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Effect of Host Genetic Variation on the Pharmacokinetics and Clinical Response of Non-nucleoside Reverse Transcriptase Inhibitors

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Abstract

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) have been used widely for treating human immunodeficiency virus type 1 (HIV-1) infected patients as a component of highly active antiretroviral therapy (HAART) and for the prevention of mother-to-child transmission (MTCT). Cytochrome P450 (CYP) 2B6 is an important hepatic isoenzyme responsible for the metabolism of NNRTIs including efavirenz and nevirapine. Recent pharmacogenetic studies have shown that *CYP2B6* genetic variants alter hepatic CYP2B6 protein expression and function, and the pharmacokinetics of several CYP2B6 substrates. In particular, the *CYP2B6*-G516T polymorphism in exon 4 affects the pharmacokinetics of efavirenz. Other studies have shown associations of the *CYP2B6*-G516T genotype with nevirapine pharmacokinetics and central nervous system adverse effects related to efavirenz use. In total, *CYP2B6* genetic variants are important determinants of efavirenz and nevirapine pharmacokinetics . Further studies are needed to identify the associations of *CYP2B6* genetic variants with the development of NNRTI resistant viruses.

Keywords

Non-nucleoside reverse transcriptase inhibitors; efavirenz; nevirapine; CYP2B6; ABCB1; pharmacokinetics; clinical response; adverse effect; resistant virus

Introduction

The morbidity and mortality associated with HIV infection in adults [1,2] and children [3] have been improved significantly due to durable virologic suppression, immunologic recovery, and clinical improvement achieved by highly active antiretroviral therapy (HAART). Current treatment guidelines for the use of HAART in antiretroviral naïve adults [101] and children [102] recommend the use of two nucleoside reverse transcriptase inhibitors (NRTIs) in combination with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI), or in selected cases, three NRTI-based regimens (3 NRTI). NNRTI-based regimens have been a preferred choice for many patients compared to PI-based regimens because of lower pill burdens allowing for better compliance to antiretroviral therapy [4] and the better lipid profile associated with NNRTI usage [5,6].

Currently, three NNRTIs including efavirenz (EFV), nevirapine (NVP), and delavirdine (DLV) are licensed for use in HIV-infected patients in the United States. EFV has been included in the majority of treatment guidelines as the preferred first-line regimen for HIV-infected adults [101] and children >3 year old [102] in the United States as well as outside of the United States [103]. NVP has been used in HIV-infected infants, children and adults not only as a component of HAART [101-103], but also for the prevention of mother-to-child transmission (MTCT) [7-11].

Most patients experience an excellent response to NNRTI containing regimens, However a subset of individuals respond poorly, have slow virologic suppression and $CD4^+$ lymphocyte increases, increased numbers of side effects or rapidly develop resistance. Although there are a number of reasons for these differential responses, recent pharmacogenetic studies suggest that at least some of these variable responses to NNRTI containing regimens are predictable based on variants in genes responsible for metabolizing and transporting antiretrovirals including PIs, NNRTIs and NRTIs [12]. Compelling data, confirmed by several cohorts, demonstrate that the single nucleotide polymorphism (SNP) in *CYP2B6* (*CYP2B6*-G516T or *CYP2B6*6*) significantly alters EFV pharmacokinetics in HIV-infected patients [13-21]. In addition, other studies have shown the importance of the *CYP2B6* SNP on central nervous system (CNS) adverse effects related to EFV use [14,15] and NVP pharmacokinetics [15,22,23].

This article reviews the metabolism of EFV and NVP, the impact of *CYP2B6* genetic variants on hepatic CYP2B6 expression and function, and the effects of other genetic variants on pharmacokinetics, adverse events, and clinical responses to NNRTIs.

