

Expert Opinion on Drug Metabolism & Toxicology

ISSN: 1742-5255 (Print) 1744-7607 (Online) Journal homepage: http://www.tandfonline.com/loi/iemt20

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To cite this article: Gabriel Stillemans, Leila Belkhir, Dennis A. Hesselink, Vincent Haufroid & Laure Elens (2018): Pharmacogenetic associations with cytochrome P450 in antiretroviral therapy: what does the future hold?, Expert Opinion on Drug Metabolism & Toxicology, DOI: 10.1080/17425255.2018.1478964

To link to this article: https://doi.org/10.1080/17425255.2018.1478964

Accepted author version posted online: 18 May 2018.
Published online: 28 May 2018.

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EXPERT OPINION ON DRUG METABOLISM & TOXICOLOGY
https://doi.org/10.1080/17425255.2018.1478964

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REVIEW

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Pharmacogenetic associations with cytochrome P450 in antiretroviral therapy: what does the future hold?

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ABSTRACT

Introduction: Several antiretroviral drugs used to treat infection with the human immunodeficiency virus (HIV) are substrates of enzymes belonging to the cytochrome P450 (CYP) superfamily, which are polymorphically expressed. It may therefore be useful to take into account the genetic variation in these enzymes to predict the likelihood of anti-HIV treatment success, toxicity and the potential for drug–drug interactions.

Areas covered: In this manuscript, the authors discuss the current state of knowledge regarding pharmacogenetic associations between CYP and all major antiretrovirals, as well as the importance of these associations.

Expert opinion: While many pharmacogenetic associations for CYP have been described in the literature, replication studies are sometimes lacking. The implementation of this knowledge in clinical practice also remains difficult. Further efforts are required both to expand this field of knowledge and to enable its use in everyday clinical practice.

ARTICLE HISTORY
Received 30 January 2018
Accepted 17 May 2018

KEYWORDS
Antiretroviral; cytochrome P450; human immunodeficiency virus; non-nucleoside reverse transcriptase inhibitor; pharmacogenetics; pharmacogenomics; protease inhibitor

1. Introduction

With the advent of antiretroviral therapy (ART), treatment of patients infected with the human immunodeficiency virus (HIV) is now widely available, although an actual cure for the infection has yet to be discovered. ART aims at decreasing the viral load to undetectable levels and restoring the immune function of the host, thereby reducing HIV-related morbidity and mortality [1,2], as well as decreasing the risk of HIV transmission [3].

ART typically involves the combination of several drugs acting at different stages of the viral cycle in order to prevent the selection of drug-resistance mutations. Indeed, mutations in the viral genome are frequent, and inadequate choice of treatment, insufficient drug exposure or low adherence may lead to the selection of resistant strains. The drugs available include nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), protease inhibitors (PIs), fusion inhibitors and CCR5 antagonists. For treatment-naive patients, therapy usually combines a dual NRTI backbone with an NNRTI, INSTI or PI.

Some of these antiretrovirals are substrates of enzymes belonging to the cytochrome P450 (CYP) superfamily, which are responsible for the phase I metabolism of many marketed drugs. With CYP metabolism being a key determinant of drug exposure, knowledge of the major isoforms involved in the biotransformation of a given drug, and characterization of the extent of this metabolism is critical to predict the likelihood of treatment success, toxicity and potential for drug–drug interactions (DDI), especially for a lifelong treatment such as ART. Suboptimal doses and subsequent underexposure can lead to anti-viral failure and selection of drug-resistance mutations, conditioning the choice of ART further down the line. Likewise, overexposure can lead to toxicity, non-adherence and possibly viral failure. This is a particular concern for antiretrovirals with a low genetic barrier (e.g. efavirenz (EFV), nevirapine (NVP), rilpivirine (RPV)), for which resistance mutations can emerge very quickly.

It is well known that genetic polymorphisms can alter the level of expression and/or intrinsic activity of enzymes, with the most prevalent form being single nucleotide polymorphisms (SNPs). Characterizing the functionality of these genetic variants and their impact on drug pharmacokinetics (PK) and pharmacodynamics (PD) is the goal of pharmacogenomics (or pharmacogenetics, as it would be called for single drug–gene interactions). The frequency of these SNPs can vary across ethnicities, which partly explains why race is sometimes found to influence clinical outcomes.

Such information could potentially be incorporated in new treatment algorithms: patients presenting a given polymorphism (or combination thereof) could be assigned to a therapy that maximizes their chance of success and/or minimizes the

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Article highlights

- Several antiretrovirals are known substrates of CYP.
- Taking into account the genetic background of patients may prove useful in individualizing treatment, thereby increasing effectiveness and reducing toxicity.
- Polymorphisms in the *CYP2A6, CYP2B6, CYP3A4* and *CYP3A5* genes (among others) have been studied.
- In some cases, pharmacogenetic information has been used to perform genotype-guided dose adjustments.
- Proper guidelines and tools must be made available to clinicians.

This box summarizes key points contained in the article.

risk of toxicity and DDI. Therapeutic drug monitoring (TDM) or predictive dosing based on pharmacogenetic information could also be performed.

