

Leading Factors Affecting the Therapeutic Effects of the Efavirenz-Rifampicin Combination Use

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Abstract: Efavirenz-containing regimens are commonly prescribed to patients who are receiving rifampicin-containing therapy for tuberculosis. Their drug interaction maintains its effects through the CYP enzyme family, mainly CYP2B6 in metabolism of Efavirenz. Rifampicin is expected to accelerate the metabolism of the Efavirenz, thus lowering its plasma EFV concentration, the lower concentration of EFV is assumed to relate with the regimen failure, while the higher is related with serious CNS effects. But the variety of EFV concentration amongst patients receiving EFV-based antiretroviral regimen and RIF-based anti-tuberculosis regimen was observed, which may be related to sex, weight, ethnicity, and most dominantly, a single-nucleotide polymorphism (SNP) of CYP2B6. We summarize the evidence from the literature and discuss leading factors affecting the therapeutic effects of the EFV-RIF combination in different clinical trials and thus give recommendations for efavirenz prescription.

1. Introduction

Tuberculosis (TB) is a leading cause of death in human immunodeficiency virus (HIV)-positive individuals. TB is one of the deadliest diseases of the 20th. Just while TB rates were starting to decline, HIV epidemic cooperated the sharp new increase of TB incidence between the end of the 1980s and the 1990s [1]. Immune-suppressed HIV-positive individuals are more vulnerable to TB active infection and the reactivation of latent TB infection (LTBI). The dual burden of TB and HIV infection increases the likelihood of dying compared with having either disease separately, looming into the first place to claim for major cause of mortality among HIV-positive patients.

TB case notifications in 2020 was estimated by WHO to a best estimate of 4.1 million as a big global drop in TB case notifications compared with 7.1 million in 2019 and 6.4 million in 2017, while TB incidence was relatively stable at around 10 million cases per year. The impact of the disruptions related to the COVID-19 pandemic needs to be assessed in the TB case diagnosis and treatment. The global coverage of HIV testing among people diagnosed with TB remained high in 2020, at 73% (up from 70% in 2019). Thanks to a continuously rising use of WHO recommended rapid molecular test, in 87 countries and territories, at least 90% of people diagnosed with TB knew their HIV status. The coverage of antiretroviral therapy (ART) among people co-infected with HIV and TB was 88% in 2020, the same level as in 2019. TB treatment and provision of ART to HIV-positive people diagnosed with TB are estimated to have averted 66 million deaths between 2000 and 2020.

ART is highly effective in reducing the risk of progression of HIV infection, preventing the development of AIDS and death, as well as reducing viral transmission. Thus, it is not surprising that ART lowers the incidence of TB. The principles of TB treatment in HIV-infected patients are the same as in HIV-uninfected ones. All identified patients should start a standard TB regimen as soon as the diagnosis is made. Ideally, TB treatment in TB/HIV co-infected patients could achieve success rates

similar to those of HIV-uninfected patients, provided that treatment is started early, and that HIV infection is concomitantly treated. Randomized clinical trials show that adding ART to TB treatment in co-infected patients improve treatment outcome and reduce mortality, regardless of the level of the CD4 cell count [2].

The WHO recommends that any newly diagnosed TB patient be treated with a standard regimen consisting, for the initial intensive phase of 2 months, of four drugs (namely rifampicin, isoniazid, pyrazinamide, and ethambutol), followed by a continuation phase of two drugs (rifampicin and isoniazid) for a period of at least 4 months [3].

The treatment of HIV-associated TB is very common in resource-limited settings, and many patients require concomitant antiretroviral therapy (ART) and rifampicin-based antitubercular therapy. The non-nucleoside reverse transcriptase inhibitor (NNRTI) efavirenz is widely prescribed in first-line ART [4]. However, in 2015 the U.S. Department of Health and Human Service reassigned efavirenz-based regimens from the “recommended” to the “alternative” therapy category based on the evidence that efavirenz is notable for central nervous system [5]. CNS side effects were observed in 24%, 9%, and 0% of patients with plasma efavirenz concentrations of greater than 4 µg/mL, 1 to 4 µg/mL, and less than 1 µg/mL, respectively [6].

Although a lot of previous studies have examined the efficacy of rifampicin in EFV-based regimens within specific cohorts. For example, In 8 Spanish patients taking efavirenz 600 mg daily, addition of rifampicin-based antitubercular therapy decreased median efavirenz peak concentration, area under the curve and trough concentration by 24%, 18% and 10% respectively [7]. However, a large prospective cohort study in South Africa and a randomized clinical trial in Thailand failed to show any significant effect when a standard dose of efavirenz (600mg daily) was used with rifampin [4,8]. More recent pharmacokinetics studies in Europe [9], India [10], and Africa [4] demonstrated no significant decrease in efavirenz concentrations in the presence of rifampicin-based TB treatment.

