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REVIEW

Pharmacogenetics as a tool to tailor antiretroviral therapy: A review

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Abstract

Highly active antiretroviral therapy (HAART) has substantially changed human immunodeficiency virus (HIV) infection from an inexorably fatal condition into a chronic disease with a longer life expectancy. This means that HIV patients should receive antiretroviral drugs lifelong, and the problems concerning with a chronic treatment (tolerability, side effects, adherence to treatment) have now become dominant. In this context, strategies for the treatment personalization have taken a central role in optimizing the therapeutic response and prevention of adverse drug reactions. In this setting, the study of pharmacogenetics features could be a very useful tool in clinical practice; moreover, nowadays the study of genetic profiles allows optimizations in the therapeutic management of People Living With HIV (PLWH) through the use of test introduced into clinical practice and approved by international guidelines for the adverse effects prevention such as the genetic test HLA-B*5701 to detect hypersensitivity to Abacavir. For other tests further studies are needed: CYP2B6 516 G > T testing may be able to identify patients at higher risk of Central Nervous System side effects following standard dosing of Efavirenz, UGT1A1*28 testing before initiation of antiretroviral therapy containing Atazanavir may aid in identifying individuals at risk of hyperbilirubinaemia. Pharmacogenetics represents a research area with great growth potential which may be useful to guide the rational use of antiretrovirals.

Key words: Pharmacogenetics; Pharmacogenomics; Single nucleotide polymorphism; Pharmacokinetics; Highly active antiretroviral therapy; Polymorphism; Phenotype; Pharmacodynamic

Core tip: The wide availability of drugs and therapeutic regimens for the human immunodeficiency virus infection treatment and the presence of associated adverse effects related to interindividual variability leads the clinician to look for an individualized therapy as much as possible. Pharmacogenetics can provide useful tools for this purpose and can propose models of genetics tests that, however, need to be further studied. This paper aim is to provide a critical and understandable review of published literature and a guidance about future

prospects in this field.

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INTRODUCTION

The concept of personalized therapy is of increasing interest in the management of antiretroviral therapy and PLWH [people living with *human immunodeficiency virus* (HIV)], especially now, because we must confront with a chronic therapy that can count on a large number of possible combinations, but also on a number of individual issues of effectiveness, toxicity, tolerability and convenience. Pharmacogenomics, as well as the need for specific diagnostic tests for therapy customization, drug-drug interactions and TDM (Therapeutic Drug Monitoring) are emerging topics that, in a long-term management of HIV infection, will need to be explored during the doctor-patient interview.

Pharmacogenetics deals with the role of genes in response to drugs and it is well known that there is a variability between individuals in drugs response due to hereditary genetic factors.

The purpose of pharmacogenetics is to identify candidate genes, define the differences in the candidate genes among individuals, and to correlate the phenotype's changes - defined by a specific drug response - with the patient's genotype.

These studies, using technologies of high capacity for DNA analysis (such as DNA microarrays or DNA chips), have been extended, more recently, to the whole human genome analysis, taking into account the possibility that the drug response is influenced by a multitude of genes, not just those ones that code for proteins directly involved in the drug action, but also by the genes power to alter this response, exactly called "modifiers". The development of this research gave impetus to the development of pharmacogenomics.

"SNPs" (single nucleotide polymorphism) are the result of a single pair of bases substitution in DNA sequence. They are very common and present in every 1000 base pairs. The entire genome contains 3000000-10000000 SNPs and of these, one million and eight hundred thousand were characterized by SNP consortium. It is believed that each gene has between five and ten SNPs, although only less of 1% has got biological significance. This biological significance may come from substitution of an amino acid in a protein or by alterations in the expression of the protein due to SNPs in the promoter region. Polymorphisms affect the concentration and the half-life of the drug in the blood.

Drugs with concentrations and half-life in the blood higher than the average population indicate a decreased drug metabolism. However, a reduction of the drug concentration and half-life in the blood is indicative of a high metabolism of the drug. In the first case the adverse effects are increased, in the second case therapeutic effects are reduced. This example shows the importance of pharmacogenomics and the analysis of the whole genome to discover the complex mechanisms that determine the response to drugs.

The potential of pharmacogenomics is to identify patients with the same diagnosis but genetically different about the response to drugs in terms of efficacy anwd adverse reactions. Patients with an unfavourable pharmacogenetic profile must be treated with alternative drugs or different doses. Individuals with a pharmacogenetic profile compatible with a favorable response can be treated with medication and conventional doses. The results of genetic testing may be used by the physician to choose which drug can be used for the patient's treatment, to optimize the dose and to minimize the risk of side effects. The utility of the pharmacogenetic test, therefore, consists in the possibility of being able to evaluate the response of a patient to a certain drug on the basis of a genetic test routine, to customize the therapy.

Pharmacogenomics is thus an important key to achieve a predictive medicine aim to provide personalized therapy: the right drug at the right dose for the right patient.

Highly active antiretroviral therapy (HAART) against HIV infection has considerably increased life expectancy and in this statement there is its great application in clinical daily. These drugs, however, have the disadvantage of relatively high incidence of side effects and a lack of response to therapy by some subjects. Pharmacogenomics could be particularly useful in the case of drugs, such as antiretrovirals, which have a narrow therapeutic index associated with pharmacokinetic and pharmacodynamic variables.

An example of pharmacogenomics, applied in the context of antiretroviral treatment and more generally in the pharmacological field, is evident in the use of the screening test for the HLAB5701 in clinical practice, able to detect hypersensitivity to Abacavir, recommended by international guidelines as a preparatory test to use this drug in an HIV patient's treatment regimen. This paper aim is to provide a critical and understandable review of published literature and a guidance about future prospects in this field.

PHARMACOGENETICS AND HAART TOXICITY

Nucleoside reverse transcriptase inhibitors

Abacavir is a nucleoside reverse transcriptase inhibitor used in conjunction with other antiretroviral agents in the treatment of HIV infection and it is a popular choice for first-line treatment. Abacavir is generally well tolerated but can cause hypersensitivity in 5% to 8% of patients during the first 6 wk of treatment[1,2]; symptoms include fever, rash, constitutional symptoms, gastrointestinal tract symptoms, and respiratory symptoms (HRS -

Hypersensitivity Reaction Syndrome)[3]. Symptoms worsen with continued usage and can be potentially life threatening if the patient is rechallenged after discontinuation[4].

Hypersensitivity to Abacavir is immunologically mediated, driven by MHC-I antigen presentation and activation of HLA-B*5701. HLA-B*5701 activation restricted to CD8+ T-cells results in the secretion of inflammatory mediators (TNF-α and IFN-γ) and induces the delayed-type hypersensitivity reaction[5,6].

HLA-B*5701 allele occurs at approximately 5% frequency in European populations, 1% in Asian populations, and less than 1% in African populations. In immunologically confirmed hypersensitivity, HLA-B*5701 genotyping is associated with a negative predictive value of nearly 100% and a positive predictive value of approximately 50%: patients without the allele are highly unlikely to develop an immunological hypersensitivity to Abacavir, but only about half of those with the allele will develop HRS.

