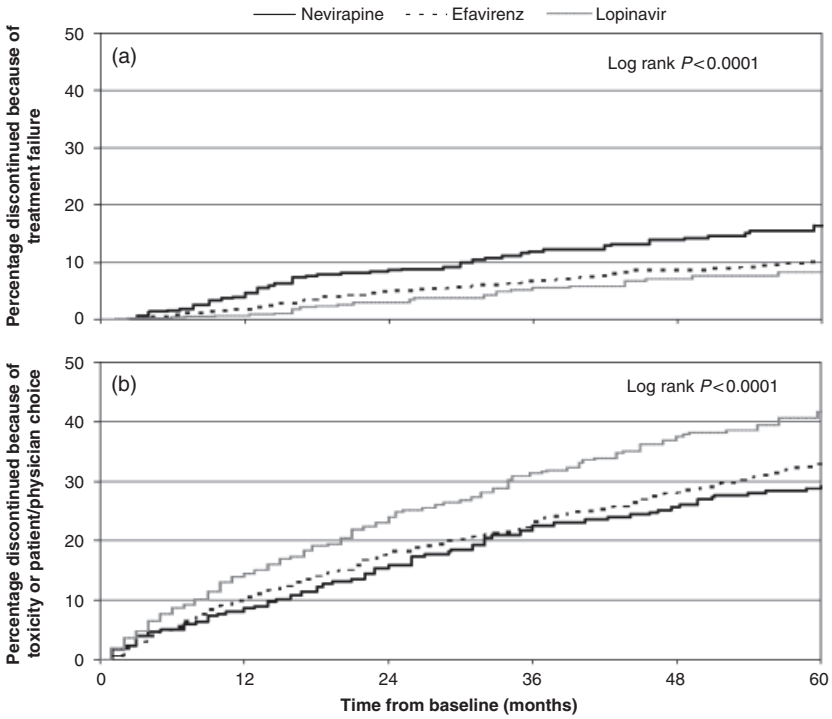


**Fig. 3** Kaplan–Meier risk of discontinuation because of (a) treatment failure and (b) toxicity or patient/physician choice.

95% CI 0.81–1.08; $P = 0.35$) compared with those on nevirapine. After adjustment in Cox proportional hazards models there remained a lower rate of discontinuation because of treatment failure for patients on efavirenz (HR 0.49; 95% CI 0.35–0.69; $P < 0.0001$) and lopinavir (HR 0.46; 95% CI 0.25–0.64; $P = 0.0001$). There was a nonsignificantly higher rate of discontinuation because of toxicity/patient choice in patients on efavirenz (HR 1.05; 95% CI 0.89–1.24; $P = 0.55$) and lopinavir (HR 1.11; 95% CI 0.92–1.34; $P = 0.0002$) compared with those on nevirapine. Competing risks analysis showed results consistent with the main analysis (data not shown).

A total of 1036 patients were antiretroviral naïve at the time of starting their regimen [166 (16%) on nevirapine, 561 (55%) on efavirenz and 309 (29%) on lopinavir] and 412 patients discontinued nevirapine (68; 41%), efavirenz (217; 39%) or lopinavir (127; 41%) for any reason while under follow-up. After adjustment for gender, age, and nadir CD4 cell count, patients on lopinavir had a marginally significantly higher rate of discontinuation for any reason (HR 1.36; 95% CI 0.95–1.95; $P = 0.09$) than patients on nevirapine; there was no significant difference between patients on efavirenz and those on nevirapine (HR 0.92; 95% CI 0.67–1.26; $P = 0.61$). Only 32 antiretroviral-naïve patients discontinued because of treatment failure [13 (8%) on nevirapine, 16 (3%) on efavirenz and three (1%) on lopinavir], limiting the ability to perform further analyses. A higher number of patients discontinued because of toxicity or patient choice: 34 (20%) discontinued nevirapine, 118 (21%) efavirenz and 84 (27%) lopinavir. Patients on lopinavir had a significantly higher rate of discontinuation because of toxicity or patient choice compared with patients on nevirapine (HR 1.69; 95% CI 1.06–2.76; $P = 0.02$); there was no significant difference between patients on efavirenz and those on nevirapine (HR 0.98; 95% CI 0.64–1.48; $P = 0.91$) after adjustment for nadir CD4 cell count and hepatitis C status.

