Efficacy and safety of once-daily combination therapy with didanosine, lamivudine and nevirapine in antiretroviral-naive HIV-infected patients

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Background: Simplified antiretroviral regimens are needed to improve patient adherence and quality of life. The purpose of this study was to evaluate the efficacy and safety of a once-daily regimen consisting of didanosine (ddI), lamivudine (3TC) and nevirapine (NVP) for adult antiretroviral-naive patients with HIV-1 infection.

Methods: This was a prospective, one-arm, multicentre pilot study. Daily drug dosage was 250 or 400 mg didanosine, 300 mg lamivudine and 400 mg nevirapine. The primary outcome measure was the percentage of patients with a plasma HIV-RNA level <50 copies/ml at 12 months on an intention-to-treat (ITT) basis.

Results: Seventy patients were enrolled in the study. At baseline, mean plasma HIV-1 RNA was 5.10 log10 copies/ml, and mean CD4 cell count was 262 cells/µl. At month 12, 67% (95% CI: 56–78) of patients maintained a viral load of <50 copies/ml in the ITT analysis and CD4 counts increased a median of 201 cells/µl. The treatment was more effective in patients with baseline CD4 counts >100 cells/µl than in those with a poorer immunological status at baseline, although the number of patients with CD4 counts <100 was low. Four patients died during the study period. Therapy was discontinued in 18 patients due to virological failure in 11, adverse events in seven, loss to follow-up or withdrawal of consent in four and death in one. Eight out of nine patients with available genotype after virological failure showed resistance mutations to NVP (Y181C and others) and 3TC (M184V/I), and four of them also had ddI resistance (L74V). The lipid profile was favourable, with a decrease in the ratio of total-to-high density lipoprotein cholesterol.

Conclusion: A once-daily combination of ddI, 3TC and NVP seems to be an effective, safe and easy-to-take regimen in antiretroviral-naive patients, at least in those who do not have severe immunodepression at baseline.


Introduction

Antiretroviral therapy (ART) has proved to be very effective in suppressing viral load and improving clinical outcome in patients with HIV infection. However, the virus cannot be eradicated and the current goal of ART is to achieve sustained suppression of viral replication using a combination of potent antiretroviral agents that has to be maintained indefinitely [1]. The efficacy of current ART is high when adherence is optimal, as has been demonstrated with directly observed treatments [2]. However, treatment failure rates of 20–50% have been reported in clinical practice within the first year of triple-drug therapy [3]. Lack of adherence and toxicity are the most important factors related to these high rates of virological failure [4]. It seems reasonable to suppose that a well-tolerated regimen in which the drugs can all be administered in one daily dose would optimize adherence to treatment and thereby improve viral suppression. Moreover, once-daily ART has potential advantages for use as directly observed therapy or as first-line therapy in patients with hectic lifestyles. In fact, administration of ART once daily is creating extraordinary interest...
among members of the scientific community and also among those who receive the therapy [5–9].

Since the introduction of highly active ART (HAART), the number of drugs that can be administered once daily has grown. Didanosine (ddI), which was initially administered twice daily, has undergone notable pharmaceutical modifications that have enabled it to be administered in one daily capsule, with much better tolerance than the former buffered tablets [10,11]. Lamivudine (3TC) was marketed for administration at 150 mg twice daily. It was later demonstrated that this dose was equivalent to 300 mg once daily, and the drug was then produced in 300 mg tablets [12]. Nevirapine (NVP) has not yet been approved for once-daily administration, but some pharmacokinetic and clinical studies have shown the feasibility of a once-daily schedule [10,13,14].

In this study, we evaluated the efficacy and safety of a once-daily regimen consisting of ddI, 3TC and NVP in ART-naive patients with HIV-1 infection.

**Materials and methods**

**Study population**

Between October 2001 and September 2002, 70 consecutive ART-naive subjects were recruited from the outpatient clinics of five different hospitals in Catalonia, Spain, for participation in the study.

Eligible patients were adults (>18 years old) with laboratory-documented HIV-1 infection, in whom ART was indicated according to Spanish guidelines [1] and who had never received ART. There were no restrictions in CD4 cell count or HIV viral load for enrollment in the study. Many of the common exclusion criteria used in clinical trials, such as active opportunistic infection in the previous 3 or 6 months, CD4 cell count <50, <100 or <200/µl, and alterations in transaminases and other laboratory parameters were not applied; hence our patients were representative of a treatment-naive patient population beginning ART.

