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Pharmacokinetic interactions between rifampicin and efavirenz in HIV-TB coinfections

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ABSTRACT

The increased percentage of patients with HIV-TB coinfection leads to inevitable interactions between rifampicin and efavirenz. Efavirenz is a potent non-nucleoside reverse transcriptase inhibitor (NNRTI) for the treatment of HIV infection. The use of this drug combination with rifampicin causes problems in determination of the optimal dosage of efavirenz when administered concomitantly with rifampicin. Efavirenz is metabolized by the enzyme cytochrome P-450 (CYP), i.e. the CYP2B6 and CYP3A4 isozymes, of which rifampicin is an inducer. The induction of cytochrome P-450 by rifampicin is mediated by pregnane X (PXR) and constitutive androstane receptors (CAR) in the cell nucleus, resulting in a wide variation in the plasma efavirenz concentrations, such that a therapeutic failure or the occurrence of toxic effects are to be expected. The optimal dosage of efavirenz is commonly determined through pharmacokinetic studies, but this is problematic in the combined use of the drug with rifampicin, due to the wide variation in study design, method, and sample size of each study. Ethnic factors and genetic polymorphism of the enzymes that metabolize efavirenz contribute to the problem of determining the optimal dose of this drug. Pharmacokinetic studies with good measurement parameters and methods are still necessary as the basis for determining the optimal dose of efavirenz in the Indonesian population.

Keywords: Drug interaction, efavirenz, rifampicin, HIV, TB

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INTRODUCTION

Tuberculosis (TB) is one of the opportunistic infections frequently encountered in patients with Human Immunodeficiency Virus (HIV) infection. The results of a survey conducted by the Department of Pulmonology and Respiratory Medicine of the Faculty of Medicine, University of Indonesia and the *Persahabatan* Hospital in the years 2000-2005 revealed an sharp increase in the percentage of TB in patients with HIV from 5.88% in 2000 to

33% in 2005.[1] HIV infection is the main risk factor of TB reactivation. Forty percent of patients with HIV against only 5% of those without HIV are said to be potentially liable to TB reactivation.[1] The mortality rate of patients with HIV accompanied by TB exceeds 50%.[2]

In the therapeutic regimen for TB the use of rifampicin is absolutely necessary for the successful outcome of the treatment of patients with HIV who are coinfected with TB. Clinical trials have demonstrated that therapeutic regimens for TB that do not use rifampicin or only in the initial two months of treatment show an increase in the therapeutic failure or relapse rates.[3]

Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) recommended by the WHO as one of the components for the initial first-line treatment of patients with HIV.[4] The combined use of efavirenz and rifampicin gives rise to the problem of drug interaction.[5] Rifampicin is a potent inducer of the enzyme cytochrome P450 which metabolizes a number of drugs, including efavirenz, thus significantly decreasing plasma levels of this NNRTI.

The problem concerns the determination of the optimal dosage of efavirenz when administered concomitantly with rifampicin. Longitudinal studies conducted by Friedland et al.[6] showed a wide variation in the plasma drug concentrations of efavirenz when administered in combination with rifampicin. This causes the patients who are exposed to subtherapeutic doses to be at risk of therapeutic failure and the development of drug resistance, whereas patients exposed to high doses of the drug are at high risk of experiencing central nervous system side effects.

The purpose of this literature review is to discuss opportunistic TB infections in patients with HIV, the interactions of efavirenz and rifampicin (in relation to nuclear receptors), and to trace the extent to which the interactions between these two drugs may be applied to the determination of the optimal dose of efavirenz.

Opportunistic TB infections in patients with HIV

HIV causes difficulties in the management of tuberculosis, and *vice versa*. HIV infection increases the risk of reactivation of latent TB, while individuals already infected with HIV and only afterwards become infected with TB have a higher progressivity of the disease.[7]

$CD4^+$ T lymphoctes and macrophages play an important role in the immune response to infection with *Mycobacterium tuberculosis*. Infection with TB leads to the release by $CD4^+$ lymphocytes of proinflammatory cytokines, such as interferon-γ (IFN-γ), interleukin (IL)-1, IL-2, and tumor necrosis factor-α (TNF-α). These cytokines subsequently activate macrophages and kill intracellular TB organisms. The production of cytotoxic T cells is an additional protective mechanism in the response to TB infection.[8]

