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Review

Pharmacogenetics of antiretrovirals☆

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ABSTRACT

The introduction of highly active antiretroviral therapy (HAART) as standard of care has changed the natural history of HIV infection into a manageable chronic disease requiring long-term antiretroviral (ARV) treatment. However, response to HAART is often limited by the occurrence of toxicity or by the emergence of drug resistance. Antiretroviral treatment is characterized by differing rates of adverse events and responses. Genetic variations between human beings account for a relevant proportion of this variability. A relevant number of associations between human genetic variants and predisposition to adverse events have been described and for some antiretroviral drugs a clear and casual genotype–phenotype correlation has already been established. The strong association between abacavir hypersensitivity reaction and HLA-B*5701 has been demonstrated in both observational and blinded randomized clinical trials in racially diverse populations and represents the best example of the clinical utility of pharmacogenetic screening in HIV medicine. Genotyping for HLA-B*5701 before prescribing an abacavir containing regimen has been introduced into routine clinical practice as the standard of care for all patients. Other well-established associations include CYP2B6 alleles and efavirenz central nervous system side effects, UGT1A1 alleles and atazanavir-associated hyperbilirubinemia and HLA class II allele HLA-DRB*0101 and nevirapine-associated hypersensitivity. Despite genetic associations having been described for peripheral neuropathy, lipodystrophy, hyperlipidaemia, pancreatitis and renal proximal tubulopathy, numerous barriers exist to the successful introduction of widespread genetic testing to the clinic. Future prospects point in the direction of individualization of antiretroviral therapy through insights from host genetics. The present paper is aimed to provide a comprehensive review of the published literature and to summarize the state of research in this area.

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1. Introduction

The introduction of highly active antiretroviral therapy (HAART) as a standard of care has considerably enhanced the life expectancy among HIV-infected individuals. Over the last 20 years antiretroviral (ARV) therapy have moved from almost ineffective monotherapy to combination multidrug regimens able to virtually suppress viral replication in most HIV-infected patients. As a consequence, the natural history of HIV infection has been changed into a manageable chronic disease requiring long-term ARV treatment. However, response to HAART is a complex phenomenon and is often limited by the occurrence of acute or chronic toxicities or by the emergence or drug resistance. Drug metabolism and toxicity may vary greatly between individuals, affecting both efficacy and toxicity. It is believed that genetic variations between human beings account for a relevant proportion of this variability. As a matter of fact HIV-infected patients consist of individuals who differ genetically with regard to their response to both the virus and the ARV drugs.

The term pharmacogenetics refers to the effects of polymorphisms within human genes on drug therapy outcomes. By definition, single-nucleotide polymorphisms (SNPs) are defined as sequence variations that occur in human DNA with single-nucleotide changes occurring at an allele frequency greater than 1% (Hoehe et al., 2003). Nucleotide changes occurring with a frequency lower than this are referred to as mutations. Recent advances in technologies for genetic analyses are generating great opportunities to disclose the role of sequence variation in human genome influencing disposition, metabolism, efficacy and toxicity of ARV drugs.

The possibility to perform genome-wide analyses has recently disclosed new possibilities of research (Syvanen, 2005). However, up to now most genotype–phenotype studies have employed a direct, hypothesis-driven candidate gene approach. In most cases the study hypotheses were to verify a plausible link between a genetic variations of probable impact on drug metabolism and/or on drug toxicity and phenotype under study. According to the hypothesis-driven candidate gene approach variability in the host genome influencing ARV efficacy and tolerability has explored genetic factors involved into immunological and pharmacokinetic determinants of responses.

