The Pharmacogenetics of HIV Treatment: A Practical Clinical Approach

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Abstract

HIV therapy is known to be associated with a large variability in efficacy and toxicity among different individuals even at standard doses. The reasons for this large inter-individual variability include race, gender, concomitant medications, drug compliance, underlying diseases and host genetic factors. Pharmacogenetic studies have focused on drug-metabolizing enzymes and membrane drug transporters to provide a better understanding of the mechanism underlying the interindividual variations in drug exposure and response. Despite of the high number of genetic polymorphisms discovered over the past few years, only a few of them became of clinical significance. In this review, the most relevant genetic polymorphisms affecting the activity and/or the expression of key drug-metabolizing enzymes and membrane drug transporters are summarized.

Keywords: HIV; Antiretroviral therapy; Pharmacogenetics

Introduction

The introduction of Highly Active Antiretroviral Therapy (HAART) as standard of care has changed the natural history of HIV infection into a manageable chronic disease requiring long-term Antiretroviral (ARV) Treatment. However, despite of the long-time experience and the vast drug armamentarium available for HIV infection, variability in efficacy and toxicity remains an important limitation for managing HIV infection. There are multiple factors affecting the variability of ARV response, including ethnicity, gender, age, body weight, drug-drug and drug-food interactions, binding to plasma proteins, hepatic impairment, disease status, pregnancy, and host genetic factors. Genetic variations in pathways of drug absorption, disposition, metabolism and excretion (ADME) may explain the interpatient variability and therefore, genes encoding for transport proteins, drug-metabolizing enzymes or nuclear receptors that encode for both transporters and enzymes, have been the main targets of HIV pharmacogenetic studies so far (Figure 1).

“Pharmacogenetics” is the discipline that analyses the genetic basis for the interindividual variation in the body disposition of drugs. The initial candidate genes studies, in which genetic variants of host factors that were already known to play a role in HIV-infection were tested, have lead to genome wide association studies (GWAS), in which not only one gene but in fact the whole genome is studied.

A number of associations between human genetic variants and predisposition to ARV drug toxicity or risk of virologic failure has been described in recent years. One of the most significant association is the one established between HLA-B*5701 and Abacavir hypersensitivity reaction and therefore, the genetic test prior prescribing Abacavir has been introduced into antiretroviral guidelines as the standard of care for all patients. Other well-established associations include HLA class II allele HLA-DRB*0101 and nevirapine-associated hypersensitivity, CYP2B6 alleles and efavirenz central nervous system side effects, UGT1A1 alleles and polymorphisms at genes coding for P-glycoprotein related with atazanavir-associated hyperbilirubinemia and polymorphisms in the ABCC2 gene associated with TDF renal proximal tubulopathy.

Since pharmacogenetic factors impact the clinical outcome of HIV patients, this review provides examples of the most relevant genetic polymorphisms affecting the most common prescribed ARVs as a tool for individualizing HIV therapy in the clinical setting. They are all summarized in table 1.

Pharmacogenetics of non nucleoside reverse transcriptase inhibitors (NNRTIs)

NNRTIs are used in combination with Nucleoside Reverse Transcriptase Inhibitors (NRTIs) or Protease Inhibitors (PIs) as first line treatment for HIV infection. They are metabolized in the liver by the cytochrome P450 (CYP450) and their absorption and distribution is affected by the drug transporter P-glycoprotein (P-gp) [1,2]. Polymorphisms affecting these targets may explain the large variability that exists in NNRTI plasma levels and they may be also related with the adverse effects associated with them.

Pharmacogenetics of efavirenz

Efavirenz (EFV) is one of the most used NNRTIs in the first-line antiretroviral therapy for HIV-infected patients, as well as the preferred third drug in patients with tuberculosis (TB) coinfection requiring rifampin-containing therapy.

The fixed dose of 600 mg once daily of EFV is related with a significant intervariability in EFV plasma exposure and clinical effects. EFV shows a narrow therapeutic range (1-4 µg/mL) and there is a potential risk of infra or supra-therapeutic concentrations that are related with virological failure or central nervous system (CNS) symptoms. Furthermore, increased EFV exposure has been associated not only with CNS toxicity but also with the development of resistance after drug discontinuation [3].