HIV infection results in dysfunction of $CD4^+$ cells and a reduction in their absolute numbers,[8] causing patients with HIV to be at high risk of experiencing reactivation of latent TB, this risk being similar to the risk of acquiring a new TB infection. Conversely the TB infection itself may increase HIV progressivity. The presence of the TB organism and its major cell wall antigen (lipoarabinomannan) within the body leads to upregulation of the genes coding for the proinflammatory cytokines IL-1, IL-2, IL-6, and TNF-α. The induced cytokines increase HIV replication by activation of the transcription factors nuclear factor kB (NF-kB) and Il-6, thus increasing the transcription of the long terminal repeats (LTRs) of HIV. This process is directly and indirectly stimulated by IL-1 and TNF-α, cytokines which in normal conditions play a role in the defense mechanisms against TB infection. In contrast, in HIV-TB coinfection the above

process accelerates the progressivity of HIV to the advanced stages.[8]

In principle, adequate chemotherapy of tuberculosis should be administered to all individuals receiving treatment for TB, irrespective of the presence of HIV infection in the individual in question. This therapeutic principle for TB includes the use of standard combinations of antituberculosis drugs, of which the first-line drugs are isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. In the standard therapeutic regimen for TB, these drugs should always be used in combinations of two or more agents. The standard regimen of 6-9 months consists of 2 months treatment with isoniazid, rifampicin, pyrazinamide, and ethambutol (base-line), followed by 4-7 months of treatment using isoniazid and rifampicin (end-line). For all responsive TB cases, this standard therapeutic regimen is presumably adequate both in HIV-infected and in non-infected patients.[9]

Drug interactions

Drug interaction occurs if the effect of a drug is modified by the presence of another.[3] Drug interactions are divided into pharmacodynamic and pharmacokinetic interactions. Pharmacokinetic interactions occur if the presence of a drug is capable of modifying the absorption, distribution (transport), metabolism, and excretion of another drug given concomitantly, so as to affect the bioavailability of the latter. Pharmacokinetic interactions include changes in gastric pH and drug absorption, altered drug metabolism mediated by CYP450, modulation of P-glycoproteins (cellular transport proteins), and alterations in renal drug elimination. Pharmacodynamic interactions are interactions between drugs acting on the same receptor system, site of action or physiological system. The induced responses may be additive, synergistic, or antagonistic. Pharmacodynamic interactions do not alter the plasma concentrations of the interacting drugs.[10] Pharmacokinetic interactions frequently occur in metabolic processes located in the liver (and less frequently in the intestines). These metabolic interactions take place when two drugs compete for being metabolized by the same enzyme, where one of the most important metabolic interactions occurring is through the enzyme CYP450.

Drugs may affect CYP450 in two ways, namely by induction or inhibition. Inhibition of CYP450 results in the slower metabolism of the drug that is the substrate of the enzyme, leading to accumulation of the drug in the blood, thus potentially causing toxicity. Induction of CYP450 leads to increased metabolism of the drug that is the substrate of the enzyme, thus reducing the efficacy of the treatment. Drug interactions are the main problem in optimization of dosage. All drugs of the rifamycin group are CYP450 inducers of varying potency.[11]

Drug metabolism and cytochrome P-450

The process of biotransformation plays an important role in discontinuing the action of a drug and the main organ for biotransformation is the liver. The biotransformation process consists of several phases. Phase I comprises oxidation, reduction, and hydrolysis, commonly mediated by CYP450. Phase II comprises conjugation, mediated by uridine diphosphate-glucuronosyl-transferase (UGT), sulfotransferase (SULT), and glutathione-S-transferase (GST). In general, this process gives rise to metabolites that are more polar, more easly ionized (more easily eliminated by the kidneys), or more fat-soluble (excreted into the bile and subsequently into the feces).[12]

CYP450 is particularly found in the smooth endoplasmic reticulum of the hepatic cells and the epithelial enterocytes of the small intestine. In general, CYP450 plays a role in 80% of the oxidative metabolism and in nearly 50% of the

elimination of a drug.[12] Currently 57 human genes for CYP450 have been identified, but only a small number code for proteins (particularly the CYP1, CYP2 and CYP3 families), and contribute to drug metabolism. CYP450 is classified on the basis of amino acid homology, designated by a digit indicating the family, a letter standing for the subfamily, and a final number referring to the individual enzyme, e.g. CYP3A4, 2D6, 2C19.[12]

Nuclear receptors and induction of cytochrome P-450

Xenobiotics may affect the rate of drug metabolism by activating the transcription process and induce the expression of genes coding for the enzymes that metabolize the drug through interactions between the nuclear receptor superfamily and their ligands.[12]

The nuclear receptor superfamily are transcription factors functioning as sensors of lipophilic xenobiotics, including drugs.[13] Activation of certain nuclear receptors by xenobiotics that are the ligands of the nuclear receptors induce the transcription of a series of target genes (among them CYP and drug transporters), which function as an adaptive defense mechanism against toxic substances or xenobiotics.[13] The structure of a nuclear receptor is depicted in Figure 1.