A great number of associations have been reported between host genetic polymorphisms and responses to ARV drugs. These include drug pharmacokinetics and pharmacodynamics, hypersensitivity reaction syndromes, hepatotoxicity, central nervous system side effects, hyperbilirubinemia, peripheral neuropathy, lipodystrophy, hyperlipidaemia, pancreatitis and renal toxicity. However, it must be underlined that numerous barriers exist to the direct translation of this body of knowledge toward the ultimate goal represented by the individualization of ARV therapy. The risk of false discoveries caused by multiple testing is a well-known problem in statistical genetics. Thus, some early reports on genotype–phenotype associations must be considered with caution until replicated in additional studies. Most studies published to date have significant limitations represented by small study size, lack of adequate statistical power and presence of selection bias. Moreover, the carriage of variant alleles is very often linked to ethnicity. As a consequence, the risk of ethnic bias exists in almost all studies of genotype–phenotype association. Thus, several prerequisites exist for successful introduction of a pharmacogenetic test into routine clinical practice. The test must be clinically relevant with high sensitivity and specificity. The evidence showing genotype–phenotype association should be ideally based on randomized, double-blind, prospective studies involving patients of different ethnicities. Large clinical trials and observational cohorts conducted across racially diverse populations are also extremely useful for association studies. Moreover, the genotypic assay should be rapid and simple to interpret. Finally, robust cost-effectiveness data should be provided to support its reimbursement.The present paper is aimed to provide a critical and comprehensive review of the published literature, to summarize the state of research and to provide insights into future prospects in this area.

2. Nucleoside reverse transcriptase inhibitors (NRTIs)

Nucleoside reverse transcriptase inhibitors (NRTIs) are a class of antiretroviral drugs whose chemical structure constitutes a modified version of a natural nucleoside. These compounds, after intracellular phosphorylation to form the active metabolites, suppress HIV replication by interfering with the reverse transcriptase enzyme. Regarding NRTIs metabolism, unlike non-nucleoside reverse transcriptase inhibitor (NNRTIs) and protease inhibitors (PIs) there is very little involvement of cytochrome P450 enzymes. Zidovudine (ZDV) and abacavir (ABC) are predominantly metabolized by the liver. On the other end, lamivudine (3TC) and tenofovir (TDF) are renally excreted virtually unchanged (van Leeuwen et al., 1992; Robbins et al., 1998).

Given the little involvement of cytochrome P450 enzymes in NRTI metabolism (Muñoz de Benito and Arribas López, 2006) there is no evidence that genetic polymorphisms of P450 could influence NRTI disposition. By contrast, since the drug transporter multidrug-resistance proteins (MRP), members of the ATP-binding cassette (ABC) superfamily, are known to play a role in the cellular efflux of NRTIs (Schuetz et al., 1999), genetic variations in MRP4 and MRP2 have been studied for their association with intracellular levels on some NRTIs.

Most studies on pharmacogenetic determinants of NRTIs toxicity have focused on hypersensitivity reaction syndromes and the HLA system. Genes involved in drug transport, like *ABCC2* gene encoding for MRP2 have also been studied regarding toxicity associated with some NRTIs. Finally, polymorphisms in mitochondrial genomes and tumor necrosis factor (TNF)-alpha have also been investigated regarding NRTI toxicity.

2.1. Zidovudine (ZDV) and lamivudine (3TC) intracellular levels

P-glycoprotein (P-gp) is a human transporter protein that carries many types of molecules, such as fats, sugars, amino acids, and drugs, across cell membranes. P-gp is widely expressed in normal cells such as liver cells, renal proximal tubular cells and capillary endothelial cells. P-gp is encoded by the multidrug-resistance gene 1 (*MDR1*), which is also called *ABCB1*. P-gp and the multidrug-resistance-associated proteins MRP2 and MRP4 are known to play an important role in determining intracellular concentration of NRTIs. Anderson et al. (2006) investigated relationships among 3TC-triphosphate, and ZDV-triphosphate pharmacokinet-

ics and pharmacodynamics with polymorphisms in MDR1, MRP2 and MRP4. Among the 33 subjects studied 3TC-triphosphate concentrations were elevated 20% in MRP4 4131T>G variant carriers. Moreover, there was a trend for elevated ZDV-triphosphates in MRP4 3724G>A variant carriers. The clinical significance of this preliminary report is still to be determined.

2.2. Abacavir (ABC)-associated hypersensitivity reaction syndrome (HRS)

ABC is a potent and well-tolerated NRTI. Unfortunately, a subset of individuals (between 1% and 9%) exposed to ABC may develop, generally after a few weeks upon initiation of therapy, an HRS of potentially lethal outcome. Clinically, ABC HRS is characterized by multisystem involvement (Hetherington et al., 2001) with a variable combination of symptoms like rash, fever, gastrointestinal, constitutional and respiratory manifestations (Clay, 2002).