EFV is oxidized primarily by hepatic CYP2B6 to form 8-hydroxy and 7-hydroxy efavirenz, and in a lesser extent by CYP3A4/5 and CYP2A6. Genetic polymorphisms of CYP2B6 are the most frequently

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| Drug | Gene (Protein) | Variants (ref.) | Genetic consequence | Clinical impact | Clinical relevance | References |
|------|---------------|----------------|-------------------|----------------|------------------|------------|
| **NNRTIs**<br>EFV | CYP2B6 (CYP2B6) | 516C>T<br>(rs3745274) | Gln172His Discontinued function | Yes<br>Higher plasma levels | Yes<br>CNS adverse effects | EFV range: 1-4 µg/mL. TT genotype associated with more risk for CNS adverse effects. [6-9,13] |
| 785A>G<br>(rs2279343) | Lys262Arg Discontinued function | Yes<br>Higher plasma levels | Yes<br>CNS adverse effects | Genotype 516/983 associated with increased CNS events [10-14] |
| 983T>C<br>(rs28399499) | Ile328Thr Decreased protein expression | Yes<br>Higher plasma levels | Yes<br>CNS adverse effects | Genotype 516/983 associated with increased CNS events [11-13] |
| **ABCB1 (P-gp)**<br>NVP | CYP2B6 (CYP2B6) | 516C>T<br>(rs3745274) | Gln172His Discontinued function | Yes<br>Higher plasma levels | No<br>- | [23,31-33] |
| 983T>C<br>(rs28399499) | Ile328Thr Decreased protein expression | Yes<br>Higher plasma levels | No<br>- | [35,36] |
| 3435C>T<br>(rs1045642) | Ile1145le Synonymous substitution. In LD with ABCB1 1236 and 2677 | No<br>No | T allele associated with lower risk of hepatotoxicity [37,39] |
| **HLA-DQ**<br>DRB1*0101 | - | - | No<br>Yes | HSR<br>Greater risk for hypersensitivity reaction [24,25] |
| **HLA-C**<br>CW*8 | - | - | No<br>Yes | HSR<br>Greater risk for hypersensitivity reaction. [26,27] |
| **HLA-B** | B3505<sup>5</sup> | - | No<br>Yes | NVP skin rash [28] |
| **IPs**<br>ATV | UGT1A1 (UGT1A1) | *28<br>(rs8175347)<br>(rs887829) | *280=Promoter region. (Insertion at TATA Box) | No<br>No | Yes<br>Gilbert's syndrome. Increased levels of bilirubin. Higher risk of hyperbilirubinemia. [48,61-63] |
| **ABCB1 (P-gp)**<br>NVP | CYP2B6 (CYP2B6) | 3435C>T<br>(rs1045642) 2677G>T<br>(rs2032585) | Ile1145le Synonymous substitution. Ala893Ser | Yes<br>Lower ATV plasma levels. | No<br>No | ATV minimum effective concentration= 0.15 µg/mL. No<br>No | Risk of subtherapeutic levels in TT carriers. [47-49] |
| **NR1I2 (PXR)** | 6396C>T<br>(rs2472677) | - | Yes<br>Lower ATV plasma levels | T allele associated with lower risk of KTD. [53,54] |
| **LPV** | SLC01B1 (OATP1B1) | 5217C<br>(rs4149056) | Val174Arg Reduced transport activity | Yes<br>Higher LPV plasma levels with CC genotype | -<br>- | NVP skin rash [28] |
| **NRTIs**<br>ABC | HLA-B<br>ABC-B*57:01 | NA | - | No<br>Yes | Abacavir Hypersensitivity Reaction (ABC-HSR) [72-73] |
| **HLA complex P5 (HCPS)** | 335T>G<br>(rs2395029) | Val112Gly | No<br>No | Yes<br>Alternative marker for screening of individuals at risk for ABC-HSR [82-85] |
| **TFV** | ABC2 (MRP3) | CATC<br>Haploptype<br>(-24, 1249, 3563, 3972)<br>(rs717620, rs2273697, rs187694, rs3740066)<br>-24CC<br>(rs717620) | NA<br>Val417Ile<br>Val1188Glu<br>Ile1324Ile | No<br>No<br>No | Yes<br>CATC Haploptype associated with greater risk of KTD. -24CC associated with higher risk of KTD [99-100] |
| **ABCC4 (MRP4)** | 463A>G<br>(rs1751034) | - | Yes<br>Higher intracellular TFV-DP | No<br>- | [98] |
| **ABCC4 (MRP4)** | 569C>T<br>(rs893949) | - | No<br>Yes | Risk for KTD [100] |
| **ABCC10 (MRP7)** | Intron-4<br>(rs9349256) | - | No<br>Yes | Urine phosphate wasting and 82-microglobulinuria [100] |
| **II RAL** | UGT1A1*28<br>[A(TA7)TAA] | *28<br>(rs8175347) | *280=Promoter region. (Insertion at TATA Box) | No<br>No | No<br>- | [109,110] |
| **ABCB1 (P-gp)** | CYP2B6 (CYP2B6) | 3435C>T<br>(rs1045642) | Ile1145le Synonymous substitution. | Yes<br>No | Allele T is associated with lower RAL plasma exposure [113] |