One of the most important induction mechanisms is effected through a type 2 nuclear receptor, belonging to the same superfamily as the steroid hormones. Type 2 nuclear receptors play an essential role in drug metabolism and therapy. The group of receptors and ligands belonging to the type 2 nuclear receptors are pregnane X receptor (PXR) with rifampicin as ligand, constitutive androstane receptor (CAR) with its ligand phenobarbital, and peroxisome proliferators activated receptor (PPAR) whose ligand is fibrate.[11]

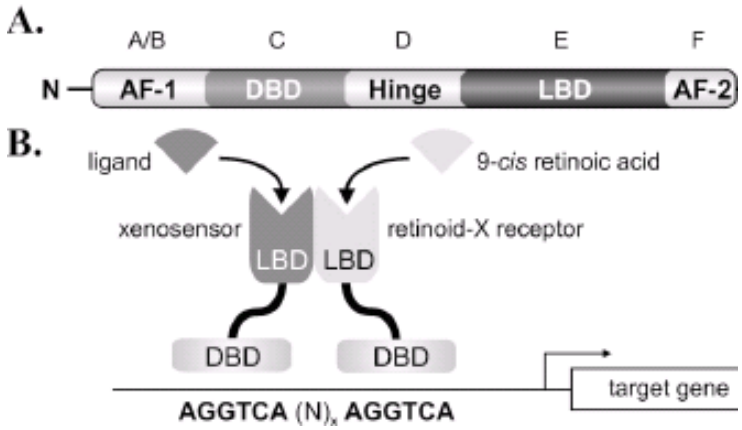

Figure 1. Structure of a nuclear receptor.[13]

A. The nuclear receptor consists of 4 domains, viz. the N-terminal region containing the activation function 1 (AF-1), DNA binding domain (DBD), hinge domain, and ligand binding domain (LBD) containing the activation function 2 (AF-2).
B. DNA binding domain of the nuclear receptor. PXR and CAR are members of the nuclear receptor superfamily functioning as sensors for the presence of lipophilic xenobiotics, including drugs. When the nuclear receptor senses the presence of a xenobiotic, it binds to RXR (heterodimer) of the responsive element of the target gene and triggers the transcription of nucleotide hexamers.

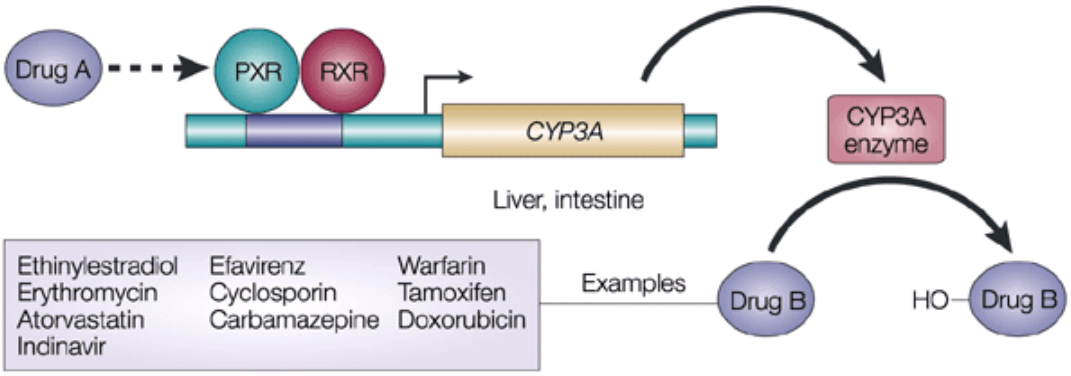

Figure 2. Drug interaction at molecular level[15]

Nuclear receptor PXR is a transcription factor regulating the expression of the CYP3A gene (yellow) in the liver and small intestine. In order to function PXR binds to the nuclear receptor RXR forming a heterodimer. Binding of drug A to PXR and induction of expression of enzyme CYP3A (pink) accelerates the metabolism of drug B, which is the substrate of CYP3A. CYP = cytochrome P450; OH = hydroxyl group; PXR= pregnane X receptor; RXR= retinoid X receptor.

PXR is activated by a number of drugs, one of them being rifampicin. PXR is expressed in the same tissue where CYP3A4 is expressed. Activation of PXR induces expression of CYP3A4, and of genes coding for drug transporters (e.g. P-glycoprotein), and phase II enzymes including UGT and SULT.[13]

The genes induced by CAR include those encoding several CYP enzymes (CYP2B6, CYP2C9, and CYP3A4), a number of phase II GST, UGT and SLUT enzymes, and endobiotic transporters. CYP3A4 is induced by PXR and CAR, such that the level of this enzyme is considerably affected by many drugs and xenobiotics.[13]

Induction of cytochrome P-450 by rifampicin

The mechanism by which rifampicin induces the enzyme CYP3A4 is mediated by activation of the nuclear receptor PXR (also known as "steroid X receptor") and CAR. Rifampicin functions as a ligand that activates the transcription factor when bound to PXR. This process is followed by the formation of a heterodimer with the retinoid X receptor (RXR), the heterodimer ultimately binding to the responsive elements of DNA in the regulator region of the CYP3A gene. The outcome is upregulation of DNA transcription resulting in increased synthesis of the CYP3A4 enzyme and increased oxidative metabolism of the substrate of the enzyme.[14] Drug interaction at molecular level is illustrated in Figure 2.

