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Pharmacogenetics of Adverse Effects Due To Antiretroviral Drugs

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Abstract

The availability of highly active antiretroviral therapy has markedly improved the survival rate and quality of life in patients infected with HIV. At present, however, there is still no cure for HIV and those undergoing treatment have to do so for life. The use of antiretroviral drugs has been associated with several toxicities that limit their success. Some acute and chronic toxicities associated with these drugs include hypersensitivity reactions, neurotoxicity, nephropathy, liver damage, and the appearance of body fat redistribution syndrome and the different metabolic alterations that accompany it. Some of these toxicities are family- or even drug-specific. Since not all patients that take a particular antiretroviral medication develop the adverse effect that has been attributed to that drug, it has therefore been postulated that there must be a genetically conditioned individual predisposition to developing the adverse effect. Pharmacogenetics is the science that studies interindividual variations in the response to and toxicity of pharmaceuticals due to variations in the genetic composition of individuals – in other words, how a person's genetic make-up influences the favorable or adverse effects of a certain treatment. Sufficient advances have been made in this discipline to allow this fertile field of research to move out of the basic science laboratory and into clinical applications. The present article reviews the investigations that have been published regarding the association between genetic determinants of persons infected with HIV and clinical toxicity resulting from different antiretroviral drugs. Special emphasis is devoted to the studies that have resulted in clinical applications such as that of the pre-screening of HLA B*5701 for avoiding abacavir-related hypersensitivity syndrome. **(AIDS Rev. 2010;12:15-30)**

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Introduction

The impact of highly active antiretroviral treatments (HAART) on improving the survival rate and quality of life in patients infected with HIV is of such a magnitude that it has led some to claim that "medical miracles" do indeed exist[1]. This is due to the powerful suppressor effect that current antiretroviral drugs have on the viral load, which is observed in a significant number of patients who take these medications appropriately. As a result, a substantial qualitative and quantitative improvement in the immune system occurs, which translates into an increase in the absolute $CD4^+$ T lymphocyte count and the recovery of lost functions. This improvement often permits the prophylaxis of opportunistic infections to be suppressed[2,3].

At present, however, there is still no cure for HIV and those undergoing treatment for it have to do so for life. The use of antiretroviral drugs has been associated with several toxicities that limit their efficacy. Some

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acute and chronic toxicities associated with these drugs include hypersensitivity reactions (HSR)[4], nephropathy[5], liver damage[6], and the appearance of body fat redistribution syndrome and the different metabolic alterations that accompany it[7,8]. Some of these toxicities are family- or even drug-specific. An intriguing fact is that not all patients that take a particular antiretroviral medication develop the adverse effect that has been attributed to that drug. It has therefore been postulated that there must be a genetically conditioned individual predisposition to developing the adverse effect[9,10].

Pharmacogenetics is the science that studies inter-individual variations in the response to and toxicity of pharmaceuticals due to variations in the genetic composition of individuals – in other words, how a person's genetic make-up influences the favorable or adverse effects of a certain treatment. Sufficient advances have been made in this discipline to allow this fertile field of research to move out of the basic science laboratory and into the realm of potential clinical applications.

The analysis of the human genome indicates that the most common genetic variations are single-nucleotide polymorphisms (SNP), which are alterations in the sequence of nucleotides that occur every 100-300 bases in the three billion base pairs of the human genome[11]. These changes in the DNA sequence do not always affect the genetic expression (phenotype). The combination of multiple SNP inherited together is called a haplotype. Haplotypes provide a more accurate prediction of genetic activity because they reflect the sum of the effects of the different SNP. Most of the data on genetic susceptibility to a specific antiretroviral-related toxicity are based on gene-association studies, in which researchers attempt to determine the relationship between candidate SNP and their consequences by means of statistical analyses[12]. Some of these studies are also based on prior evidence of gene-toxicity associations for the general population, as is the case, for example, with the studies of SNP associated with dyslipidemia[13]. But in many cases the hypothetical association is not confirmed in the end, which has led to the recent publication of preliminary guides for conducting such studies in order to prevent the diffusion of false-positive results[14,15].

With the quickly decreasing cost of genotype testing and the forecasted increase in its use as a toxicogenetic predictive tool in clinical practice related to HIV infection, some aspects of associations between genetic markers and a specific event must be considered. These include their replicability with high positive-predictive values of the associations of SNP with well-defined clinically relevant adverse events as well as the preference for studies that evaluate the contribution of SNP in the context of the analysis of multiple SNP and haplotypes, and finally, the validation of the genetic markers in large independent cohorts[10].

The international consortium on the haplotype map of the human genome[11] has identified a minimum group of SNP that are sufficiently representative of human genetic variation, which allows for the study of candidate genes associated with increased susceptibility to the development of adverse effects.

Genetic determinants of the adverse effects of antiretroviral treatment

Below we have compiled the most recent information on studies of the association between genetic determinants of people infected with HIV and clinical toxicity resulting from different antiretroviral drugs. Studies reported have been designed to investigate the effect of a single gene on a given toxicity phenotype, have assessed the effect of multiple genes together (multigene models) or have used genome-wide approach. Table 1 contains the most noteworthy adverse effects, the drugs that such effects are attributed to, and the different "genetic markers" studied, the most representative clinical application of which is the determination of HLA B*5701 as a predictive factor of HSR resulting from the use of abacavir.

Dyslipidemia

Apolipoproteins A5, C3, and E

Dyslipidemia associated with HAART, and in particular with protease inhibitors (PI), and its negative impact on cardiovascular risk has been widely studied[16-20]. These alterations in the lipid metabolism include hypertriglyceridemia, increased total cholesterol and cholesterol bound to low-density lipoproteins (LDL-C), and decreased cholesterol bound to high-density lipoproteins (HDL-C), all of which are independent risk factors for cardiovascular disease[21]. Variability in the susceptibility of patients with similar pharmacological histories and the same demographic characteristics to develop secondary dyslipidemia while undergoing HAART leads us to presume that genetic factors are involved.

In the study of the association between secondary dyslipidemia in patients undergoing HAART and genetic factors, it has been postulated that polymorphisms in

Table 1. Some adverse effects of HAART, the drugs presumably involved, and the main genetic variants that have been studied

Adverse effect	Drug/s	Genes studied
Dyslipidemia	PI	ApoC3, A5, E, TNFα, IL-6, PPARγ, SREBP1, resistin
Insulin resistance	NRTI/PI	TNFα, IL-6, PPARγ, resistin
Lipodystrophy	NRTI/PI	TNFα, IL-6, APOC3 IL-1β, PPAR-γ, lamin, resistin, mitochondrial DNA
Atherosclerosis	NRTI/PI	MCP-1, SDF-1, CX3CR1
Neurotoxicity	EFV	CYP2B6, CYP3A4
HSR, Liver disease	NVP	HLA, CYP2B6, MDR1
Hyperbilirubinemia	ATV	UGT1A1
Peripheral neuropathy. Lactic acidosis	NRTI	Mitochondrial DNA
Renal damage	TFV	MRP2, MRP4, hOAT
HSR	ABC	HLA-B*5701

HSR: hypersensitivity reaction; NRTI: nucleoside analogue reverse transcriptase inhibitor; PI: protease inhibitor; EFV: efavirenz; NVP: nevirapine; ATV: atazanavir; TFV: tenofovir; ABC: abacavir.

genes that encode the apolipoproteins A5, C3, and E (APOA5, APOC3, APOE), cholesterol ester transport proteins (CETP), the ATP binding cassette transporter A1 (ABC-A1), and the sterol regulatory element binding protein (SREBP-1) may be involved[10,13,22-26]. The apolipoproteins A5 and C3 regulate the metabolism of triglycerides in opposite directions. Apolipoprotein APOA5 reduces plasma levels of triglycerides, possibly by inhibiting the hepatic production of very low-density lipoproteins (VLDL) and accelerating the hydrolysis of triglycerides mediated by lipoprotein lipase[27]. A longitudinal study of 229 patients infected with HIV-1 concluded that patients under treatment with PI and who are also carriers of the *APOA5 -1131C* allele (*APOA5-1131T→C*) present faster deterioration of the lipid profile at the expense of an increase in total cholesterol and triglycerides, a decrease in HDL-C, and an increase in the total cholesterol/HDL-C fraction compared to patients with the same treatment who are carriers of the wild-type gene (*APOA5-1131T*) or patients whose HAART is not based on PI[22].

As opposed to APOA5, APOC3 decreases the lipolysis of lipoproteins rich in triglycerides and the hepatic clearance of triglycerides by inhibiting lipoprotein lipase and hepatic lipase[28]. The best studied polymorphisms of *APOC3* are *APOC3-482 C→G, –455C→T* and *+3238C→G* (also called the *SstI* polymorphism). Several recent studies[23-25] have found significant increases in plasma triglycerides in patients infected with HIV in treatment with different PI who are also carriers of variants in *APOC3* and *APOE* genes.

The APOE serves as a ligand for chylomicrons and VLDL particles that are cleared from the bloodstream by APOE binding to the LDL receptor. This lipoprotein presents three isoforms and the most common genotype is *APOE ε3/ε3*[29]. The *APOE ε3/ε4* variant has been associated with an increase in LDL-C and with lower triglyceride levels, and *APOE ε3/ε2* has been associated with an increase in cardiovascular risk. There are documented cases of patients infected with HIV who are carriers of the *APOE ε3/ε4* or *ε3/ε2* variants and in whom severe dyslipidemia was triggered by the start of HAART[30,31], although the data are inconsistent[23].

Sterol regulatory element binding protein-1

One of the pathogenic pathways of secondary lipid alterations as a result of HAART that has been proposed are the effects of PI on SREBP proteins, which are fundamental to lipid metabolism and whose alteration provokes changes that give rise to hyperlipidemia, insulin resistance, and adipocyte apoptosis[32]. There are clear discrepancies in the possible relationship of the polymorphism of the SREBP-1 protein with lipid alterations secondary to antiretroviral treatments. One study which included 67 patients receiving PI treatment, homozygous for *SREBP-1c 3322C→G* SNP, found a

small increase in total cholesterol and triglycerides[26], a result that could not be confirmed further[33].

Multigene models

Previous studies have found a significant number of patients with lipid alterations despite having a favorable *APOC3/APOE* genotype profile[24], which suggests the involvement of other genes in the lipid response to HAART. On the basis of these findings, a longitudinal study was conducted over more than four years with 438 patients infected with HIV, which evaluated the role of 20 SNP of 13 genes associated with dyslipidemia in the general population[13]. The goal was to more accurately predict patients at risk of developing secondary dyslipidemia as a result of HAART. The study found that variants in five genes (*ABCA1, APOA5, APOC3, APOE,* and *CETP*) contribute to the explanation of plasma levels of triglycerides and HDL-C, especially in the context of a HAART that contains ritonavir.