**Abbreviations:** NNRTIs: non nucleoside reverse transcriptase inhibitors; EFV: efavirenz; NVP: nevirapine; IPs: protease inhibitors; ATV: atazanavir; LPV: lopinavir; NRTIs: nucleoside reverse transcriptase inhibitors; ABC: abacavir; TFV: tenofovir; II: integrase Inhibitors; RAL: raltegravir; CYP2B6: cytochrome P-450 2B6 isooform; ABCB1: ATP-binding cassette subfamily B member1, P: P-gp: P-glycoprotein; HLA: human leukocyte antigen; MRP: multidrug resistance-associated protein 7; UGT: uridine 5'-diphospho-glucuronosyltransferase 1A1; NR1I2: nuclear receptor subfamily 1, group I, member 2; PXR: Pregnane X Receptor; SLC01B1: solute carrier organic anion transporter 1B1; OATP1B1: organic anion transporter 1B1; HCPS: human leukocyte antigen complex P5; ABC2C: ATP-binding cassette subfamily C, membrane 2; ABC4: ATP-binding cassette subfamily C, member 4; ABC10: ATP-binding cassette subfamily C, member 10; MRP2: Multidrug resistance-associated protein 2; MRP4: Multidrug resistance-associated protein 4; MRP7: multidrug resistance-associated protein 7; Gln: glutamine; His: histidine; Lys: lysine; Arg: arginine; Ile: isoleucine; Thr: threonine; Ala: alanine; Ser: serine; Val: valine; Gly: glycine; Glu: glutamic acid; CNS: central nervous system; HSR: hypersensitivity reaction; KDF: kidney tubular dysfunction. **Table 1:** Summary of most relevant genetic variants that affect antiretroviral pharmacokinetics and toxicity.
studied so far. The CYP2B6 gene is highly polymorphic and as a consequence, there is a considerable interindividual variability in expression and function [4,5]. Since EFV shows a narrow therapeutic range, the risk of virological failure and toxic effects on the CNS is worrisome. One of the most relevant polymorphisms is the change 516G>T that leads to a lower enzyme activity of CYP2B6 and therefore, to a greater EFV exposure. Thus, patients with the slow metabolizer genotype CYP2B6-516TT exhibit higher EFV plasma levels compared with genotypes GG or GT, being more prone to develop CNS adverse reactions [6-9] (Figure 2). The prevalence of the genotype CYP2B6-516TT is above 5% for different ethnicities (20% in black population and 6% in Caucasians) [6], and for this reason, the probability of dealing with patients harbouring the TT genotype may be quite common in clinical practice.

In addition, extensive CYP2B6 genotyping of relevant single nucleotide polymorphisms (SNPs) studies have identified more variants that account for the variability in EFV pharmacokinetics. Subjects homozygous for the CYP2B6*6 allele, that contains both 516G>T and the 785A>G polymorphisms, display significantly higher EFV plasma levels than heterozygous subjects or those with the common genotype [10]. The 983T>C polymorphism, a less frequent polymorphism only described in Hispanic and black population, has been shown to impact in EFV exposure as well [11,12]. In a recent study, Ribaudo et al. [13] established that the CYP2B6*18 allele, that harbours the 516G>T and 983T>C polymorphisms, better predict EFV pharmacokinetics and also, slow-metabolizer genotypes were associated with increased CNS events among white patients and decreased virologic failure among black patients. Similarly, the CYP2B6*16 allele, that contains both 785A>G and 983T>C polymorphisms, has been associated with greater EFV exposure [14]. Moreover, novel alleles such as the allele *28 (defined by 1132C>T), that results in protein truncation, have been also associated with a greater risk of showing high EFV plasma levels [15].

