**Name of journal: *World Journal of Virology***

**ESPS Manuscript NO: 16392**

**Columns: Editorial**

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

Asensi V *et al.*Pharmacogenomics and antiretroviral therapy

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, Hospital Universitario Central de Asturias, Oviedo University School of Medicine, Calle San Francisco, 1, 33013 Oviedo, Spain

**Author contributions:** All authors contributed to this paper.

**Conflict-of-interest:** The authors do not have any conflict of interest related to this paper.

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**Correspondence to: Victor Asensi, MD, PhD,** Infectious Diseases-HIV Unit, Hospital Universitario Central de Asturias, Oviedo University School of Medicine,33013 Oviedo, Spain.e-mail:vasensia@gmail.com

**Telephone:** +34-985-108000-36442

**Received:** January 15, 2015

**Peer-review started:** January 16, 2015

**First decision:** April 27, 2015

**Revised:** May 8, 2015

**Accepted:** June 9, 2015

**Article in press:**

**Published online:**

**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.

Asensi V, Collazos J, Valle-Garay E. Can antiretroviral therapy be tailored to each human immunodeficiency virus-infected individual? Role of pharmacogenomics. *World J Virol* 2015; In press

**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].

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 andis 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* SNPhas 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 becausetenofovir 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/day 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* SNPshave been linked tohyperlipidemia 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* haplotypesand *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 ARTincluded 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.

**REFERENCES**

1 **Pirmohamed M**, Back DJ. The pharmacogenomics of HIV therapy. *Pharmacogenomics J* 2001; **1**: 243-253 [PMID: 11908767]

2 **Fox J**, Boffito M, Winston A. The clinical implications of antiretroviral pharmacogenomics. *Pharmacogenomics* 2006; **7**: 587-596 [PMID: 16753006 DOI: 10.2217/14622416.7.4.587]

3 **Quirk E**, McLeod H, Powderly W. The pharmacogenetics of antiretroviral therapy: a review of studies to date. *Clin Infect Dis* 2004; **39**: 98-106 [PMID: 15206060 DOI: 10.1086/421557]

4 **Tarr PE**, Telenti A. Toxicogenetics of antiretroviral therapy: genetic factors that contribute to metabolic complications. *Antivir Ther* 2007; **12**: 999-1013 [PMID: 18018758]

5 **Phillips EJ**, Mallal SA. Pharmacogenetics and the potential for the individualization of antiretroviral therapy. *Curr Opin Infect Dis* 2008; **21**: 16-24 [PMID: 18192781 DOI: 10.1097/QCO.0b013e]

6 **Vidal F**, Gutiérrez F, Gutiérrez M, Olona M, Sánchez V, Mateo G, Peraire J, Viladés C, Veloso S, López-Dupla M, Domingo P. Pharmacogenetics of adverse effects due to antiretroviral drugs. *AIDS Rev* 2010; **12**: 15-30 [PMID: 20216907]

7 **Tozzi V**. Pharmacogenetics of antiretrovirals. *Antiviral Res* 2010; **85**: 190-200 [PMID: 19744523 DOI: 10.1016/j.antiviral.2009.09.001]

8 **Vidal F**, Domingo P, Viladés C, Peraire J, Arnedo M, Alcamí J, Leal M, Villarroya F, Gatell JM. Pharmacogenetics of the lipodystrophy syndrome associated with HIV infection and combination antiretroviral therapy. *Expert Opin Drug Metab Toxicol* 2011; **7**: 1365-1382 [PMID: 21999362 DOI: 10.1517/17425255.2011.621941]

9 **Pavlos R**, Phillips EJ. Individualization of antiretroviral therapy. *Pharmgenomics Pers Med* 2012; **5**: 1-17 [PMID: 23226059 DOI: 10.2147/PGPM.S15303]

10 **Arab-Alameddine M**, Décosterd LA, Buclin T, Telenti A, Csajka C. Antiretroviral drug toxicity in relation to pharmacokinetics, metabolic profile and pharmacogenetics. *Expert Opin Drug Metab Toxicol* 2011; **7**:609-622 [PMID: 21500966 DOI: 10.1517/17425255.2011.562891]

