AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 22, Number 4, 2006, pp. 321–329

Long-Term Safety and Efficacy of Nevirapine-Based Approaches in HIV Type 1-Infected Patients

ANNA BONJOCH,[1] ROGER PAREDES,[1] PERE DOMINGO,[2] MANEL CERVANTES,[3] ENRIC PEDROL,[4] ESTEVE RIBERA,[5] LLUÍS FORCE,[6] JOSEP M. LLIBRE,[7] JOSEP VILARÓ,[8] DAVID DALMAU,[9] JOSEP CUCURULL,[10] JAUME MASCARÓ,[11] ANGELS MASABEU,[12] NÚRIA PÉREZ-ÁLVAREZ,[1] JORDI PUIG,[1] DENISE CINQUEGRANA,[1] and BONAVENTURA CLOTET[1]

ABSTRACT

Using a multicenter, cross-sectional, observation study, the long-term safety, metabolic profile, and viral efficacy of nevirapine (NVP)-based approaches in HIV-1-infected patients treated for at least 2 years were assessed. For 4 months, all consecutive HIV-1-infected patients who had been receiving an NVP-containing regimen for at least 2 years were recruited. A total of 613 patients were included with a median follow-up period of 43 months (IQR: 31–51). At baseline, 24.5% (150 patients) were treatment naive, 41.5% (254 patients) switched for simplification purposes, and 34% (209 patients) were failing HAART. Increases by five times or more in AST/ALT values were observed in fewer than 2% of patients. Only 5.7% of all adverse events reported during the investigation were attributable to NVP. The percentage of patients with normal HDL cholesterol levels rose from 17.7% at baseline to 35.4% at the last visit. At the latest time point available for analysis, 76% of naive and 74% of those who had switched had HIV-1 RNA loads of <50 copies/ml, while 59% of salvage patients achieved this level of viral suppression. Factors associated with viral suppression at the latest visit were adequate adherence (OR: 2.58, 95% CI: 0.85–7.78, $p < 0.001$), first-line treatment (OR: 3.02, 95% CI: 1.52–6.00, $p = 0.002$), and baseline CD4 cells >400 cells/μl (OR: 2.34, 95% CI: 1.22–4.47, $p = 0.010$). Exposure to nevirapine for up to 4 years is safe. Liver toxicity is infrequent and generally mild. HDL cholesterol levels consistently increase over time and viral suppression is maintained.

INTRODUCTION

NEVIRAPINE (NVP) HAS BEEN ESTABLISHED as an effective, convenient, and well-tolerated anti-HIV therapy, which often leads to prolonged virological and immunological responses.[1–4] The major concern with its use is liver toxicity.[5,6] More specifically, the short-term risk of liver toxicity associated with the use of NVP has been reported in certain populations, such as HIV-1-infected patients with hepatitis B virus (HBV) and/or hepatitis C (HCV) coinfection,[7,8] subjects with active alcoholism,[9] those carrying the HLA-DRB*0101 haplotype,[10] men with CD4 counts over 400 cells/mm^3, as well as women with CD4$^+$ counts above 250 cells/mm^3, and also those who are pregnant.[11,12] Other side effects of NVP-based therapies include skin rash and anaphylactic reactions, which lead to Stevens–Johnson syndrome in less than 0.5% of patients.[13]

Importantly, the previous findings about the occurrence and causes of NVP-related hepatotoxicity are conflicting regarding the groups of patients who are more likely to experience these adverse events.[12–14] Nevertheless, the majority of previous investigations have shown that liver toxicity and cutaneous reactions are most likely to occur within the first 6–18 weeks of NVP-based treatment.

On the other hand, NVP-based regimens have also been shown to achieve significant metabolic benefits, most importantly on patient lipid profiles. Thus, NVP may help to improve dyslipidemia and to decrease long-term patient cardiovascular risk.[1,2]

Given the high cost of current antiretroviral treatments, the development and implementation of safe, effective, and eco-

[1]Lluita contra la SIDA Found, AIDS Care Unit, Universitat Autònoma de Barcelona, Hospital Germans Trias i Pujol, Badalona, [2]Hospital de la Santa Creu i St Pau, Barcelona, [3]Parc Tauli, Sabadell, [4]Hospital General de Granollers, [5]Hospital Vall d'Hebron, Barcelona, [6]Hospital de Mataró, [7]Hospital de Calella, [8]Hospital General de Vic, [9]Mútua de Terrassa, [10]Hospital de Figueres, [11]Hospital J. Trueta, Girona, and [12]Hospital de Palamós, Barcelona, Spain.

nomical HIV therapies are urgently needed. Thus, low-cost approaches, such as those based on nevirapine, must be assessed for their use in the long term. Currently available controlled clinical studies[15–18] do not precisely predict the clinical outcomes of patients receiving NVP beyond 48 weeks.

Our aim was to assess the safety, metabolic profile, and efficacy of NVP-based regimens after very prolonged patient exposure, in light of recent warnings regarding NVP-associated liver toxicity in the short term.

MATERIALS AND METHODS

Study design and population

This was a multicenter, cross-sectional, and observational study performed in 12 tertiary care hospitals in Spain. Adult HIV-1-infected patients were included if they had been receiving an NVP-containing highly active antiretroviral therapy (HAART) regimen for at least 2 years, regardless of the reason for its initiation (first-line, salvage, or simplification). Participants were identified by unselected consecutive recruitment from outpatient clinic visits during a total period of 4 months.

Study measurements

Data were collected using a standardized record sheet, which included three time points for analysis: baseline (the data of initiation of the NVP-containing regimen), 2 years after baseline, and the last clinical visit available for each patient.