## Discussion

This analysis compared the long-term durabilities of nevirapine-, efavirenz- and lopinavir-based cART regimens in patients. Therefore, patients were only included in the analysis once virological suppression had been achieved and after at least 3 months on the drug to exclude discontinuations because of early-onset potentially treatment-limiting toxicities. No significant difference was found in the rate of discontinuation for any reason among the three treatment regimens, although differences were found in the rate of discontinuation for specific reasons. Patients on nevirapine had a higher rate of discontinuation because of reported treatment failure and a lower rate of

**Table 2** Multivariate Poisson regression analysis comparing the risk of developing or worsening of selected clinical and laboratory markers across the three treatment regimens

| | Number included | Number of events | IR (95% CI) | Adjusted IRR | 95% CI | *P*-value |
|---|---|---|---|---|---|---|
| Non-AIDS clinical event* | | | | | | |
| Nevirapine | 603 | 49 | 1.51 (1.09–1.94 | 1.00 | – | – |
| Efavirenz | 1465 | 81 | 1.14 (0.89–1.39) | 0.75 | 0.52–1.09 | 0.13 |
| Lopinavir | 818 | 53 | 1.69 (1.24–2.15) | 1.10 | 0.72–1.69 | 0.66 |
| Worsening anaemia† | | | | | | |
| Nevirapine | 360 | 110 | 6.38 (5.19–7.57) | 1.00 | – | – |
| Efavirenz | 721 | 222 | 7.69 (6.68–8.70) | 1.16 | 0.91–1.46 | 0.23 |
| Lopinavir | 351 | 75 | 5.87 (4.54–7.20) | 0.82 | 0.29–1.13 | 0.22 |
| Losing >10% of body weight‡ | | | | | | |
| Nevirapine | 299 | 50 | 3.83 (2.77–4.90) | 1.00 | – | – |
| Efavirenz | 755 | 134 | 4.34 (3.61–5.08) | 1.13 | 0.81–1.56 | 0.46 |
| Lopinavir | 435 | 67 | 4.63 (3.52–5.74) | 1.15 | 0.79–1.67 | 0.46 |
| Total cholesterol >6.2 mmol/L§ | | | | | | |
| Nevirapine | 309 | 103 | 7.93 (6.40–9.46) | 1.00 | – | – |
| Efavirenz | 699 | 228 | 8.89 (7.74–10.05) | 1.04 | 0.58–1.32 | 0.72 |
| Lopinavir | 386 | 120 | 10.58 (8.69–12.47) | 1.22 | 0.92–1.64 | 0.17 |
| HDL cholesterol <0.9 mmol/L¶ | | | | | | |
| Nevirapine | 194 | 46 | 5.81 (4.13–7.49) | 1.00 | – | – |
| Efavirenz | 489 | 123 | 6.90 (5.68–8.12) | 1.16 | 0.82–1.65 | 0.39 |
| Lopinavir | 256 | 81 | 11.01 (8.62–13.41) | 1.80 | 1.22–2.66 | 0.003 |
| AST >2 times upper limit of normal‖ | | | | | | |
| Nevirapine | 296 | 38 | 2.61 (1.78–3.44) | 1.00 | – | – |
| Efavirenz | 637 | 65 | 2.35 (1.78–2.92) | 0.86 | 0.57–1.29 | 0.46 |
| Lopinavir | 454 | 48 | 2.96 (2.13–3.80) | 1.14 | 0.72–1.80 | 0.59 |
| ALT >2 times upper limit of normal** | | | | | | |
| Nevirapine | 310 | 74 | 5.40 (4.17–6.62) | 1.00 | – | – |
| Efavirenz | 811 | 175 | 5.31 (4.52–6.09) | 0.98 | 0.73–1.30 | 0.87 |
| Lopinavir | 491 | 77 | 4.53 (3.52–5.54) | 0.84 | 0.60–1.18 | 0.30 |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HDL, high-density lipoprotein; IR, unadjusted incidence rate; IRR, adjusted incidence rate ratio.
*Adjusted for gender, ethnic origin, HIV exposure group, region of Europe, hepatitis C status, prior antiretroviral treatment, anaemia, hypertension, diabetes, smoking status, age, prior AIDS diagnosis, nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone, nadir CD4 cell count and maximum recorded viral load.
†Adjusted for HIV exposure group, region of Europe, hepatitis B and C status, NRTI backbone, prior treatment, maximum viral load, year of starting regimen and haemoglobin level at baseline.
‡Adjusted for HIV exposure group, hepatitis C status, CD4 cell count at starting treatment and weight at baseline.
§Adjusted for gender, ethnic origin, HIV exposure group, region of Europe, hepatitis B and C status, current body mass index (BMI), age, date of starting regimen and total cholesterol at baseline.
¶Adjusted for gender, ethnic origin, HIV exposure group, region of Europe, hepatitis C status, age, date of starting regimen and HDL cholesterol at baseline.
‖Adjusted for HIV exposure group, region of Europe, hepatitis C status, age, viral load, date of starting regimen and baseline AST level.
**Adjusted for gender, HIV exposure group, region of Europe, hepatitis B and C status, prior AIDS diagnosis, NRTI backbone, age and ALT level at baseline.