Metabolism of NNRTIs

Efavirenz—EFV is metabolized by the hepatic CYP. Among the CYP isoenzymes, CYP2B6 is the major enzyme converting EFV to its predominant metabolite, 8-hydroxyefavirenz [24], which is further hydroxylated to 8, 14-dihydroxyefavirenz by CYP2B6 (Figure 1) [25]. EFV is also converted to 7-hydroxyefavirenz, which is a minor pathway, possibly by CYP2B6 and CYP2A6 [25,26]. Their conjugated metabolites are excreted predominantly in the urine as glucuronides and sulfate conjugates [24,25].

Nevirapine—NVP is also metabolized by the hepatic CYP and converted to its metabolites. Among the metabolites, 2-hydroxynevirapine, 3-hydroxynevirapine, 8-hydroxynevirapine and 12-hydroxynevirapine are the major metabolites, mainly transformed by CYP3A4, CYP2B6, CYP3A4 and CYP2D6, respectively [27,28]. The NVP metabolites are eliminated primarily in the urine in four glucuronidated conjugates of hydroxylated metabolites (Figure 2). The percentage of each metabolite found in urine is 23%, 32%, 2%, and 29% of total metabolites, respectively [28].

Delavirdine—DLV is extensively biotransformed into several inactive metabolites, primarily by *CYP3A4* with minor involvement of *CYP2D6* [29]. It is excreted into the urine and feces, primarily as dealkyl delavirdine and pyridinecleaved delavirdine [30]. The hepatic *CYP2B6* does not appear to be involved with DLV metabolism.

CYP2B6 gene polymorphisms and hepatic CYP2B6 expression and function

Over 100 SNPs have been identified within the *CYP2B6* gene located on chromosome 19 [104]. Among them, several important SNPs have been found to be associated with hepatic *CYP2B6* expression and function (for summary see recent review [31]). In *in vitro* assays using human liver microsomes, several studies have demonstrated the impact of genetic variants on *CYP2B6* protein expression and hydroxylation of *CYP2B6* substrates. Lang *et al*.

analyzed the expression of the *CYP2B6* protein and its substrate metabolic transformation using *S*-mephenytoin *N*-demethylase activity in human liver samples. They observed significantly reduced CYP2B6 protein expression and decreased activity in human liver samples with the *CYP2B6*-C1459T (rs3211371) [*CYP2B6*5* and *CYP2B6*7*] [32]; although these findings are yet to be confirmed. In contrast, Hesse *et al.* demonstrated that carrying the *CYP2B6*6B* allele was an important predictor of bupropion hydroxylation when the data were stratified with alcohol use; however, no effect of the genotype was found to be associated with CYP2B6 mRNA or protein expression [33]. In another study, Xie *et al.* showed that the *CYP2B6*6* variant enhanced cyclophosphamide hydroxylation [34]. Lamba *et al.* evaluated CYP2B6 splicing variants in human liver samples and demonstrated that the *CYP2B6*-G516T, –C1459T, and intron 3 C15582T genotypes were predictors of hepatic *CYP2B6* activity and varied according to sex and ethnicity [35]. In an additional study by Desta *et al.*, bupropion protein expression and activity, and EFV hydroxylation were significantly decreased in subjects with the *CYP2B6*5*, or *CYP2B6*6* [26]. Recent studies have shown several novel single nucleotide polymorphisms including *CYP2B6**16 [18,20], *CYP2B6**27 and *28 [20], *CYP2B6**26 [36] which significantly altered EFV pharmacokinetics. In total, the *CYP2B6*-G516T genotype may serve as a tag SNP for several haplotypes and is an important predictor of hepatic CYP2B6 protein expression and hydroxylation of CYP2B6 substrates.

CYP2B6 genotypes and NNRTI pharmacokinetics

Efavirenz—Several studies have identified a relationship between *CYP2B6*-G516T gene polymorphisms and plasma EFV pharmacokinetics in HIV-infected adults [13-20] and children [21] (Table 1). All available data have shown that the subjects with the *CYP2B6*-516-T/T genotype (homozygous variants) have consistently higher EFV concentrations compared to those with the *CYP2B6*-516-G/T (heterozygous variant) and G/G genotype (wild type). Additional research also identified differences in EFV pharmacokinetics in subjects with the *CYP2B6*-516-G/T and those with the *CYP2B*6-516-G/G genotypes [14,16,19,20].