This review aims at summarizing the current state of knowledge regarding the pharmacogenomics of the various antiretroviral drugs available on the market. A separate section will be dedicated to each drug currently recommended by international guidelines. We will then consider how such information can be used in clinical practice, to what extent it is currently done, and what obstacles remain for routine clinical implementation.

1.1. Overview of CYP

The human CYP superfamily is composed of 57 genes and numerous pseudogenes. For the purpose of this review, we will focus on isoforms that are relevant to ART. Key information on the most frequently described SNPs will be given in the following section. Table 1 summarizes all SNPs of importance and the corresponding allelic frequencies in various populations.

The *CYP2A6* gene is located on chromosome 19. A variety of SNPs have been studied in the context of ART, most notably c.-47A>C (*CYP2A6*9*, rs28399433), g.1836G>T (*CYP2A6*9B*, rs8192726) and c.1093G>A (*CYP2A6*17*, rs28399454).

CYP2B6 can represent up to 10% of hepatic CYP and is also expressed in the central nervous system (CNS). The corresponding gene is located on chromosome 19 and is known to be polymorphic. It has been extensively studied in the context of ART: its most commonly described decrease- or loss-of-function SNPs include c.516G>T (*CYP2B6*9*, rs3745274), c.983T > C (*CYP2B6*18*, rs28399499), and c.1459C>T (*CYP2B6*5*, rs3211371). Variant *CYP2B6*9* has been linked to a major splicing defect [5] and is more frequent in Africans than in Caucasians. *CYP2B6*18* is believed to be a null allele [6] and *CYP2B6*5* results in lower levels of hepatic CYP2B6 [7]. In contrast, variant c.785A>G (*CYP2B6*4*, rs2279343) has been linked to a gain-of-function. However, it is often part of the *CYP2B6*6* haplotype, which is characterized by the presence of both the c.785A>G and the c.516G>T alleles, resulting in an overall decrease-of-function (it should be noted that the *CYP2B6*9* allele has sometimes been erroneously referred to as *CYP2B6*6*).

CYP2C19 (located on chromosome 10) is also worth mentioning. Its two main loss-of-function alleles are c.681G>A (*CYP2C19*2*, rs4244285), leading to a splicing defect, and c.636G>A (*CYP2C19*3*, rs4986863). A gain-of-function allele responsible for the ultra-rapid metabolizer status has also been described: variant c.-806C>T (*CYP2C19*17*, rs12248560).

The *CYP3A* subfamily is comprised of four genes (all located on chromosome 7): *CYP3A4, CYP3A5, CYP3A7* and *CYP3A43*. Whereas *CYP3A7* is usually only expressed in the fetal liver, *CYP3A4* and *CYP3A5* are expressed predominantly within adult hepatic tissue, where they account for 30% of total CYP content. Both enzymes present a certain degree of substrate overlap and are responsible for the phase I metabolism of many marketed drugs.

Several *CYP3A4* polymorphisms (mostly in non-coding regions) have been identified. Variant *CYP3A4*1B* (rs2740574) is characterized by a substitution at position c.-392A>G, which seems to be associated with decreased activity, and is found more frequently in African populations. However, the role of this SNP is debated and it is in strong linkage disequilibrium with the *CYP3A5*1* allele, something to keep in mind when considering pharmacogenetic associations. Meanwhile, the creation of an alternate splice site in intron 6 results in decreased hepatic mRNA levels in individuals with the partial loss-of-function allele *CYP3A4*22* (rs35599367) [8].

Table 1. Allelic frequencies of SNPs relevant to antiretroviral therapy.

				Variant allele frequency				
Allele	rs number	Nucleotide change	Variant type	African	American	East asian	European	South asian
*CYP2A6*9*	rs28399433	c.-47A>C	Upstream gene variant	0.082	0.099	0.239	0.072	0.154
*CYP2A6*9B*	rs8192726	g.1836G>T	Intronic variant	0.082	0.043	0.180	0.069	0.131
*CYP2A6*17*	rs28399454	c.1093G>A	Missense variant	0.117	0.006	0.001	0	0
*CYP2B6*4*	rs2279343	c.785A>G	Missense variant	0.065	0.034	0.030	0.037	0.176
*CYP2B6*5*	rs3211371	c.1459C>T	Missense variant	0.011	0.072	0.003	0.112	0.089
*CYP2B6*9*	rs3745274	c.516G>T	Missense variant	0.374	0.373	0.215	0.236	0.381
*CYP2B6*15*	rs4803419	c.1172T>A	Missense variant	0.082	0.352	0.436	0.320	0.342
*CYP2B6*18*	rs28399499	c.983T>C	Missense variant	0.082	0.010	0	0	0
*CYP2C19*2*	rs4244285	c.681G>A	Splicing defect	0.170	0.105	0.312	0.145	0.358
*CYP2C19*17*	rs12248560	c.-806C>T	Upstream gene variant	0.235	0.120	0.015	0.224	0.136
*CYP3A4*1B*	rs2740574	c.-392A>G	Upstream gene variant	0.766	0.105	0.004	0.028	0.040
*CYP3A4*22*	rs35599367	g.20493C>T	Intronic variant	0.001	0.026	0	0.050	0.006
*CYP3A5*3*	rs776746	g.6986A>G	Intronic variant	0.180	0.797	0.713	0.943	0.668
*CYP3A5*6*	rs10264272	g.14690G>A	Splicing defect	0.154	0.023	0	0.003	0
*CYP3A5*7*	rs76293380	g.27131_27132insT	Frameshift variant	0	0	10^{-4}	0	0