11 **Mallal S**, Nolan D, Witt C, Masel G, Martin AM, Moore C, Sayer D, Castley A, Mamotte C, Maxwell D, James I, Christiansen FT. Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; **359**: 727-732 [PMID: 11888582 DOI: 10.1016/S0140-6736(02)07873-X]

12 **Mallal S**, Phillips E, Carosi G, Molina JM, Workman C, Tomazic J, Jägel-Guedes E, Rugina S, Kozyrev O, Cid JF, Hay P, Nolan D, Hughes S, Hughes A, Ryan S, Fitch N, Thorborn D, Benbow A. HLA-B\*5701 screening for hypersensitivity to abacavir. *N Engl J Med* 2008; **358**: 568-579 [PMID: 18256392 DOI: 10.1056/NEJMoa0706135]

13 **Cargnin S**, Jommi C, Canonico PL, Genazzani AA, Terrazzino S. Diagnostic accuracy of HLA-B\*57: 01 screening for the prediction of abacavir hypersensitivity and clinical utility of the test: a meta-analytic review. *Pharmacogenomics* 2014; **15**: 963-976 [PMID: 24956250 DOI: 10.2217/pgs.14.52]

14 **Izzedine H**, Hulot JS, Villard E, Goyenvalle C, Dominguez S, Ghosn J, Valantin MA, Lechat P, Deray AG. Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy. *J Infect Dis* 2006; **194**: 1481-1491 [PMID: 17083032 DOI: 10.1086/508546]

15 **Moss DM**, Neary M, Owen A. The role of drug transporters in the kidney: lessons from tenofovir. *Front Pharmacol* 2014; **5**: 248 [PMID: 25426075 DOI: 10.3389/fphar.2014.00248]

16 **Maher B**, Alfirevic A, Vilar FJ, Wilkins EG, Park BK, Pirmohamed M. TNF-alpha promoter region gene polymorphisms in HIV-positive patients with lipodystrophy. *AIDS* 2002; **16**: 2013-2018 [PMID: 12370499 DOI: 10.1097/00002030-200210180-00005]

17 **Nolan D**, Moore C, Castley A, Sayer D, Mamotte C, John M, James I, Mallal S. Tumour necrosis factor-alpha gene -238G/A promoter polymorphism associated with a more rapid onset of lipodystrophy. *AIDS* 2003; **17**: 121-123 [PMID: 12478078]

18 **Tarr PE**, Taffé P, Bleiber G, Furrer H, Rotger M, Martinez R, Hirschel B, Battegay M, Weber R, Vernazza P, Bernasconi E, Darioli R, Rickenbach M, Ledergerber B, Telenti A. Modeling the influence of APOC3, APOE, and TNF polymorphisms on the risk of antiretroviral therapy-associated lipid disorders. *J Infect Dis* 2005; **191**: 1419-1426 [PMID: 15809899 DOI: 10.1086/429295]

19 **Veloso S**, Olona M, Peraire J, Viladés C, Pardo P, Domingo P, Asensi V, Broch M, Aguilar C, López-Dupla M, Aragonés G, Garcia-Pardo G, Sirvent JJ, Vendrell J, Richart C, Vidal F. No relationship between TNF-α genetic variants and combination antiretroviral therapy-related lipodystrophy syndrome in HIV type 1-infected patients: a case-control study and a meta-analysis. *AIDS Res Hum Retroviruses* 2011; **27**: 143-152 [PMID: 20854131 DOI: 10.1089/aid.2009.0312]

20 **Asensi V**, Rego C, Montes AH, Collazos J, Carton JA, Castro MG, Alvarez V, Fernández C, Maradona JA, Valle-Garay E. IL-1beta (+3954C/T) polymorphism could protect human immunodeficiency virus (HIV)-infected patients on highly active antiretroviral treatment (HAART) against lipodystrophic syndrome. *Genet Med* 2008; **10**: 215-223 [PMID: 18344712 DOI: 10.1097/GIM.0b013e3181632713]