We evaluated the association between the *CYP2B6*-G516T genotype and EFV pharmacokinetics in 71 HIV-1 infected children receiving HAART [21]. Children with the T/T genotype had significantly lower EFV oral clearance rates (3.0 L/h/m^2) than those with the G/T genotype (5.7 L/h/m^2, P = 0.02) and the G/G genotype (7.0 L/h/m^2, P = 0.003) (Figure 3A). A multivariate analysis for EFV oral clearance including age, gender, race/ethnicity, and *CYP2B6*-G516T genotype also showed that age (P = 0.03) and the *CYP2B6*-G516T genotype (P = 0.005) were independently and statistically associated with EFV oral clearance.

Numerous studies have investigated the relationship between the *CYP2B6*-C1459T genotype and plasma EFV pharmacokinetics in HIV-infected adults [14,17,20,37] and children [21]. However, to date, no significant effect has been observed.

Nevirapine—Compared to EFV, few studies have evaluated the relationship between the *CYP2B6* genotypes and NVP pharmacokinetics [15,22,23] (Table 1). Rotger *et al.* assessed the *CYP2B6*-G516T in 59 HIV-infected subjects who received NVP as a component of HAART [15]. Individuals with the *CYP2B6*-516-T/T had 1.7-fold higher mean plasma levels than those with the *CYP2B6*-516-G/G. Similarly, Penzak *et al.* evaluated 23 HIV-infected adults who received NVP and showed that the median NVP concentration in individuals with the *CYP2B6*-516-T/T (7.6 μg/mL) was higher than those in individuals with the G/G genotype (4.2 μg/mL) or with the G/T genotype (5.6 μg/mL) [22]. Our recent data analyzing 126 HIV-1 infected children receiving NVP as a component of HAART

demonstrated a significant association between the *CYP2B6*-G516T and NVP oral clearance [23]. NVP oral clearance in children with the *CYP2B6*-516-T/T genotype (1.6 L/hr/m^2) was significantly decreased compared to those with the -G/G (2.3 L/hr/m^2, P = 0.001) and -G/T genotype (2.1 L/hr/m^2, P = 0.003) (Figure 3B). A multivariate analysis for NVP oral clearance showed that the *CYP2B6*-G516T genotype (T/T genotype, P = 0.02) and concomitant PI (P = 0.05) were independently associated with NVP oral clearance. The *CYP2B6*-C1459T genotype was not associated with NVP oral clearance (P = 0.95).

CYP2B6 genotype and adverse effects associated with NNRTI use

Efavirenz—Several major adverse effects are associated with EFV use including skin rash, abnormal liver enzymes, and notably CNS symptoms including insomnia, abnormal dreams, confusion, amnesia, and hallucination [101,102]. These CNS adverse effects are associated with the higher levels of EFV in plasma [38-40], while others failed to demonsrate the association [41,42]. Two studies have demonstrated the association between the *CYP2B6* genotype and the incidence of CNS adverse effects [14,15]. Haas *et al.* evaluated 156 patients who received EFV with different combinations of NRTI demonstrating that the *CYP2B6*-G516T genotype was associated with CNS symptoms at 1 week after initiation of treatment [14]. Similarly, Rotger *et al.* evaluated 167 patients who received EFV as a component of HAART and demonstrated that the *CYP2B6*-516-T/T genotype was associated with a higher incidence of sleep disorders and fatigue [15].

EFV is contraindicated for women of child bearing potential because it is known to be teratogenic, causing neural tube defects [43-45]. The impact of the *CYP2B6*-G516T genotype on the incidence of neural tube defect is currently unknown; however, it is possible that the *CYP2B6*-G516T genotype, which is associated with altering the plasma EFV levels, may impact on the incidence of neural tube defect in infants whose mothers are exposed to higher levels of EFV during the early pregnancy. In any event, women who are planning or at risk for becoming pregnant should be offered alternative antiretroviral regimens whenever possible.