Variant allele frequencies were retrieved from the Ensembl database [10], except for CYP2B6*4 and CYP3A5*7, which were retrieved using the ExAC Browser [4]. Refer to these databases for the exact composition of subpopulations. SNP: single nucleotide polymorphism.

There is also much heterogeneity in *CYP3A5* expression. The most commonly described SNP, rs776746, defines the *CYP3A5*3* allele. The g.6986A>G substitution creates a cryptic splice site resulting in a truncated, inactive protein [9]. Allelic frequencies for this SNP are high, ranging from 0.2 in Africans to 0.65 in East Asians and 0.9 in Caucasians [10]. Other polymorphisms worth mentioning include *CYP3A5*6* (rs10264272) and *CYP3A5*7* (rs41303343). Considering the former variant, g.14690G>A leads to the formation of a cryptic splice site and skipping of exon 7, producing an inactive enzyme [9]. For the latter, a premature stop codon is generated by the insertion g.27131_27132insT.

Other, seldom discussed isoforms (at least in the context of ART) include CYP1A2, CYP2D6, and CYP2C9.

1.2. Literature search strategy

A systematic search was conducted in the MEDLINE database using relevant terms, such as 'cytochrome,' 'antiretroviral,' 'genotype,' 'polymorphism,' 'pharmacogenetic,' 'pharmacogenomic,' 'pharmacokinetic,' 'variant' and the names of the various drugs of interest. As mentioned in the introduction, we chose to focus on currently recommended antiretrovirals that are known substrates of CYP (i.e. EFV, NVP, RPV, atazanavir (ATV), darunavir (DRV), lopinavir (LPV) and elvitegravir). All articles written in English were screened for relevancy. Case reports, poster presentations, reviews, studies that did not include PK and/or PD analyses, small-scale studies, duplicate studies, and articles of poor quality (unclear rationale, inadequate clinical or statistical methodology) were discarded. When replication studies were abundant, our main selection criteria were: large sample size, methodological strength, new information, and/or reporting of new alleles. Elvitegravir was eventually excluded due to a lack of pharmacogenetic studies.

2. Review

2.1. Efavirenz

Thanks to its relatively low cost and once-daily dosing schedule, EFV is a widely used NNRTI in developing countries, while it is less favored in developed countries, in part due to a high rate of CNS side effects, including dizziness, insomnia, somnolence, abnormal dreams, anxiety and depression. These symptoms occur in up to two-thirds of patients [11,12] and can increase the odds of treatment non-adherence or discontinuation. However, they are most frequently reversible, resolving within a few weeks for some (but not all) patients. Initially, a dose of 600 mg once-daily was recommended. It is still the standard dose in most guidelines, while low-dose EFV (400 mg) is only found as an option in the WHO guidelines [13]. Based on clinical observations, it has been suggested to set the therapeutic index as plasma mid-dose concentrations of 1–4 mg/l (in treatment-naive patients) [14–17]. It should be noted that while the link between plasma PK and CNS toxicity is rather well established, the same does not hold true for a PK/efficacy relationship.

EFV is primarily metabolized by CYP2B6, and to a lesser extent by CYP3A4, CYP3A5, CYP1A2 and CYP2A6 [18,19]. Its main metabolite, 8-hydroxy-EFV, can be further oxidized by CYP2B6 into 8,14-hydroxy-EFV, while the formation of the 7-hydroxy metabolite is catalyzed by CYP2A6 only. Formation of sulfate and glucuronide conjugates has also been described [20]. Of note is the ability of EFV to induce its own metabolism.

A wealth of evidence is available regarding the effect of the *CYP2B6*9* variant. This polymorphism leads to reduced metabolism and increased EFV plasma concentrations [21–67]. Some studies have also suggested that this genotype and the resulting increased exposure could be correlated to a higher incidence of CNS toxicity [21–25]. The effect of the genotype on exposure seems to be proportional to the number of variant alleles, being stronger for TT homozygotes than for GT heterozygotes.

Another commonly studied SNP that can result in increased plasma exposure is *CYP2B6*18* [23,29–31,33,51–62,68,69], although a few studies have failed to replicate this association [34,36,41].

While the magnitude of the effect is much smaller than for the previous polymorphisms, variant g.15582C>T could also play a role [29,36,54,64]. It is usually not a major predictor of exposure when other SNPs are already taken into account; however, it can aggravate a metabolic deficit.

Finally, even though it has been linked with lower levels of enzyme in the liver, variant *CYP2B6*5* does not appear to affect EFV PK [23,27,30,61,70].

