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Published in:
The Journal of Infectious Diseases

DOI:
10.1086/514002

Link to publication

Citation for published version (APA):
de Jong, M. D., Vella, S., Carr, A., Boucher, C. A. B., Imrie, A., French, M., ... Reiss, P. (1997). High-dose nevirapine in previously untreated human immunodeficiency virus type 1-infected persons does not result in sustained suppression of viral replication. The Journal of Infectious Diseases, 175, 966-970. DOI: 10.1086/514002

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High-Dose Nevirapine in Previously Untreated Human Immunodeficiency Virus Type 1–Infected Persons Does Not Result in Sustained Suppression of Viral Replication


High-dose nevirapine treatment has been reported to confer sustained antiretroviral effects, despite a rapid development of resistance. The use of this strategy was evaluated in 20 previously untreated human immunodeficiency virus type 1 (HIV-1) p24 antigenemic persons with CD4 cell counts between 100 and 500/mm$^3$. Treatment consisted of 400 mg of nevirapine, after a 2-week lead-in dose of 200 mg. Rash was the most frequently reported adverse event, occurring in 25%. While sustained declines in p24 antigen levels were observed in the majority, serum HIV-1 RNA load and CD4 cell counts returned to baseline values within 12 weeks in virtually all subjects. The resistance-conferring tyrosine-to-cysteine substitution at reverse transcriptase position 181 was detected after 4 weeks in most subjects. These observations suggest that plasma drug levels attained with high-dose nevirapine were not sufficient to inhibit nevirapine-resistant virus, although they were $\approx 2$-fold higher than reported IC$_{50}$ values of resistant virus.

Treatment with nevirapine, a nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT), results in potent antiretroviral effects [1]. However, at dosages up to 200 mg/day, these effects are transient because of a rapid development of nevirapine resistance [1, 2], which is not prevented by concomitant or alternating treatment with zidovudine [1–3].

Theoretically, sustained antiviral activity despite the development of resistance could be achieved by the attainment of active drug levels exceeding concentrations that inhibit drug-resistant virus in vitro. A recent study of nevirapine at a high dose of 400 mg/day in antiretroviral-experienced patients with advanced HIV disease indeed showed sustained reductions in serum p24 antigen levels and HIV-1 RNA load [4]. In the present study, we evaluated the same principle of treatment with nevirapine in previously untreated, predominantly asymptomatic HIV-1–infected persons.

Patients and Methods

Study population and treatment. Previously untreated HIV-1 p24 antigenemic (\(\geq 25 \text{ pg/mL}\)) patients with CD4 lymphocyte
counts between 100 and 500/mm³ were treated with nevirapine at a single daily dose of 400 mg, after a 2-week period of treatment with a daily dose of 200 mg. This lead-in dose was aimed at reducing the incidence of rash, which is a major dose-limiting toxicity of high-dose treatment [4, 5]. The study period was 28 weeks. The addition of nucleoside analogue therapy was allowed beyond 6 weeks of treatment, if p24 antigen levels returned to baseline values.

**Clinical and laboratory evaluation.** Patients were evaluated weekly up to week 4, biweekly up to week 8, and monthly thereafter. At each visit, blood was collected for assessment of hematology, chemistry, serum p24 antigen level, and lymphocyte subset enumeration. Serum p24 antigen levels were measured in real time using the Abbott Enzyme ImmunoAssay and quantitation panels (Abbott, Abbott Park, IL). Immune complex–dissociated (ICD) and non-ICD p24 antigen levels (pg/mL) were measured in stored serum obtained at screening and at weeks 0, 4, 12, and 28 for the whole study group and at all time points in a subset of 4 subjects [6]. The relative amounts of HIV-1 RNA containing the nevirapine resistance–conferring tyrosine-to-cysteine substitution at RT position 181 were measured at baseline and at weeks 4 and 12, using a primer-guided nucleotide incorporation assay [7]. Trough plasma nevirapine levels were measured in stored plasma [8].

**Results**

**Study population.** Twenty previously untreated p24 antigenemic men were enrolled. Baseline characteristics are shown in table 1. Fifteen patients completed 28 weeks of treatment. Zidovudine was added to treatment of 4 of these patients at weeks 8, 16, and 24, respectively. Four patients discontinued treatment prematurely because of adverse events, and 1 patient was lost to follow-up at day 141. Treatment interruptions of >1 week occurred in 3 of 15 subjects who completed the study period (duration 10, 12, and 58 days). In 2 of these, nevirapine was initially reinstituted at a reduced dose for a period of 19 and 33 days, respectively.