Another nuclear receptor, CAR, is also involved in the activation of transcription factor CYP3A4. CAR exhibits cross-talk[16] (functional interaction between 2 or more signaling pathways) with PXR, in the sense that both nuclear receptors bind to the same responsive element in the promoter region of the gene for CYP3A4 as well as CYP2B6 (Figure 3).

Cross-talk enables the two nuclear receptors to induce activation of the transcription factor of the CYP3A4 and CYP2B6 genes as a result of rifampicin administration. In addition, the occurrence of cross-talk causes CAR and PXR to jointly compensate for loss or malfunction of each nuclear receptor.[17] The effect of rifampicin on CAR is smaller than on PXR.[17] Efavirenz and nevirapin induce the genes for CYP2B6 and CYP3A4 principally through activation of CAR.[16]

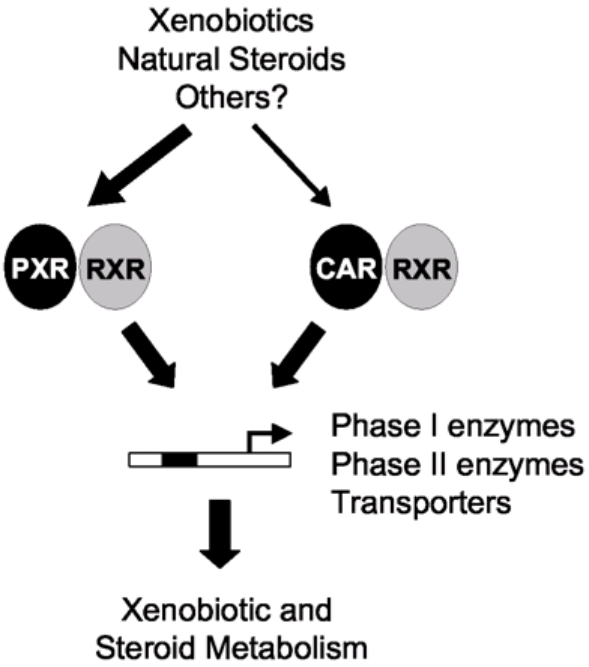

Figure 3. Cross-talk between PXR and CAR signaling pathways.[16]

Both nuclear receptors PXR and CAR are modulated by xenobiotics and steroids. To become active, PXR and CAR bind to RXR to form a heterodimer at the responsive element of the regulator region of the genes involved in the metabolism of xenobiotics and steroids, including those coding for phase I and phase II enzymes and transporters.

RIFAMPICIN

Currently there are 3 types of rifamycin that are used in clinical practice, namely rifampicin (rifampin), rifapentin, and rifabutin. The use of rifapentin is not recommended for treatment of TB in HIV-positive patients, due to the high microbiological failure rate.[18] Rifabutin is recommended more for use in HIV patients with concomitant TB infection, as the risk of its potential interaction with ARV (protease inhibitor and NNRTI) is the lowest among the existing rifamycins.

Rifamycin acts to inhibit deoxyribonucleic acid (DNA)-dependent ribonucleic acid (RNA) polymerase of mycobacteria and other microorganisms (Figure 4). Inhibition of DNA-dependent RNA polymerase leads to suppression of the initiation of DNA chain formation (but not of chain extension) required for microbacterial replication.[19]

Rifampicin is well-absorbed following oral administration, the peak concentration being reached within 2-4 hours. After being absorbed, the drug is rapidly eliminated into the bile and enters the enterohepatic circulation. The half-life of rifampicin is from 2- 5 hours. The half-life is progressively shortened within 14 days of therapy, due to the ability of rifampicin to induce hepatic microsomal enzymes and accelerate the deacetylation process that plays an important role in drug elimination. Elimination of rifampicin in the urine is only 30%, and in the feces 60-65%, less than half in intact form. Therefore its dose does not need to be adjusted with impaired renal function.[18] The pharmacokinetic profile of rifampicin is shown in Table 1.