Rifampicin has been shown to reduce the mean peak (C_{max}) and trough (C_{min}) plasma efavirenz concentrations as well as the area under the concentration-time curve (AUC) by more than 20%, albeit with significant interpatient variability. These effects can be overcome by adjusting the administered dosage of efavirenz from the standard 600 mg/day to 200-800 mg/day for different genotypes.

In the present manuscript, we review and synthesize the literature on the interactions between rifampin and efavirenz in order to summarize the possible pharmaceutical effects, collect and analyze the factors influencing drug-drug interaction between the two drugs, and eventually give a practical recommendation on how to optimize antiretroviral and antitubercular therapies in patients co-infected with HIV and M. tuberculosis infections.

2. Mechanism

The preferred combined regimen for the concomitant treatment of HIV and TB is efavirenz (EFV)-based antiretroviral therapy (ART) with rifampin-based TB treatment. Efavirenz is a potent inhibitor of HIV type-1 (HIV-1) replication, with a relatively narrow therapeutic index and large inter-individual variability in pharmacokinetics, due in part to variants in the CYP2B6 (cytochrome P450 (CYP) 2B6 gene (CYP2B6)) [5]. Efavirenz is metabolized primarily by the hepatic cytochrome P450 isoenzyme 2B6 (CYP2B6) to form inactive hydroxylated metabolites.

Rifampin is known to be one of the potent inducers of CYP2B6 in vitro and enhances the elimination of known CYP2B6 substrates like methadone, ketamine and bupropion. Base on the existing data and evidence that Efavirenz 8-hydroxylation is the primary clearance mechanism of efavirenz in liver and this pathway is predominantly catalyzed by CYP2B6 [5], rifampin is expected to enhance efavirenz elimination and lower plasma efavirenz exposure.

In a cross-over placebo control trial in healthy subjects, a single 600mg oral dose of efavirenz was administered after pretreatment with placebo or rifampin (600mg/day for 10 days). Pharmacokinetics status centered on EFV and its major inactive metabolites 8-hydroxyefavirenz (and 8,14-dihydroxyefavirenz) showed that rifampin enhances CYP2B6-mediated efavirenz 8-hydroxylation in vivo, with no significant differences between male and female subjects observed [11]. Drug interaction

studies in healthy volunteers evaluating the effects of rifampin on EFV PK showed reductions in EFV concentrations based on modeling work [8,12].

3. The syndemic interaction between HIV and TB as well as the scale of the problem

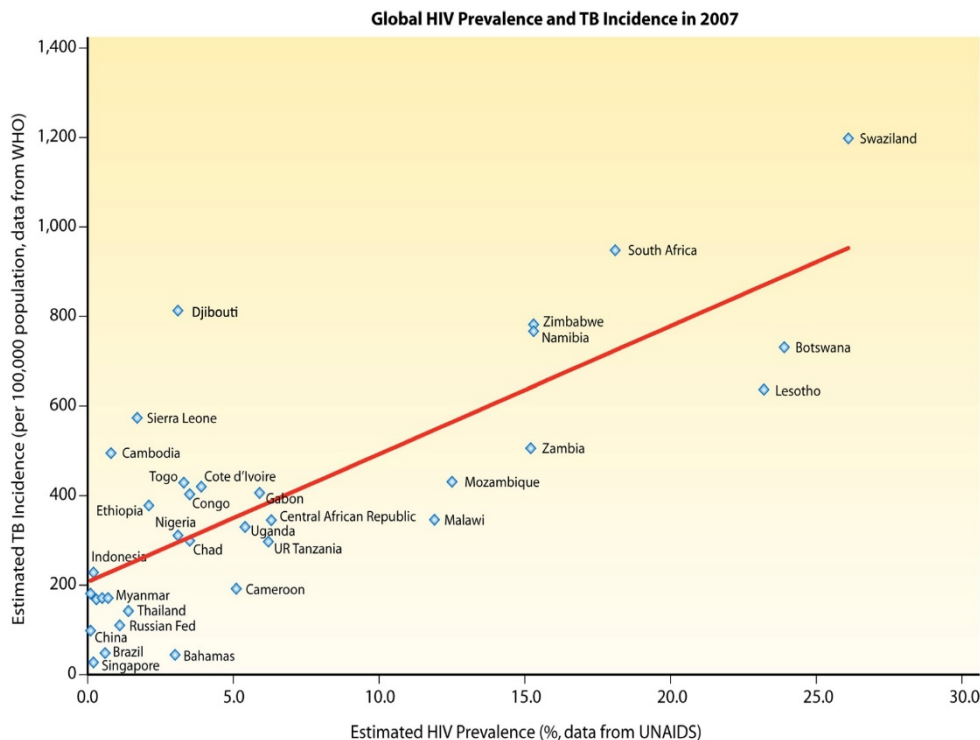


Figure 1. Higher HIV prevalence rates are associated with higher TB incidence rates. We used data from 132 countries from the UNAIDS/WHO 2008 report on the global AIDS epidemic for HIV prevalence (250) and from the WHO 2009 report tuberculosis control for TB incidence (263) and generated a scatter plot showing a positive linear correlation. The Pearson coefficient (r) was 0.799, with a (two-tailed) P value of <0.01 using SPSS statistical software.