The underlying immunologic mechanism of ABC HRS is thought to be an HLA-B5701-restricted immune response to the NRTI drug. Generally speaking, HRSs have been associated with specific human leukocyte antigen (HLA) alleles within the major histocompatibility complex (MHC) (Chung et al., 2007; Martin et al., 2004). The HLA system is the name of the MHC in humans. It contains a large number of genes related to immune system function. This group of genes, that resides on chromosome 6, encodes a relevant number of antigen-presenting proteins and many other genes. It is believed that the ABC HRS is triggered when the HLA-encoded molecule presents the NRTI drug for T-cell activation. The release of inflammatory cytokines and chemokines initiates a cascade of events responsible for the clinical features of ABC HRS. Aside from ABC HRS, another important HRS syndrome associated with the use of ARV drugs is the nevirapine (NVP) HRS.

The association between HLA type HLA-B*5071 and ABC HRS is by far the best example of casual genotype–phenotype correlation in HIV medicine. The involvement of host genetic factors was first suggested by the occurrence of ABC HRS in members of the same family (Peyrieère et al., 2001). Subsequently, several groups demonstrated a strong association between a specific HLA and ABC HRS. A strong association between ABC HRS and the haplotype comprising HLA-B*5701, HLA-DR7, and HLA-DQ3 was first reported by Mallal et al. (2002). This association was further confirmed in other cohorts of different ethnicities (Hetherington et al., 2002; Hughes et al., 2004a; Rauch et al., 2006). More importantly, the clinical utility of pharmacogenetic screening for HLA- B*5701 was established in a large randomized, double-blind, prospective study enrolling 1956 patients in 19 countries. In this study, patients were randomly assigned to undergo prospective HLA-B*5701 screening, with subsequent exclusion of ABC prescription in HLA-B*5701-positive subjects (prospective screening group), or to undergo ABC use without HLA-B*5701 screening (control group). Because of suboptimal specificity when using clinical criteria alone, in all patients with suspected ABC HRS a confirmatory skin-patch testing was performed (immunologically confirmed HRS). Prospective screening for HLA-B*5701 eliminated (0% compared with 2.7% in the control group) immunologically confirmed hypersensitivity reactions to ABC (negative predictive value of 100%) and significantly reduced the rate of clinically suspected HRSs (from 7.8% to 3.4%) (Mallal et al., 2008). Thus, HLA-B*5701 screening was clearly shown to be clinically useful in preventing ABC HRS. Finally, a cost-effectiveness analysis demonstrated that genetic testing for HLA-B*5701 was cost-effective (Hughes et al., 2004b).

On the basis of the results of these studies pharmacogenetic screening for HLA-B*5701 has already entered routine clinical practice. Most guidelines for the treatment of HIV-infected patients recommend that a screening for HLA-B*5701 should be performed before starting an ABC-containing regimen in all subjects. HLA-B*5701-positive patients should not be prescribed ABC and the status of HLA-B*5701 positivity should be recorded as an ABC allergy in the patient's medical record (DHHS, 2008; Gazzard, 2008; Hammer et al., 2008).

2.3. Tenofovir (TDF)-associated renal proximal tubulopathy

TDF is among the most widely prescribed ARV drug. However, its use has been associated with renal proximal tubulopathy, especially in patients with advanced HIV infection (Madeddu et al., 2008).

TDF is a drug with extensive renal excretion mediated by the multidrug-resistance protein (MRP) transporters located on the brush border of the proximal renal tubule. The *ABCC2* gene encodes for the multidrug-resistance protein 2 (MRP2), a member of the superfamily of ATP-binding cassette (ABC) transporters that transport various molecules, including drugs, across cellular membranes. The mechanism of TDF nephrotoxicity could be linked to an impaired active TDF efflux from the renal proximal tubular cells by the MRP2 transporter. Recent observations (Izzedine et al., 2006) suggest that renal proximal tubulopathy could be associated with a single G>A substitution at position 1249 of ATP-binding cassette, sub-family C, member 2 (*ABCC2*) gene. In this study, after controlling for age, sex, and duration of HIV infection, ABCC2 haplotypes were significantly associated with the onset of TDF-induced renal proximal tubulopathy. This preliminary report, suggesting an association of proximal tubulopathy with polymorphisms in the *ABCC2* gene encoding for the MRP2 transporter, needs to be confirmed in independent populations. Moreover, although a putative role MRP2 polymorphisms in the renal toxicity associated with TDF use has been proposed, it is important to note that TDF is a substrate for MRP4, but not for MRP2 (Imaoka et al., 2007). Thus, the mechanisms underlying these findings remain elusive and further studies in this field are needed.