The study protocol was approved by the institutional review boards of all the participating centres and written informed consent was obtained from all patients.

**Trial design**

This was an exploratory, prospective, open-label, one-arm, multicentre, clinically based cohort study in which all the patients received the following three drugs once daily in the morning before breakfast: ddI (250 or 400 mg enteric coated capsules) at 250 mg daily for patients weighing <60 kg and 400 mg daily for those weighing 60 kg or more; 3TC (150 mg tablets initially, changed to 300 mg tablets when available) at 250 mg daily; 400 mg enteric coated capsules) at 250 mg daily for those weighing <60 kg and 400 mg daily for those weighing 60 kg or more; 3TC (150 mg tablets initially, changed to 300 mg tablets when available) at

Follow-up, assessments and endpoints

Clinical and laboratory evaluations were performed at baseline and at months 1, 3, 6, 9 and 12. Baseline assessment included demographic data and previous AIDS-defining diseases according to the CDC classification 1993. All patients underwent medical history taking and physical examination, determination of CD4 cell count and HIV RNA (lower limit of quantification, 50 copies/ml) and analyses of routine clinical and laboratory parameters (hematology, liver and kidney function tests, blood lipids and amylase). Patients were in a fasting state for blood collection. Adverse events were graded in severity according to the World Health Organization (WHO) toxicity grading scales. Isolated rises in γ-glutamyl transferase were not considered indicative of hepatotoxicity because they reflect only enzyme induction caused by NVP. For all patients stopping treatment, the reason and time of treatment cessation were recorded. All adverse drug reactions were documented.

Self-reported adherence was investigated at each study visit by a validated questionnaire [simplified medication adherence questionnaire (SMAQ)] [15]. The need for strict adherence was emphasized at each study visit. Health-related quality of life was assessed using the EuroQol technique [16]. Subjects recorded their perception of overall health-related quality of life in a visual analogue scale ranging from 0–100, with 0 denoting the worst imaginable health state and 100 denoting the best imaginable health state.

The primary endpoint of the study was the percentage of subjects with therapeutic success (viral load ≤50 copies/ml) at month 12 on the basis of the intention-to-treat, non-complete (missing or switch) equals failure (ITT, nc=f) population. Therapeutic failure was defined as a plasma HIV-RNA level >50 copies/ml (confirmed by a second viral load determination) and/or discontinuation of the study therapy for any reason (adverse events, death, consent withdrawal or loss to follow-up). Patients missing two consecutive scheduled visits were considered dropouts.

Secondary outcome measures included virological efficacy according to on-treatment (OT) analysis, percentage of subjects who maintained a plasma HIV-RNA level of <500 copies/ml at month 12 in the ITT and OT analyses, immunological response (mean change in CD4 cell counts), occurrence of adverse events and percentage of patients who discontinued the treatment.
Statistical analysis
Statistical analyses were performed with SPSS for Windows (v12.0; SPSS Inc, Chicago, Il, USA). For quantitative variables, the means ±SD were used as measurements of central tendency and dispersion. The number of patients in each category and the corresponding percentages are given for qualitative variables. Between-group comparisons were made with the chi-square test or Fisher’s exact test for categorical variables, the t-test or the Mann–Whitney test for unpaired quantitative variables and the paired t-test or the Wilcoxon rank sum test for paired quantitative variables. All reported P values were 2-sided, and a value <0.05 was considered statistically significant. Bonferroni’s method was used to adjust the definition of significance for multiple comparisons.

Results
Baseline characteristics
Seventy consecutive patients were enrolled in the study. None were excluded from the analysis. Baseline demographic characteristics and biological values are summarized in Table 1. Seventeen patients had a clinical AIDS diagnosis at entry and 14 of them developed 16 AIDS-defining opportunistic diseases during the 3 months prior to starting ART (six wasting syndrome, five Pneumocystis jiroveci pneumonia, three Kaposi’s sarcoma, one cerebral toxoplasmosis and one non-Hodgkin lymphoma). The mean CD4 cell count was 262 ±184 cells/µl. Baseline CD4 cell counts were less than 100 cells/µl in 14 patients, between 100 and 200 cells/µl in 16 patients and more than 200 cells/µl in 40 patients. Mean plasma HIV-RNA level was 5.1 ±0.65 log10 copies/ml. Baseline plasma HIV-1 RNA viral load was >100 000 copies/ml in 29 patients and <100 000 copies/ml in 41 patients.