The syndemic interaction between HIV and TB epidemics has had deadly consequences around the world. This shows that HIV infection with TB at the same time can have a serious impact on the body, and makes treatment more difficult to carry on. To further prove that HIV infection is one of the important risk factors for TB, scientists collected and concluded their data reversely, and there were nearly 1.4 million (15%) of people were coinfecting with HIV in 9.4 million cases of TB. In addition, HIV-associated TB accounted for 29% of deaths among incident TB cases, even though it contributed to 15% of all incident TB cases from FIG 1 (HIV-associated TB contributes disproportionately to TB-related deaths), the estimated death rate of incident TB was up to 2-fold higher for patients infected with HIV (37%) than those without HIV (16%) from FIG 1 [13-15].

The reason for high death rate of TB in HIV-infected individuals can be summarized as follows: (i) the failure of immune system and immune response to restrict the growth of Mycobacterium tuberculosis; the rapid progression of the disease. (ii) atypical presentation and lower rates of sputum smear positivity, result the delayed diagnosis and treatment of TB infection. (iii) stigma/ insufficient uptake of HIV testing in TB clinics, results the delayed diagnosis of HIV infection (iv) delayed start or lack of access to combination antiretroviral therapy (ART). (v) The high rates of multidrug-resistant (MDR) TB (MDR-TB) leading to a delayed initiation of effective therapy [16-18]

In addition, the FIG 2 illustrated the burden of death from HIV-associated TB was highest in those countries include: South Africa, Nigeria, India, Zimbabwe, Ethiopia, the United Republic of Tanzania, Mozambique, Uganda, and Kenya and mortality in most of these countries [19].

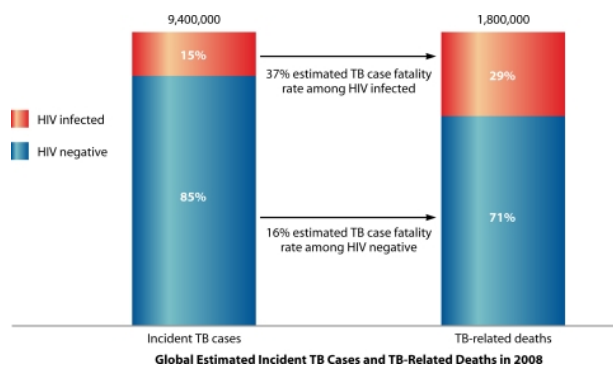


Figure 2. HIV-associated TB contributes disproportionately to TB-related deaths. (Data are from WHO global Tuberculosis control: a Short Update to the 2009 report.) Although HIV-associated TB accounted for 15% of all incident TB, it contributed to 29% of deaths among incident TB cases in 2008. The estimated case-fatality rate if incident Tb was more than 2-fold higher for people infected with HIV (37%) than for those without HIV (16%).

4. The expression of CYP2B6 and genetics variability of CYP2B6

Efavirenz is generally recommended for use with other antiretrovirals. The mechanism for efavirenz therapy has been proved as metabolized by CYP enzymes to form inactive hydroxylated metabolites and by UDP- glucuronosyltransferases (UGT)-mediated direct N-glucuronidation. The 8-hydroxy-efavirenz is the major efavirenz metabolite, which is generated primarily by CYP2B6 and lacks antiviral activity to achieve therapy efficiency. CYP2B6 is encoded by the CYP2B6 gene. Current identified single nucleotide poly morphism (SNPs) types for CYP2B6 are beyond 100. In addition, there are 38 known variant alleles and multiple sub-alleles for CYP2B6, Alleles can be divided into functional groups as follows: normal function such as CYP2B6*1, decreased function such as CYP2B6*6 and *9, and non- functional group as

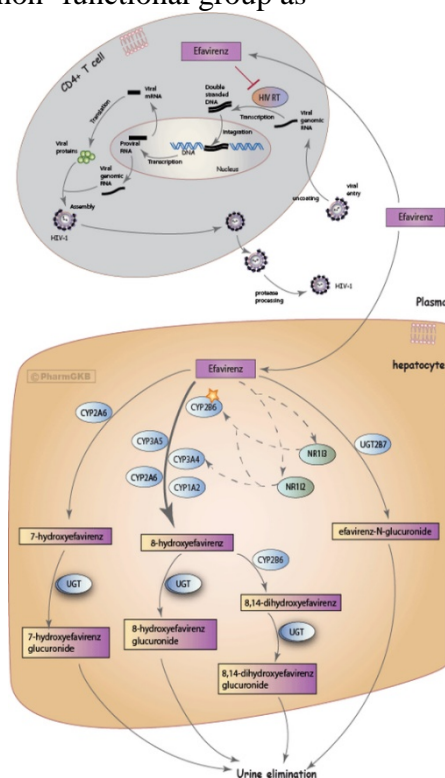


Figure 3. Schematic representation of efavirenz metabolism and mechanism of action against HIV. An interactive version of the pathway is available at: <https://www.pharmgkb.org/pathway/PA166123135>). Image reproduced and is licensed under CC BY-SA 4.0 from PharmGKB.