The baseline evaluation included sociodemographic characteristics (age, gender, risk factors for HIV infection), treatments (antiretroviral treatment history, current HAART, medical visit schedule, weeks on NVP-based strategies), lipodystrophy, HIV/AIDS disease stage according to the 1993 Centers for Disease Control classifications, quantification of plasma HIV-1 RNA, $CD4^+$ and $CD8^+$ cell counts (determined in whole blood by flow cytometry), serum chemistry including fasting lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides), and liver enzymes: aspartate aminotransferase (AST), alanine, aminotransferase (ALT), and γ-glutamyltransferase (GGT). At the subsequent time points (2 years and the last clinical visit), the following data were collected: lipodystrophy assessment, adherence, complete blood cell count, $CD4^+$ and $CD8^+$ T cell counts, HIV-1 RNA levels, and a complete serum chemistry including the fasting lipid profile and liver function.

Liver enzymes and lipid values were classified as abnormal according to the standard range of normal values determined by each hospital. Liver toxicity was defined as a 2.5-fold increase above the upper limit of the standard normal range or an increase of 2.5 times from baseline values. Severe hepatotoxicity was defined as a 5-fold or greater increase in liver parameters according to the standardized toxicity grade scale modified by the AIDS Clinical Trial Group, corresponding to grade III–IV of toxicity on this scale.[19] Acute clinical hepatitis was defined as the presence of physical signs and/or symptoms consistent with hepatitis concomitantly with abnormal liver chemistry.

Safety profiles, determined by analyzing liver enzymes, were compared between males with $CD4^+$ cell counts of more or less than 400 cells/μl, and between females with $CD4^+$ cell counts of more or less than 250 cells/μl, as well as between coinfected and noncoinfected patients.

Adherence reports were obtained from clinical notes. The proportion of compliance was calculated by dividing the number of pills consumed during the last month by the number of pills prescribed in the same period. Patients who consumed at least 95% of the prescribed doses during the treatment period were considered to have good adherence. Adherence was considered regular if patients took 90–95% of the prescribed therapy or if patients had a treatment interruption of up to 2 days. Bad adherence was considered to be the intake of less than 90% of the prescribed doses or the occurrence of an unplanned drug cessation for more than 2 days.

Statistical analysis

The longitudinal evolution of data collected at baseline, 2 years, and the last clinical visit was analyzed.

Differences in all parameters at baseline, 2 years, and the last visit of follow-up were determined. Comparison of means between groups was performed by the *t* test or Mann–Whitney *U* test, as appropriate. The proportion of patients with altered liver or lipid profiles was compared between groups by means of the χ^2 or Fisher's exact test for proportions, as appropriate. Results were considered significant at $p \leq 0.05$.

We used a logistic regression model to determine the factors related to having an undetectable viral load at the last measurement. The following covariates were included in the model to investigate their possible influence: gender, CDC stage, age, years of HIV infection, lipodystrophy (categorized as yes/no), coinfection with hepatitis B or C viruses, NVP as a first line treatment, time on an NVP-containing treatment regimen, PI, EFV, or d4T in previous therapy, adherence (categorized as good, regular, or bad), baseline CD4 cell count (categorized as

Table 1. Baseline Patients Characteristics

Patients included	*613*
CDC A (%)	49
CDC B (%)	26
CDC C (%)	25
Age median (IQR)	41 (37–46)
Male (%)	70.8%
Patients on PI at enrollment (%)	35 (5.7%)
Treatment with NVP by	
Simplification therapy (%)	215 (35%)
First therapy (%)	150 (24.5%)
Rescue therapy (%)	209 (34%)
Switch due to intolerance (%)	39 (6.5%)
Good adherence (%)	56%
Coinfected patients, *n* (%)	189 (31%)
Lipodystrophy, *n* (%)	95 (15.5%)
CD4 cells count $\leq$350 cell/μl at baseline, *n* (%)	221 (37.2%)
Viral load >10,000 copies/ml at baseline *n* (%)	181 (30.7%)
Viral load >100,000 copies/ml at baseline *n* (%)	63 (10.2%)

TABLE 2. LIVER ENZYMES EVOLUTION[a]

	Baseline	*Second year*	*Last measurement*
ALT median, IQR	28 (18.5;49.5)	32 (21;52)	33 (21.25;52)
AST median, IQR	28 (20;44)	28 (20.5;44.5)	28 (21;48)
GGT median, IQR	30 (19;61)	67 (37;137)	63 (37;133.75)

[a]AST, aspartate aminotransferase, ALT, alanine aminotransferase, GGT, γ-glutamyltransferase; IQR, intraquartile rank.

>100, 200, 350, and >400 cell/μl), and baseline HIV-RNA viral load (categorized as <10,000, >10,000, copies/ml).

A backward stepwise procedure was used to select the best set of predictors of virological success.

RESULTS

Patient baseline characteristics

A total of 613 patients were included in this study. Baseline characteristics are summarized in Table 1. The median follow-up time period was 43 months [interquartile range (IQR) 31–51]. At the time of entry into the study, 41.5% (254 patients) had undetectable HIV-1 RNA levels (<50 copies/ml) and switched to an NVP-based strategy because of intolerance to the prior regimen or for simplification purposes, 24.5% (150 patients) were antiretroviral-naive, and 34% (209 patients) were on a failing previous regimen. Forty-nine percent of patients were classified as CDC stage A, 26% were stage B, and 25% were stage C. Lipodystrophy was present in 15.5% of patients. Coinfection with hepatitis B or C viruses was present in 31% of the patients ($n = 189$). The most frequent nucleoside analogue backbone was zidovudine/lamivudine (29.7%) followed by didanosine/lamivudine (24.22%). A protease inhibitor was concomitantly administered in 5.7% of patients.

Tolerability and adverse events

Overall, 17% of patients reported experiencing adverse events during the study. The most frequent adverse event was lipodystrophy (29% of patients). Nine patients (5.7% of all adverse events) developed adverse effects that could be attributed to nevirapine, predominantly liver toxicity. Three cases of acute hepatitis were detected: two cases occurred in 2 hepatitis C virus-coinfected patients with a persisting alcoholic habit and one episode occurred in a pregnant HCV coinfected woman. Eighty patients (13%) discontinued therapy beyond 2 years, mostly due to virological rebound (37 patients, 6%). Hepatic toxicity was the reason for discontinuation in only 7 patients (1.1%).