Lipodystrophy

The lipodystrophy syndrome associated with HAART encompasses different forms of abnormal distribution of body fat and metabolic alterations, which often occur concomitantly in the same individual. The morphological changes related to the disorder include the loss of subcutaneous fat (lipoatrophy), the accumulation of fat (lipohypertrophy), or a combination of both. Despite several proposals[34], to date there is no consensus on the objective definition of lipodystrophy. This syndrome has been associated with the use of PI[35-38] and of nucleoside analog reverse transcriptase inhibitors (NRTI)[39-42], but factors other than antiretroviral drugs probably play a role in its pathogenesis, such as the HIV infection itself and genetic factors of the host.

Variations in the mitochondrial DNA sequence

One of the physiopathological mechanisms involved in the development of lipodystrophy, and above all of lipoatrophy, is mitochondrial dysfunction[43]. The NRTI inhibit DNA polymerase gamma (POLγ), which is an indispensable enzyme for the replication and repair of mitochondrial DNA (mtDNA). However, mtDNA depletion has also been documented in patients infected with HIV who have never received antiretroviral treatment[44]. Several authors have investigated the impact of alterations in the mtDNA sequence on the development of lipoatrophy[45-48] and an association has been found between lipoatrophy and the accumulation of mutations in the mtDNA, which has also been observed in animal models of aging. Nevertheless, these results are currently difficult to extrapolate to what happens in patients infected with HIV due to a lack of consensus in the criteria that define lipodystrophy, and because the existing studies were carried out with small samples that require further replication.

Mutations in the LMNA gene

Lipodystrophy associated with HIV infection has phenotypic similarities to some primary or hereditary lipodystrophies[49]. Familial partial lipodystrophy is a heterogeneous group of illnesses that are inherited in an autosomal dominant manner and can express several phenotypes. The most common variety is that described by Dunnigan, et al.[50] and is characterized by a progressive loss of subcutaneous fat in the extremities, which usually begins to manifest at puberty and gradually affects the fat of the abdominal wall and the thorax as well[51]. Patients can also present with an accumulation of fat in the face, neck, intraabdominal region, and metabolic alterations such as insulin resistance, dyslipidemia, and atherosclerosis. The genetic foundation of this disease is the mutation in the gene that encodes for lamin A/C[52]. Lloyd, et al. identified an interaction between lamin A and the SREBP-1 adipocyte maturation factor[53]. Several subsequent studies have investigated the physiopathological role of lamin alterations in the lipodystrophy syndrome associated with HAART. In some animal models, PI (indinavir and nelfinavir) have been associated with an alteration in the maturation of lamin A/C, in SREBP-1 nuclear localization and in adipocyte differentiation[54]. In HIV-infected patients with lipodystrophy, mutations in the *LMNA* gene, a gene which is associated with hereditary forms of lipodystrophy, have not been identified[55].

Tumor necrosis factor alpha

Tumor necrosis factor alpha (TNFα) has been studied in an attempt to identify genetic factors associated with lipodystrophy because many of its actions on the adipocyte level mimic the *ex vivo* findings observed in adipose tissue samples of patients with lipodystrophy. The homeostasis of TNFα is profoundly altered by antiretroviral therapy[56], as evidenced by the systemic hyperproduction and increase in TNFα mRNA documented in samples of subcutaneous fat from patients

with lipodystrophy[57]. Therefore, several studies have been carried out to determine if polymorphisms in the promoter region of the TNFα gene are associated with the development of lipodystrophy[24,58,59], but the results are inconclusive. A seminal British study assessed 61 patients infected with HIV with lipodystrophy, 35 without lipodystrophy, and 239 healthy controls and found a higher representation of *TNFα-238A* genetic variant in the group of patients with lipodystrophy. The authors argued that this genetic variant in itself is neither sufficient nor absolutely necessary to induce the disease, although its presence may increase the risk of developing it[58]. A Swiss cohort study, however, was unable to reproduce these findings[24]. An Australian longitudinal study found that being a carrier of the allelic variant *-238A* of the *TNFα* gene is associated with an earlier start and a faster progression of lipodystrophy[59]. To date, hence, the involvement of *TNFα* genetic variants in lipodystrophy remain controversial.

Interleukin 1 beta and interleukin 6

The importance of inflammatory phenomena among the pathogenic mechanisms of the redistribution of body fat associated with HIV infection and antiretroviral treatment has focused attention on the polymorphisms of genes that encode for cytokines involved in that response and whose homeostasis (such as that of TNFα mentioned above) is altered in patients with lipodystrophy. Among these, it has recently been found that the polymorphic *T allele (+3954C/T*) of the interleukin 1 beta (*IL-1β)* gene is less present in populations with lipodystrophy than in those without the disorder[60]. This finding was related to the low modulation of the inflammatory response of this allele, which is based on lower circulating levels of TNFα in patients lacking it. In this and other studies, no association has been found between the presence of lipodystrophy and the polymorphism of the interleukin 6 (*IL-6)* gene[60,61].

Peroxisome proliferator-activated receptor gamma

Peroxisome proliferator-activated receptor gamma (PPARγ) is a ligand-dependent master transcription factor controlling adipocyte differentiation and is thought to be involved in obesity and in some components of the metabolic syndrome. A study was performed in Caucasian Spaniards to determine whether *PPARγ Pro12Ala* polymorphism is associated with the risk of developing lipodystrophy and its associated metabolic disturbances in 278 patients infected with HIV-1 and treated with HAART (139 with lipodystrophy and 139 without) and in 105 uninfected controls. Results indicated that *PPARγ Pro12Ala* genotype distribution and allele frequencies were non-significantly different between both HIV-1-infected categories, lipodystrophy vs. non-lipodystrophy (p = 0.9 and 0.87, respectively). Lipodystrophy patients harboring the rare *X/Ala* genotype (*Ala/Ala* plus *Pro/Ala*) had significantly greater plasma total and LDL cholesterol levels compared with carriers of the common *Pro/Pro* genotype (p = 0.029 and 0.016, respectively) at univariate analyses, but at multivariate analyses these associations were no longer significant[62]. This study confirmed the lack of association between *PPARγ* polymorphism and lipodystrophy reported previously in an Italian study which involved multiple genes (See Multigene Studies)[63].

Multigene studies

Other studies have tried to evaluate the impact of host genetics on the development of lipodystrophy and its associated metabolic derangements through a multigene approach involving several candidate plausible genes. A study performed with 255 patients from the ICoNA cohort assessed the distribution of diverse genes that encode for proteins involved in cell apoptosis and in adipocyte metabolism. Polymorphisms investigated were *Fas -670 A→G* SNP, *ApoC3 -455C→T* and *-482C→T* SNP, *C161T* silent substitution in the *PPARγ* gene, the adrenergic beta3 receptor *(ARbeta3)* codon *64T→C* variant, and two SNP in the adrenergic beta2 receptor *(ARbeta2* codon *16A→G* and *ARbeta2* codon *27C→G)*[64]. In a multivariate model, after adjusting for confounding, the following genotypes resulted protective against lipoatrophy: *ApoC3 -455CC* genotype (p = 0.037), *ARbeta3* codon *64 TT* genotype (p = 0.066), and *Fas -670GG* genotype (p = 0.053). With regard to fat accumulation, the *ARbeta2* codon *27CC* genotype resulted protective (p = 0.0006), whereas the *ARbeta2* codon *16AA* genotype was associated with higher risk (p = 0.0026). These data suggest that polymorphisms in some genes involved in apoptosis and in adipocyte metabolism are associated with HAART-related lipodystrophy[63].

Resistin, also known as FIZZ-3 (found in inflammatory zone 3), is a pleiotropic cytokine that acts as an immune and inflammatory mediator. It is an adipocyte-secreted peptide and it has been nominated to connect obesity with diabetes. With the purpose to ascertain the role of host genetic variation in influencing the risk of lipodystrophy and metabolic complications associated with HAART,

a study was performed in 189 patients enrolled in ACTG5005s, the metabolic substudy of ACTG384[64]. Three hundred SNP in 135 candidate genes were evaluated, among them that of resistin. A subset of patients was identified that had a normal metabolic profile at baseline, but developed significantly elevated lipids and insulin resistance on HAART. Candidate gene analysis revealed that an SNP in the resistin gene was significantly associated with elevated lipids and insulin resistance ($p = 0.0003$). This subset of patients also experienced significant body composition changes, particularly limb fat loss[64]. These data suggest that resistin genetic variants may modulate the appearance of lipodystrophy and metabolic disturbances in HIV-infected patients treated with HAART.

Atherosclerosis

Inflammatory phenomena play an important role in the development of atherosclerosis and can be a predictive factor in the progression of cardiovascular disease[65]. In this context, chronic infections, like the HIV infection itself, can trigger an inflammatory stimulus, initiating or exacerbating atherogenesis[66]. Research has been done in recent years into the role of various genetic polymorphisms related to inflammation in the development of atherosclerosis in patients infected with HIV. The most frequently studied polymorphisms are those in stromal cell-derived factor-1 (SDF-1)[67] and in monocyte chemotactic protein-1 (MCP-1)[68,69].

Stromal cell-derived factor-1

Stromal cell-derived factor-1 is a chemotactic cytokine of lymphocytes and monocytes that is associated with plaque activation and aggregation and its expression is elevated in atheromatous plaques[70]. The SDF-1 plays an important role in HIV infection because it is a natural ligand of the CXCR4 coreceptor through which HIV penetrates cells[71]. Research has shown that the polymorphism *SDF1-3'UTR-801 G→A* (abbreviated *SDF1-3'A*) is linked to a lesser expression of SDF-1 and influences the progression of HIV infection[72]. *In vitro* studies have found an association between SDF-1 and atherosclerosis[70,73], results that have also been found in patients infected with HIV[67] in that patients carrying the allele *SDF1-3'A* present a lesser degree of subclinical carotid atherosclerosis in echographic evaluations.

Monocyte chemotactic protein-1

Monocyte chemotactic protein-1 is a protein with powerful activating action for mononuclear phagocytes (monocytes and macrophages) in that when its receptor (CCR2) is stimulated, the monocytes migrate to the subendothelium and initiate the phagocytosis of modified lipoproteins[74]. One study evaluated the influence of genetic variants of *MCP-1* on the development of atherosclerosis in patients infected with HIV and found that patients carrying the *MCP-1–2518G* genetic variant are five-times more likely to develop subclinical atherosclerosis, evaluated by ultrasonography[69].

