Published in final edited form as:

J Clin Pharmacol. 2008 September ; 48(9): 1032–1040. doi:10.1177/0091270008321790.

Pharmacokinetics of Efavirenz when Co-administered with Rifampin in TB/HIV Co-infected Patients: Pharmacogenetic Effect of *CYP2B6* Variation

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Abstract

The goal of this study was to determine the effect of *CYP2B6* genetic variation on the steady-state pharmacokinetics of efavirenz (600 mg/day) in TB/HIV co-infected patients receiving concomitant rifampin, a potent *CYP* inducer. In the 26 patients studied, *CYP2B6* c.516GG, GT and TT genotype frequencies were 0.27, 0.50 and 0.23, respectively. Mean plasma efavirenz area-under-the-curve was significantly higher in patients with *CYP2B6* c.516TT than in those with GT (107 vs. 27.6 µg.h/mL, $P < 0.0001$), or GG genotype (107 vs. 23.0 µg.h/mL, $P < 0.0001$). Apparent oral clearance (CL/F) was significantly lower in patients with *CYP2B6* c.516TT than in those with GT genotype (2.1 vs. 8.4 mL/min/kg, $P < 0.0001$), and GG genotype (2.1 vs. 9.9 mL/min/kg, $P < 0.0001$). No differences in efavirenz exposure or CL/F existed between patients with *CYP2B6* c.516GT and GG genotypes. Our results indicate that *CYP2B6* c.516TT genotype can be used to identify efavirenz poor metabolizers in patients co-treated with rifampin.

Keywords

Cytochrome P450 2B6; genetic polymorphisms; efavirenz exposure; rifampin

Tuberculosis (TB) is the most common complication of human immunodeficiency virus (HIV) infection and is associated with high fatality rates.^{1,2} While highly active antiretroviral therapy (HAART) improves survival in co-infected patients,³⁻⁵ potential overlapping drug toxicities, and cytochrome P450 (*CYP*)-mediated drug-drug interactions constitute major challenges to early initiation of HAART. The magnitude of drug-drug interactions due to rifampin is a major factor in selecting an effective HAART regimen.⁶⁻⁸ Rifampin is a critical component of TB therapy,⁹ but is also a potent inducer of *CYP* enzyme activity,¹⁰⁻¹² as well as the P-glycoprotein (P-gp) transport system.¹³ As a result, the exposure to the HIV protease inhibitors (PIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs) is reduced during

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CONFLICTS OF INTEREST

A. Kwara has received research funding from Bristol-Myers Squibb and is a member of the speaker's bureau. The other authors declare no conflict of interest.

concomitant rifampin therapy.⁶⁻⁸ The reduction in exposure is more pronounced for the PIs and often co-administration with rifampin is contraindicated.⁶⁻⁸ Of the NNRTIs, current treatment guidelines consider the interactions between rifampin and efavirenz to be manageable, and an efavirenz-based regimen is preferred in patients on rifampin.⁶⁻⁸

Efavirenz is primarily metabolized by hepatic *CYP2B6*, with minor contributions from *CYP3A4/5* and *CYP2A6*.^{14,15} In the setting of impaired *CYP2B6* function, it is hypothesized that alternate metabolic pathways are critical for the clearance of efavirenz.¹⁶ The *CYP2B6* gene is highly polymorphic,¹⁷ and is subject to pronounced interindividual variability in expression and activity. The single nucleotide polymorphism (SNP) c.516G>T (Q172H), a marker for the *CYP2B6**6*6 [Q172H and c.785A>G (K262R)] allele, is significantly associated with elevated efavirenz plasma concentrations¹⁸⁻²² and a higher likelihood of efavirenz-related central nervous system (CNS) symptoms.^{21,22} The low clearance of efavirenz in *CYP2B6**6*6 haplotype has been associated with a reduced *CYP2B6* protein expression in the liver.¹⁵