Efficacy
Figure 1 shows the disposition of the patients after 12 months of therapy. Treatment failed in 23 out of 70 patients because of virological failure in 11, discontinuation of treatment due to adverse events in seven, loss to follow-up or withdrawal of consent in four and death in one. Four patients died during the study period (two due to lymphomas diagnosed during the first month of therapy, one due to bacterial endocarditis and one due to bacterial pneumonia); however in three of them, treatment had failed previously because of virological failure in two cases and adverse effects requiring discontinuation of treatment in one case.

At month 12 of follow-up, 67% of the subjects (95% CI: 56–78) had a maintained a viral load of <50 copies/ml in the ITT analysis (Figure 2A). In the

Table 1. Demographic and baseline clinical and biological characteristics of HIV-infected patients enrolled in the study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>39 ±11</td>
</tr>
<tr>
<td>Sex, males</td>
<td>53 (76%)</td>
</tr>
<tr>
<td>HIV route</td>
<td></td>
</tr>
<tr>
<td>IDU</td>
<td>22 (31%)</td>
</tr>
<tr>
<td>Men who have sex with men</td>
<td>22 (31%)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>21 (30%)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>CDC Stage C</td>
<td>17 (24%)</td>
</tr>
<tr>
<td>Body weight, kg</td>
<td>67 ±10</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.7 ±3.2</td>
</tr>
<tr>
<td>CD4 cell count, cells/µl</td>
<td>262 ±184</td>
</tr>
<tr>
<td>CD8 cell count, cells/µl</td>
<td>1093 ±603</td>
</tr>
<tr>
<td>HIV RNA, log10 copies/ml</td>
<td>5.1 ±0.65</td>
</tr>
<tr>
<td>HCV-positive</td>
<td>26 (37%)</td>
</tr>
<tr>
<td>HBsAg-positive</td>
<td>5 (7%)</td>
</tr>
<tr>
<td>Haemoglobin, g/dl</td>
<td>13.3 ±1.1</td>
</tr>
<tr>
<td>White blood cell count, cells/µl</td>
<td>4964 ±2463</td>
</tr>
<tr>
<td>Platelets, cells/µl</td>
<td>191 ±68</td>
</tr>
<tr>
<td>AST, UI/l</td>
<td>50 ±46</td>
</tr>
<tr>
<td>ALT, UI/l</td>
<td>57 ±48</td>
</tr>
<tr>
<td>Alkaline phosphatase, UI/l</td>
<td>125 ±73</td>
</tr>
<tr>
<td>Amylase, UI/l</td>
<td>64 ±28</td>
</tr>
<tr>
<td>Total cholesterol, mg/dl</td>
<td>155 ±35</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>139 ±79</td>
</tr>
<tr>
<td>Glycaemia, mg/dl</td>
<td>95 ±26</td>
</tr>
</tbody>
</table>

Data are expressed in number (percentage) of patients or mean ±SD. Normal ranges: ALT and AST 10–40 UI/l, alkaline phosphatase 35–110 UI/l, amylase 10–75 UI/l, total cholesterol 130–220 mg/dl, triglyceride levels 40–200 mg/dl and glucose 75–115 mg/dl. ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CDC, Centres for Disease Control; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; IDU, intravenous drug user.

Figure 1. Disposition of the patients during the follow-up

*Four patients died during the study period, but in three, treatment had failed previously.
OT analysis, plasma viral load was <50 copies/ml in 80% of the subjects (95% CI: 69–90) (Figure 2A).

In the ITT analysis, 33%, 66%, 69%, 71% and 70% of patients maintained plasma viral load at <500 copies/ml at months 1, 3, 6, 9 and 12, respectively. In the OT analysis 36%, 75%, 80%, 85% and 83% of subjects maintained plasma viral load <500 copies/ml at months 1, 3, 6, 9 and 12, respectively.

Antiviral efficacy tended to be higher at month 12 in the stratum of patients with baseline HIV-1 RNA levels above 100 000 copies/ml than in patients with values below this level; however, differences were not statistically significant by either ITT nc=f analysis (P=0.21) or OT analysis (P=0.13) (Figure 2B).