Globally, median AST and ALT values remained within the standard normal range throughout follow-up. Median AST values were 28 U/L (IQR 20; 44), 28 U/L (IQR 20.5; 44.5), and 28 U/L (IQR 21; 48) at baseline, 2 years, and the last visit, respectively. Median ALT values were 28 U/L (IQR 18.5; 49.5), 32 U/L (IQR 21; 52), and 33 U/L (IQR 21.2; 52) at baseline, 2 years, and the last visit, respectively. Median GGT values increased from 30 U/L (IQR: 19; 61) to 67 U/L (IQR: 37; 137) at 2 years and to 63 U/L (IQR: 37; 133,75) at the last visit (Table 2).

Grade III/IV toxicity, according to the standardized toxicity grade scale modified by the AIDS Clinical Trial Group, was infrequent in our cohort of patients (less than 2% in AST and ALT values). Median GGT values increased from 4% at baseline to 14% at the second year and to 13% at the last visit.

Overall, coinfected patients showed a greater percentage of moderate/severe hepatotoxicity than noncoinfected patients (1.8% in noncoinfected patients in comparison with 4.4% in coinfected patients at baseline, and 4.7% in noncoinfected patients versus 20.3% in coinfected patients at the last control visit). GGT levels also showed a greater increase over time in coinfected patients than other liver enzymes, for which abnormalities remained under 4% through the follow-up (Table 3).

Patients with HBV and/or HCV coinfection displayed significantly higher baseline liver enzymes than noncoinfected patients [median AST: 41 U/L (IQR 29; 64) vs. 23 U/liter (IQR 18; 32); median ALT 42 U/L (IQR 26; 71) vs. 24 U/liter (IQR 17; 35), respectively]. Liver enzymes remained stable and without significant longitudinal changes in both groups (Fig. 1). Patients concomitantly receiving PIs also showed higher AST and GGT values at baseline than the remaining patients. During the two follow-up time points, although AST and GGT values were higher in patients receiving PIs, differences did not reach statistical significance.

A comparative analysis between females with $CD4^+$ cell counts greater than 250 cells/mm^3 and females with fewer than 250 $CD4^+$ cells/mm^3 did not show differences regarding adverse events and evolution of liver enzymes. Males with $CD4^+$ cell counts greater than 400 cells/mm^3, as compared to those with

TABLE 3. PROPORTION OF ABNORMALITIES IN LIVER ENZYMES GRADE III OR IV[a]

	Baseline		*Second year*		*Last measurement*	
	Noncoinfected	*Coinfected*	*Noncoinfected*	*Coinfected*	*Noncoinfected*	*Coinfected*
ALT % (*n*)	0.9 (2)	3.8 (7)	1.3 (3)	2.7 (5)	0 (0)	3.7 (7)
AST % (*n*)	0.4 (1)	4.3 (8)	0 (0)	2.7 (5)	0.4 (1)	3.7 (7)
GGT % (*n*)	1.8 (4)	4.4 (8)	6 (14)	22.6 (42)	4.7 (11)	20.3 (38)

[a]In noncoinfected patients (negative serologies of hepatitis C or B viruses) versus coinfected patients (positive serologies of hepatitis C or B viruses).

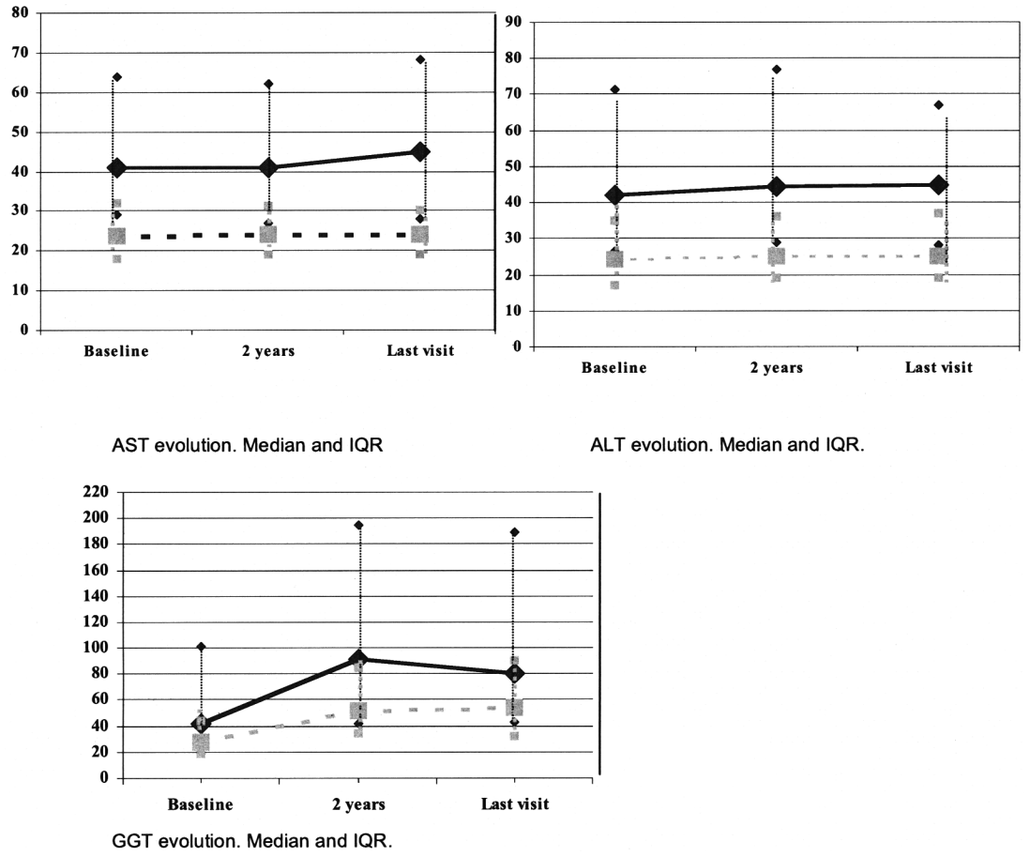


FIG. 1. Liver enzymes evolution. Black line: coinfected patients. Gray dashed line: noncoinfected patients. AST, ALT, and GGT values are expressed in median and IQR (interquartile rank).

