Efavirenz Plasma Concentrations and HIV Viral Load in HIV/AIDS-tuberculosis Infection Patients Treated with Rifampicin

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ABSTRAK

Tujuan: *untuk mengetahui pengaruh penggunaan obat tuberkulosis rifampisin terhadap kadar plasma efavirenz dan viral load pasien HIV/AIDS-Tuberkulosis yang telah mendapat terapi antiretrovirus 3-6 bulan.* ***Metode:*** *kadar efavirenz dan viral load pasien HIV/AIDS yang telah mendapat terapi antiretroviral berbasis efavirenz dosis 600 mg/hari selama 3-6 bulan terapi dan pasien HIV/AIDS-Tuberkulosis dengan terapi antiretroviral yang sama ditambah terapi antituberkulosis berbasis rifampisin di RSPI Prof. DR Sulianti Saroso dalam periode Februari-Mei 2015 diukur. Kadar efavirenz pada kedua kelompok dibandingkan dengan menggunakan uji Mann-Whitney, sedangkan proporsi pasien dengan viral load ≥40 kopi/mL dianalisis dengan uji kai kuadrat.* ***Hasil:*** *dari 45 pasien (27 dengan HIV/AIDS dan 18 dengan infeksi HIV/AIDS-tuberkulosis). Median konsentrasi plasma efavirenz pada kelompok HIV/AIDS 0,680 mg/L (range 0,24-5,67 mg/L) dan pada kelompok HIV/AIDS-tuberkulosis 0,685 mg/L (range 0,12-2,23 mg/L tidak berbeda bermakna antara kedua kelompok. Proporsi pasien dengan viral load ≥40 kopi/mL setelah 3-6 bulan pengobatan ARV pada kelompok HIV/AIDS 51,9%, dan kelompok HIV/AIDS-tuberkulosis 72,2% juga tidak berbeda bermakna (uji kai kuadrat, p=0,291).* ***Kesimpulan:*** *kadar plasma efavirenz pada pasien HIV/AIDS–tuberkulosis yang mendapat antiretroviral dan rifampisin tidak berbeda bermakna dengan pasien HIV/AIDS tanpa tuberkulosis. Proporsi pasien dengan viral load ≥40 kopi/mL lebih tinggi pada pasien yang mendapat antiretroviral dan rifampisin dibandingkan dengan pasien yang tidak mendapat rifampisin, namun secara statistik perbedaan ini tidak bermakna. Diperlukan penelitian dengan jumlah pasien yang lebih besar untuk klarifikasi pengaruh rifampisin terhadap kadar plasma eavirenz dan terhadap viral load.*

Kata kunci: *HIV, tuberkulosis, efavirenz, rifampisin, viral load.*

ABSTRACT

Aim: *to determine the effect of a rifampicin-containing tuberculosis regimen on efavirenz plasma concentrations and viral load in HIV/AIDS-Tuberculosis infection patients who received efavirenz-based antiretroviral therapy.* ***Methods:*** *plasma efavirenz concentrations and HIV viral load were measured in HIV/AIDS patients treated with 600 mg efavirenz-based antiretroviral for 3 to 6 months and in HIV/AIDS-Tuberculosis infection patients treated with similar antiretroviral regimen plus rifampicin-containing antituberculosis in Sulianti Saroso Infectious disease Hospital, Jakarta. Plasma efavirenz concentration in both groups were compared using Mann-Whitney test, while proportion of patients with viral load ≥40 copy/mL were analyzed with chi-square test.* ***Results:*** *forty five patients (27 with HIV/AIDS and 18 with HIV/AIDS-Tuberculosis infections) were recruited during the period of February to May 2015. The median efavirenz plasma concentration obtained from HIV/AIDS group was 0,680 mg/L(range*

0,24 to 5,67 mg/L and that obtained from HIV/AIDS-Tuberculosis group was 0.685 mg/L (0.12 -2.23 mg/L) which was not significantly different statistically. The proportion of patients with viral load ≥40 copies/mL after 3-6 months of ARV treatment in the HIV/AIDS group was 51.9%, and in the HIV/AIDS-Tuberculosis group was 72.2%, which was not significantly different statistically (Chi Square test, p=0.291). ***Conclusion:*** *plasma efavirenz concentration in HIV/AIDS-tuberculosis patients receiving antiretroviral and rifampicin is not significantly different from that on HIV/AIDS patients without tuberculosis. Proportion of patients with viral load of ≥40 copy/mL is higher in HIV/AIDS-tuberculosis patients receiving rifampicin compared to HIV/AIDS patients that not receive rifampicin. However, this difference did not reach statistical significance. Confirmatory studies with bigger sample size are needed to clarify the influence of rifampicin on plasma level of efavirenzand and on viral load.*