With regards to transport proteins, the efflux transporter P-gp, which is encoded by the ABCB1 (MDR1) gene, has been the most widely studied. The synonymous polymorphism 3435C>T in the ABCB1 gene is related with lower expression of P-gp [16], and the allele T has been associated with lower EFV plasma concentrations [1,17]. In spite of this fact, the clinical consequences remain a matter of controversy with contradictory results [1,18,19]. Similarly, genetics polymorphisms in genes encoding for other transporters such as the multidrug resistance proteins (MRPs) are being investigated.

In a recent study conducted in 128 HIV Caucasian patients, a pharmacokinetic/pharmacogenetic (PK/PG) model was proposed as a tool to optimize EFV dosage. The model included the CYP2B6*6 allele, the polymorphism ABCC4-19497C>T and the level of gamma glutamyl transpeptidase (GGT) as the major factors influencing the EFV oral clearance [19]. However, this type of PK/PG models need to be further validated in another populations in order to become into a useful tool for individualizing the therapy.

**Pharmacogenetics of nevirapine**

Nevirapine (NVP) is also widely prescribed for HIV-1 infection, especially in source poor-settings and pregnant women (or those who are trying to achieve it) and their children. Nevertheless, its use is limited due to the related-adverse effects that appear more frequently during the first 6 weeks of treatment and a fragile genetic barrier to the development of drug resistance [20]. The main adverse effects associated with NVP use are rash, that can affect up to 15% of patients initiating NVP, an increase in transaminases even 5 times the normal level in about 20% of patients, fever, and the immune-mediated hypersensitivity reaction (HSR) that may manifests as hepatotoxicity [21,22]. The mechanism involved in the development of the adverse events related with NVP is not well understood. Cutaneous effects are most likely MHC class I-mediated, influenced by NVP CYP2B6 metabolism, whereas hepatic toxicity is most likely MHC class II-mediated and unaffected by such metabolism [23].
Several human leukocyte antigens (HLA) class I and II alleles have been associated with rash and/or hepatitis reactions development. The simultaneous presence of allele HLA-DRB1*01:01 and a CD4+ T lymphocyte count greater than 25% significantly increases the risk for hypersensitivity and hepatototoxicity reactions to NVP [24,25]. Similar associations have also been established for other HLA class I alleles such as HLA-B*14:02, HLA-Cw08 and HLA-B*35:05 [26-28].

Up to the present year, the majority of these studies were focused on white populations, however, in 2013, Phillips et al. [29] published the first study to be carried out in black population, where they highlight the need for HLA studies to be performed across other populations, more specifically those where different HLA alleles may be prevalent. In this study, both HLA-B*58:01 and HLA-DRB1*01:02 were independently associated with increased hepatotoxicity during NVP therapy [29]. In relation to rash reaction, a GWAS study conducted in Thai population has recently reported that genetic variations within CCHCR1 (rs1265112) on chromosome 6p12.3 are strongly associated with NVP-induced rash [30].

NVP is metabolized primarily by CYP3A4 and 2B6 enzymes into its major metabolites 2-hydroxyetravirine and 3-hydroxyetraviripine, respectively, with a minor contribution from CYP3A5 [31]. Several studies have reported that the polymorphisms 516G>T and 983T>C in the CYP2B6 gene are associated with variations in NVP pharmacokinetics in ethnically diverse populations [32-36], although the clinical impact remains uncertain since an association between greater NVP exposure and toxic effects has not been fully demonstrated.

In regards to P-gp, it has been hypothesized that polymorphisms affecting its activity might influence intracellular concentrations, and therefore, the related toxicity. The polymorphism ABCB1-3435C>T has been associated with a decreased risk of hepatotoxicity in patients receiving NVP [37-39]; nevertheless, this observation is paradoxical since a lower expression of P-gp would lead to a greater accumulation of NVP inside the hepatocytes.