Nevirapine—Several major adverse effects are associated with NVP use including skin rash and abnormal liver enzymes. The frequency of Grade 3 or 4 increased liver enzymes in patients on NVP (4-18%) appears to be higher than those on EFV (1-8%) based on several clinical trials and cohort studies [46]. Factors associated with hepatotoxicity include female gender, higher baseline and actual $CD4^+$ T-cell counts [47,48], and *HLA-DRB1*0101* [49]. Although NVP is not a substrate of P-glycoprotein [50], the ATP binding cassette, subfamily B, member 1 (*ABCB1*), which encodes P-glycoprotein, the *ABCB1*-C3435T (rs1045642) genotype has been reported to be associated with the incidence of hepatotoxicity in HIV-1 infected adults receiving NVP containing HAART regimens [51,52]. Richie *et al.* evaluated the possible significant genotypes in 13 patients who developed NVP-associated hepatotoxicity with 49 matched controls [52]. Using univariate analysis, the *ABCB1*-3435-T allele and the status of hepatitis B surface antigen were associated with a decreased likelihood of hepatotoxicity. Haas *et al.* also demonstrated the association between the *ABCB1*-C3435T genotype and NVP-associated hepatotoxicity in 53 patients compared to 108 controls [51]. Using multivariate analysis, the *ABCB1*-C3435T genotype was significantly associated with reduced risk of NVP-associated hepatotoxicity. Interestingly, the *CYP2B6*-G516T genotype was not associated with risk of hepatotoxicity when assessed in multivariate analyses in both studies. The exact mechanism why *ABCB1*-C3435T was associated with a reduced risk of NVP-associated hepatotoxicity is currently unknown; however, it is possible that altered P-glycoprotein activity in the intestine associated with the *ABCB1* variants [53] alters disposition of NVP and/or its metabolites that affects intracellular concentrations of NVP and toxicity in liver.

Impact of genetic variants on clinical responses

The actual influence of the *CYP2B6*-G516T genotypes on clinical responses has been evaluated in only a few studies [14,17,21,54] (Table 1). Haas *et al.* evaluated the impact of the *CYP2B6* genotype on virologic and immunologic responses over 24 weeks in 157 HIV-infected adults receiving EFV as a component of HAART and have shown no differences in immunologic (P = 0.15) or virologic responses (P = 0.74) among the patients with the *CYP2B6*-G516T genotypes after 24 weeks of therapy [14]. A recent larger study in adults by Haas *et al.* also showed no correlation between the presence of *CYP2B6*-G516T polymorphisms and long-term virologic or immunologic response for up to three years [17]. Another study by Motsinger *et al.* reported that virologic failure in patients receiving EFV was associated with a two-locus interaction between *ABCB1*-G2677T and *CYP2B6*-G516T [54]. Our previous data in 72 children who received EFV as a component of HAART [21] did not demonstrate differences in immunologic or virologic outcomes when analyzed in association with *CYP2B6*-G516T gene polymorphisms despite significant differences in EFV oral clearance. However, our recent study in 126 children with advanced HIV infection who received NVP as a component of HAART demonstrated different findings [23]. Children with the *CYP2B6*-516-T/T genotype had the greatest increase in $CD4^+$ T-cell percentages (+9.0%) compared to those with the -G/G (+3.2%, P = 0.008) and -G/T genotype (+5.0%, P = 0.04) at week 12. This trend continued for $CD4^+$ T cell percentages in children with the *CYP2B6*-516-T/T genotype (+10.5%) compared to those in children with the -G/G genotype (+4.7%, P = 0.01) and -G/T genotype (+8.2%, P = 0.06) at week 24. A multivariate analysis for change in $CD4^+$ T-cell percentages showed that the *CYP2B6*-516-T/T genotype was the only covariate associated with a change in $CD4^+$ T-cell percentages from baseline to week 12 (P = 0.03). Virologic response at weeks 12 and 24 was also evaluated among the three groups; however, no differences were observed (P = 0.86, P = 0.24, respectively). Although there are many factors involved in determining the response to antiretroviral therapy in HIV-infected patients, our study was the first report demonstrating that *CYP2B6* genetic variants can significantly affect the clinical response to NNRTI-containing regimens. It is important to note the differences between our first and second studies. In our initial report, children were carefully monitored early in their treatment course with pharmacokinetic analysis. For children whose EFV plasma concentrations failed to achieve predetermined target levels, the dose of EFV was adjusted. Thus, the impact of specific CYP genotypes on virologic and immunologic clinical outcomes was limited because of the intensive pharmacokinetic monitoring of the children participating in this study. In contrast in our more recent study, HIV-1 infected children were treated with regimens containing an NNRTI without real-time monitoring of drug levels. Therefore, we believe that our current findings are more representative of children receiving chronic NNRTI containing antiretroviral therapy when routine pharmacokinetics is not performed.

