

ORIGINAL RESEARCH

A randomized controlled trial investigating the efficacy and safety of switching from a protease inhibitor to nevirapine in patients with undetectable viral load

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Objective

To assess the antiviral efficacy and safety of switching from a protease inhibitor (PI) to nevirapine in patients with long-term HIV-1 RNA suppression on PI-containing regimens, and to assess its influence in the adherence to treatment.

Methods

In an open-label multicentre study, 160 HIV-infected patients with undetectable viral load for at least 6 months on a PI-containing regimen were randomized to either continue with their PI regimen ($n = 79$) or replace PI with nevirapine ($n = 81$). Clinical assessment included plasma HIV-1 RNA, blood chemistry, haematology, lymphocyte counts and adverse events reports. Adherence to treatment and lipodystrophy syndrome were assessed by patient self-reporting.

Results

Treatment efficacy was equivalent in the two arms, for patients with viral loads either above or below 100 000 HIV-1 RNA copies/mL. The increase in CD4 cell count was significant in both arms ($P < 0.00001$) but the average CD4 cell count at 48 weeks was slightly higher in the nevirapine arm (596 vs. 569; $P = 0.1588$). The number of patients with severe hypertriglyceridaemia (>400 mg/dL) after 48 weeks of treatment decreased in the nevirapine arm (from 11 to six), but increased in the PI arm (from four to 11) and led to treatment discontinuation in two patients. Lipodystrophy changes increased in 15% of patients in the PI arm but decreased in 4% of patients in the nevirapine arm. Finally, although adherence was similar in the two arms, patients reported that it required significantly less effort to stay on treatment in the nevirapine arm.

Conclusions

The results indicate that switching from PI to nevirapine is as effective as continuing with PI for maintaining viral control, even in patients with baseline viral load above 100 000 copies/mL. In addition, reductions in hypertriglyceridaemia and lipodystrophy and in the effort required to stay on treatment were observed.

Keywords: nevirapine, protease inhibitor – sparing highly active antiretroviral therapy, simplification

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Introduction

The introduction of protease inhibitor (PI)-based highly active antiretroviral treatment (HAART) has significantly reduced the morbidity and mortality of patients infected with HIV [1,2]. However, PI-containing regimens have several limitations: the complicated dosing regimens with dietary requirements, the high daily pill burden and the risk of metabolic disorders, such as lipodystrophy, may reduce the patient's quality of life and drug adherence [3,4]. In addition, elevation of blood lipids by PI treatment may increase the long-term risk of cardiovascular morbidity. These issues have motivated HIV researchers to investigate whether it is safe to switch patients on a PI-based regimen

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and with optimal viral suppression to a simplified maintenance therapy with nonnucleoside reverse transcriptase inhibitors (NNRTIs) or with a third nucleoside reverse transcriptase inhibitor (NRTI) instead of the PI [5,6]. Some of these studies showed the efficacy of this strategy; however, most of them were either noncomparative or included a small number of patients [7–14]. In fact, a recently published meta-analysis showed that more comparative data are necessary [6].

In the case of nevirapine (NVP), there are only three prospective, comparative and randomized simplification studies [9,13,14]. In the study by Negredo *et al.* [9], 77 subjects were randomized to switch from PI therapy to NVP therapy ($n = 26$) or to efavirenz therapy ($n = 25$), or to continue PI therapy ($n = 26$). At month 12, viral suppression was 96, 92 and 92%, respectively. A significant increase in CD4 count was observed in all three groups. In the NVP group, lipid profiles and quality of life improved, whereas levels of γ-glutamiltransferase and alanine aminotransferase significantly increased. Ruiz *et al.* [13] randomized 106 HIV-infected adults with clinically evident lipodystrophy, who sustained HIV RNA suppression for at least 6 months with PI regimens, to replacement of the PI with NVP for 48 weeks vs continuing the prior PI. Viral suppression and increase of CD4 count were good and similar in both arms, and fasting total cholesterol and triglyceride levels decreased in the NVP group. The study by Maggiolo *et al.* [14] was carried out in 124 HIV-infected patients with undetectable viraemia (<50 HIV-1 RNA copies/mL) who were randomized to continue with PI ($n = 62$) or to replace it with NVP ($n = 62$). After 48 weeks, viral suppression was similar in both arms but the percentage of interruption was higher in the PI group. The adverse events in the NVP group were mainly attributable to intolerance or acute toxicity occurring in the first 2 months after treatment switch (rash in five cases), while in the PI group the majority of adverse events were related to metabolic disturbances.

