

Influence of Rifampicin on Nevirapine Plasma Concentration in HIV-TB Coinfected Patients

Nafrialdi¹, Agus W. Nugroho¹, Evy Yuniastuti², Meta S.S. Wiria¹

¹ Department of Pharmacology, Faculty of Medicine, Universitas Indonesia. Jl. Salemba Raya 6, Jakarta, Indonesia. Correspondence mail: nafrialdi@yahoo.com.

² Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

ABSTRAK

Tujuan: mempelajari pengaruh rifampisin terhadap kadar plasma nevirapin pada penderita dengan ko-infeksi HIV-TB. **Metode:** studi potong lintang pada 40 pasien penderita HIV (16 dengan ko-infeksi HIV-TB, dan 24 HIV tanpa TB). Dilakukan di Kelompok Studi Khusus (Pokdisus) AIDS Rumah Sakit Cipto Mangunkusumo, Jakarta, mulai Oktober-November 2008. Pasien yang telah mengkonsumsi rifampisin dan nevirapin bersamaan selama minimal 2 minggu dimasukkan dalam studi ini. Kadar nevirapin plasma diukur menggunakan HPLC, dan perbandingan antara kedua kelompok dilakukan dengan menggunakan uji-t tidak berpasangan. **Hasil:** kadar plasma nevirapin (mean±SD) pada pasien HIV adalah 7,5±2,2 ug/ml, sedangkan pada penderita HIV-TB 5,5±2,7 ug/ml (p=0,018). Pada sebagian besar pasien kadar plasma nevirapin masih dalam rentang terapeutik. **Kesimpulan:** pemakaian rifampisin bersama nevirapin menyebabkan penurunan kadar nevirapin secara bermakna, namun kadar ini masih dalam rentang terapeutik.

Kata kunci: rifampisin, nevirapin, koinfeksi HIV-TB, interaksi obat.

ABSTRACT

Aim: to evaluate the influence of rifampicin on nevirapine plasma concentration in HIV-TB coinfecting patients. **Methods:** this was a cross sectional study on 40 HIV patients (16 with HIV-TB coinfection, and 24 HIV without TB) conducted in HIV-AIDS study group (Pokdisus AIDS) of Cipto Mangunkusumo Hospital, Jakarta in October-November 2008. Those who had consumed both drugs for at least 2 weeks were recruited. Plasma nevirapine level was measured by using HPLC method, and the comparison between the two groups was done by unpaired t-test. **Results:** Nevirapine plasma level (mean±SD) in HIV patient was 7.5±2.2 ug/ml, while in HIV-TB patients it was 5.5±2.7 ug/ml (p=0.018). In most of patients receiving rifampicin, the plasma nevirapine concentration was still in therapeutic range. **Conclusion:** co-administration of rifampicin was associated with a significant decrease in nevirapine plasma concentration. However, this level was still in therapeutic range.

Key words: rifampicin, nevirapine, HIV-TB coinfection, drug interaction.

INTRODUCTION

The burden of HIV/AIDS is continuously increasing worldwide, including in Indonesia. Data in Indonesia showed that the incidence of HIV/AIDS was estimated 110000 in 2002, and increased to 190000 in 2006,¹ and accordingly reach 240 000 in 2010.² Typical cellular immunity

impairment is observed in HIV patients as reflected by the decrease in CD4 counts. This implicates the increase of opportunistic infections, especially those related with the failure of cellular immunity, such as tuberculosis. USAIDS report estimated the incidence of HIV to be 33 million worldwide, with one third of the patients are

coinfected with tuberculosis. Patients infected with HIV and TB are 30 times more likely to progress to active TB disease. On the other hand, TB infection will enhance the replication of HIV and will accelerate the progression to full blown AIDS.³ In Indonesia, the prevalence of TB-HIV coinfection is approximately 55-66.9%.^{1,4}

The main treatment of HIV/AIDS consists of antiretroviral combination therapy. The most widely used are dual reverse transcriptase inhibitors (NRTI or NNRTI) combined with one protease inhibitor (PI),^{5,6} Nevirapin or efavirenz are the most commonly used NNRTI.^{7,8}

Rifampicin is a cornerstone in TB therapeutic regimen which contributes greatly in the success of TB treatment and significantly shortens the duration of treatment compared to the regimen without rifampicin. Thus, concomitant administration of ARV and rifampicin is unavoidable in the management of TB-HIV coinfection. However, since rifampicin is well known as a strong inducer of cytochrome P-450, this combination is subject to drug-drug interaction which potentially affect the therapeutic outcome.