Currently, it is not known whether *CYP* induction by rifampin will affect the relationship between *CYP2B6* c.516G>T genotype and efavirenz exposure. The reported magnitude of induction of *CYP2B6* activity by rifampin in primary human hepatocytes varies. While some authors reported a 7 – 13-fold induction,^{10,11} others found only 2.5-fold increase in activity.¹² In one *in vivo* study, *CYP2B6* activity in the presence of rifampin was only 2.1 times that in the absence of rifampin.²³ Co-administration of rifampin with efavirenz 600 mg daily caused a 22% reduction in efavirenz area under the curve (AUC) in HIV/TB co-infected patients, which was overcome by increasing the dose to 800 mg/day.²⁴ This finding led some experts to recommend an increased efavirenz dose when co-administered with rifampin.^{6,7,25} Although an increased efavirenz dose might be appropriate for some persons, it does not take into consideration the variable effect of rifampin on *CYP2B6* activity. In the aforementioned pharmacokinetic study, the change in efavirenz AUC with concomitant rifampin ranged from a decrease of 65% to an increase of 37%.²⁴ Furthermore, variability in efavirenz concentrations is greater in the presence of rifampin than without rifampin.^{26,27}

The *CYP2B6* genotype most frequently associated with the slow-metabolizer phenotype (c.516TT) occurs with high frequency in native African populations,^{28,29} and dose reduction has been proposed in patients with this variant.²⁹ Globally, efavirenz-based HAART is often needed in HIV/TB co-infected patients on rifampin. Consequently, understanding the potential modifying influence of enzyme induction and *CYP2B6* genetic polymorphisms could enhance optimization of efavirenz dosage.

In this study, we determined whether the *CYP2B6* c.516G>T genotype is predictive of efavirenz plasma concentrations in TB/HIV co-infected patients on rifampin. To our knowledge, this is the first study to evaluate whether variability in efavirenz exposure during co-administration with rifampin is related to *CYP2B6* polymorphisms.

METHODS

Study design and patients

A steady-state pharmacokinetic study of efavirenz was performed in HIV and TB co-infected patients in Ghana, West Africa. HIV/TB co-infected patients with CD4 count ≤ 250 cells/mm³ receiving rifampin therapy were prospectively enrolled between November 2005 and February 2007. Patients aged 18 years or older were considered for inclusion if they were antiretroviral therapy naïve, had a new diagnosis of TB in the induction phase of therapy, and were available for follow-up at the study site for antiretroviral therapy. Patients were excluded if they were pregnant or breast-feeding, had any other opportunistic infections within 30 days

of study entry, hemoglobin of < 6 g/dl, leucocyte count $< 2,500$ /mm³, serum creatinine > 1.5 mg/dl, and aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2 times upper limit of normal. All females with the potential for pregnancy were required to use two non-hormonal methods of contraception.

Tuberculosis diagnosis was based on a positive sputum smear for acid-fast bacilli (AFB), or a clinical presentation consistent with active disease. All patients received antituberculosis therapy consisting of isoniazid 5 mg/kg (max, 300 mg) daily, rifampin 10 mg/kg (max 600 mg) daily, pyrazinamide 25 mg/kg (2 gm daily) and ethambutol 15 mg/kg (max 2 gm) daily for at least 2 months, followed by isoniazid and ethambutol daily for 6 to 10 months in accordance with Ghana National TB treatment guidelines in 2005. HAART was started between 2 to 10 weeks of starting TB therapy. The HAART regimen consisted of efavirenz 600 mg daily plus either lamivudine 150 mg and zidovudine 300 mg twice daily, or lamivudine 150 mg and stavudine 40 mg twice a daily for those with hemoglobin was ≤ 8 g/dl. The Institutional Review Board (IRB) for the protection of human subjects of the University of Ghana Medical School, Ghana, and Lifespan Hospitals, Providence, Rhode Island reviewed and approved the study protocol.

Clinical and laboratory monitoring

Each participant was evaluated at study entry and relevant clinical data collected using standardized forms. Baseline measurement of complete blood count, blood urea nitrogen, serum creatinine, liver function tests, CD4 cell count and HIV-1 plasma viral load were done prior to starting HAART. All study participants were re-evaluated at week 2 of HAART, and at one month. Drug-related side effects, and clinical responses and medication adherence were recorded at follow-up visits. Hemoglobin and liver function tests were repeated at one month of HAART and toxicity graded according to the Division of AIDS table for grading severity of adult adverse experiences.³⁰

Pharmacokinetic sampling

Pharmacokinetic sampling was performed on day 14 of concurrent HAART. The median duration of rifampin therapy before initiation of HAART was 35 days (range, 14–70 days). Patients were instructed to switch their evening efavirenz administration to mornings three days prior to admission to the hospital for sampling. Blood samples obtained prior to medication dosage and at times 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, and 24 hours after observed administration of antituberculous and antiretroviral drugs. Seven to 10 milliliters of blood were collected in heparinized plastic tubes, then centrifuged at 3000 g for 10 minutes. Plasma was separated into labeled 1.2 mL cryovials and frozen at -70°C until shipping. The frozen plasma samples were shipped on dry ice for analysis and were received in good condition. Plasma samples were stored at -70°C until testing.

