Efavirenz to Nevirapine Switch in HIV-1–Infected Patients with Dyslipidemia: A Randomized, Controlled Study

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Many antiretroviral therapies, including efavirenz, are associated with increased serum concentrations of low-density lipoprotein cholesterol. In a small 52-week randomized study, we found that switching from efavirenz to nevirapine was associated with significantly decreased low-density lipoprotein cholesterol levels, compared with continuation of efavirenz therapy (P < .04). A switch to nevirapine was associated with no severe adverse events.

Coronary heart disease (CHD) is a growing problem in patients with HIV infection who are receiving antiretroviral therapy [1], because these drugs are associated with increases in serum lipid levels. For example, a 48-week exposure to efavirenz (EFV) in antiretroviral-naïve patients was associated with an 18% increase in fasting low-density lipoprotein cholesterol (LDL-c) levels [2], a risk factor for CHD. One reason to modify effective antiretroviral therapy is to improve long-term tolerability—in particular, antiretroviral–related metabolic abnormalities that could increase CHD risk. Consequently, switching from therapy with a protease inhibitor (PI) continues to be an area of intense research.

We hypothesized that switching patients with EFV-associated dyslipidemia to nevirapine (NVP) would decrease fasting LDL-c levels. Additionally, we explored the dose–effect relationship between drug plasma levels and subsequent LDL-c levels. To our knowledge, this is the first randomized study to evaluate the impact of switching from EFV to NVP therapy on LDL-c levels.

Methods. This investigator-lead, phase IV, open-label, parallel group, active control, randomized, multicenter trial was conducted from June 2003 to February 2006 at 7 centers in France. All patients provided written, informed consent and received dietary counseling before randomization.

Eligible patients were adults (age, ≥18 years) who had received at least 6 months of EFV therapy and who had HIV RNA levels of <400 copies/mL, LDL-c dyslipidemia, and risk factors for CHD. Details for patient eligibility are available at http://www.clinicaltrials.gov/ct/show/NCT00405171. Patients who were randomized to switch to NVP received 200 mg daily for 2 weeks, then 200 mg twice daily for the remaining 50 weeks. Investigators could not modify the nucleoside reverse-transcriptase inhibitor backbone or introduce lipid-lowering drugs during the study. Patients in the NVP arm of the study were contacted via telephone at weeks 1 and 3. Medical examinations and liver enzyme analyses were performed at weeks 2, 4, 6, and 8. All patients were evaluated at weeks 12, 36, and 52 for clinical, biological, and immunovirologic parameters. For safety monitoring, we used the Agence Nationale de Recherche sur le SIDA toxicity grading scale. Neuropsychiatric evaluations were conducted using a standardized self-questionnaire administered at baseline and at 12 weeks [3]. Physical activity, emotion, and social activities were assessed by Dartmouth Primary Care Cooperative Information Project (COOP) charts.

Fasting serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels were measured using an enzymatic method. LDL-c was calculated using the Friedewald formula. Consequently, patients with triglyceride levels of >4.6 mmol/L were excluded from the study. Steady-state plasma EFV or NVP levels were measured at week 12. Lipid and pharmacologic analyses were performed in a central laboratory at the end of the study.

Assuming a baseline LDL-c level of 4.1 mmol/L and a SD of ±1.3 mmol/L in control subjects (SD extrapolated for total cholesterol level after 52 weeks of EFV therapy [4]), 90% power, and a 2-sided type I error of 0.05, inclusion of at least 36 patients was necessary to demonstrate a 35% reduction in the experimental arm.

The primary efficacy population was the intent-to-treat population. Centralized fasting LDL-c level changes (from baseline January 2019.
to week 52) in each study arm were compared using the independent Student’s t test for small sample size. Goodness-of-fit tests did not reject the hypothesis that lipid change was normally distributed. Multivariate analysis of the primary outcome was performed using generalized linear models, including the arm of randomization and baseline factors associated with primary outcome at P<.20 in the univariate analysis. Dose-effect relationships were explored using least-squares linear regression analysis among patients assigned to the NVP or EFV arms. The strength of the relationship between the week-12 drug level (predictor) and the week-52 lipid level was assessed using the variance explained (R^2). Statistical analyses were performed using SAS software, version 9.1 (SAS Institute), all tests were 2-sided, and a P value of <.05 was considered to be statistically significant.

