Plasma Nevirapine Levels and 24-Week Efficacy in HIV-Infected Patients Receiving Nevirapine-Based Highly Active Antiretroviral Therapy with or without Rifampicin

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Bamrasnaradura Infectious Diseases Institute and the Ministry of Public Health approved the study.

Materials and methods. The study design was a prospective cohort study involving 140 Thai HIV-infected patients (70 patients per group) in the Bamrasnaradura Infectious Diseases Institute. Enrollment was from November 2004 to March 2005. Inclusion criteria for both groups were as follows: (1) HIV-infected individuals ≥15 years old, (2) a CD4+ cell count of <350 cells/mm³, and (3) a willingness to participate and provide a consent form. Additional inclusion criteria for the NVP-RFP group were as follows: (4) having a diagnosis of active tuberculosis and (5) receipt of a rifampicin-containing antituberculous regimen ≥1 month prior to enrollment. An additional inclusion criterion for the NVP group was as follows: (4) not having received rifampicin within 1 month prior to enrollment. Exclusion criteria for both groups were as follows: (1) receipt of previous HAART, (2) being pregnant, (3) receipt of a medication that has drug-drug interactions with nevirapine or rifampicin, and (4) having aspartate aminotransferase and alanine aminotransferase levels >5 times the upper limit of the normal range. The institutional ethics committees of the Bamrasnaradura Infectious Diseases Institute and the Ministry of Public Health approved the study.

The dosage of rifampicin was 450 mg per day for patients...
with a body weight ≤ 50 kg and 600 mg per day for patients with a body weight > 50 kg. The patients had follow-up visits at 2, 4, 8, 12, 18, and 24 weeks after initiation of therapy, at which time they were assessed clinically and evaluated for adverse events. After 8 and 12 weeks of HAART, blood samples were obtained from patients 12 h after they were observed to have taken a dose to analyze nevirapine levels at the HIV Netherlands-Australia-Thailand Research Pharmacokinetic Laboratory (Bangkok, Thailand) by high performance liquid chromatography assay.

Power and Sample Size, version 1.01 (Dupont and Plummer), was used to calculate sample size by testing for equivalence of plasma nevirapine level. The equivalence of plasma nevirapine level was a difference of < 1 mg/L between the plasma nevirapine levels of the 2 treatment groups. The probabilities of committing type I and type II errors were 0.05 and 0.20, respectively. The estimated loss of patients to follow-up was 15%. Sample size needed for the study was 140 patients. Mean (± SD) or median (interquartile range) and frequency values were used to describe patients’ characteristics for continuous and categorical data, respectively. A Mann-Whitney test was used to compare plasma nevirapine levels between groups. A χ² test was used to compare the number of patients with a plasma nevirapine level < 3.4 mg/L and the number of patients who achieved an undetectable HIV RNA level between groups. A P value < 0.05 was considered to be statistically significant. All analyses were performed using SPSS software, version 11.5 (SPSS).

Results. A total of 140 patients (70 patients per group) were eligible and enrolled to receive 30 or 40 mg of stavudine, 150 mg of lamivudine, and 200 mg of nevirapine every 12 h. During the first 2 weeks, all patients received a lead-in dosage of 200 mg of nevirapine once daily prior to escalation to 200 mg twice daily. The NVP-RFP group had a higher proportion of male patients (80% vs. 56%; P = .002) and patients with a younger age (mean age [± SD], 34.4 ± 6.2 vs. 37.2 ± 8.7 years; P = .028) than the NVP group. The other baseline characteristics, including body weight, body mass index, baseline CD4+ cell count, baseline HIV RNA level, and baseline liver function test results, were similar between the 2 groups (P > .05). Both study groups had very low CD4+ cell counts (median count [interquartile range], 29 cells/mm³ [14–79 cells/mm³]) and the average body weight was ~54 kg.