discontinuation because of toxicity or patient/physician choice compared with those on efavirenz and lopinavir. There was no significant difference in the development of any non-AIDS-related clinical event, worsening of anaemia, severe weight loss, or increased ALT or AST levels. Patients on lopinavir had a higher rate of low HDL cholesterol compared with patients on nevirapine; however, there was no difference in the rate of low HDL cholesterol between patients on efavirenz and those on nevirapine.

Earlier cohort studies [19–21] found that, in antiretroviral-naïve and -experienced patients [22], patients on efavirenz had a significantly lower rate of treatment failure compared with those on nevirapine; part of the explanation for this is that nevirapine has been associated with several early-onset side effects, such as hypersensitivity [20]. This present analysis examined the longer term durability of nevirapine in patients who do not develop these early-onset tolerability issues. More recent randomized trials found that nevirapine and efavirenz showed similar efficacy [23,24]. In addition, the Atazanavir/Ritonavir on a background of Tenofovir and Emtricitabine (Truvada) versus Nevirapine (ARTEN) study [25] demonstrated noninferiority between nevirapine and atazanavir, a ritonavir-boosted PI, in a population of antiretroviral-naïve patients. The definition of treatment failure in the 2NN clinical trial [23] was a combined endpoint of virological failure, disease progression or therapy change and the main reason given for treatment failure was a change in therapy. Annan *et al.* [24] defined treatment failure as either virological failure or discontinuation of therapy. Our analyses were based on reported reason for

discontinuation of treatment, rather than treatment failure defined using virological or immunological measurements, in patients who had initially tolerated and responded to treatment. This definition is closer to the definition of treatment failure used in the more recent studies and our results are consistent with their findings.

It has previously been reported that the choice of NRTI backbone is a significant predictor of virological success and treatment failure [24]; however, even after adjustment for this, significant differences remained. In patients with extensive resistance to other drug classes, nevirapine has been associated with an inferior virological outcome compared with patients on efavirenz [26], and therefore accumulation of resistance from previous drug regimens could also affect the rate of discontinuation because of treatment failure. Around 36% of the patients included in the analysis were treatment naïve at the time of starting their regimen. In naïve patients very few discontinuations, in any group, were because of reported treatment failure. Therefore, in treatment-naïve patients, our results suggest that, if the regimen can be successfully tolerated in the first few months and viral suppression achieved, nevirapine is a durable treatment strategy, in terms of discontinuation because of treatment failure, compared with efavirenz and lopinavir.