Thus, although the carriage rate of the HLA-B*5701 allele is low, stratification of patients for Abacavir treatment based on HLA-B*5701 genotyping could virtually eliminate immunologically confirmed hypersensitivity, and appears to be a cost effective healthcare practice[7].

Screening for HLA-B*5701 prior to initiation of Abacavir therapy is widely and strictly recommended for naïve HIV subjects that are going to start antiretroviral treatment; HLA-B*5701 - positive individuals should not be prescribed Abacavir. It should be also remarked that a negative HLA-B*5701 test does not preclude the development of a non-immunologic hypersensitivity reaction to Abacavir or of a clinical hypersensitivity reaction to another antiretroviral agent that may be given along with Abacavir, therefore genotyping should not substitute for clinical vigilance, but can greatly reduce the incidence of Abacavir hypersensitivity by identifying patients at high risk before they are treated[8-14].

Although other nucleoside/nucleotide analogues reverse transcriptase can induce renal damage (in particular, have been reported with Didanosine and Abacavir) there is no doubt that the drug of this class more involved in this effect is Tenofovir (TDF), a nucleotide analogue of adenosine 5 monophosphate administered orally at a dose of 300 mg once daily, in combination with other antiretroviral agents in naive patients' treatment. It is one of the most widely used drugs in patterns of antiretroviral therapy, being placed between the molecules to be preferred in all international guidelines. It can cause damage at the level of the proximal renal tubule[15].

TDF can cause renal toxicity (proximal tubular type), possible acute renal failure, Fanconi syndrome, creatinine dysfunction and hypophosphatemia. Tenofovir renal elimination includes a glomerular step and tubular phase of active secretion, that's why toxicity involves both a reduction in glomerular filtration and tubular function damage.

TDF penetrates, in fact, across the basolateral membrane of the tubular cells mainly through OAT1 and less through OAT3. The extracellular elimination is an active process dependent on MRP2 and MRP4 (members of a superfamily of ATP transporters, involved in the carriage of various molecules and drugs across cell membranes), proteins encoded by *ABCC4* and *ABCC2* genes. The nephrotoxicity mechanism of Tenofovir could be related to a compromised active efflux of TDF through the proximal renal tubule cells by the transporter called MRP2.

According to some studies, the renal proximal tubular epithelium is associated with genetic polymorphism (1249G > A) in the gene encoding the ABCC2-MRP2 transporter, but the positive value of screening in order to identify patients at risk of tubulopathy related to TDF is uncertain, considering this test low sensitivity[16].

Among the NRTIs (Nucleoside Reverse Transcriptase Inhibitors), involved in pharmacogenetic studies, there are Lamivudine (3TC) and Zidovudine (AZT), usually in a fixed dose combination drug, for many years considered a very important however still widely used.

In particular, there are many studies that focus on the relationship between 3TC/AZT pharmacokinetic and pharmacodynamic profile and MDR1, MRP2 and MRP4 polymorphisms.

P-glycoprotein 1 (Permeability glycoprotein, P-gp) is a membrane glycoprotein pump function with the known activity to remove neutral or weakly basic amphipathic substances from the cytoplasm which were penetrated into the cell consuming ATP; it is encoded by *MDR1* gene (multidrug resistance protein 1), also known as ATP-binding cassette sub-family B member 1 (ABCB1). P-gp, MPR2 and MPR4 play a main role in determining the intracellular concentration of nucleoside reverse transcriptase inhibitors. Concerning 3TC/FTC, it was observed in a 33 HIV patients population on antiretroviral regimen that included above formulation, that 3TC concentrations were elevated in 20% of subjects with MRP4 4131T > G variant carriers and that there was a trend of higher AZT concentrations in patients with MRP4 3724G > A variant carriers. However, this study and its subsequent observation are of uncertain clinical significance.

The onset of pancreatitis is related with the use of NRTIs and in particular with Didanosine.

It has been reported in 7% of patients treated with this drug; in a higher percentage of cases showed only increased amylase. In the field of genetic medicine, an increased risk of pancreatitis in the general population has been correlated with mutations in the CFTR (cystic fibrosis transmembrane regulator) responsible for several other clinical conditions such as cystic fibrosis and male infertility, and the mutations of serin protease inhibitor kazal-1 (SPINK-1) encoding a trypsin inhibitor in the cytoplasm of pancreatic acinar cells.

A case-control study conducted in the Swiss court aimed to asses the frequency of mutations in the CFTR and SPINK-1 polymorphisms in HIV-positive patients on antiretroviral regimen containing Didanosine with asymptomatic hyperamylasaemia or symptomatic pancreatitis;

this study suggests that CFTR mutations 1717-1G > A, IV585T and SPINK-1 polymorphism 112C > T are frequent in the studied population and may increase the susceptibility to pancreatitis in patients treated with NRTIs also exposed to additional risk factors, but further studies are needed to confirm these results[17].

Finally, some studies have been conducted to identify a possible correlation between specific mitochondrial polymorphisms and susceptibility to develop peripheral neuropathy (PN) in patients treated with NRTIs. Peripheral neuropathy complicates the clinical picture of HIV patients treated with NRTIs. This adverse event is definitely correlated to drugs belonging to this class because it has been reported also when these ones were taken as monotherapy. In particular, the neuropathy can occur with Didanosine, Zalcitabine and Stavudine. Clinical features of the drug-related PN are similar to the HIV-related neuropathy, but if there is a iatrogenic source PN has an onset and a more rapid progression and it is dose-related[18-20]. Prolonged exposure to NRTIs is associated with skeletal myopathy, lipoatrophy, fatty liver, metabolic acidosis and peripheral neuropathy that occurs with distal symmetrical anesthesia and/or paraesthesia painful structural abnormalities associated with mitochondrial DNA depletion. It has been investigated the association between polymorphisms MTND1 LHON4216C and MTND2 LHON4917G associated with LHON (Leber's Hereditary Optic Neuropathy) and PN in HIV-infected patients treated with NRTIs. The study found that 4917G polymorphism may increase susceptibility to the development of PN in patients treated with NRTIs. However, when subjects with 4917G were excluded from the analysis, the association with 4216C was no longer observed[21].

Considering the association between iron deficiency (essential for mitochondrial function) and some peripheral neuropathies in the general population, some studies have been conducted to examine a possible association between hemochromatosis gene mutations and susceptibility to peripheral neuropathy NRTI-induced, concluding that the iron burden mutations such as C282Y mutation might be associated with a reduced risk of PN in the course of NRTIs[22-25]. Nevertheless this association is particularly controversial.