2.4. NRTI-associated pancreatitis

The use of didanosine (ddI) alone and of ddI in combination with stavudine (d4T) has been associated with the development of pancreatitis (DHHS, 2008). Cystic fibrosis transmembrane conductance regulator (CFTR) and serine protease inhibitor kazal-1 (SPINK-1) mutations have been reported to increase the risk of pancreatitis in the general population. CFTR mutations are involved in a number of clinical conditions including cystic fibrosis, male infertility and idiopathic pancreatitis. SPINK-1 encodes for a trypsin inhibitor in the cytoplasm of pancreatic acinar cells and is a genetic risk factor for pancreatitis in the general population.

For these reasons Felley et al. (2004) conducted a case–control study to evaluate the frequency of CFTR mutations and SPINK-1 polymorphisms in patients with either asymptomatic hyperamylasemia or with symptomatic pancreatitis. Among patients with asymptomatic hyperamylasemia those with CFTR or SPINK-1 mutations had higher amylase levels when compared with those without mutations. CFTR mutations and SPINK-1 polymorphisms were also associated with clinical pancreatitis.

These preliminary observations suggest that CFTR mutations and SPINK-1 polymorphisms may increase the susceptibility to pancreatitis in patients treated with NRTIs that are exposed to additional risk factors. Further studies are needed to confirm these findings.

2.5. NRTI-associated peripheral neuropathy

The use of first generation NRTIs such as zalcitabine (ddC), ddI and d4T has been associated with the potential development

of peripheral neuropathy (Keswani et al., 2002). NRTIs require intracellular phosporylation for activity and toxicity. Long-term toxicities associated with NRTIs may be related to overactivation of NRTI intracellular phosphorylation and/or to a mitochondrial injury due to the inhibition of mitochondrial DNA polymerase-gamma by the NRTI drug (Keswani et al., 2002; Anderson et al., 2004). The inhibition of mitochondrial DNA polymerase-gamma caused by the NRTI drug could possibly lead to mitochondrial DNA depletion and mitochondrial dysfunction. Mitochondrial DNA, a maternally inherited genome located within the mitochondria in each human cell, encodes for proteins involved in oxidative phosphorylation and cellular energy production. Mitochondrial DNA undergoes sequence evolution much faster than nuclear DNA (Wallace et al., 1999). Certain combinations of mitochondrial DNA single-nucleotide variants (mitochondrial DNA haplogroups) are presumed to have remained largely unchanged within populations through genetic drift and selection (Wallace, 2003). Mitochondrial haplogroups have recently being associated with human neurodegenerative disorders like Parkinson disease (van der Walt et al., 2003). Hulgan et al. (2005) studied mitochondrial haplogroups in patients exposed to NRTIs. They found that peripheral neuropathy was associated with the presence of mitochondrial haplogroup T, defined by point mutation 7028C>T, 10398G>A, and 13368G>A. Similarly, Carter et al. studied two non-synonymous mitochondrial DNA polymorphisms, 4216C and 4917G that are both found in haplogroup T, in 250 HIV-infected patients exposed to NRTIs. After adjusting for age, baseline CD4 count, plasma HIV RNA level, and drug exposure, both 4216C and 4917G were independently associated with peripheral neuropathy (Canter et al., 2008).

Human mitochondrial genomes exhibit considerable genetic variation between individuals. Susceptibility to peripheral neuropathy could be associated with polymorphisms in the mitochondrial genome, especially with the mitochondrial haplogroup T (Hulgan et al., 2005). The signature haplogroup T polymorphism at position 13368 is located in the ND5 region of the mitochondrial gene and does not result in amino acid changes. Although molecular mechanisms underlying functional differences between haplogroups are only partly understood, polymorphisms in the mitochondrial genome may affect efficiency of oxidative phosphorylation and impair energy production, triggering the clinical onset of peripheral neuropathy after the exposure to some NRTIs.

