Body Weight Cutoff for Daily Dosage of Efavirenz and 60-Week Efficacy of Efavirenz-Based Regimen in Human Immunodeficiency Virus and Tuberculosis Coinfected Patients Receiving Rifampin[▽]

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Seventy-one human immunodeficiency virus-infected patients with tuberculosis who were receiving a rifampin (rifampicin)-containing regimen were initiated on treatment with efavirenz at 600 mg/day plus stavudine-lamivudine. Fasting efavirenz concentrations at 12 h after dosing (C_{12}) were monitored. The mean $\pm$ standard deviation efavirenz C_{12} at weeks 6 and 12 and after rifampin discontinuation were 4.5 ± 4.3 , 3.8 ± 3.5 , and 3.5 ± 2.7 mg/liter, respectively. High body weight was associated with a low efavirenz C_{12} at weeks 6 and 12 ($P = 0.003$, $r = -0.255$). The efavirenz C_{12} regression prediction line at 1 mg/liter intercepted a mean body weight of 57.5 kg.

N₂R was a randomized clinical trial comparing the clinical efficacies of two nonnucleoside reverse transcriptase inhibitor-based highly active antiretroviral therapy (HAART) regimens for patients coinfecting with human immunodeficiency virus (HIV) and tuberculosis who received rifampin (rifampicin) (9). A secondary objective was to assess body weight as a cutoff for selecting the daily dosage of efavirenz. Patients were enrolled and followed through 60 weeks after HAART. Inclusion criteria were described previously (9). All patients were started on twice-daily stavudine-lamivudine and efavirenz at 600 mg/day at bedtime. The dosages of rifampin were 450 mg/day for body weights of ≤ 50 kg and 600 mg/day for body weights of > 50 kg. Fasting efavirenz concentrations at 12 h after dosing (C_{12}) were measured with a validated high-performance liquid chromatography assay at weeks 6 and 12 and at 6 to 12 weeks after rifampin discontinuation. This assay was developed at the Department of Clinical Pharmacology of the University Medical Center Nijmegen, Nijmegen, The Netherlands (5).

All statistical analyses were performed with SPSS version 11.5 (SPSS Inc., Chicago, IL). Pearson's correlations were used to study the relationships between parameters. Factors possibly predictive of efavirenz C_{12} and an elevated serum alanine aminotransferase (ALT) activity at week 12 were evaluated with a linear-regression model. Inter- or inpatient variability was expressed as a coefficient of variation (CV). The institutional ethics committees of the Bamrasnaradura Infectious

Diseases Institute and the Thai Ministry of Public Health approved this study.

Seventy-one patients were enrolled; 65% were male, and the mean $\pm$ standard deviation (SD) baseline body weight was 53 ± 10 kg. The mean $\pm$ SD baseline CD4 cell count was $75 \pm 68/\mu\text{l}$, the median (interquartile range) log plasma HIV type 1 RNA copy number was 5.8 (range, 5.6 to 5.8), and the mean $\pm$ SD serum ALT activity was 29 ± 18 U/liter. Six (8.5%) patients were positive for hepatitis B surface antigen, and 18 (25.4%) were positive for hepatitis C antibody. The mean $\pm$ SD efavirenz C_{12} at weeks 6 and 12 and after rifampin discontinuation are shown in Fig. 1. After stratification into four groups by body weight (35 to 45, 46 to 55, 56 to 65, and > 66 kg) at week 6, the mean C_{12} were 7.6 mg/liter, 4.1 mg/liter, 2.4 mg/liter, and 1.8 mg/liter, respectively. Three (4.3%) of 70, 2 (3.1%) of 64, and 2 (3.3%) of 60 patients, respectively, had efavirenz C_{12} of < 1 mg/liter at weeks 6 and 12 and after rifampin discontinuation ($P > 0.05$). Twenty-four (34.3%), 16 (25.0%), and 14 (23.3%) patients had efavirenz C_{12} of > 4 mg/liter at the corresponding periods ($P > 0.05$). High interpatient variability at weeks 6 (CV, 105%) and 12 (CV, 107%) and after rifampin discontinuation (CV, 77%), as well as high inpatient variability between weeks 6 and 12 (CV, 136%) were observed in the efavirenz C_{12} . Figure 2 shows the relationship between efavirenz C_{12} at the different time points. In the separate multivariate analysis model, at the different time points, low C_{12} at weeks 6 and 12 were associated with higher body weights ($P = 0.028$), as shown in Table 1. This correlation was not significant ($P = 0.244$) after discontinuation of rifampin.

By intent-to-treat and on-treatment analyses at 60 weeks, 70.4% (50 of 71) and 81.9% (50 of 61) of the patients achieved HIV type 1 RNA levels of < 50 copies/ml, respectively. Two

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FIG. 1. Distributions of efavirenz C_{12} after 6 and 12 weeks of HAART (in patients concurrently receiving efavirenz and rifampin) and after rifampin discontinuation. *, P value for comparison of efavirenz C_{12} means between time points by repeated-measurement analysis.