CYP2B6*18, and increased function CYP2B6*4, from which CYP2B6*6 is the main frequent decreased function allele. There are different SNPs in the CYP2B6 gene such as 516G>T (rs3745274) and 983T>C (rs28399499), according to their combination as haplotypes, may lead to different degrees of slow and/or fast EFV/NVP metabolizer phenotype. The 516G>T (rs3745274) and 983T>C (rs28399499) are associated with a significant loss of CYP2B6 function, and it will lead to reduced clearance and prolonged half-life both for EFV and NVP (Nevirapine), the 516G>T SNP influences mainly the EFV metabolism and the 983>T SNP affects the metabolism of both EVF and NVP. Efavirenz (EFV) and Nevirapine (NVP), these two drugs are largely used for HIV combination treatment in some countries. In addition, there are two more SNP like 785A>G (rs2279343) and -82T>C (rs34223104) associated with a gain of CYP2B6 function, and 785A>G SNP increases EFV and NVP metabolism. However, most attention has been focused on CYP2B6 516G>T and 983T>C SNPs in pharmacogenetic studies of EFV and NVP. The minor metabolic pathways are CYP2A6-mediated hydroxylation to 7-hydroxy-efavirenz and UGT2B7-mediated glucuronidation to efavirenz N-glucuronid [20-22].

The contribution of these pathways may be different following a single dose of efavirenz versus chronic dosing. Efavirenz increases CYP2B6 expression via activation of the constitutive androstane receptor. Therefore, chronic dosing of efavirenz enhances its own metabolism which is called autoinduction. There are some relations between the magnitude of efavirenz autoinduction among individual and it is affected by variation in the CYP2B6 gene. For example, Table 1 showed the relationship between CYP2B6 genotype and apparent oral clearance for efavirenz and there is considerable CYP2B6 induction with the CYP2B6*1/*1 and *1/*6 genotypes and little or no autoinduction with CYP2B6*6/*6. There are plenty of evidence from previous studies that there is a strong relationship between CYP2B6 genotype with variability in plasma efavirenz concentration and with adverse effect, and the impact of CYP2B6 c.516G>T and c.983T>C have been examined from most studies, which means these two variants provide basis for our clinical recommendation. The tables 1&2 showed that the evidence associating these two variants with increased plasma efavirenz concentration was strong. In addition, CYP2B6 poor metabolized genotype that shown in table 2 is associated with decreased efavirenz clearance and significantly increased the risk for efavirenz CNS adverse effects and treatment discontinuation (toxicity) Although antiretroviral Therapy (ART) has significantly treated for many HIV diseases, the treat of HIV drug resistance can reduce the positive effect of ART, which makes ART become lower efficiency. For example, occurrence of drug toxicity, suboptimal patient's compliance, suboptimal virologic responses, incomplete immune reconstitution, and emergence of drug resistance limit therapeutic outcomes, these are all factors need to be considered carefully. Because of the sub-therapeutic ARV drug exposure and/or acquisition of drug-resistant strains, the HIV drug resistance is more likely to occur. Moreover, HIV-diagnosed individuals with virologic failure are more likely to stay on virologically failing regimens for prolonged periods, the reason for that is because of lack of adequate virological follow-up. This may further result in an ineffective drug exposure potentially causing drug toxicity and a higher risk of selecting and transmitting drug-resistant viruses. Furthermore, the researchers also found that the presence of HIV drug resistance mutations (DRMs) in minor viral populations is related to an increased risk of virologic failure, especially in NNRTI-based ART regimens, regardless of adherence, ethnicity, and immunovirological basal characteristics of patients [23-26].

In summary, different CYP2B6 genotypes can influence immuno-virological response and toxicity by affecting EFV and NVP plasma concentration. Therefore, the researchers designed the experiment and aim to explore the impact of CYP2B6 genotype and haplotype variation on the risk of developing EFV/NVP drug resistance mutations (DRMs) in HIV-1 patients receiving EFV-/ NVP-containing regimens in Botswana.