Rifampicin is in general well-tolerated. Less than 4% of patients experience side effects, the most common in treatment of TB being skin rashes, fever, nausea, and vomiting. Rarely hepatitis and hepatic failure may occur.[19]

The most important interactions of the members of the rifamycin class occur mainly with the CYP3A4 and CYP2C8/9 isozymes. In addition to these two CYP isozymes, rifampicin also induces the activity of isozymes CYP2C19 and CYPB6 to a smaller extent.[5] The members of the rifamycin class differ in CYP induction potential, and in order of decreasing potency these are rifampicin > rifapentin > rifabutin, with a difference in induction potential of approximately 3:2:1.[20] In addition to being a potent CYP inducer, rifampicin also upregulates the synthesis of cytosolic enzymes involved in the metabolic reactions of phase II drugs, e.g. uridine diphosphate-glucuronosyltransferase and sulfotransferase.[12]

Table 1. Pharmacokinetic profile of rifampicin[19]

	Rifampicin
Bioavailability (%)	68
Effect of food	↓AUC* 6%, ↓Cmax** 36%
Main metabolic pathway	Deacetylation, hydrolysis to formal derivatives
Effect on CYP3A4 induction	Excellent
Autoinduction	Yes
Half life	2-5
Bound protein (%)	85

* AUC = area under the time-concentration curve

** Cmax = maximal drug concentration

EFAVIRENZ

Efavirenz is one of four NNRTI drugs licensed by the Food and Drug Administration (FDA) for treatment of HIV. The other three agents are nevirapin, delaverdin, and etravirdin. Among these, delavirdin is rarely used in clinical practice because of its relatively lower potency and higher frequency of administration when compared to the others. Etravirdin is reserved for cases resistant to the other NNRTI. All four drugs have differing structures, but a common mechanism of action.

NNRTI act as noncompetitive inhibitors of the reverse transcriptase of the Human Immunodeficiency Virus type-1 (HIV-1), that transcribes viral RNA into DNA. Binding of NNRTI to the hydrophobic pocket in the HIV-1 reverse transcriptase subunit p66 induces conformational changes and disturbs the catalytic activity of the enzyme, thus resulting in inhibition of viral DNA synthesis.[21]

Orally administered efavirenz is well-absorbed in the digestive tract, with a peak concentration within 5 hours. The bioavailability of the drug is increased by 22% on simultaneous intake of foods high in fat. Over 99% of the drug is bound to plasma proteins. The metabolism of efavirenz is mainly mediated by CYP2B6 to produce 8-hydroxyefavirenz, followed by oxidation into 8,14-dihydroxyefavirenz. Other isozymes (CYP3A4, 3A5, and 1A2) contribute only minimally to the metabolism of efavirenz.[22] Efavirenz is an inducer of CYP3A4, thus being able to induce its own metabolism.[21] The autoinduction of efavirenz results in a difference in the half-times of the drug on administration of a single dose (52-76 hours) as compared with administration of multiple doses (after reaching a stable level) with half-life of 40-55 hours. Elimination of the unmodified drug by way of the kidneys is insignificant (< 1%), thus no dose adjustment is necessary in renal dysfunction.[21] The pharmacokinetic profile of efavirenz is shown in Table 2.

The commonly encountered side effects of efavirenz are skin rashes, disorders of the central nervous system (dizziness, disturbed concentration, dysphoria, nightmares, and insomnia) including psychotic episodes (depression, hallucinations, and/or mania). The central nervous system side effects are generally tolerated and disappear within the initial 4 weeks of therapy. To reduce the side effects, the drug is taken on an empty stomach at bedtime. Other reported side effects are headaches and increased levels of hepatic transaminases and serum cholesterol. Administration of the drug to pregnant women results in malformations of the fetal brain and spinal cord.[21]

Table 2. Pharmacokinetic profile of efavirenz[21,23]

	Efavirenz
Bioavailability (%)	Unknown
Effect of food	Taken on empty stomach. Admistration with food increases AUC by 20% & Cmax by 40-50%.
Main metabolic pathway	CYP2B6, CYP3A4 (minimal)
Effect on CYP3A4 induction	Induction
Autoinduction	Yes (no need for dose adjustment)
Half life	40-55
Bound protein (%)	>99

All NNRTI drugs are metabolized by CYP450, but by different isozymes. Nevirapin is the substrate of CYP3A4 whilst efavirenz is mainly metabolized by CYP2B6, such that its concentration is less affected by administration of other drugs modifying the activity of the CYP3A4 enzymes, e.g. rifampicin, when compared with other members of the NNRTI group.[21]