Notable differences in antiviral efficacy were observed when patients were stratified according to baseline CD4 counts. The largest difference was found comparing patients with baseline CD4 above 100 cells/µl and those below this value (Figure 2C). The percentage of patients with HIV-1 RNA below 50 copies/ml at month 12 (ITT nc=f) was 77% (95% CI: 66–88) in patients with baseline CD4 cell counts of ≥100 cells/µl and 29% (95% CI: 5–53) in patients with baseline CD4 cell counts of <100 cells/µl (P=0.001, statistically significant with Bonferroni's correction) (Figure 2C). In the stratum of patients with baseline CD4 cell counts between 100 and 199 cells/µl, antiviral efficacy tended to be lower than in patients with ≥200 cells/µl; however, the difference was not significant (ITT nc=f, 69% compared with 80%, P=0.38).

After the start of treatment, there was a rapid reduction in HIV-1 RNA levels and a progressive increase in CD4 cell counts. Changes in plasma HIV RNA and CD4 cell counts are indicated in Figure 3.

It was possible to assess compliance with therapy in 63 patients. According to the SMAQ questionnaire, 53 patients (84.1%) were adherent and 10 (15.9%) were non-adherent. Five non-adherent patients (50%) and 12 adherent patients (19%) experienced treatment failure (P=0.07).

Genotypical analyses of plasma samples were obtained from nine out of 11 patients who experienced virological failure (Table 2). One non-adherent patient experienced failure with a wild-type virus. The other eight patients had isolates showing mutations associated with resistance to the study drugs. Resistance mutations to NVP (eight Y181C, four V108I, two K103N and two G190A) and to 3TC (M184V/I) were detected in all samples. Four samples also carried the L74V mutation associated with ddI resistance.

Safety and tolerability

Skin rash was the most common adverse event, appearing in 13 patients (18.6%), 10 men and three women (18.9% and 17.6%, respectively, P=1.0). NVP was permanently withdrawn because of moderate or severe rashes in five patients (7.1%), four men and one woman (7.5% and 5.9%, respectively, P=1.0). The remaining eight patients presented mild (seven patients) or moderate (one patient) rashes that did not require withdrawal of the drug. The patients received symptomatic treatment with antihistamines and/or corticosteroids and the rashes resolved without recurrence. Patients with a baseline CD4 cell count below or above 250/µl showed a similar incidence of rash (7/36=19.4% and 6/34=17.6%, P=1.0) and of treatment-limiting rash (2/36=5.6% and 3/34=8.8%, P=0.67) (Table 3).

Other clinical adverse events were methadone withdrawal symptoms in four cases, leading to interruption of NVP in one case, and gastric intolerance in one patient, in whom ddI was removed.

In six patients, biological toxicity could not be assessed because treatment was withdrawn before the first follow-up visit at 1 month of treatment. Six of the remaining 64 patients (9.3%) developed at least one episode of grade 3 or 4 (alanine aminotransferase or aspartate aminotransferase >5 x upper limit of normal) liver-associated toxicity, detected by laboratory analysis. However, none of them had symptoms of acute liver disease, and laboratory hepatic toxicity improved without treatment discontinuation. Hepatic toxicity was not associated with a skin rash in any of these six patients.

The metabolic profile (Figure 4) showed significant rises in total cholesterol, with a mean of 28% between baseline and month 12. There was an increase in both high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol. Mean plasma values of HDL and LDL cholesterol at month 12 were 46% and 16% higher than baseline values, respectively. The mean ratios between total cholesterol and HDL cholesterol were 4.4 ±1.7, 4.1 ±1.5, 4.0 ±1.5, 3.7 ±1.2, 3.6 ±1.2, and 3.5 ±1.1 at baseline and months 1, 3, 6, 9 and 12, respectively (decreases of 5%, 5%, 6%, 13%, and 12%, respectively; P<0.05 between baseline and months 9 and 12). There were no significant changes in fasting plasma triglycerides during the follow-up.

Plasma concentrations of glucose, urea and creatinine did not differ significantly from the beginning of treatment to month 12.

None of the patients had symptoms of acute pancreatitis. Three patients (4.7%) developed at least one episode of laboratory grade 3 pancreatic toxicity; none of the patients had grade 4 toxicity. Amylase levels improved without treatment discontinuation.