Analytical and pharmacokinetic analysis

Efavirenz concentrations were determined by a modified validated reverse-phase high-performance liquid chromatography (HPLC) with an ultraviolet absorbance detector.³¹ Ritonavir (Norvir, Abbott Laboratories, Abbott Park, IL) was used as the internal standard. The retention times of the internal standard and efavirenz were 9.9 and 16.9 minutes, respectively. Calibration curves were linear in the range of from 0.05 $\mu\text{g/L}$ to 12.5 $\mu\text{g/L}$ (mean $R^2 = 0.992$; SD = 0.003) and the limit of detection was 0.05 $\mu\text{g/L}$. Recovery of efavirenz ranged from 110 to 120%. Intra-day variability (expressed as a coefficient of variation) ranged from 8.8 to 13.7%, while inter-day variability ranged from 10.8 to 14.3%.

CYP2B6 genotyping

Exons 4, 5 and 7 of *CYP2B6* gene were sequenced to determine the c.516G>T (Q172H, rs3745274), c.785G>A (K262R, rs2279343) and c.983T>C (I328T, rs28399499) c.SNP genotypes in each study participant. We chose these SNPs because they are relatively common in native Africans populations and have been associated with altered *CYP2B6* function *in vivo*¹⁸⁻²² and/or *in vitro*.¹⁵ Since we used direct sequencing for genotyping, it was also possible to evaluate whether rarer cSNPs reported in African populations with established effects on *CYP2B6* function were also present including c.1006C>T (R336C, rs34826503), c.503C>T (T168I, rs36056539), and c.593T>C (M198T, rs36079186). Genomic DNA was isolated from blood spots collected on Whatman FTA Classic Cards (Whatman International Ltd, Kent, United Kingdom) according to the manufacturer's protocol. Polymerase chain reaction (PCR) was performed using three sets of primers designed to amplify target exons including exon-intron boundaries. The primers used were: GGT CTG CCC ATC TAT AAA C (forward), and CTG ATT CTT CAC ATG TCT GCG (reverse) for exon 4; ACA GCA AGG GAG ATG AGG AGA GGT (forward), and TCT TTC TGC CTC TGT GAG TTT TTT CTC T (reverse) for exon 5; and AAT CCA CCC ACC TCA ACC TCC AAA AT (forward) and CCA AAC AGG AGG GCT ATG GGG (reverse) for exon 7. SNP genotypes were determined by direct inspection of sequence chromatograms (FinchTV, Geospiza, Inc., Seattle, WA) and were used to infer the *CYP2B6**1*1 (reference), *CPY2B6**1*4 (K262R), *CPY2B6**6*6 (Q172H, K262R), *CPY2B6**1*9 (Q17H), *CPY2B6**1*16 (K262R, I328T) and *CPY2B6**1*18 (I328T) haplotypes for each subject (<http://www.cypalleles.ki.se/cyp2b6.htm>).

Pharmacokinetic analysis

Peak plasma concentration (C_{max}), time to C_{max} (T_{max}), concentration at 12 hours ($C_{12hours}$) and trough concentration at 24 hours (C_{min}) were obtained by visual inspection of the plasma efavirenz concentration-time profile for each patient. Other pharmacokinetic parameters were determined by non-compartmental methods from plasma drug concentration-time data. The $AUC_{0-24\text{ hour}}$ from time zero to 24 hours was determined using the trapezoidal method. Apparent oral clearance of efavirenz (CL/F) was calculated by dividing the administered efavirenz daily dose (600 mg) by the $AUC_{0-24\text{ hour}}$. Clearance was normalized to body weight ($CL/F/W$) at study entry in kilograms.