Results from studies on the impact of any of these alleles on the probability of treatment success reveal a complex situation: the CYP2B6 slow metabolizer phenotype could compensate for intermittent non-compliance by keeping plasma concentrations high, but the accumulation of the drug could also lead to an increased incidence of side effects (most notably CNS symptoms) and more treatment discontinuations – at least in the early months, while late treatment failure would be less likely in those individuals. This could explain why some studies have found a relationship between *CYP2B6* genotype and treatment end points, while others have not. The results could also differ due to the use of different definitions for treatment success/failure (such as different viral load thresholds), different follow-up periods and time frames (early initiation in naïve patients versus established therapy), etc. Turning to cerebrospinal fluid (CSF) concentrations, the slow metabolizer phenotype can lead to high CSF concentrations, but also a low rate of conversion to phase I metabolites (which could participate to the overall toxicity of the drug) – hence, paradoxically, slow and fast metabolizer status both could be risk factors for CNS toxicity.

Similarly, non-CNS side effects could be more frequent in some individuals. For instance, a study in healthy volunteers showed that repeated administration of EFV significantly lengthened the QT interval in *CYP2B6*6* homozygotes but not in heterozygous or wild-type homozygous subjects [61]. An increased risk of hepatotoxicity has also been found in *CYP2B6*9/*9* individuals [71].

Fewer studies are available for *CYP3A* variants. Neither the presence of the *CYP3A4* loss-of-function alleles *CYP3A4*1B* [27,41,54,67,72] or *CYP3A4*22* [64], nor enzymatic activity (as assessed by 1′-hydroxymidazolam formation after administration of the parent drug) [72] seems to be significantly correlated with EFV exposure. Regarding *CYP3A5*, most studies have reported no association at all between exposure and the *CYP3A5*3*

[25,27,29,34,36,41,54,60,61,67,68,71–73] or the *CYP3A5*6* and *CYP3A5*7* alleles [34,36,51,67,68,71]. Only one study described increased plasma concentrations of EFV in *CYP3A4*1B* carriers and decreased concentrations in *CYP3A5*3* carriers (a rather paradoxical observation, which has never been replicated) [21]. Overall, the impact of *CYP3A* polymorphisms on EFV PK appears to be quite small, possibly because these isoforms are only involved in secondary metabolic pathways.

The same holds true for *CYP2A6*, for which polymorphisms (most often *CYP2A6*9B* and *CYP2A6*17*) have a negligible impact (or none at all) on EFV PK [31,34,36,38,41,43,51,54,55,58,61,67,68] or viral response [74]. However, in some instances, the composite genotype *CYP2A6*9/*17B* has been found to be predictive of EFV PK, even when CYP2B6 metabolizer status was already taken into account [52,64]. Information regarding the *CYP2A6* genotype of an individual may be of limited use in subjects with functional CYP2B6, whereas it could help further refine predictions in CYP2B6 slow metabolizers.

To account for these numerous sources of genetic variability, some authors have proposed the use of multiple or composite genotypes (or haplotypes), most often involving *CYP2B6*. These would be weighted according to their individual relevance to EFV metabolism, for example, in population PK models involving multiple SNPs [60,75] or using risk scores based on the number of CYP decrease- or loss-of-function alleles to predict the probability of treatment success or discontinuation [76,77]. CYP2B6 slow metabolizer status has also been shown to be protective against viral failure [78], while the risk of suicidality increased with the number of *CYP2B6*- and *CYP2A6*-variant alleles (a significant hazard ratio was found in Whites and Hispanics, but not Blacks) [79].

Based on these observations, *CYP2B6* genotype-based dose recommendations are conceivable. In a study conducted in Japanese patients, those with plasma concentrations above 6 mg/l and who harbored the *CYP2B6*6* or **26* haplotypes (the latter being a combination of the *CYP2B6*6* haplotype and c.499C>G) were assigned to a dose reduction protocol [80]. The dose was safely reduced from the standard, once-daily 600 mg to 400 mg or 200 mg while maintaining viral suppression. Therapy was then initiated at lower doses for a group of treatment-naive patients possessing those alleles with similar results. An improvement of CNS symptoms was also noted, although the design of this study did not allow the authors to exclude the possibility of a placebo effect.

Although its protocol was not to adjust the dose based on genotype, but rather on plasma concentrations and the occurrence of CNS toxicity, yet another study demonstrated the importance of considering the c.516G>T polymorphism [81]. Most subjects whose dose was lowered to 400 mg possessed at least one variant allele, and all subjects with a 200 mg dose were TT homozygotes. This dose reduction greatly improved CNS symptoms and allowed for substantial cost savings.

Unfortunately, the design of some of these studies makes it difficult to conclude whether the resolution of symptoms was truly a result of dose adjustments. Regardless, it is important to reiterate that the toxicity of EFV, which has caused it to fall out of favor as a first-line treatment option in some countries, could be mitigated by using dose reduction approaches possibly guided by pharmacogenetics.