Studies on the interactions of rifampicin and efavirenz

The optimal dose of efavirenz when administered concomitantly with rifampicin is still the subject of controversy. Several pharmacokinetic studies that have been conducted will be discussed here. The pharmacokinetic study by Lopez-Cortez et al.[23] in Spain on 24 patients with concomitant infections of HIV and tuberculosis was of non-blinded randomized design. Group A (n=16) received antituberculosis drugs without rifampicin (comprising isoniazid, pyrazinamide, and streptomycin), but with added antiretroviral therapy containing efavirenz 600 mg/day, on days 1–7. The patients were then switched to a standard antituberculosis regimen containing rifampicin (plus isoniazid and pyrazinamide) with an antiretroviral regimen containing efavirenz 600 mg/day (group A1; n=8) or efavirenz 800 mg/day (group A2; n=8). The second treatment group, i.e. group B (n=8), received standard TB therapy containing rifampicin on days 1-7, with the addition of an antiretroviral regimen containing efavirenz 800 mg/day on day 8. The plasma concentration of efavirenz was determined on days 7 and 14. The levels of AUC, C_{max}, and C_{min} of efavirenz decreased respectively 24%, 25%, and 22%, after addition of rifampicin to the efavirenz of 600 mg/day (treatment A1 vs A). The exposure to efavirenz in group A2 (efavirenz 800 mg/day with rifampicin) and group A (efavirenz 600 mg/day without rifampicin) yielded similar results. The investigators stated that there was a positive association between body weight, dose of efavirenz (dose/kg), and the pharmacokinetic parameters of efavirenz. However, when the data were analyzed by body weight (<50 kg vs ≥50 kg), it was apparent that the concentration of efavirenz with 800 mg daily dose administered concomitantly with rifampicin was identical to that seen with the dose of 600 mg/day without rifampicin, independent of body weight. Because of the uncertainty regarding the minimum plasma concentration of efavirenz required for virological suppression, the investigators suggested increasing the dose of efavirenz from 600 mg/day to 800 mg/day as a single dose, irrespective of body weight of the patients on concomitant rifampicin.

Manosuthi et al.[24,25] conducted an non-blinded randomized clinical trial for respectively 24 and 48 weeks on 84 patients with HIV-TB coinfection in Thailand. Patients receiving rifampicin for more than 1 month were randomized into 2 groups of identical size, to whom was given a therapeutic regimen containing efavirenz 600 mg/day (n=42), or efavirenz 800 mg/day (n=42). The plasma concentrations of efavirenz were determined respectively 12 hours after drug administration and on day 14. The numbers of $CD4^+$ cells and the levels of HIV RNA were also assessed on weeks 16, 24, and 48. The study results indicated similar means of body weight in the two groups (50.6 kg vs 52.9). Both groups had 12-hr efavirenz concentrations (C_{12}) of similar magnitude (median 3.02 mg/L vs 3.39 mg/L); but the upper C_{12} levels were higher in the group receiving efavirenz at the dosage of 800 mg/day (21.3 mg/L) in comparison with the group on 600 mg/day (12.2 mg/L). In general, AUC and C_{min} were important predictor parameters used for finding a correlation between antiretroviral exposure and virological response.[24] Other data indicate that the 12-hr efavirenz concentration was also useful for predicting virological failure, similar to the central nervous system side effects occurring as a result of efavirenz administration.[26] Follow up studies were done up to 48 weeks in order to assess the virological and imunological responses. On the 48th week, 31 of 34 patients (91.2%) in the group on 600 mg/day, and 27 of 31 patients (87.1%) in the group on 800 mg/day attained HIV RNA levels of <50 copies/mL. In addition, there were no differences in $CD4^+$ levels between the two groups on the 24th and 48th weeks. The conclusion of this study was that efavirenz with a dose of 600 mg/day is adequate for the majority of HIV-infected patients in Thailand (with a body weight of around 50 kg) receiving rifampicin concomitantly. The investigators also state that the recommended dosages should not be applied to other ethnic groups, or to populations with a higher body weight (>50 kg).

The study conducted by Brennan-Benson et al.[28] was aimed at determining the effects of higher body weights and differing ethnicities on exposure to efavirenz. This observational study involved 9 patients with body weights of over 50 kg (mean 66.4 kg; range 52-107 kg). The patients received an antiretroviral regimen containing efavirenz 800 mg/day and antituberculosis therapy containing rifampicin. During a time period of 2 years the clinical toxicity and plasma concentrations of efavirenz were monitored. Seven out of the 9 patients with HIV/TB coinfection experienced clinical toxicity, namely central nervous system toxicity in 6 persons, and hepatitis in 1 person. The induced toxicity necessitated a reduction of the doses or cessation of therapy. All patients experiencing toxicity had supratherapeutic trough concentrations of efavirenz (median 11.7 mg/L; range 5.37-19.6 mg/L). The target therapeutic range of trough concentrations of efavirenz were between 1.2 and 4.0 mg/L. Among the 7 patients experiencing toxicity, 6 of them were ethnic Black Africans, and one was a Caucasian. The investigators were of the opinion that CYP2B6 polymorphism contributes heavily to the high rate of central nervous system toxicity. Around 20% of ethnic Black Africans possess homologous G516T alleles versus 3% of Caucasians.[28] This CYP2B6 polymorphism is associated with exposure to higher concentrations of efavirenz and with central nervous system toxicity due to slower clearance of efavirenz.[28]