Keywords: *HIV, tuberculosis, rifampicin, efavirenz, viral load.*

INTRODUCTION

Efavirenz is metabolized by the enzyme cytochrome P-450 (CYP), i.e. the CYP2B6 and CYP3A4 isozymes, of which rifampicin is an inducer. Earlier studies in the white population and in healthy volunteers reported that rifampicin coadministration decreases plasma levels of efavirenz. The therapeutic range of efavirenz was considered to be 1-4 mg/L, as previously reported. Sub-therapeutic drug concentrations may increase the risk of drug resistance and treatment failure. Otherwise, studies from diverse populations, mainly in black and Asian populations, reported no effect of rifampicin on efavirenz plasma concentration or the increase in efavirenz plasma concentration during rifampicin-based anti-TB treatment.[1-3] However, studies that prove the impact of rifampicin co-administration on efavirenz-based antiretroviral therapy outcome is understudied.[3]

Monitoring the efficacy of antiretroviral treatment is generally done after 6 months. Routine virologic monitoring (viral load measurement every 3-6 months) has been the standard of care for earlier detection of treatment failure in many middle and high-income nations.[3,4]

US Food and Drug administration (FDA) approved to increase the dose of efavirenz from 600 to 800 mg/day when coadministrared with rifampicin in patients with pretreatment bodyweight of >50 kg.[2] However, the appropriate dose of efavirenz during rifampicin-based tuberculosis treatment remains debated.[3,5] On the other hand, concentrations above the therapeutic range may increase drug related toxicities, such as neuropsychiatric side effects, which may lead to the emergence of resistance resulting from treatment interruptions.[6] Administration of standard doses of efavirenz results in significant variations in plasma drug concentrations between populations. The reasons for the large inter-individual variability of efavirenz concentration are multifactorial, and involve ethnicity or CYP2B6 pharmacogenetic variations and drug-drug interactions.[7]

In this study, we aimed to determine the effect of rifampicin-containing tuberculosis regimen on efavirenz plasma concentrations and viral load in HIV/AIDS-TB infection patients who have received efavirenz-based antiretroviral therapy for 3 to 6 months.

METHODS

Plasma efavirenz concentrations and HIV viral load were measured in HIV/AIDS patients treated with 600 mg efavirenz-based antiretroviral for 3 to 6 months and in HIV/AIDS-TB infection, patients treated with similar antiretroviral regimen plus rifampicin-containing antituberculosis in Sulianti Saroso Infectious Disease Hospital, Jakarta, during the period of February to May 2015, and the results were compared.The estimated sample size was 52 patients consisted of 26 groups of HIV/AIDS and 26 groups of HIV/AIDS-TB. Poor adherence was defined as a value of pill consumption <95% pills, and patients with poor adherence were excluded.

Blood samples were collected early in the morning on EDTA tubes 14 ± 2 hours after efavirenz intake. After centrifugation, plasma was transferred and stored at -80ºC until

analysis.The plasma concentrationsof efavirenz were determined using High Performance Liquid Chromatography (HPLC) method with UV detection at Pharma Metric laboratories. Viral load was measured using Polymerase Chain Reaction (PCR) method in referral laboratories at Sulianti Saroso Infectious Disease Hospital, Jakarta.

Efavirenz plasma concentrations between HIV/AIDS group and HIV/AIDS-TB group were compared using Mann-Whitney U test, and proportional data was analysed using Chi Square tests. All statistical analyses were performed using SPSS program version 14.

RESULTS

During the study periode, only 45 patients (27 with HIV/AIDS and 18 with HIV/AIDS-TB infections) were recruited in accordance with the inclusion and exclusion criterias due to limited patients availability. Characteristic and clinical profile of the 45 patients are shown in **Table 1** and **Table 2**.

The median efavirenz plasma concentration obtained from HIV/AIDS group was 0.680 mg/L (range 0.24 to 5.67 mg/L) and that obtained from HIV/AIDS-TB group was 0.685 mg/L (range 0.12-2.23 mg/L). Statistically they were not significantly different (Mann-Whitney U test, p=0.480). **Table 3** shows the proportion of patients with sub-therapeutic efavirenz plasma concentration (<1 mg/L) in the HIV/AIDS group and HIV/AIDS-TB group. There was no significant difference (chi square, p=0.948) between the proportion of patients with subtherapeutic efavirenz plasma concentration in the groups.