Table 1. Assignment Of Likely Cyp2b6 Phenotypes Based on Genotypes

Likely phenotype	Genotypes	Examples of CYP2B6 diplotypes ^b
CYP2B6 ultrarapid metabolizer	An individual carrying two increased function alleles	*4/*4, *22/*22, *4/*22
CYP2B6 rapid metabolizer	An individual carrying one normal function allele and one increased function allele	*1/4, *1/*22
CYP2B6 normal metabolizer	An individual carrying two normal function alleles	*1/*1
CYP2B6 intermediate metabolizer	An individual carrying one normal function allele and one decreased function allele OR one normal function allele and one no function allele OR one increased function allele and one decreased function allele OR one increased function allele and one no function allele ^a	*1/*6, *1/*18, *4/*6, *4/*18, *6/*22, *18/*22,
CYP 2B6 poor metabolizer	An individual carrying two decreased function alleles OR two no function alleles OR one decreased function allele and one no function allele	*6/*6, *18/*18, *6/*18

^aSee text for discussions regarding CYP2B6 rs4803419.

^bPlease refer to the diplotype to phenotype translation table online for a complete list.

By using different kinds of Statistical Analysis, for example, the scientists used the Arlequin software 53 to test for Hardy–Weinberg Equilibrium (HWE) and the genetic fixation index (FST) with default settings, and Linkage Disequilibrium (LD) was tested using the Expectation- Maximization (EM) algorithm with 20,000 permutations and three initial conditions. BLR (Binary Logistic Regression) also used for predicting association between two variables.

BLR analysis showed an association between EFV/NVP resistance and CYP2B6 516G allele (OR: 2.26; 95% CI: 1.27–4.01; P=0.005), Binary Logistic Regression is used to predict the relationship between our independent variables (age, BMI, baseline CD4+ T- cell count and viral load, CYP2B6 genotype) and the dependent variable (drug resistance), and the dependent variable is binary. Furthermore, haplotype analysis showed that the proportion of EFV/ NVP-resistant infections was higher among CYP2B6 faster than extensive/slow metabolizers (30.8% vs 16.8%; P=0.035).

Table 2 Efavirenz Dosing Recommendations Based on Cyp2b6 Phenotype In Children ≥40 Kg And Adult Patients

CYP2B6 phenotype	Implications for efavirenz pharmacology measures	Therapeutic recommendations	Classification of recommendations
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CYP2B6 ultrarapid phenotype	Slightly lower dose-adjusted trough concentrations of efavirenz compared with normal metabolizers	initiate efavirenz with standard dosing (600mg/day)	strong
CYP2B6 rapid metabolizer	Slightly lower dose-adjusted trough concentrations of efavirenz compared with normal metabolizers	initiate efavirenz with standard dosing (600mg/day)	strong
CYP2B6 normal metabolizer	Normal efavirenz metabolism	initiate efavirenz with standard dosing (600mg/day)	strong ^c
CYP2B6 intermediate metabolizer	Higher dose-adjusted trough concentrations of efavirenz compared with normal metabolizers; increased risk of CNS adverse events	Consider initiating efavirenz with decreased dose of 400mg/day ^{a,b}	Moderate
CYP2B6 poor metabolizer	Slightly lower dose-adjusted trough concentrations of efavirenz compared with normal metabolizer; significantly increased risk of CNS adverse events and treatment discontinuation	Consider initiating efavirenz with decreased dose of 400mg or 200mg /day ^{a,b}	Moderate

^aIf therapeutic drug monitoring is available and a decreased efavirenz dose is prescribed, considering obtaining steady-state plasma efavirenz concentrations to ensure concentrations are in the suggested therapeutic range (1 to 4ug/mL).

^bTo prescribe efavirenz at a decreased dose of 400mg/day or 200mg/day in a multidrug regimen may require prescribing more than one pill once daily. If so, the provider should weigh the potential benefit of reduced dose against the potential detrimental impact of increased pill number.

^cThe ENCORE study showed that in treatment-naïve patients randomized to initiate efavirenz-based regimens (combined with tenofovir and emtricitabine), 400mg/day was non-inferior to 600mg/day regardless of CYP2B6 genotype (32).

In conclusion, CYP2B6*6 allele (516G) is associated with the presence of EFV/NVP resistance, thus also strengthening the need to assess the CYP2B6 genetic profiles in HIV-infected patients in order to improve the virologic outcomes of NNRTI containing ART.

Table 3 Estimated and Maximum-Likelihood(HL) Haplotype Frequencies by Phenotype and for All the Samples Combined. Maximum-Likelihood Haplotype Frequencies are Shown in Parenthesis with Their Standard Deviations (SD).