In this paper, we report and discuss the results of a randomized, prospective, multicentre study to evaluate the effectiveness of switching from PI to NVP in maintaining viral control and limiting undesirable side effects in 160 HIV-infected patients with long-term viral suppression.

Patients and methods

Patients

One hundred and sixty HIV-infected patients were enrolled at four clinical centres. All patients met the following criteria: first HAART regimen including a PI (PI alone or boosted with ritonavir) and two NRTIs; undetectable viral load for at least 6 months; no previous experience with NNRTIs; absence of lipid-lowering drugs and methadone use; age above 18 years; and signing of the informed consent form. Patients with the following characteristics were excluded: with opportunistic infections; with severe hepatic disease; on treatment for any other severe acute disease, such as active pulmonary tuberculosis; requiring medication which may interact with the drugs under study. Pregnant or breast-feeding women were also excluded.

After screening and baseline assessments, patients were followed up at weeks 4, 12, 24, 36 and 48. The following measurements were taken at each visit in the fasting state: blood cell counts; concentrations of serum glucose, creatinine, Na^+, K^+, Ca^{2+}, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), γ-glutamyltranspeptidase (GGT), alkaline phosphatase (PA), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and triglycerides; CD4 and CD8 counts; HIV-1 RNA viral load (VL) (branched-DNA technique; Chiron Corp., Emeryville, CA, with a detection limit of 50 copies/mL).

Any side effect or evidence of HIV disease progression, according to the Centers for Disease Control and Prevention (CDC) grade categories, was recorded. Patients were specifically asked to report any changes in their body shape and to grade them on a scale from 0 to 3.

Treatment adherence was measured every 3 months by two different methods: patient self-reporting according to a scale of 12 questions with multiple-choice answers, and the pharmacy record of monthly drug delivery to patients.

The effort involved in taking the drugs was reported by the patients according to a scale of increasing effort from 1 to 10.

Treatment drugs

Nevirapine was administered in 200 mg tablets four times a day (qid) for the first 2 weeks, and twice a day (bid) thereafter. Corticosteroids were not allowed to be used during the first weeks of NVP introduction but antihistamines were permitted at the investigator's discretion. PIs and NRTIs were used according to their data sheet recommendations. PI ritonavir-boosted doses were allowed.

Trial design

Patients were randomly assigned to either continue their PI-containing HAART regimen (PI group) or change the PI for NVP (NVP group) without changes in the NRTIs. Randomization was stratified by baseline VL, before HAART, below or above 100 000 copies/mL.

Endpoints

The primary endpoint was the evaluation of therapeutic failure after 48 weeks of treatment. Secondary endpoints were to assess immunology, serum lipid profile, body-shape modifications, adherence and effort in taking the treatment.

Definitions

Therapeutic failure was defined as VL rebound, the presence of any HIV-associated clinical complication, as defined by the CDC, and/or the presence of significant toxicity to any drug that required treatment discontinuation. VL rebound was defined as a VL of more than 200 copies/mL in two different blood samples taken at least 2 weeks apart. Hypertriglyceridaemia was defined as fasting serum triglyceride levels higher than 400 mg/dL. Hypercholesterolaemia was defined as fasting total serum cholesterol levels higher than 240 mg/dL. Hepatic toxicity was defined as at least a 5-fold increase in baseline ALAT or ASAT levels with or without symptoms of hepatitis.