Neurotoxicity associated with the use of efavirenz

Treatment with efavirenz causes side effects at the central nervous system (CNS) level in up to half the patients who use it[75,76]. Symptoms tend to appear during the first days or weeks of treatment and in most cases consist of dizziness, insomnia, nightmares, instability, drowsiness, and alterations in the ability to concentrate[75-77], which usually improve gradually in a few weeks. However, severe depression, psychosis, aggression, mania, and paranoid reactions have also been described[76-80]. Several studies have shown that there is great interindividual variability in the plasma concentrations of efavirenz, and that patients who reach the highest concentrations of the drug run a higher risk of developing neuropsychiatric symptoms[76,77,79-81].

Efavirenz is a nonnucleoside reverse transcriptase inhibitor (NNRTI), which is metabolized in the liver by means of the CYP450 enzyme complex, as with protease inhibitors and other NNRTI. Efavirenz is metabolized mainly, but not exclusively, by means of the CYP450 isoenzyme 2B6 (CYP2B6), which is responsible for the clearance of 90% of circulating efavirenz[82]. Up to 28 alleles in the gene that encode for this isoenzyme have been described, meaning that it is an extraordinarily polymorphic gene, especially in the black population[83]. There is also great interindividual variability in the quantity and catalytic activity of this isoenzyme in the human liver[84]. The allelic variant of the gene that seems to most affect the expression of CYP2B6 in the liver and which most alters the metabolism of efavirenz is a change from *G→T* in codon *516* (*516G→T* SNP), allele marker *CYP2B6*6*[85,86]. Several different studies have shown that patients carriers of the T variant allele, especially homozygotes with two copies of non-functioning alleles (*TT* genotype), present higher plasma concentrations of efavirenz[85-90] and may run a higher risk of developing severe adverse neuropsychiatric effects[79,80,85,86].

Although other CYP450 isoenzymes have also been implicated in the metabolism of efavirenz, including

CYP2A6, CYP3A4, and CYP3A5, their influence on plasma concentrations of efavirenz seems to be limited[82,85,89]. The close link between the *CYP2B6 516G→T* polymorphism and plasma concentrations of efavirenz has been confirmed in other studies[86-89]. One study analyzed the *516G→T* polymorphism in 100 Caucasian patients treated with efavirenz. Of the patients, 52% had the wild-type genotype (*GG*), 43% the heterozygote genotype (*GT*), and 5% the homozygote genotype (*TT*)[87]. The highest plasma concentrations of efavirenz were found in the patients with the *TT* genotype and the lowest in the group with the *GG* genotype; concentrations of the drug in *GT* genotype subjects were in-between. In this study, 40% of the patients with the homozygote genotype and 20% of those with the heterozygote genotype had excessive plasma concentrations of efavirenz (> 4 µg/ml). Meanwhile, only 5% of the subjects with the wild-type *GG* genotype were found to have elevated plasma concentrations and 20% had subtherapeutic concentrations of the drug (< 1 µg/ml)[87]. Another study conducted in patients from the Swiss cohort evaluated the presence of this allele as a pharmacogenetic marker of the pharmacokinetics and toxicity of efavirenz in 167 patients. Concentrations of efavirenz in plasma and peripheral blood mononuclear cells were measured[88]. Just as in the study described earlier, individuals carrying the *TT* genotype were found to have higher plasma and intracellular concentrations of efavirenz. Furthermore, intracellular concentrations and carriage of the *CYP2B6 516TT* genotype were predictors for the development of neuropsychiatric toxicity[88].

In addition to the most well known allelic variants, new polymorphisms have recently been described that are associated with the loss or decrease in CYP2B6 enzyme activity. These include *983T→C* and *785A→G* (markers of the *CYP2B6*16* allele)[91], *593T→C* (marker of the *CYP2B6*27* allele)[92] and *1132C→T* (marker of the *CYP2B6*28* allele)[92] which, especially in homozygote individuals, imply an elevated risk of developing excessive plasma concentrations of efavirenz. Although efavirenz is not a substrate of P-glycoprotein, it has been suggested that polymorphism in the *ABCB1* gene, which encodes for that protein, may be associated with very low plasma concentrations of the drug[93].

While CYP2B6 is the main enzyme responsible for efavirenz metabolism, in individuals in which CYP2B6 function is impaired, the role of other enzymes able to metabolize this drug, such as CYP2A6, may be relevant. In this respect, di Iulio, et al.[94] studied the effect of *CYP2A6* gene variation (14 alleles) in 169 individuals from the Swiss cohort previously characterized for functional variants in *CYP2B6* (18 alleles). Plasma concentrations of efavirenz and its primary metabolites were measured in different genetic scenarios *in vivo*. Results indicated that the accessory metabolic pathway CYP2A6 has a critical role in limiting drug accumulation in individuals characterized as CYP2B6 slow metabolizers. These data suggest that dual CYP2B6 and CYP2A6 slow metabolism may occur in humans and this may lead to extremely high efavirenz exposure[94]. In a further study with the same cohort, it was estimated that besides *CYP2B6* genetic variants, both *CYP2A6* and *CYP3A4/5* allelic diversity may contribute to efavirenz exposure, particularly when CYP2B6 is impaired. Dosage adjustment in accordance with the type of polymorphism (*CYP2B6, CYP2A6*, or *CYP3A4*) may help clinicians to prescribe the appropriate dose of efavirenz to maintain it within the therapeutic levels[95].

Most pharmacogenetic studies conducted up to now have focused on the effect of individual polymorphisms. However, pharmacokinetic processes and the response to medications are complex phenomena, in which interactions among proteins encoded by multiple genes are likely. Preliminary studies suggest that combined analyses of several genes might improve the predictive ability of plasma exposure, of response to treatment, and even of the toxicity of efavirenz[96]. In the genetic substudy of the ACTG 384 trial in which didanosine (ddI) plus stavudine (d4T) was compared to azidothymidine (AZT) plus lamivudine (3TC), and efavirenz was compared to nelfinavir, the analysis model that included the alleles *CYP2B6 516G→T* and *ABCB1 2677G→T* was the best predictor of plasma exposure to efavirenz in Caucasian patients[96]. Furthermore, the interaction between these two genes better predicted the response to treatment, whereas for failure due to toxicity, the model with the better predictive capacity was that which included the genes *ABCB1 2677G→T* and *ABCB1 3435C→T*[96].

The recognition that certain genetic polymorphisms can influence the metabolism of efavirenz and determine marked pharmacokinetic differences between individuals could have implications in antiretroviral therapy. Currently, efavirenz is administered at a fixed dosage of 600 mg once a day. The possibility that a lower dosage might reduce the incidence of adverse events without compromising the drug's efficacy in patients with *CYP2B6* allelic variants associated with a higher exposure to the drug is particularly attractive. This strategy has already been used successfully in isolated cases[79]. Also, in a recent study in which lower doses of efavirenz were administered to patients carriers

of the *CYP2B6 516T* allele, CNS symptoms were reduced in 10 of 14 cases that received adjusted doses according to plasma concentrations of the drug (200-400 mg/day), and the virologic efficacy of the treatment was maintained[97]. *CYP2B6* genotyping might, therefore, prove useful as an adjuvant for a personalized therapy strategy based on measurements of plasma concentrations of efavirenz with the goal of increasing the safety of and tolerance to the drug, although prospective, randomized studies are needed to confirm this hypothesis.

Hypersensitivity reactions associated with nevirapine

Hypersensitivity reactions related to the use of nevirapine occur in approximately 5% of HIV-infected patients treated with the drug and present with fever with hepatitis and/or cutaneous exanthema and sometimes produce multi-systematic symptoms[98,99]. Although such symptoms are generally resolved upon termination of the treatment with this drug, in some cases the reaction can be fatal[99]. The characteristics of the HSR suggest that it may be the result of a genetic predisposition and that the manifestations are caused by an immunological response dependent on $CD4^+$ T lymphocytes, which is triggered by specific antigens associated with nevirapine. The reaction generally appears in the second or third week of treatment and occurs faster and is more severe when the drug is reintroduced[98,99]. A low CD4 count before initiating treatment is protective. The reaction develops more frequently and is more severe in uninfected persons who receive the drug for postexposure prophylaxis[100].

Several independent studies suggest that this reaction may have an immunogenetic base and that it is associated with major histocompatibility complex (MHC) HLA antigens[101-103]. In an Australian cohort of 235 patients treated with nevirapine, 26 presented hypersensitivity reactions. Patients who were carriers of the haplotype *HLA-DRB1*0101* and who also had a percentage of lymphocytes CD4 > 25% were found to be 17-times more likely to develop HSR manifested as hepatitis or systemic symptoms, with positive and negative predictive values of 40 and 96%, respectively[101]. Neither of the two variables were separately associated with a higher risk of developing HSR in the multivariate analysis, which suggests that the genetic predisposition may be a prerequisite, but is insufficient in itself to develop HSR, and the reaction may be attenuated or abolished if the $CD4^+$ T lymphocyte count is low[101].

The role of HLA antigens in HSR due to nevirapine has been confirmed in other studies[102,103]. In Sardinian patients, an unusually elevated incidence of HSR due to nevirapine was documented as compared to other population groups and a study was conducted to find out if it was related to specific HLA antigens[102]. Forty-nine patients infected with HIV receiving treatment with nevirapine and 82 patients infected with HIV not receiving treatment with the drug were studied. Twenty-six percent of the patients exposed to nevirapine developed an HSR. The *HLA-A, HLA-Cw, HLA-B* and *HLA-DR* alleles were typed in both groups: 46% of the patients with HSR had haplotypes *HLA-Cw*8–HLA B*14* compared to 5% of the nevirapine-tolerant group[102]. The frequency of haplotypes *HLA-Cw*8–HLA B*14* found in the patients with HSR was 7.5-9.5 times higher than that found in the general population of the island and of the nevirapine-tolerant group. Although it was not possible in this study to determine which of the two haplotypes was principally associated with HSR, in a subsequent study in the Japanese population in which the haplotype *HLA-B14* was not present, the *HLA-A, HLA-B, HLA-Cw, HLA-DRB1,* and *HLA-DQB1* alleles were typed in 309 patients[103]. The allelic frequency of *HLA-Cw8* and *HLA-B14* was 13 and 0%, respectively. The group with HSR to nevirapine included 11 patients (group 1) and the tolerant group 29 (group 2). The frequency of the *HLA-Cw*8* allele was 42, 10, and 9-14% for group 1, group 2, and the general Japanese population, respectively, which confirms the association between the haplotype *HLA-Cw*8* and the risk of developing an HSR with nevirapine[103].