Impact of *CYP2B6* genotype on the development of NNRTI resistant virus

One of the major concerns for patients who receive an NNRTI as part of their antiretroviral regimen is the development of resistant viruses, which requires only a single point mutation to confer high-level, cross-class resistance among NNRTIs [55]. The impact of the *CYP2B6* genotype on the development of NNRTI resistant virus is currently unknown; however, Ribaudo *et al.* [19] demonstrated that *CYP2B6*-G516T genotypes, which were associated with plasma EFV levels, predicted the duration of plasma EFV levels exceeding 95% inhibitory concentration. They concluded that the *CYP2B6*-516-T/T genotype or a prolonged half-life of EFV may predict increased risk for developing EFV resistance virus among patients who discontinued EFV-containing regimens.

We investigated the impact of the *CYP2B6*-G516T genotype and EFV oral clearance on HIV-1 infected children who developed NNRTI mutations (K103N and G190S) during the

early stage of HAART (n = 10) and those who sustained undetectable plasma HIV-1 RNA during HAART (n = 31) [21]. There was no difference in the distribution of the *CYP2B6*-G516T genotype or EFV oral clearance rate between two groups. It should be noted, however, that this was the same cohort of children who had dose adjustments based on EFV pharmacokinetics early in their treatment and the relatively small number of subjects available for study may have resulted in inadequate power to demonstrate a difference.

Impact of *CYP2B6* genotype on HIV-1 MTCT and development of NVP resistant virus

NVP has been used widely to prevent HIV-1 MTCT in developing countries [7-11]. However, a single dose of NVP is associated with the development of NVP resistant virus in mothers and their infants who become infected with HIV [56]. The impact of the *CYP2B6* genotype on the development of NVP resistant virus in mother and infant is unknown.

Impact of the *ABCB1* genotype on NNRTI pharmacokinetics and clinical response to HAART regimens containing NNRTI

Although NVP or EFV is not a substrate of P-glycoprotein [50], associations have been reported between the *ABCB1* genotype and EFV pharmacokinetics [57], and virologic outcome in HIV-infected adults receiving EFV containing HAART regimens [17]. In addition, an inverse correlation between NVP intracellular concentrations and P-glycoprotein expression in PBMC has been reported [58], while another study demonstrated no association between EFV intracellular conc entrations and P-glycoprotein expression in PBMC [56]. Recent data have suggested that the genetic polymorphisms for *ABCB1*-G2677T (rs2032582), which is highly associated with the *ABCB1*-C3435T genotype, influence the virologic outcome combined with the *CYP2B6*-G516T genotype in patients who receive EFV containing HAART regimens [54]. In total, these data suggest that EFV, NVP, or their metabolites may be a substrate of P-glycoprotein.