Haplotype	MS	Phenotype	Estimated and ML Frequencies ±SD		
			Overall*	EFV/NVP-Redistant	EFV/NVP-Susceptible

TGAT	0	Extensive	201(0.441±0.023)	43(0.526±0.065)	162(0.430±0.029)
TGAC	-1	Slow	24(0.054±0.013)	5(0.065±0.035)	19(0.052±0.015)
CGAT	1	Rapid	12(0.019±0.008)	3(0.039±0.024)	5(0.008±0.006)
CGGT	2	Ultra-rapid	2(0.004±0.003)	2(0.024±0.018)	0(0.000±0.000)
TTAT	-1	Slow	37(0.078±0.015)	6(0.082±0.036)	27(0.073±0.017)
TTAC	-2	Very slow	10(0.441±0.023)	1(0.013±0.017)	9(0.230±0.011)
TGGT	1	Rapid	16(0.041±0.011)	3(0.046±0.023)	13(0.041±0.011)
TTGC	-1	Slow	41(0.083±0.015)	6(0.073±0.032)	35(0.085±0.016)
TTGT	0	Extensive	107(0.236±0.020)	11(0.132±0.046)	96(0.252±0.026)
TGGC	0	Extensive	2(0.006±0.005)	0(0.000±0.000)	2(0.006±0.006)
CGAC	0	Extensive	201(0.002±0.003)	0(0.000±0.000)	1(0.003±0.003)
ATAT	0	Extensive	1(0.009±0.009)	0(0.000±0.000)	5(0.013±0.006)
CTGT	1	Rapid	0(0.000±0.000)	0(0.000±0.000)	0(0.005±0.005)

The Order of Nucleotides in the Reconstructed Haplotypes is Made According to the SNP Position in the CYP2B6 Gene(-82>C,516G>T,785A>G,923T>C)

Note: "The combination of susceptible and resistant dataset does not necessarily result in a "sum" of the two haplotype counts estimated separately. Different sample counts in each group have an effect on the accuracy of the estimates.

Abbreviation: Ms, metabolic score: N/A, not applicable; NC, not calculated (because of lack of estimated haplotype frequency).

Table 4 EFV/NVP Resistance by CYP2B6 Metabolic Phenotype

EFV/NVP Resistance Status	EFV/NVP Metabolic Phenotype	
	MS≤0 ^a	MS≥1 ^b
Resistant,n(%)	72(16.8%)	8(30.8%)
Susceptible,n(%)	356(83.2%)	18(69.2%)
Total	428(100%)	26(100%)

NOTE: Resistance and susceptible haplotypes were counted according to MS as from Table4. The z statistic is 1.812. The one-tailed P-value is 0.035. aMS≤0: extensive, slow and very slow EFV/NVP metabolizers. bMS≥1: rapid and ultra-rapid EFV/NVP metabolizers

5. Efavirenz Plasma Concentrations with Neuropsychiatric Adverse Events Correlation and racial differences

Although the prevalence of neurocognitive diseases has decreased in the age of HAART, neurological consequences caused by antiretroviral toxicity have become a growing burden in HIV-positive individuals. Despite the undeniable benefits, there is widespread worry about the negative effects of efavirenz usage, notably neuropsychiatric problems. Efavirenz crosses the blood–brain barrier to reach therapeutic concentrations in the brain, with cerebral spinal fluid values ranging from

0.5 to 1.2 % of plasma concentrations [28]. In clinical studies, dizziness (28%), depression (19%), insomnia (16%), anxiety (9%), impaired concentration (8%), somnolence (7%), nervousness (7%), abnormal dreams (6%), and hallucinations (1.2%) were reported in more than half of the patients who started taking efavirenz [29].

Liver metabolism of Efavirenz is predominantly by CYP2B6. Efavirenz concentrations vary widely amongst patients, which may be related to sex, weight, ethnicity, drug-drug interactions, as well as SNPs of CYP2B6 [30]. When rifampicin-containing anti-tuberculous therapy is co-administered, HIV-infected individuals with TB should receive efavirenz-containing antiretroviral therapy. Rifampicin may increase the activity of CYP enzymes, lowering efavirenz plasma concentrations. Early pharmacokinetic investigations showed that when efavirenz was given with rifampicin, the concentration of efavirenz was reduced by 26% [31]. In vitro studies have recently revealed that CYP3A4, CYP2A6, and UGT2B7 also responsible for efavirenz hepatic metabolism in addition to CYP2B6.

Ethnicity plays an important part on efavirenz plasma levels, with Caucasians having the lowest overall plasma levels per standard dose as an indigenous population and Africans having the highest. These variations in plasma levels are linked to ethnic disparities in efavirenz clearance and metabolism, which can have clinical implications. The CYP2B6 gene is highly polymorphic, with several SNPs linked to functional implications, resulting in interindividual heterogeneity among groups. The single strongest predictor of higher efavirenz plasma concentrations is the CYP2B6 G516T polymorphism. The CYP2B6 G516T genotype is quite common among all ethnic populations studied (24%–38%), Although the CYP2B6 G516T allele frequency varies by ethnicity, it is more common in African and Hispanic groups than in Caucasian and Asian ones. The CYP2B6 G516T variant allele, which inhibits efavirenz metabolism, [32] and its effects on efavirenz plasma concentrations may outweigh the rifampicin co-administration counter effect. The allele frequency of CYP2B6 G516T varies among the different ethnicities, ranging from 14% to 21% in Asian populations, 22% to 30% in Caucasians, and up to near 50% in Africans. The CYP2B6-G516T has three genotypes, GG (wild-type), GT (heterozygous mutant) and TT (homozygous mutant). GT heterozygotes, and in particular the TT homozygotes, metabolize efavirenz more slowly than GG homozygotes, and as a result, their efavirenz plasma levels are elevated. However, Slower metabolizers, on the other hand, have a higher risk of efavirenz-induced psychosis, including hallucinations, which subsides when lower dosages of efavirenz are given to these patients [33].