$CD4^+$ counts less than 400 cells/mm^3, showed a statistical difference in GGT levels ($p = 0.001$, 0.001, and 0.002 in baseline, second year, and last measurement, respectively). No differences in AST and ALT values were observed between these male groups. Globally, male patients showed greater values of AST and ALT than females, but a higher proportion of coinfected patients was male (138 patients, 73%). Global adverse events did not show differences between genders ($p = 0.707$).

Lipid profile

Overall, median lipid values remained within the standard normal range throughout the study. However, there was a statistically significant increase in total cholesterol, HDL cholesterol, and triglyceride levels at the second year and at the last visit time points, with respect to baseline values ($p < 0.01$ for all values). LDL cholesterol values remained stable through follow-up.

The proportion of patients with normal HDL cholesterol levels increased from 17.7% at baseline to 34.9% at 2 years and to 35.4% at the last clinical visit ($p < 0.001$ at both follow-up visits). The percentage of patients with normal LDL cholesterol values (64.6% to 59.1% and 62.2% at baseline, 2 years, and the last visit) and normal triglycerides (67.4% to 66.1% and 71.1%, respectively) remained stable during the course of the follow-up period.

Significant differences were found in lipid profiles when controlling for the different motives for beginning an NVP-based regimen (Table 4). Antiretroviral naive patients who started NVP as a first-line regimen showed a significant increase in HDL cholesterol from baseline values to the second year and the last visit ($p < 0.001$ in both time points). Total cholesterol and LDL fractions also increased from baseline to the second year ($p < 0.001$ and $p = 0.031$, respectively) but remained stable afterward. Triglycerides remained stable at all time points analyzed in this group of patients.

Patients initiating NVP as a salvage regimen showed a significant increase in HDL cholesterol from baseline to the second year and to the last visit ($p < 0.001$ for both time points), as well as in total cholesterol values at the last visit ($p = 0.001$).

Patients who switched to NVP due to simplification or toxicity achieved an improvement in HDL cholesterol at 2 years and at the last visit ($p < 0.001$ for both time points). Indeed, LDL cholesterol also improved at the last visit ($p = 0.024$), and total cholesterol improved between the second year and the last visit ($p = 0.018$). In addition, triglyceride levels significantly improved at the last visit with respect to baseline ($p = 0.023$).

All lipid profile changes described are summarized in Fig. 2.

The proportion of patients with normal lipid profiles increased for all relevant parameters in the simplification group. In the remaining arms, while the percentage of patients with normal HDL fractions and triglycerides increased, the proportion of patients with normal LDL and total cholesterol values decreased at the last visit, with respect to baseline values.

Table 4. Lipid Profile Evolution by Treatment Groups

Purpose of NVP use	*Median (mg/dl) (IQR) % of normal values*			p *values* *BL vs. 2 years (%)*	p *values* *2 years vs. last visit (%)*	p *values* *BL vs. last visit (%)*
	Baseline	*2 years*	*Last visit*			
Naive ($n = 150$)						
Total cholesterol	169	194	188.8			
	(148.8–193)	(166–219)	(165–214.75)	$p < 0.001$	$p =$ ns	$p < 0.001$
	83%	63%	65%	($p = 0.001$)	($p < 0.001$)	($p = 0.008$)
HDL cholesterol	41	52	54			
	(33.5–46.5)	(42–63.5)	(43.7–65.7)	$p < 0.001$	$p =$ ns	$p < 0.001$
	44%	49%	53%	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)
LDL cholesterol	91.5	107	107.75			
	(67.5–113.5)	(88.95–136)	(84.75–135)	$p = 0.031$	$p =$ ns	$p =$ ns
	95.5%	75.3%	75.4%	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)
Triglycerides	127	108.8	102			
	(90–178.75)	(78–173)	(73.65–169)	$p =$ ns	$p =$ ns	$p =$ ns
	76.3%	77%	78%	($p = 0.003$)	($p < 0.001$)	($p = 0.014$)
Intolerance or simplification ($n = 254$)						
Total cholesterol	209	211.5	200.8	$p =$ ns	$p =$ ns	($p = 0.018$)
	(174.5–244.5)	(177–240)	(174.4–244)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)
	45.5%	43%	50%			
HDL cholesterol	39	47	45.5			
	(32–43.25)	(39–58)	(39.4–56.4)	$p < 0.001$	$p =$ ns	$p < 0.001$
	07%	26%	25%	($p = 0.004$)	($p < 0.001$)	($p = 0.001$)
LDL cholesterol	137	132	130.4	$p =$ ns	$p =$ ns	$p = 0.024$
	(106–172)	(102–158)	(100.2–159.5)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)
	43%	49%	49.7%			
Triglycerides	143	142	140	$p =$ ns	$p =$ ns	$p = 0.023$
	(95–233)	(95–244)	(102.6–227.4)			
	60%	57%	64.4%	($p < 0.001$)	($p < 0.001$)	($p = 0.002$)
Coming from HAART failure ($n = 209$)						
Total cholesterol	189	204	203			
	(164–218)	(184–229)	(174–229)	$p < 0.001$	$p =$ ns	$p = 0.01$
	67%	51%	52%	($p < 0.001$)	($p < 0.001$)	($p = 0.009$)
HDL cholesterol	41	48	48	$p < 0.001$	$p =$ ns	$p < 0.01$
	(33–47)	(38–61)	(39–60)	($p < 0.001$)	($p < 0.001$)	($p < 0.001$)
	14%	39.5%	38%			
LDL cholesterol	115	123	120			
	(92–135)	(84–210)	(95–142)	$p =$ ns	$p =$ ns	$p =$ ns
	70.5%	59%	67%	$p =$ ns	($p < 0.001$)	($p = 0.022$)
Triglycerides	129	142.25	140			
	(92.5–207)	(96–244)	(102.6–227)	$p =$ ns	$p = 0.026$	$p =$ ns
	71%	66.5%	73.5%	($p < 0.001$)	($p < 0.001$)	($p = 0.002$)

