Can antiretroviral therapy be tailored to each human immunodeficiency virus-infected individual? Role of pharmacogenomics

Victor Asensi, Julio Collazos, Eulalia Valle-Garay

Abstract
Pharmacogenetics refers to the effect of single nucleotide polymorphisms (SNPs) within human genes on drug therapy outcome. Its study might help clinicians to increase the efficacy of antiretroviral drugs by improving their pharmacokinetics and pharmacodynamics and by decreasing their side effects. HLAB*5701 genotyping to avoid the abacavir-associated hypersensitivity reaction (HSR) is a cost-effective diagnostic tool, with a 100% of negative predictive value, and, therefore, it has been included in the guidelines for treatment of human immunodeficiency virus (HIV) infection. HALDRB*0101 associates with nevirapine-induced HSR. CYP2B6 SNPs modify efavirenz plasma levels and their genotyping help decreasing its central nervous system, hepatic and HSR toxicities. Cytokines SNPs might influence the development of drug-associated lipodystrophy. APOA5, APOB, APOC3 and APOE SNPs modify lipids plasma levels and might influence the coronary artery disease risk of HIV-infected individuals receiving antiretroviral therapy. UGT1A1*28 and ABCB1 (MDR1) 3435C>T SNPs modify atazanavir plasma levels and enhance hyperbilirubinemia. Much more effort needs to be still devoted to complete large prospective studies with multiple SNPs genotyping in order to reveal more clues about the role played by host genetics in antiretroviral drug efficacy and toxicity.

Key words: Pharmacogenomics; Pharmacokinetics; Antiretroviral drugs; Adverse effects; Human immunodeficiency virus infection; Single nucleotide polymorphisms

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Core tip: Pharmacogenetics may play an important role in
the near future for the treatment of human immunodeficiency virus-infection, as exemplified by the HLAB*5701 genotyping to prevent the abacavir-associated hypersensitivity reaction. Diverse other single nucleotide polymorphisms have been described as related to certain pharmacokinetic characteristics and adverse effects of antiretroviral drugs. In this Editorial we summarize the current knowledge on this rapidly evolving field.

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INTRODUCTION

Antiretroviral therapy (ART) has become so effective that human immunodeficiency virus (HIV) infection is not any more the deadly plague of the past, but a chronic, easy to handle condition. Although ART is much less toxic nowadays than it was in the past, it is still not free of side effects. The choice of the most effective and safe ART regimen is the daily task of HIV clinicians throughout the world. An aim that has been made easier by the existence of ART guidelines that are updated yearly by different agencies and societies.

Another approach, much more cumbersome, is the use of pharmacogenetics to prescribe ART. The same antiretrovirals administered at the same doses produce different antiviral effects and toxicities in different individuals, suggesting that genetic factors of the host may also play a role. The term pharmacogenetics refers to the effect of polymorphisms within human genes on drug therapy outcome. Single-nucleotide polymorphisms (SNPs) are sequence variations in human DNA with single nucleotide changes occurring at an allele frequency greater than 1%. Nucleotide changes occurring with a lower frequency are referred to as mutations.

SNPs are candidates for a causal role for a given phenotype when they are associated with changes in protein function, which occurs more likely when the SNP is located in an exon, a DNA protein-coding region, and lead to changes in the encoded amino acid. However more than 95% of SNPs are located in non-coding gene regions, such as those of the promoter, untranslated, introns and intergenic regions. Such non-exonic SNPs can still alter protein function or expression by changes in gene transcription, mRNA splicing, mRNA stability or alterations in translation and conformation of the protein. Therefore, pharmacogenetics gives ground to individualized therapy.

This genetic tool might help clinicians to enhance ART efficacy by improving the pharmacokinetics and pharmacodynamics of antiretroviral drugs and by decreasing their side effects\(^{1,12}\). The use of HLAB*5701 genotyping to avoid the abacavir-associated hypersensitivity reaction (HSR) is a cost-effective diagnostic tool, which have a negative predictive value of 100% for all ethnic groups and, consequently, it has been included in all ART guidelines\(^{11,12}\). Unluckily, pharmacogenetics cannot offer so bright solutions to other ART problems at present, although it might still be of some help to the clinician, however.