Last but not least, a cost-effectiveness analysis compared three different strategies: standard EFV therapy, universal dose reduction to 400 mg (as seen in the ENCORE1 trial) or genotype-based dosing [82]. The latter was found to be cost-effective. In contrast, based on the results from the pharmacogenetic subsection of the ENCORE1 trial, the authors concluded that while a dose of 400 mg was safe and could help reduce toxicity, genotype-guided dosing would be of limited use [64]. It could be argued that a universal dose reduction would be a more effective approach – at least in some population types (depending on the frequency of the various SNPs of interest). Caution should still be exercised; for instance, PK simulations using data from pregnant women showed a higher risk of suboptimal exposure or toxicity if the dose reduction was not guided by *CYP2B6* genotyping [83].

Thus, it appears that knowledge of *CYP2B6* genotype could prove useful in individualizing EFV therapy (Table 2). In particular, the role of *CYP2B6*9* has been demonstrated by numerous studies, including genome-wide association studies (GWAS). With loss-of-function alleles being more frequent in Africans compared to Caucasians, there is a need for population-specific guidelines (for both western and developing countries). However, the PK/PD and genotype/PD relationships of EFV have yet to be fully elucidated.

2.2. Nevirapine

NVP is the oldest NNRTI, and is still widely used worldwide. Side effects include potentially life-threatening skin reactions (Stevens–Johnson syndrome and toxic epidermal necrolysis) and hepatotoxicity. To reduce the risk of these side effects, it is recommended to proceed as follows: after a two-week run-in phase of 200 mg once-daily, the dosage can be increased to 200 mg twice-daily (or the patient may start taking NVP extended release 400 mg once-daily). The risk of hepatotoxicity is also higher when NVP is initiated in antiretroviral-naive women and men with CD4 counts <250 cells/µl or <400 cells/µl, respectively. Therefore, NVP-based therapy is contraindicated in these patients [84,85]. It has been proposed to set the minimal effective plasma concentration of NVP to 3 mg/l (no clear upper boundary is currently defined) [86,87].

Like EFV, NVP is a substrate of CYP2B6, and much research has focused on the same SNPs for both drugs. In addition to CYP2B6, CYP3A4 plays some role in the metabolism of NVP [88,89], as do CYP3A5 and CYP2C9 isoforms to a lesser extent. NVP is also an inducer of its own metabolism.

*CYP2B6*9* has been shown to increase the plasma levels of NVP in most [22,30,90–100], but not all studies [61,101]. The effect is usually apparent in *CYP2B6*9* homozygotes only.

Similarly, some studies have reported an association between allele *CYP2B6*18* and exposure [30,90,92–96,100], while others have not [61,91]. Interestingly, NVP exposure could sometimes be predicted using a combination of variants (*CYP2B6*6* homozygotes or **6/*18* heterozygotes versus other genotypes) that were not significant in univariate analysis [61].

Variant *CYP2B6*4* was not significant in any of the studies conducted so far [61,101,102], except for one, where a weak association was detected, albeit in univariate analysis only [90].

Table 2. Relevance of CYP polymorphisms to non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy.

Allele	rs number	Nucleotide change	Clinical outcome	Level of evidence
*CYP2A6*9*	rs28399433	c.-47A>C	No effect on EFV PK	Low
*CYP2A6*9B*	rs8192726	g.1836G>T	No effect on EFV PK	Low
*CYP2A6*17*	rs28399454	c.1093G>A	Increased exposure to EFV	Low
			No effect on NVP PK	Low
*CYP2B6*4*	rs2279343	c.785A>G	Increased exposure to EFV	Low
			No effect on NVP PK	Low
*CYP2B6*5*	rs3211371	c.1459C>T	No effect on EFV or NVP PK	Low
*CYP2B6*6*		c.516G>T, c.785A>G	(cfr. CYP2B6*9 and CYP2B6*4)	
*CYP2B6*9*	rs3745274	c.516G>T	Increased exposure to EFV and NVP	High
			Increased risk of EFV CNS symptoms, fewer viral failures	Medium
			Increased risk of NVP cutaneous toxicity	Low
*CYP2B6*15*	rs4803419	c.1172T>A	Increased exposure to EFV	Medium
			No effect on NVP PK	Low
*CYP2B6*18*	rs28399499	c.983T>C	Increased exposure to EFV and NVP	High
			Increased risk of EFV CNS symptoms, fewer viral failures	Medium
			Increased risk of NVP cutaneous toxicity	Low
*CYP2C19*2*	rs4244285	c.681G>A	No effect on RPV PK	Low
*CYP2C19*17*	rs12248560	c.-806C>T	No effect on RPV PK	Low
*CYP3A4*1B*	rs2740574	c.-392A>G	No effect on EFV or NVP PK	Low
*CYP3A4*22*	rs35599367	g.20493C>T	No effect on EFV, NVP or RPV PK	Low
*CYP3A5*3*	rs776746	g.6986A>G	No effect on EFV or NVP PK	Medium
			No effect on RPV PK	Low
*CYP3A5*6*	rs10264272	g.14690G>A	No effect on EFV PK	Low
*CYP3A5*7*	rs76293380	g.27131_27132insT	No effect on EFV PK	Low

Level of evidence (low/medium/high) was assigned based on the amount and quality of available evidence. CNS: central nervous system; EFV: efavirenz; NVP: nevirapine; PK: pharmacokinetics; RPV: rilpivirine.