Associations with hemochromatosis (*HFE*) gene mutations and peripheral neuropathy have also been reported. Hereditary hemochromatosis is a multisystem iron overload disorder in most cases due to mutations in the *HFE* gene that alter iron adsorption and transport. Since iron transport is dysregulated in HIV infection and disorders in iron metabolism are linked to mitochondrial disorders, it has been hypothesized that *HFE* gene mutation could modulate the risk of peripheral neuropathy. Kallianpur et al. (2006) reported that patients with HFE 845G>A, resulting in the C282Y substitution, might develop peripheral neuropathy significantly less often than C282Y non-carriers. However, the association between HFE mutations and peripheral neuropathy is controversial. No evidence of relation between peripheral neuropathy and presence of *HFE* gene mutations was reported in a recent case–control study of HIV-infected patients with and without peripheral neuropathy (Costarelli et al., 2007).

In conclusion, more studies are needed to better identify relationships between host genetic variants and peripheral neuropathy.

2.6. NRTI-associated lipoatrophy

A relevant proportion of patients exposed to some NRTIs, particularly the tymidine analogues d4T and to lesser extent ZDV, may develop peripheral lipoatrophy (Lichtenstein et al., 2003). Lipoatrophy is characterized by peripheral fat loss of gradual onset manifested as facial thinning and as thinning of extremities and buttocks. Lipoatrophy is particularly worrisome since it may stigmatize the patient and affect his quality of life. The pathogenesis of NRTI-associated lipoatrophy is multi-factorial and genetic factors may be associated with an increased risk of developing peripheral fat wasting since this condition does not occur in all treated patients and there is a very large interindividual variability in the emergence and severity of the symptoms (Lichtenstein et al., 2003).

Tumor necrosis factor (TNF)-alpha, a cytokine promoting adipocyte apoptosis, has many actions that are consistent with the features of lipodystrophy and shows high levels of expression in adipose tissue in HIV-infected patients. A polymorphism in the TNF-alpha promoter region (TNF −238G>A) has been associated with TNF promoter activity and with serum levels of TNF (Hajeer and Hutchinson, 2001). Maher et al. (2002) investigated whether polymorphisms in the promoter region of the *TNF-alpha* gene could be associated with the development of lipoatrophy. They found that TNF-alpha 238G>A polymorphism was significantly more frequent in HIV-positive patients with lipoatrophy than in those without lipoatrophy. Furthermore, Nolan et al. (2003) reported an association between TNF-alpha 238G>A polymorphism and more rapid onset of lipoatrophy. By contrast, data from the Swiss HIV Cohort Study failed to show an association between TNF-alpha 238G>A polymorphism and development of lipoatrophy (Tarr et al., 2005). Thus, the association between TNF-alpha polymorphisms and more rapid onset of lipoatrophy remains controversial.

Additional genes involved in lipid metabolism and apoptosis could possibly play a role in the development of lipoatrophy. These include apolipoproteins (APO), adrenergic receptors and Fas and its ligand (FasL). Apolipoproteins are lipid-binding proteins which are the constituents of the plasma lipoproteins. There are five major classes of apolipoproteins (A, B, C, D, E), and several subclasses. Apolipoprotein C3 (ApoC3) is located on very low-density lipoprotein (VLDL) and is a marker of triglyceride-rich lipoprotein's metabolism and clearance. Adrenergic receptors are G-protein-coupled receptors for catecholamines. Adrenergic receptors are essential components of the autonomic nervous system, which control various physiological functions including metabolism of glucose and lipids and the beta-3 adrenergic receptor protein has been shown to play a major role in lipolysis in subcutaneous fat (Yasuda et al., 2006). Fas and its ligand (FasL) represent the main genes that control apoptosis in the immune system. Recently, the influence of these genetic polymorphisms on NRTI-associated lipoatrophy was investigated in a large observational cohort (Zanone Poma et al., 2008). After adjusting for gender, HIV exposure, age, current viral load, hepatitis C virus (HCV) serology and NRTI use ApoC3 −455 CC genotype, adrenergic receptor beta-3 codon 64 TT genotype and Fas −670 GG genotype resulted protective against lipoatrophy. These preliminary observations need to be confirmed in other cohorts.

In conclusion, although genetic polymorphisms of genes involved in apoptosis and adipocyte metabolism have been associated with the risk of developing lipoatrophy, to date, genetic prediction of fat loss is not possible.

3. Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) are a class of antiretroviral drugs that act as noncompetitive inhibitors of the reverse transcriptase of HIV-1. Licensed NNRTIs include efavirenz (EFV), nevirapine (NVP) and etravirine (ETR).