21 **Montes AH**, Valle-Garay E, Suarez-Zarracina T, Melon S, Martinez E, Carton JA, Collazos J, Asensi V. The MMP1 (-16071G/2G) single nucleotide polymorphism associates with the HAART-related lipodystrophic syndrome. *AIDS* 2010; **24**: 2499-2506 [PMID: 20852404 DOI: 10.1097/QAD.0b013e32833e922c]

22 **Viladés C**, Escoté X, López-Dupla M, Martinez E, Domingo P, Asensi V, Leal M, Peraire J, Inza MI, Arnedo M, Gutiérrez M, Valle-Garay E, Ferrando-Martinez S, Olona M, Alba V, Sirvent JJ, Gatell JM, Vidal F. Involvement of the LPS-LPB-CD14-MD2-TLR4 inflammation pathway in HIV-1/HAART-associated lipodystrophy syndrome (HALS). *J Antimicrob Chemother* 2014; **69**: 1653-1659 [PMID: 24535275 DOI: 10.1093/jac/dku032]

23 **Egaña-Gorroño L**, Martínez E, Pérez I, Escribà T, Domingo P, Gatell JM, Arnedo M. Contribution of genetic background and antiretroviral therapy to body fat changes in antiretroviral-naive HIV-infected adults. *J Antimicrob Chemother* 2014; **69**: 3076-3084 [PMID: 25185137 DOI: 10.1093/jac/dku266]

24 **Domingo** **P**, Mateo MG, Pruvost A, Torres F, Salazar J, Gutierrez MD, Cabeza MC, Domingo JC, Fernandez I, Villarroya F, Vidal F, Baiget M, de la Calle-Martín O. Polymorphisms of Pyrimidine Pathway Enzymes Encoding Genes and HLA-B\*40∶01 Carriage in Stavudine-Associated Lipodystrophy in HIV-Infected Patients. *PLoS One* 2013; **8**: e67035 [PMID: 23840581 DOI: 10.1371/journal.pone.0067035]

25 **Domingo P**, Cabeza Mdel C, Torres F, Salazar J, Gutierrez Mdel M, Mateo MG, Martínez E, Domingo JC, Fernandez I, Villarroya F, Ribera E, Vidal F, Baiget M. Association of thymidylate synthase polymorphisms with acute pancreatitis and/or peripheral neuropathy in HIV-infected patients on stavudine-based therapy. *PLoS One* 2013; **8**: e57347 [PMID: 23468971 DOI: 10.1371/journal.pone.0057347]

26 **Hulgan T**, Haas DW, Haines JL, Ritchie MD, Robbins GK, Shafer RW, Clifford DB, Kallianpur AR, Summar M, Canter JA. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. *AIDS* 2005; **19**: 1341-1349 [PMID: 16103764 DOI: 10.1038/sj.tpj.6500470]

27 **Canter JA**, Haas DW, Kallianpur AR, Ritchie MD, Robbins GK, Shafer RW, Clifford DB, Murdock DG, Hulgan T. The mitochondrial pharmacogenomics of haplogroup T: MTND2\*LHON4917G and antiretroviral therapy-associated peripheral neuropathy. *Pharmacogenomics J* 2008; **8**: 71-77 [PMID: 17684475]

28 **Kallianpur AR**, Hulgan T, Canter JA, Ritchie MD, Haines JL, Robbins GK, Shafer RW, Clifford DB, Haas DW. Hemochromatosis (HFE) gene mutations and peripheral neuropathy during antiretroviral therapy. *AIDS* 2006; **20**: 1503-1513 [PMID: 16847405 DOI: 10.1097/01.aids.0000237366.56864.3c]

29 **Costarelli S**, Torti C, Gatta LB, Tinelli C, Lapadula G, Quiros-Roldan E, Izzo I, Castelnuovo F, Biasiotto G, Arosio P, Carosi G. No evidence of relation between peripheral neuropathy and presence of hemochromatosis gene mutations in HIV-1-positive patients. *J Acquir Immune Defic Syndr* 2007; **46**: 255-256 [PMID: 17895769 DOI: 10.1097/QAI.0b013e3180ed44d9]

30 **Felley C**, Morris MA, Wonkam A, Hirschel B, Flepp M, Wolf K, Furrer H, Battegay M, Bernasconi E, Telenti A, Frossard JL. The role of CFTR and SPINK-1 mutations in pancreatic disorders in HIV-positive patients: a case-control study. *AIDS* 2004; **18**: 1521-1527 [PMID: 15238770]