A major problem of the SNP-phenotype association studies in the field of ART is the lack of reproducibility. This might be related to the relatively small size of the populations genotyped, the lack of statistical power of the study or a selection bias. Other times the SNP association of the observed effect is found only within a specific ethnic group but not in others. Also, some of the reported positive associations might have been obtained after multiple statistical comparisons, giving place to potentially spurious associations due to chance. Likewise, only positive results are usually reported, which means that some published associations may not have been overtly refuted by other authors that found no such a relationship.

On the other hand, a SNP-phenotype association might not be necessarily due to the functional effect of the gene variant, but to the presence of other variant on the same chromosome in linkage disequilibrium, combination that is referred to as a haplotype. Finally, most of the pharmacogenetic studies are retrospective or cross-sectional. A large prospective study on a multiethnic population, with simultaneous genotyping of multiple SNPs known to be relevant in the general population, would be much more informative.

In the following lines we will focus on the most frequent associations of genetic variants with the pharmacokinetic changes and toxicity of antiretroviral drugs, the most relevant of which are summarized in Table 1.

ABACAVIR-ASSOCIATED HSR

As mentioned above, the use of HLAB*5701 genotyping to avoid the abacavir-associated HSR is the ideal example of a genotype-phenotype correlation in HIV medicine. The involvement of host genetic factors was first suggested by the observation of abacavir-associated HSR in members of the same family. Later, several groups demonstrated a strong association between abacavir and the haplotype comprising HLAB*5701, HLA-DR7 and HLA-DQ3 genotypes\(^{11}\).

The clinical utility of HLAB*5701 genotyping was confirmed in a large, randomized, double-blind, international, multiethnic prospective study. HIV-infected patients with a positive HLAB*5701 genotype were excluded from abacavir prescription (prospective screening group) while other HIV-infected patients received abacavir without HLAB*5701 genotyping (control group). Patients with clinically suspected HSR underwent a confirmatory skin-patch testing (immunologically confirmed HSR). Prospective HLAB*5701 screening eliminated immunologically confirmed HSR with a negative predictive value of 100% and significantly reduced the rate of clinically suspected HSR from 7.8% to 3.4%\(^{15}\)
### Table 1  Summary of most relevant genetic determinants of antiretroviral drug pharmacokinetics and toxicity

| Drug/drug class | Gene, allele(s)/SNPs | SNP | Reported associations | Additional observations | Ref. |
|-----------------|----------------------|-----|-----------------------|------------------------|------|
| Abacavir        | HLA-B*5701           | 2395029 | ↑ risk of HSR         | Cost effective test and included in all ART guidelines | [11-13] |
| Tenofovir       | ABC2C (MRP2)12349G > A | 2273697 | ↑ risk of renal proximal tubulopathy in French populations | To be confirmed in other populations | [14,15] |
| Lamivudine, Zidovudine | ABC44 (MRP4) 3724G > A, 4313T > G | 2273697 | ↑ intracellular exposure of stavudine triphosphate | Uncertain clinical significance | [15,53] |
| NRTIs           | TNFa-308G > A        | 361525  | Earlier onset of lipoatrophy | Negative findings reported by others | [16-20] |
| Stavudine, NRTIs | IL1β +3954C > T      | 1143634 | ↓ risk of lipodystrophy in Spanish populations | To be confirmed in other populations | [20] |
| Stavudine, NRTIs | MMP1-16071G > 2G     | 1799750 | ↑ risk of lipodystrophy in Spanish populations | To be confirmed in other populations | [21] |
| APOE            | 1799750              |       | ↑ risk of renal proximal tubulopathy in French populations | To be confirmed in other populations | [11,13] |
| CYP2B6          | 516G > T             |       | ↑ modest plasma levels | Clinically no significant | [57] |