The distributions of the median plasma nevirapine levels between the 2 treatment groups are shown in figure 1. Mean (± SD) plasma nevirapine levels at weeks 8 and 12 were 5.40 ± 3.53 mg/L for the NVP-RFP group and 6.56 ± 3.11 mg/L for the NVP group (P = .048). At 8 weeks, 29.7% of patients in NVP-RFP group and 6.8% of patients in NVP group had nevirapine levels < 3.4 mg/L (P = .001). At 12 weeks, 27.4% and 8.5% of patients in the corresponding patient groups had nevirapine levels < 3.4 mg/L (P = .020). Most patients who had a plasma nevirapine level < 3.4 mg/L at week 8 still had a plasma nevirapine level < 3.4 mg/L at week 12.

A multiple linear regression analysis was performed that included the following factors: sex, age, body weight, and whether receipt of rifampicin indicated that receipt of rifampicin was a significant predictive factor of plasma nevirapine level (P = .018). The proportions of patients who had a plasma HIV RNA level of < 50 copies/mL were not different between the NVP-RFP and NVP groups, with respect to the intent-to-treat analysis (72.9% vs. 65.7%; P = .464) and the on-treatment analysis (87.9% vs. 82.1%; P = .388). There was no significant difference in CD4+ cell count at 24 weeks (P = .667) and plasma alanine aminotransferase level at 8 and 12 weeks of HAART (P = .647) between the 2 groups. The incidence (7.0%) of nevirapine-associated skin rashes in the NVP-RFP group was not different from that in the NVP group (8.6%; P = 1.000).

Discussion. In the present study, we have shown that the trough plasma nevirapine level was reduced by 17.7% with concomitant administration of nevirapine and rifampicin. Despite reduction in nevirapine levels produced by rifampicin, the
majority (>70%) of trough plasma nevirapine levels in the NVP-RFP group are still higher than the recommended trough nevirapine level (>3.4 mg/L). Our cohort study demonstrates that HIV-infected patients who concurrently receive nevirapine and rifampicin have a comparable short-term virological and immunological response.

Among 17 patients in NVP-RFP group who had trough plasma nevirapine levels <3.4 mg/L, 14 (82.4%) of 17 patients had achieved an undetectable plasma HIV RNA level (<50 copies/mL) after 24 weeks of nevirapine-based HAART. This may be explained by the data demonstrating that nevirapine has a high therapeutic index. With the standard dose of nevirapine (400 mg per day), the mean (± SD) minimum plasma level in a steady state is 6.56 ± 3.11 mg/L, which is much greater than the usual IC_{50} for this drug (0.0025–0.025 mg/L) [9]. Nevertheless, long-term virological and immunological outcomes of these patients need to be monitored.

In the present study, we also have shown that the incidences of elevated alanine aminotransferase level and nevirapine-associated skin rashes are not higher among patients taking rifampicin with nevirapine. However, this should be interpreted with caution. The sample size may not be large enough to detect the difference of a relatively low incidence of this adverse event. A retrospective study shows that the administration of antituberculous drugs with nevirapine is predictive of clinical hepatitis and skin rashes [10]. Thus, the concurrent administration of nevirapine and rifampicin should be closely monitored.

Nevirapine-based HAART is a common regimen that is widely used for treatment of HIV-infected patients in resource-limited countries because of its affordability. In addition, nevirapine is also recommended for use in 2 of the 4 World Health Organization–recommended generic combinations for the treatment of HIV-infected patients in resource-limited countries [11]. Until the other options are more accessible, nevirapine-based HAART is still a key regimen to scale up treatment of HIV-infected patients in resource-limited countries. The results from the present study may support the recent guideline [12] and provide additional data regarding efficacy and safety to support the physicians’ use of nevirapine-based HAART for the concomitant treatment of HIV-infected patients with tuberculosis who are receiving rifampicin.

In conclusion, HIV-infected patients who concurrently receive nevirapine and rifampicin have lower plasma nevirapine levels. However, the incidence of adverse events and short-term virological and immunological outcomes are similar between the 2 groups. A HAART regimen containing nevirapine-based HAART may be suitable for patients with HIV infection and active tuberculosis, particularly in resource-limited countries. However, additional studies of long-term virological and immunological outcomes and a re-evaluation of the appropriate therapeutic level of nevirapine are needed.

Acknowledgments

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References