31 **Martin AM**, Nolan D, James I, Cameron P, Keller J, Moore C, Phillips E, Christiansen FT, Mallal S. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1\*0101 and abrogated by low CD4 T-cell counts. *AIDS* 2005; **19**: 97-99 [PMID: 15627041]

32 **Vitezica ZG**, Milpied B, Lonjou C, Borot N, Ledger TN, Lefebvre A, Hovnanian A. HLA-DRB1\*01 associated with cutaneous hypersensitivity induced by nevirapine and efavirenz. *AIDS* 2008; **22**: 540-541 [PMID: 18301070 DOI: 10.1097/QAD.0b013e3282f37812]

33 **Littera R**, Carcassi C, Masala A, Piano P, Serra P, Ortu F, Corso N, Casula B, La Nasa G, Contu L, Manconi PE. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. *AIDS* 2006; **20**: 1621-1626 [PMID: 16868443 DOI: 10.1097/01.aids.0000238408]

34 **Gatanaga H**, Yazaki H, Tanuma J, Honda M, Genka I, Teruya K, Tachikawa N, Kikuchi Y, Oka S. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. *AIDS* 2007; **21**: 264-265 [PMID: 17197830 DOI: 10.1097/QAD.0b013e32801199d9]

35 **Haas DW**, Bartlett JA, Andersen JW, Sanne I, Wilkinson GR, Hinkle J, Rousseau F, Ingram CD, Shaw A, Lederman MM, Kim RB. Pharmacogenetics of nevirapine-associated hepatotoxicity: an Adult AIDS Clinical Trials Group collaboration. *Clin Infect Dis* 2006; **43**: 783-786 [PMID: 16912957 DOI: 10.1086/507097]

36 **Ritchie MD**, Haas DW, Motsinger AA, Donahue JP, Erdem H, Raffanti S, Rebeiro P, George AL, Kim RB, Haines JL, Sterling TR. Drug transporter and metabolizing enzyme gene variants and nonnucleoside reverse-transcriptase inhibitor hepatotoxicity. *Clin Infect Dis* 2006; **43**: 779-782 [PMID: 16912956 DOI: 10.1086/507101]

37 **Carr DF**, Chaponda M, Cornejo Castro EM, Jorgensen AL, Khoo S, Van Oosterhout JJ, Dandara C, Kampira E, Ssali F, Munderi P, Lalloo DG, Heyderman RS, Pirmohamed M. CYP2B6 c.983T& gt; C polymorphism is associated with nevirapine hypersensitivity in Malawian and Ugandan HIV populations. *J Antimicrob Chemother* 2014; **69**: 3329-3334 [PMID: 25147095 DOI: 10.1093/jac/dku315]

38 **Zanger UM**, Klein K. Pharmacogenetics of cytochrome P450 2B6 (CYP2B6): advances on polymorphisms, mechanisms, and clinical relevance. *Front Genet* 2013; **4**: 24 [PMID: 23467454 DOI: 10.3389/fgene.2013.00024]

39 **Haas DW**, Smeaton LM, Shafer RW, Robbins GK, Morse GD, Labbe L, Wilkinson GR, Clifford DB, D'Aquila RT, De Gruttola V, Pollard RB, Merigan TC, Hirsch MS, George AL, Donahue JP, Kim RB. Pharmacogenetics of long-term responses to antiretroviral regimens containing Efavirenz and/or Nelfinavir: an Adult Aids Clinical Trials Group Study. *J Infect Dis* 2005; **192**: 1931-1942 [PMID: 16267764 DOI: 10.1086/497610]

40 **Marzolini C**, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001; **15**: 71-75 [PMID: 11192870 DOI: 10.1038/sj.clpt.6100072]

41 **Rotger M**, Tegude H, Colombo S, Cavassini M, Furrer H, Décosterd L, Blievernicht J, Saussele T, Günthard HF, Schwab M, Eichelbaum M, Telenti A, Zanger UM. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther* 2007; **81**: 557-566 [PMID: 17235330]