**NRTIs**

| Drug/drug class | Gene, allele(s)/SNPs | SNP | Reported associations | Additional observations | Ref. |
|-----------------|----------------------|-----|-----------------------|------------------------|------|
| NRTIs | Mitochondrial DNA (haplogroup T): MTND1*HON4216C, MTND2*HON4917G, 7028C > T, 1038G > A, 1336G > A | 2232582 | ↑ risk of lipodystrophy in Spanish populations | To be confirmed in other populations | [22] |
| NRTIs | HFE845G > A          |       | ↓ expression and ↑ activity genotypes | Negative findings reported by others | [28,29] |
| NRTIs | CFTR 1717-1G > A, IVS8 5T, SPINK-1 112C > T | 28357980 | ↑ risk of peripheral neuropathy | Tissue specific mitochondrial DNA depletion may also play some role in NRTI toxicity | [7,26,27] |
| Nevirapine      | HLA-DRB1*10101       | 1801131 | ↑ risk of lipodystrophy and peripheral neuropathy in Spanish populations | Stevens-Johnson syndrome or toxic epidermal necrolysis, but no other HSR | [37] |
| Nevirapine      | CYP2B6 983T > C      | 28399499 | ↑ risk of HSR in Malawian and Ugandan populations | Stevens-Johnson syndrome or toxic epidermal necrolysis, but no other HSR | [37] |
| Nevirapine, Efavirenz | ABCB1 (MDR1) 3435C > T | 1045642 | ↓ risk of hepatotoxicity | Negative findings reported by some authors | [35,36] |
| Efavirenz       | ABCB1 (MDR1) 3435C > T | 1045642 | ↓ plasma exposure | Negative findings reported by some authors | [51-53] |
| Efavirenz       | CYP2B6 *1/*1 haplotype |       | ↑ plasma concentrations | Stevens-Johnson syndrome or toxic epidermal necrolysis, but no other HSR | [45] |
| Efavirenz       | ABCB1 (MDR1) 3435C > T | 1045642 | ↑ HDL-cholesterol in Spanish populations | Stevens-Johnson syndrome or toxic epidermal necrolysis, but no other HSR | [45] |
| Efavirenz       | CYP2B6 516G > T, 983T > C | 3745274, 28399499 | ↑ plasma exposure and ↑ risk of CNS side effects | To be confirmed in other populations | [39,42,44, 46,48,49] |
| Efavirenz       | CYP2A6 48T > G, UGT1A1-1249T > A, 735A > G | 28399433, 28565062 | ↑ plasma concentrations in Black and White, but not in Hispanic individuals from the United States | To be confirmed in other populations | [47] |
| Efavirenz, Nevirapine | CYP2B6 516G > T, 983T > C | 28399499 | ↑ plasma exposure in African populations | To be confirmed in other populations | [43] |
| NNRTIs | ABCA1/Hepatic Lipase (LIPC)/Cholesteryl Ester Transfer Protein (CETP) | 4149313, 173539 | ↑ HDL-cholesterol in Spanish populations | To be confirmed in other populations | [61] |
| PIs | ABCA1 2982A > G | 3764261 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [60] |
| PIs | CETP 279A > G | 662799 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [60] |
| PIs | APOA4-1131T > C, 64G > C | 662799 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [60,62] |

**Antiretrovirals**

| Drug/drug class | Gene, allele(s)/SNPs | SNP | Reported associations | Additional observations | Ref. |
|-----------------|----------------------|-----|-----------------------|------------------------|------|
| Antiretrovirals | APOE2 > c3 haplotypes | 1801278 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [18] |
| Antiretrovirals | Insulin Receptor Substrate 1 (IRS1) | 1801278 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [18] |
| Antiretrovirals | UGT1A1*5b > 28 | 1801278 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [18] |
| Antiretrovirals | UGT1A1*28 | 1801278 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [18] |
| Antiretrovirals | UGT1A1*28 | 1801278 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [18] |

**Other**

| Drug/drug class | Gene, allele(s)/SNPs | SNP | Reported associations | Additional observations | Ref. |
|-----------------|----------------------|-----|-----------------------|------------------------|------|
| Indinavir       | UGT1A1*26*28, UGT1A1*28 | 1801278 | ↑ risk of hyperlipidemia | To be confirmed in other populations | [18] |
A recent meta-analysis has quantified the utility of HLAB*5701 testing[3]. The pooled odds ratio to detect abacavir-induced hypersensitivity on the basis of clinical criteria was 33.07 (95%CI: 22.33-48.97), while diagnostic odds ratio for detection of immunologically confirmed abacavir hypersensitivity was 1141 (95%CI: 409-3181). The meta-analysis also found that prospective HLA-B*5701 testing significantly reduced the incidence of abacavir-induced hypersensitivity. These results strongly support the clinical value of HLAB*5701 screening to avoid this condition. Therefore, HLAB*5701 genotyping has proved to be cost-effective and is already included as a routine tool in all ART guidelines.