Most studies on pharmacogenetic determinants of NNRTI disposition, efficacy and toxicity have focused on genes involved in NRTI

metabolism (i.e. genetic polymorphisms of cytochrome P450), drug transport (i.e. genetic polymorphisms of P-gp) and hypersensitivity reactions (i.e. genetic polymorphisms of the HLA system).

EFV is predominantly metabolized by cytochrome 2B6 (CYP2B6) with a minor contribution from cytochrome P450 3A4 (CYP3A4). NVP is predominantly metabolized by CYP3A4 and CYP2B6 with a minor contribution from cytochrome P450 3A5 (CYP3A5). Cytochrome P450, a superfamily of heme-binding proteins responsible for the oxidative metabolism of many drugs, may exhibit genetic polymorphisms resulting in enzymes with reduced expression and activity. As a consequence, there is a considerable interindividual variability in NNRTI metabolism and disposition. For these reasons, *CYP2B6*, *CYP3A4*, and *CYP3A5* genes have been extensively studied with respect to pharmacokinetics, pharmacodynamics, treatment response, and toxicity of both EFV and NVP.

Oral absorption and tissue penetration of NNRTIs are affected by the drug transponder P-gp, a human transporter protein encoded by MDR1. Polymorphisms in the *MDR1* gene can be associated with differences in P-gp activity and, thus, in drug disposition. As a consequence, the association between allelic variance of *MDR1* gene and NNRTI plasma concentrations was studied rather comprehensively.

The HLA system has also been extensively studied with respect to NVP-associated HRS (Martin et al., 2005; Vitezica et al., 2008; Littera et al., 2006; Gatanaga et al., 2007a,b).

3.1. Nevirapine (NVP)-associated HRS and NNRTI-associated hepatitis

NVP use has been associated with HRS characterized by various combinations of fever, hepatitis, and rash. NVP hypersensitivity resembles ABC HRS, since it can be sometimes serious with fatal events reported (Baylor and Johann-Liang, 2004) and since it occurs in about 5% of cases, generally within the first six weeks of treatment (Dieterich et al., 2004; Taiwo, 2006). NVP HRS occurs with significantly higher frequency in the treatment of naïve female patients with CD4 cell count greater than 250 cells/mm^3 and in the treatment of naïve male patients with CD4 cell count greater than 400 cells/mm^3. By contrast, low CD4 cell count appears to be protective (Dieterich et al., 2004). This suggests that the underlying mechanism could be a CD4 T-cell-dependent immune response to NVP-associated antigens and the participation of HLA Class II alleles.

Clinical hepatitis or asymptomatic serum transaminase elevations have also been associated with NVP use. Usually, NVR-associated hepatitis occurs within the first 12 weeks of therapy and is often associated with the occurrence of skin rash. Although with a lower frequency, serum transaminase elevations may occur during EFV treatment.

An association of both NVP HRS and NNRTI hepatotoxicity with host genetic factors has been reported. NVP HRS has been associated with an interaction of HLA-DRB1*0101 and CD4 percentage, consistent with the hypotheses of CD4+ T-lymphocyte dependent immune response to NPV-associated antigens (Martin et al., 2005). The simultaneous presence of both HLA-DRB1*0101 and CD4 cell percentage greater then 25% was associated with the highest risk of hepatic or systemic NVP reactions. Moreover, the carriage of HLA-DRB1*0101 was also associated with hepatic/systemic reactions but not with isolated rash. According to this study, the interaction between host genetics and host immune factors could play a major role in determining NVP HRS, with both HLA haplotype and CD4+ cell percentage determining the probability of NVP HRS. More recently, the occurrence of isolated rash in Caucasian patients treated with EFV or NVP was associated with the presence of HLA-DRB1*0101 but not with CD4 percentages (Vitezica et al., 2008). Thus, different mechanisms could be involved in determining the risk of isolated rush vs. hepatotoxicity in NVP adverse events. Moreover, additional HLA alleles have been recently associated with NVP hepatotoxicity in Sardinian (HLA-Cw8/HLA-B14) (Littera et al., 2006) and Japanese (HLA-Cw8) (Gatanaga et al., 2007b) patients.