Median triglycerides, LDL, HDL, and total cholesterol values tended to be lower in HBV and HCV coinfected patients than in the remaining subjects, although differences between groups were not statistically significant at any time point, for any of these parameters.

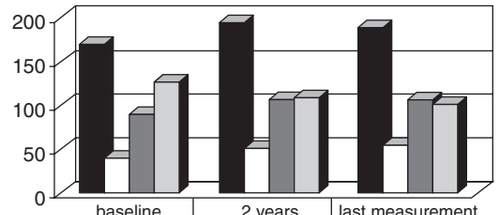
Regarding the association between treatment combinations and lipid abnormalities, patients receiving concomitant PI treatment had higher LDL and total cholesterol levels ($p < 0.001$) than patients not receiving PIs. Moreover, patients receiving d4T had lower HDL and higher LDL cholesterol levels than those on d4T-sparing regimens ($p = 0.008$ and $p = 0.049$, respectively, from baseline). No particular associations could be established between lipodystrophy and treatment combinations.

Adherence

Adherence data were available for more than 80% of the study subjects throughout the follow-up period. Up to 60% of patients achieved good adherence during the follow-up (defined as the consumption of at least 95% of the prescribed doses). These patients were more likely to achieve and maintain undetectable HIV-1 RNA levels at the second year and last visit time points.

A

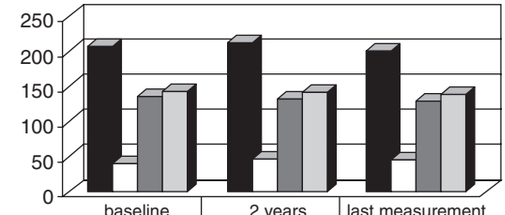
Evolution of lipid profile in naïve patients (median values, mg/dl).



	baseline	2 years	last measurement
■ Total Cholesterol	169	194	188,8
□ HDL-Cholesterol	41	52	54
■ LDL-Cholesterol	91,5	107	107,75
□ Triglycerides	127	108,8	102

B

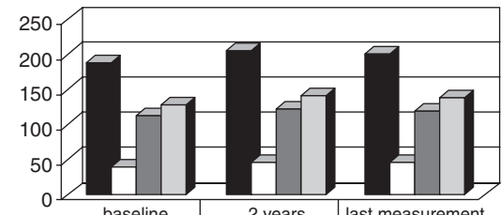
Intolerance or simplification (median values, mg/dl).



	baseline	2 years	last measurement
■ Total Cholesterol	209	211,5	200,8
□ HDL-Cholesterol	39	47	45,5
■ LDL-Cholesterol	137	132	130,4
□ Triglycerides	143	142	140

C

Coming from HAART failure (median values, mg/dl).



	baseline	2 years	last measurement
■ Total Cholesterol	189	204	203
□ HDL-Cholesterol	41	48	48
■ LDL-Cholesterol	115	123	120
□ Triglycerides	129	142,25	140

FIG. 2. Evolution of lipid profile according to NVP use expressed in median values (mg/dl).

Virological and immunological outcomes

At the latest time point available (median follow-up of 43 months), of 76% of treatment-naive patients, 74% of patients switched for simplification strategies, and 59% of patients on salvage approaches had undetectable viral loads (plasma HIV-1 RNA <50 copies/ml). Additionally, patients from the salvage therapy group showed a decrease in viral load from the baseline median (IQR) of 0.58 $\log_{10}$ (−1.85; 0).

The median $CD4^+$ cell count increased from baseline values by 224 cells/μl in treatment-naive patients, and by 134 cells/μl from baseline in patients on salvage therapies. Patients who changed regimens due to intolerance or simplification showed an increase from baseline in their $CD4^+$ cell counts of 77 cells/μl. Virological and immunological results are summarized in Table 5.

Predictors of virological outcome

In the univariate analysis, factors associated with an HIV-1 RNA load of <50 copies/ml at the final visit in patients with detectable viral loads at baseline were male gender [odds ratio: 1.68 (95% CI: 1.02; 2.78), $p = 0.043$], duration of HIV infection [odds ratio: 0.92 (95% CI: 0.86; 0.99) $p = 0.022$], being treatment naïve [odds ratio: 2.74 (95% CI: 1.69; 4.44) $p < 0.001$], adequate adherence [odds ratio: 2.97 (95% CI: 1.02; 8.71), $p < 0.001$], and baseline CD4 cell count >400 cells/μl [odds ratio: 1.77 (95% CI: 1, 13; 2.77), $p = 0.012$]. In the multivariate analysis, factors related to a higher likelihood of having an HIV-1 RNA load of <50 copies/ml were being treatment-naive [odds ratio: 3.02 (95% CI: 1.52; 6.00) $p = 0.002$], adequate adherence [odds ratio: 2.58 (95% CI: 0.85; 7.78) $p < 0.001$], and baseline CD4 cell counts greater than 400 cells/μl [odds ratio: 2.34 (95% CI: 1.22; 4.47), $p = 0.010$].

Other parameters such as age, gender, or years of infection were not associated with a particular virological response in our study (Table 6).