Statistical methods

A descriptive analysis was performed for all variables recorded with the following statistics: number of observations, mean, standard deviation, quartiles and extreme values, for continuous variables; number of observations and frequencies, for discrete variables. The sample size calculation was made to detect differences between the percentages of failure for each treatment (35% and 15%, respectively) and to obtain 80% power. The primary efficacy analysis was performed on the per protocol group of subjects and in an intent–to-treat analysis. This analysis was calculated by χ^2 statistics to test the null hypothesis of equal effects in the two treatment groups with a significance level of 5%. All tables were created and biostatistical tests performed using SAS version 8.2 (SAS Institute, Cary, NC, USA).

Results

Patients characteristics

One hundred and sixty patients, enrolled between 22 May 2001 and 12 May 2002, were randomized to continue with their treatment (PI group; $n = 79$) or to substitute the PI with NVP (NVP group; $n = 81$). Table 1 shows that no significant differences were found between the patient groups. The distribution of PIs used before randomization was as follows: NVP, 56 patients (35%); indinavir, 77 patients (48.12%); indinavir/ritonavir, 18 patients (11.2%); saquinavir/ritonavir, two patients (1.25%); saquinavir, three patients (1.85%); lopinavir/ritonavir, one patient (0.6%), and ritonavir, three patients (1.85%).

Table 1 Characteristics of the patients

	P-value	PI	NVP
Number of patients		79	81
Age (years) (average)	0.1787	39.29	40.60
Sex (male)	0.5106	91.67	87.72
HIV risk factor (%)	0.6629		
Intravenous drug user		47.37	49.38
Homosexual		30.26	37.04
Heterosexual		18.42	11.11
Time with undetectable VL (months)	0.8128	19.48	20.03
Basal VL > 100 000 copies/mL (% of patients)	0.9154	60.52	59.74
CD4 count pre-HAART (cells/μL)	0.6747	349.49	329.56
CD4 at randomization (cells/μL)	0.1492	502.41	570.22
HCV coinfection (%)	0.6428	54.55	50.98
HBV coinfection (%)	0.1616	2.27	5.45
NRTI (%)			
Zidovudine	0.0832	53.16	39.02
Didanosine	0.6921	12.66	14.63
Lamivudine	0.5584	86.08	82.93
Stavudine	0.0970	44.30	62.20
Zalcitabine	0.3248	7.59	2.44
Types of therapeutic failure			
Viral rebound		3	3
HIV complication		1	1
Adverse reaction		7	8
Protocol violation		0	3
Lost to follow-up		10	8
Total failures		21	23

PI, protease inhibitor; NVP, nevirapine; VL, viral load; HAART, highly active antiretroviral therapy; HCV, hepatitis C virus; HBV, hepatitis B virus; NRTI, nucleoside reverse transcriptase inhibitor.

The study patient flow chart is shown in Fig. 1. These patients were also subanalysed according to their VL before beginning HAART (> 100 000 copies/mL, 94 patients; < 100 000 copies/mL, 66 patients).

Efficacy

In an intent–to-treat analysis, at 48 weeks from the randomization, the percentage of patients with therapeutic failure (loss = failure) was similar in the two arms (21 of 79 patients, 27%, in the PI arm; 23 of 81 patients, 28%, in the NVP arm; $P = 0.7914$). The different types of therapeutic failure are showed in the Table 1. Patients with baseline VL above 100 000 copies/mL before HAART had higher rates of therapeutic failure (30 of 94 patients, 40%) compared with patients with baseline VL before HAART < 100 000 copies/mL (14 of 66 patients, 21%), although this difference did not reach statistical significance ($P = 0.1355$) as neither reached statistical difference between both arms (< 100 000