Non-nucleoside reverse transcriptase inhibitors

NVP is a similar non-nucleoside reverse transcriptase inhibitor (NNRTI) widely prescribed for HIV treatment. Although generally well tolerated and effective, some individuals exposed to NVP show hepatotoxicity and severe cutaneous adverse reactions, including SJS/TEN during the first weeks of therapy (on average 12 d after starting therapy)[26]. This hypersensitivity reaction looks like Abacavir HRS and it is frequent when naive young women with CD4 > 250 cells/μL and naive males with CD4 > 400 cells/μL are treated, these elements suggest that genetic factors may play an important predisposing role[27].

The results of some studies that evaluated the influence of genetic variability in response to NNRTIs treatment, suggest that the development of SJS/TEN is dependent on an immune mechanism. Some studies show a correlation between certain HLA alleles (HLA-B*58:01 and HLA-B*15:02) and the SJS/TEN induced by allopurinol or carbamazepine.

The HLA-DRB1*01 and CYP2B6 gene polymorphisms have been associated with the onset of rash from NVP[28]. Another study has identified the involvement of HLA-B*35:05 in the rash caused by NVP in a Thai population. In addition, an ABCB1 polymorphism (1 member of the ATP-binding cassette subfamily B), also known as MDR1 (encoding the multidrug resistance protein 1) was associated with a lower risk of developing hepatotoxicity. The ABCC10 (encoding the multidrug resistance-associated protein 7) polymorphism rs2125739 has recently been associated with plasma concentrations of NVP. Several studies have finally emphasized the role of NVP hepatotoxicity by CYP2B6 gene polymorphism (516G > T), with the 516TT genotype associated with higher plasma concentrations.

To date, no study, however, assessed the involvement of genetic factors in the SJS/TEN caused by NVP: the gene polymorphisms of cytochromes that metabolize the drug or transporters have been studied only in relation to hepatotoxicity and skin rash. For this reason, a retrospective study was conducted in a population of Mozambique treated with NVP, to test whether the genetic variability of the cytochromes genes metabolizing NVP (CYP2B6, CYP3A4, CYP3A5) and transporters (ABCB1 and ABCC10) could be involved in susceptibility to SJS/TEN. This study describes the relationship between genetic variants of CYP2B6 and the onset of SJS/TEN. In particular, it was found that the 983C allele confers a higher risk of these adverse reactions. It is clear that, since the SJS/TEN is a complex disease, CYP2B6 is just one of many factors involved.

It has been suggested that variants of the MDR1 gene coding for P-gp (the pump transporter efflux of many drugs) can influence Nevirapine toxicity, in particular polymorphism C > T position 3435 of MDR1 was associated with reduced risk of hepatotoxicity[29-33].

Efavirenz is a widely prescribed drug for the HIV infection treatment and in combination with two NRTIs is recommended as a first-line regimen in patients starting antiretroviral therapy. From a pharmacological point of view, Ffavirenz is a non-nucleoside reverse transcriptase inhibitors (NNRTIs) whose metabolism is mediated by Cytochrome P450 2B6 (CYP2B6), which is a genetically polymorphic enzyme. This drug is generally characterized by a good toxicity profile and high efficacy: however, some episodes of viral failure and conditions affecting the central nervous system (CNS) such as nightmares, dizziness, drowsiness, insomnia, inability to concentrate have been reported in some patients with a frequency that can involve approximately half of the patients especially within the first few weeks of treatment[34].

In ACTG 5095 and 5097s it was demonstrated that the presence of a single nucleotide polymorphism (SNP) at position 516 of the CYP2B6 gene correlates with either

the presence of elevated Efavirenz plasma levels and the appearance of CNS adverse events. Subsequent papers also confirmed these findings. In other studies, moreover, similar associations even with the presence of a second polymorphism at position 983 of the CYP2B6 gene have been demonstrated. These two SNPs have a higher frequency in the African population; this phenomenon could therefore explain the particularly higher Efavirenz plasma levels observed in Africans subjects than in individuals of other ethnicities[35-37].

Finally, there is preliminary evidence that the presence of polymorphisms of other genes, such as ABCB1 coding for P-glycoprotein or *CYP3A5* gene, may significantly influence the viral response and/or the daily exposure to the drug in patients treated with Efavirenz. It has been amply demonstrated that the polymorphism increases the predictive value of 516/983 SNPs on the Efavirenz pharmacokinetics; instead, other genetic variants in genes *CYP2B6*, *CYP3A5* and *ABCB1* don't improve the predictive value of the model based on the 516/983 genotype[38].

Finally, this work suggests that the slow metabolizer genotype, according to the polymorphism 516 (G > T) and 983 (T > C), can lead to viral beneficial and that the reduction of the drug dose may increase the risk of viral failure.

The best models to predict the Efavirenz pharmacokinetics are based on the polymorphisms 516 and 983 genotypes: slow metabolizers of white ethnicity are at risk for CNS adverse events, while there is a reduction of the probability of viral failure in black patients.

The presence of a G > T single nucleotide polymorphism (SNP) at position 516 of *CYP2B6* gene results in a Gln-His (Glutamine- Histidine) amino acid change associated with higher plasma EFV concentrations leading to increased drug- related side effects.

The *C3435T* change at a wobble position in exon 26 on chromosome 7 of the human genome has pharmacological consequences, and has been reported in a number of African populations and other ethnic groups in different populations. The frequency of the *C3435T* mutation is significantly influenced by ethnicity with marked differences in genotypes seen between different populations. Several studies have reported a high prevalence of the CC genotype in different African populations, and this prevalence implies overexpression of P-gp. In individuals with CC genotype, access of HIV protease inhibitors to major cellular targets known to express P-gp is restricted and this could have serious implications in the use of protease inhibitors. Patients with the T homozygous genotype have been shown to have low expression of P-gp. The C3435T SNP is also correlated with P-gp expression and function on lymphocytes but not on placenta. Several studies have reported significantly greater CD4 cell count in patients with the MDR1 3435TT genotype and these patients tend towards less pronounced viral infection than those patients with the CT or CC genotype[39,40].

Characterization of MDR1 and CYP2B6 enzymes and utilization of pharmacogenomic testing for identification of different alleles in patients may provide a useful tool for therapy optimization with drugs that are substrates of P-gp and those that are metabolised through the CYP2B6 pathway. CYP2B6 genotyping seems to be a useful tool to predict Efavirenz toxicity and resistance allowing patients to know that as poor metabolizers are at greater risk of increased plasma exposure of the drug and therefore of its adverse effects and probably resistance in case of drug discontinuation[41-47].

Protease inhibitors

Protease inhibitors (PIs) are mainly metabolized by CYP3A4 (the predominant form of Cytochrome P450) of which they also are inhibitors; especially ritonavir is an inhibitor of CYP3A4 and it is used as a booster to increase the plasma exposure of other PI. In view of the PI dual function as substrates and inhibitors, the impact of their polymorphisms is difficult to assess. Finally, PIs are also substrate of Pg-P.