42 **Wyen C**, Hendra H, Vogel M, Hoffmann C, Knechten H, Brockmeyer NH, Bogner JR, Rockstroh J, Esser S, Jaeger H, Harrer T, Mauss S, van Lunzen J, Skoetz N, Jetter A, Groneuer C, Fätkenheuer G, Khoo SH, Egan D, Back DJ, Owen A. Impact of CYP2B6 983T& gt; C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. *J Antimicrob Chemother* 2008; **61**: 914-918 [PMID: 18281305 DOI: 10.1093/jac/dkn029]

43 **Wang J**, Sönnerborg A, Rane A, Josephson F, Lundgren S, Ståhle L, Ingelman-Sundberg M. Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. *Pharmacogenet Genomics* 2006; **16**: 191-198 [PMID: 16495778 DOI: 10.1097/01.fpc.0000189797.03845.90]

44 **Aurpibul L**, Chotirosniramit N, Sugandhavesa P, Kosashunhanan N, Thetket S, Supindham T, Piyamongkol W, Supparatpinyo K. Correlation of CYP2B6-516G & gt; T Polymorphism with Plasma Efavirenz Concentration and Depression in HIV-Infected Adults in Northern Thailand. *Curr HIV Res* 2012; **10**: 653-660 [PMID: 22950382 DOI: 10.2174/157016212803901338]

45 **Manosuthi W**, Sukasem C, Lueangniyomkul A, Mankatitham W, Thongyen S, Nilkamhang S, Manosuthi S, Sungkanuparph S. Impact of pharmacogenetic markers of CYP2B6, clinical factors, and drug-drug interaction on efavirenz concentrations in HIV/tuberculosis-coinfected patients. *Antimicrob Agents Chemother* 2013; **57**: 1019-1024 [PMID: 23254426 DOI: 10.1128/AAC.02023-12]

46[**Sinxadi PZ**](http://www.ncbi.nlm.nih.gov/pubmed/?term=Sinxadi%20PZ%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [Leger PD](http://www.ncbi.nlm.nih.gov/pubmed/?term=Leger%20PD%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [McIlleron H](http://www.ncbi.nlm.nih.gov/pubmed/?term=McIlleron%20H%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [Smith P](http://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20P%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [Dave JA](http://www.ncbi.nlm.nih.gov/pubmed/?term=Dave%20JA%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [Levitt NS](http://www.ncbi.nlm.nih.gov/pubmed/?term=Levitt%20NS%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [Maartens G](http://www.ncbi.nlm.nih.gov/pubmed/?term=Maartens%20G%5BAuthor%5D&cauthor=true&cauthor_uid=25611810), [Haas DW](http://www.ncbi.nlm.nih.gov/pubmed/?term=Haas%20DW%5BAuthor%5D&cauthor=true&cauthor_uid=25611810). Pharmacogenetics of plasma efavirenz exposure in HIV-infected adults and children in south Africa. *Br J Clin Pharmacol* 2015; Epub ahead of print [PMID: 25611810 DOI: 10.1111/bcp.12590]

47 **Haas DW**, Kwara A, Richardson DM, Baker P, Papageorgiou I, Acosta EP, Morse GD, Court MH. Secondary metabolism pathway polymorphisms and plasma efavirenz concentrations in HIV-infected adults with CYP2B6 slow metabolizer genotypes. *J Antimicrob Chemother* 2014; **69**: 2175-2182 [PMID: 24729586 DOI: 10.1093/jac/dku110]

48 **Gatanaga H**, Hayashida T, Tsuchiya K, Yoshino M, Kuwahara T, Tsukada H, Fujimoto K, Sato I, Ueda M, Horiba M, Hamaguchi M, Yamamoto M, Takata N, Kimura A, Koike T, Gejyo F, Matsushita S, Shirasaka T, Kimura S, Oka S. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 \*6 and \*26. *Clin Infect Dis* 2007; **45**: 1230-1237 [PMID: 17918089 DOI: 10.1086/522175]