Hepatotoxicity associated with the use of nevirapine

Hepatotoxicity associated with nevirapine may be accompanied by other manifestations of hypersensitivity or manifest in isolation. In a recent meta-analysis on the safety of nevirapine in different populations of patients infected with HIV, 4.9% of those treated with the drug developed symptomatic hepatic adverse events[99]. As with efavirenz, the hepatic biodegradation of nevirapine is conducted mainly by the CYP4502B6 isoenzyme, although other isoenzymes including CYP3A4 have also been implicated in its metabolism. Although P-glycoprotein (encoded by the gene *ABCB1* [also known as *MDR-1*]) transports multiple substrates including protease inhibitors, it does not seem to operate as a transporter of NNRTI[104]. However, a recent study found an inverse correlation between the concentrations of nevirapine in peripheral blood mononuclear cells and the levels of expression of P-glycoprotein, which

suggests that this protein may play a role in the transport of nevirapine[105].

An observational study investigated the relationship between the genetic polymorphisms of *CYP2B6, CYP3A4,* and *MDR-1* and hepatotoxicity during antiretroviral treatment with NNRTI in 423 patients who began a regimen containing efavirenz (222 patients) or nevirapine (201 patients). Of the patients, 4.7% experienced severe hepatotoxicity (14 nevirapine, six efavirenz)[106]. Surprisingly, the risk of hepatotoxicity was related to variations in the *MDR-1* gene. The polymorphism *C→T* at position *3435* of *MDR-1* was associated with a decrease in the likelihood of developing hepatotoxicity. In the multivariate analysis, the interaction between the polymorphisms *MDR-1 3435 C→T* and *CYP2B6 1459 C→T* predicted the risk of hepatotoxicity with 74% accuracy. In a similar study conducted by the same research group, the relationship between the polymorphisms of *CYP2B6, CYP3A,* and *MDR-1* and hepatotoxicity due to nevirapine was analyzed in naive patients that participated in the Gilead Sciences FTC-302 trial, a double-blind study conducted in South Africa in which emtricitabine was compared with lamivudine and nevirapine with efavirenz[107]. Of the 385 patients assigned to nevirapine, 17% presented with hepatotoxicity. In this study as well, carriage of the *MDR-1 3435T* variant allele was associated with a lower risk of developing hepatotoxicity. The mechanism by which this polymorphism can reduce the risk of hepatotoxicity due to nevirapine is unknown. It has been proposed that this allelic variant might alter the export activity of P-glycoprotein in the intestinal tract, which would affect the pharmacokinetics of nevirapine or its metabolites in such a way that its intracellular concentrations and toxicity would decrease[107].

These results were replicated in a recent case-control study conducted in Mozambique, which assessed *ABCB1*, *CYP2B6, CYP3A4,* and *CYP3A5* gene variants in 78 HIV-infected patients with nevirapine-induced liver damage and in 78 nevirapine-tolerant individuals. The *ABCB1 c.3435C→T* SNP was associated with hepatotoxicity ($p = 0.038$), with the variant *T* allele showing some protective effect (OR: 0.42). It was also observed that diverse SNP within the *CYP2B6* and *CYP3A5* genes modulated the degree of liver damage[108].

Hyperbilirubinemia associated with the use of atazanavir or indinavir

Twenty to fifty percent of patients treated with atazanavir and 5-25% of those that receive indinavir develop hyperbilirubinemia due to increased unconjugated bilirubin and, in about 6% of cases, overt jaundice[109,110]. This effect is attributable to a competitive inhibition by atazanavir and indinavir of the UGT1A1 enzyme responsible for the conjugation and clearance of bilirubin[111] and it occurs more frequently in individuals with Gilbert syndrome, a process characterized by a genetically determined alteration in the conjugation of bilirubin. This syndrome is associated with carriers of the *UGT1A1*28* allele, defined by the presence of seven repetitions of the TA dinucleotide (TA_7) in the promoter region of the gene which encodes for the UGT1A1 enzyme, which causes reduced activity of that enzyme and asymptomatic hyperbilirubinemia[112]. In these patients, the incidence of hyperbilirubinemia due to atazanavir or indinavir varies depending on the genotype of the promoter region of the gene that encodes the UGT1A1: from 15% in those that have the wild-type allele to 90% in homozygote individuals for the *UGT1A1*28* allele. The latter group is that in which the highest levels of bilirubin are reached and in which overt jaundice is most likely[111,113-115].

The relative contribution of the *UGT1A1*28* allele to hyperbilirubinemia associated with antiretroviral treatment was evaluated in 96 patients (92 Caucasian) infected with HIV of the Swiss cohort and treated with antiretrovirals for a period of six years[115]. The effect of the different drugs and the *UGT1A1*28* allele were estimated using bilirubin concentrations. The analysis confirmed the association between this allele and the risk of hyperbilirubinemia in that 67% of the homozygote individuals for the *UGT1A1*28* allele that received atazanavir or indinavir had at least two episodes of hyperbilirubinemia in the jaundice range (> 2.5 mg/dl), compared to 7% observed in those treated with neither of the drugs. The authors modeled the theoretical impact that a genotyping policy before the initiation of antiretroviral treatment might have on the incidence of jaundice. According to their estimations, the universal administration of atazanavir or indinavir without prior genotyping would cause hyperbilirubinemia in the jaundice range in 21.6% of patients, whereas treatment based on prior *UGT1A1*28* genotyping would reduce that rate to 5.8%[115].

In a study conducted in Spain in 118 patients treated with atazanavir/ritonavir, Rodríguez-Nóvoa, et al.[116] found the *UGT1A1*28* allele in 55% of patients (48% heterozygote individuals, 7% homozygote individuals). The proportion of grade 3-4 hyperbilirubinemia patients (total bilirubin > 3.2 mg/ml) was 80% in homozygote carriers of the variant, 29% in heterozygote carriers of the variant, and 18% in those with the wild-type *UGT1A1*

genotype. In the multivariate analysis, being a carrier of at least one *UGT1A1*28* allele was independently associated with the development of severe hyperbilirubinemia (OR: 2.96)[113]. The same researchers found a correlation between bilirubin values and plasma concentrations of atazanavir and that the *3435C→T* polymorphism in the *MDR-1* gene that encodes P-glycoprotein influences plasma concentrations of atazanavir (wild-type genotype carriers presented higher concentrations than the *C/T* or *T/T* genotypes)[113-116].

Unlike Caucasian subjects, in Thai patients treated with indinavir a different allele, *UGT1A1*6*, may predispose to hyperbilirubinemia more than the *UGT1A1*28* allele[114].

Peripheral neuropathy and lactic acidosis due to nucleoside reverse transcriptase inhibitors

Nucleoside reverse transcriptase inhibitors block viral replication by means of a competitive mechanism with endogenous nucleosides to enter proviral DNA. Although they act relatively specifically on the reverse transcriptase of HIV, to a lesser or greater extent they also inhibit mtDNA polymerase γ, an enzyme responsible for the replication of mtDNA and which is encoded in the *POL*γ gene located in the nucleus. The depletion of mtDNA can damage the oxidative metabolism and cause the accumulation of pyruvic and lactic acid, which can give rise to various adverse effects including peripheral neuropathy and lactic acidosis[117]. The manifestations of mitochondrial toxicity comprise one of the main complications of NRTI, although they only develop in some patients. On the other hand, there are many similarities between these manifestations and certain congenital (genetic) alterations of mitochondrial function. All of this suggests that genetic factors may be important determiners of the individual predisposition to developing mitochondrial toxicity in patients treated with NRTI.

Peripheral neuropathy can develop in up to 15% of patients infected with HIV[118]. Although it may be a complication of untreated HIV infection, most cases are caused by antiretroviral treatment, particularly with the use of ddI and/or d4T[119,120].

To determine whether certain genetic polymorphisms can influence the susceptibility to developing peripheral neuropathy associated with NRTI, Hulgan, et al.[121] conducted an exploratory genetic analysis in 509 patients who had participated in the ACTG 384 study, a randomized clinical trial in which ddI plus d4T was compared to AZT plus 3TC. During the three years of the trial, 147 patients (29%) developed peripheral neuropathy, 108 (73%) of whom had been randomized to receive ddI plus d4T and 39 (27%) of whom received AZT plus 3TC ($p < 0.001$). The researchers studied European haplotype groups of the mitochondrial genome[121]. Mitochondrial DNA contains 38 genes, 13 of which are structural genes that encode for different subunits of the enzymatic complexes of the oxidative phosphorylation system. The largest non-coding region, known as the control region or D-loop, stands out for its high rate of mutation and for varying markedly from population to population. Nine different mitochondrial haplotype groups were studied and only the haplotype T group was found more frequently in patients who developed peripheral neuropathy. In Caucasian patients who developed peripheral neuropathy, 17% belonged to the haplotype T group compared to 6.7% who did not develop peripheral neuropathy (OR: 2.8). The association was closer when the patients assigned to the ddI plus d4T group were analyzed. In this subgroup, 10 of the 48 (20.8%) who developed peripheral neuropathy belonged to the haplotype T group compared to four of 89 (4.5%) who did not develop it (OR: 5.4). In the multivariate analysis, the main independent predictors of the development of peripheral neuropathy were the assignment to the ddI plus d4T group (OR: 2.57), a more advanced age at the time the neuropathy was diagnosed (OR: 1.05 per year) and a mitochondrial haplotype T group (OR: 2.89)[121]. In a subsequent analysis, the authors characterized a specific mitochondrial polymorphism within the haplotype T group, *MTND2 (*) LHON 4917G*, which may be associated with an increased susceptibility to the development of peripheral neuropathy due to nucleoside analogs[122].

Because alterations in the metabolism of iron have been linked to mitochondrial dysfunction and other degenerative processes, one study evaluated whether mutations in the hemochromatosis gene (*HFE*) could influence the susceptibility to developing peripheral neuropathy in patients that had participated in the ACTG 384 study[123]. The *HFE C282Y* and *H63D* genotypes were analyzed. Of the 506 patients of the ACTG 384 study, of those in whom the *HFE C282Y* locus was genotyped, 47 were heterozygotes; none were homozygotes. With the *HFE H63D* locus, 74 heterozygotes and no homozygotes were found. In the patients that received treatment with ddI plus d4T, the incidence of peripheral neuropathy was lesser in heterozygotes for the *HFE C282Y* genotype (in all races/ethnicities) and in heterozygotes for the *HFE H63D*

genotype (only in Caucasian subjects). In the multivariate analysis, however, only the *HFE C282Y* genotype remained as a protective factor against the development of peripheral neuropathy (OR: 0.30), even after adjusting for the mitochondrial haplotype T[123].