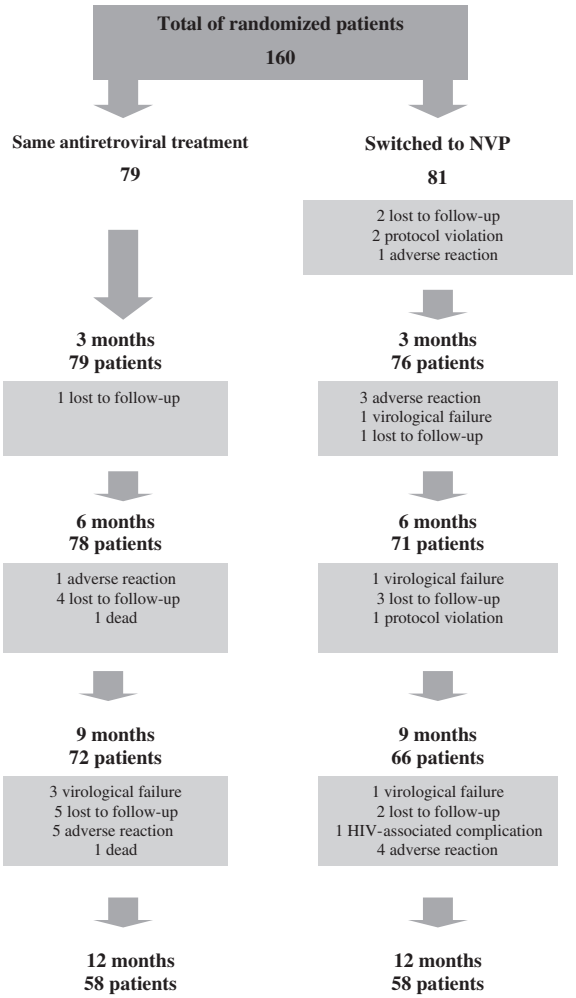

Fig. 1 Flow chart for the study patients. NVP, nevirapine.

copies/mL: seven failures in the NVP group vs. seven failures in the PI group; > 100 000 copies/mL: 16 failures in the NVP group vs. 14 failures in the PI group).

In an on-treatment analysis, the number of patients with viral rebound at 48 weeks was equal in the two groups (three of 58 patients in both treatment arms; 5%, $P = 1$), so the proportion of patients with undetectable VL was also the same (96%; $P = 0.9751$). Time until failure was similar in the two arms. Five of the six patients with viral rebound had a baseline VL > 100 000 copies/mL (three in the PI group and two in the NVP group) and only one (in the NVP group) had baseline VL < 100 000 copies/mL.

CD4 cell count

The increase in CD4 cell count throughout the study was significant in both arms ($P < 0.00001$), with no significant differences between the PI and NVP groups. The average CD4 cell count at 48 weeks was slightly higher in the NVP arm (596 vs. 569 cells/μL: $P = 0.1588$) but it was also slightly higher at baseline in this arm.

Table 2 Incidence of different types of adverse events

Adverse events	PI	NVP
Lipid profile alteration	6	2
Lipoatrophy	8	3
Diarrhoea	1	0
Renal toxicity	1	0
Obstructive uropathy	4	0
Hepatotoxicity	0	4
Hyperglycaemia–diabetes	2	1
Gastrointestinal intolerance	1	0
Rash	0	5
Upper gastrointestinal tract haemorrhage	1	0
CNS alterations	1	0
Concomitant infections	2	3
Arterial hypertension	0	1
Others	1	2*
Total	28	21
Withdrawal because of drug toxicity		
Diarrhoea	1	0
Renal toxicity	1	0
Obstructive uropathy	2	0
Upper gastrointestinal haemorrhage	1	0
Hepatitis	0	4
Hyperglycaemia–diabetes	2	0
Exanthema	0	4
Total	7	8

PI, protease inhibitor; NVP, nevirapine; CNS, central nervous system.
*One death from Hodgkin's lymphoma.

Adverse events

Although patients in the PI arm showed a higher rate of adverse events than those in the NVP arm (35% vs. 26%, respectively; $P = 0.095$), there was no statistically significant difference between the incidence of treatment discontinuation because of drug toxicity between the two arms (10% in the NVP arm vs. 10% in the PI arm; $P = 0.9580$) (Table 2). The most common adverse events in the PI group were metabolic disturbances: hypertriglyceridaemia, hypercholesterolaemia and lipodystrophy. Four patients with indinavir in their regimens had obstructive uropathy. In the NVP group, the most important adverse events were hepatitis and rash. Two patients died at week 48 in the PI group, one of them because of multiorgan failure associated with recurrent leishmaniasis, the other because of an oesophageal varix leading to an upper gastrointestinal tract haemorrhage. In the NVP group, one patient died as a consequence of non-Hodgkin's lymphoma.