There were no signs or symptoms of haematological toxicity. On the other hand, some haematological disorders that were present at the baseline assessment improved with ART. Median plasma haemoglobin concentrations increased from 13.3 ±1.1 at baseline to...
Figure 2. Percentage of subjects who achieved plasma HIV RNA levels <50 copies/ml through to study month 12, according to an ITT nc=f analysis and an OT analysis.

(A) For all patients enrolled in the study. (B) For patients with baseline HIV-RNA above or below 100 000 copies/ml. (C) For patients with baseline CD4+ cell counts above or below 100 cells/µl. 100K = 100 000. ITT, intent-to-treat; incomplete=failure; OT, on treatment; VL, viral load.
The percentage of patients with anaemia (haemoglobin <11.0 g/dl in women or <12.0 g/dl in men) decreased from 13% at baseline to 2% at month 12. Total white blood cell, neutrophil and lymphocyte counts did not differ significantly from the start of treatment to month 12. Median platelet count increased from 191 ± 68 at baseline to 228 ± 93 cells/µl at month 12 (P<0.01). The percentage of patients with a low platelet count (<150 cells/µl) decreased from 26% at baseline to 13% at month 12.

The mean scores for health-related quality of life at baseline, month 6 and month 12 were 69 ± 17, 78 ± 15 and 85 ± 12, respectively. Differences were significant between baseline and month 6 (P=0.002), between baseline and month 12 (P<0.001), and between month 6 and month 12 (P=0.018).

**Discussion**

The capacity of ART to suppress HIV replication is linked to the potency of the antiretroviral regimen, but also to the patient’s adherence to the prescribed treatment [2,4]. Once-daily therapeutic combinations with a small number of pills can improve adherence and therapeutic success [3,4]. For the regimen used in this study, we chose a single daily dose of ddI and 3TC as the nucleoside analogue combination. There is considerable experience with this combination, which shows elevated efficacy and little toxicity [17–20]. For the third drug we chose NVP. NVP-containing regimens are effective in ART-naive patients, producing a durable virological and immunological response [21]. In the Spanish guidelines for 2004, the combination of ddI, 3TC and NVP is considered one of the preferred treatment regimens for naive patients [1]. A pharmacokinetic study has suggested that NVP can be administered once daily [13], and some clinical trials have shown similar efficacy with once- and twice-daily schedules [10,14]. There is no previous clinical experience regarding administration of NVP in full once-daily therapeutic regimens in ART-naive patients.

The results of this study suggest that a once-daily regimen of ddI, 3TC and NVP is effective in ART-naive subjects. According to the ITT analysis, 67% of all patients and 77% of patients with a baseline CD4 cell count higher than 100 cells/µl showed viral suppression to <50 copies/ml after 12 months of therapy.
data on regimens that can be administered once daily showed the following proportions of patients achieving <50 copies/ml at month 12: 77–83% for ddI, 3TC or emtricitabine and efavirenz (EFV) [17–20,22,23]; 77–82% for tenofovir, 3TC and EFV [24,25]; and 64–76% for abacavir, 3TC and EFV [26–29]. However, most of these studies have more restrictive exclusion criteria than those we used, making the present study more representative of common clinical practice. Some studies exclude patients with a baseline CD4 cell count of <200 cells/µl [20,22]. In addition, some studies allow a change from EFV to nelfinavir [23] or NVP [24] because of toxicity, without considering this change therapeutic failure. The dissimilar criteria used for inclusion and exclusion in the studies makes it difficult to compare the efficacy of the various therapeutic regimens described. In the randomized 2NN trial, the difference in the percentage of patients with treatment failure between NVP twice daily and EFV was not significant (5.9%, 95% CI: –0.9 to 12.8); however the twice daily NVP arm failed to demonstrate non-inferiority to the EFV arm.