Lactic acidosis is a serious manifestation of mitochondrial toxicity that occasionally occurs in patients undergoing treatment with nucleoside analogs, especially with d4T and ddI[124]. Not all patients who are treated with d4T or ddI present with lactic acidosis, which leads to the suspicion that there may be a genetic predisposition for developing the disorder. A group of Japanese investigators sequenced 22 exons of the *POL*γ gene, which encodes the catalytic subunit of mtDNA polymerase γ, in 11 patients infected with HIV with a history of hyperlactatemia induced by d4T and in five patients that had received prolonged treatment with d4T and who had normal levels of serum lactate. They were able to identify a new mutation in codon *964* of the *POL*γ gene (*R964C*) in a Thai patient with lactic acidosis. When they characterized the biochemical effect of this mutation through recombinant analysis, they found that it produced a marked decrease in the enzyme activity of mtDNA polymerase, which was 14% of the enzyme activity produced by the wild-type gene. Furthermore, the cultivation with d4T of lymphoblastoid cells derived from the patient with the *R964C* mutation significantly reduced mtDNA levels compared to that found with cells with the wild-type gene[125]. Although the mutation was only found in one patient, it is biologically plausible that this mutation may predispose to the development of mitochondrial toxicity induced by nucleoside analogs.

Renal toxicity and tenofovir

The primary adverse effect of tenofovir is renal toxicity, which is usually caused by damage to the proximal tubule and which manifests as different alterations in tubular function and/or acute renal insufficiency[126-130]. Treatment with this drug has also been associated with a decrease in glomerular filtration and chronic renal insufficiency[131,132]. The best characterized factors that predispose for nephrotoxicity due to tenofovir are the presence of a prior chronic renal disorder, the concomitant use of other nephrotoxic drugs, low body weight, advanced age, and a low $CD4^+$ T lymphocyte count[133]. Some clinical studies have found that the coadministration of tenofovir with certain antiretroviral drugs, especially boosted protease inhibitors and didanosine, may be associated with a higher risk of nephrotoxicity[130,134-138]. However, discordant results were obtained in experimental studies that evaluated the effect of the combination of tenofovir with other antiretrovirals[139-141].

Tenofovir is excreted by glomerular filtration and active tubular secretion. Active tubular secretion is mediated by two types of specific transporters in the cells of the renal proximal tubules: (i) those located in the basolateral membranes, which take in the small, soluble molecules from the systemic circulation to facilitate their entrance to the interior of the cells, and (ii) those located in the apical membranes, which export the drugs from the interior of the cells to the urine. In the case of tenofovir, the proteins that transport the drug from the bloodstream to the interior of the tubular cells have been well characterized[142]. It is known that at the level of the basolateral membrane of the proximal tubules it is captured by human organic anion transporter 1 (hOAT1) and 3 (hOAT3). Tenofovir has an affinity 20-times higher for hOAT1 than for hOAT3. However, the expression of hOAT3 in the proximal tubules is much higher than that of hOAT1, which suggests that hOAT3 may be a parallel route of low affinity but high transport capacity[142]. In terms of export proteins, although the proteins associated with resistance to multiple drugs MRP2 and MRP4 and P-glycoprotein are present in the apical membranes of the proximal renal tubules, and there is indirect evidence that MRP2 may play a role[143], the most robust experimental data indicate that tenofovir is not a substrate of MRP2 nor of P-glycoprotein, but of MRP4, which would be the protein that would transport tenofovir to the urine[144]. It has been proven in different *in vitro* systems that tenofovir accumulates in concentrations five-times lower in cells that overexpress MRP4, and that the accumulation increases when an MRP inhibitor is added[144].

Izzedine, et al.[145] posed the hypothesis that certain variations in the genes that encode the transporter proteins may condition an intracellular accumulation of tenofovir, which increases the risk of tubular toxicity. These researchers performed an exploratory analysis of the genes that encode the proteins MRP2 (ABCC2), MRP4 (ABCC4) and P-glycoprotein (ABCC1) in 30 Caucasian patients infected with HIV treated with tenofovir. The patients were divided into two groups: 13 patients who had developed proximal renal tubulopathy secondary to treatment with tenofovir (group 1) and 17 patients without renal anomalies (group 2). A mutational screening was conducted for the genes *ABCC2 (MRP2)* and *ABCC4 (MRP4)* in group 1 and all the SNP identified were genotyped in the control group to analyze the association by means of a case-control study. The

30 patients included in the study were also genotyped for three functional SNP of the gene *ABCB1 (3435C→T, 2677G→T/A* and *1236G→T*). The development of tubulopathy was significantly associated with the polymorphism *1249G→A* of gene *ABCC2 (MRP2)* and with a haplotype of the same gene that consisted of four polymorphisms including *1249G→A* (unadjusted OR: 4.25; lower bound of 95% CI: 1.25). No significant differences were found between groups 1 and 2 regarding the analysis of the genes *ABCC4 (MRP4)* and *ABCB1* (P-glycoprotein), although a synonymous polymorphism (i.e. one that does not alter the amino acid sequence of the encoded protein) in gene *ABCC4* was associated with the development of tubulopathy and was entered in the multivariate analysis of the *ABCC2* haplotypes as a co-variable. The authors concluded that *ABCC2* haplotypes are associated with proximal tubulopathy induced by tenofovir as they significantly influence the susceptibility to developing tubular dysfunction: *CATC* as a haplotype favoring toxicity (it was found in 40.9% of the cases and 13.7% of the controls; $p < 0.01$) and *CGAC* as a protective haplotype (it was not found in any of the cases and was present in 20.2% of the controls; $p < 0.01$)[145].

A Spanish group recently carried out a pharmacogenetic association study of predictors of renal tubular dysfunction induced by tenofovir[146]. The polymorphisms of *ABCC2, ABCC4, SLC22A6* (encodes hOAT1), *SCL22A11* (encodes hOAT3), and *ABCB1* (encodes for P-glycoprotein) genes were studied in a cohort of patients treated with tenofovir who had renal damage. A significant association was found between being a homozygote carrier of the *C* allele in position *-24* of *ABCC2* and tubular dysfunction in patients treated with tenofovir. The fact that this genetic variant is detected in only 24% of patients with renal damage associated with the use of tenofovir suggests that this genetic determinant may favor this toxicity but is not the only determining factor[146].

The results of these studies should be interpreted with caution, given the small sample size and scant differences found between the groups. On the other hand, the functional effect of the polymorphisms described is unknown, as are the mechanisms by which these variants can increase susceptibility to the toxicity of tenofovir, considering that tenofovir is not a substrate of MRP2 but of MRP4[144]. Although definitive data linking *MRP4* polymorphisms with tubulopathy secondary to treatment with tenofovir are lacking, Kiser, et al. have recently identified a relationship between *ABCC4 3463A→G* SNP and intracellular tenofovir diphosphate concentrations in 30 HIV-infected patients. In this study, carriers of the *ABCC4 3463G* variant had concentrations 35% higher than that of carriers of the wild-type allele ($p = 0.04$), suggesting that genetic variations of this drug transporter may play a role in the intracellular accumulation of tenofovir[147].

Hyperamylasemia and acute pancreatitis

Elevated amylase or lipase is common in patients infected with HIV and is frequently associated with antiretroviral treatment[148]. In most cases these elevations are asymptomatic, although occasionally they can cause acute pancreatitis[149].

In a population not infected with HIV, certain mutations in the CFTR gene (cystic fibrosis transmembrane conductance regulator) and the SPINK-1 gene (serine protease inhibitor Kazal-1), which encode for a trypsin inhibitor in the cytoplasm of pancreatic acinar cells, have been associated with a higher risk of developing pancreatitis[150,151]. Swiss cohort researchers analyzed whether those mutations predispose for the development of pancreatic alterations in patients infected with HIV receiving antiretroviral treatment[152]. In a cross-sectional study, they identified 51 cases (4.5% of all patients evaluated) with pancreatic alterations (10 had suffered from acute pancreatitis and 41 presented an asymptomatic elevation of pancreatic enzymes) and they compared them to 51 controls matched for age, sex, viral load, $CD4^+$ T lymphocyte count and antiretroviral drugs. In total, they found 13 carriers of mutations in the *CFTR* and *SPINK-1* genes (12.7%). The concentrations of amylase were not significantly different in the patients with and without mutations; however, among the patients with hyperamylasemia, those with mutations were found to have higher concentrations of plasma amylase. Furthermore, the mutations were present in four of the 10 (40%) cases with acute pancreatitis and only in seven of the 51 (14%) patients in the control group ($p = 0.01$)[152].

Hypersensitivity reactions caused by abacavir

Hypersensitivity reaction in patients who receive abacavir is characterized by exanthema and fever, often accompanied by malaise and gastrointestinal and respiratory alterations. It is therefore a multiorgan syndrome. This adverse effect occurs during the first six weeks of treatment with abacavir[153] and completely resolves upon suspension of the drug. There is, however, a risk of a potentially fatal reaction if abacavir is reintroduced in patients who have developed HSR[154].

Hypersensitivity reaction due to abacavir occurs in 5-8% of Caucasian patients who receive the drug, while the risk in black patients is lower, at about 3%[153,155,156]. Hypersensitivity reaction due to abacavir is idiosyncratic, genetically determined, in that it is impossible to clinically predict the likelihood with which a person might develop it. However, several variables have been identified that are associated with a higher risk of presenting with HSR due to abacavir, including being Caucasian and having a high $CD8^+$ T-cell count[157].

Because the HLA system is involved in the majority of hypersensitivity reactions to medications, two initial independent pharmacogenetic studies evaluated the possible association between HLA system genotypes/haplotypes and HSR due to abacavir. Both studies found that the haplotypes *HLA-B*5701, HLA-DR7,* and *HLA-DQ3* were associated with the presence of this syndrome[158,159], findings which have been replicated in subsequent observational studies[160,161].