In total, only 7 out of 45 patients (15.6%) had viral load values ranged from 54,800 to over 1,000,000 copies/ml before ARV therapy. **Figure 1** showed a comparison of viral load before and after 3-6 months of ARV therapy in 7 patients.

In a total of 45 patients, the proportion of patients with successful virological suppression (viral load <40 copies/ml) after 3-6 months of ARV therapy were 48.1% in HIV/AIDS group and 27.8% in HIV/AIDS-TB group. Viral load ≥40 copies/ml were seen in the HIV/AIDS group (51,9%), and in HIV/AIDS-TB group (72.2%), including the 3 patients (6.67%) in HIV/AIDS-TB

Table 1. Subject's characteristics

	HIV/AIDS group (n=27)	HIV/AIDS-TB group (n=18)
Sex (male), n (%)	22 (81.48)	14 (77.78)
Age (years), median (range)	32 (22-38)	32 (24-45)
Weigth (kg), median (range)	64 (45-86)	54 (44-69)
Heigth (cm), median (range)	170 (150-181)	160 (147-175)
Body mass index, n (%)		
- <18.5	1 (3.70)	4 (22.2)
- >18.5	26 (96.3)	14 (77.8)

Table 2. Clinical profiles of subjects

	HIV/AIDS group (n=27)	HIV/AIDS-TB group (n=18)
Baseline CD4 counts, n (%)		
- <350 sel/μL	21 (77.8)	18 (100.0)
- >350 sel/μL	6 (22.2)	0 (0.0)
WHO staging, n (%)		
- Stage I/II	22 (81.5)	0 (0.0)
- Stage III/IV	5 (18.5)	18 (100.0)
ART, n (%)		
- AZT+3TC+EFV	3 (11.1)	7 (38.9)
- TDF+3TC+EFV	17 (62.9)	8 (44.5)
- TDF+FTC+EFV	7 (25.9)	3 (16.7)
Rifampicin 450/INH	0 (0.0)	16 (88.8)
Rifampicin 600/INH	0 (0.0)	2 (11.12)
Oral candidiasis	4 (14.8)	10 (55.6)
Hepatitis B	0 (0.0)	1 (5.56)
Hepatitis C	0 (0.0)	1 (5.56)
Toxoplasmosis	0 (0.0)	1 (5.56)

Table 3. The proportion of patients with sub-therapeutic efavirenz plasma concentration (<1 mg/L) in the HIV/AIDS group and HIV/AIDS-TB group

	Efavirenz Plasma Concentration	
	Subtherapeutic n (%)	Therapeutic n (%)
HIV/AIDS group (n=27)	18 (66.7)	9 (33.3)
HIV/AIDS-TB group (n=18)	13 (72.2)	5 (27.8)

Chi Square test, p=0,948

* Two of 9 patients from HIV/AIDS group had efavirenz plasma concentration ≥ 4 mg/L (supratherapeutic) ie 5,34 mg/L and 5,67 mg/L

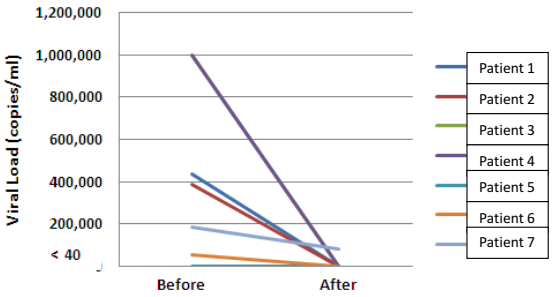

Figure 1. comparison of viral Load before and after 3-6 months of ARV therapy in 7 patients from HIV/AIDS and HIV/AIDS-TB group

Table 4. Viral load after 3-6 months of ARV therapy in HIV/AIDS group and HIV/AIDS-TB group

	HIV/AIDS group n (%)	HIV/AIDS-TB group n (%)
Viral load		
<40 copies/mL	13 (48.1)	5 (27.8)
≥40 copies/mL	14 (51.9)	13 (72.2)
Chi square test p=0.291		

group that have viral load >1000 copies/ml. (**Table 4**) There was no significant difference (Chi square, p = 0.291) between the patient with viral load <40 copies/ml and ≥40 copies/ml in those 2 groups.