49 **Martín AS**, Gómez AI, García-Berrocal B, Figueroa SC, Sánchez MC, Calvo Hernández MV, Gonzalez-Buitrago JM, Valverde Merino MP, Tovar CB, Martín AF, Isidoro-García M. Dose reduction of efavirenz: an observational study describing cost-effectiveness, pharmacokinetics and pharmacogenetics. *Pharmacogenomics* 2014; **15**: 997-1006 [PMID: 24956253 DOI: 10.2217/pgs.14.48]

50 **Marzolini C**, Paus E, Buclin T, Kim RB. Polymorphisms in human MDR1 (P-glycoprotein): recent advances and clinical relevance. *Clin Pharmacol Ther* 2004; **75**: 13-33 [PMID: 14749689 DOI: 10.1016/j.clpt.2003.09.012]

51 **Fellay J**, Marzolini C, Meaden ER, Back DJ, Buclin T, Chave JP, Decosterd LA, Furrer H, Opravil M, Pantaleo G, Retelska D, Ruiz L, Schinkel AH, Vernazza P, Eap CB, Telenti A. Response to antiretroviral treatment in HIV-1-infected individuals with allelic variants of the multidrug resistance transporter 1: a pharmacogenetics study. *Lancet* 2002; **359**: 30-36 [PMID: 11809184 DOI: 10.1016/S0140-6736(02)07276-8]

52 **Winzer R**, Langmann P, Zilly M, Tollmann F, Schubert J, Klinker H, Weissbrich B. No influence of the P-glycoprotein polymorphisms MDR1 G2677T/A and C3435T on the virological and immunological response in treatment naïve HIV-positive patients. *Ann Clin Microbiol Antimicrob* 2005; **4**: 3 [PMID: 15659247 DOI: 10.1186/1476-0711-4-3]

53 **Anderson PL**, Lamba J, Aquilante CL, Schuetz E, Fletcher CV. Pharmacogenetic characteristics of indinavir, zidovudine, and lamivudine therapy in HIV-infected adults: a pilot study. *J Acquir Immune Defic Syndr* 2006; **42**: 441-449 [PMID: 16791115 DOI: 10.1097/01.qai.0000225013.53568.69]

54 **Rotger M**, Taffe P, Bleiber G, Gunthard HF, Furrer H, Vernazza P, Drechsler H, Bernasconi E, Rickenbach M, Telenti A. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. *J Infect Dis* 2005; **192**: 1381-1386 [PMID: 16170755 DOI: 10.1086/466531]

55 **Rodríguez-Nóvoa S**, Martín-Carbonero L, Barreiro P, González-Pardo G, Jiménez-Nácher I, González-Lahoz J, Soriano V. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. *AIDS* 2007; **21**: 41-46 [PMID: 17148966 DOI: 10.1097/QAD.0b013e328011d7c1]

56 **Wenning LA**, Petry AS, Kost JT, Jin B, Breidinger SA, DeLepeleire I, Carlini EJ, Young S, Rushmore T, Wagner F, Lunde NM, Bieberdorf F, Greenberg H, Stone JA, Wagner JA, Iwamoto M. Pharmacokinetics of raltegravir in individuals with UGT1A1 polymorphisms. *Clin Pharmacol Ther* 2009; **85**: 623-627 [PMID: 19279563 DOI: 10.1038/clpt.2009.12]

57 **Rodríguez Nóvoa S**, Barreiro P, Rendón A, Barrios A, Corral A, Jiménez-Nacher I, González-Lahoz J, Soriano V. Plasma levels of atazanavir and the risk of hyperbilirubinemia are predicted by the 3435C--& gt; T polymorphism at the multidrug resistance gene 1. *Clin Infect Dis* 2006; **42**: 291-295 [PMID: 16355344 DOI: 10.1086/499056]

58 **D'Avolio A**, Carcieri C, Cusato J, Simiele M, Calcagno A, Allegra S, Sciandra M, Trentini L, Di Perri G, Bonora S. Intracellular accumulation of atazanavir/ritonavir according to plasma concentrations and OATP1B1, ABCB1 and PXR genetic polymorphisms. *J Antimicrob Chemother* 2014; **69**: 3061-3066 [PMID: 24997317 DOI: 10.1093/jac/dku234]