These findings encouraged a multinational, multicenter, randomized clinical trial called PREDICT-1[162]. In this study, patients undergoing treatment with abacavir and those not previously treated with the drug were randomized into two groups. A prospective *HLA-B*5701* test was given to a group of more than 900 patients before initiating treatment with abacavir and, if the result was positive, abacavir was not administered to the patient (prospective pharmacogenetic evaluation group). The patients included in the second group ($n > 900$) were treated with abacavir according to common clinical practice, without a prior genetic test (control group). All patients that began treatment with abacavir were monitored for six weeks and those that presented cutaneous exanthema were given an immunological confirmation test by means of an epicutaneous test with abacavir that confirmed (in the event of a positive result) or excluded (if the result was negative) HSR due to abacavir.

The prevalence of *HLA-B*5701* in the (mostly white) population studied was 5.6%. In the prospective pharmacogenetic evaluation group, the incidence of clinical HSR attributed to abacavir was 3.4%, while in the control group it was 7.8% ($p < 0.001$). When HSR was confirmed with the epicutaneous patch, the immunologically confirmed incidence of HSR due to abacavir was 0% in the prospective pharmacogenetic evaluation group and 2.7% in the control group ($p < 0.001$). These data indicated a negative predictive value for HSR of 100% in *HLA-B*5701* negative individuals and a positive predictive value for HSR of 47.9% in *HLA-B*5701* positive individuals. For the first time it was demonstrated that prescreening with a pharmacogenetic test reduced the incidence of a serious adverse event. Additionally, this was demonstrated through a randomized clinical trial. The publication of these results led to an important change with regard to pharmacogenetic testing prior to prescribing abacavir[162]. As mentioned above, the population studied in PREDICT-1 was mainly white – a population with a high prevalence of *HLA-B*5701*. Subsequent studies have confirmed the efficacy of prior pharmacogenetic evaluation in black individuals[163].

The results of the PREDICT-1 study indicate that pretesting for *HLA-B*5701* before prescribing abacavir and avoiding administering it to *HLA-B*5701* positive patients will significantly reduce the risk of HSR due to this drug and make its administration safer. In fact, this screening represents the first pharmacogenetic test with a robust clinical application intended to improve the impact of a prescribed drug. The evaluation of this genetic determinant before prescribing abacavir is now recommended in clinical guides on treating patients infected with HIV and forms part of our day-to-day clinical practice[164-166].

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References

1. Gazzard B. Antiretroviral therapy for HIV: medical miracles do happen. Lancet. 2005;366:346-7.
2. Furrer H, Opravil M, Bernasconi E, Telenti A, Egger M. Stopping primary prophylaxis in HIV-1-infected patients at high risk of. Toxoplasma encephalitis. Swiss HIV Cohort Study. Lancet. 2000;355:2217-8.
3. López Bernaldo de Quirós J, Miró J, Peña J, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after highly active antiretroviral therapy in patients with HIV infection. Grupo de Estudio del SIDA 04/98. N Engl J Med. 2001;344:159-67.
4. Martin A, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by *HLA-B*5701* and a haplotypic *Hsp70-Hom* variant. Proc Natl Acad Sci USA. 2004;101:4180-5.
5. Berns J, Kasbekar N. Highly active antiretroviral therapy and the kidney: an update on antiretroviral medications for nephrologists. Clin J Am Soc Nephrol. 2006;1:117-29.

6. Núñez M. Hepatotoxicity of antiretrovirals: incidence, mechanisms and management. J Hepatol. 2006:44(Suppl 1):S132-9.
7. Mallon P. Pathogenesis of lipodystrophy and lipid abnormalities in patients taking antiretroviral therapy. AIDS Rev. 2007;9:3-15.
8. Oh J, Hegele R. HIV-associated dyslipidaemia: pathogenesis and treatment. Lancet Infect Dis. 2007;7:787-96.
9. Cressey T, Lallemant M. Pharmacogenetics of antiretroviral drugs for the treatment of HIV-infected patients: An update. Infect Genet Evol. 2007;7:333-42.
10. Tarr P, Telenti A. Toxicogenetics of antiretroviral therapy: genetic factors that contribute to metabolic complications. Antivir Ther. 2007; 12:999-1013.
11. The International HapMap Consortium. A haplotype map of the human genome. Nature. 2005;437:1299-320.
12. Hattersley A, McCarthy M. What makes a good genetic association study? Lancet. 2005;366:1315-23.
13. Arnedo M, Taffé P, Sahli R, et al. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. Pharmacogenet Genomics. 2007;17:755-64.
14. Colhoun H, McKeigue P, Davey S. Problems of reporting genetic associations with complex outcomes. Lancet. 2003;361:865-72.
15. Freimer N, Sabatti C. Guidelines for association studies in Human Molecular Genetics. Hum Mol Genet. 2005;14:2481-3.
16. Bozzette S, Ake C, Tam H, et al. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. N Engl Med. 2003;348:702-10.
17. Mary-Krause M, Cotte L, Simon A, et al. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. AIDS. 2003;17:2479-86.
18. Friis-Moller N, Sabin C, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. N Engl J Med. 2003; 349:1993-2003.
19. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med. 2005;352:48-62.
20. Friis-Moller N, Reiss P, Sabin C. Class of antiretroviral drugs and the risk of myocardial infarction. N Engl J Med. 2007;356:1723-35.
21. Executive summary of the third report of the National Cholesterol Education Program (NECP). Expert panel on detection, evaluation and treatment of high blood cholesterol in adults (Adult Treatment Panel III). JAMA. 2001;285:2486-97.
22. Guardiola M, Ferré R, Salazar J, et al. Protease inhibitor -associated dyslipidemia in HIV-infected patients is strongly influenced by the APOA5-1131T>C gene variation. Clin Chem. 2006;52:1914-9.
23. Fauvel J, Bonnet E, Ruidavets J, et al. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. AIDS. 2001;15:2397-406.
24. Tarr P, Taffe P, Bleiber G, et al. Modeling the influence of APOC3, APOE and TNF polymorphisms on the risk of antiretroviral therapy-associated lipid disorders. J Infect Dis. 2005;191:1419-26.
25. Foulkes A, Whol D, Frank I, et al. Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. PLoS Med. 2006;3:e52.
26. Miserez A, Muller P, Barella L, et al. A single-nucleotide polymorphism in the sterol-regulatory element-binding protein 1c gene is predictive of HIV-related hyperlipoproteinaemia. AIDS. 2001;15:2045-9.
27. Schaap F, Rensen P, Voshol P, et al. APOAV reduces plasma triglycerides by inhibiting very low density lipoprotein-triglyceride (VLDL-TG) production and stimulating lipoprotein lipase-mediated VLDL-TG hydrolysis. J Biol Chem. 2004;279:27941-7.
28. Li W, Dammerman M, Smith J, et al. Common genetic variation in the promoter of the human apo CIII gene abolishes regulation by insulin and may contribute to hypertriglyceridemia. J Clin Invest. 1995;96:2601-5.
29. Mahley R, Rall S. Apolipoprotein E: far more than a lipid transport protein. Annu Rev Genomics Hum Genet. 2000;1:507-37.
30. Behrens G, Schmidt H, Stoll M, et al. ApoE genotype and protease-inhibitor-associated hyperlipidaemia. Lancet. 1999;354:76.
31. Lister R, Youle M, Nair D, et al. Latent dysbetalipoproteinaemia precipitated by HIV-protease-inhibitors. Lancet. 1999;353:1678.
32. Caron M, Auclair M, Vigouroux C, et al. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. Diabetes. 2001;50:1378-88.
33. Yang A, King M, Han L, et al. Lack of correlation between SREBP1 genotype and hyperlipidemia in individuals treated with highly active antiretroviral therapy. AIDS. 2003;17:2142-3.
34. Carr A, Emery S, Law M, et al. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. Lancet. 2003;361:726-35.
35. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS. 1998;12:F51-8.
36. Lo J, Mulligan K, Tai V, et al. "Buffalo hump" in men with HIV-1 infection. Lancet. 1998;351:867-70.
37. Miller K, Jones E, Yanovski J, et al. Visceral abdominal-fat accumulation associated with the use of indinavir. Lancet. 1998;351:871-5.
38. Martínez E, Mocroft A, Garcia-Viejo M, et al. Risk of lipodystrophy in HIV-1 infected patients treated with protease inhibitors: a prospective cohort study. Lancet. 2001;357:592-8.
39. Saint-Marc T, Partisani M, Poizot-Martin I, et al. A syndrome of peripheral fat wasting (lipodystrophy) in patients receiving long-term nucleoside analogue therapy. AIDS. 1999;13:1657-67.
40. Mallal S, John M, Moore C, et al. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. AIDS. 2000;14:1309-16.
41. Joly V, Flandre P, Meiffredy V, et al. Increased risk of lipoatrophy under stavudine in HIV-1-infected patients: results of a substudy from a comparative trial. AIDS. 2002;16:2447-54.
42. Mallon P, Miller J, Cooper D, et al. Prospective evaluation on the effects of antiretroviral therapy on body composition in HIV-1 infected men starting therapy. AIDS. 2003;17:971-9.
43. Nolan D, Hammond E, Martin A, et al. Mitochondrial DNA depletion and morphologic changes in adipocytes associated with nucleoside reverse transcriptase inhibitor therapy. AIDS. 2003;17:1329-38.
44. Miro O, Lopez S, Martínez E, et al. Mitochondrial effects of HIV infection on the peripheral blood mononuclear cells of HIV-infected patients who were never treated with antiretrovirals. Clin Infect Dis. 2004;39:710-6.
45. Zaera M, Miro O, Pedrol E, et al. Mitochondrial involvement in antiretroviral therapy-related lipodystrophy. AIDS. 2001;15:1643-51.
46. Shikuma C, Hu N, Milne C, et al. Mitochondrial DNA decrease in subcutaneous adipose tissue of HIV-infected individuals with peripheral lipoatrophy. AIDS. 2001;15:1801-9.
47. Walker U, Bickel M, Lutke Volksbeck S, et al. Evidence of nucleoside analogue reverse transcriptase inhibitor-associated genetic and structural defects of mitochondria in adipose tissue of HIV-infected patients. J Acquir Immune Defic Syndr. 2002;29:117-21.
48. Martin A, Hammond E, Nolan D, et al. Accumulation of mitochondrial mutations in human immunodeficiency virus-infected patients treated with nucleoside-analogue reverse-transcriptase inhibitors. Am J Hum Genet. 2003;72:549-60.
49. Garg A. Acquired and inherited lipodystrophies. N Engl J Med. 2004; 350:1220-34.
50. Dunnigan M, Cochrane M, Kelly A, Scott J. Familial lipoatrophic diabetes with dominant transmission: a new syndrome. Q J Med. 1974; 43:33-48.
51. Garg A, Peshock R, Fleckenstein JL. Adipose tissue distribution pattern in patients with familial partial lipodystrophy (Dunnigan variety). J Clin Endocrinol Metab. 1999;84:170-4.
52. Shackleton S, Lloyd D, Jackson S, et al. LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. Nat Genet. 2000;24:153-6.
53. Lloyd D, Trembath R, Shackleton S. A novel interaction between lamin A and SREBP1: implications for partial lipodystrophy and other laminopathies. Hum Mol Genet. 2002;11:769-77.
54. Caron M, Auclair M, Sterlingot H, et al. Some HIV protease inhibitors alter lamin A/C maduration and stability, SREBP-1 nuclear localization and adipocyte differentiation. AIDS. 2003;17:2437-44.
55. Domingo P, Baiget M, Arroyo J, et al. Absence of mutations in exon 8 of the gene in combination antiretroviral therapy-associated partial lipodystrophy. J Acquir Immune Defic Syndr. 2002;30:457-8.
56. Ledru E, Christeff N, Patey O, et al. Alteration of tumor necrosis factor-alpha T-cell homeostasis following potent antiretroviral therapy: contribution to the development of human immunodeficiency virus-associated lipodystrophy syndrome. Blood. 2000;95:3191-8.
57. Johnson J, Albu J, Engelson E, et al. Increased systemic and adipose tissue cytokines in patients with HIV-associated lipodystrophy. Am J Physiol Endocrinol Metab. 2004;286:E261-71.
58. Maher B, Alfirevic A, Vilar F, et al. TNF-alpha promoter region gene polymorphisms in HIV-positive patients with lipodystrophy. AIDS. 2002;16:2013-8.
59. Nolan D, Moore C, Castley A, et al. Tumour necrosis factor-alpha gene -238G/A promoter polymorphism associated with a more rapid onset of lipodystrophy. AIDS. 2003;17:121-3.
60. Asensi V, Rego C, Montes A, et al. IL-1b (+3954C/T) polymorphism could protect HIV-infected patients on HAART against the lipodystrophic syndrome. Gen Med. 2008;10:215-23.
61. Saumoy M, López-Dupla M, Broch M, et al. A study of the IL-6 system in HIV-1-infected patients with combination antiretroviral therapy-related fat redistribution syndromes. AIDS. 2008;22:893-6.
62. Saumoy M, Veloso S, Alonso-Villaverde C, et al. PPARgamma Pro12Ala Polymorphism in HIV-1-infected Patients with HAART-related Lipodystrophy. Curr HIV Res. 2009;7:533-40.
63. Zanone Poma B, Riva A, Nasi M, et al. Genetic polymorphisms differently influencing the emergence of atrophy and fat accumulation in HIV-related lipodystrophy. AIDS. 2008;22:1769-78.
64. Ranade K, Geese W, Noor M, et al. Genetic analysis implicates resistin in HIV lipodystrophy. AIDS. 2008;22:1561-8.
65. Ross R. Atherosclerosis: an inflammatory disease. N Engl J Med. 1999;340:115-26.

