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PharmGKB Summary: Efavirenz Pathway, Pharmacokinetics (PK)

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Keywords

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Background

Efavirenz (EFV) is used as part of a highly active anti-retroviral therapy (ART) regimen (HAART) against HIV-1 infection [1, 2]. It is important to achieve correct dosage of anti-viral medications: too high a concentration of plasma EFV may increase risk for toxicity, including neurologic toxicity (such as sleep disorders and hallucinations) [3-6], whereas too low a concentration may be associated with virologic failure [7, 8]. A therapeutic EFV range of 1-4 μg/mL is suggested, although patients with EFV plasma concentrations of >4 μg/mL do not experience substantially greater side effects than those with lower concentrations, and it is unclear whether concentrations of <1 μg/mL are associated with increased virologic failure in patients adhering to EFV treatment [9, 10]. Enzymes involved in the breakdown of EFV have an important role in this balance. Drugs taken concomitantly by HIV patients can affect EFV levels by inhibiting or inducing these enzymes, and EFV itself induces its own metabolism by increasing the expression of or activating some of these enzymes. Polymorphisms in the genes that encode these enzymes may also affect EFV concentrations, helping to explain some of the high variability in EFV plasma concentrations observed between individuals when given the same recommended daily dose [8, 11-13]. In this summary we focus on the latter interaction: the pharmacogenetics of EFV. An interactive version of this summary can be viewed at https://www.pharmgkb.org/pathway/PA166123135.

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Conflicts of Interest

RBA and TEK are stockholders in Personalis, Inc.

Pharmacodynamics

An array of antiretroviral drugs are now available that target different stages of the HIV-1 life-cycle (for a comprehensive review see [2]). EFV is amongst the molecules that target HIV-1 reverse transcriptase, preventing the formation of viral double-stranded DNA from the single-stranded viral RNA genome (Figure 1) [2]. These drugs can be divided into two classes: analogs of nucleoside substrates (nucleoside reverse transcriptase inhibitors: NRTIs) and non-NRTIs (NNRTIs) that bind to a non-catalytic site of the reverse transcriptase enzyme; EFV is in the latter class [2]. Mutations in the gene encoding the HIV-1 reverse transcriptase enzyme are associated with resistance to NRTIs and NNRTIs, including EFV [14]; however, in this summary we focus on variants in the human genome and their effect on EFV pharmacokinetics and treatment.

Pharmacokinetics

The major route of EFV metabolism is to 8-hydroxyefavirenz (8-hydroxy-EFV), formed predominately by CYP2B6 (Figure 1) [15-17]. Studies within human liver microsomes have shown that the formation rate of 8-hydroxy-EFV displays considerable variability in different samples [17]. CYP3A4, CYP3A5, CYP1A2 and CYP2A6 may play minor contributing roles in this xenometabolic step [15-17]. CYP2B6 is also the major enzyme involved in formation of the secondary metabolite 8,14-dihydroxy-EFV [15, 16]. Furthermore, EFV can be hydroxylated to 7-hydroxy-EFV by CYP2A6, a minor pathway of EFV metabolism accounting for around 23% of overall EFV metabolism *in vitro* [16, 17]. Hence, there are three hydroxylated EFV metabolites: 8-hydroxy-EFV, 8,14-dihydroxy-EFV and 7-hydroxy-EFV.

The predominant mode of EFV excretion is as glucuronides in the urine, with 8-hydroxy-EFV-glucuronide as the major metabolite found [18]. Multiple UDP-glucuronosyltransferase (UGT) isoforms (including UGT1A1, 1A3, 1A7, 1A8, 1A9, 1A10, and 2B7) can act upon the three hydroxylated EFV metabolites to produce glucuronide forms [18-20]. *In vitro* studies have shown that EFV can be directly glucuronidated to EFV-*N*-glucuronide by UGT2B7 (though this is a minor pathway after the first dose of EFV) [18-22]. The formation rate of EFV-*N*-glucuronide shows large variability between human microsome samples, whereas formation of 7-hydroxy-EFV-G, 8-hydroxy-EFV-G and 8,14-hydroxy-EFV-G do not [23].

EFV-enzyme interactions and drug-drug interactions

The transcription factors pregnane X receptor (PXR, *NR1I2*) and constitutive androstane receptor (CAR, *NR1I3*) are activated to different extents by different drugs. Their target genes include those involved in xenobiotic metabolism and elimination, and therefore may underlie drug-drug interactions [9, 24, 25]. EFV is thought to enhance its own metabolism (autoinduction) by inducing the expression of *CYP2B6* and *CYP3A4* via activation of NR1I3 and NR1I2 [24, 26-28]. Other drugs can also induce *CYP2B6* and *CYP3A4* expression, including rifampin (an anti-tuberculosis drug often taken concomitantly with EFV in patients with HIV and tuberculosis co-infection) via the activation of NR1I2 [24, 25, 28]. *In*

vitro, EFV has been seen to competitively inhibit bupropion 4-hydroxylation by CYP2B6, as well as inhibiting CYP2C8, CYP2C9 and CYP2C19 activity [29, 30].

Pharmacogenetic studies have provided insight into the variability seen in EFV PK between patients [31].The effect EFV has on metabolizing enzymes, and the drug-drug interactions between EFV and other antiretrovirals or medications commonly taken concomitantly by HIV patients, may influence the safety, adherence, and efficacy of treatment; however, these effects vary between patients and thus are difficult to predict [31]. For example, when comparing samples on day 1 and day 14 in patients treated with EFV-based HAART, some patients exhibit an increase in EFV oral clearance (autoinduction) whilst others do not, and between those that do, the extent of the increase in oral clearance is variable [32]. Importantly, the time-points of samples collected and compared could influence the extent of autoinduction observed [33]. EFV autoinduction is also influenced by a patient's genotype; for example, patients with the *CYP2B6*1* allele may exhibit long-term EFV autoinduction [33, 34]. In selected situations, therapeutic drug monitoring of antiretroviral therapy may help to address these issue by individualizing dosage to minimize side effects while maintaining antiviral efficacy [31, 35], although it is important to note that EFV is often co-formulated in a fixed dose as part of an anti-viral regimen, adding a layer of complexity to individualization of dosage.