59 **Alonso-Villaverde C**, Coll B, Gómez F, Parra S, Camps J, Joven J, Masana L. The efavirenz-induced increase in HDL-cholesterol is influenced by the multidrug resistance gene 1 C3435T polymorphism. *AIDS* 2005; **19**: 341-342 [PMID: 15718846]

60 **Arnedo M**, Taffé P, Sahli R, Furrer H, Hirschel B, Elzi L, Weber R, Vernazza P, Bernasconi E, Darioli R, Bergmann S, Beckmann JS, Telenti A, Tarr PE. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. *Pharmacogenet Genomics* 2007; **17**: 755-764 [PMID: 17700364 DOI: 10.1097/FPC.0b013e32814db8b7]

61 **Egaña-Gorroño L**, Martínez E, Cormand B, Escribà T, Gatell J, Arnedo M. Impact of genetic factors on dyslipidemia in HIV-infected patients starting antiretroviral therapy. *AIDS* 2013; **27**: 529-538 [PMID: 23262498 DOI: 10.1097/QAD.0b013e32835d0da1]

62 **Guardiola M**, Ferré R, Salazar J, Alonso-Villaverde C, Coll B, Parra S, Masana L, Ribalta J. Protease inhibitor-associated dyslipidemia in HIV-infected patients is strongly influenced by the APOA5-1131T-& gt; C gene variation. *Clin Chem* 2006; **52**: 1914-1919 [PMID: 16887900 DOI: 10.1373/clinchem.2006.069583]

63 **Fauvel J**, Bonnet E, Ruidavets JB, Ferrières J, Toffoletti A, Massip P, Chap H, Perret B. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. *AIDS* 2001; **15**: 2397-2406 [PMID: 11740190]

64 **Rotger M**, Glass TR, Junier T, Lundgren J, Neaton JD, Poloni ES, van 't Wout AB, Lubomirov R, Colombo S, Martinez R, Rauch A, Günthard HF, Neuhaus J, Wentworth D, van Manen D, Gras LA, Schuitemaker H, Albini L, Torti C, Jacobson LP, Li X, Kingsley LA, Carli F, Guaraldi G, Ford ES, Sereti I, Hadigan C, Martinez E, Arnedo M, Egaña-Gorroño L, Gatell JM, Law M, Bendall C, Petoumenos K, Rockstroh J, Wasmuth JC, Kabamba K, Delforge M, De Wit S, Berger F, Mauss S, de Paz Sierra M, Losso M, Belloso WH, Leyes M, Campins A, Mondi A, De Luca A, Bernardino I, Barriuso-Iglesias M, Torrecilla-Rodriguez A, Gonzalez-Garcia J, Arribas JR, Fanti I, Gel S, Puig J, Negredo E, Gutierrez M, Domingo P, Fischer J, Fätkenheuer G, Alonso-Villaverde C, Macken A, Woo J, McGinty T, Mallon P, Mangili A, Skinner S, Wanke CA, Reiss P, Weber R, Bucher HC, Fellay J, Telenti A, Tarr PE. Contribution of genetic background, traditional risk factors, and HIV-related factors to coronary artery disease events in HIV-positive persons. *Clin Infect Dis* 2013; **57**: 112-121 [PMID: 23532479 DOI: 10.1093/cid/cit196]

**P-Reviewer:** Bare P, Bisen P, Cruciani M, Davis DA, Yu G **S-Editor:** Ji FF **L-Editor: E-Editor:**

**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* | 22736973742106 | ↑ 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 (haplogroupT): *MTND1\*LHON4216C, MTND2\*LHON4917G, 7028C > T,10398G > A,13368G > A,* | [28357980](http://www.snpedia.com/index.php/Rs28357980) | ↑ 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* | 374527428399499 | ↑ 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)* | 41493131735393764261 | ↑ 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](http://www.snpedia.com/index.php/Rs662799)  | ↑ risk of hyperlipidemia |  | [60,62] |
| Antiretrovirals  | *APOE/LDL Receptor (LDLR)* | 4055092228671 | ↑ 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](http://www.snpedia.com/index.php/Rs2854117)[2854116](http://www.snpedia.com/index.php/Rs2854116)[5128](http://www.snpedia.com/index.php/Rs5128) | ↑ 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.