Atazanavir is a widely used PI because of its long-term tolerability, its reduced pill burden and its power. The *UGT1A1* gene codes for the UDP glucuronosyltransferase enzyme (UGT1A1), which mediates bilirubin conjugation with glucuronic acid in the liver, then excreted in the bile. Atazanavir inhibits *UGT1A1*, leading to hyperbilirubinaemia and jaundice in certain subjects. The UGT1A1*28 allele is associated with increased risk of hyperbilirubinaemia during Atazanavir based treatment, and genotyping for UGT1A1*28 before starting antiretroviral treatment containing the aforementioned drug may aid to identify patients at higher risk of hyperbilirubinaemia. Subjects whit two copies of the gene variant (UGT1A1*28 homozygotes) have been reported to have the highest risk and UGT1A1*28 heterozygotes show an intermediate risk of developing hyperbilirubinaemia[48,49].

Atazanavir metabolism is partially due to P-gp efflux pump encoded by the *MDR1* gene, which seems to increase plasma concentrations of Atazanavir in presence of 3435 variable genetic homozygosis C/C, exposing the patient to a risk of hyperbilirubinemia and severe jaundice.

In summary, genotyping for *UGT1A1* and *MDR13435* before starting Atazanavir may help the clinician to identify those subjects at increased risk of exposure to high plasma levels of the drug and the consequent development of side effects[50,51].

In the post-HAART era the occurrence of treatment-related metabolic disorders was observed, among which the most frequent are dyslipidemia, insulin resistance, diabetes mellitus, lipodystrophy, all considered risk factors for cardiovascular events[52]. The genesis of these disorders is multifactorial so the genetic susceptibility of the single patient represents a new field of investigation.

Lipodystrophy is a long-term complication that deeply affects the quality of life of PLWH leading to the need to identify genetic predisposing factors that could optimize the therapeutic management. TNF expression in the adipose tissue plays an important pathogenic role in the abnormal visceral fat distribution; therefore

Table 1 Pharmacogenetics and highly active antiretroviral therapy toxicity

ARVs	Polymorphisms	Effects
NRTIs		
Abacavir (ABC)	HLA-B*5701	Hypersensitivity Reaction Syndrome
Tenofovir (TDF)	ABCC2-MRP2 (1249G > A)	Increased risk of tubulopathy
Lamivudine (3TC)	MRP4 4131T > G	Increased plasma concentrations
Zidovudine (AZT)	MRP4 3724 G > A	Increased plasma concentrations
Didanosine (ddI)	CFTR 1717-1G > A, IV585T,	Higher risk of pancreatitis
Didanosine (ddI), Zalcitabine (ddC), Stavudine (d4T)	SPINK-1 112C > T MTND1 LHON4216C, MTND2 LHON4917G	Leber's Hereditary Optic Neuropathy, Peripheral Neuropathy
NNRTIs		
Nevirapine (NVP)	HLA-B*58:01, *15:02, *35:05 ABCC10rs2125739, CYP2B6 516G > T	Cutaneous rash, SJS/TEN Increased plasma concentration, hepatotoxicity Reduced risk of hepatotoxicity
Efavirenz (EFV)	MDR1 3435C > T CYP2B6 G516T, T983C	Higher plasma concentrations, SNC side effects
PIs		
Atazanavir (ATV)	UGT1A1*28, MDR1 3435C/C	Hyperbilirubinemia and jaundice
All PIs	TNF gene 238G > A APOA5 (1131T > C, 64G > C), APOC3 (482C > T, 455C > T, 3238C > G) ABCA1 2962A > G APOE (ε2, ε3 haplotypes)	Early onset of lypodistrophy High risk of dyslipidemia
Others		
Maraviroc (MVC)	SLC01B1 521T > C (rs4149056)	Increased plasma concentrations
Raltegravir (RAL)	UGT1A1*28	Increased plasma concentrations

several studies have been conducted in order to identify the genetic variants involved. It has been shown that the 238 variant was significantly more represented in HIV-infected patients with lipodystrophy than in those without. In particular polymorphism 238G > A appears to be related in some studies but not in others, to an early onset of lypodistrophyc process[53-59].

Regarding dyslipidemia, it is known that there is a correlation in the general population with genetic polymorphisms in apolipoproteins genes; some studies have attempted to reproduce this model even in the HIV population. Several studies showed promising results such as the demonstration of an association between *APOA5* gene polymorphisms (1131T > C and 64G > C) and an increased risk of hyperlipidemia.

Furthermore multiple studies identified some polymorphisms of APOC3 (482C > T, 455C > T, 3238C > G), ABCA1 (2962A > G) and APOE (ε2 and ε3 haplotypes) that are associated with a high risk of dyslipidemia[60-67].

Other antiretrovirals

Maraviroc (MVC), the only coreceptor CCR5 antagonist approved for clinical use, is a therapeutic chance for the treatment of the multiexperienced HIV patients (*i.e.*, with resistance to traditional drugs)[68-70]. A close correlation between MVC plasma levels and therapeutic effectiveness has been described, with the identification of a MEC (Minimum Effective Concentration) of 50 ng/mL. MVC plasma concentrations are the result of absorption, distribution, metabolic and elimination processes mediated by several proteins in different tissues. The hepatic uptake of MVC, and therefore its metabolism, is influenced by the action of a carrier protein, OATP1B1, encoded by *SLCO1B1* gene. It has been shown that the presence, in the heterozygous or homozygous status, C variant allele in the polymorphism 521T > C (rs4149056) SLC01B1 gene is correlated with an increase MVC plasma concentration. Genetic screening before prescribing this drug could be a help for the clinician for a customized therapy.

Raltegravir (RAL) is the first drug of a new antiretroviral class, the Integrase Inhibitors (INI). It is metabolized by UGT1A1 and its variant allele *28 in the homozygous status is associated to a reduction of the enzyme activity resulting in mild higher RAL plasma concentrations, but not statistically significant[71] (Table 1).

PHARMACOGENETICS AND HAART RESPONSE

It is well known that combination antiretroviral therapy has dramatically improved the survival rate and the quality of life of PLWH due to the powerful effect on the viral suppression and immune recovery, that's why the most important surrogate parameters used for the evaluation of the HAART response are represented by the viral load (HIV-RNA) and the CD4+ count.

Several pharmacogenetic studies have been conducted in order to establish a relationship between patients' genetic predisposition and susceptibility to the antiretroviral therapy efficacy, but the obtained data are inconsistent and often conflicting, this is probably due to a partial genetic analysis, different categorization of poor immune recovery or due to small numbers of patients

Table 2 Pharmacogenetics and highly active antiretroviral therapy response

Polymorphisms	Drug response
CYP3A5*1	Increased PIs clearance
CYP2B6 rs3475274, rs28399499	Increased EFV and NVP plasma concentrations
ABCB1 3435C > T	Better viral responses to EFV exposure
ABCB1 rs1045642 (3435T > C)	CT/CC genotype associated with higher CD4 count in EFV, 3TC, NVP containing regimen

PIs: Protease inhibitors; NVP: Nevirapine; EFV: Efavirenz.

evaluated[72].