Variant *CYP2B6*5* has not been found to be predictive of NVP PK either [30,61,91,101,102].

Moving on to CYP3A, neither *CYP3A4*1B* [91,97,102], nor *CYP3A4*22* [96], nor *CYP3A5*3* [61,91,96,101,102] seems to be associated with NVP PK.

Toxicogenetic studies of NVP have mostly investigated SNPs related to the immune system, but also occasionally to phase I metabolism. A GWAS in individuals of various ethnicities found *CYP2B6*9* (as well as two non-coding SNPs in linkage disequilibrium with it) to be a significant predictor of adverse cutaneous reactions [103]. This finding was replicated in a candidate gene study in Caucasians [101], while another one in Africans was only able to demonstrate a trend toward association [104], and several others could not replicate these results. Other SNPs, including *CYP2B6*4* [105], *CYP2B6*5* [105], as well as *CYP3A4*1B* [104,105], *CYP3A5*3* [104,105] and *CYP3A5*6* [105], do not appear to be relevant to cutaneous toxicity. *CYP2B6*18*, however, was strongly associated with the risk of such side effects [104,106]. Unfortunately, the sensitivity and specificity of these markers may not be sufficient for a clinical application. As for hepatotoxicity, neither of the available GWAS has revealed any association with CYP polymorphisms [103,105].

The increased exposure in CYP2B6 slow metabolizers (defined based on *CYP2B6*9* and *CYP2B6*18*) can also protect against viral failure in patients receiving standard doses [78]. Simulations based on population PK models have shown that an off-label dose of 400 mg once-daily (immediate release), rather than the recommended 200 mg twice-daily, could reduce NVP exposure to unacceptable levels [92,97]. However, safe exposure can be maintained in CYP2B6 slow metabolizers with 400 mg once-daily, meaning genotyping for *CYP2B6*9* and *CYP2B6*18* could help in determining an appropriate dosing schedule (with the once-daily schedule potentially improving patient compliance). Other simulations suggest that standard dosing may actually result in subtherapeutic concentrations in a small proportion of patients with functional CYP2B6 [90].

NVP is a good candidate for pharmacogenetics-guided therapy (Table 2). However, perhaps due to a lack of conclusive data, the available knowledge has not yet matured into any therapeutic recommendations. Initiating treatment only in subjects with normal CYP2B6 metabolism as well as using reduced doses or once-daily dosing schedules in individuals harboring *CYP2B6* defective alleles could potentially improve treatment outcomes.

2.3. Rilpivirine

RPV is the latest NNRTI. It is a substrate of CYP3A4 and to a lesser extent of CYP2C19.

Only one pharmacogenetic study is currently available. None of the following SNPs were associated with drug clearance: *CYP2C19*2, CYP2C19*17, CYP3A4*22* or *CYP3A5*3* [107] (Table 2).

Further investigations are needed to assess the pharmacogenetics of RPV in Asian and African populations, as well as the impact of other SNPs.

2.4. Ritonavir, cobicistat

Several antiretrovirals, especially among PIs, are coadministered with a PK booster in order to increase exposure to the active molecule. The booster can be either ritonavir (RTV) (a PI with no activity at the dose used for boosting) or cobicistat (COB) (a structural derivative of RTV that is completely inactive against HIV). Both boosters are strong inhibitors of CYP3A4 and CYP3A5. RTV can also induce other CYP isoforms, such as CYP1A2, CYP2C9 and CYP2C19.

Pharmacogenetic studies have focused on the active antiretrovirals rather than the boosters, but it is important to consider the possibility of an indirect effect of SNPs on antiretroviral PK through RTV or COB PK. Additionally, boosters complicate the interpretation of results by introducing a powerful DDI (see further).

2.5. Atazanavir

ATV is a PI administered in a standard dose of 300 mg once-daily in combination with either 100 mg RTV or 150 mg COB. Unboosted ATV may also be used at 400 mg once-daily in stable patients. Drug-specific side effects include icterus, sometimes hepatitis or cholelithiasis, and rarely nephrolithiasis; while lipodystrophy is considered a class effect for PIs.

ATV is metabolized by CYP3A4 and CYP3A5, as well as UDP-glucuronosyl-transferases (UGTs); a small percentage is also excreted unchanged in the urine. It is an inhibitor of CYP3A4, though less so than RTV or COB.

Pharmacogenetic studies have investigated the effect of CYP decrease-of-function alleles on ATV PK, often in conjunction with SNPs in phase II enzymes and/or transport proteins. CYP3A5 non-expressor status (defined as homozygosity for loss-of-function alleles *CYP3A5*3, CYP3A5*6* or *CYP3A5*7*) was predictive of slower clearance in healthy volunteers receiving unboosted ATV, while this effect was no longer observed in all subjects in the RTV-boosting phase of the study [108].