Statistical analysis

All statistical analyses were performed using Sigmasat 3.0 software (Systat, San Jose, CA). Values of $AUC_{0-24\text{ hr}}$, C_{max} , C_{min} , CL/F , and $CL/F/W$ among *CYP2B6* c.516GG, GT, and TT groups were compared using Kruskal-Wallis analysis of variance (ANOVA) on ranks. Individual groups were pairwise compared using the Student-Newman-Keuls procedure adjusting for multiple comparisons. Correlations between efavirenz $AUC_{0-24\text{ hour}}$ and C_{min} , and between efavirenz $AUC_{0-24\text{ hour}}$ and $C_{12hours}$, were evaluated by Spearman correlation analysis. Genotype frequencies were tested for consistency with expected Hardy-Weinberg equilibrium by Chi-squared test.

RESULTS

Study population

Between January 2006 and February 2007, 55 patients with TB/HIV coinfection were screened for inclusion in the study. Of these, 25 patients met at least one exclusion criteria. Of 25 patients excluded from the study, 10 patients had ALT or AST levels > two times the upper limit of normal, seven died before consent, four had total white blood cell count < 2.5 and four had elevated serum creatinine > 1.5 mg/dl.

Of the 30 enrolled patients, 26 completed both pharmacogenetic and pharmacokinetic testing. The demographic and baseline characteristics of the 26 patients who were included in the final analysis are summarized in Table 1. The mean age was 39 years (range, 22 – 54 years), 18 patients (69.2%) were males, 16 patients (62.0%) had a history of alcohol ingestion and the mean body weight was 55.7 kg. There were no differences in baseline characteristics between patients in the three major *CYP2B6* c.516G>T genotypic groups (Table 1).

Frequency of *CYP2B6* genotypes and haplotypes

We first analyzed for *CYP2B6* genotypic variants of the non-synonymous c.516G>T exon 4 c.SNP for all 30 enrolled patients and found the GG genotype in 8 patients (27.0%), GT genotype in 15 patients (50.0%) and TT genotype in 7 patients (23.0%), which is consistent with the predicted Hardy-Weinberg distribution ($X^2=0.00004$; $P=0.995$). Additional genotype analysis of the exons 5 and 7 c.SNPs enabled unambiguous haplotype inference for 5 different alleles, including *CYP2B6**I*I (reference), *CYP2B6**I*4 (K262R), *CYP2B6**6*6 (Q172H, K262R), *CYP2B6**I*9 (Q172H), and *CYP2B6**I*18 (I328T) (Table 2). The most common *CYP2B6* haplotypes in the 30 patients studied patients were *CYP2B6**I*6 (13 patients), *CYP2B6**6*6 (7 patients) followed by *CYP2B6**I*I (5 patients). Rarer haplotypes included *CYP2B6**I*18 (2 patients), *CYP2B6**I*4 (one patient) and *CYP2B6**I*9 (one patient). One patient was heterozygous for all 3 c.SNPs and so was either *CYP2B6**I*16 or *CYP2B6**6*18 (Table 2). We did not find any of the rarer exon 4 or exon 5 c.SNPs in any of the subjects.

Efavirenz concentrations and *CYP2B6* genotype correlations in the presence of rifampin

The variability in total plasma efavirenz exposure was 110%, and was strongly associated with *CYP2B6* c.516G>T genotype. Efavirenz AUC, C_{max} , and C_{min} values were all significantly higher in patients with the c.516TT genotype compared to subjects with either the c.516GG or c.516GT genotypes (Figure 1A, Table 3). However, there were no statistically significant differences in efavirenz concentrations, and $AUC_{0-24\text{ hour}}$ between the patients with c.516GT and c.516GG genotypes. The inclusion of K262R and I328T SNPs into the phenotype-genotype analysis (as haplotypes) did not improve prediction of the slow metabolizer phenotype over c.516G>T alone (Figure 1B). Apparent oral clearance of efavirenz (CL/F) and CL/F normalized for body weight were significantly lower in patients with c.516TT genotype than in those with c.516GG or c.516GT genotypes but no differences were found between those with c.516GT compared to c.516GG (Table 3).

Further phenotype-genotype analysis of data from individuals with the most common *CYP2B6* haplotypes (*I*I, *I*6, and *6*6) indicated that patients with *CYP2B6**6*6 haplotype had significantly higher AUC than those with the *CYP2B6**I*I or *CYP2B6**I*6 haplotypes (Figure 2). Because of the relatively low frequency of the remaining haplotypes with one patient each, it was not possible to test differences for statistical significance (Figure 2).