Drug metabolism through CYP450 system has emerged as an important determinant of several drugs interactions and several efforts are conducted to demonstrate its utility to target an optimal therapeutic regimen in term of drug response.

Among this family of enzymes, the majority of drugs actually used in clinical practice are metabolized by CYP3A4 and CYP3A5 which currently show the most individual variations of gene expression, mainly caused by Single Nucleotide Polymorphisms (SNPs).

As mentioned before there are currently six different classes of antiretrovirals which interferes with the HIV life cycle at a different stage.

CYPs that are primarily involved in the metabolism of NNRTIs and NRTI are CYP2B6 and to a lesser extent CYP3A4. By contrast to the NNRTIs, the large part of PIs are metabolized by the CYP3A enzyme system. CYP enzymes in human liver, in particular CYP3A4, play a pivotal role in PI biotransformation, converting these agents to inactive metabolites[73].

Associations between human CYP3A4 and CYP3A5 genetic variants and predisposition to therapy failure has often been hypothesized and described, mainly in HIV-infected patients treated with Protease Inhibitors whose metabolism is affected by induction or inhibition of CYP3A

Indeed, several recent studies have suggested that the disposition of certain PIs might predicted by CYP3A5*1 genotype. A report published by Mouly *et al*[74] show an association between increased Saquinavir clearance and this genetic variant of the enzyme. The CYP3A5*1 genotype has also been related to 44% faster Indinavir oral clearance in 11 HIV patients[20].

One of the most of robust examples of a pharmacokinetic association is observed with genetic variation in the *CYP2B6* gene and the NNRTI efavirenz and nevirapine. CYP2B6 loss of function alleles (rs3475274 and rs28399499) are associated with pharmacokinetic characteristics of NNRTIs. The metabolizer phenotype predicts Efavirenz and Nevirapine plasma concentrations and clinical response to these drugs[75-77].

Regarding clinical response an association between the metabolizer phenotype and virological failure in African-American has been suggested[78].

The minor allele T at rs3745274 causes a decreased expression and activity of CYP2B6 in the liver. In some studies it has been demonstrated that carriers of the TT genotype compared to GG/GT genotypes experienced an over 3-fold increase in Efavirenz concentrations[79].

Patients with CYP2B6 intermediate and slow metabolizer phenotypes achieve undetectable viral loads after treatment with NNRTIs: the association of the phenotype and response to drugs has important potential for clinical decision-making.

Polymorphisms in ABCB1, which encodes P-glicoprotein, may predict altered pharmacokinetics of some drugs. Two studies suggested that ABCB13435C → T predicted more favourable viral responses to Efavirenz containing regimens[80].

Many studies have assessed the potential association of ABCB1 polymorphisms with changes in drug response, some of these have specifically examined a potential association of genotype with outcome in HIV infected patients; it has been studied the relationship between rs1045642 (3435T > C) genotype with viral load and CD4 count in HIV patients treated with Efavirenz and Nevirapine containing regimens; after 6 mo of these therapies, people having TT genotype showed a significantly higher CD4 count than those having a CT/CC genotype; on the contrary no correlation statistically significant was found with viral load.

Similar results emerged from studies about 3TC and Nevirapine[81] (Table 2).

CONCLUSION

The wide availability of drugs and therapeutic regimens for the HIV infection treatment and the presence of associated adverse effects related to interindividual variability leads the clinician to look for an individualized therapy as much as possible. Pharmacogenetics can provide useful tools for this purpose and can propose models of genetic tests that, however, need to be further studied.

The correlation between genetic variables and the HRS to Abacavir is now recognized as such and therefore its administration is related to the presence of favorable genotypes (negative HLAB5701). The genetic variability related to the adverse effects of Efavirenz and Atazanavir are similarly promising, but not yet present in clinical practice. It is desiderable, considering the need for tailored regimes, pursuing further studies to identify a statically significant correlation between specific genetic profiles and adverse effects related to other antiretroviral drugs (Nevirapine hepatotoxicity, proximal tubulopathy due to Tenofovir, peripheral neuropathy, lipodystrophy, metabolic alterations).

Pharmacogenomics seems to be potentially useful not only in its ability to identify individual susceptibility to drug toxicity, but also in terms of pre-treatment assessment of the patient's individual response to a particular drugs combination. Despite several studies recognize this potential, actually there are no strong

enough data. The analysis of the literature reveals a need for further studies that provide greater sample size, but also a valid model for genetic analysis.

In conclusion, pharmacogenetics represent a way to go toward the goal of personalized medicine in the field of HIV infection, to obtain a therapeutic response optimization of the single patient, a reduction of toxicity HAART related, a lower risk of drug-drug interactions, a right therapeutic dose.

REFERENCES

1 **Hetherington S**, Hughes AR, Mosteller M, Shortino D, Baker KL, Spreen W, Lai E, Davies K, Handley A, Dow DJ, Fling ME, Stocum M, Bowman C, Thurmond LM, Roses AD. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002; **359**: 1121-1122 [PMID: 11943262 DOI: 10.1016/S0140-6736(02)08158-8]

2 **Hetherington S**, McGuirk S, Powell G, Cutrell A, Naderer O, Spreen B, Lafon S, Pearce G, Steel H. Hypersensitivity reactions during therapy with the nucleoside reverse transcriptase inhibitor abacavir. *Clin Ther* 2001; **23**: 1603-1614 [PMID: 11726000 DOI: 10.1016/S0149-2918(01)80132-6]

3 **Clay PG**. The abacavir hypersensitivity reaction: a review. *Clin Ther* 2002; **24**: 1502-1514 [PMID: 12462283 DOI: 10.1016/S0149-2918(02)80057-1]

4 **Escaut L**, Liotier JY, Albengres E, Cheminot N, Vittecoq D. Abacavir rechallenge has to be avoided in case of hypersensitivity reaction. *AIDS* 1999; **13**: 1419-1420 [PMID: 10449301 DOI: 10.1097/00002030-199907300-00026]

5 **Chung WH**, Hung SI, Chen YT. Human leukocyte antigens and drug hypersensitivity. *Curr Opin Allergy Clin Immunol* 2007; **7**: 317-323 [PMID: 17620823 DOI: 10.1097/ACI.0b013e3282370c5f]

6 **Martin AM**, Nolan D, Gaudieri S, Almeida CA, Nolan R, James I, Carvalho F, Phillips E, Christiansen FT, Purcell AW, McCluskey J, Mallal S. Predisposition to abacavir hypersensitivity conferred by HLA-B*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci USA* 2004; **101**: 4180-4185 [PMID: 15024131 DOI: 10.1073/pnas.0307067101]