Pharmacogenetics of etravirine

Etravirine (ETV) is a second generation NNRTI approved by Food and Drug Administration (FDA) in 2008. It is metabolized by CYP3A, 2C9, and 2C19 and the resultant metabolites are glucuronidated by uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes [40]. ETV concentrations are highly variable, explained in part by interactions with food intake and other medications.

The contribution of host genetic factors was investigated in a recent study in which, patients who carried the allele CYP2C19*2, that leads to a truncated protein, had lower ETV clearance [41]; however, this finding may not have clinical impact.

Pharmacogenetics of protease inhibitors

Protease Inhibitors (PIs) family includes the major number of ARVs and they are also the preferred third drug as part of HAART.

PIs have marked inter-individual variability in bioavailability and plasma pharmacokinetics, which might be explained by variation in drug metabolism. PIs are not only metabolized by CYP3A4 but also inhibitors of the CYP3A. Some of them are inhibitors of the UGT1A1, the enzyme responsible for bilirubin glucuronidation.

Furthermore, drug transporters, such as Pgp, play an important role in the disposition, metabolism and clearance of the PIs. Thus, genetic polymorphisms affecting the expression/activity of enzymes and transport proteins may affect the bioavailability and body distribution of PIs [2,42-44].

Pharmacogenetics of atazanavir

Atazanavir (ATV) is currently recommended in first-line regimens for treatment-naive HIV-infected patients as well as switch regimens for patients with intolerances to other ARV drugs.

Several drawbacks are associated with its clinical use, such as poor and highly variable oral bioavailability, the extensive metabolism of ATV by CYP3A4 in the liver and intestine as well as a large number of drug-drug interactions. In addition, the associated jaundice side effect is one of the main deterrents for patients’ compliance.

Polymorphisms affecting efficacy of atazanavir: ATV bioavailability shows high interpatient variability and ATV plasma concentrations are influenced by many processes that are mediated by different transport proteins and metabolizer enzymes. Since ATV plasma concentrations correlate with treatment response, and in fact, a minimum effective concentration of 150 ng/mL has been proposed as a target in treatment guidelines, polymorphisms affecting ATV disposition affect its clinical efficacy.

P-gp has been demonstrated to transport ATV [45,46]. The polymorphism ABCR1-3435C>T has been associated with variations in ATV plasma levels regardless of the dosage. Patients with the CC genotype display higher ATV levels than those with CT/TT genotype [47,48]. This nucleotide change does not change the encoded amino acid and therefore, it would not be the cause of altered activity of the transporter but may be associated with one or more causal variants in the poorly characterized stretch of linkage disequilibrium (LD) surrounding it [49]. It has been proposed that polymorphism 2677G>T/A is responsible for the aforementioned functional consequences due to the fact that it is frequently linked to the 3435 SNP [50,51]. Nucleotide substitution at 2677G>T/A results in changes in the amino acid 893, Ala893Ser/Thr, but the functional implication remains unknown so far.

Other transport proteins such as MRPs seem to play a minor role in ATV efflux from cells whereas organic anion transporter 1B1 (OATP1B1), encoded by SLCO1B1, is involved in the ATV uptake inside the cells [46,52]. Studies focus on polymorphisms at these genes could be of great interest.

The transcription of metabolic enzymes and transport proteins is regulated by nuclear receptors (NR). One of the most important ones is the Pregnane X Receptor (PXR) encoded by the NR1I2 gene. PXR regulates the expression of CYP3A4, ABCB1 (P-gp) and SLCO1B1 (OATP1B1) and consequently, genetic variations in this receptor may affect the antiretroviral pharmacokinetics [46]. The most studied polymorphism at NR1I2 is the 63396C>T, which has been associated with an increased activity of CYP3A4, leading to variations in ATV exposure. In this regard, homozygosity for the NR1I2-63396-T genotype is a predictor for sub-therapeutic ATV levels [53,54].

In the matter of the above, ATV plasma concentrations are associated with several SNPs involved in its distribution and metabolism. In a study conducted by Siccardi et al. [53], a score based in 3 SNPs, ABCB1 (3435C>T), SLCO1B1 (521T>C) and PXR (63396C>T), was proposed as the best predictor of unboosted ATV plasma exposure in the clinical setting [55]. The pharmacogenetic score was calculated as the sum of favourable genotypes. An “unfavourable genotype”, defined as having none or 1 of the SNPs mentioned above present, was associated with...
lower ATV plasma levels while "favourable genotype" which has 2 or 3 of the SNPs, was associated with greater ATV plasma levels. More recently, Bonora et al. [56] have shown that individualisation of ATV schedule according to the score based on these SNPs allowed to optimise ATV exposure when administered with TDF/FTC.