We evaluated 14 pairs of cerebrospinal fluid (CSF) and plasma NVP levels from 11 children with known or suspected HIV encephalopathy, or presence of symptoms consistent with neurological decline attributable to HIV-related neurologic diseases [23]. The median NVP CSF: plasma ratio was 0.62 in children with the *ABCB1*-3435-C/T or - T/T compared to 0.43 in children with the *ABCB1*-3435-C/C genotype (P = 0.01). No significant difference was observed when the ratios were compared with the *CYP2B6*-G516T genotype (P = 1.00). Although the number of CSF samples was limited, this finding provides additional support for NVP or its metabolites being substrates of P-glycoprotein [59].

Age is an important factor that can alter the association of NNRTI pharmacokinetics and CYP2B6 genotypes

Although there are no data available regarding the impact of age on hepatic CYP2B6 expression in children and adults, hepatic CYP activity is known to change with age and is often greater in young children (1-4 years old) compared to adults [60]. This is also supported by studies showing that the clearance of CYP substrates including warfarin [61], antipyrine [62], and nelfinavir [63,64] are increased in young children. Therefore, we examined if the *CYP2B6*-G516T genotype in young children would have a greater impact on EFV oral clearance than older children [21,23]. EFV oral clearance was significantly greater for the younger children <5 years with the G/G genotype (9.7 L/h/m^2) compared to those with ≥5 years with the G/G genotype (6.6 L/h/m^2) (P = 0.03). However, no differences were observed in children with the G/T genotype (P = 0.71), or T/T genotype (P = 0.86). These data suggest that hepatic enzyme levels determined by age may need to be considered when evaluating the impact of genetic variants on drug pharmacokinetics of younger children. We performed the same analysis using the NVP cohort; however, no significant difference was observed when we analyzed the data by age [23]. Because other CYP isoenzymes including

CYP3A4 or CYP2D6 involve in NVP metabolism and the developmental maturation of each hepatic isoenzyme is different among the isozymes [65], the variations in these genes may affect the expression of hepatic CYP isoenzymes, which may lead to differences in NVP pharmacokinetics.

Clinical implications

Recent articles illustrate the feasibility of translating HIV pharmacogenomics into clinical practice [36,66]. Gatanaga *et al.* demonstrated that patients with the CYP2B6 *6/*6 and *6/*26, who had extremely high plasma EFV concentrations, had persistently suppressed plasma HIV-1 RNA while receiving reduced doses of EFV (200-400 mg/day, instead of 600 mg). They also showed improvement of CNS-related symptoms after the dose adjustment. In addition, Torno *et al.* presented a case of an HIV-infected patient who has maintained durable virologic suppression of HIV infection with a 400 mg daily dose of EFV and the pharmacogenetic study and therapeutic drug monitoring supported the dose reduction. They suggested that the potential applications of combined pharmacogenetic testing/therapeutic drug monitoring in guiding efavirenz-based therapy.

CONCLUSIONS

Several important genetic variants have been reported that alter NNRTI pharmacokinetics and the risk for adverse effects. The *CYP2B6*-G516T is associated with EFV and NVP pharmacokinetics, and the incidence EFV-related CNS adverse effects. In addition, the *ABCB1*-C3435T genotype has been associated with the incidence of NVP hepatotoxicity, although NNRTI are thought not to be a substrate of P-glycoprotein. At present, therefore, the relationship between the *ABCB1* genotype and hepatic P-glycoprotein functional activity remain uncertain.

In total, currently available data suggest that *CYP2B6* variants are important predictors of EFV and NVP pharmacokinetics. It is likely, therefore, as antiretroviral therapy evolves to the optimization of treatment regimens for the individual patient that determination of the *CYP2B6* genetic variants will be important for optimizing NNRTI containing regimens.