Safety and tolerability

There was one death that was attributed to extensive pulmonary TB in a patient who had already received two months of TB treatment before initiating HAART. Drug susceptibility testing was not available to determine if this patient had resistant TB. Two patients (*CYP2B6* c.516GG and c.516GT genotypes) developed grade 2 AST and ALT abnormalities, while one patient (c.516GT genotype) developed a grade 3 hemoglobin abnormality at week 4. None of the patients discontinued TB therapy or HAART as a result of adverse treatment effects.

Correlation between timed discrete efavirenz concentrations and AUC_{0–24 hour}

Finally, we evaluated the correlation between dosage timed efavirenz concentrations including $C_{\min}$ and $C_{12 \text{ hour}}$, which are more convenient for therapeutic drug monitoring of efavirenz therapy than AUC_{0–24 hour}. As shown in Figure 3, we found strong linear correlations between both $C_{\min}$ and AUC_{0–24 hour} ($R_s = 0.962$, $P < .0001$) and also between $C_{12 \text{ hour}}$ and AUC_{0–24 hour} and $C_{\min}$ ($R_s = 0.969$, $P < .0001$).

DISCUSSION

Our findings show that the wide interindividual variability of efavirenz concentrations in rifampin-treated HIV/TB co-infected patients is strongly associated with *CYP2B6* c.516TT genotype status. A substantial number of pharmacogenetic studies of efavirenz disposition conducted previously have found significant differences in efavirenz concentrations in patients associated with *CYP2B6* c.516G>T genotype with the rank order of c.516TT > GT > GG genotype.^{18–22} However, none of these studies were performed in the presence of rifampin and it was not clear what effect this drug would have on the *CYP2B6* genotype-phenotype relationship. While we did not find an intermediate phenotype for *CYP2B6* c.516GT genotype as previously established,^{18–22} the c.516TT genotype was strongly predictive of high efavirenz exposure in patients with TB/HIV who are taking rifampin.

We had hypothesized that rifampin co-administration would minimize differences in efavirenz clearance related to *CYP2B6* genotype either through enhancement of residual *CYP2B6* activity in those individuals with the intermediate and normal metabolizer genotypes (*CYP2B6* c.516 GT and GG), or perhaps via induction of alternate efavirenz clearance pathways, including *CYP* enzymes (other than *CYP2B6*) that metabolize efavirenz such as *CYP3A4/5* and *CYP2A6*. In support of this contention, our results showed no difference in efavirenz clearance between individuals with the *CYP2B6* c.516GT and GG genotypes. This contrasts with several previous studies in the absence of rifampin that showed a clear intermediate metabolizer phenotype with an average 24 to 27% lower clearance in *CYP2B6* c.516GT heterozygotes versus c.516GG homozygotes.^{18–22}

However, we also showed significantly lower efavirenz clearance in *CYP2B6* c.516TT individuals indicating that rifampin treatment does not fully reverse the poor metabolizer phenotype in this genotype group. Recent *in vitro* work indicates that the *CYP2B6* c.516G>T polymorphism alters a splice enhancer site and results in aberrant mRNA splicing, with deletion of critical protein domains, and nonfunctional enzyme protein.³² Consequently, enhancement of *CYP2B6* gene transcription via effects of rifampin on pregnane-X receptor will lead to enhanced *CYP2B6* mRNA, but much of this mRNA will likely be aberrantly spliced and will not produce active enzyme.

It should also be noted that efavirenz metabolism undergoes significant autoinduction following repeated dosing through constitutive androsterone receptor (CAR) mediated enhancement of *CYP2B6* gene expression.^{34,35} Other CAR regulated CYPs such as *CYP3A4* may also be induced with repeated efavirenz dosing. Consequently it is possible that any additional effect of rifampin on efavirenz metabolism in our patients may be limited to those enzymes that are regulated mainly by PXR and not by CAR. Furthermore, our patients may have been exposed to other potential enzyme inducers such as alcohol, which in previous work in our laboratory has been associated with enhanced *CYP2B6* activity *in vitro*.³³

A limitation of this study is that we did not include a comparator group of patients who had not received rifampin to determine whether there are differential effects of rifampin on each genotype. However, it should be noted that the average efavirenz oral clearance for patients in this study was 2.1 to 2.7 times higher than published values for subjects receiving a similar

dose of efavirenz in the absence of rifampin.^{36,37} This is consistent with enhancement of efavirenz clearance by pregnane X-receptor/constitutive androstane receptor mediated induction of *CYP2B6* protein expression,^{11,38-40} although it could also be the result of differences in the populations studied (sub-Saharan African in this study versus mostly Caucasians in the other studies).