Polymorphisms related with Hyperbilirubinemia due to Atazanavir treatment: ATV is known to cause indirect hyperbilirubinemia by inhibiting the enzyme UGT1A1, which is responsible for bilirubin conjugation in the liver to be eliminated from the body. About 20%-50% of patients exposed to ATV may develop hyperbilirubinemia that can be severe in about 6% of cases [57]. Several studies have shown the correlation between ATV plasma levels and the risk of bilirubin elevations [47,48,58]. Polymorphisms at the UGT1A1 gene have been related with a diminished activity of the enzyme, affecting the metabolism of bilirubin. The variant allele UGT1A1*28 is associated with Gilbert’s syndrome, an inherited unconjugated hyperbilirubinemia disorder [59,60]. Allele *28 contains seven repeats of the dinucleotide TA (TA7) at the promoter of the gene instead of six (TA6) typically of the common allele (UGT1A1*1). In this setting, plasma bilirubin levels are further increased in ATV recipients when the UGT1A1*28 allele is present [48,61,62] (Figure 3). Another polymorphism in the UGT1A1 promoter (rs887829) associated with ATV hyperbilirubinemia has been proposed as the strongest genetic predictor of peak bilirubin in a GWAS conducted very recently. In this study, the likelihood of on-treatment hyperbilirubinemia in ATV recipients increased with higher baseline bilirubin and hemoglobin, and further increased with rs887829 [63].

Pharmacogenetics of lopinavir

Lopinavir (LPV) is mainly metabolized by CYP3A enzymes and is also a substrate of the efflux transporters encoded by ABCB1, ABCB1 and ABCC2 genes, which contribute to its low and variable oral bioavailability.

A common SNP in the SLCO1B1 gene, 521T>C, has been associated with higher plasma levels of LPV [64-67], but the clinical significance is still uncertain and further studies are needed to confirm this association and to assess the impact on LPV pharmacokinetics.

Likewise, an association between 4544G>A polymorphism in ABCC2 and LPV accumulation in peripheral blood mononuclear cells has been reported in a small cohort of HIV-infected patients [68]. Nevertheless, further investigations are needed to confirm this association and to explore the real pharmacodynamic impact.

Pharmacogenetics of nucleos(t)ide reverse transcriptase inhibitors

Nucleos(t)ide reverse transcriptase inhibitors (NRTIs) are the back bone commonly used in ARV therapy. Since its metabolism is little mediated by CYP450 enzymes, there is no evidence that genetic polymorphisms of P450 affect NRTI disposition. By contrast, MRPs are known to play a role in the cellular efflux of NRTIs and therefore, genetic variations in these proteins have been associated with intracellular levels of NRTIs [69]. In the other hand, pharmacogenetic studies of the HLA system may explain some of the toxicity reactions associated with this class of ARVs.

Pharmacogenetics of abacavir

Abacavir (ABC) is widely prescribed as part of the HAART regimen although about 5-8% of Caucasian patients who receive ABC develop a HSR within the first 6 weeks of treatment [70,71]. Symptoms include fever, rash, gastrointestinal disturbances, and lethargy. It normally improves after 24h of ABC discontinuation but subsequent rechallenge with ABC is extremely dangerous, resulting in a recurrence of symptoms and lastly, life threatening complications and death.

Fortunately, it has been discovered a strong association between ABC-HSR and the 57.1 haplotype at the HLA (defined by the presence of HLA-B*57:01, HLA-DR7 and HLA-DQ3) [72-74]. The HLA region is the most polymorphic locus in the genome, which further complicates studies. Nevertheless, this association has been confirmed in different ethnicities despite of the fact that the prevalence of the HLA-B*57:01 across different ethnic groups is heterogeneous (Caucasians 4%, Asians 2%, Hispanics 1% and Blacks 0.5%) [75-78]. One of the most important studies supporting the clinical usefulness of the screening of the HLA-B*57:01 was the one published by Mallal et al. [75] in 2008 in which a large number of patients were enrolled. Prospective studies as well as cost-effectiveness studies of HLA-B*57:01 testing have force its incorporation in the HIV treatment guidelines before prescribing ABC [78-81]. In fact, the HLA-B*57:01 testing has been the first pharmacogenetic test used in the clinical practice to the management of HIV infection.