Friedland et al.[6] revealed the existence of a wide variability in efavirenz concentrations among 19 ethnic Black Africans with HIV/TB coinfection (mean body weight 59.4 kg; range 45-97 kg) who received efavirenz 600 mg/day concomitantly with rifampicin. The investigators

monitored the minimal plasma concentrations of efavirenz (C_{min}) intermittently during a 6-month combination therapeutic regimen for TB containing rifampicin and antiretroviral drugs, and 15 months after cessation of TB therapy. The study results indicated that inter-subject variability in efavirenz concentrations was greater if the drug was administered with rifampicin (coefficient of variation [CV] 157%) compared with the inter-subject variability after discontinuation of rifampicin (58%), with relatively consistent intra-subject variation over time (CV 24%). $C_{min,}$ however, was not significantly different during versus post TB therapy. Efavirenz concentration was not correlated with body weight, irrespective of concomitant rifampicin administration. Of the 17 patients who completed the HIV/TB therapy, 16 had an HIV RNA level of <50 copies/mL. Seven persons (35%) reportedly had dizziness and poor concentration during the initial weeks of efavirenz therapy, but no association was found between plasma efavirenz concentrations and neuropsychiatric symptoms. The investigators were of the opinion that the optimal dosage of efavirenz should be mainly determined on the basis of studies assessing clinical outcomes and supported by pharmacokinetic data for informing their design. Notwithstanding the variability in plasma efavirenz concentrations during rifampicin administration, excellent HIV clinical treatment outcomes were obtained. The authors support the use of a routine dose of efavirenz 600 mg/day on concomitant administration of rifampicin for African patients with HIV/TB coinfection. A summary of studies assessing the interactions between efavirenz and rifampicin in patients with HIV/TB may be seen in Table 3.

The determination of the optimal dosage is generally based on pharmacokinetic studies. However, assessing the optimal dosage of efavirenz for use in combination with rifampicin is not a simple question. This is due to the wide variation in the following aspects of the studies: the study design used (randomized[24-26] vs observational);[6,27] the duration of follow-up; the time of administration of efavirenz. (In some studies the drug was given with meals, whereas in others it was given to fasting patients). The food factor contributes to the difficulties in determining the optimal dose of efavirenz, and is connected with the occurrence of side effects. Administration of efavirenz with meals increased the AUC and C_{max} of the drug by 20% and 40-50%, respectively.[21] The studies did not provide important information in connection with the collection of pharmacokinetic data, such as time of sample collection or the methods used for assessing the relevant pharmacokinetic parameters. Most studies used an inadequate pharmacokinetic sample size because the investigators believed that the study subjects would not consent to repeated blood sampling for an extended period of time. In studies providing pharmacokinetic parameters, the available pharmacokinetic data for assessing exposure to efavirenz were extremely variable (C_{12h}, C_{min}, AUC). The relationship between C_{12h} and C_{min} is still unclear. In addition, assessment of the efficacy and safety of efavirenz based on C_{12h} concentration has still to be validated.

The majority of patients in the study had a body weight of ≤50 kg; the data showed that efavirenz 600 mg/day was adequate for maintaining virological and immunological control up to the 48th week on concomitant admininstration of rifampicin. However, considerable amounts of data are still required on patients with body weights of >50 kg, because some studies have demonstrated toxicity of efavirenz necessitating reduction of dosages or cessation of treatment in patients with higher body weights.[24,25,27]

Table 3. Summary of studies on concomitant efavirenz and rifampicin administration in patients with HIV and TB coinfection