Pharmacogenetics

Variants within genes of enzymes involved in the EFV PK pathway have been investigated for association with PK parameters, clinical outcomes and side effects, such as neurologic (CNS) toxicity, one of the most commonly reported adverse events in patients taking EFV.

CYP2B6 variants

As CYP2B6 is the main enzyme involved in EFV metabolism, polymorphisms in the *CYP2B6* gene have been extensively investigated for associations with EFV PK parameters, toxicity, and treatment responses. These are summarized in Table 1, with two of the variants described in more detail below.

1) 516G>T, rs3745274—A large number of studies have investigated the effect of the *CYP2B6* 516G>T SNP on EFV PK, efficacy and side effects, and it is the most investigated variant in relation to the EFV PK pathway. The T allele of this polymorphism is present in several *CYP2B6* haplotypes: **6A-C*, **7A*, **7B*, **9*, **13A*, **13B*, **19*, **20*, **26*, **34*, **36*, **37*, **38* [36]. Studies using human liver samples suggest that it results in a *CYP2B6* mRNA splice variant that lacks exons 4 to 6 (named SV1) and consequently results in lower levels of functional *CYP2B6* mRNA [37]. Correlating with its effect on *CYP2B6* expression, the T allele is associated with increased EFV plasma concentrations and median estimated C_{min} values in HIV patients as compared to patients with the G allele [9, 38, 39].

Numerous studies have reported an association in HIV-infected patients between the TT genotype and increased EFV plasma concentrations, reduced clearance, or increased exposure to drug compared to patients with the GG and/or GT genotype (Table 1). The TT genotype is more common in African-Americans and Blacks than in European-Americans or

Caucasians, and this may underlie differences seen in EFV plasma concentrations between these populations [40, 41]. Patients with the GT genotype also have increased EFV plasma concentrations and exposure as compared to patients with the GG genotype (Table 1). Moreover, a gene-dose effect is observed in many studies, with EFV clearance following the pattern TT<GT<GG, and EFV concentrations following the pattern TT>GT>GG [40, 42]. The TT and GT genotypes are also associated with higher intracellular peripheral blood mononuclear cell (PBMC) EFV concentrations and exposure as compared to the GG genotype (Table 1).

Clifford *et al* showed that EFV-treated patients experienced significantly more CNS symptoms during the first week of treatment as compared to the non-EFV group, but differences between the groups decreased rapidly and were no longer significant by four weeks of treatment [43]. The clinical relevance of increased exposure to EFV in HIV patients with the T allele has been investigated; however, results remain unclear for an association with toxicity, treatment termination, or efficacy, with some studies finding a significant association, while others do not (Table 1).

Genotyping for this variant may be helpful for individualizing EFV dosages in some situations. In one cohort of HIV-infected children the GG genotype was associated with a 50-70% probability of developing sub-therapeutic EFV plasma concentrations, and patients with the GG genotype required a higher dose adjustment [44]. Conversely, Taiwanese patients with the GT or TT genotype were at a significantly increased risk of plasma EFV concentrations associated with toxicity (>4 mg/L) - two patients discontinued EFV treatment due to neurotoxic side effects, and both had EFV plasma levels above 4mg/L [45].

It has been proposed that *CYP2B6* genotyping could be used as a screen to identify individuals who may be either slow or fast metabolizers of EFV and may benefit the most from early therapeutic drug monitoring (TDM), in order to optimize dosage as a function of exposure before or during the initiation of drug therapy [35, 46]. For example, one retrospective study reported that therapeutic dose monitoring and dose reduction in 31 patients with one or two 516 T alleles from a standard 600 mg/day dose of EFV to 400 mg/day, reduced the mean EFV C_{min} (5.7 +/−3.4 mg/l at 600 mg/day) to within therapeutic range (2.39 +/− 1.28 mg/l at 400 mg/day) [47]. The authors also report that decreasing dosage in those patients also correlated with a decrease in the percentage of patients reporting CNS adverse events (from 89.3% to 9.7%), an increase in $CD4^+$ lymphocyte counts (from 483.9-×10^6 cells/ μl to 600.8 × 10^6 cells/μl), and an increase in the percentage of patients with undetectable HIV viral load (from 93.5% to 100%.) Interestingly, all of the patients with the 516 T/T genotype required a further reduction to 200 mg/day EFV, supporting reduction in EFV dose for slow-metabolizers [47]. An important caveat before considering dose adjustment based on pharmacogenetic testing is that EFV and other anti-retrovirals are prescribed as part of a more complex regimen (ART and HAART) and may be administered as part of a fixed-dose co-formulation.

In conclusion, there is a clear association between the *CYP2B6* 516G>T variant and EFV plasma concentrations, although a lack of a clear relationship between this variant and

response to EFV treatment may indicate a wide therapeutic window, as well as the complexities of drug-drug interactions of an anti-HIV regimen [48].

2) 983T>C, rs28399499—The C allele is the sole variant of the **18* allele and is also present in *CYP2B6*16* (along with 785A>G). The C allele is associated with increased EFV plasma concentrations compared to the T allele [38]. Genotype CC and/or CT have been reported to be associated with increased EFV plasma concentrations and drug exposure compared to the TT genotype in several studies; however, other studies report no significant difference in EFV concentrations between the CT genotype and TT genotype (Table 1). Adjustment for the *CYP2B6* 516G>T genotype may be required for an association to be observed between estimated C_{min} EFV with 983T>C (as was shown with trough EFV concentrations in [39]). Another factor influencing the discrepancy between studies may be the low or absent allele frequency of C in some populations: the C allele was found at a frequency of 0.05-0.08 in African, Black, or African-American populations but was not identified in Caucasian, Asian, or Chilean populations [9, 38, 49, 50]. The clinical relevance of this polymorphism is unclear. In a cohort of 170 Black and Caucasian individuals, the only two patients with the CC genotype were withdrawn from EFV-containing HAART therapy due to toxicity [38]. On the other hand, CC and CT genotypes were not associated with risk of immunological failure or central nervous system (CNS) toxicity as compared to the TT genotype in Ghanian patients treated with EFV [51].