Nevirapine is widely used in Indonesian patients due to its availability and relatively low cost. In TB-HIV coinfection, it is indeed suggested to avoid the concomitant use of rifampicin and nevirapine since the last drug is metabolized by CYP3A4. Efavirenz is recommended as an alternative. However, considering that nevirapine is more readily available in the market and less costly, a considerable number of coinfecting patients still receive nevirapine. The induction of CYP3A4 by rifampicin may decrease plasma concentration of nevirapine. But it is not known whether this will really have clinical implication. The study of Ribera et al.⁹ reported a variable reduction of nevirapine trough level of 10-68%, which potentially fall below therapeutic range. Other study by Martinelli et al.¹⁰ showed that concomitant treatment of rifampicin and nevirapine for 48 weeks resulted in trough plasma concentration of nevirapine of 3.54 ug/mL, which was still in therapeutic range (3.000–4.599 ug/mL).^{10,11} In the present study, we are interested in evaluating the plasma concentration of nevirapine with or without concomitant rifampicin treatment in HIV patients.

METHODS

This was a cross sectional study conducted at the Department of Internal Medicine, Faculty of Medicine, University of Indonesia – Cipto Mangunkusumo hospital from October to November 2008. The study protocol had been approved by the Ethics Committee of the Faculty of Medicine, University of Indonesia.

Study subjects were HIV/AIDS patients with TB coinfection (inpatients or out patients) at the Department of Internal Medicine, Cipto Mangunkusumo hospital and have received concomitant treatment of rifampicin with full dose nevirapine (200 mg twice daily) for at least 2 weeks. This period was given to allow complete induction of CYP3A4 by rifampicin. Control group had HIV/AIDS patients without TB coinfection and had received full dose nevirapine for at least 2 weeks. Written informed consent were obtained from each study participants prior to enrollment in the study. Those with irregular medication intake, and those taking other medication that can alter CYP3A4 activity such as cimetidine, fenitoin, carbamazepine, and azole antifungal were excluded from the study.

Blood Sampling and Measurement

Five milliliters of venous blood was withdrawn from each subject and collected in EDTA containing tube. The blood was centrifuged for 10 minutes at 3000 rpm, and the plasma was separated for measurement of nevirapine concentration with HPLC (Waters Alliance 2695 with UV detector 2487. As much as 500 uL plasma was mixed with 25 uL carbamazepine solution in methanol (100 ug/mL) as internal standard. One hundred uL of NaOH was then added and the mixture was homogenized with vortex for 60 seconds, followed by centrifugation (3000 rpm, 10 minutes). The samples were extracted with 2 mL of diethyl ether and evaporated at 65°C. The residues was then dissolved in 200 uL methanol and injected into HPLC.

Statistical Consideration

Sample size was calculated based on the formula for two mean comparisons of numeric data: $[n_1 = n_2 = 2 \{(Z\alpha + Z\beta) SD\}^2 / (x_1 - x_2)^2]$. By taking the α value of 5% ($Z\alpha = 1.96$), the power of 80% and the difference of 1.5 ug/mL in mean concentration considered as clinically significant, the samples needed in each group

was 24. Plasma concentration of nevirapine in both groups was compared by using unpaired t-test. P value of <0.05 was taken as the limit of statistical significance.

RESULTS

As many as 40 patients have been recruited in this study. Twenty four patients (20 male and 4 female) without TB coinfection received nevirapine, while 16 patients (11 male and 5 female) with TB coinfection received nevirapine plus rifampicin.

Table 1. Demographic data of HIV/AIDS patients without and with TB co-infection

Variables	Without TB co-infection	With TB co-infection
Sex		
- Male	20	11
- Female	4	5
Age (mean \pm SD) (yrs)	33.16 \pm 5.86	30.56 \pm 5.80
Body weight (mean \pm SD) (kg)	58.64 \pm 8.85	52.19 \pm 9.10
Height (mean \pm SD) (Cm)	167.4 \pm 4.04	164.3 \pm 4.64

Plasma nevirapine concentrations in patients with and without TB coinfection was 7.95 ± 2.64 ug/mL and 5.55 ± 2.73 ug/mL, respectively ($p = 0.0084$).

Figure 1 shows distribution of individual plasma nevirapine concentration. In group without rifampicin co-treatment, all plasma nevirapine concentrations fall within therapeutic range. In two of them, nevirapine concentration was higher than upper limit therapeutic level (12 ug/mL), but no adverse event was reported.

In group with rifampicin co-treatment, the plasma nevirapine concentration is significantly lower than the first group. Even in two of them, plasma nevirapine concentration was far below lower limit of therapeutic level (0.29 and 0.23 ug/mL).