7 **Hughes DA**, Vilar FJ, Ward CC, Alfirevic A, Park BK, Pirmohamed M. Cost-effectiveness analysis of HLA B*5701 genotyping in preventing abacavir hypersensitivity. *Pharmacogenetics* 2004; **14**: 335-342 [PMID: 15247625 DOI: 10.1097/00008571-200406000-00002]

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

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

10 **Hoehe MR**, Timmermann B, Lehrach H. Human inter-individual DNA sequence variation in candidate genes, drug targets, the importance of haplotypes and pharmacogenomics. *Curr Pharm Biotechnol* 2003; **4**: 351-378 [PMID: 14683431 DOI: 10.2174/1389201033377300]

11 **Hughes AR**, Mosteller M, Bansal AT, Davies K, Haneline SA, Lai EH, Nangle K, Scott T, Spreen WR, Warren LL, Roses AD. Association of genetic variations in HLA-B region with hypersensitivity to abacavir in some, but not all, populations. *Pharmacogenomics* 2004; **5**: 203-211 [PMID: 15016610 DOI: 10.1517/phgs.5.2.203.27481]

12 **Easterbrook PJ**, Waters A, Murad S, Ives N, Taylor C, King D, Vyakarnam A, Thorburn D. Epidemiological risk factors for hypersensitivity reactions to abacavir. *HIV Med* 2003; **4**: 321-324 [PMID: 14525543 DOI: 10.1046/j.1468-1293.2003.00166.x]

13 **Peyrieère H**, Nicolas J, Siffert M, Demoly P, Hillaire-Buys D, Reynes J. Hypersensitivity related to abacavir in two members of a family. *Ann Pharmacother* 2001; **35**: 1291-1292 [PMID: 11675863 DOI: 10.1345/aph.1A022]

14 **Rauch A**, Nolan D, Martin A, McKinnon E, Almeida C, Mallal S. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* 2006; **43**: 99-102 [PMID: 16758424 DOI: 10.1086/504874]

15 **Madeddu G**, Bonfanti P, De Socio GV, Carradori S, Grosso C, Marconi P, Penco G, Rosella E, Miccolis S, Melzi S, Mura MS, Landonio S, Ricci E, Quirino T. Tenofovir renal safety in HIV-infected patients: results from the SCOLTA Project. *Biomed Pharmacother* 2008; **62**: 6-11 [PMID: 17574807 DOI: 10.1016/j.biopha.2007.04.008]

16 **Imaoka T**, Kusuhara H, Adachi M, Schuetz JD, Takeuchi K, Sugiyama Y. Functional involvement of multidrug resistance-associated protein 4 (MRP4/ABCC4) in the renal elimination of the antiviral drugs adefovir and tenofovir. *Mol Pharmacol* 2007; **71**: 619-627 [PMID: 17110501 DOI: 10.1124/mol.106.028233]

17 **Felley C**, Morris MA, Wonkam A, Hirschel B, Flepp M, Wolf K, Furrer H, Battegay M, Bernasconi E, Telenti A, Frossard JL. The role of CFTR and SPINK-1 mutations in pancreatic disorders in HIV-positive patients: a case-control study. *AIDS* 2004; **18**: 1521-1527 [PMID: 15238770 DOI: 10.1097/01.aids.0000131356.52457.7a]

18 **Keswani SC**, Pardo CA, Cherry CL, Hoke A, McArthur JC. HIV-associated sensory neuropathies. *AIDS* 2002; **16**: 2105-2117 [PMID: 12409731 DOI: 10.1097/00002030-200211080-00002]

19 **Anderson PL**, Kakuda TN, Lichtenstein KA. The cellular pharmacology of nucleoside- and nucleotide-analogue reverse-transcriptase inhibitors and its relationship to clinical toxicities. *Clin Infect Dis* 2004; **38**: 743-753 [PMID: 14986261 DOI: 10.1086/381678]

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

21 **Canter JA**, Haas DW, Kallianpur AR, Ritchie MD, Robbins GK, Shafer RW, Clifford DB, Murdock DG, Hulgan T. The mitochondrial pharmacogenomics of haplogroup T: MTND2*LHON4917G and antiretroviral therapy-associated peripheral neuropathy. *Pharmacogenomics J* 2008; **8**: 71-77 [PMID: 17684475 DOI: 10.1038/sj.tpj.6500470]

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

23 **Wallace DC**, Brown MD, Lott MT. Mitochondrial DNA variation in human evolution and disease. *Gene* 1999; **238**: 211-230 [PMID: 10570998 DOI: 10.1016/S0378-1119(99)00295-4]

24 **Wallace DC**. Mitochondrial DNA sequence variation in human evolution and disease. *Proc Natl Acad Sci USA* 1994; **91**: 8739-8746 [PMID: 8090716 DOI: 10.1073/pnas.91.19.8739]

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

26 **Baylor MS**, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr* 2004; **35**: 538-539 [PMID: 15021321 DOI: 10.1097/00126334-200404150-00014]

27 **Dieterich DT**, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis* 2004; **38** Suppl 2: S80-S89 [PMID: 14986279 DOI: 10.1086/381450]

28 **Martin AM**, Nolan D, James I, Cameron P, Keller J, Moore C, Phillips E, Christiansen FT, Mallal S. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1*0101 and abrogated by low CD4 T-cell counts. *AIDS* 2005; **19**: 97-99 [PMID: 15627041 DOI: 10.1097/00002030-200501030-00014]

29 **Wang D**, Johnson AD, Papp AC, Kroetz DL, Sadée W. Multidrug resistance polypeptide 1 (MDR1, ABCB1) variant 3435C& gt; T affects mRNA stability. *Pharmacogenet Genomics* 2005; **15**: 693-704 [PMID: 16141795 DOI: 10.1097/01.fpc.0000178311.02878.83]

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

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

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

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

34 **Haas DW**, Ribaudo HJ, Kim RB, Tierney C, Wilkinson GR, Gulick RM, Clifford DB, Hulgan T, Marzolini C, Acosta EP. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004; **18**: 2391-2400 [PMID: 15622315]

35 **Rotger M**, Tegude H, Colombo S, Cavassini M, Furrer H, Décosterd L, Blievernicht J, Saussele T, Günthard HF, Schwab M, Eichelbaum M, Telenti A, Zanger UM. Predictive value of known and novel alleles of CYP2B6 for efavirenz plasma concentrations in HIV-infected individuals. *Clin Pharmacol Ther* 2007; **81**: 557-566 [PMID: 17235330 DOI: 10.1038/sj.clpt.6100072]

36 **Rotger M**, Colombo S, Furrer H, Bleiber G, Buclin T, Lee BL, Keiser O, Biollaz J, Décosterd L, Telenti A. 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 [PMID: 15864119 DOI: 10.1097/01213011-200501000-00001]

37 **Saitoh A**, Fletcher CV, Brundage R, Alvero C, Fenton T, Hsia K, Spector SA. Efavirenz pharmacokinetics in HIV-1-infected children are associated with CYP2B6-G516T polymorphism. *J Acquir Immune Defic Syndr* 2007; **45**: 280-285 [PMID: 17356468 DOI: 10.1097/QAI.0b013e318040b29e]