**Adverse events.** Frequently reported nevirapine–associated adverse events were rash and fever, frequently coincident, occurring in 25% and 20% of patients, respectively. Four patients discontinued treatment because of adverse events. One patient experienced a mild rash during the lead-in period, which progressed to Stevens-Johnson syndrome on dose escalation. One patient experienced a severe rash with fever, facial edema, and elevations of plasma transaminase levels during the lead-in period. Recovery was complete in both patients after therapy withdrawal. A third patient developed a rash with mouth ulcers on day 24, which resolved after interrupting treatment but immediately worsened on re-initiation. The fourth patient discontinued therapy at day 98 because of persistent elevations of transaminase levels.

**Plasma nevirapine levels.** Plasma nevirapine levels were sequentially measured in 19 of 20 subjects while receiving study drug. During the lead-in period, mean trough levels were 12.8 ± 4.9 μM and 10.9 ± 3.8 μM at weeks 1 and 2, respectively. On dose escalation, average trough nevirapine levels increased, ranging from 14.7 ± 4.9 to 18.5 ± 7.9 μM. Of note, in the 2 subjects developing a severe rash early during treatment, nevirapine levels during the lead-in period ranked second and third highest. Nevirapine levels were not measured in the third subject who discontinued treatment because of a rash.

**Immunologic and virologic responses.** The number of CD4 lymphocytes increased sharply during the first week of treatment but returned toward baseline values at subsequent weeks (figure 1A).

A rapid reduction of ICD and non-ICD p24 antigen levels was observed in virtually all patients and was sustained throughout the 28-week study period in the majority of subjects who continued treatment (figure 1B). When only considering the 11 subjects who were treated with nevirapine alone for the complete study period, a median decline of 59% (range, 8%–94%) was still observed after 28 weeks.

Changes in HIV-1 RNA load were measured in 18 subjects. A mean decline of 0.46 ± 0.47 log RNA copy numbers was observed after 4 weeks of treatment, with a return to baseline values within 12 weeks (figure 1C). In only 1 subject, a sustained reduction at weeks 12 and 28 was observed (0.54 and 0.58 log, respectively), after a maximum decline of 1.34 log at week 4. Of note, nevirapine levels in this subject were relatively low (range, 5.3–12.4 μM).

In the subgroup of 4 subjects in whom RNA load was measured at all time points, maximum declines of 1.45–1.72 logs (mean, 1.52 ± 0.19 log) were invariably observed during the first 2 weeks of treatment (figure 1C). During subsequent weeks, virus load resurred in these subjects and reached baseline values within 6 weeks of treatment.

**Proportions of 181 cysteine-variant HIV-1 RNA.** The relative amounts of 181 cysteine-variant HIV-1 RNA were measured...
Figure 1. A. Mean changes in CD4 lymphocyte counts ± SE; B, median percentage changes in immune complex–dissociated (ICD) (□) and non-ICD (●) p24 antigen levels; C, mean changes in log HIV-1 RNA load ± SE in all subjects (●) and in a subgroup of 4 patients (−). Baseline values are defined as measurements at week 0 only, to avoid influence of regression to mean effects [9]. Numbers in lower part of each graph indicate number of subjects tested at each time point.
sured at weeks 0, 4, and 12 in 15, 15, and 13 subjects, respectively. In none of the subjects was 181 cysteine-variant RNA detectable at baseline. After 4 and 12 weeks of treatment, a 100% 181 cysteine-variant RNA population was detected in 5 of 15 subjects and 3 of 13 subjects, respectively, while a fully 181 wild type population was observed in 4 of 15 and 6 of 13 subjects, respectively. In the remaining subjects, percentages of 181 cysteine-variant virus ranged from 25% to 95% at week 4 and from 14% to 81% at week 12.

In the 2 patients who added zidovudine to nevirapine treatment at week 8, 181 cysteine-variant populations of, respectively, 100% and 95% at week 4 were reverted to a fully 181 wild type tyrosine population at week 12. The subject with a sustained RNA load decline harbored a 55% 181 cysteine-variant virus population at week 12.

