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EDITORIAL

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

Victor Asensi, Julio Collazos, Eulalia Valle-Garay

Victor Asensi, Infectious Diseases-HIV Unit, Hospital Universitario Central de Asturias, Oviedo University School of Medicine, 33013 Oviedo, Spain

Julio Collazos, Infectious Diseases Unit, Hospital de Galdácano, 48960 Vizcaya, Spain

Eulalia Valle-Garay, Biochemistry and Molecular Biology Department, Oviedo University School of Medicine, 33006 Oviedo, Spain

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Correspondence to: Victor Asensi, MD, PhD, Infectious Diseases-HIV Unit, Hospital Universitario Central de Asturias, Oviedo University School of Medicine, Avenida de Roma s/n, 33013 Oviedo, Spain. vasensia@gmail.com
Telephone: +34-985-108000-36442

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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

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[1-10]. 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%[12].

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	*ABCC2 (MRP2)1249G > A*	2273697	↑ risk of renal proximal tubulopathy in French populations	To be confirmed in other populations	[14,15]
Lamivudine, Zidovudine	*ABCC4 (MRP4) 3724G > A, 4131T > G*	2273697 3742106	↑ intracellular exposure of stavudine triphosphate	Uncertain clinical significance	[15,53]
NRTIs	*TNFα238G > 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]
NRTIs	*MMP1-16071G > 2G*	1799750	↑ risk of lipodystrophy in Spanish populations	To be confirmed in other populations	[21]
Stavudine, Zidovudine	*TS* ↓ expression and *MTHFR 1298 A > C* ↑ activity genotypes	1801131	↑ risk of lipodystrophy and peripheral neuropathy in Spanish populations	To be confirmed in other populations	[24,25]
NRTIs	*LPS-binding protein (LBP) T > C*	2232582	↑ risk of lipodystrophy in Spanish population	To be confirmed in other populations	[22]
NRTIs	Mitochondrial DNA (haplogroup T): *MTND1*LHON4216C, MTND2*LHON4917G, 7028C > T, 10398G > A, 13368G > A*	28357980	↑ risk of peripheral neuropathy	Tissue specific mitochondrial DNA depletion may also play some role in NRTI toxicity	[7,26,27]
NRTIs	*HFE845G > A*		↓ risk of peripheral neuropathy	Negative findings reported by others	[28,29]
NRTIs	*CFTR 1717-1G > A, IVS8 5T, SPINK-1 112C > T*		↑ risk of pancreatitis	Reported also in the general population	[30]
Nevirapine	*HLA-DRB1*0101*		↑ risk of HSR and hepatotoxicity	CD4 cell % > 25% associated with ↑ risk	[31,32]
Nevirapine	*HLA-cw8*		↑ risk of HSR in Italian and Japanese populations		[33,34]
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		[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	In patients receiving antituberculosis treatment	[45]
Efavirenz	*ABCB1 (MDR1 3435C > T*	1045642	↑ HDL-cholesterol in Spanish populations	To be confirmed in other populations	[60]
Efavirenz	*CYP2B6 516G > T, 983T > C*	3745274 28399499	↑ plasma exposure and ↑ risk of CNS side effects	Reports of successful efavirenz dose individualization	[39,42,44, 46,48,49]
Efavirenz	*CYP2A6 48T > G, UGT2B7 735A > G*	28399433 28365062	↑ 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 3764261	↑ LDL-cholesterol in Spanish populations	To be confirmed in other populations	[61]
PIs	*ABCA1 2962A > G*		↑ risk of hyperlipidemia		[60]
PIs	*CETP 279A > G*		↑ risk of hyperlipidemia		[60]
PIs	APOA5-1131T > C, 64G > C	662799	↑ risk of hyperlipidemia		[60,62]
Antiretrovirals	*APOE/LDL Receptor (LDLR)*	405509 2228671	↑ risk of trunk fat gain in Spanish populations	To be confirmed in other populations	[23]
PIs	*APOC3 482 C > T, 455 C > T, 3238 C > G*	2854117 2854116 5128	↑ risk of hyperlipidemia		[18,63]
PIs	*APOE ε2 and ε3* haplotypes		↑ risk of hyperlipidemia		[18]
Antiretrovirals	*Insulin Receptor Substrate 1 (IRS1)*	1801278	↑ risk of limbs lipoatrophy in Spanish populations	To be confirmed in other populations	[23]
Raltegravir	*UGT1A1*28/*28*		↑ modestly plasma levels	Clinically no significant	[57]
Atazanavir, Indinavir	*UGT1A1*28*		Unconjugated hyperbilirubinemia and jaundice		[54,55]

Atazanavir	*ABCB1 (MDR1) 3435C > T*	1045642	Unconjugated hyperbilirubinemia and jaundice	↑ plasma levels	[57]
Atazanavir	*ABCB1 (MDR1) 2677 G > T*	2032582	↑ intracellular/plasma concentration ratios	For GG homozygous as compared with GT and TT genotypes	[58]
Nelfinavir	*CYP2C19*2 (681G > A)*	4244285	↑ drug exposure in Italian and multiracial Americans	To be confirmed in other populations	[39]
Indinavir	*CYP3A5*3 (A6986G)*		↑ oral clearance	To be confirmed in other populations	[53]
Maraviroc	*CCR5WT/Δ32*		No effect on virologic response	Clinically not significant	[7]

SNP: Single-nucleotide polymorphisms; HSR: Hypersensitive reaction; ART: Antiretroviral therapy; CNS: Central nervous system; NRTIs: Nucleoside reverse transcriptase inhibitors; NNRTIs: Non-nucleoside reverse transcriptase inhibitors; PIs: Protease inhibitors.

A recent meta-analysis has quantified the utility of *HLAB*5701* testing[13]. 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[14], 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[15].

NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS-ASSOCIATED LIPODYSTROPHY

British and Australian researchers have reported an association of the *TNFα238G > A* SNP with the earlier onset of lipoatrophy in Caucasian HIV-infected patients under nucleoside reverse transcriptase inhibitors (NRTI)[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, have 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 lipoatrophy in the same Spanish Caucasian cohort[23]. Low-expression thymidylate synthase SNPs have also been associated with lipodystrophy in HIV-infected patients exposed to estavudine[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*LHON4216C* and *MTND2*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[7,26,27].

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[33] and Japanese[34] 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.

EFAVIRENZ 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[45].

SNPs in other CYP enzymes such as *CYP3A5* SNPs have also been associated with faster clearance of other antiretroviral drugs such as indinavir[53].

ATAZANAVIR AND INDINAVIR-ASSOCIATED HYPERBILIRRUBINEMIA

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 UGTA1, 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[18,60-63].

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[62].

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 currently the *HLAB*5701* genotyping, which has proven to be highly efficacious to prevent the abacavir-associated HSR and, consequently, it has been included as a routine tool for the care of HIV-infected patients in all ART guidelines.

In this short review we have focused more on the possible role of pharmacogenetics to prevent ART side effects than in pharmacokinetics. However, the reader must be aware of the value of pharmacogenetics to modulate 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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