38 **Marzolini C**, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001; **15**: 71-75 [PMID: 11192870 DOI: 10.1097/00002030-200106150-00023]

39 **Winzer R**, Langmann P, Zilly M, Tollmann F, Schubert J, Klinker H, Weissbrich B. No influence of the P-glycoprotein genotype (MDR1 C3435T) on plasma levels of lopinavir and efavirenz during antiretroviral treatment. *Eur J Med Res* 2003; **8**: 531-534 [PMID: 14711599]

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

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

42 **Motsinger AA**, Ritchie MD, Shafer RW, Robbins GK, Morse GD, Labbe L, Wilkinson GR, Clifford DB, D'Aquila RT, Johnson VA, Pollard RB, Merigan TC, Hirsch MS, Donahue JP, Kim RB, Haas DW. Multilocus genetic interactions and response to efavirenz-containing regimens: an adult AIDS clinical trials group study. *Pharmacogenet Genomics* 2006; **16**: 837-845 [PMID: 17047492 DOI: 10.1097/01.fpc.0000230413.97596.fa]

43 **Ribaudo HJ**, Haas DW, Tierney C, Kim RB, Wilkinson GR, Gulick RM, Clifford DB, Marzolini C, Fletcher CV, Tashima KT, Kuritzkes DR, Acosta EP. Pharmacogenetics of plasma efavirenz exposure after treatment discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis* 2006; **42**: 401-407 [PMID: 16392089 DOI: 10.1086/499364]

44 **Torno MS**, Witt MD, Saitoh A, Fletcher CV. Successful use of reduced-dose efavirenz in a patient with human immunodeficiency virus infection: case report and review of the literature. *Pharmacotherapy* 2008; **28**: 782-787 [PMID: 18503405 DOI: 10.1592/phco.28.6.782]

45 **Tsuchiya K**, Gatanaga H, Tachikawa N, Teruya K, Kikuchi Y, Yoshino M, Kuwahara T, Shirasaka T, Kimura S, Oka S. 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**: 1322-1326 [PMID: 15194512 DOI: 10.1016/j.bbrc.2004.05.116]

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

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

48 **Busti AJ**, Hall RG, Margolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. *Pharmacotherapy* 2004; **24**: 1732-1747 [PMID: 15585441 DOI: 10.1592/phco.24.17.1732.52347]

49 **Monaghan G**, Ryan M, Seddon R, Hume R, Burchell B. Genetic variation in bilirubin UPD-glucuronosyltransferase gene promoter and Gilbert's syndrome. *Lancet* 1996; **347**: 578-581 [PMID: 8596320 DOI: 10.1016/S0140-6736(96)91273-8]

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

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

52 **Wohl DA**, McComsey G, Tebas P, Brown TT, Glesby MJ, Reeds D, Shikuma C, Mulligan K, Dube M, Wininger D, Huang J, Revuelta M, Currier J, Swindells S, Fichtenbaum C, Basar M, Tungsiripat M, Meyer W, Weihe J, Wanke C. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis* 2006; **43**: 645-653 [PMID: 16886161 DOI: 10.1086/507333]

53 **Hajeer AH**, Hutchinson IV. Influence of TNFalpha gene polymorphisms on TNFalpha production and disease. *Hum*