CYP2A6 variants

Variants within the *CYP2A6* gene have been associated with EFV plasma concentrations, though the clinical relevance of this effect is not clear (Table 2). An association between rs28399433 (c.-48A>C) genotypes AC and CC with increased EFV plasma concentrations, as compared to the AA genotype, has been observed in several studies, whereas others report no association with this SNP and EFV plasma levels (Table 2). As compared to CYP2B6, CYP2A6 is a minor player in EFV metabolism and associations between *CYP2A6* polymorphisms and EFV PK parameters may be dependent on a patient's underlying *CYP2B6* genotype. For example, in Thai patients with the *CYP2B6*1/*1* genotype (excluding patients with variant alleles at positions *CYP2B6* rs8192709, rs3826711, rs3745274, rs2279343, rs3211369, rs3211371, rs8192719), *CYP2A6* rs28399433 genotypes were not significantly associated with EFV plasma concentrations [12]. This was confirmed in a separate genomewide association study (GWAS) in 856 individuals that found no association between rs28399433 and estimated plasma trough concentrations of EFV [39]. However, when investigating only individuals with a *CYP2B6* slow metabolizer genotype (defined by genotypes 516TT, or 516T/983C or 983CC of two SNPs rs3745274 and rs28399499) a significant association was observed between the *CYP2A6* rs28399433 AC genotype and higher EFV plasma concentrations (as compared to AA genotype) [52]. The clinical relevance of this SNP on EFV treatment is unclear since no association with immunological failure, virologic response, or CNS toxicity has been reported (Table 2).

UGT2B7 variants

Several variants within the *UGT2B7* gene have been investigated for associations with EFV PK parameters, toxicity or immunological failure, though most studies report no significant

association (Table 3). Again, considering *CYP2B6* genotype may be important for revealing an association with other variants; in patients with an underlying *CYP2B6* slow metabolizer genotype the *UGT2B7* rs28365062 genotype GG was associated with higher EFV plasma concentrations, and this SNP along with *CYP2A6* rs28399433 A>C explained 21% variance in EFV plasma concentrations in these patients using a multivariate linear regression model [52].

CYP3A5 and *CYP3A4* variants

Associations for variants in the *CYP3A5* and *CYP3A4* genes can be seen in Table 4. In patients with the *CYP2B6*1/*1* genotype (excluding patients with variant alleles at positions *CYP2B6* rs8192709, rs3826711, rs3745274, rs2279343, rs3211369, rs3211371, rs8192719), rs776746 (*CYP3A5*), rs28371759 (*CYP3A4*) or rs2740574 *(CYP3A4*) genotypes were not found to be significantly associated with EFV plasma concentrations in 100 Thai HIV patients [12].

NR1I3 variants

A SNP (rs2307424) that results in a G>A substitution in the *NR1I3* (CAR) gene has been investigated for effects in patients treated with EFV (Table 5). In a cohort of Chilean patients with HIV, the G allele was associated with higher EFV plasma concentrations, and along with *CYP2B6* rs3745274 allele A, was a statistically significant predictor of EFV plasma concentrations in multivariate stepwise linear regression analysis [9]. The A allele may therefore enhance *NR1I3* activity, resulting in increased expression of *CYP2B6* and thus reduced EFV plasma concentrations [9]. Genotype GG was independently associated with increased risk of discontinuation of EFV treatment within 3 months of treatment along with other risk factors in a mixed population cohort [53]. In Ghanaian patients, a study found no statistically significant association between this polymorphism and EFV plasma concentrations, CNS toxicity, or risk of immunological failure [51]. Two other studies also reported no significant associations between rs2307424 G>A and plasma concentrations of EFV after taking three *CYP2B6* polymorphisms into account [39, 52].

Conversely, the *NR1I3* rs3003596 genotype GG has been associated with lower EFV plasma concentrations compared to the AA and AG genotypes (Table 5). When stratifying for the *CYP2B6* 516G>T genotype, the significant effect is only seen in patients with the *CYP2B6* c.516 TT genotype [54]. The same study found no statistically significant association with other *NR1I3* or *NR1I2* SNPs and EFV plasma concentrations, including rs2307424 [54].

ABCB1 variants

ABCB1 (P-gp, MDR1) has not been shown to have a direct role in EFV transport; however, several studies have investigated the effects of EFV on *ABCB1* expression and the effects of *ABCB1* polymorphisms on EFV PK (Table 6). PBMC mRNA expression of *ABCB1* was significantly reduced at day 14 from day 1 of EFV treatment in healthy volunteers, though P-gp enzymatic activity in PBMCs was not altered by treatment [55, 56]. Polymorphisms in *ABCB1* may influence the PK of drugs taken concomitantly with EFV, and thus may affect EFV levels via drug-drug interactions. Mixed results are reported for the effect of the rs1045642 SNP on EFV PK and toxicity, but for associations related to drug efficacy, the A

allele seems to be associated with favorable outcomes in patients with HIV (Table 6). In contrast, an association between the A allele and a lower increase in CD4+ T cell count was reported in Belgian patients after initiation of EFV-containing therapy [57]. More studies are required to evaluate the clinical relevance of *ABCB1* variants on response to treatment that includes EFV.

Other genes

Polymorphisms in other genes, such as *CYP1A2* and *HTR2A* have been investigated for an association with EFV PK parameters, toxicity, or efficacy (Table 7).

Multivariate analysis

It is likely that multiple polymorphisms in genes involved in EFV metabolism contribute to overall EFV plasma concentrations and resulting efficacy and toxicity outcomes. Recent studies have examined multiple factors influencing variance in EFV PK parameters; these results are summarized below.