The *MDR1* gene encodes for P-gp, the multidrug efflux pump transporter that promotes active efflux of many drugs from human cells. It has been hypothesized that MDR1 variants might influence intracellular concentration and, as a consequence, NVP toxicity (Ritchie et al., 2006). Recently, two groups have independently reported an association between MDR1 polymorphisms and NNRTI-associated hepatotoxicity. Ritchie et al. (2006) performed a case–control study of patients initiating NVP-based HAART. They found that the C>T polymorphism at MDR1 position 3435 was significantly associated with decreased risk of hepatotoxicity. The association between MDR1 3435C>T polymorphism and reduced risk of NVP hepatotoxicity was confirmed in a randomized study (Haas et al., 2006). The potential mechanisms underlying genotype–phenotype association for MDR1 3435C>T polymorphism and NVP hepatotoxicity are uncertain. Although MDR1 3435C>T polymorphism do not alter amino acid sequence, it has been hypothesized that this polymorphism may reduce mRNA stability (Wang et al., 2005).

In conclusion, the presence of the HLA class II allele HLA-DRB*0101 is associated with an increased risk of NVP-associated HRS and hepatotoxicity, and the risk is attenuated by low CD4 cell count. NNRTI hepatotoxicity is also associated with *MDR1* gene polymorphism, since 3435 CT genotype appears to confer a reduced risk (Ritchie et al., 2006; Haas et al., 2006). Genetic screening for NVP hypersensitivity and NNRTI hepatotoxicity appears to be a promising approach toward a safer use of NNRTIs in clinical practice. However, these findings need to be extended in populations of different ethnicities before they could be considered of clinical utility.

3.2. Efavirenz (EFV) disposition and central nervous system (CNS) side effects

In most guidelines, treatment with efavirenz (EFV) plus two NRTIs is recommended among the first line regimens in patients initiating HAART. Thus, EFV is among the most widely used antiretroviral drug. However, EFV treatment may be associated with central nervous system (CNS) side effects, represented by abnormal dreams, dizziness, somnolence, insomnia and impaired concentration (Haas et al., 2004). The frequency of CNS side effects may be as high as up to one-half of patients, occurring generally during the first weeks of treatment.

Since there is a considerable interindividual difference in EFV drug levels and half-life after oral administration, it has been suggested that the occurrence of CNS side effects could reflect increased EFV plasma levels. EFV is mainly metabolized by CYP2B6. Since the variability in expression and function of CYP2B6 is considerable, a substantial interindividual variability exists in EFV exposure and CNS side effects. For these reasons CYP2B6 polymorphisms and their association with EFV disposition and side effects have been extensively studied. Haas et al. (2004) found that the CYP2B6 T/T genotype at position 516 was associated with greater EFV plasma exposure. The median values for EFV area under the concentration-time curve from 0 to 24 h according to G/G, G/T, and T/T genotype were 44, 60, and 130 μg h/mL, respectively. G/T and T/T genotypes were also associated with more severe CNS symptoms. Increased EFV exposure has been associated not only with CNS side effects but also with the development of resistance after treatment discontinuation (Marzolini et al., 2001). A strong association between CYP2B6 516 T/T genotype and both greater EFV plasma exposure and increased CNS toxicity was also reported by

Rotger et al. (2005a). Moreover, the association between CYP2B6 G516T polymorphisms and EFV oral clearance was reported in HIV-infected children (Saitoh et al., 2007). Furthermore, Rotger et al. (2007) performed extensive CYP2B6 genotyping and assessed associations with EFV drug levels. They found that patients with a poor metabolizer genotype were at greater risk of showing very high EFV plasma levels. Similarly, subjects homozygous for the CYP2B6*6 allele that contains both 516G>T and 785A>G polymorphisms, have been shown to experience significantly higher EFV plasma levels than heterozygous subjects or subjects without the CYP2B6 allele (Tsuchiya et al., 2004). In addition, the CYP2B6*16 allele, that contains the 983T>C and the 785A>G polymorphisms, is associated with greater EFV exposure (Wang et al., 2006). Finally, it has been recently shown that heterozygosity for CYP2B6 983T>C is also associated with higher NVP plasma exposure (Wyen et al., 2008).