We assayed for several c.SNPs other than c.516G>T (Q172H) including K262R and I328T that have been associated with altered *CYP2B6* activity. However, inclusion of these additional SNPs into the phenotype-genotype analysis (as haplotypes) did not improve prediction of the slow metabolizer phenotype over c.516G>T alone either because of low frequency in the population (I328T), or linkage with c.516T as part of the *CYP2B6**6 haplotype (K262R is in linkage with Q172H).

Although we measured complete efavirenz concentration profiles over 24 hours in order to accurately derive segmental AUC values, such intensive monitoring is not always practical particularly for studies involving larger patient populations. Consequently, we evaluated the correlation between AUC values and single plasma concentrations collected at defined time points relative to dose ($C_{\min}$ and $C_{12\text{hour}}$). In both instances, excellent correlations were observed validating the use of such measures as a surrogate for AUC in future (and previous) studies.

In conclusion, the results of this study demonstrate that *CYP2B6* c.516TT genotype is highly predictive of reduced clearance of efavirenz in rifampin treated TB/HIV co-infected patients. *A priori* dose reduction of efavirenz in patients with *CYP2B6* 516TT genotype or *CYP2B6**6*6 haplotype with a goal of minimizing toxicity⁴¹ as well as reducing cost²⁹ may be important especially in resource-poor settings. Any future controlled trials of reduced efavirenz dose in carriers of *CYP2B6* 516TT genotype should not exclude individuals requiring concurrent rifampin therapy as co-administration does not appear to reverse the poor metabolizer phenotype associated with this genotype. Although our data suggests that the effect of rifampin on efavirenz clearance might differ depending on patient *CYP2B6* genotype, the lack of an appropriate control group limits any firm conclusions. Consequently, a controlled 2-way crossover pharmacokinetic interaction study examining the effect of rifampin within each subject is currently underway to directly address this hypothesis.

ACKNOWLEDGMENTS

We thank the study participants, the study coordinator, Adjoa Obo-Akwa and her assistant, Esther Manche as well as the study nurse, Janet May Ayi of Korle Bu Teaching Hospital. We are grateful to Aba Hayford and Makafui Seshie of Clinical Virology, UGMS for laboratory support. We thank Drs Charles Carpenter and Timothy Flanigan, as well as Vicki Godleski of Lifespan/Tufts/Brown CFAR for valuable comments and administrative support and Dr David Haas for comments on the manuscript. This research was funded in part by a 2004 developmental grant from the Lifespan/Tufts/Brown Center for AIDS Research and NIH K23 and K23 developmental award (NIH K23 AI071760) to A. Kwara. The project described was supported by Grant Number P30AI042853 from the National Institute of Allergy and Infectious Diseases. Dr. Greenblatt is supported by grants AG-17880 and AI-58784, and Dr Court is supported by grants GM-74369, and GM-61834 from the Department of Health and Human Services. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy And Infectious Diseases or the National Institute of Health.

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Figure 1.

Mean ($\pm$ SEM) efavirenz concentrations at each timed point stratified by *CYP2B6* c.516G>T genotype (A) and by *CYP2B6* haplotype (B) in HIV/TB co-infected patients receiving rifampin-containing TB treatment. Efavirenz concentrations at all time points were significantly higher in patients with *CYP2B6* c.516TT than those with GG or GT genotypes.

Figure 2. Efavirenz AUC₀₋₂₄ hour values stratified by *CYP2B6* c.516G>T genotype (A) and by *CYP2B6* haplotype (B) in HIV/TB co-infected patients receiving rifampin-containing TB treatment. Genotype and haplotype group differences were evaluated by Kruskal-Wallis analysis of variance (ANOVA) on ranks with pairwise group comparisons by the Student-Newman-Keuls procedure. Horizontal bars represents the median.

Figure 3. Correlations between efavirenz AUC₀₋₂₄ hour and C_{min} (A), and between efavirenz AUC₀₋₂₄ hour and C₁₂hour (B). Also shown on each plot are the fitted lines and Spearman correlation coefficients (Rs) and P values.