Multiple SNPs in CYP2B6—rs3745274 c.516G>T and rs28399499 c.983T>C are the two SNPs in *CYP2B6* that are most often reported to demonstrate an association with variability in EFV trough concentrations. In a cohort of Belgian patients, *CYP2B6* c.516 genotype GT and TT, *CYP2B6* c.983 genotype TC, and Asian origin, were all factors that contributed significantly to interindividual variability in estimated log-transformed trough EFV concentrations [57]. Moreover, *CYP2B6* c.516G>T, *CYP2B6* c.983T>C, BMI, and time post-dose were all significantly associated with EFV plasma concentrations in a multivariate analysis of a cohort of 174 Caucasian and Black patients on stable EFV-containing HAART [38]. Additionally, mean log EFV trough concentrations increased with the number of *CYP2B6* loss-of-function alleles in Ugandan and Zimbabwean patients [58]. After correcting for c.516 G>T and c.983 T>C, an intronic polymorphism in *CYP2B6*, rs4803419 C>T, also showed an association with variability in EFV trough concentrations in a GWAS. Together, the three SNPs explained 33% of the interindividual variability in EFV concentrations in a cohort of n=856 in linear regression analysis [39]. Slow metabolizers (women with two 516T alleles or two 983C alleles, or one of each allele) were more likely to respond to NNRTI-based treatment (undetectable viral load up to 54 weeks after initiation) compared to fast metabolizers (no variant alleles at these positions) [59]. Conversely, some studies do not show these genotypic associations with response to EFV treatment; multiple SNP analyses examining different genotype combinations of *CYP2B6* rs3745274, rs28399499 and rs4803419 found no association with virologic response at 48 weeks in 359 HIV-infected Haitian patients treated with an EFV-containing anti-retroviral regimen, or with other SNPs examined [60]. Multivariate analysis in another study in Ghanaian patients reported *CYP2B6* c.516G>T (n=496), *CYP2B6* c.983T>C (n=494), and body weight as independent factors associated with EFV plasma concentration; however, neither EFV plasma concentration nor SNPs could predict clinical failure in univariate analysis [51].

Multiple gene analysis—Several studies examine the effect of polymorphisms in multiple genes on EFV plasma concentration. A stepwise multiple linear regression analysis

identified *CYP2B6* rs3745274 c.516 genotype TT, *UGT2B7*1a* carrier status (no variant alleles at rs7439366 C>T or rs28365062 A>G), and *CYP2A6*9* (rs8192726 C>A), or *CYP2A6*17* (rs28399454 C>T) as independent predictors of EFV plasma concentration (mid-dose at weeks 4 and 8) in 94 Ghanaian patients, accounting for 45.2%, 10.1% and 8.6% of the total variance in EFV plasma concentrations, respectively [61]. Furthermore, a multivariate linear regression model including *CYP2A6* rs28399433 A>C and *UGT2B7* rs28365062 A>G explained 21% variance in EFV plasma concentrations in patients with the *CYP2B6* slow metabolizer genotype (defined by genotypes 516TT, or 516T/983C, or 983CC of two SNPs: rs3745274 and rs28399499). In addition, when coupled with *CYP2B6* rs28399499 T>C the variance explained reached 22% [52].

Similarly, in 207 Chilean HIV patients, multivariate stepwise linear regression analysis revealed that the *CYP2B6* rs3745274 allele T and *NR1I3* rs2307424 allele G were significant predictors for EFV plasma concentrations [9]. More patients were above the suggested minimum toxic concentration of plasma EFV (4μg/mL) who had three to four high EFV concentration-associated alleles (*CYP2B6* rs3745274 allele T and *NR1I3* rs2307424 allele G) than those with zero, one, or two of these alleles. Conversely, more patients were below the suggested minimum effective concentration (1μg/mL) that had zero or one of these alleles compared to those with three or four [9]. Examining patients who were within the EFV therapeutic range (1-4 μg/mL), more were carriers of one or two of these variants [9]. Furthermore, in a separate cohort from the German Competence Network for HIV/AIDS, *CYP2B6* rs3745274 allele T and *NR1I3* rs2307424 allele G were classified as 'discontinuation-associated' alleles because the higher the number of these alleles possessed by the patients, the higher the rate of treatment discontinuation due to increased EFV plasma toxicity [53]. Additionally, multivariate backward logistic regression found that *CYP2B6* rs3745274 genotype TT, *NR1I3* rs2307424 genotype GG, ethnicity, and smoking status were independently associated with the discontinuation of EFV within 3 months of treatment. In conjunction, an association was observed where patients possessing an increased number of these risk factors were more likely to discontinue treatment [53].

Genes involved in metabolism of other drugs taken concomitantly with EFV— In patients also being treated for TB infection, polymorphisms in genes involved in other drug PK pathways could also influence EFV PK. In a multivariate regression analysis of 62 patients from Rwanda being treated for HIV and TB infection, *CYP2B6* c.516G>T, *CYP2B6* c.983T>C, and *CYP2A6* c.1093G>A contributed 43%, 29%, and 27% of the total variance in EFV plasma levels, respectively [50]. Another study took into account the *NAT2* genotype, and found that patients with the *CYP2B6* c.516G>T genotype TT and a *NAT2* slow acetylator genotype (two "slow" alleles *NAT2*5*, **6* or **7* determined by genotyping rs1801280, rs1801279, rs1799930 and rs1799931) had the lowest apparent EFV clearance when treated concomitantly with anti-TB drugs [62]. On the other hand, patients with the *CYP2B6* c.516G>T genotype GG with the *NAT2* rapid acetylator genotype had the highest levels of clearance [62]. When TB treatment was discontinued, EFV plasma concentrations decreased in *NAT2* slow acetylators and rose in *NAT2* rapid acetylators [62].

Conclusions

Large variability in EFV plasma concentrations exists between patients given the same dose of the drug. Polymorphisms in genes underlying EFV metabolism have been associated with EFV exposure; however, the clinical consequences of these variants are unclear. Genotyping and inclusion of multiple variables may help establish the dose of EFV required by an individual to achieve therapeutic levels. Personalizing EFV dosages for HIV treatment may help to reduce EFV exposure as well as CNS toxicity in individuals with the *CYP2B6* slow metabolizer genotype. However, EFV is often co-formulated with other anti-retroviral agents in a fixed dose regimen for HAART and this should be considered before genotype-based dose adjustment.