**TENOFOVIR-ASSOCIATED RENAL PROXIMAL TUBULOPATHY**

Tenofovir, the most widely prescribed antiretroviral nowadays, has shown to produce renal proximal tubulopathy and bone toxicity in the long run. Tenofovir is introduced in the renal proximal tubular cell by the human organic anion transporters 1 and 3. Multidrug resistance-associated proteins (ABCC/MRP) 2 and 4 are located in the apical membranes of the proximal renal tubules and transport different drugs from the tubular cells to the urine. Variations in the genes that encode ABCC2 (MRP2) and ABCC4 (MRP4) proteins might block tenofovir excretion, enhancing intracellular tenofovir levels and increasing the risk of renal tubular toxicity. In fact, ABCC2 (MRP2)1249G > A SNP has been linked to tenofovir-associated renal proximal tubulopathy in HIV-infected French patients[24], a genetic association that needs to be confirmed in other populations. However, this finding needs further explanation because tenofovir is not a substrate for ABCC2, although this genetic variant might be in linkage disequilibrium with other SNPs in genes coding for unidentified factors that might exacerbate tenofovir toxicity[25].

**NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS-ASSOCIATED LIPODYSTROPHY**

British and Australian researchers have reported an association of the TNFα238G > A SNP with the earlier onset of lipatrophy in Caucasian HIV-infected patients under nucleoside reverse transcriptase inhibitors (NRTIs)[16,17], findings that have not been reproduced by others and need further confirmation[18-20]. IL1β + 3954C > T SNP, which decreases TNF-α plasma levels, has been associated with protection against lipodystrophy in HIV-infected Spanish individuals on stavudine[20].

Metalloproteases (MMPs), involved in extracellular matrix remodeling, can modulate adipocyte differentiation[8]. MMP1 - 16071G > 2G SNP induces increased MMP-1 plasma levels and has also been associated with lipodystrophy[21]. Increased lipopolysaccharide (LPS) plasma levels have been found in HIV-infected subjects. Lipopolysaccharide-binding protein (LBP), which transports LPS, has been linked to obesity and metabolic perturbations. LPS-binding protein (LBP)T > C SNP has been associated with lipodystrophy in Spanish HIV-infected individuals[22]. Specific SNPs in APOE and LDL receptor (LDLR) genes (rs 405509 and rs 2228671) have been related to trunk fat gain in HIV-infected individuals on ART. Insulin Receptor Substrate 1 (IRS1) SNPs (rs 1801278) has been associated with increased risk of limbs lipatrophy in the same Spanish Caucasian cohort[23]. Low-expression thymidylate synthase SNPs have also been associated with lipodystrophy in HIV-infected patients exposed to stavudine[24].

**NRTI-ASSOCIATED PERIPHERAL NEUROPATHY AND PANCREATITIS**

Low-expression thymidylate synthase SNPs have been related to increased stavudine triphosphate intracellular levels[24]. Methylenetetrahydrofolate reductase (MTHFR) 1298 A > C SNP has been associated with decreased activity of this enzyme and abnormalities of folate metabolism. The conjunction of a low-expression thymidylate synthase plus a MTHFR genotype in HIV-infected patients exposed to stavudine has been associated with the development of peripheral neuropathy and lipodystrophy in HIV-infected individuals[24,25]. Mitochondrial haplogroup T MTND1*LHON4216G and MTND2-6*LHON4917G genotypes and mitochondrial haplogroup T and 7028C > T, 10398G > A, and 13368G > A, SNPs were independently linked to increased susceptibility to...
NRTI-associated peripheral neuropathy\(^{26,27}\).

Iron transport is dysregulated in HIV infection and disorders of iron metabolism are linked to mitochondrial dysfunction and other neurodegenerative disorders. Hemochromatosis (HFE) gene SNPs alter the structure of HFE protein dysregulating intestinal iron absorption and its cellular transport. The carriage of the hemochromatosis (HFE) 845G>A SNP decreased the risk of NRTI-associated peripheral neuropathy, although this finding could not be reproduced by others\(^{28,29}\).