Lipid profile

Triglyceride levels decreased in patients who switched to NVP, whereas they increased in the PI group (Figs 2a and b).

The difference between the two arms was significant (in the PI group the average triglyceride level increased from 187.4 mg/dL at baseline to 197.9 mg/dL at 48 weeks of treatment, whereas in the NVP group the average evolution was from 178.3 to 155.6 mg/dL; $P = 0.0086$). In addition, the number of patients with triglyceride levels above 400 mg/dL after 48 weeks of treatment decreased in the NVP arm (from 11 to six) but increased in the PI arm (from four to 11), and high triglyceride levels led to treatment discontinuation in two patients. Four patients discontinued PI because of elevation of triglycerides to above 750 mg/dL. The decision to switch these patients to NVP was made by the responsible physician following the clinical practice in the participating clinic.

Serum total cholesterol, HDL and LDL levels were similar in the two groups throughout the study. At 48 weeks, average serum total cholesterol was 204.34 ± 52.04 in the PI group and 200.04 ± 40.18 in the NVP group ($P = 0.9420$). The proportion of patients with hypercholesterolaemia (> 240 mg/dL) was also equivalent in the two treatment arms (12.5% vs. 12.7%; $P = 0.9712$).

Lipoatrophy

Patient self-reported lipoatrophy increased in 15% of patients in the PI arm but decreased in 5% of patients in the NVP arm (Fig. 3).

Adherence

Treatment adherence according to patient self-reporting was over 95% in both treatment groups throughout the course of the study. According to pharmacy drug delivery the adherence was 100%. However, the average score of effort to stay on treatment was significantly lower in the NVP arm (1.44 NVP vs. 2.47 PI; $P = 0.0002$).

Discussion

In the last few years, the use of PI-sparing HAART regimens, switching from PI to an NNRTI or a third NRTI, has become common in clinical practice either as treatment initiation or simplification after the use of PIs. Some studies showed the efficacy of this strategy, but most of these studies were either noncomparative or included a small number of patients [7–14]. Recently, a prospective and randomized study showed that switching to efavirenz or NVP is a safe therapeutic option for maintaining viral control, and it seems to be better than switching to abacavir, particularly for those patients with single or double therapy before HAART initiation [15].

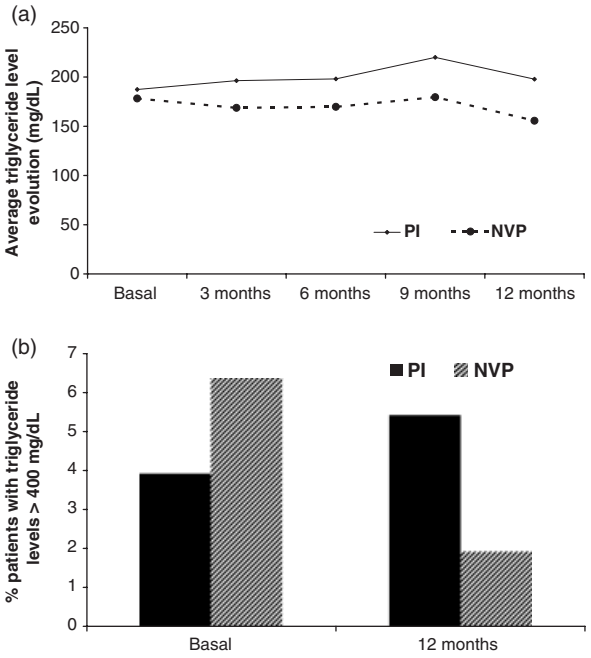

Fig. 2 Lipid profile in the two arms, PI and NVP. (a) Evolution of mean triglyceride serum levels throughout the study period. $P = 0.0086$. (b) Proportion of patients with serum triglycerides > 400 mg/dL at baseline and 12 months after switch. $P = 0.33$. PI, protease inhibitor; NVP, nevirapine.