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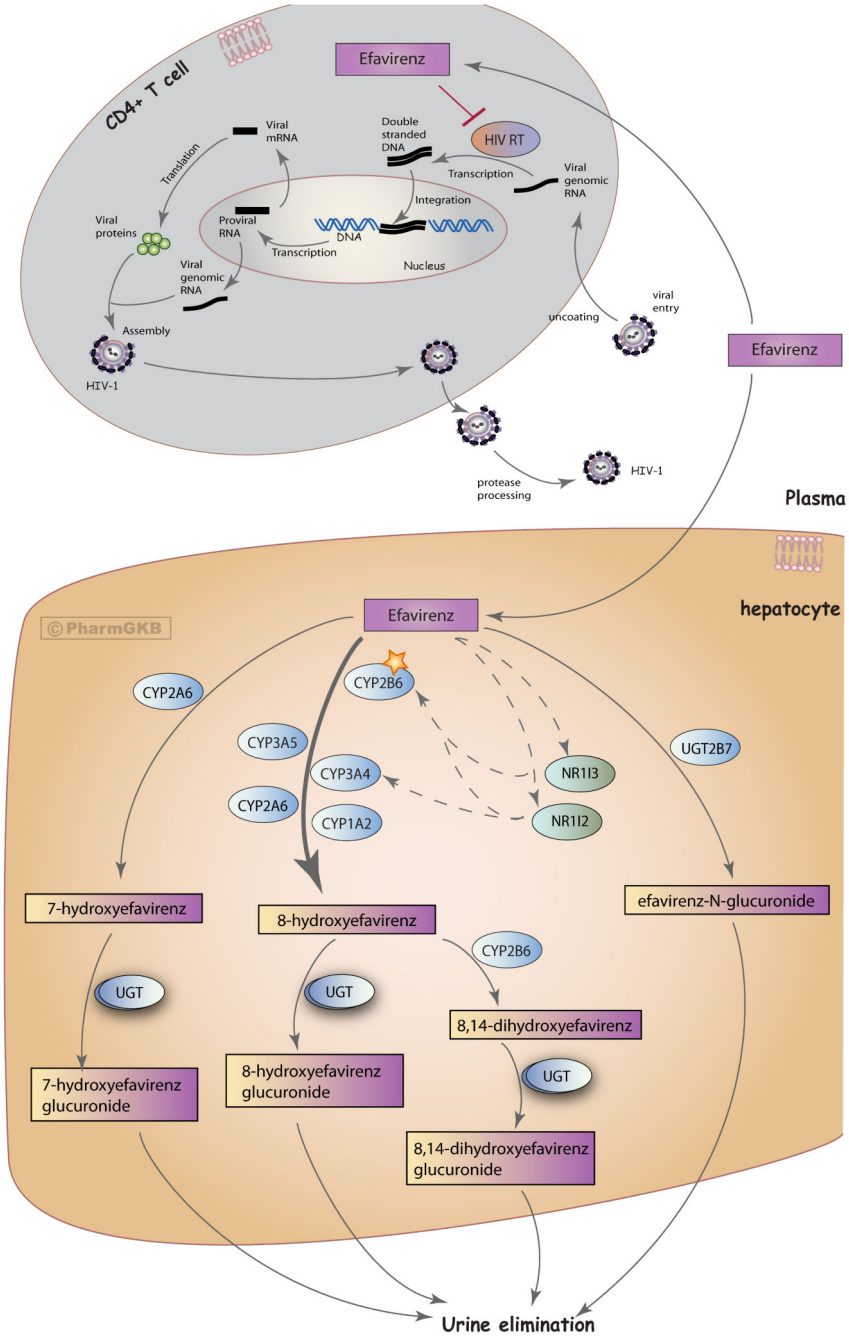

Figure 1.

Stylized cells depicting the metabolism and mechanism of action of efavirenz. A fully interactive version is available at PharmGKB http://www.pharmgkb.org/pathway/PA166123135.

Table 1

Summary of EFV PGx associations for variants in the *CYP2B6* gene

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
1) 516G>T	rs3745274 NM_000767.4:c.516G>T, NP_000758.1:p.Gln172His	The TT genotype is associated with increased EFV plasma concentrations, reduced clearance and increased drug exposure or plasma exposure compared to the GG and/or GT genotype.	PK	[PMID: 19659438, 18281305, 15622315, 2308025, 20625352, 20723261, 19779319, 24080498, 20860463, 19371316, 19779319, 24551111, 24316028, 23399569, 23172109, 23970651, 16267764, 18839779, 22927450, 24145522, 15864119, 23254426, 20441246, 15825040, 17356468, 22057858, 24956253, 20338069, 22950382, 22481606, 19704172, 18728241, 19124658, 20952418].
		The TT genotype is associated with prolonged EFV plasma concentrations (up to 14 days) after discontinuation of therapy, as compared to GG (around 6 days) and GT (7 days) genotypes.	PK	[PMID: 16392089]
		The GT genotype is associated with increased EFV plasma concentrations or plasma exposure compared to the GG genotype.	PK	[PMID: 24551111, 15622315, 24316028, 23399569, 23172109, 19371316, 23970651, 23254426, 15825040]
		Genotypes of the SNP are not associated with EFV plasma concentrations at 2 weeks of treatment.	PK	[PMID: 20723261]
		The GT and TT genotypes are associated with	PK	[PMID: 20860463, 15864119]

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
		increased PBMC-associated EFV concentration/exposure compared to the GG genotype.		
		Patients with the GG genotype may require a higher dose adjustment.	PK	[PMID: 18839779]
		The TT genotype or T allele is associated with sleep disorders and fatigue when treated with an EFV-containing regimen.	Toxicity	[PMID: 15864119, 23734829, 24956253]
		The GT genotype is associated with increased likelihood of worse sleep quality as compared to the GG genotype at 6 months of EFV treatment, but not at 4 or 12 months (sleep quality was not associated with EFV plasma levels in this study).	Toxicity	[PMID: 23970651]
		Genotypes TT and GT are associated with a higher change in median symptom score for central nervous system side effects (CNS) at week 1 from baseline compared to genotype GG, but no difference between genotypes was seen at week 24.	Toxicity	[PMID: 15622315]
		Genotype TT and male gender were associated with an increased risk of CNS side-effects when treated with an EFV-containing regimen.	Toxicity	[PMID: 24517233]
		Patients with the TT genotype experienced a higher number of overall side effects compared to those with the GG genotype, but this was not statistically significant.	Toxicity	[PMID: 20723261]
		The TT genotype is associated with EFV treatment discontinuation within 3 months of treatment.	Toxicity	[PMID: 21715435]
		Genotypes of the SNP are not associated with toxicity-related treatment failure when treated with an EFV-containing regimen.	Toxicity	[PMID: 16267764]