Virological failure was seen mainly in patients with baseline CD4 cell counts of <100 cells/µl. In this stratum, only 29% of patients showed therapeutic success at month 12. Nevertheless, the number of patients in the study with this baseline immunological status was small, hence this result should be interpreted with caution. Moreover, half these patients (seven out of 14) had presented AIDS-defining opportunistic diseases during the 3 months prior to starting ART, a factor that could have contributed to their poor evolution. In a retrospective study including 118 naive patients initiating HAART including NVP and with baseline CD4 cell counts <200 cells/µl, 54% of patients had less than 50 copies/ml at 12 months in the ITT analysis [30]. The importance of a low CD4 count as a predictor of poor virological outcome has been stated in many studies, using a variety of drug combinations [17,31]. The baseline viral load shows a much weaker relationship with virological evolution than CD4 lymphocyte count. We found that treatment tended to be more effective in patients with a baseline viral load below 100 000 copies/ml, but differences were not significant. A meta-analysis showed that baseline viral load does not affect virological outcome in ART-naive HIV-infected patients treated with NVP-containing regimens [32]. In the 2NN study, a higher probability of treatment or virological failure was found in patients with a high baseline viral load [14]. The magnitude of the difference observed between patients with high and low baseline viral loads was similar to that found in the present study, but because of the large number of patients in the 2NN study, the result was statistically significant.

One drawback of the regimen may be the high level of genotypical resistance in patients with virological failure. Mutations conferring resistance to NVP (Y181C and others) and to 3TC (M184V/I) were observed in eight out of nine patients with an available resistance test, four of whom also had associated ddI resistance (L74V). In Spain, the frequency of mutations conferring antiretroviral resistance is low in naive individuals and it is likely that the majority of mutations observed in our patients with virological failure developed with the treatment. Unfortunately, we do not have basal resistance studies to assure that baseline genotypes were wild-type, and that primary resistance mutations could not explain virological failure in some patients.

In the present study, the patients reported a high level of treatment adherence, and the trend toward better therapeutic response in adherent compared with non-adherent subjects was not statistically significant. The treatment was easy to take and the perception of health during therapy improved. All these characteristics indicate that any patient would benefit from this therapeutic regimen, but the benefit could be greater in patients whose lifestyle makes it difficult to set routines, or patients who, for social or psychological reasons, need the support of third parties to reinforce or guarantee adherence to treatment. This once-daily regimen with ddI, 3TC and NVP has been previously administered to 70 intravenous drug users. The
majority of patients were using methadone or polamidone and many had received a range of antiretroviral agents prior to enrollment. In approximately half of the patients, therapy discontinuation was recorded because of a loss to follow-up or adverse events (rash, methadone/polamidone withdrawal syndrome, etc). Despite the expected high dropout rate in this population, the regimen appeared to be effective on an OT basis [33].

The study regimen was generally well tolerated. There was no evidence indicating that the drugs contributed to any new or unexpected adverse clinical manifestations. The most common adverse event was a skin rash, which occurred in 19% of patients and led to permanent discontinuation of NVP in 7% of patients. This incidence is within the reported range, which varies from 7–32%, and it led to drug discontinuation in approximately 4–10% of patients [34,35], without significant differences when NVP was administered once or twice a day [10,14,36]. We found no differences in the frequency of rash between women and men, a finding identical to that reported in controlled clinical trials in which the primary endpoint was the development of a rash [34,35]. In three retrospective studies, a much higher incidence of rash was seen in women than in men [37–39].

Although many of our patients were coinfected with hepatitis C or hepatitis B virus (37% and 7%, respectively), biological grade 3 or 4 hepatotoxicity was only observed in six (9%) patients and none of them required discontinuation of therapy for this reason. The frequency of hepatic laboratory abnormalities was similar to rates reported in clinical studies, in which about 5–10% of HIV-positive patients treated with NVP had grade 3 or grade 4 hepatotoxicity [40]. The majority of these liver enzyme elevations are asymptomatic. Nevertheless, cases of severe hepatic failure have been reported, particularly in pregnant and nonpregnant women with high CD4 cell counts and in non-HIV-infected patients taking NVP for postexposure prophylaxis, and were mainly associated with rash (hypersensitivity syndrome) [41]. In the 2NN study, patients assigned to NVP once daily had a slightly higher frequency of hepatic laboratory abnormalities than those assigned to take the drug twice daily, although clinical hepatotoxicity was similar [14].

The lipid profile in our patients was favourable. In approximately half of the patients, therapy discontinuation was recorded because of a loss to follow-up or adverse events (rash, methadone/polamidone withdrawal syndrome, etc). Despite the expected high dropout rate in this population, the regimen appeared to be effective on an OT basis [33].

In summary, our study shows that a once-daily combination of ddI, 3TC and NVP can be an effective, safe and easy-to-take regimen in ART-naive patients, at least in those who are not severely immunodpressed. These encouraging exploratory results require confirmation in comparative trials.

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References


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