FUTURE PERSPECTIVE

Pharmacogenetics promises to provide important clues to understanding the variable responses of patients to antiretroviral treatment regimens. Our findings and those of others support an important effect of *CYP2B6*-G516T genotypes on EFV pharmacokinetics in HIV-1 infected children and adults. In addition, there are several genetic variants reported to alter the concentrations of plasma EFV and NVP that are associated with the risk for adverse effects. These findings will require validation in additional cohorts.

Several important areas remain to be investigated. First, the impact of *CYP2B6* genotypes on MTCT and development of resistant virus in mothers and their infants after receiving a single dose of NVP is of particular interest. Second, the association of genetic variants with the development of NNRTI resistance with different antiretroviral backgrounds is an area in need of investigation. Third, because NVP is an inducer of CYP, the effect of CYP2B6 genotypes on long-term antiretroviral treatment remains to be examined. Fourth, the relationships between NNRTI and P-glycoprotein in lymphocytes, the blood brain barrier, and other anatomical sites warrants further investigation. Fifth, because age is an important factor to determine the metabolism of drugs in children, the contribution of age into PK data needs to be in consideration when analyzing the pharmacogenetic data in children. Finally, studies of genetic variations of nuclear receptors which regulate

the transcription of CYP and other transporters responsible for metabolizing and transporting NNRTIs are of considerable importance.

These and other questions will need to be addressed in order for determination of genetic variation to become a useful tool in optimizing the treatment of patients.

EXECTIVE SUMMARY

Importance of NNRTIs in treatment of HIV-1 infection

- An NNRTI (EFV) in combination with two NRTIs is an important option for first line therapy of antiretroviral naïve HIV-infected patients.
- Wide inter-individual variation of plasma NNRTI concentrations is an important consideration in patients. Adverse effects, development of resistant virus, and treatment failure are the major concerns which are associated with the variation of NNRTI levels.

Metabolism of NNRTIs

- EFV is exclusively metabolized by hepatic CYP2B6 isoenzyme.
- NVP is also metabolized by CYP2B6, but other CYP isoenzymes including CYP3A4 and CYP2D6 are also involved.

Genetic variants and hepatic CYP2B6

- Several studies have shown that *CYP2B6* gene polymorphisms significantly affect the expression and function of hepatic CYP2B6.
- *CYP2B6*5* (C1459T) and *CYP2B6*6* (G516T and A785G) variants are the most significant gene polymorphisms affecting the hepatic CYP2B6 expression and hydroxylation of its metabolites.

Genetic variants and NNRTI pharmacokinetics

- The *CYP2B6*-G516T gene polymorphism is an important determinant of EFV and NVP pharmacokinetics in HIV-1 infected children and adults.
- In addition to *CYP2B6*-G516T genetic variants, several factors are known to influence the EFV and NVP pharmacokinetics including age, concomitant medications, race/ethnicity, and other possible genetic variants.

Genetic variants and clinical responses

- A few studies have shown an association between *CYP2B6* genotype and immunologic and virologic responses in HIV-1 infected patients receiving NNRTI containing HAART regimens; however, this effect remains controversial..

Genetic variants and adverse effects

- The *CYP2B6*-G516T genotype, which is associated with a higher level of EFV, is associated with a greater incidence of central nervous system adverse effects.
- The *ABCB1*-C3435T genotype is associated with increased risk of NVP hepatotoxicity.

Conclusion

- The *CYP2B6*-G516T gene polymorphism is an important determinant of EFV and NVP pharmacokinetics.
- The *CYP2B6*-G516T genotype has been found in some studies to be associated with the incidence of EFV related CNS adverse effects.
- The *ABCB1*-C3435T genotype is associated with the incidence of NVP related hepatotoxicity, although the relationship between the *ABCB1* genotype and hepatic P-glycoprotein functional activity remains uncertain.
- *CYP2B6*-G516T genetic variants are likely to be important when strategies are developed to optimize antiretroviral therapy for individual patients.