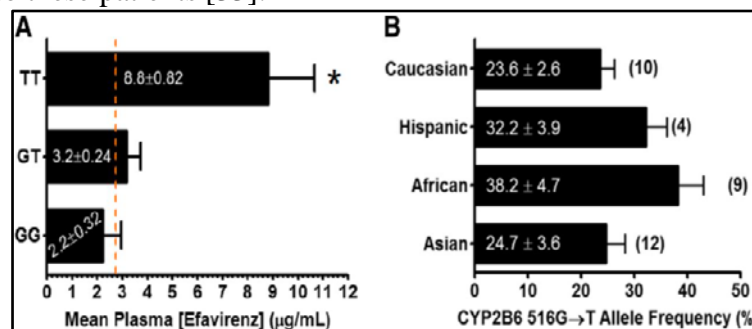


Figure 4. High plasma concentrations are associated with slow metabolizing CYP2B6G-T

Higher plasma concentrations are related with a slow metabolising CYP2B6 516GT allelic load, as shown in (A fig.4). Individuals with the slow metabolising TT genotype have four times greater mean plasma concentrations of efavirenz than those with the fast-metabolising GG genotypes, and GT haplotypes have intermediate values closer to the faster metabolising GG genotype. And (B fig.4) demonstrates that the frequency of the CYP2B6 516GT allele varies as much as 1.6-fold across major ethnic groupings, with Africans having the highest frequency and Caucasians having the lowest [34].

For example, 124 Thai adult rifampicin recipients with concurrent HIV-1/TB coinfection were treated with efavirenz (600 mg/day) (n = 65) based antiretroviral therapy in clinical research (ART). GG, GT, and TT genotypes of CYP2B6-G516T were found in 38.46 percent, 47.69 percent, and 13.85 percent of the population, respectively. At weeks 6 and 12 of ART and 1 month following rifampicin

withdrawal, the mean 12-hour post-dose plasma efavirenz concentration in patients with the TT genotype. (10.97 ± 2.32 , 13.62 ± 4.21 and 8.48 ± 1.30 mg/L, respectively) were significantly higher than those with GT (3.43 ± 0.29 , 3.35 ± 0.27 and 3.21 ± 0.22 mg/L, respectively) ($p < 0.0001$) or GG genotypes (2.88 ± 0.33 , 2.45 ± 0.26 and 2.08 ± 0.16 mg/L, respectively) ($p < 0.0001$). Compared with the effects of CYP2B6-516TT genotype, we could observe only small effects of rifampicin on plasma efavirenz levels. There is no difference in efavirenz mid-dosing interval concentrations or time to virologic suppression [35].

Another clinical trial found 122 adult rifampicin recipients in South Africa who were also infected with HIV and TB. 60 (49%) were G/G homozygotes, 46 (38%) were G/T heterozygotes, and 16 (13%) were T/T homozygotes. And the 13% of participants who had a 32% allele frequency. High efavirenz plasma concentrations were substantially linked to the CYP2B6 516G>T polymorphism. Low efavirenz levels were linked to a 12.5-fold greater probability of virological failure, while high efavirenz levels were linked to significant sleep disruption. The *6 allele of the CYP2B6 516G>T polymorphism has been linked to high efavirenz concentrations. A high proportion of Southern Africans have the CYP2B6 516G>T polymorphism, which impairs the metabolism of efavirenz [36].

An efavirenz dose-adjustment algorithm has been presented, based on the importance of sex, weight, and the CYP2B6-G516T SNP genotype in efavirenz metabolism. If the patient is homozygous for G516T (TT genotype), the efavirenz dose is reduced to 200 mg, rather than the typical dose of 600 mg, according to this method. If the patient is heterozygous (GT), the weight of the patient should be considered: if the weight is less than 62 kg, a dose of 600 mg be sufficed. Consider the sex for patients weighing less than 62 kg. Men should receive a 600-mg dose, while women should receive a 400-mg dose [37].