Immunol 2001; **62**: 1191-1199 [PMID: 11704281 DOI: 10.1016/S0198-8859(01)00322-6]
54 **Maher B**, Alfirevic A, Vilar FJ, Wilkins EG, Park BK, Pirmohamed M. TNF-alpha promoter region gene polymorphisms in HIV-positive patients with lipodystrophy. *AIDS* 2002; **16**: 2013-2018 [PMID: 12370499 DOI: 10.1097/00002030-200210180-00005]
55 **Wand H**, Calmy A, Carey DL, Samaras K, Carr A, Law MG, Cooper DA, Emery S. Metabolic syndrome, cardiovascular disease and type 2 diabetes mellitus after initiation of antiretroviral therapy in HIV infection. *AIDS* 2007; **21**: 2445-2453 [PMID: 18025881 DOI: 10.1097/QAD.0b013e3282efad32]
56 **Yasuda K**, Matsunaga T, Adachi T, Aoki N, Tsujimoto G, Tsuda K. Adrenergic receptor polymorphisms and autonomic nervous system function in human obesity. *Trends Endocrinol Metab* 2006; **17**: 269-275 [PMID: 16860568 DOI: 10.1016/j.tem.2006.07.001]
57 **Arnedo M**, Taffé P, Sahli R, Furrer H, Hirschel B, Elzi L, Weber R, Vernazza P, Bernasconi E, Darioli R, Bergmann S, Beckmann JS, Telenti A, Tarr PE. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. *Pharmacogenet Genomics* 2007; **17**: 755-764 [PMID: 17700364 DOI: 10.1097/FPC.0b013e32814db8b7]
58 **Asensi V**, Rego C, Montes AH, Collazos J, Carton JA, Castro MG, Alvarez V, Fernández C, Maradona JA, Valle-Garay E. IL-1beta (+3954C/T) polymorphism could protect human immunodeficiency virus (HIV)-infected patients on highly active antiretroviral treatment (HAART) against lipodystrophic syndrome. *Genet Med* 2008; **10**: 215-223 [PMID: 18344712 DOI: 10.1097/GIM.0b013e3181632713]
59 **Carr A**, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353**: 2093-2099 [PMID: 10382692]
60 **Fauvel J**, Bonnet E, Ruidavets JB, Ferrières J, Toffoletti A, Massip P, Chap H, Perret B. An interaction between apo C-III variants and protease inhibitors contributes to high triglyceride/low HDL levels in treated HIV patients. *AIDS* 2001; **15**: 2397-2406 [PMID: 11740190 DOI: 10.1097/00002030-200112070-00007]
61 **Foulkes AS**, Wohl DA, Frank I, Puleo E, Restine S, Wolfe ML, Dube MP, Tebas P, Reilly MP. Associations among race/ethnicity, ApoC-III genotypes, and lipids in HIV-1-infected individuals on antiretroviral therapy. *PLoS Med* 2006; **3**: e52 [PMID: 16417409 DOI: 10.1371/journal.pmed.0030052]
62 **Guardiola M**, Ferré R, Salazar J, Alonso-Villaverde C, Coll B, Parra S, Masana L, Ribalta J. Protease inhibitor-associated dyslipidemia in HIV-infected patients is strongly influenced by the APOA5-1131T-> C gene variation. *Clin Chem* 2006; **52**: 1914-1919 [PMID: 16887900 DOI: 10.1373/clinchem.2006.069583]
63 **Lichtenstein KA**, Delaney KM, Armon C, Ward DJ, Moorman AC, Wood KC, Holmberg SD. Incidence of and risk factors for lipoatrophy (abnormal fat loss) in ambulatory HIV-1-infected patients. *J Acquir Immune Defic Syndr* 2003; **32**: 48-56 [PMID: 12514413 DOI: 10.1097/00126334-200301010-00007]
64 **Safrin S**, Grunfeld C. Fat distribution and metabolic changes in patients with HIV infection. *AIDS* 1999; **13**: 2493-2505 [PMID: 10630518 DOI: 10.1097/00002030-199912240-00002]
65 **Santos CP**, Felipe YX, Braga PE, Ramos D, Lima RO, Segurado AC. Self-perception of body changes in persons living with HIV/AIDS: prevalence and associated factors. *AIDS* 2005; **19** Suppl 4: S14-S21 [PMID: 16249648 DOI: 10.1097/01.aids.0000191485.92285.c7]
66 **Tarr PE**, Taffé P, Bleiber G, Furrer H, Rotger M, Martinez R, Hirschel B, Battegay M, Weber R, Vernazza P, Bernasconi E, Darioli R, Rickenbach M, Ledergerber B, Telenti A. Modeling the influence of APOC3, APOE, and TNF polymorphisms on the risk of antiretroviral therapy-associated lipid disorders. *J Infect Dis* 2005; **191**: 1419-1426 [PMID: 15809899]
67 **Zanone Poma B**, Riva A, Nasi M, Cicconi P, Broggini V, Lepri AC, Mologni D, Mazzotta F, Monforte AD, Mussini C, Cossarizza A, Galli M. Genetic polymorphisms differently influencing the emergence of atrophy and fat accumulation in HIV-related lipodystrophy. *AIDS* 2008; **22**: 1769-1778 [PMID: 18753860 DOI: 10.1097/QAD.0b013e32830b3a96]
68 **Westby M**, van der Ryst E. CCR5 antagonists: host-targeted antiviral agents for the treatment of HIV infection, 4 years on. *Antivir Chem Chemother* 2010; **20**: 179-192 [PMID: 20413825 DOI: 10.3851/IMP1507]
69 **Eugen-Olsen J**, Iversen AK, Garred P, Koppelhus U, Pedersen C, Benfield TL, Sorensen AM, Katzenstein T, Dickmeiss E, Gerstoft J, Skinhøj P, Svejgaard A, Nielsen JO, Hofmann B. Heterozygosity for a deletion in the CKR-5 gene leads to prolonged AIDS-free survival and slower CD4 T-cell decline in a cohort of HIV-seropositive individuals. *AIDS* 1997; **11**: 305-310 [PMID: 9147421 DOI: 10.1097/00002030-199703110-00007]
70 **Liu R**, Paxton WA, Choe S, Ceradini D, Martin SR, Horuk R, MacDonald ME, Stuhlmann H, Koup RA, Landau NR. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* 1996; **86**: 367-377 [PMID: 8756719 DOI: 10.1016/S0092-8674(00)80110-5]
71 **Wenning LA**, Petry AS, Kost JT, Jin B, Breidinger SA, DeLepeleire I, Carlini EJ, Young S, Rushmore T, Wagner F, Lunde NM, Bieberdorf F, Greenberg H, Stone JA, Wagner JA, Iwamoto M. Pharmacokinetics of raltegravir in individuals with UGT1A1 polymorphisms. *Clin Pharmacol Ther* 2009; **85**: 623-627 [PMID: 19279563 DOI: 10.1038/clpt.2009.12]
72 **Peraire J**, Viladés C, Pacheco YM, López-Dupla M, Domingo P, Gutiérrez M, Rosado I, Leal M, Richart C, Vidal F. Evaluation of the pharmacogenetics of immune recovery in treated HIV-infected patients. *Expert Opin Drug Metab Toxicol* 2014; **10**: 81-101 [PMID: 24256435 DOI: 10.1517/17425255.2014.854330]
73 **Cotreau MM**, von Moltke LL, Greenblatt DJ. The influence of age and sex on the clearance of cytochrome P450 3A substrates. *Clin Pharmacokinet* 2005; **44**: 33-60 [PMID: 15634031 DOI: 10.2165/00003088-200544010-00002]
74 **Mouly SJ**, Matheny C, Paine MF, Smith G, Lamba J, Lamba V, Pusek SN, Schuetz EG, Stewart PW, Watkins PB. Variation in oral clearance of saquinavir is predicted by CYP3A5*1 genotype but not by enterocyte content of cytochrome P450 3A5. *Clin Pharmacol Ther* 2005; **78**: 605-618 [PMID: 16338276 DOI: 10.1016/j.clpt.2005.08.014]
75 **Zanger UM**, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem* 2008; **392**: 1093-1108 [PMID: 18695978 DOI: 10.1007/s00216-008-2291-6]
76 **Ingelman-Sundberg M**, Sim SC, Gomez A, Rodriguez-Antona C. Influence of cytochrome P450 polymorphisms on drug therapies: pharmacogenetic, pharmacoepigenetic and clinical aspects. *Pharmacol Ther* 2007; **116**: 496-526 [PMID: 18001838 DOI: 10.1016/j.pharmthera.2007.09.004]
77 **Wang H**, Tompkins LM. CYP2B6: new insights into a historically overlooked cytochrome P450 isozyme. *Curr Drug Metab* 2008; **9**: 598-610 [PMID: 18781911 DOI: 10.2174/138920008785821710]
78 **Ribaudo HJ**, Liu H, Schwab M, Schaeffeler E, Eichelbaum M, Motsinger-Reif AA, Ritchie MD, Zanger UM, Acosta EP, Morse GD, Gulick RM, Robbins GK, Clifford D, Haas DW. Effect of CYP2B6, ABCB1, and CYP3A5 polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. *J Infect Dis* 2010; **202**: 717-722 [PMID: 20662624 DOI: 10.1086/655470]
79 **Price AL**, Zaitlen NA, Reich D, Patterson N. New approaches to population stratification in genome-wide association studies. *Nat Rev Genet* 2010; **11**: 459-463 [PMID: 20548291 DOI: 10.1038/nrg2813]
80 **Frasco MA**, Mack WJ, Van Den Berg D, Aouizerat BE, Anastos K, Cohen M, De Hovitz J, Golub ET, Greenblatt RM, Liu C, Conti DV, Pearce CL. Underlying genetic structure impacts the association between CYP2B6 polymorphisms and response to efavirenz and

nevirapine. *AIDS* 2012; **26**: 2097-2106 [PMID: 22951632 DOI: 10.1097/QAD.0b013e3283593602]
81 **Zhu P**, Zhu Q, Zhang Y, Ma X, Li Z, Li J, Chen J, Luo L, Ring HZ, Ring BZ, Su L. ABCB1 variation and treatment response in AIDS patients: initial results of the Henan cohort. *PLoS One* 2013; **8**: e55197 [PMID: 23372834 DOI: 10.1371/journal.pone.0055197]

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