Among the 18 patients in the HIV/AIDS-TB group, 4 (30.8%) had viral load <40 copies/ml with sub-therapeutic efavirenz plasma concentration after 3-6 months of ARV therapy. Among the 27 in the HIV/AIDS group, 10 (55.6%) had viral load <40 copies/ml with sub-therapeutic efavirenz plasma concentration after 3-6 months of ARV therapy. **Figure 2** shows a comparison between efavirenz plasma concentration and viral load in the groups.

In a total of 45 patients, 35 (77.78%) had adverse effects.Efavirenz has been related to CNS effect. Nineteen (70.3%) had central nervous system (CNS) side effects. One of 2 patients in the HIV/AIDS group with supratherapeutic efavirenz plasma concentration (5.67 mg/L) had CNS side effects. Generally, some patients experienced more than one side effects (**Table 5**). Side effects usually occurs within the first few weeks of treatment.

Table 5. Side effects of Efavirenz

	HIV/AIDS group (n=27)	HIV/AIDS-TB group (n=18)
CNS effect, n (%)	19 (70.3)	10 (55.6)
- dizziness	6	4
- halusination	2	2
- insomnia	3	4
- headache	2	4
- nightmares	3	2
- somnolence	5	-
- dementia	1	-
Hepatotoxicity, n (%)	1 (3.70)	3 (16.7)
Gastrointestinal effect, n (%)	8 (29.6)	3 (16.7)
- nausea vomitus	8	3
- diarrhea (dehydration)	1	-
- constipation	1	-
Skin effect, n (%)	4 (14.8)	4 (22.2)
- rash	4	4

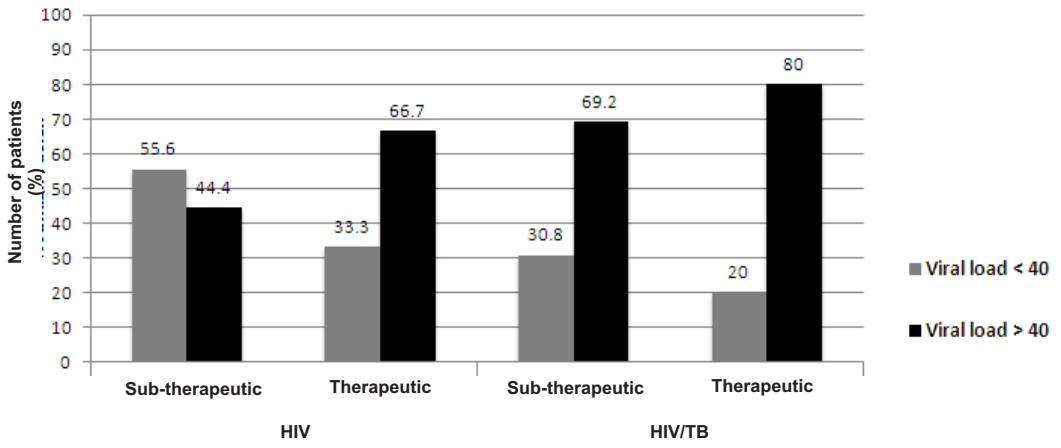

Figure 2. Comparison between efavirenz plasma concentration and viral load in the groups.

DISCUSION

Our results show that after administration of a daily dose of 600 mg efavirenz-based antiretroviral therapy for 3-6 months, efavirenz plasma concentrations were not significantly different between group of HIV/AIDS-TB patients receiving anti-TB therapy and HIV/AIDS patients receiving efavirenz-based therapy only. Yenny et al studied the pharmacokinetics effect of rifampicin on plasma efavirenz concentrations in healthy volunteers and reported that rifampicin reduced efavirenz's AUC by 20.4%.[9] Other studies have been conducted to assess the effect of rifampicin or rifampicin based tuberculosis treatment co-administration on efavirenz concentrations, which reported results different from our report here.[10,11]

Our results are in agreement with several studies from Sub-Saharan Africa and Cambodia.[2,3,12] Those studies concluded that efavirenz plasma concentrations were not significantly different between group of HIV/AIDS-TB patients and group of HIV/AIDS patients who received efavirenz-based only.