**Results.** Thirty-seven patients with a mean of 41 months (range, 7–80 months) of exposure time to EFV therapy were randomized into 1 of the 2 study arms. Participants were well balanced between the study arms (NVP [n = 18] vs. EFV [n = 19]) for mean age (48.7 years vs. 46.1 years), male sex (83% vs. 89%), and mean body mass index (25.1 vs. 25.6, calculated as weight in kilograms divided by the square of height in meters), CD4 cell count (504 vs. 567 cells/μL), duration of HIV infection (10.0 vs. 10.7 years), and LDL-c level (4.47 vs. 3.97 mmol/L). Stavudine was prescribed for 3 and 2 patients in the NVP and EFV arms, respectively. More patients in the EFV arm received an abacavir- or tenofovir-based regimen (8 vs. 3 in the NVP arm, P = .15 using Fisher’s exact test), and the emotional disability score was higher in patients who were randomized to receive NVP (2.2 vs. 1.4 in the EFV arm, P<.02). Nine men had CD4 cell counts that were >400 cells/μL before they switched to NVP therapy.

No patient had HIV RNA levels of >400 copies/mL, and the mean CD4 cell count change between baseline and week 52 was +34.0 cells/μL in the EFV arm and −8.8 cells/μL in the NVP arm (P = .29). Mean aspartate transaminase and alanine transaminase levels did not differ between arms at any time. No severe hepatotoxicity or cutaneous reactions occurred after the switch to NVP. One patient discontinued EFV therapy at week 24 because of a psychiatric disorder (grade 2). Another patient discontinued NVP therapy at week 24 because of musculoskeletal pain (grade 2). Severe or life-threatening adverse events were reported by 2 patients receiving EFV: headache and back pain (grade 3) requiring hospitalization in 1 patient, and elevated liver enzymes (>10 times the upper limit of normal; grade 4), which resolved after EFV therapy interruption, in another patient.

Three patients were excluded from analysis because of missing data. The mean LDL-c level decreased significantly from baseline in the NVP arm (n = 17) but not in the EFV arm (n = 17; mean change, −0.43 mmol/L [95% CI, −0.81 to −0.05 mmol/L] vs. −0.09 mmol/L [95% CI, −0.40 to 0.22 mmol/L]). Variables that were positively associated with decreases in LDL-c levels from baseline were a switch to NVP (P = .15), receipt of an abacavir- or tenofovir-based regimen (P = .09), female sex (P = .03), and physical activity (P = .07). In the multivariate model, being randomized to receive NVP (P<.04) and receiving an abacavir- or tenofovir-based regimen (P<.04) were both significantly and independently associated with a decrease in LDL-c levels after 1 year, adjusting for sex (P = .23) and physical activity (P = .12). One-year changes in total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels did not differ between the study arms.

In a linear regression model (figure 1), week-12 NVP plasma levels significantly predicted week-52 LDL-c levels. No such relationship existed for patients in the EFV arm. Observed slope coefficients differed significantly between the arms (P<.001). The mean neuropsychiatric evaluation score at week 12 decreased significantly from baseline in the NVP arm, representing an improvement in neuropsychiatric status, but not in the EFV arm (mean change, −5.4 [95% CI, −9.5 to −1.4] vs. 0.5 [95% CI, −3.4 to 4.5], respectively).

**Discussion.** Switching from EFV to NVP decreased LDL-c levels in our population. This decrease corresponds to a 20% decrease in the 10-year relative risk for major cardiac events, according to the Framingham equation. Higher NVP plasma levels predicted lower LDL-c levels with the variance of NVP explaining 45.4% of the LDL-c variance, reinforcing the role of NVP in this reduction. NVP therapy was considered to be safe, with no severe adverse events reported, and provided optimal efficacy.