	Study design[@]	Number of subjects	Body weight badan (kg)	Dose of efavirenz (single dose)	Pharmacokinetics & virology	Side effects
Lopez-Cortez et al.[24] (Spain)	Randomized, unblinded, controlled, prospective; follow up 2 weeks	24	Median 54; range 38-80	600 mg (n= 8) 800 mg (n= 16)	Addition of RFP to EFV 600 mg caused C_{min} EFV ↓25%, AUC ↓22%. Exposure to EFV 800 mg + RFP identical to EFP 600 mg only, irrespective of body weight (<50 kg vs ≥ 50 kg)	600 mg: SSP (4), rash (1), ↑liver functions (1). 800 mg: SSP (1), ↑ liver functions (2)
Manosuthi et al.[25,26] (Thailand)	Randomized, unblinded, controlled; follow up 48 weeks.	84	Mean 50.6 (600 mg group) Mean 52.9 (800 mg group)	600 mg (n= 42) 800 mg (n= 42)	Median EFV C_{12h} identical in both groups, but upper range of C_{12h} higher in 800 mg (21,3 mg/L) group vs 600 mg (12,2 mg/L) group. Virological and immunological outcomes at week 48 identical in both groups.	600 mg: rash (1), headache (1) 800 mg: rash (1), hepatitis (1)
Brennan-Benson et al.[28] (England)	Obervational, unblinded, prospective; follow up 2 years	9	Mean 66.4; range 52-107	800 mg	Median C_{min} 11.7 mg/L (range 5.4-19.6 mg/L) in 7 patients (therapeutic range 1.2-4 mg/L)	Seven out of 9 patients had efavirenz toxicity necessitating dose reduction or cessation of therapy. CNS (6), hepatitis (1)
Friedland et al.[6] (South Afrika)	Observational, unblinded, prospective; follow up 21 months	20	Mean 59.4; range 45-97	600 mg	Mean C_{min} EFV identical, with or without concomitant RFP; ↑↑ intersubject variability of EFV on concomitant RFP. Sixteen out of 17 patients completing treatment had HIV RNA <50 copies/mL in month 21	CNS (7)

EFV = Efavirenz; RFP = rifampicin; CNS = central nervous system
@ single center; except study by Manosuthi et al. (two-center study)

Ethnicity and pharmacogenetics provide important contributions and should be considered in connection with the wide variability among the patients to efavirenz exposure. The majority of patients in the study were Asians or ethnic Black Africans, whilst Caucasians were underrepresented. Ethnicity plays an important role because ethnic Black Africans are frequently of the homologous CYP2B6 516-T/T genotype in comparison to other ethnic groups.[28] This fact is supported by the study conducted by Friedland et al.[6] where the study results indicated that Black African patients suffered more frequently from central nervous system side effects although receiving a dose of 600 mg with rifampicin. The significant toxicity of efavirenz leading to a dose reduction was also reported in predominantly ethnic Black Africans receiving 800 mg efavirenz with rifampicin.[27]

A study performed in Japan on patients with HIV infection had the goal of determining the possibility of a dose reduction of efavirenz on the basis of genotype. Among 456 patients of whom the genotype was determined, 16 were found to be carriers of 516-T/T. In all 16 patients a concentration of efavirenz of >6000 ng/mL was found when given a standard dose of 600 mg/day. For 12 patients a dose reduction was effected to 400 mg/day, and among 11 subjects the dose was reduced further to 200 mg/day in 7 subjects. Among 4 persons receiving an initial dose of 400 mg, 2 of them had persistently high efavirenz concentrations, thus necessitating a dose reduction to 200 mg/day. The ascertained dosages were continued for >6 months, in which period HIV levels were still undetectable. These study results demonstrate the successful outcome of a dose reduction of efavirenz to 400 mg/day or 200 mg/day in Japanese 516-T/T carriers with HIV (without TB infection). Dose reduction according to genotype resulted in reduction of central nervous system side effects and was capable of maintaining virological control. These findings indicate that an increase in dosage of up to 800 mg/day on concomitant administration of rifampicin may not be necessary in patients with the homologous allele variant 516T/T.[29] Other studies demonstrated intersubject variability in pharmacokinetics of efavirenz due to another CYP2B6 polymorphism, namely C1459T.[30]

Clinical application

To date several guidelines have been prepared by clinicians on the use of efavirenz with rifampicin. The recommendation issued by the British HIV Association (BHIVA)[31] in the therapeutic guidelines for HIV/TB in 2009 currently favors a dose of efavirenz of 600 mg/day for patients with a body weight of < 50 kg, and recommends consideration of increasing the dosage to 800 mg/day for patients with a body weight of >50 kg[31] or >60 kg.[9] Cipto Mangunkusumo Hospital uses a dose of efavirenz 600 mg for patients with HIV/TB, irrespective of body weight, in accordance with the guidelines issued by the World Health Organization (WHO)[4] which only recommend a dose of 600 mg, without regard to body weight. The Food and Drug Administration[32] states that the available data are inadequate for supporting a recommendation of the dosages of efavirenz when used concomitantly with rifampicin.

CONCLUSIONS

Concomitant use of rifampicin with efavirenz leads to unavoidable drug interactions. Interactions between the two drugs result in a wide variation in the plasma efavirenz concentrations, thus being capable of affecting therapeutic outcomes or the occurrence of toxic effects. This leads to problems in determining the optimal dosage of efavirenz in patients with HIV/TB coinfection. Before assessing the

optimal dosage, it is necessary to study the patterns of interaction of the two drugs. Pharmacokinetic studies with good measurement parameters and methods are still needed as the basis for determining the optimal dosage of efavirenz in the Indonesian population.

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