Discussion

The initially potent activity of nevirapine at dosages up to 200 mg/day has encouraged research into strategies to delay or circumvent the development of drug resistance, thereby sustaining antiviral activity [1, 3]. In theory, the consequences of drug resistance could be circumvented by the attainment of effective drug levels exceeding concentrations that inhibit drug-resistant virus in vitro. In a recent study of high-dose nevirapine treatment in antiretroviral-experienced patients with advanced HIV disease, sustained reductions in p24 antigen and HIV-1 RNA levels were indeed observed [4].

In the present study, the same principle of treatment was evaluated in previously untreated, predominantly asymptomatic HIV-1–infected persons. Although this study confirms that high-dose nevirapine results in sustained p24 antigen reductions in the majority of patients, declines in serum HIV-1 RNA load were transient in all but 1 of the patients, similar to what has been observed during treatment at lower doses [1]. As in the previous study [4], increases in CD4 lymphocyte counts were also transient and, in our study, mirrored the changes in RNA load.

Previous studies have unequivocally shown a rapid emergence of highly drug-resistant virus during nevirapine treatment, regardless of the initial CD4 cell count, virus load, or nevirapine dose [1–3, 10]. Although drug susceptibilities were not assessed, it thus seems most likely that the loss of HIV-1 RNA load suppression in our study is due to the development of drug resistance, which is substantiated by the detection of RT codon 181 cysteine-variant virus in the majority of our patients. As previously reported, alternative resistance-conferring mutations are found in a proportion of nevirapine-treated patients [2], which may have accounted for the absence of 181 variant virus in some of our patients.

Although Havlir et al. [4] concluded that the development of nevirapine resistance can no longer be equated with therapeutic failure, this conclusion appeared to be largely based on the observed sustained declines in p24 antigen levels. On the basis of p24 antigen responses, our conclusion would have been identical. However, at least in previously untreated asymptomatic persons, this conclusion does not seem to hold true when considering the responses in HIV-1 RNA load. This suggests that, although plasma levels were of a similar magnitude as in Havlir’s study (i.e., ~2-fold higher than reported IC50 values of resistant virus) [4], they do not seem sufficient to overcome nevirapine-resistant virus. Of note, trough nevirapine levels were, in fact, relatively low in the only subject who showed a sustained decline in HIV-1 RNA load.

The cause of the discrepancy between responses in HIV-1 RNA load and p24 antigen levels, which has also been observed in other antiretroviral studies [11, 12], remains unclear and requires further research. High levels of anti-core antibody appear to interfere with p24 antigen detection, even after immune complex dissociation of p24 antigen [13]. It can be hypothesized that during the period of maximal suppression of viral replication, an excess of anti-core antibodies is attained, which captures circulating p24 antigen for extended periods of time. However, we qualitatively measured anti-core antibodies (Abbott HIVAB p24 EIA) at weeks 2 and 24 in 4 subjects and did not observe a clear pattern in the relationship between anti-core antibody status and p24 antigen levels (data not shown), which argues against this hypothesis.

An alternative hypothesis for the discrepancy is that nevirapine-induced changes in the virus result in a more efficient production of intact virions, reflected by a decreased production of circulating free p24 antigen. Finally, the mere presence of nevirapine in serum may have a direct negative influence on the performance of the p24 antigen assay, resulting in the inadvertent measurement of low p24 antigen levels. An observation that would favor this hypothesis is that the discrepancy between p24 antigen and HIV-1 RNA responses seems unique to high-dose nevirapine treatment and is not observed at lower doses [1].

Overall, high-dose nevirapine was well tolerated in our patients, as has been reported in larger studies using the same dose-escalation schedule for nevirapine administration [14, 15]. Although severe rashes were observed in 2 patients, these rashes occurred during the low-dose lead-in period. Of note, these 2 cases were associated with exceptionally high nevirapine levels during this lead-in period. The development of Stevens-Johnson syndrome in 1 of these patients might have been prevented if the dose had not been escalated after onset of the rash.

In conclusion, high-dose nevirapine monotherapy does not result in sustained antiviral effects in previously untreated patients. However, the initial suppression of viral replication is substantial. Further attempts to achieve sustained effects by using nevirapine in combination with multiple other antiretroviral drugs may prove worthwhile. Indeed, the addition of nevirapine and didanosine to existing zidovudine treatment shows promising antiviral effects [14], while preliminary results indicate that in previously untreated patients, this particular triple
combination provides even greater benefits and may even prevent the development of nevirapine resistance [15].

References