Patients on lopinavir and efavirenz had a higher rate of discontinuation because of toxicities or patient/physician choice. Other studies found that nevirapine was associated with a higher rate of toxicities when compared with efavirenz [1,23] and the ARTEN study [25] found that discontinuation was higher in those on nevirapine compared with atazanavir. However, most of the discontinuations because of toxicity in nevirapine have been reported in the first few months on therapy [16,20,25]. As mentioned previously this analysis focused on patients who had tolerated the first 3 months of therapy. Thus, short-term toxicities, such as hypersensitivity, leading to early discontinuation would have been excluded. Lodwick *et al.* [27] found that, compared with patients on efavirenz, there was no significant difference in toxicities in patients on nevirapine but a significantly increased rate of changes because of toxicity in patients on lopinavir, using similar inclusion criteria to this study but only including antiretroviral-naïve patients; this is consistent with our sensitivity analysis in antiretroviral-naïve patients.

To investigate longer term durability, in addition to clinical events, laboratory values were used as surrogate markers of risk of disease; i.e. total cholesterol and HDL cholesterol can be used as surrogate markers for risk of cardiovascular disease and ALT and AST levels for risk of liver disease. No significant differences among the regimens were found in the risk of developing or worsening anaemia, severe weight loss, or increased AST or ALT levels. Patients on lopinavir had a higher incidence of development of HDL cholesterol $<0.9$ mmol/L compared with patients on nevirapine. Nevirapine and efavirenz have both been found to increase HDL cholesterol level [28,29]. The ARTEN study also found that nevirapine had a more favourable lipid profile than atazanavir [25]. In this study there was no significant difference in the incidence of developing high total cholesterol or low HDL cholesterol between patients on efavirenz and nevirapine; however, the 2NN study [30] found a significantly greater increase in HDL cholesterol on nevirapine compared with efavirenz.

There are a number of limitations to this study which should be noted. The analysis was based on data from a cohort study and, although many biases can be accounted for in the adjusted analysis, there may still be unmeasured confounders that we did not account for. Time to discontinuation analyses were stratified by centre to minimize the effect of different clinical experiences in different centres. Cohort studies are not randomized and bias as a result of confounding by indication or some other unknown factors is difficult to exclude. Additionally, some selection bias may have been introduced as a higher proportion of patients on nevirapine were excluded because of having been exposed to prior treatment with one of the three drugs. This study differs from previous analyses comparing nevirapine-based cART regimens with efavirenz- or boosted PI-based regimens in that a significant number of both treatment-naïve and treatment-experienced patients were included in the analysis. This analysis also looked at time to discontinuation of treatment rather than virological endpoints and only patients who had achieved an initial response to the regimen were included. Unlike previous studies that followed patients from treatment initiation, the first 3 months were excluded from this analysis so that the focus was on the development of long-term toxicities and serious adverse events. It is also worth noting that treatment for HIV infection is currently expected to be lifelong. Although we found few differences in the long-term outcomes we considered, it is possible that there will be long-term differences in outcomes for those who discontinue treatment for treatment failure and those who discontinue because of toxicities or patient/physician choice as a consequence of the rate at which available alternative regimens are used.

In conclusion, in patients in routine clinical practice across Europe who had achieved an initial response and tolerated the first 3 months of their regimen, nevirapine-based cART regimens were found to have similar durability, based on risk of all-cause discontinuation and development of serious clinical events, to regimens based on efavirenz and lopinavir. However, patients on nevirapine had a higher rate of discontinuation because of reported treatment failure and those on efavirenz and lopinavir had a

higher rate of discontinuation because of toxicity or patient/physician choice. Sensitivity analysis in naïve patients found that very few discontinuations, in any group, were because of reported treatment failure; the rate of discontinuation because of toxicity or patient/physician choice remained increased in patients on lopinavir compared with those on nevirapine.

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## Supporting information

Additional supporting information may be found in the online version of this article:

**Appendix S1.** The EuroSIDA study group.

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