Efavirenz plasma exposure is mainly influenced by CYP2B6 genotype.[2] The common clinical practice of administering the same dose to all patients leads to profound differences in drug plasma concentration, which is correlated with patient genotype. Several polymorphisms in the gene CYP2B6 may influence isoenzyme activity and therefore the hepatic metabolism and clearance of efavirenz.[14] Efavirenz are primarily metabolized by hepatic CYP2B6, with some contributions from CYP3A4. Differences in various studies show that there is a dominant activity of CYP2B6 over CYP3A4 in various populations.[9]

Identification of slow and extensive metabolizers for the category of drugs metabolized by CYP2B6 is important for understanding the differences in efavirenz plasma concentrations and in clinical response of drugs metabolized by this enzyme. The patients with an extensive metabolizer genotype, causing a subtherapeutic efavirenz plasma concentration. The patients with a slow metabolizer genotype predicted to increase efavirenz concentrations.[8,14] We observed a large proportion of patients with sub-therapeutic efavirenz concentrations in HIV/AIDS group (66.7%) and in HIV/AIDS-TB group (72.2%). One of the plausible reasons is the dominant activity of extensive metabolizer genotype. Even though, in Indonesia, no studies have identified the CYP2B6enzyme activity.

Extensive rifampisin-efavirenz interaction studies evaluated not only the effect on efavirenz concentration, but also its effecton HIV antiretroviral treatment outcome.[3] Overall, our results show differences in virologic suppression after 3-6 months ARV therapy between the HIV/AIDS-TB group and the HIV/AIDS group; indicating that it takes longer time to reach virology success during dual TB–HIV co-infection as compared to HIV-only infection, but there was no significant difference (p=0.291) between the proportions of patients with viral load <40 copies/mL and ≥40 copies/mL in the groups. This non-significancy might be due to the small number of patients included in this study, a larger study is needed to see whether the differences is indeed true.

In total, there was no significant difference between the proportion of patients with subtherapeutic efavirenz plasma concentration in the groups with viral load <40 copies/mL and ≥40 copies/mL. This may indicate that after administration of a daily dose of 600 mg efavirenz-based antiretroviral therapy for 3-6 months in the groups, although with subtherapeutic efavirenz concentration, overall, virological response was still good. In our report, three patients in the HIV/AIDS-TB group with sub-therapeutic efavirenz concentration had viral load >1,000 copies/mL. Virologic failure was defined as a viral load of >1,000 copies/mL, but to detect early treatment failure, having two viral load monitorings within the first year, would be ideal.[8] Only 1 out of 3 patients had two viral load monitoring, i.e viral load 185.758 copies/mL to 81.954 copies/mL, and after ARV initiation has shown significant improvement of virologic outcomes.

In our study, the proportion of patients with CNS side-effects in the HIV/AIDS group was 70.3% and in the HIV/AIDS-TB group was 55.6%. The cause of CNS side-effects probably was efavirenz high lipophilic nature, its easily

penetrates the blood brain barier. Although most patients' plasma efavirenz concentrations are sub-therapeutic, efavirenz was known to be distributed in the cerebrospinal fluid at 0.26% to 1.19% from the concentrations of efavirenz in plasma.[15]

Based on efficacy data, in terms of virologic response, obtained in this study; as well as the fairly high incidence of CNS side effects, the recommended increase in the dose of efavirenz from 600 mg/day to 800 mg/day in patients with HIV/AIDS-TB receiving rifampicin seems not necessary. On the other hand, it had been shown that the provision of antiretroviral therapy along with antituberculosis in patients with HIV/AIDS-TB had no drug interaction, so it might be better to treat both diseases simultaneously than to delay therapy.

The limitation of our study is that the sample size was small (27 with HIV/AIDS and 18 with HIV/AIDS-TB infections). The sample of HIV/TB did not reach the minimum target, so our study was not adequately powered to detect the differences. Some other things need to be investigated, such as the cause of subtherapeutic efavirenz concentrations, however, these concentration still show therapeutic efficacy in terms of viral count, as well as high numbers of side effects. Does it mean that our dosage is too high for Indonesians?

CONCLUSION

Plasma efavirenz concentration in HIV/AIDS-tuberculosis patients receiving antiretroviral and rifampicin is not significantly different from those with HIV/AIDS without tuberculosis. Proportion of patients with viral load of ≥40 copy/mL is higher in HIV/AIDS-tuberculosis patients receiving rifampicin compared to HIV/AIDS patients that not receive rifampicin. However, this difference did not reach statistical significance. Confirmatory studies with bigger sample size are needed to clarify the influence of rifampicin on plasma level of efavirenz and on viral load.

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