Our results agree with previously published reports. Switching patients with protease inhibitor–associated dyslipidemia to NVP or EFV resulted in significantly different reductions in LDL-c levels, favoring NVP (−25.2% for NVP vs. −10.2% for EFV; P<.05) [5]. EFV and NVP elicited different changes in lipid profiles among patients in nonspecific randomized trials [4, 6] and cohort studies [7–9].

NVP demonstrated a noninferior efficacy against EFV [10], with a noninferiority margin of 13.5 in a large, randomized trial [11] that compared the use of the 2 drugs in virologically suppressed patients. The potential long-term benefit of the NVP switch–associated LDL-c reduction in regard to CHD mortality should be balanced against the short-term risk of potentially fatal hepatotoxicity in patients with CD4 cell counts of >250 cells/μL (in female patients) or >400 cells/μL (in male patients). It is unknown whether switching from EFV to NVP when CD4 cell counts are above these thresholds is associated with the same risk as starting NVP de novo. Among the studies that evaluate the switch from EFV to NVP, no severe hepatotoxicity or cutaneous reactions were reported [12, 13]. Additionally, the
Figure 1. Plasma levels of efavirenz (A) and nevirapine (B) and their dose-effect relationships with low-density lipoprotein (LDL) cholesterol levels. A, Observed slope coefficient $\beta \pm SD$, $-6.2 \times 10^{-5} \pm 14.8 \times 10^{-5}$; $P = .68$; $R^2 = .012$. B, Observed slope coefficient $\beta \pm SD$, $-26.0 \times 10^{-5} \pm 7.6 \times 10^{-5}$; $P = .0042$; $R^2 = .454$. One dose is missing.
EuroSIDA cohort study [14] observed a lower incidence of toxicity \( (P = .027) \) in antiretroviral-experienced patients with elevated CD4 counts versus antiretroviral-naïve patients with elevated CD4 counts after NVP was introduced. Nevertheless, appropriate patient monitoring is warranted.

Neuropsychiatric effects are the most commonly reported adverse effect of EFV that leads to drug discontinuation, but these are generally considered to be transient. However, systematic neuropsychiatric evaluations have reported long-term mild neuropsychiatric disturbances [3, 15, 16]. In our study, the switch to NVP was associated with 12-week improvements in patients’ neuropsychiatric evaluation scores.

The small sample size and inclusion criteria on the basis of LDL-c level could limit the interpretation of nonsignificant results that are not associated with the decrease in LDL-c level. On the other hand, the selection of a specific dyslipidemic population with room for improvement increased the power of this study to detect differences in LDL-c levels.

In conclusion, switching from EFV to NVP therapy was associated with a significant reduction in LDL-c levels at 52 weeks, compared with EFV continuation. We suggest that exposure to the drug (i.e., NVP or EFV), rather than to an antiretroviral class (i.e., nonnucleoside reverse-transcriptase inhibitors), may be informative to assess the role of these drugs on the incidence of CHD in large cohorts of patients with HIV infection.

**The Switch of Nonnucleoside Reverse-Transcriptase Inhibitors to Reduce the Occurrence of Cardiovascular Complications (SIROCCO) study team.** Investigators: J-J. Parienti (10 screenings), R. Verdon (5 screenings), and C. Bazin (1 screening; Hôpital Côte de Nacre, Caen, France); D. Rey (9 screenings; Hôpitaux Universitaires, Strasbourg, France); P. Poubeau (5 screenings; Hôpital St Pierre, La Réunion, France); F. Rafi (2 screenings) and S. Bouchez (2 screenings; Hôpital Hôtel-Dieu, Nantes, France); T. May (2 screenings; Hôpital Brabois, Vandoeuvre les Nancy, France); C. Daniel (1 screening) and S. Le Moal (1 screening; Hôpital Y. Le Foll, St Brieuc, France); G. Le Moal (1 screening; Hôpital Universitaire, Poitiers, France); E. Bouvet (Hôpital Bichat, Paris, France); and F. Borsa-Lebas (Hôpital C. Nicolle, Rouen, France).

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