Cystic fibrosis transmembrane conductance regulator (CFTR) and serine protease inhibitor Kazal-1 (SPINK-1) mutations have been reported to increase the risk of pancreatitis in the general population. CFTR 1717-1G > A, IVS8 5T, and SPINK-1 112C > T SNPs are also frequent among HIV-positive patients suffering from acute pancreatitis, what suggests that these mutations might increase the susceptibility to pancreatitis if the patients are exposed to environmental risk factors such as thymidine NRTIs (stavudine, didanosine)\(^{30}\).

NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS-ASSOCIATED HSR AND HEPATITIS

Carriage of the class II allele HLA-DRB1*0101 has been linked with nevirapine-associated hepatotoxicity and HSR (but not with isolated rash) in HIV-infected Western Australians, especially in those individuals with a CD4 cell count > 25%\(^{31}\). A similar association with cutaneous hypersensitivity has also been reported for nevirapine and efavirenz in French Caucasian patients regardless of the CD4 values\(^{32}\).

Additional HLA alleles (HLA-cw8/HLA-B14) have been recently associated with nevirapine hepatotoxicity in Sardinian (Sardinia)\(^{33}\) and Japanese (Japan) HIV-infected patients. On the other hand, ABCB1 (MDR1) 3435C > T SNP has been found to decrease the risk of nevirapine-associated hepatotoxicity in multiethnic South African and American individuals\(^{35,36}\).

Likewise, an association between the CYP2B6 c.983T > C SNP and the development of nevirapine-induced Stevens-Johnson syndrome or toxic epidermal necrolysis, but not other hypersensitivity reactions, has been described in Malawian and Ugandan HIV-infected individuals\(^{37}\). Considering that this SNP is found in a small part of African populations, but not in Caucasians, these findings would point out to an ethnic-specific predisposing factor.

EFAVIREN扎 DISPOSITION AND CENTRAL NERVOUS SYSTEM SIDE EFFECTS

The cytochrome P450 (CYP) enzyme CYP2B6, primarily expressed in the liver, is involved in the biotransformation of efavirenz. CYP2B6 is one of the most polymorphic CYP genes in humans and its variants have shown to affect transcriptional regulation, splicing, mRNA and protein expression and catalytic activity\(^{38}\). CYP2B6 516G > T, 983T > C, 785A > G and 21563C > T SNPs have been associated with greater efavirenz plasma exposure and the development of more severe central nervous system (CNS) effects in different HIV-infected populations, including African and Thai patients\(^{39-46}\).

Likewise, increased efavirenz concentrations were associated with CYP2A6 -48T > G and with GG homozygosity for UGT2B7 735, a SNP of the microsomal enzyme uridine 5’-diphospho-glucuronosyltransferase (UGT), in Black and White, but not in Hispanic individuals from the United States\(^{47}\).

Also, CYP2B6 *6/*6 and *6/*26 carriers have been found to be associated with extremely high plasma concentrations of efavirenz in Japanese patients receiving standard doses of the drug\(^{48}\). Efavirenz doses were substantially reduced down to 200 mg/d in these patients without loss of antiviral efficacy and improvement in CNS symptoms. In addition, CYP2B6 516G > T genotyping has been found to reduce treatment costs, even considering only the sparing related to efavirenz dose reduction\(^{49}\). These two reports constitute examples of practical applications of genotyping and how pharmacogenomics may be useful for the management of HIV-infected individuals receiving antiretroviral drugs.

On the other hand, there are conflicting results about the effect of ABCB1 (MDR1) 3435C > T SNPs in decreasing efavirenz plasma exposure\(^{50-52}\), and an independent association between low efavirenz plasma concentrations and the CYP2B6 *1/*1 haplotype has also been found in patients receiving antituberculosis drugs\(^{53}\).

SNPs in other CYP enzymes such as CYP3A5 SNPs have also been associated with faster clearance of other antiretroviral drugs such as indinavir\(^{54}\).

ATAZANAVIR AND INDINAVIR-ASSOCIATED HYPERBLIRUBINURIA

The most common side effect of atazanavir is hyperbilirubinemia (observed in 20%-50% of patients exposed to this drug), a mostly minor disturbance that in 6% of cases can reach the range of clinical jaundice. Bilirubin needs to be conjugated with glucuronic acid to be excreted in the bile. This step is mediated by the microsomal enzyme UGT, which can cause unconjugated hyperbilirubinemia when its activity is reduced. Fifteen UGT isoforms with different substrate specificities, including the bilirubin-specific isoform UGT1A1, have been identified. UGT1A1*28 SNP has been associated with hyperbilirubinemia in HIV-infected Swiss and Spanish Caucasian individuals starting atazanavir or indinavir\(^{54,55}\), and this SNP might modify raltegravir plasma levels as well\(^{56}\).