DISCUSSION

Tuberculosis is an opportunistic infection in HIV/AIDS patients with special characteristics due to its chronicity and the needs of long-term combination treatment of rifampicin with antiretrovirals. It is well known that rifampicin is a potent inducer of cytochrome P450. On the other hand, some antiretroviral drugs are substrate of these enzymes which will be affected during concomitant treatment. Nevirapine is a non-nucleoside reverse transcriptase inhibitor (NNRTI) commonly used in developing countries as this drug is readily available and relatively inexpensive. This drug is metabolized by cytochrome P450, specifically by CYP3A4 isoenzyme. Co-administration with rifampicin may lead to the decrease of plasma concentration of nevirapine with the consequence of possible treatment failure. However, some clinical studies on rifampicin-nevirapine interaction gave variable results.

Manosuthi et al.¹³ conducted a study on 140 HIV patients in Thailand and reported a 18% decrease of nevirapine plasma concentration in patients receiving rifampicin compared to patients receiving nevirapine only ($p=0.048$). The study of Cohen et al.¹⁴ reported that nevirapine levels fell below therapeutic concentration (<3 ug/mL) in 6 out of 16 patients (37.5%) under concomitant

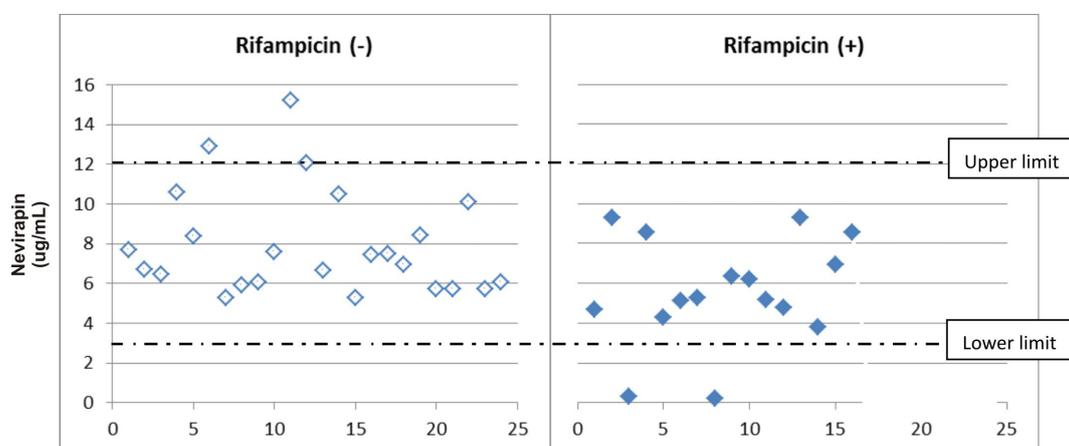


Figure 1. Plasma nevirapine concentration in group receiving rifampicin (panel A) and in group without rifampicin (panel B).

treatment. While Autar et al.¹⁵ reported the subtherapeutic concentration of nevirapine in 7 out of 74 patients (9.5%) receiving rifampicin and in 2 patients without rifampicin.

In the present study, we recruited 24 HIV patients without TB, while for those with TB coinfection we could only recruit 16 patients with rifampicin-nevirapine co-treatment since most of patients received efavirenz, instead of nevirapine. The patients were selected among those who have taken full dose nevirapine (200 mg twice daily) for at least 2 weeks to allow steady state plasma concentration, or had taken rifampicin + nevirapine for at least 2 weeks to allow complete induction of CYP. We found that the mean plasma concentration of nevirapine was significantly lower in group receiving concomitant treatment (5.55 ± 2.73 ug/mL) compared to those only received nevirapine (7.95 ± 2.64 ug/mL).

The sub-therapeutic concentration of nevirapine was observed in 2 of 16 (0.32%) patients receiving rifampicin, while none in patients receiving nevirapine alone. Our results were not greatly different from that of Autar et al. who found plasma nevirapine concentration of 5.47 ± 2.66 and 8.72 ± 3.98 mg/l, respectively in groups without and with rifampicin cotreatment,¹⁵ with many more patients having the subtherapeutic concentration (9.5%). Gillian et al.¹⁶ reported a non significant difference of NRTI in patients receiving concomitant rifampicin treatment.

The subtherapeutic concentration of nevirapine in two patients was extremely low, suggesting that this could not fully be attributed to drug interaction. Contribution of other factors such as nonadherence, cannot be ruled out. On the contrary, in two or three of the patients, the nevirapine concentration was revealed to be above therapeutic range. However, no specific adverse reaction was detected.

