Efavirenz is a potent and effective non-nucleoside reverse transcriptase inhibitor that is a preferred component of first-line antiretroviral therapy (ART) for HIV-1-infected individuals in both wealthy and resource-limited countries [1,2]. The use of efavirenz in clinical practice has further increased in recent years, especially in developing countries. It is usually prescribed at a fixed dosage of 600 mg once daily. Some patients who receive efavirenz have experienced adverse effects such as neuropsychiatric manifestations, skin rash, hepatitis and dyslipidemia [1,3]. In clinical practice, concern over neuropsychiatric adverse effects often plays a role in the decision of whether or not to include efavirenz as part of ART. Prediction of therapeutic efficacy and the likelihood of developing psychiatric disorders have been associated with plasma efavirenz concentrations [4]. The preferable mid-dosing plasma level of efavirenz is 1000–4000 ng/ml to allow for optimized antiretroviral potency and to minimize the risk of neuropsychiatric toxicity. HIV-1-infected patients who receive standard-dose efavirenz and have plasma efavirenz concentration of <1000 ng/ml appear to have a higher risk for virological failure and emergence of selective drug resistance, while those with high plasma efavirenz concentrations of >4000 ng/ml may experience adverse CNS effects more frequently [4]. Many studies have highlighted the potential for serious psychiatric complications with efavirenz, including depression, psychosis, amnesia, extreme excitability, aggressive behavior, post-traumatic stress disorder symptoms and induced suicidal effect [3,4]. However, increased neuropsychiatric adverse effects were typically reported only during the first month after starting this medication [4–6]. Clinical trials have reported CNS side effects in >50% of patients following initiation of efavirenz-based ART. In patients initiating efavirenz therapy for the first time, the development of adverse effects may negatively influence adherence and subsequent treatment failure [6]. The effect of genetic polymorphisms on efavirenz pharmacokinetics is markedly considered because the plasma concentration of efavirenz has been found to be a reliable predictor of treatment failure and risk of neurologic side effects.

**CYP2B6 polymorphisms, efavirenz concentrations & CNS adverse effects**

Genetic variance among individuals influences the metabolism, distribution and elimination of drugs. Higher plasma efavirenz concentrations may be a result of genetic differences in the metabolism of this drug. Efavirenz is metabolized by CYP2B6, CYP2A6 and UGT2B7 [7]. However, CYP2B6 is the major metabolizing enzyme involved in the metabolism of efavirenz, and its genetic polymorphism is associated with increased plasma efavirenz concentration and a higher incidence of neurotoxicity during initial treatment [8]. The allelic variant 516G>T is associated with diminished activity of the CYP2B6 isoenzyme, increased plasma efavirenz concentrations and increased incidence of efavirenz-associated neuro-psychological toxicity [4,5,7–9]. Gounder et al. found correlation between CYP2B6 516TT genotype and efavirenz concentrations, which resulted in increased incidence of fatigue, mood and sleep disorders after initiation of efavirenz [5]. Moreover, a previous study has established that CYP2B6 T983C increases the predictive capability of CYP2B6 G516T for efavirenz pharmacokinetics. Associations between increased plasma efavirenz exposure, CYP2B6 516G>T
and 983T>C have been consistent across multiple studies and populations [12]. In addition, our studies of CYP2B6 polymorphisms showed significant allelic variants (CYP2B6 c.516G>T and c.785A>G polymorphisms), which may decrease the clearance of efavirenz by reducing the activity of the CYP2B6 enzyme and thereby increase plasma efavirenz concentration [9–11]. Prospective CYP2B6 c.516G>T, c.785A>G and c.783T>C genotyping has been proposed for identifying patients at risk of neurotoxicity for efavirenz-based ART in HIV-infected patients.

**CYP2B6 polymorphisms & risk for treatment failure**

Efavirenz has a low genetic barrier to HIV drug resistance. A single mutation, most frequently K103N in the reverse transcriptase gene, results in efavirenz resistance. The development of efavirenz resistance mutations may be due to repetitive exposure to subtherapeutic drug levels. Treatment failure has been found to be more frequent in patients with low efavirenz trough levels compared with those with high levels (>1100 ng/ml). As for efavirenz, some investigators have suggested that the lower limit for the therapeutic range of efavirenz should be raised from 1000 to 2300 ng/ml [13,14]. The median efavirenz concentration for patients with g.18492 heterozygous variants or homozygous variants was significantly lower than those with the wild-type genotype [Sukasem C, Manosuthi W, Koomdee N et al. Low efavirenz pharmacokinetics in HIV-1 infected Thai adults are associated with CYP2B6 polymorphism (2013), Submitted]. The information given by this SNP analysis may help to effectively identify HIV-infected individuals who might have a risk for treatment failure. Because the T allele in CYP2B6 g.18492C>T has a high frequency among the HIV-infected population, its role as an indicator of clinical outcomes needs to be defined in this population.