This highlights an important (and sometimes unavoidable) drug interaction for PIs boosted with RTV or COB: inhibition of CYP could produce a slow metabolizer phenotype, regardless of the actual CYP genotype (a hypothesis that also applies to other boosted PIs, e.g. DRV and LPV).

In HIV patients, *CYP3A5*3* was associated with exposure in subjects receiving boosted ATV [109], but not in those receiving the unboosted drug [110]. The latter study also found a lower rate of virological failure in CYP3A5 expressors, adding to the confusion.

The role of *CYP3A4*1B* is even less clear. One study found an association with higher drug exposure [108], while another could not link the genotype to either plasma or intracellular concentrations [111].

Lastly, a GWAS failed to detect any significant association between ATV exposure and polymorphisms in phase I drug metabolism pathways, casting doubt on the relevance of previous observations [112].

Thus, SNPs in CYP may not play a major role in ATV PK (Table 3). SNPs in UGT may be more relevant to individualization of therapy, as evidenced by guidelines produced by the Clinical Pharmacogenetics Implementation Consortium [113], although this is out of the scope of this review.

2.6. Darunavir

DRV is the most recently approved – and one the most frequently used – PI. Like several other drugs of this class, it is combined with a PK booster. The standard regimen is 800 mg DRV + 100 mg RTV (or 150 mg COB) once-daily, while 600 mg DRV + 100 mg RTV twice-daily is recommended in treatment-experienced patients. DRV has the advantage of being less toxic than some of the older PIs, although hepatotoxicity remains a potential issue.

DRV is a substrate of CYP3A4, with all of its metabolites exhibiting low activity [114,115].

In a population PK study of 60-predominantly Caucasian patients, none of the studied SNPs (*CYP3A5*3, CYP3A7* variants rs10211 and rs2257401; *CYP3A4*1B* and rare variants rs4987161 and rs4646437) were associated with DRV clearance [116].

Table 3. Relevance of CYP polymorphisms to protease inhibitor (PI) therapy.

Allele	rs number	Nucleotide change	Clinical outcome	Level of evidence
*CYP3A4*1B*	rs2740574	c.-392A>G	No effect on ATV, DRV, or LPV PK	Low
*CYP3A4*22*	rs35599367	g.20493C>T	Increased exposure to LPV	Low
*CYP3A5*3*	rs776746	g.6986A>G	No effect on LPV PK	Medium
			Increased exposure to DRV	Low
			No effect on ATV PK	Low
*CYP3A5*6*	rs10264272	g.14690G>A	No effect on ATV or LPV PK	Low
*CYP3A5*7*	rs76293380	g.27131_27132insT	No effect on ATV PK	Low

Level of evidence (low/medium/high) was assigned based on the amount and quality of available evidence. ATV: atazanavir; CNS: central nervous system; DRV: darunavir; LPV: lopinavir; PK: pharmacokinetics.

Meanwhile, a study conducted in 135 African and Caucasian patients demonstrated lower drug exposure for subjects harboring the variant *CYP3A5*1*, but only in patients receiving etravirine, a known CYP inducer, while no effect was discernible at the population level [117]. This highlights the importance of taking DDI into consideration, including for RTV- or COB-boosted antiretrovirals.

There is currently not enough data to make any genotype-based dose recommendations for DRV (Table 3). Studies of additional SNPs and of ethnically heterogeneous populations are required.

2.7. Lopinavir

LPV is a PI administered at 400 mg + 100 mg of RTV twice-daily. Drug-specific side effects include QT interval prolongation and an increased risk of myocardial infarction. It is metabolized by – and can inhibit – CYP3A isoforms.

The largest study to date investigated over 1500 polymorphisms and 115 genes in a Caucasian population [118]. LPV clearance was reduced by 18% in subjects harboring the variant rs6945984, an intergenic tag SNP in linkage disequilibrium with *CYP3A5*3* and *CYP3A7*2* (a gain-of-function allele). Oddly, the related functional SNPs were not significant at the chosen threshold. Also, another large-scale study could not demonstrate an association between rs6945984 and the risk of treatment discontinuation [76].

Studies of smaller scale were no more successful at demonstrating a clear relationship between LPV PK/PD and SNPs such as *CYP3A4*1B* [119,120], *CYP3A5*3* [119–123] and *CYP3A5*6* [119–121]. One study found that homozygosity for *CYP3A4*22* was associated with a major reduction in clearance [124]. The fact that *CYP3A4*22* homozygotes are quite rare could explain why this is an isolated finding.

As with other boosted PIs, *CYP3A* polymorphisms may play a role in the PK/PD variability of LPV, with RTV mitigating this effect, but there is currently too little evidence to make any recommendations (Table 3).

3. Conclusion

Several antiretroviral drugs are substrates of CYP enzymes, for which functional genetic polymorphisms exist. These polymorphisms can alter the PK of antiretrovirals, with an impact

on treatment efficacy, toxicity and potential for DDI. We summarized the main pharmacogenetic associations described in the literature and how they could shape therapeutic guidelines. In most cases, pharmacogenetic information has not yet led to specific dose recommendations.