66. Danesh J, Collins R, Peto R. Chronic infections and coronary heart disease: is there a link? Lancet. 1997;350:430-6.
67. Coll B, Alonso-Villaverde C, Parra S, et al. The stromal derived factor-1 mutated allele (SDF1-3'A) is associated with a lower incidence of atherosclerosis in HIV-infected patients. AIDS. 2005;19:1877-83.
68. Coll B, Parra S, Alonso-Villaverde C, et al. HIV-infected patients with lipodystrophy have higher rates of carotid atherosclerosis: the role of monocyte chemoattractant protein-1. Cytokine. 2006;34:51-5.
69. Alonso Villaverde C, Coll B, Parra S, et al. Atherosclerosis in patients infected with HIV is influenced by a mutant monocyte chemoattractant protein-1 allele. Circulation. 2004;110:2204-9.
70. Abi-Younes S, Sauty A, Mach F, et al. The stromal cell-derived factor-1 chemokine is a potent platelet agonist highly expressed in atherosclerotic plaques. Circ Res. 2000;86:131-8.
71. Simmons G, Reeves J, Hibbitts S, et al. Co-receptor use by HIV and inhibition of HIV infection by chemokine receptor ligands. Immunol Rev. 2000;177:112-26.
72. Soriano A, Martínez C, Garcia F, et al. Plasma stromal cell-derived factor (SDF)-1 levels, SDF1-3'A genotype, and expression of CXCR4 on T lymphocytes: their impact on resistance to human immunodeficiency virus type 1 infection and its progression. J Infect Dis. 2002; 186:922-31.
73. Gear A, Camerini D. Platelet chemokines and chemokine receptors: linking hemostasis, inflammation and host defence. Microrcirculation. 2003;10:335-50.
74. Han K, Tangirala R, Green S, et al. Chemokine receptor CCR2 expression and monocyte chemoattractant protein-1-mediated chemotaxis in human monocytes: a regulatory role for plasma LDL. Arterioscler Thromb Vasc Biol. 1998;18:1983-91.
75. Staszewski S, Morales-Ramírez J, Tashima K, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. N Engl J Med. 1999;341:1865-73.
76. Marzolini C, Telenti A, Decosterd L, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. AIDS. 2001;15:1193-4.
77. Gutiérrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. Clin Infect Dis. 2005;41:1648-53.
78. Csajka C, Marzolini C, Fattinger K, et al. Population pharmacokinetics and effects of efavirenz in patients with human immunodeficiency virus infection. Clin Pharmacol Ther. 2003;73:20-30.
79. Hasse B, Gunthard H, Bleiber G, Krause M. Efavirenz intoxication due to slow hepatic metabolism. Clin Infect Dis. 2005;40:e22-3.
80. Lowenhaupt E, Matson K, Qureishi B, Saitoh A, Pugatch D. Psycosis in a 12-year-old HIV-positive girl with an increased serum concentration of efavirenz. Clin Infect Dis. 2007;45:e128-30.
81. Stahle L, Moberg L, Svensson J, Sonnerborg A. Efavirenz plasma concentrations in HIV-infected patients:inter-and intraindividual variability and clinical effects. Ther Drug Monit. 2004;26:267-70.
82. Ward B, Gorski J, Jones D, Hall S, Flockhart D, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. J Pharmacol Exp Ther. 2003;306:287-300.
83. Klein K, Lang T, Saussele T, et al. Genetic variability of CYP2B6 in populations of African and Asian origin: allele frequencies, novel functional variants, and possible implications for anti-HIV therapy with efavirenz. Pharmacogenet. Genomics. 2005;15:861-73.
84. Lang T, Klein K, Fischer J, et al. Extensive genetic polymorphism in the human CYP2B6 gene with impact on expression and function in human liver. Pharmacogenetics. 2001;11:399-415.
85. Haas D, Ribaudo H, Kim R, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Group study. AIDS. 2004;18:2391-400.
86. Tsuchiya K, Gatanaga H, Tachikawa N, et al. Homozygous CYP2B6 *6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. Biochem Biophys Res Commun. 2004;319:1322-6.
87. Rodriguez-Nóvoa S, Barreiro P, Rendón A, Jiménez-Nacher I, Gonzalez-Lahoz J, Soriano V. Influence of 516 G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. Clin Infect Dis. 2005;40:1358-61.
88. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenet Genomics. 2005;15:1-5.
89. Haas D, Smeaton L, Shafer R, et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an Adult Aids Clinical Trials Group Study. J Infect Dis. 2005;192:1931-42.
90. Ribaudo H, Haas D, Tierney C, et al. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group study. Clin Infect Dis. 2006;42:401-7.
91. Wang J, Sonnerborg A, Rane A, et al. Identification of a novel specific CYP2B6 allele in Africans causing impaired metabolism of the HIV drug efavirenz. Pharmacogenet Genomics. 2006;16:191-8.
92. Rotger M, Tegude H, Colombo S, et al. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. Clin Pharmacol Ther. 2007;81:557-66.
93. Fellay J, Marzolini C, Meaden ER, et al. Response to antiretroviral treatment in HIV-infected individuals with allelic variants of the multidrug resistant transporter 1: a pharmacogenetics study. Lancet. 2002;359:30-6.
94. Di Iulio J, Fayet A, Arab-Alameddine M, et al. In vivo analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. Pharmacogenet Genomics. 2009;19:300-9.
95. Arab-Alameddine M, Di Iulio J, Buclin T, et al. Pharmacogenetics-based population pharmacokinetic analysis of efavirenz in HIV-1-infected individuals. Clin Pharmacol Ther. 2009;85:485-94.
96. Motsinger A, Ritchie M, Shafer R, et al. Multilocus genetic interactions and response to efavirenz-containing regimens: an adult AIDS clinical trials group study. Pharmacogenet Genomics. 2006;16:837-45.
97. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P4502B6 *6 and *26. Clin Infect Dis. 2007;45:1230-7.
98. Dieterich D, Robinson P, Love J, Stern J. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. Clin Infect Dis. 2004;38(Suppl 2):S80-9.
99. Stern J, Robinson P, Love J, Lanes S, Imperiale M, Mayers D. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. J Acquir Immune Defic Syndr. 2003;34(Suppl 1):S21-33.
100. Patel S, Johnson S, Belknap S, Chan J, Sha B, Bennett C. Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV infected individuals. J Acquir Immune Defic Syndr. 2004;35:120-5.
101. Martin M, Nolan D, James I, et al. Predisposition to nevirapine hypersensitivity associated with HLA-DBR1*0101 and abrogated by low CD4 T-cell counts. AIDS. 2005;5:97-9.
102. Littera R, Carcassi C, Masala A, et al. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. AIDS. 2006;20:1621-6.
103. Gatanaga H, Yazaki H, Tanuma J, et al. HLA-Cw8 primarily associated with hypersensitivity to nevirapine. AIDS. 2007;21:264-5.
104. Stormer E, von Moltke L, Perloff M, Greenblatt D. Differential modulation of P-glycoprotein expression and activity by non-nucleoside HIV-1 reverse transcriptase inhibitors in cell culture. Pharm Res. 2002;19:1038-45.
105. Almond L, Edirisinghe D, Dalton M, Bonington A, Back D, Khoo S. Intracellular and plasma pharmacokinetics of nevirapine in human immunodeficiency virus-infected individuals. Clin Pharmacol Ther. 2005; 78:132-42.
106. Ritchie M, Haas D, Motsinger A, et al. Drug transporter and metabolizing enzyme gene variants and nonnucleoside reverse transcriptase inhibitor hepatotoxicity. Clin Infect Dis. 2006;43:779-82.
107. Haas D, Barlett J, Andersen J, et al. Pharmacogenetics of nevirapine associated hepatotoxicity: an adult AIDS Clinical Trials Group collaboration. Clin Infect Dis. 2006;43:783-6.
108. Ciccacci C, Borgiani P, Ceffa S, et al. Nevirapine-induced hepatotoxicity and pharmacogenetics: a retrospective study in a population from Mozambique. Pharmacogenomics. 2010;11:23-31.
109. Plosker G, Noble S. Indinavir: a review of its use in the management of HIV infection. Drugs. 1999;58:1165-203.
110. Busti A, Hall R, Margolis D. Atazanavir for the treatment of human immunodeficiency virus infection. Pharmacotherapy. 2004;24:1732-47.
111. Zucker S, Qin X, Rouster S, et al. Mechanism of indinavir-induced hyperbilirubinemia. Proc Natl Acad Sci USA. 2001;98:12671-6.
112. Huang C, Huang M, Lin M, Yang S, Teng H, Tang K. Genetic factors related to unconjugated hyperbilirubinemia amongst adults. Pharmacogenet Genomics. 2005;15:43-50.
113. Rodríguez-Nóvoa S, Martín-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. AIDS. 2007;21:41-6.
114. Boyd MA, Srasuebkul P, Ruxrungtham K, et al. Relationship between hyperbilirubinemia and UDP-glucuronosyltransferase 1A1(UGT1A1) polymorphism in adult HIV-infected Thai patients treated with indinavir. Pharmacogenet Genomics. 2006;16:321-9.
115. Rotger M, Taffé P, Bleiber G, et al. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. J Infect Dis. 2005;192:1381-6.
116. Rodríguez Nóvoa S, Barreiro P, Rendón A, et al. Plasma levels of atazanavir and the risk of hyperbilirubinemia are predicted by the 3435C–>T polymorphism at the multidrug resistance gene 1. Clin Infect Dis. 2006;42:291-5.
117. Lewis W, Copeland W, Day B. Mitochondrial DNA depletion, oxidative stress, and mutation: mechanisms of dysfunction from nucleoside reverse transcriptase inhibitors. Lab Invest. 2001;81:777-90.
118. Keswani S, Pardo C, Cherry C, Hoke A, McArthur J. HIV-associated sensory neuropathies. AIDS. 2002;16:2105-17.