**Integrating CYP2B6 pharmacogenetics in clinical practices**

Efavirenz dose reduction or initiation of efavirenz treatment at reduced dose must be considered in CYP2B6*6/*6 (516TT and 785GG) homozygotes, which could eliminate the problem of efavirenz-associated CNS symptoms. It may also decrease the risk of development of efavirenz resistance, an important issue in resource-limited countries. It is recommended to establish CYP2B6 genotype in patients receiving efavirenz in order to predict their metabolizing behavior. Accordingly, to obtain efavirenz steady-state concentrations within the therapeutic range (1000–4000 ng/ml), it would be advisable to implement a gradual reduction in dose to 400 or 200 mg/day for patients that are intermediate or poor metabolizers, respectively [15].

Haas et al. reported on a patient with the CYP2B6 516GT/T genotype who had chronic CNS symptoms and extremely high efavirenz concentration while receiving a 600-mg dose, but the symptoms were resolved by reducing the efavirenz dose to 200 mg [8]. Gatananga et al. showed that patients with the CYP2B6 516G>T SNP had significantly higher plasma efavirenz concentrations (>6000 ng/ml) on the standard dosing regimen. In that study, the reduction of the initial efavirenz dosages to either 400 or 200 mg resulted in the lowering of efavirenz concentrations towards the therapeutic range and an improvement in CNS-related symptoms in the majority of patients [15]. The HIV-1 load was successfully suppressed below the detection limit (50 copies/ml) at dosages that were reduced from 600 to 400 and 200 mg. Importantly, individuals who suffered from chronic CNS-related symptoms at the standard dosage showed an improvement with efavirenz dose reduction. Taken together, the quality of life of CYP2B6 516GT/T genotype carriers who suffer from CNS-related symptoms can be improved by reducing efavirenz dose from the standard 600 to 400 or even 200 mg once daily [8,15].

"...the CYP2B6 18492 C>T genotype is associated with low plasma efavirenz concentrations, and may require a higher dose of efavirenz."

Therefore, a genotyping test for common functional variants of CYP2B6*6, which contains both the 516G>T and 785A>G polymorphisms, prior to the initiation of therapy is recommended for identifying patients at risk of efavirenz-associated neurotoxicity in clinical practice. Conversely, the CYP2B6 18492 C>T genotype is associated with low plasma efavirenz concentrations, and may require a higher dose of efavirenz. A cost–effectiveness study indicated that genotyping has been proposed for identifying patients at risk of efavirenz-asso-
Would a CYP2B6 test help HIV patients being treated with efavirenz?

In summary, pharmacogenetic testing of CYP2B6 in HIV-infected patients offers evidence that this test can be used clinically to improve outcomes for patients receiving an efavirenz-based regimen. For this reason we suggest the testing of CYP2B6 polymorphisms in routine clinical practice where the prevalence of the CYP2B6 516TT genotype is high. In the future, CYP2B6 genotyping will likely move into clinical practice for HIV-infected patients treated with efavirenz and increasingly enables doctors to prescribe the right dosage of efavirenz for the first time for everyone. This would mean that patients will receive medicines that are safer and more effective, leading to better healthcare overall. However, this tool should not take the place of careful adherence counseling and monitoring, but rather should augment clinical practice.

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Thai adults are associated with CYP2B6 polymorphism (2013). Submitted. Thus, the pharmacogenetics of CYP2B6 may be used to guide efavirenz dosages. Additionally, genetic information about CYP2B6 may prove to be useful for the *a priori* dosing of efavirenz. Hence, CYP2B6 genotyping should be introduced into routine clinical practice, where clinicians’ decisions can be guided by the patient’s genotype. Antiretroviral prescribing strategies could be improved by understanding whether certain individuals are genetically predisposed to CNS-related adverse effects or virological failure with efavirenz.

“In the future, CYP2B6 genotyping will likely move into clinical practice for HIV-infected patients treated with efavirenz and increasingly enable doctors to prescribe the right dosage of efavirenz for the first time for everyone.”

Would a CYP2B6 test help HIV patients being treated with efavirenz?