DISCUSSION

In this cross-sectional, multicenter study we have shown that the prolonged use of nevirapine, beyond 2 years of treatment, constitutes a safe and potent approach. Moreover, we found that the safety of NVP in patients continuously treated beyond 2 years of exposure is independent of gender and initial $CD4^+$ cell count, although hepatitis B/C coinfected patients have significant, major increases in AST/ALT values.

Our results, obtained under routine clinical conditions, concur with other studies regarding the low frequency of long-term severe hepatotoxicity.[2,5,20–23] These studies demonstrated that clinically relevant hepatotoxicity related to nevirapine predominantly occurs early and in patients with high CD4 counts (particularly women with CD4 counts >250 cells/mm at initiation of therapy). When treating patients with lower CD4 counts (women <250 and men <400), the use of nevirapine appears to have a remarkably low rate of drug-related adverse events in both the short[10–12] and long term.

We recognize that our patient population is biased because of the exclusion of those patients who discontinued treatment with NVP within the first 2 years due to adverse events. However, we would like to stress that in contrast to previous studies, our aim was to determine if very prolonged exposure to nevirapine could be associated with late-onset toxicity in those who had tolerated the drug initially.

Recent studies have warned of the risk of early nevirapine-associated hepatotoxicity, especially in patients presenting with hepatitis B or C coinfection, pregnant women, and women with $CD4^+$ cell counts above 250 cells/mm^3. However, the conclusions of these investigations are discordant in reference to the

TABLE 5. CD4 CELLS/μl AND HIV-1 RNA VIRAL LOAD EVOLUTION FOR PATIENTS BY NVP USE[a]

	Baseline		*2 years*		*Last visit*	
NVP use	*CD4 median (IQR)*	*log_{10} VL median (IQR)*	*CD4 median (IQR)*	*log_{10} VL median (IQR)*	*CD4 median (IQR)*	*log_{10} VL median (IQR)*
Naive (n = 150)	384 (209.5;597.5)	4.41 (3.73;5.09)	619 (375.5;844.5)	1.7 (1.7;2.3)	608 (402.25;903)	1.7 (1.7;2.3)
Intolerance or simplification (n = 254)	504 (327.5;732)	2.3 (1.7;2.3)	572 (398.75;855.75)	1.7 (1.56;2.3)	581 (403;800)	1.7 (1.6;2.3)
Coming from HAART failure (n = 209)	373 (208;560.75)	3.52 (2.3;4.28)	515 (336;714)	2.3 (1.7;2.97)	510 (340;657.5)	2.3 (1.7;3.16)

[a]IQR, interquartile rank; VL, HIV-1 RNA viral load.

groups that are most likely to suffer from NVP-related hepatotoxicity.[1,11–14] Despite such conflicting results, these studies have concordantly reported that the appearance of liver toxicity occurs within the first weeks of initiating nevirapine-based treatment.

In our study, a large proportion (approximately 31%) of the patients were coinfected with B or C hepatitis viruses. Contrary to the results of previous investigations,[7,8] we found that both coinfected and noncoinfected patients present similar liver pro-

TABLE 6. PREDICTORS OF VIROLOGICAL SUCCESS IN 330 PATIENTS WHO RECEIVED NVP FOR AT LEAST 2 YEARS AND HAD BASELINE DETECTABLE VIRAL LOAD

			Univariate analysis		*Multivariate analysis*	
Characteristic at baseline (reference category)	*Undetectable viral load (n = 200)*	*Detectable viral load (n = 130)*	p-*value*[a]	*Odds ratio (95% CI)*	p-*value*[a]	*Odds ratio (95% CI)*
Gender (male)	133/200	100/130	0.043	1.68 (1.02;2.78)		
CDC stage						
C	44/184	32/118	0.794			
B	40/184	26/118		1.12 (0.57;2.19)		
A	100/184	60/118		1.21 (0.69;2.11)		
Age (years) median (IQR)	40 (36;44)	41 (38;47)	0.157	0.98 (0.96;1.01)		
Duration of HIV infection (years) median (IQR)	8 (5;12)	10 (6.75;13.25)	0.022	0.92 (0.86;0.99)		
Lipodystrophy (yes)	15/141	11/64	0.196	1.74 (0.75;4.04)		
Coinfection (yes)	71/154	37/70	0.349	1.31 (0.74;2.31)		
Being treatment naive (no)	103/99	97/130	<0.001	2.74 (1.69;4.44)	0.002	3.02 (1.52;6.0)
Time on NVP treatment (>5 years)	34/199	14/130	0.119			
2 years	17/199	9/130		0.78 (0.28;2.16)		
2–3 years	44/199	47/130		0.39 (0.18;0.81)		
3–4 years	59/199	36/130		0.68 (0.32;1.43)		
4–5 years	45/199	24/130		0.77 (0.35;1.71)		
PI in previous therapy (no)	109/147	39/57	0.411	0.76 (0.39;1.48)		
EFV in previous therapy (no)	143/147	55/57	0.766	0.77 (0.14;4.32)		
d4T in previous therapy (no)	125/147	40/57	0.017	0.41 (0.20;0.86)		
Adherence						
Bad	8/152	7/70	<0.001		<0.001	
Regular	136/152	40/70		0.30 (0.08;1.11)		0.29 (0.08;1.09)
Good	8/152	23/70		2.97 (1.02;8.71)		2.58 (0.85;7.78)
CD4 baseline (>350)	98/197	77/129	0.079	1.50 (0.95;2.34)		
CD4 baseline (>200)	144/197	98/129	0.562	1.16 (0.70;1.94)		
CD4 baseline (>100)	174/197	120/129	0.168	1.76 (0.79;3.94)		
CD4 baseline (>400)	79/197	70/129	0.012	1.77 (1.13;2.77)	0.010	2.34 (1.22;4.47)
VL baseline (>10,000)	107/200	69/130	0.940	0.98 (0.63;1.53)		
VL baseline (>100,000)	43/200	19/130	0.120	0.62 (0.35;1.13)		

[a]Logistic regression model.