119. Browne M, Mayer K, Chafee S, et al. 2', 3'-didehydro-3'-deoxythymidine (d4T) in patients with AIDS or AIDS-related complex: a phase I trial. J Infect Dis. 1993;167:21-9.
120. Kelleher T, Cross A, Dunkle L. Relation of peripheral neuropathy to HIV treatment in four randomized clinical trials including didanosine. Clin Ther. 1999;21:1182-92.
121. Hulgan T, Haas D, Haines J, et al. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS Clinical Trial Group study. AIDS. 2005;19:1341-9.
122. Canter J, Haas D, Kallianpur A, et al. The mitochondrial pharmacogenomics of haplogroup T: MTND2 (*) LHON4 917G and antiretroviral therapy-associated peripheral neuropathy. Pharmacogenomics J. 2008;8:71-7.
123. Kallianpur A, Hulgan T, Canter J, et al. Hemochromatosis (HFE) gene mutations and peripheral neuropathy during antiretroviral therapy. AIDS. 2006;20:1503-13.
124. Lactic Acidosis International Study Group. Risk factors for lactic acidosis and severe hyperlactataemia in HIV-1-infected adults exposed to antiretroviral therapy. AIDS. 2007;21:2455-64.
125. Yamanaka H, Gatanaga H, Kosalaraksa P, et al. Novel mutation of human DNA polymerase χ associated with mitochondrial toxicity induced by anti-HIV treatment. J Infect Dis. 2007;195:1419-25.
126. Coca S, Parazella M. Acute renal failure associated with tenofovir: evidence of drug-induced nephrotoxicity. Am J Med Sci. 2002;324:342-4.
127. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. Clin Infect Dis. 2003;36:1070-3.
128. Rifkin B, Perazella M. Tenofovir-associated nephrotoxicity: Fanconi syndrome and renal failure. Am J Med. 2004;117:282-4.
129. Padilla S, Gutiérrez F, Masiá M, Cánovas V, Orozco C. Low frequency of renal function impairment during one-year of therapy with tenofovir-containing regimens in the real-world: a case-control study. AIDS Patient Care STDS. 2005;19:421-4.
130. Saumoy M, Vidal F, Peraire J, et al. Proximal tubular kidney damage and tenofovir: a role for mitochondrial toxicity? AIDS. 2004;18:1741-2.
131. Gallant J, Parish M, Keruly J, Moore R. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. Clin Infect Dis. 2005;40:1194-8.
132. Mocroft A, Kirk O, Gatell J, et al. Chronic renal failure among HIV-1-infected patients. AIDS. 2007;21:1119-27.
133. Nelson M, Katlama C, Montaner J, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. AIDS. 2007;21:1273-81.
134. Zimmermann A, Pizzoferrato T, Bedford J, Morris A, Hoffman R, Braden G. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. Clin Infect Dis. 2006;42:283-90.
135. Murphy M, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing didanosine. Clin Infect Dis. 2003;36:1082-5.
136. Crane H, Kestenbaum B, Harrington R, Kitahata M. Amprenavir and didanosine are associated with declining kidney function among patients receiving tenofovir. AIDS. 2007;21:1431-9.
137. Masiá M, Gutiérrez F, Padilla S, Ramos J, Pascual J. Didanosine-associated toxicity: a predictable complication of therapy with tenofovir and didanosine? J Acquir Immune Defic Syndr. 2004;35:427-8.
138. Masiá M, Gutiérrez F, Padilla S, Ramos J, Pascual J. Severe toxicity associated with the combination of tenofovir and didanosine: case report and review. Int J STD AIDS. 2005;16:646-8.
139. Vidal F, Domingo J, Guallar J, et al. In vitro cytotoxicity and mitochondrial toxicity of tenofovir alone and in combination with other antiretrovirals in human renal proximal tubule cells. Antimicrob Agents Chemother. 2006;50:3824-32.
140. Venhoff N, Setzer B, Melkaoui K, Walker U. Mitochondrial toxicity of tenofovir, emtricitabine and abacavir alone and in combination with additional nucleoside reverse transcriptase inhibitors. Antivir Ther. 2007; 12:1075-85.
141. Cihlar T, Ray A, Laflamme G, et al. Molecular assessment of the potential for renal drug interactions between tenofovir and HIV protease inhibitors. Antivir Ther. 2007;12:267-72.
142. Motohashi H, Sakurai Y, Saito H, et al. Gene expression levels and immunolocalization of organic ion transporters in the human kidney. J Am Soc Nephrol. 2002;13:866-74.
143. Miller D. Nucleoside phosphonate interactions with multiple organic anion transporters in renal proximal tubule. J Pharmacol Exp Ther. 2001;299:567-74.
144. Ray A, Cihlar T, Robinson K, et al. Mechanism of active renal tubular efflux of tenofovir. Antimicrob Agents Chemother. 2006;50:3297-304.
145. Izzedine H, Hulton J, Villard E, et al. Association between ABCC2 gene haplotypes and tenofovir-induced proximal tubulopathy. J Infec Dis. 2006;194:1481-91.
146. Rodriguez-Nóvoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. Clin Infect Dis. 2009;48:e108-16.
147. Kiser J, Aquilante C, Anderson P, et al. Clinical and genetic determinants of intracellular tenofovir diphosphate concentrations in HIV-infected patients. J Acquir Immune Defic Syndr. 2008;47:298-303.
148. Argiris A, Mathur-Wagh U, Wilets I, Mildvan D. Abnormalities of serum amylase and lipase in HIV-positive patients. Am J Gastroenterol. 1999;94:1248-52.
149. Cappell M, Marks M. Acute pancreatitis in HIV-seronegative patients: a case control study of 44 patients. Am J Med. 1995;98:243-8.
150. Cohn J, Friedman K, Noone P, Knowles M, Silverman L, Jowell P. Relation between mutations of the cystic fibrosis gene and idiopathic pancreatitis. N Engl J Med. 1998;339:653-8.
151. Pfützer R, Barmada M, Brunskill A, et al. SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology. 2000;119:615-23.
152. Felley C, Morris M, Wonkam A, et al. The role of CFTR and SPINK-1 mutations in pancreatitis disorders in HIV-positive patients: a case-control study. AIDS. 2004;18:1521-7.
153. Hethrerington S, McGuirk S, Powell G, et al. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. Clin Ther. 2001;23:1603-14.
154. Escaut L, Liotoer J, Albengres E, et al. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. AIDS. 1999;13:1419-20.
155. Cutrell A, Hernández J, Fleming J, et al. Updated clinical risk factor analysis of suspected hypersensitivity reactions to abacavir. Ann Pharmacother. 2004;38:2171-2.
156. Easterbrook P, Waters A, Murad S, et al. Epidemiological risk factors for hypersensitivity reactions to abacavir. HIV Med. 2003;4:321-4.
157. Brothers C, Wannamaker P, Sutherland-Philips D. Lower reported rate of suspected hypersensitivity reaction to abacavir among black patients. 46th ICAAC San Francisco 2006; [abstract H-1065].
158. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B*5701, HLA-DR7 and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. Lancet. 2002;459;727-32.
159. Hethrerington S, Hughes A, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. Lancet. 2002;359:1121-2.
160. Martin A, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 abd haplotypic Hsp70-Hom variant. Proc Natl Acad Sci USA. 2004;101:4180-5.
161. Rauch A, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in Western Australian HIV cohort study. Clin Infect Dis. 2006;43.99-102.
162. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. N Engl J Med. 2008;358:568-79.
163. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-B*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. Clin Infect Dis. 2008;46:1111-8.
164. Goldman M, Faruki H. Abacavir hypersensitivity: a model system for pharmacogenetic test adoption. Genet Med. 2008;10:874-9.
165. Philips E, Mallal S. Successful translation of pharmacogenetics into the clinic: the abacavir example. Mol Diagn Ther. 2009;13:1-9.
166. GESIDA Expert Panel. National AIDS Plan. GESIDA/AIDS National Plan recommendation with respect to antiretroviral treatment in adults infected with HIV (February 2009 update). Enferm Infecc Microbiol Clin. 2009;27:222-35.