6. Discussion

In our survey, we noticed that many clinical trials were conducted to evaluate when to start ART for people with active TB considering the risk of TB-IRIS (Immune reconstitution inflammatory syndrome, IRIS) or adverse effects of drugs against HIV disease progression risk. The time to initiate antiretroviral therapy exerts a paradoxical influence on the therapeutic index of patients in tuberculosis therapy with confirmed tuberculosis and HIV coinfection. In a prospective open-label, randomized, controlled trial in Durban and South Africa, an analysis of 642 patients shows a consistent association between antiretroviral therapy and survival in coinfecting patients [2]. Along with many other HIV treatment programs in South Africa, Thailand, Madrid we investigate [38, 39], findings are similar to show a significant decrease in mortality rate among patients who began integrated antiretroviral therapy, as compared with those who did not receive simultaneous antiretroviral therapies (sequential therapy). Although the outcomes manifest an exhilarating survival benefit in integrated HIV-tuberculosis treatment, major concerns follow up, including the increasing likelihood of immune reconstitution inflammatory syndrome, additive toxic effects, and the potential adverse effect on outcomes of tuberculosis therapy. It is reassuring that recent studies indicate that the risk of such episodes can be tempered by the survival benefit showed in the early initiation of ART in patients coinfecting with tuberculosis. But we still recommend that close clinical monitoring for the CD4+ count in the first few months after the initiation of ART in accordance with WHO guideline for the integration of tuberculosis and HIV care.

A therapeutic range of 1-4mg/L has been suggested for efavirenz mid dosing interval concentrations, as efavirenz concentrations below 1mg/L are associated with an increased risk of virological failure and concentrations above 4mg/L are associated with central nervous system side effects. Although rifampicin does accelerate the metabolism of efavirenz, there is no enough evidence eligible to prove significant difference exists between median efavirenz concentrations less than 1mg/L and concomitant rifampicin-based antitubercular therapy when EFV is given at a standard dose (600mg daily). Remarkably, a high interindividual variability in the pharmacokinetic parameters is consistent with previous reports we reviewed when rifampicin-based antitubercular therapy is

concomitantly accepted with efavirenz-based antiretroviral therapy, and may suggest that therapeutic drug monitoring (TDM) should be recommended for patients taking EFV in combination with RIF.

Recent findings in Italy show that the systemic bioavailability, C_{max} values and C_{trough} values of EFV 800 mg dose in association with RIF is similar to that of EFV 600 mg alone in a group of patients of largely Caucasian ethnicity and weight well above 60 kg. Similarly, in a larger uncontrolled study of EFV 800mg per day with rifampicin in Spain [40] no association was observed between EFV C_{min} and the rate of virological failure throughout the follow-up period. Similar results were reported for co-infected subjects in resource limited settings including South Africa and Thailand [41], This can be explained that efavirenz is an inducer of CYP2B6 and thereby enhances its own metabolism (autoinduction). Thus, it is possible that CYP2B6 is near maximally induced under efavirenz steady-state setting, eliminating the full intrinsic induction potential of rifampin on this enzyme.

However, it is feared that increasing the dose of EFV would cause upgraded rates of side effects, which are supposed to be dose dependent. Thus, it is understandable that some research whose subject is refined to a specific ethnicity will mark in particular that their experimental results should be strictly applied to a specific group of the ethnicity. Manosuthi et al. first reported similar plasma EFV concentrations in two groups of patients assuming rifampicin with either EFV 600 mg or EFV 800 mg. The author concluded that EFV 600 mg/day should be merely applicable to most Thai HIV-TB coinfecting patients with body weight approximately 50 kg. Since ethnicity is linked to polymorphism of genes of the CYP enzyme, this could largely affect EFV's pharmacokinetic parameters along with patient's weight, age, and sex. Indeed, Doo-Yeoun Cho et al assume that rifampin had marginal effect on certain genotypes (*2/*2 and one subject with *6/*6 genotype that coexists with another SNP tagging the *14 allele), while two subjects with *6/*6 genotype were equally susceptible to rifampin-mediated induction as those with *1/*1 and *1/*6 genotypes. Thus, it is highly possible that individuals with an extensive CYP2B6 metabolizer status represents a subpopulation at particularly high risk of treatment failure when EFV is given with rifampin-containing tuberculosis treatment [8].

7. Conclusion

In conclusion, CYP2B6 genotype and haplotype variations substantially influence the metabolism of the EFV, resulting to significant differences even in the typically fixed-dose regulation, which allows for one pill, once-daily dosing of EFV. Basically, other than the CYP2B6 genotype, autoinduction by EFV also plays a role in its metabolism through the form of a positive feedback regulation. The participation of another accelerator, the RIF, makes the profile more complicated. Rifampicin's expected function in accelerating the metabolism of Efavirenz can be tempered by the specific CYP2B6 genotypes like CYP2B6 *6/*6, consistent with autoinduction level. Therefore, therapeutic drug monitoring is advisable for patients taking concomitant EFV and RIF treatment considering the large interindividual variability in pharmacokinetic profile. A rapid CYP2B6 genotyping test to identify subgroups of patients at particular risk for low EFV concentrations (i.e., pregnant women, children, and individuals for whom tuberculosis treatment has been co-administered) would be useful.

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