NVP, nevirapine; PI, protease inhibitors; EFV, efavirenz; VL, HIV-1 RNA viral load.

file evolutions in the long term, despite significantly higher baseline values in coinfected patients. More specifically, both hepatitis coinfected and noncoinfected patients exhibited a similar increase and kinetics of liver enzymes over time, although median AST and ALT values tended to be higher in HBV or HCV coinfected patients from baseline to the final visit. The proportion of grade III or IV toxicity was three times more frequent in coinfected patients than noncoinfected subjects.

Also, in contrast to recent warnings[11,13] regarding liver toxicity in the short-term in HIV-infected women starting NVP with CD4 cell counts of >250 cells/μl, we found no relationship between the female gender, immunosuppression, and an increase of toxicity in our cohort of patients with exposure beyond 2 years. The difference in findings may result from the long-term focus of our study, in contrast to the short-term focus of the studies referenced above that warn of early-onset hepatoxicity. Regarding differences between genders, we observed a statistical increase of liver enzymes in males, as compared to females. A possible explanation for this phenomenon is that most of the coinfected patients were male (73%).

Some authors consider the pathogenesis of hepatic toxicity to be related to immunological depletion[15] or recovery,[6,22] while others have not found a relationship between immune status and hepatotoxicity.[24] On the other hand, a possible increase in NVP concentration in patients with previous hepatic dysfunction is postulated as a possible cause of liver toxicity.[25–27] We stratified the analyses of liver toxicity according to different $CD4^+$ levels and have been unable to establish any relationship between liver toxicity and the degree of immune depression in the long term.

In concordance with other studies,[2,5] we observed that NVP-containing treatments caused higher and more frequent increases in GGT levels than in ALT, AST, total bilirubin, or alkaline phosphatase levels. Although the total rise in GGT levels was statistically significant, it reached a plateau after 2 years. This has also been shown in the meta-analyses performed by Murphy.[22] The clinical significance of GGT increases remains unclear. One trial postulated that this parameter should be interpreted as a marker of microsomal induction,[16] rather than a sign of hepatic cellular damage. Importantly, GGT increases are not related to clinical hepatitis in our study.

In terms of patient lipid profiles, our results agree with those of previous studies, showing that NVP-containing regimens contributed to ameliorate the lipid profile of HIV-experienced patients. Mean lipid values were stable over time, with a significant improvement in triglycerides and HDL cholesterol values. The improvement seen in naive and switching strategies may be related to the intrinsic impact on HDL metabolism by NNRTI drugs,[28,29] and also to the withdrawal of PIs, which are known to worsen lipid metabolism.[1,2,30] Likewise, our results showed a lasting improvement in HDL cholesterol and total cholesterol HDL ratios (two parameters linked to cardiovascular risk) associated with long-term nevirapine use. Consequently, one benefit of treatment with NVP could be the achievement of an antiatherogenic lipid profile.[29,31]

The favorable initial virological response achieved with nevirapine use was maintained throughout this prolonged exposure in almost 70% of patients who were either on a simplification approach or on first-line therapy. Factors associated with viral suppression in our study were baseline CD4 cell counts, adequate adherence, and first-line antiretroviral treatment. Furthermore, we have observed that the favorable virological response seen both in our patients and in those of different studies[3,4,17] may be maintained for very prolonged time periods without a subsequent significant increase in toxicity.

In conclusion, liver toxicity associated with the use of nevirapine beyond 2 years was generally mild and infrequent, and no unexpected long-term toxicities have been documented in our cohort. Long-term exposure to NVP was associated with favorable lipid profiles as well as virological and immunologic responses for up to 43 months of follow-up. Those on first-line treatment, those with baseline CD4 cell counts of more than 400 cells/μl, and those with optimal adherence were more likely to have undetectable viral loads at the last clinical visit. Our results confirm the prolonged clinical utility of nevirapine-based regimens in the routine clinical setting as a safe and effective approach.

REFERENCES

1. Martinez E, Arnaiz J, Podzamczer D, Dalmau D, Ribera E, Domingo P, *et al*.: Substitution of nevirapine, efavirenz or abacavir for protease inhibitors in patients with human immunodeficiency virus infection. N Engl J Med 2003;349:1036–1046.
2. Negredo E, Cruz L, Paredes R, Ruiz L, Fumaz C, Bonjoch A, *et al*.: Virological, immunological and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with long-lasting viral suppression. Clin Infect Dis 2002;34:504–510.
3. Podzamczer D, Ferrer E, Consiglio E, Gatell JM, Perez P, Perez JL, *et al*.: A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (COMBINE study). Antiviral Ther 2002;7:81–90.
4. Lange J: Efficacy and durability of nevirapine in antiretroviral drugs naive patients. J Acquir Immune Defic Syndr 2003;34:S40–52.
5. Martinez E, Blanco JL, Arnaiz J, Perez-Cuevas J, Mocroft A, Cruceta A, *et al*.: Hepatotoxicity in HIV-1 infected patients receiving nevirapine-containing antiretroviral therapy. AIDS 2001;15:1261–1268.
6. Kontorinis N and Dieterich DT: Toxicity of non-nucleoside analogue reverse transcriptase inhibitors. Semin Liver Dis 2003;23: 173–181.
7. Sulkowski MS, Thomas DL, Chaisson RE, and Moore RD: Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. JAMA 2000;283:74–80.
8. Sulkowski M, Thomas D, Mehta S, Chaisson R, and Moore R: Hepatotoxicity associated with nevirapine or efavirenz containing antiretroviral therapy: Role of hepatitis C and B infections. Hepatology 2002;35:182–189.
9. Kresina TF, Flexner CW, Sinclair J, Correira MA, Stapleton JT, Adeniyi-Jones S, *et al*.: Alcohol use and HIV pharmacotherapy. AIDS Res Hum Retroviruses 2002;18:757–770.
10. Martin A, Cameron P, Nolan D, James I, Keller J, Phillips E, *et al*.: Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*01 and higher CD4+ T cell counts. In: *XV International AIDS Conference, Bangkok, Thailand, 2004*. Abstract LbOrB13. International AIDS Society, Stockholm.
11. Kramer F, Stek A, Du WB, and Kovaks A: Nevirapine tolerability in HIV-infected women in pregnancy. 11th Conference on Retroviruses and Opportunistic Infections, February 8–11, 2004, San Francisco, CA (abstract 923).
12. Bershoff-Matcha SJ, Mundy LM, and Henry JV: Adverse events