(66.7%) of 3 patients with efavirenz C_{12} of <1 mg/liter at week 6 and 18 (16.9%) of 67 patients with efavirenz C_{12} of ≥ 1 mg/liter at week 6 developed treatment failure. The mean $\pm$ SD serum ALT activity increased from the baseline at week 12 (38 ± 32 U/liter; $P = 0.046$, paired t test). At 12 weeks, two patients developed grade III hepatotoxicity. Multivariate analysis of ALT activity-predictive factors at week 12 showed that

positivity for hepatitis B surface antigen was a predictor of high serum ALT activity during concurrent efavirenz and rifampin administration ($P = 0.005$). Three patients developed grade II/III cutaneous reactions.

The range of acceptable efavirenz C_{12} is currently proposed to be 1 to 4 mg/liter (7). To date, clinical trials evaluating weight-based cutoffs for efavirenz dosing during coadministra-

FIG. 2. Relationship between body weight at timing of concentration and pooled efavirenz C_{12} at weeks 6 and 12 (in patients receiving efavirenz and rifampin) (A) and at weeks 6 and 12 after rifampin discontinuation (B). Broken lines represent regression prediction and 95% confidence intervals for the mean. Open squares represent C_{12} at weeks 6 and 12, and filled squares represent C_{12} after rifampin discontinuation. There appears to be a relationship between high body weight and low combined efavirenz C_{12} at weeks 6 and 12 ($P = 0.003$, $r = -0.255$). Conversely, when the regression line was plotted by defining efavirenz C_{12} as an independent variable, efavirenz C_{12} at 1 mg/liter intercepted body weight at a mean of 57.5 (95% CI, 54.9 to 60.1) kg. The same trends were found at weeks 6 ($P = 0.033$, $r = -0.257$) and 12 ($P = 0.058$, $r = -0.234$) and were also found in efavirenz C_{12} at weeks 6 and 12 and after rifampin discontinuation, as shown in panel B ($P = 0.001$, $r = -0.239$).

TABLE 1. Summary of multivariate analysis of efavirenz concentration and patients' parameters at weeks 6 and 12

Parameter	Efavirenz C_{12} at:					
	Wk 6			Wk12		
	Beta	95% CI	P value	Beta	95% CI	P value
Body wt	-0.289	-0.254 to -0.015	0.028	-0.310	-0.207 to -0.019	0.020
Baseline serum creatinine	0.122	-3.988 to 10.284	0.381	0.192	-0.006 to 0.049	0.125
Age	-0.095	-0.183 to 0.081	0.440	0.176	-0.030 to 0.175	0.162
Serum ALT	-0.008	-0.006 to 0.005	0.947	0.103	-3.388 to 7.821	0.432

tion of rifampin are limited (1, 2, 6–8, 10, 12). In the present study, almost one-third of the patients had body weights of ≥ 60 kg during monitoring. Nevertheless, most achieved concentrations above the minimum recommended level. The efavirenz C_{12} decreased 16% relative to that at week 6, as patients gained an average of 3 kg of body weight, but this decrease did not change the percentage of patients with a C_{12} of <1 mg/liter. Interestingly, an efavirenz concentration of 1 mg/liter intercepted a mean body weight of 60 kg at the upper limit of the 95% confidence interval (CI) of the beta value of the correlation coefficient. Therefore, increasing efavirenz dosing, practically to 800 mg/day, in patients weighting >60 kg to compensate for the effect of rifampin coadministration may be considered.

Efavirenz concentrations persistently decreased from 25% to 46% for every 10-kg increase in body weight. In addition, a high body weight was found to be an important predictive factor of a low drug concentration. These models did not include gender because this parameter had a highly positively correlated with body weight ($P < 0.001$). A cross-sectional study showed that body weight was an independent predictive factor for efavirenz concentration (16). Furthermore, marked interpatient and inpatient variabilities were observed in this study during concurrent the use of both drugs, and this trend was found to be consistent over time. The previous studies showed low inpatient variability in patient receiving efavirenz alone (11). This may be explained by the extensive difference of genetic polymorphism that influences *CYP2B6* enzyme expression (17).

A number of limitations should be acknowledged. First, this study collected C_{12} instead of the minimal drug concentration to assess drug exposure. A number of studies attempted to demonstrate the ability of C_{12} to predict clinical efficacy and adverse reactions (3, 11). Second, there are no studies that clearly show that therapeutic drug monitoring improved patients' clinical outcomes. Third, a persons with the *CYP2B6* polymorphism 516G>T had higher efavirenz concentrations (4, 13, 15). The frequency of this allele ranges from 15% in Asians to 50% in Africans (4, 15). Ultimately, previous studies demonstrated that many factors and issues contribute to pharmacokinetic variability, including biological factors, environmental factors, and genetic issues (14).

A standard-dose efavirenz-based regimen is appropriate for HIV patients with tuberculosis who are receiving rifampin and have body weights of <60 kg. In clinical practice, a weight-based cutoff for efavirenz dosing is a practical therapeutic approach. However, further study is needed to explore the appropriate escalating daily efavirenz dosage in

patients with higher body weights. In addition, the issue of ethnic pharmacogenetic differences should be taken into account.

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We have no conflicts of interest to declare.

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