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
		Genotypes GT and TT are not associated with increased risk of CNS toxicity.	Toxicity	[PMID: 24080498]
		Genotypes of the SNP are not associated with switching to a completely new treatment regimen when treated initially with an EFV-containing regimen or with EFV treatment termination.	Toxicity/ efficacy	[PMID: 16267764, 15622315]
		Genotypes of the SNP are not significantly associated with virologic failure, plasma HIV-1 RNA copy number, viral loads at 3 or 6 months of treatment, or CD4+ T cell count when treated with an EFV-containing regimen.	Efficacy	[PMID: 16267764, 15622315, 20723261, 20338069]
		Factors that were associated with increased risk of immunological failure in Ghanaian patients treated with EFV were; genotype GG (compared to genotype TT), less than 95% adherence to treatment, and low baseline CD4+ T cell counts.	Efficacy	[PMID: 24080498]
		Genotypes of the SNP are not associated with HIV genotypic drug resistance when treated with an EFV-containing regimen.	Efficacy	[PMID: 16267764]
2) 983T>C	rs28399499 NM_000767.4:c.983T>C NP_000758.1:p.Ile328Thr	The CC and/or CT genotype are associated with increased EFV plasma concentrations and drug exposure compared to the TT genotype.	PK	[PMID: 24080498, 23080225, 18281305, 22927450, 20860463, 22481606]
		No significant difference was found with EFV concentrations between the CT and TT genotype.	PK	[PMID: 19371316, 19779319, 19239339]
		CC and CT were not associated with risk of immunological failure or CNS toxicity as compared to the TT genotype in Ghanaian patients treated with	Toxicity	[PMID: 24080498]

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
		EFV.		
		Genotype TT is associated with an increased risk of CNS side effects.	Toxicity	[PMID: 24517233]
3) 785A>G	rs2279343 NM_000767.4:c.785A>G NP_000758.1:p.Lys262Arg	The GG genotype is associated with increased EFV concentrations as compared to the AA genotype.	PK	[PMID: 23399569, 23254426, 20441246, 22481606]
		The AG genotype is associated with increased EFV concentrations as compared to the AA genotype.	PK	[PMID: 23399569, 23254426]
		Genotypes of this SNP are not associated with EFV concentrations.	PK	[PMID: 20625352]
4) g.18492T>C	rs2279345	Genotypes CC and CT are associated with lower EFV plasma concentrations as compared to the TT genotype. Removing the potential influence of other underlying *CYP2B6* SNPs, this association is maintained when examining only patients with a *CYP2B6*1/*1* haplotype background (determined by genotyping 7 SNPs [PMID: 24477223, 24293076], and patients co-infected with TB with a *CYP2B6*1/*1* haplotype background [PMID: 24492364].	PK	[PMID: 24477223, 24293076, 24492364, 23254426]
5) g.27103G>A	rs36118214 NM_000767.4:c.1294+586G>A NG_007929.1:g.27103G>A	Genotype AA is associated with significantly lower EFV plasma levels as compared to the AG or GG genotype. This association was maintained amongst extensive metabolizers (those with rs3745274 genotype GG or rs28399499 genotype TT, removing the influence of variant alleles of these two SNPs). Though the clinical relevance cannot be determined in such a small patient group, an individual with rs36118214 genotype AA, rs1872121 genotype	PK	[PMID: 19659438]

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
		AA and rs12721649 genotype AG displayed extremely low EFV plasma concentrations at both week 2 and 4 of anti-retroviral treatment and experienced virologic failure at week 24.		
6) 1459C>T	rs3211371 Arg487Cys NP_000758.1 NM_000767.4	Genotypes of this SNP are not significantly associated with EFV plasma concentrations or exposure.	PK	[PMID: 18281305, 16267764, 23254426, 16433869, 23399569]
7) 485-18C>T	rs4803419 NM_000767.4 : 485-18C>T	In patients without variant alleles at rs3745274 (516C>T) and rs28399499 (983T>C), allele T was associated with higher median estimated EFV C_{min} values though the effect size was smaller than the rs3745274 T allele.	PK	[PMID: 23080225]
8) 64C>T	rs8192709 (Arg22Cys : NP_000758.1, 64C>T : NM_000767.4)	Genotype CC is associated with higher EFV concentrations (higher mid-dose EFV plasma concentrations at 12 weeks) in Thai patients.	PK	[PMID: 23399569]
		Genotypes of this SNP are not associated with EFV plasma concentrations (after at least 4 weeks of treatment or 12 hours after dosing) in Thai patients.	PK	[PMID: 23254426]
9) 136A>G	rs35303484 CYP2B6*11, NM_000767.4:c.136A>G	In a Belgian cohort of 50 patients, only one patient had the AG genotype, with no patients with the GG genotype, and no significant association was seen in variability of minimum plasma or PBMC concentrations of EFV compared to the AA genotype.	PK	[PMID: 20860463]
		Genotypes of this SNP are not significantly associated with neurotoxicity syndromes (sleep disorders, hallucinations and cognitive effects) when treated with EFV-containing ART.	Toxicity	[PMID: 23734829]

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
10) *CYP2B6*6*	According to CYP nomenclature, *6A is defined as 516G>T and 785A>G.	Diplotypes *1/*6, *5/*6 and *6/*6 are associated with increased EFV plasma concentrations and decreased clearance, and *1/*1 is associated with low EFV plasma concentrations.	PK	[PMID: 23254426, 23399569, 24142869, 25096076, 20952418]
		Significantly lower CYP2B6 protein is observed in microsomes from Caucasians with *CYP2B6* genotypes **1/*5*, **1/*6*, **5/*6*, **6/*6* compared to *1/*1, correlating with significantly lower EFV 8-hydroxylation in **6/*6* samples.	PK	[PMID: 17559344]