4. Expert opinion

In order for theoretical knowledge to be of practical use, several hurdles must be overcome. First, this knowledge must be well established and rigorously validated, so that it can be trusted. Second, the individuals who can make use of it must be sensitized to the issue. Third, the knowledge must be incorporated in a framework that enables its use by the interested individuals. As far as pharmacogenetic associations in ART are concerned, all of these hurdles have yet to be fully overcome, although much progress has been made.

A good example of pharmacogenetic testing for antiretrovirals is the guidelines for the use of abacavir, which requires prior screening for HLA-B*5701. Patients carrying this allele are at an increased risk of presenting major hypersensitivity reactions; despite the relatively low occurrence of such reactions (5–8%), genotyping before treatment initiation has been shown to be cost-effective in Caucasian and Hispanic populations [125] and is now mentioned in the package insert [126]. However, such examples are few and far between, especially for CYP. One should remember that strong, monogenic associations are the easiest case to study. The reality is much more complex, and taking into account multiple loci and multiple SNPs may be required to understand how the components of an individual's genetic background influence each other, as one SNP may mitigate or potentiate another.

Another complication arises from DDI. Indeed, polypharmacy is the norm rather than the exception for HIV patients, both because of the need for multiple antiretrovirals and because of comorbidities. Examples of comedications with high CYP DDI potential that HIV patients may receive include tuberculosis therapy with rifampicin (a well-known CYP inducer), or CYP inhibitors such as azole antifungals (e.g. voriconazole and itraconazole) or Hepatitis C virus PIs (e.g. simeprevir and boceprevir). As we have mentioned in this review, many antiretrovirals also happen to be CYP inducers or inhibitors themselves, or are coadministered with PK boosters. Adding or removing the perpetrator drug could lead to unexpected results in patients whose true phenotype was previously hidden due to the DDI. Possible differences between RTV and new boosters like COB should also be investigated.

While various genetic polymorphisms have been described for CYP, associations for a given SNP–drug pair are not always consistent. These discrepancies can be explained by small study sample sizes and lack of representation of some ethnicities (precluding recruitment of a sufficient number of individuals carrying rare alleles), inappropriate study design (purely retrospective study, too lax or too restrictive inclusion/exclusion criteria, and low-quality PK data) and statistical analysis (candidate gene studies with no correction for multiple comparisons), different outcome definitions, or simply more stringent methodology for establishing an association. It should also be mentioned that some studies overlook possible gene–gene interactions or epigenetics, choosing to focus solely on a handful of SNPs. Validation of available results on large cohorts would help consolidate our knowledge of how these SNPs can impact drug therapy. In addition to replication studies, experiments designed to acquire mechanistic insight into these polymorphisms and how they shape drug PK would be beneficial. The contribution of some metabolites of EFV (or NVP) to their toxicity also highlights the need to consider more than just the parent drug when it comes to pharmacogenetic associations. Finally, another area requiring greater attention is whether the impact of CYP polymorphisms on drug PK is also relevant to the long-term efficacy and safety, e.g. viral suppression and immune function recovery, emergence of resistance and biomarkers of HIV morbidity. Stronger levels of evidence will result in official guidelines or recommendations (in the form of drug label updates or as part of clinical decision support systems).

These recommendations will then have to be implemented in routine practice: a robust and cost-effective framework must be established so that pharmacogenetic information can be of use. Regarding the cost, genotyping should be compared to other strategies, such as TDM (although obviously, they can be seen as complementary). For instance, in resource-limited settings, TDM alone may be a cheaper alternative. This could change in the future as genotyping becomes more widely available and affordable. Pharmacoeconomic studies and simulations of multiple scenarios are required to weigh the benefits of the various treatments available and set strategies adapted to the needs and resources of each country (as well as the ethnic composition of the local population, which determines the allelic frequencies of various polymorphisms).

Unfortunately, a drug of interest and its corresponding CYP do not exist together in a vacuum; they are part of a larger system, composed of multiple CYP enzymes, other enzymes, influx and efflux transporters, nuclear receptors regulating biotransformation and transport of xenobiotics, PD targets (including viral genome and immune response pathways), comedications and various patient-specific characteristics, not to mention patient-, physician- and setting-related limitations (economical and practical). Simplistic recommendations such as those seen with weight-based dosing are no longer doable when one enters the realm of the so-called 'precision-based medicine' that pharmacogenetics can contribute to. Advanced mathematical models are necessary to handle this abundance of information. New methodologies (for example, population PK) will help in this regard. The development of more user-friendly tools, their incorporation in the clinical routine workflow, and the appropriate training of clinicians in the use of the software should be our next priorities.

One last caveat of genotype-tailored therapy is that appropriate pharmaceutical forms must be available; yet the increasing popularity of fixed-dose combinations for the treatment of HIV might limit opportunities for individualizing therapy.

In summary, pharmacogenetic studies have shed some light on the role of genetic polymorphisms in ART, but this knowledge must now be incorporated in decision-making systems. There is still much to be done if the field of pharmacogenomics is to see more than marginal use.

Funding

This work was funded by grant by the Fonds pour la Formation à la Recherche dans l'Industrie et dans l'Agriculture (grant no. FC16749) to G Stillemans.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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