HLA-B*57:01 testing is expensive, time consuming and requires specialized laboratories; in consequence, another genetic marker has been proposed as surrogate of the HLA-B*57:01 allele. The polymorphism 335T>G is located within the HLA complex P5 gene, HCP5, has been found to be in high linkage disequilibrium (LD) with HLA-B*57:01 [82,83]. Several studies have explored the potential of HCP5 testing to predict the ABC-HSR and they have demonstrated that HCP5 testing is cheaper, less time-consuming and easier to perform than HLA typing [82-85] and therefore, genotyping the HCP5 SNP has increasingly been adopted as a simple method to screen for susceptibility to ABC-HSR. However, the fact HCP5 occurs within a region of copy number variation and the fact LD is incomplete and may vary between ethnicities, should be considered when using the HCP5 SNP as a surrogate marker for HLA-B*57:01 [86].

Pharmacogenetics of tenofovir

Tenofovir (TFV) is a NRTI widely used for the treatment of HIV infection. It is a drug of choice both for first line therapy in naives and
Pharmacogenetics of integrase inhibitors

Integrase inhibitors (INI) are a novel family of ARVs, which prevent the integration of reverse transcribed viral cDNA into the cellular chromosomes, a key step in the HIV life cycle. Since they inhibit a different process from the classical ones, cross-resistance with other families is not expected. Raltegravir (RAL) is the first INI approved for the treatment of HIV infection for both naïve and pretreated patients and it is a very attractive option of treatment due to its potency and good safety profile.

Pharmacogenetics of raltegravir

RAL plasma concentrations display a large inter and intra-individual variability, being the coefficient of variation (CV) 212% and 122%, respectively. Gender, race, age, body mass index, food intake, renal or hepatic insufficiency have not shown a clinically meaningful effect on RAL pharmacokinetics [105-108].

RAL is mainly metabolized by UGT1A1 and therefore, polymorphisms at this enzyme, such as the allele *28 associated with the well-known Gilbert syndrome, have been studied. Plasma concentrations of RAL have been reported to be slightly higher in individuals with the UGT1A1*28/*28 genotype than in those with the UGT1A1*1/*1 genotype. However, this increase is not clinically significant, and no dose adjustment of RAL is recommended for individuals with the UGT1A1*28/*28 genotype [109,110].

RAL is not a substrate and neither induce CYP450 enzymes, nevertheless, it has been reported that RAL is a substrate of the P-gp [111,112], and consequently, polymorphisms in transport proteins might contribute to explain the large intra- and inter-individual variability of RAL exposure. A recent study in a Spanish HIV RAL-cohort showed that the polymorphism at ABCB1-3435C>T was associated with RAL concentrations. Patients carrying CT or TT genotypes displayed lower median RAL concentrations than those with the CC genotype. Although PK/PD analyses do not suggest a threshold RAL concentration associated with reduced efficacy, patients carrying CT/TT genotypes at the P-gp gene might be more prone to virological failure [113].

Moreover, it has been reported that RAL is a substrate for the influx transporters OAT1 (SLC22A6) and PEPT1 (SLC15A1) [114]. Further studies in which transport proteins involved in RAL disposition and elimination would be examined together might provide a better understanding of the pharmacokinetics of RAL.

Pharmacogenetics of entry inhibitors

HIV uses CCR5 and/or CXCR4 as a co-receptor to entry into host cells. The CCR5 is likely the most physiologically important coreceptor during natural infection and is involved in the activation of leukocytes. This protein belongs to the beta chemokine receptors family of integral membrane proteins and normal ligands for this receptor are able to suppress HIV-1 infection in vitro. Maraviroc (MVC) is the first licensed CCR5 antagonist and effectively inhibits the interaction between HIV and CCR5 [115], representing a useful clinical tool in the treatment of HAART-experienced patients harboring viruses with selective tropism for the CCR5 receptor. Patients infected with X4 or dual viruses are not benefit of MVC based regimen.