Table 2

Summary of EFV PGx associations for variants in the CYP2A6 gene

Variant common name	Variant mapping information[a]	Association with EFV in HIV-infected patients[a]	Association type	References
1) −48T>G (also referred to as *9)	**rs28399433** NM_000762.5:c.-48T>G Complemented alleles: A>C.	Genotypes AC and/or CC are associated with increased EFV plasma concentrations, as compared to the AA genotype.	PK	[PMID: 24080498, 19659438, 24729586]
		Genotypes of this SNP are not associated with EFV plasma levels.	PK	[PMID: 24316028, 23080225, 24477223]
		Genotypes of this SNP are not significantly associated with neurotoxicity syndromes (sleep disorders, hallucinations and cognitive effects) when treated with EFV-containing ART.	Toxicity	[PMID: 23734829]
		No association was found between the genotypes AC and CC and risk of immunological failure at an average follow-up of 66 months or central nervous system (CNS) toxicity as compared to the AA genotype in retrospective analysis of medical records.	Efficacy/ toxicity	[PMID: 24080498]
		No significant association with virologic response at 48 weeks of treatment with an EFV-containing anti-retroviral regimen.	Efficacy	[PMID: 24695352]
2) CYP2A6*9 *and* ***CYP2A6*17***	**rs8192726** NM_000762.5:c.493+23G>T also described as 1836G>T Complemented alleles: C>A. and **rs28399454** NM 000762.5:c.1093G>A NP_000753.3:p.Val365Met (also described as g.5056G>A) Complemented alleles: C>T.	rs8192726 allele A and rs28399454 allele T are predictive of EFV plasma concentration.	PK	[PMID:19779319, 19371316]
		rs8192726 genotypes or rs28399454 genotypes are not associated with plasma or PBMC concentrations of EFV.	PK	[PMID: 23172109, 20860463]
		Genotypes of the rs28399454 SNP are not significantly associated with neurotoxicity syndromes (sleep disorders, hallucinations and cognitive effects) when treated with EFV-containing ART.	Toxicity	[PMID: 23734829]

Variant common name	Variant mapping information[a]	Association with EFV in HIV-infected patients[a]	Association type	References
3) 1436T>G	**rs12460590** NM 000764.2:c.1436T>G NP_000755.2:p.Val479Gly Complemented alleles: A>C.	This SNP contributed significantly to EFV plasma levels in univariate regression analysis, but not multivariate analysis, in 62 Rwandan patients being co-treated for HIV and TB infection.	PK	[PMID: 24316028]

[a]The *CYP2A6* gene is found on the minus chromosomal strand, alleles for the associations outlined here have been complemented to the plus chromosomal strand.

Table 3

Summary of EFV PGx associations for variants in the *UGT2B7* gene

Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
c.802T>C	rs7439366 NM 001074.2:c.802T>C NP_001065.2:p.Tyr268His	Alleles or genotypes of this SNP are not significantly associated with EFV plasma concentrations.	PK	[PMID: 24080498, 23172109].
		No association was found for risk of immunological failure or neurotoxicity syndromes in Ghanaian patients with HIV treated with EFV-containing anti-retroviral regimen.	Toxicity/ efficacy	[PMID: 24080498]
c.802T>C and c.801A>T	rs7439366 NM 001074.2:c.802T>C NP_001065.2:p.Tyr268His rs7438284 NM 001074.2:c.801A>T NP_001065.2:p.Pro267Pro	Combined analysis of alleles of these two variants found no association with plasma or PBMC EFV concentrations in a cohort of 50 patients in Belgium.	PK	[PMID: 20860463]
c.735A>G	rs28365062 NM 001074.2:c.735A>G NP 001065.2:p.Thr245Thr	Genotypes of this SNP are not associated with plasma or PBMC EFV concentrations.	PK	[PMID: 20860463, 24080498, 23172109]
		Genotypes of this SNP are not associated with immunological failure or neurotoxicity syndromes in Ghanian patients with HIV treated with EFV-containing anti-retroviral regimen	Toxicity/ efficacy	[PMID: 24080498]
		In patients with an underlying CYP2B6 slow metabolizer genotype (defined by genotypes 516TT, or 516T/983C or 983CC of the two SNPs rs3745274 and rs28399499), rs28365062 genotype GG was associated with higher EFV plasma concentrations.	PK	[PMID: 24729586]

Table 4

Summary of EFV PGx associations for variants in the *CYP3A4 and CYP3A5*

Variant common name	Variant mapping information[a]	Association with EFV in HIV-infected patients[a]	Association type	References
1) CYP3A5 6986A>G	rs776746 Present in CYP3A5 alleles **3A-L* and **9* NC 000007.14:g.99672916 T>C Complemented alleles: T>C.	Lower EFV plasma concentrations and higher clearance in patients with the CC or CT genotype compared to those with the TT genotype.	PK	[PMID: 15622315]
		No association with plasma or PBMC EFV concentrations, or EFV plasma exposure.	PK	[PMID: 20625352, 23080225, 24316028, 16267764, 24477223]
2) CYP3A5 713G>A	Complemented alleles: C>T.	Genotypes of this SNP are not associated with EFV plasma exposure.	PK	[PMID: 16267764]
3) CYP3A4 -392G>A	rs2740574 NM_017460.5:c.−392G>A Complemented alleles: C>T.	Higher EFV plasma concentrations were observed in patients with the CC or CT genotype compared to TT in univariate analysis in n=152 subjects.	PK	[PMID: 15622315]
		No association was found between genotypes of this SNP and CC and CT and EFV plasma exposure in n=367 subjects	PK	[PMID: 16267764]
		This SNP contributed significantly to EFV plasma levels in univariate regression analysis, but not multivariate analysis, in 62 Rwandan patients being co-treated for HIV and TB infection.	PK	[PMID: 24316028]
		No significant association with virologic response at 48 weeks was found in 359 HIV patients treated with an EFV-containing anti-retroviral regimen.	Efficacy	[PMID: 24695352]

[a]The *CYP3A4* and *CYP3A5* genes are found on the minus chromosomal strand, alleles for the associations outlined here have been complemented to the plus chromosomal strand.