The greatest concern of co-treatment with rifampicin is the decrease of ARV plasma level which could potentially lead to treatment failure. In the present study, plasma concentration of nevirapine is significantly lower after induction of cytochrome by rifampicin compared to those who received nevirapine only. Fortunately, the plasma level of nevirapine in the majority of the patients was still in therapeutic range. This indicates that for those who can not afford the efavirenz, nevirapine remains an acceptable alternative for ARV treatment.

Limitations of this study were that the measurement of nevirapine concentration was only done at one point which was not exactly at the moment of trough level. However, two weeks or more of consumption would allow the obtention of steady state concentration, where the fluctuation is normally minimal. In addition, the small sample size was another limitation of this study which make the generalization of the results was quite difficult.

CONCLUSION

From the above results, we can conclude that interaction between rifampicin and nevirapine has led to significant decrease of nevirapine concentration. However, in the majority of patients, the plasma nevirapine concentration was still in therapeutic range, suggesting that in patients who can not afford efavirenz, nevirapine is an acceptable alternative.

REFERENCES

1. Djoerban Z. AIDS: from basic knowledge to HIV-TB coinfection. *Acta Med Indones*. 2008;40:113.
2. Ditjen PPM & PLP Kemenkes RI Laporan Situasi Perkembangan HIV/AIDS tahun 2010.
3. USAID. TB/HIV, MDR-TB, and other challenges. Available at: http://www.usaid.gov/our_work/global_health/id/tuberculosis/techareas/tbhiv.html. Retrieved 18 February 2012.
4. Sumantri S, Djoerban Z. Clinical manifestations and antiretroviral management of HIV/AIDS patients with tuberculosis coinfection in Kramat 128 hospital. *Acta Med Indones*. 2008;40:117-23.
5. Fauci AS, Clifford Lane H. Human immunodeficiency virus disease: AIDS related disorders. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's principle of internal medicine*. 17th ed. New York: McGraw Hill; 2008. p. 1137-203.
6. Zolopa AR, Katz MH. HIV infection and AIDS. In: Mc Phee SJ, Papadakis MA, Tierney LM, eds. *Current medical diagnosis and treatment*. New York: McGrawHill; 2008. p. 1150- 77.
7. Raffanti S, Haas DW. Antimicrobial agents antiretroviral agents. In: Hardman JG, Limbird LE, Gilman AG, eds. *Goodman & Gilman's the pharmacological basis of therapeutics*. 10th ed. New York: McGraw-Hill; 2001. p. 1349-80.
8. Gazzard BG. Viral diseases. In: Speight TM, Holford NHG, eds. *A very drug treatment*. 4th ed. Auckland: Adis International. 1997. p. 1516-43.
9. Ribera DE, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acqui Immune Defic Syndr*. 2001;28:450-3.
10. Martnelli C, Fiore C, Giuntini R, Leoncini F. Therapeutic drug monitoring (TDM) for nevirapine in

- once dosing regimen (OD) in HIV patients who had interrupted antiretroviral therapy (TARV): 48 weeks of follow up. IAS Con HIV Pathog Treat. 2005 Jul 2; Abstract No. WePe3.2CO1
11. Wang J, Kou H, Fu Q, Han Y, Qiu Z, et al. (2011) Nevirapine plasma concentrations are associated with virologic response and hepatotoxicity in Chinese patients with HIV infection. Available at : <http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0026739>. Retrieved February 22, 2012.
 12. de Vries-Sluijs TE, Dieleman JP, Arts D, Huitema AD, Beijnen JH, et al. Low nevirapine plasma concentrations predict virological failure in an unselected HIV-1-infected population. *Clin Pharmacokinet*. 2003;42:599–605.
 13. Manosuthi W, Sungkanuparph S, Thakkinstian A, Rattanasiri S, Chaovavanich A, et al. Plasma nevirapine levels and 24-weeks efficacy in HIV-infected patients receiving Nevirapine-based highly active antiretroviral therapy with or without Rifampicin. *Clin Inf Dis*. 2006;43:253-5.
 14. Cohen K, van Cutsem G, Boulle A, Mc Illeron H, Goemaere E, Smith PJ, et al. Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. *J Antimicrob Chemother*. 2008;61(2):389-93.
 15. Autar RS, Wit FW, Sankote J, Mahanontharit A, Anekthananon T, Mootsikapun P, Sujaikaew K, Cooper DA, Lange JM, Phanuphak P, Ruxrungtham K, Burger DM. Nevirapine plasma concentrations and concomitant use of rifampin in patients coinfecting with HIV-1 and tuberculosis. *Antivir Ther*. 2005;10(8):937-43.
 16. Gillian L, Back David J, deRuiter, Annemiek. Effect of tuberculosis therapy on nevirapin trough plasma concentrations. *AIDS*. 1999;13(17):2489.