CCR5-A32 is an allele of CCR5. This allele is found in 5-14% of Europeans but is rare in Africans and Asians. The A32 deletion results in a nonfunctional receptor, thus preventing HIV R5 entry. The presence of two copies of this allele provides strong protection against
HIV infection whereas the presence of one copy of this allele delays disease progression [116]. However, genetic variations in the CCR5 chemokine receptor gene have not shown to impact the virological response to MVC [117].

On the other hand, MVC is substrate of CYP3A4 and P-gp, hence, dose adjustment is frequently required when coadministered with drugs that alter its pharmacokinetics [118,119]. More recently, MVC has been identified as substrate of the transport protein OATP1B1 and the polymorphism 521T>C seems to be associated with higher MVC plasma levels [119]. The clinical usefulness of this finding needs to be tested in larger cohort of patients and validated for different dose groups.

Thus, the only genetic test that is mandatory to perform before starting MVC treatment is the determination of the viral tropism that it is not a host genetic test but a viral genetic test [120].

Conclusion and Clinical Relevance

The pharmacogenomic field is a very recent discipline but is being avidly explored to understand and better predict efficacy and toxicity of treatments in several diseases. Pharmacogenetic studies have focused on drug-metabolizing enzymes and membrane drug transporters to contribute to the understanding of the mechanism underlying the interindividual variations in drug exposure and response. Novel techniques that allow studying a vast number of genes, such as the GWAS, provide very valuable information. Despite of the high number of genetic polymorphisms discovered over the past few years, only a few of them became of clinical significance. The study design, selection of genes variants, differences regarding the ethnicity, population variability or environment influence, along with the complexity of the genetic techniques and the interpretation of the results, are some of the variables that limit the application of pharmacogenomics.

In clinical practice, two of the more common scenarios to deal with when introducing pharmacogenetics into the clinic are: a) the target affected by genetic variants is linked with a well-defined condition (HLA-B*57:01 and ABC, UGT1A1*28 and ATV, CYP2B6-516 and EFV, HLA-DRB*0101 and NVP) and b) no consensus exists for defining an altered function/parameter (ABCC genes and TDF).

In the first scenario, the target affected by genetic variants is linked with a well-defined condition, and therefore is easy to interpret. The association between HLA-B*5701 and ABC-HSR is the best example of the usefulness in bringing pharmacogenetics to the clinic. This genetic test has demonstrated to be cost-effective in most ethnic groups and current guidelines for ARV therapy advice to perform it prior to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. Lancet 359: 30-36.

Regarding NNRTIs, slow metabolizer recipients (CYP2B6-7T) could help to guide dose reductions and prevent toxicities and resistance after drug discontinuation in EFV recipients. Likewise, genetic screening for preventing the HRS and the risk hepatotoxicity would be a promising approach toward a safer use of NPV in clinical practice.

The second scenario is that in which no consensus exists for defining an altered function/parameter. This is the case of TDF and its association with kidney tubular dysfunction (KTD), in which neither the criteria to define KTD nor the mechanism implicated is well established. Several polymorphisms in renal transport proteins have been proposed to play a role in the development of KTD as well as higher TDF plasma levels. One of the main clinical consequences of the KTD is the phosphate waste which can ultimately lead to osteopenia and osteoporosis. In this regard, information derived from pharmacogenetics and pharmacokinetics studies may help to identify the subset of individuals at greater risk for developing more severe renal injury and loss of bone density.

In the lights of the above, the more tools the clinicians manage, the better clinical outcome will be achieved. Available pharmacogenetic tests combined with therapeutic drug monitoring (TDM) of parent drugs and/or metabolites, would be a complementary tool when attempts are made to individualize dosing regimen, maximize drug efficacy and enhance drug safety. In a recent review about pharmacogenomics, Rotimi and Jorde [121] also highlight the need for depth analysis of the available GWAS data, more advances in technologies and sequencing the complete genome (whole-genome sequencing-WGS-) to identify low frequency or rare variants that are associated with HIV infection. In addition, data collections should be extended to as many diverse populations as possible, being particularly important in African populations due to the high HIV prevalence rate and the high level of genetic diversity. In the future, the individualized medicine will likely consist of a combined approach using the knowledge of drug, virus, and host factors information to guide the personalized prescription in which, the right drug will be given to the right person.

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