Table 5

Summary of EFV PGx associations for variants in the *NR1I3* gene

Variant common name	Variant mapping information[a]	Association with EFV in HIV-infected patients[a]	Association type	References
c.540C>T	rs2307424 NM_001077469.2:c.540C>T NP_001070937.1:p.Pro180Pro Complemented alleles: G>A.	The G allele is associated with higher EFV plasma concentrations.	PK	[PMID: 23172109]
		Genotype GA and AA are not associated with significant differences in EFV plasma concentrations compared to the GG genotype.	PK	[PMID: 23080225, 23173844, 24080498]
		Genotype GG is associated with increased risk of discontinuation of EFV treatment within 3 months of treatment.	Toxicity/ efficacy	[PMID: 21715435]
		Genotype GA and AA are not associated with risk of central nervous system toxicity or immunological failure compared to the GG genotype.	Toxicity/ efficacy	[PMID: 24080498]
rs3003596	NM_001077469.2:c.239-1089T>C Complemented alleles: A>G.	Genotype GG and AG are associated with lower EFV plasma concentrations compared to the AA genotype.	PK	[PMID: 23173844]
		Genotypes of this SNP are not significantly associated with neurotoxicity syndromes (sleep disorders, hallucinations and cognitive effects) when treated with EFV-containing ART.	Toxicity	[PMID: 23734829]

[a]The *NR1I3* gene is found on the minus chromosomal strand, alleles for the associations outlined here have been complemented to the plus chromosomal strand.

Table 6

Summary of EFV PGx associations for variants in the *ABCB1* gene

Variant common name	Variant mapping information[a]	Association with EFV in HIV-infected patients[a]	Association type	References
1)3435 T>C/A	rs1045642 NM_000927.4:c.3435 T>C NM_000927.4:c.3435 T>A NP_000918.2:p.Ile1145= Complemented alleles: A>G/T.	Genotypes of this SNP are not associated with EFV minimum plasma concentrations, plasma drug exposure, oral clearance, apparent volume of distribution or PBMC EFV concentrations.	PK	[PMID: 20860463, 15622315, 16267764, 20625352, 24145522]
		Genotype AA is associated with increased clearance of EFV compared to AG, and genotype GG is associated with decreased clearance as compared to genotype AG.	PK	[PMID: 12545140]
		Allele A is associated with an increased likelihood of toxicity-related treatment failure when treated with an EFV-containing regimen.	Toxicity	[PMID: 16267764]– *this variant was in LD with rs2032582*.
		Allele A is associated with a reduced risk of hepatotoxicity during antiretroviral therapy when treated with EFV or nevirapine (patients were combined) as compared to allele G.	Toxicity	[PMID: 16912956]
		Genotypes of this SNP are not significantly associated with neurotoxicity syndromes (sleep disorders, hallucinations and cognitive effects) when treated with EFV-containing ART.	Toxicity	[PMID: 23734829]
		The AA genotype is associated with a lower likelihood of virologic failure compared to the AG/GG genotype in patients receiving an EFV-containing regimen.	Efficacy	[PMID: 16267764]
		Allele A is associated with a reduced likelihood of emerging viral drug resistance in patients receiving an EFV-containing regimen.	Efficacy	[PMID: 16267764].
		Genotype AA is associated with an increased likelihood of favorable virologic responses and a higher increase in CD4+ T cell count when treated with EFV or nelfinavir compared to other genotypes	Efficacy	[PMID: 11809184].
		Allele A is not associated with a reduced response to EFV in patients with AIDS.	Efficacy	[PMID: 20662624]

Variant common name	Variant mapping information[a]	Association with EFV in HIV-infected patients[a]	Association type	References
		A allele and a lower increase in CD4+ T cell count in Belgian patients after initiation of EFV-containing therapy (a multiple linear regression model).	Efficacy	[PMID: 20860463]
2) *193A>G	rs3842 NM_000927.4:c.*193 A>G Complemented alleles: T>C.	The C allele and Asian origin was associated with intra-individual variability in EFV accumulation ratio (EFV PBMC concentration/minimum concentration of EFV) in a multiple linear regression model	PK	[PMID: 20860463]
		This SNP was associated with EFV metabolism in co-variate analysis.	PK	[PMID: 24497997]
		Genotypes of this SNP are not significantly associated with neurotoxicity syndromes (sleep disorders, hallucinations and cognitive effects) when treated with EFV-containing ART.	Toxicity	[PMID: 23734829]
3)2677 A>C/T	rs2032582 NM_000927.4:c.2677 T>A NM_000927.4:c.2677 T>G NP_000918.2:p.Ser893Ala NP_000918.2:p.Ser893Thr Complemented alleles: A>C/T.	Genotypes of this SNP are not associated with EFV plasma concentrations, plasma exposure or PBMC concentrations in HIV patients.	PK	[PMID: 16267764, 20860463, 20625352, 15622315]
4) 1236T>C	rs1128503 NM_000927.4:c.1236 T>C NP_000918.2:p.Gly412Gly Complemented alleles: A>G.	Genotypes of this SNP were not associated with minimum plasma or PBMC EFV concentrations in a Belgian cohort of 50 HIV patients.	PK	[PMID: 20860463]

[a]The *ABCB1* gene is found on the minus chromosomal strand, alleles here have been complemented to the plus chromosomal strand.

Table 7

Summary of EFV PGx associations for variants in other genes

Gene	Variant common name	Variant mapping information	Association with EFV in HIV-infected patients	Association type	References
CYP1A2	-739T>G		In 62 Rwandan patients treated for both HIV and TB infection, genotype TG was associated with higher EFV plasma levels over a 6-week period as compared to patients with the TT genotype, although in multivariate analysis, none of the three *CYP1A2* SNPs investigated (−739T>G, −163C>A, and 2159G>A) contributed significantly to EFV plasma level variation.	PK	[PMID: 24316028]
HTR2A	102C>T	rs6313	This variant was associated with a decreased risk of sadness when treated with EFV in multivariate regression analysis.	Toxicity	[PMID: 23859571]
ABCG2	421C>A	rs2231142	Associated with increased risk of abnormal dreams when treated with EFV in multivariate analysis adjusted for maximum steady state plasma concentration and demographic co-variables.	Toxicity	[PMID: 23859571]