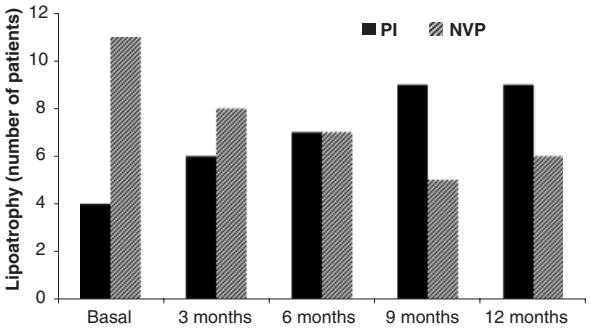

Fig. 3 Incidence of lipoatrophy during follow up. PI, protease inhibitor; NVP, nevirapine.

In our study, 160 patients with undetectable VL on a PI-containing regimen were randomized either to continue with their PI regimen or to change the PI for NVP. Results at 48 weeks after randomization showed that treatment efficacy was equivalent in the two arms, for both on-treatment and intention-to-treat analyses.

It has been reported that patients with pre-HAART high VL tend to have higher rates of therapeutic failure [16], but there is little information about this in simplification studies. We stratified the patients according to their basal (before beginning HAART) VL values, and the results

showed that patients with high VL (> 100 000 copies/mL) had higher rates of viral rebound (5%) than those with low VL (1.6%), but the rate was similar in the two treatment groups.

The increase in CD4 cell count was similar in the two arms, which is consistent with previous reports [9–14].

Changes in triglycerides after switching from PIs to NVP have been observed in some studies [7–9,12–14] but others have not shown any significant variation [6,10,11]. Our study showed a significant decrease in triglyceride levels in the group who switched to NVP. In addition, the proportion of subjects with triglyceride levels > 400 mg/dL at the time of the switch diminished by 54.5% in the NVP arm and increased by 36.3% in the PI arm. Therefore, we conclude that a large proportion of patients with high triglyceride serum levels on PI regimens do benefit from switching to NVP.

The effect of the switch on serum total cholesterol levels has also been found to vary in different studies. Some have shown significant decreases [8–12] while others have not shown any difference [6,7]. Our results did not show any significant difference after the switch either in total serum cholesterol or in the HDL and LDL fractions. These conflicting results leave the effect on cholesterol levels inconclusive.

Little information is available in simplification studies about lipoatrophy, in part because of the difficulty in assessing this complication. Although anthropometric measurements and imaging techniques, such as dual-energy x-ray absorptiometry (DEXA), have been used in assessing lipodystrophy, they are difficult to perform or not easily available in most institutions and their results are conflicting; so self-reporting of body shape changes by patients is still a valid, and probably the most realistic, method for measuring these alterations. Three previous studies showed no anthropometric changes after the switch to NVP [8,9,13] and two detected, in half of the patients, partial amelioration or subjective improvements [6,9]. In our study, lipoatrophy, measured by patients self-reporting body shape changes, decreased by 4% in patients who switched to NVP, whereas it increased by 15% in the PI group. It is interesting to note that, in the NVP group, there were 20% more patients on stavudine than in the PI group. This suggests that the withdrawal of the PI diminishes the risk of lipoatrophy in spite of maintaining stavudine.

Adherence to therapy is possibly the most important factor for treatment success [17]. In this study, adherence was good in both arms, as in many other similar studies. However, the effort to stay on treatment was significantly lower in the patients who switched to NVP. Greater effort in taking the treatment has been associated with lower adherence to treatment in the long term [18].

We conclude that switching from PI to NVP was as effective as continuing with PI for maintaining viral control, even in patients with baseline VL above 100 000 copies/mL. In addition, a reduction in hypertriglyceridaemia, toxic effects, self-reported body shape changes and effort to stay on treatment was observed in the NVP group.

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