to nevirapine therapy during pregnancy. 11th Conference on Retroviruses and Opportunistic Infections, February 8–11, 2004, San Francisco, CA (abstract 939).
13. Bersoff-Matcha S, Miller W, Aberg J, van der Horst C, Hamrick J, Powderly W, *et al*.: Sex differences in nevirapine rash. Clin Infect Dis 2001;32:124–129.
14. Hitti J, Frenkel L, Huang S, Wei L, Stevens L, Watts H, *et al*.: Toxicity with continuous nevirapine in pregnancy. Results from PACTG 1022. 11th Conference on Retroviruses and Opportunistic Infections, February 8–11, 2004, San Francisco CA (abstract 938).
15. Puoti M, Spinetti A, Ghezzi A, Donato F, Zaltron S, Putzolu V, *et al*.: Mortality for liver disease in patients with HIV infection: A cohort study. J Acquir Immune Defic Syndr 2000;24:211–217.
16. Negredo E, Moltó J, Muñoz J, Pedrol E, Ribera E, Viciana P, *et al*.: Safety and efficacy of once-daily dose didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. Antiviral Ther 2004;9:335–342.
17. van Leth F, Phanuphak P, Ruxrungtham K, Baraldi E, Miller S, Gazzard B, Cahn P, *et al*.: Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: A randomised open-label trial, the 2NN Study. Lancet 2004;17:1253–1263.
18. Parienti J, Massari V, Descamps D, Vabret , Bouvet E, Larouze B, *et al*.: Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. Clin Infect Dis 2004;38:1311–1316.
19. AIDS Clinical Trial Group: Table of grading severity of adult adverse experiences. Division of AIDS, National Institute of Allergy and Infectious Disease, Rockville, MD, 1996.
20. Palmon R, Koo B, Shoultz D, and Dieterich D: Lack of hepatotoxicity associated with nonnucleoside reverse transcriptase inhibitors. J Acquir Immune Defic Syndr 2002;29:340–345.
21. Bonnet F, Lawson-Ayayi S, Thiébaut R, Ramanampamonjy R, Lacoste D, Bernard N, *et al*.: A cohort of nevirapine tolerance in clinical practice: French Aquitaine Cohort, 1997–1999. Clin Infect Dis 2002;35:1231–1237.
22. Murphy RL: Defining the toxicity profile of nevirapine and other antiretroviral drugs. J Acquir Immune Defic Syndr 2003;34:S15–20.
23. Dieterich D, Becker S, Fusco J, Balu R, Most BM, Stern J, *et al*.: Low incidence of grade III/IV hepatotoxicity in first HAART observations from 1,237 patients followed for one year. In: *XIV International AIDS Conference, Barcelona, Spain, 2002*. Poster 4534. International AIDS Society, Stockholm.
24. Martin-Carbonero L, Núñez M, Rios P, Perez-Olmeda M, Gonzalez-Lahoz J, and Soriano V: Liver injury after beginning antiretroviral therapy on HIV/hepatitis C virus co-infected patients is not related to immune reconstitution. AIDS 2002;16:1423–1425.
25. Vento S, Garofano T, Renzini C, Casali F, Ferraro T, and Concia E: Enhancement of hepatitis C virus replication and liver damage in HIV-co-infected patients on antiretroviral combination therapy. AIDS 1998;12:116–117.
26. Lamson M, Maldonado S, Hutman H, *et al*.: The effects of underlying renal or hepatic dysfunction on the pharmacokinetics of nevirapine. In: *8th International Conference on AIDS, Durban, South Africa, 2000.* Abstract TuPeb3301. International AIDS Society, Stockholm.
27. Gonzalez de Requena D, Núñez M, Jimenez-Nacher I, Gonzalez-Lahoz J, and Soriano V: Liver toxicity caused by nevirapine. AIDS 2002;16:290–291.
28. Fontas E, Van Leth F, Sabin A, Friis-Meller N, Rickenbach M, d'Arminio Monforte A, *et al*.: Lipid profile in HIV-infected patients receiving combination antiretroviral therapy: Are different antiretroviral drugs associated with different lipid profiles? J Infect Dis 2004;189:1056–1074.
29. van der Valk M, Kasatelein J, Murphy R, van Leth F, Katlama C, Horban A, *et al*.: Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 2001;15:2407–2414.
30. Ruiz L, Negredo E, Domingo P, Paredes R, Francia E, Balaguer M, *et al*.: Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. J Acquir Immune Defic Syndr 2001;27:229–236.
31. Van Leth F, Phanuphak P, Gazzard B, Cahn P, Wood R, Bloch M, *et al*.: Lipid changes in a randomized comparative trial of a first-line antiretroviral therapy with regimens containing either nevirapine alone, efavirenz alone or both drugs combined, together with stavudine and lamivudine (2NN study). In: *10th Conference on Retroviruses and Opportunistic Infections, February 10–14, 2003, Boston, MA*. Abstract 752. Foundation for Retrovirology and Human Health, Alexandria, VA.

Address reprint requests to:
Anna Bonjoch
Fundacio Lluita contra la SIDA
Hospital Universitari Germans Trias i Puol
Ctra de Canyet, s/n
08916 Badalona, Barcelona, Spain

E-mail: abonjocj@ns.hugtip.scs.es