Table 1
Baseline characteristics of the 26 tuberculosis and human immunodeficiency virus co-infected patients who completed the study

Variable *	All (n=26)	GG (n=7)	GT (n=12)	TT (n=7)
Age (Years)				
Mean (SD)	39 (8)	39 (3)	39 (2)	41 (3)
Gender (N (%))				
Male	18 (69)	4 (57)	9 (75)	5 (60)
Female	8 (31)	3 (43)	3 (25)	2 (40)
Body weight (Kg)				
Mean (SD)	55.7 (9.8)	53.8 (3.8)	54.8 (2.9)	59.1 (3.7)
BMI (Kg/m ²)				
Mean (SD)	18.9 (3.1)	18.3 (2.6)	18.9 (2.7)	19.8 (4.3)
Entry CD4 count (cells/μl)				
Mean (SD)	130 (118)	126 (45)	155 (34)	90 (45)
Log ₁₀ HIV-1 RNA				
Mean (SD)	5.3 (0.6)	5.2 (0.7)	5.5 (0.4)	5.0 (0.8)
AST (IU/L)				
Mean (SD)	44 ((25)	57 (31)	33 (11)	49 (29)
Grade 1 or 2 (N (%))	6 (23%)	4 (57%)	0 (0%)	2 (29%)
ALT (IU/L)				
Mean (SD)	30 (18)	35 (23)	24 (12)	35 (22)
Grade 1 or 2 (N (%))	4 (15%)	2 (29%)	0 (0%)	2 (29%)

* *P* value > .05 for comparisons between genotypic groups for all variables. SD = standard deviation; N or n = number; BMI = body mass index; HIV = human immunodeficiency virus; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

Table 2
Frequency of *CYP2B6* 516G>T genotypes and haplotypes in 30 enrolled patients with tuberculosis and human immunodeficiency virus co-infection in Ghana

Exon 4	n	Percent	Exon 5	Exon 7	Haplotypes	n	Percent
c.516G>T (Q172H)			c.785A>G (K262R)	c.983T>C (I328T)			
GG	8	27%	AA	TT	*1/*1	5	17%
			AA	TC	*1/*18	2	7
			AG	TT	*1/*4	1	3%
GT	15	50%	AG	TT	*1/*6	13	43%
			AA	TT	*1/*9	1	3%
			AG	TC	*1/*16 or *6/*18	1	3%
TT	7	23%	GG	TT	*6/*6	7	23%

N = number of patients

Table 3

Steady-state pharmacokinetic parameters of efavirenz in 26 tuberculosis and human immunodeficiency virus coinfecting patients receiving rifampin stratified by CYP2B6 c.516G>T genotype

Parameter	All subjects	Median (IQR)			P value		
		GG	GT	TT	ANOVA	GG vs. GT	GG vs. TT
Number of subjects	26	7	12	7			
T _{max} (hours)	4.0 (2.0 – 5.5)	4.0 (2.5 – 4.0)	3.0 (1.5 – 4.0)	6.0 (5.0 – 8.0)	0.019	0.201	0.133
C _{max} (µg/mL)	1.6 (0.8 – 2.1)	1.6 (1.2 – 2.0)	1.8 (1.2 – 2.1)	4.3 (2.9 – 7.0)	<0.001	0.550	<0.001
C _{min} (µg/mL)	0.9 (0.4 – 1.7)	0.6 (0.2 – 0.9)	0.5 (0.3 – 1.2)	2.8 (2.1 – 4.7)	<0.001	0.293	<0.001
AUC _{0–24hour} (µg.h/mL)	31.4 (17.7 – 45.0)	24.4 (11.8 – 30.9)	24.8 (16.6 – 40.3)	74.7 (59.1 – 133.7)	<0.001	0.367	<0.001
CL/F (mL/min)	335 (222 – 629)	410 (324 – 864)	481 (307 – 647)	134 (77 – 169)	<0.001	0.579	<0.001
CL/F/W (mL/min/kg)	6.3 (3.3 – 10.6)	8.3 (6.1 – 14.3)	8.6 (5.8 – 10.9)	1.9 (1.5 – 2.6)	<0.001	0.549	<0.001

T_{max} = time to peak concentration; C_{max} = peak concentration; C_{min} = minimum concentration (24 hours after dosing); AUC 0–24 hour = total area under the curve; CL/F = apparent oral clearance; CL/F/W = apparent oral clearance normalized for body weight; IQR = interquartile range.