Correspondence

Do We Still Need Lead-In Dosing of Nevirapine in HIV-Infected Patients Who Are Receiving Rifampicin-Containing Antituberculous Therapy?

To the Editor—We read with great interest the article by Manosuthi et al [1] that compared plasma concentrations and efficacies between standard doses of efavirenz-based (600 mg per day) and nevirapine-based (400 mg per day) antiretroviral therapy among patients with concurrent human immunodeficiency virus (HIV) infection and tuberculosis who were receiving a rifampicin-containing antituberculous therapy. Although interpretation of the data should be cautious in view of the limitation of insufficient sample size, the finding of achievement of a similar virological response (HIV RNA level, <50 copies/mL) between efavirenz- and nevirapine-based antiretroviral therapy indeed adds further evidence that, along with previous studies by the authors [2, 3], moderate decreases in the plasma nevirapine level caused by concomitant rifampicin treatment did not compromise the clinical efficacy of standard-dose nevirapine-based antiretroviral therapy in patients with concurrent HIV infection and tuberculosis who have the same ethnicity and similar weight.

However, inferior virological responses and more deaths in patients with HIV infection and tuberculosis receiving nevirapine-based antiretroviral therapy than patients receiving efavirenz-based antiretroviral therapy was observed in a randomized clinical trial from India (mean weight, 42.3 kg) [4] and in an observational study from South Africa [5]. The cause of discrepancy remains unclear, but the extent of antiretroviral resistance to which the transmitting HIV isolates have developed in different regions, especially among those women who may have received nevirapine for prevention of mother-to-child transmission of HIV, and the distributions of cytochrome P450 (CYP) 2B6 polymorphisms that affect the nevirapine plasma concentrations in different ethnicities may be contributory [6, 7].

The dosing of nevirapine begins with 200 mg per day for 2 weeks (lead-in dosing), followed an increase to 200 mg every 12 h or 400 mg once daily because of autoinduction of enzymes that metabolize nevirapine in the first 2 weeks of therapy. In the study by Manosuthi et al [1] and the study by Indian investigators [4], patients with concurrent HIV infection and tuberculosis had received rifampicin for >4 weeks before commencement of either antiretroviral therapy, during which time, induction of CYP3A4 activity and expression of CYP2B6 by rifampicin are likely to reach its plateau. In a previous study of 13 HIV-infected patients in India (mean weight, 58 kg) who received regular antiretroviral therapy containing nevirapine at a dosage of 200 mg twice daily, addition of rifampicin reduced the minimum concentration and area-under-the-curve of nevirapine by 53% and 46%, respectively [8]. During the lead-in phase of nevirapine, nevirapine plasma concentrations may be reduced to a significant degree by concomitant rifampicin that encourages the emergence of HIV resistant to nevirapine.

Although more randomized studies of sufficient sample size are urgently needed in resource-limited regions where fixed-dose antiretroviral therapy containing nevirapine remains the most convenient and accessible regimen to HIV-infected patients with tuberculosis, whether lead-in dosing of nevirapine is still needed should be addressed as well if the patients are in the maintenance phase of antituberculous therapy containing rifampicin.

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Reply to Chang et al

TO THE EDITOR—Chang et al [1] raise a concern related to our study [2] regarding whether a dose escalation (lead-in) strategy of nevirapine is necessary in human immunodeficiency virus (HIV)–infected patients who are currently receiving rifampicin, because they already have undergone full induction of their cytochrome P450 system, provided that they have been taking rifampicin for a while. Nevirapine is an inducer of cytochrome P450 and also induces its own metabolism. This effect results in a reduction in the nevirapine elimination half-life from 45 to 30 h with repeated dosing after 2 weeks [3]. The recommended daily dose of nevirapine for adults is 200 mg twice daily [4]; this is preceded by a 2-week lead-in dose of 200 mg once daily because of the autoinduction of nevirapine hepatic metabolism. This lead-in strategy has been shown to reduce the frequency of rash [4].

Previous studies of Malawians and Thais have shown that 59%–79% of patients who receive 200 mg of nevirapine per day for the first 2 weeks of therapy experienced short periods of subtherapeutic drug levels [5–7]. Specifically, our recent experience with patients receiving rifampicin who initiated nevirapine at a lead-in dosage of 200 mg per day and who then increased the nevirapine dosage demonstrated that 79% of patients who received 2 weeks of nevirapine at 200 mg per day, compared with 19% of patients who received a 2-week lead-in regimen of 400 mg per day, had a detectable plasma nevirapine level at 12 h after taking less than the minimum recommended level at 2 weeks. Given the high proportion of patients who experienced suboptimal nevirapine levels during the first 2 weeks, whether nevirapine dosages should be initiated with standard dosage of 400 mg per day, without lead-in dosing to counterbalance with this drug–drug interaction, is a pertinent question. Although subtherapeutic plasma nevirapine levels occur during the lead-in period, the high inhibitory quotient indicate that the plasma nevirapine level with concomitant use of rifampicin is still greater than the 95% effective inhibitory concentration (0.19 mg/L) [8].

On the other hand, data from the same study revealed that a lead-in strategy involving 200 mg of nevirapine twice daily was associated with a higher rate of nevirapine-associated hypersensitivity reactions. Therefore, the decision making for the first 2-week lead-in of nevirapine treatment in patients with concurrent HIV infection and tuberculosis who are receiving rifampicin should weigh between a short period of subtherapeutic levels that might compromise subsequent antiretroviral efficacy and the risk of nevirapine-associated cutaneous reactions. Nevertheless, a low plasma nevirapine level during the first 2 weeks has been shown to reduce the risk of nevirapine cutaneous reaction without compromising its long-term efficacy [9, 10]. In addition, a previous study demonstrated that nevirapine-associated adverse reactions were also related to the high trough plasma nevirapine levels [8].

On the basis of the existing data to date, a strategy of beginning nevirapine therapy at 200 mg per day for 2 weeks follows by 400 mg per day in patients with concurrent HIV infection and tuberculosis who are receiving rifampicin is justified. However, additional research on the optimal pharmacokinetics and long-term treatment outcomes for nevirapine remains necessary. In addition, pharmacokinetic-based interpatient variability of drug–drug interaction needs to be taken into consideration.

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