Likewise, the P-glycoprotein, an efflux pump coded by the ABCB1 (MDR1) gene, is one of the most important transporters, especially expelling protease inhibitors outside the cell. ABCB1 (MDR1) SNPs might therefore influence atazanavir plasma concentration and, in fact,
**ABCB1 (MDR1) 3435C > T SNP has been associated with increased atazanavir plasma levels and hyperbilirubinemia in Spanish patients**\(^{[57]}\). Also, the intracellular/plasma concentration ratio of atazanavir was higher in GG carriers compared with those with GT and TT genotypes of the ABCB1 2677 G>T SNP in an Italian study\(^{[58]}\).

**PROTEASE INHIBITOR AND EFAVIRENZ-ASSOCIATED LIPIDIC ABNORMALITIES AND CORONARY ARTERY DISEASE RISK**

Hyperlipidemia is usually associated with ritonavir-boosted protease inhibitor therapy, but also with efavirenz use. ABCA1 SNPs have been linked to hyperlipidemia in HIV-infected patients treated with protease inhibitors or efavirenz. Thus, ABCA1 2962A > G SNP has been associated with increased HDL-cholesterol plasma levels after efavirenz treatment in Spanish patients\(^{[59]}\) and after ritonavir-boosted protease inhibitor therapy in the Swiss HIV cohort\(^{[60]}\). The contribution of other SNPs associated with plasma lipid levels in the general population has also been extensively studied in the same Swiss cohort and in other populations. APOA5, especially the -1131T > C and 64G > C SNPs, APOC3, especially the 482 C > T, 455 C > T and 3238 C > G SNPs, and APOE, especially the APOE ε2 and ε3 haplotypes and APOB SNP have been shown to contribute to increased plasma triglyceride, HDL-cholesterol and/or LDL-cholesterol levels during ART\(^{[61-63]}\). ABCA1, Hepatic Lipase (LIPC) and Cholesteryl Ester Transfer Protein (CETP) gene variant, especially the 279A > G SNP, were favorably associated with HDL-cholesterol when ART included non-nucleoside reverse transcriptase inhibitors (NNRTI). However an unfavorable effect on total-cholesterol and triglyceride levels was observed when ART included protease inhibitors\(^{[60]}\).

Recently, a large meta-analysis has shown the role in HIV-infected patients on ART of 23 SNPs associated with coronary artery disease (CAD) in the general population. The authors report that the effect of unfavorable genetic background was similar to traditional CAD risk factors and certain adverse antiretroviral exposures. The authors concluded that genetic testing might provide prognostic information complementary to the family history of CAD\(^{[64]}\).

**DISCUSSION AND CONCLUSION**

The field of pharmacogenetics is just beginning, but it will help the clinician to tailor and individualize ART for each HIV-infected patient. The gold standard to reach is the pharmacokinetic parameters of antiretroviral drugs. For instance, efavirenz dosage can be tailored for each individual knowing his/her CYP2B6 SNPs carriage, as CYP2B6 genetic variants seem to substantially modify efavirenz absorption and plasma levels. Moreover, genotyping has even shown to be a cost-effective measure, as the costs of the determination are compensated by savings related to efavirenz dose reduction and management of side-effects. Therefore, the clinician might adjust efavirenz doses to achieve maximal antiviral efficacy with minimal side effects. The same train of thought can be applied to UGT1A1 *28 and ABCB1 genotypings, to control the plasma and intracellular concentrations of atazanavir and to decrease the atazanavir-associated hyperbilirubinemia without modifying its antiviral effect.

The practical usefulness of other genetic testings is less clear at present, pending on the confirmation of the results observed in different studies and the discovery of new genetic variants associated with the pharmacokinetics and side-effects of antiretroviral drugs. Therefore, much more effort is needed to complete large size prospective studies with multiple SNPs genotyping, to reveal more clues about the role played by host genetics in ART response.

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Asensi V et al. Pharmacogenomics and antiretroviral therapy

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