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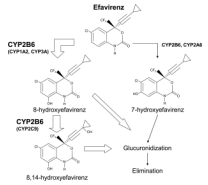

Figure 1. Efavirenz metabolic pathway and catalytic hepatic enzymes

CYP: Cytochrome P450. Larger arrows represent major pathway and smaller arrows represent minor pathway [24,25]

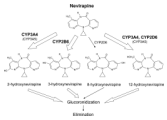

Figure 2. Nevirapine metabolic pathway and catalytic hepatic enzymes

CYP: Cytochrome P450. Larger arrows represent major pathway and smaller arrows represent minor pathway [27,28].

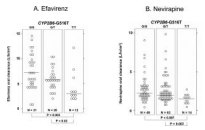

Figure 3. Oral clearance rate (L/h/m^2) for efavirenz (A) and nevirapine (B) in children with the *CYP2B6*-G516T genotypes

Each circle represents efavirenz (A) or nevirapine (B) oral clearance (L/h/m^2) in each subject with the *CYP2B6*-516-G/G genotype (left), -G/T genotype (middle), and -T/T genotype (right). The lines in the middle represent the median of oral clearance rate for efavirenz (A) or nevirapine (B).

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Table 1

A summary of studies evaluating the association between cytochrome P450 2B6 (CYP2B6) genotype and non-nucleoside reverse transcriptase inhibitors (NNRTI) pharmacokinetics, clinical responses, and adverse effects

NNRTI	Study (year)	CYP2B6 SNP	No. of patients	Ethnicity*	Pharmacokinetic Parameters†	Results‡	Clinical Response‡	Adverse effect‡	Ref.
Efavirenz	Tsuchiya *et al.* (2004)	*2-*8	44 adults	A	plasma C_{12h}	Greater in **6/*6*	NA	NA	16
	Haas *et al.* (2004)	516, 1459	157 adults	B, H, W	AUC, C_{24h}	516-TT>GT>GG	NS	CNS toxicity and 516	17
	Rotger *et al.* (2005)	516	167 adults	A, B, H, W	AUC	516-TT>GT>GG	NA	516 and CNS toxicity, and fatigue	18
	Rodriguez-Navoa *et al.* (2005)	516	100 adults	W	plasma C_{12h}	516-TT>GT>GG	NA	NA	19
	Haas *et al.* (2005)	516, 1459	340 adults	B, H, W	AUC	516-TT>GT>TT	NS	NA	20
	Burger *et al.* (2006)	1459	228 adults	A, B, W	Plasma C	NS	NA	NA	38
	Ribaudo *et al.* (2006)	516	152 adults	B, H, W	Plasma C, $T_{1/2}$ (after d/c)	516-TT>GT>GG	NA	NA	21
	Wang *et al.* (2006)	12 SNP	51 adults	B, W	Plasma C	516-TT=GT>GG, greater in *16	NA	NA	23
	Rotger *et al.* (2007)	15 SNP	169 adults	A, B, H, W	AUC	greater in *6/*6, *1/*6 lower in 1*/*4	NA	NA	23
	Saitoh *et al.* (2007)	516, 1459	71 children	B, H, W	oral clearance	516-TT<GT=GG	NS	NS	24
Nevirapine	Rotger *et al.* (2005)	516	59 adults	A, B, H, W	AUC	Greater in 516-TT	NA	NA	18
	Penzak *et al.* (2007)	516	23 adults	B	plasma trough	516-TT>GG=GT	NA	NA	25
	Saitoh *et al.* (2007)	516, 1459	126 children	A, B, H, W	oral clearance	516-TT<GT=G/G	CD4 recovery and 516	NS	26

NNRTI: non-nucleoside reverse transcriptase inhibitors; SNP: single nucleotide polymorphisms

*4: A785T and A10853G; *6: G516T and A785T; *16: A785G and T983C.

*A: Asian; B: Black; H: Hispanic; W: White

†Plasma C: Plasma concentration; AUC: Area under the curve; C_{max}: Maximum plasma concentration of NNRTI; $T_{1/2}$: half life; d/c: discontinuation

‡NA: not available; NS: Not significant.