Slow EFV metabolizer subjects could also be at risk of resistance after drug withdrawal. EFV has a half-life considerably longer than NRTIs and has a low genetic barrier to resistance. Thus, when an EFV plus two NRTIs regimen is interrupted, the persistence of detectable levels of EFV in the absence of detectable NRTI levels may expose the patient to the risk of developing EFV resistance. After EFV withdrawal, elevated drug concentrations have been shown to persist for more than 21 days in half of the patients with CYP2B6 516 T/T genotype (Ribaudo et al., 2006). Thus, patients with slow metabolizer genotypes seem to be at increased risk of developing EFV resistance after EFV withdrawal.

In conclusion, a number of studies have demonstrated that the CYP2B6 polymorphisms are associated with increased EFV plasma exposure and CNS side effects. For these reasons there is a growing interest in attempt of using CYP2B6 genotyping for individualizing EFV dose. Gatanaga et al. (2007a) performed CYP2B6 genotyping in 456 patients who received EFV treatment. All CYP2B6 *6/*6 and *6/*26 carriers had extremely high plasma EFV concentrations (>6000 ng/mL) while receiving the standard dosage. EFV dose was reduced to 400 mg for 11 patients and to 200 mg for 7 patients with persistently suppressed HIV-1 loads. Although these results were confirmed by an independent group (Torno et al., 2008), further investigations should be performed to define the potential clinical utility of this approach.

Oral absorption and tissue penetration of NNRTIs is also affected by the drug transponder P-gp that is encoded by MDR1 (Marzolini et al., 2004). For this reason polymorphisms in *MDR1* gene have been studied by several groups, although with conflicting results. Fellay et al. (2002) analyzed the association between EFV plasma levels and allelic variants of *MDR1* gene and of several other genes. They found that median EFV concentrations differed significantly between patients with MDR1 3435 TT, CT, and CC genotypes being at the 30th, 50th, and 75th percentiles, respectively. EFV drug levels were also significantly lower in patients with CYP2D6 extensive-metabolizer alleles. Although in this study patients with the MDR1 TT genotype had also a greater rise in CD4+ cell count, this last finding was not confirmed in a subsequent study (Winzer et al., 2005).

The association between CYP2B6 516G>T polymorphism and greater EFV plasma exposure was independently confirmed in patients of different ethnicities (Winzer et al., 2003; Haas et al., 2005; Motsinger et al., 2006). By contrast, the role of MDR1 polymorphisms on EFV plasma levels remains controversial since negative findings have been reported by several groups (Winzer et al., 2003; Haas et al., 2005; Motsinger et al., 2006).

In conclusion, CYP2B6 genotyping appears a promising approach toward the prediction of EFV toxicity and resistance, allowing the recognition of patients that, being slow EFV metabolizer, are at increased risk of greater plasma exposure, CNS side effects and, possibly, EFV resistance after drug withdrawal. The potential role of genotyping for MDR1 polymorphisms to increase the possibility of identifying subjects at risk of greater EFV exposure still appears controversial. It must be considered that the multiplicity of factors affecting EFV plasma levels could limit the value of isolated CYP2B6 genotyping in predicting the development of EFV toxicity and resistance. Moreover, CYP2B6 516G>T is not invariably associated with elevated EFV levels. Given the extensive use of EFV in clinical practice, the clinical utility of CYP2B6 genotyping needs to be better defined and further research in this field is warranted.

4. Protease inhibitors (PIs)

Protease inhibitors (PIs) are a class of antiretroviral drugs that inhibit HIV-1 replication by inhibiting the activity of HIV-1 protease. PIs are all metabolized to a major extent by CYP3A4 that is the predominant form of human cytochrome P450. PIs are not only substrate but also inhibitors of CYP3A. Among them, ritonavir (RTV) is a very potent CYP3A inhibitor and is therefore used as a booster to increase plasma exposure of other PIs. CYP3A polymorphisms may result in enzymes with variable drug metabolizing activity. However, since PIs are both substrate and inhibitors of CYP3A, the impact of these polymorphisms on PI disposition is difficult to predict.

PIs are also P-gp substrate (Marzolini et al., 2004). Since P-gp is extensively expressed in human cells of different tissues like liver, kidney, central nervous system, small intestine and lymphoid tissue the impact of P-gp variants in PI disposition was also extensively studied.

Some PIs act as inhibitors of uridine diphosphate-glucuronosyltransferase (UGT)1A1, an enzyme of the glucuronidation pathway that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble metabolites. Regarding PI toxicity, genetic variation in UGT1A1 enzyme has been linked to hyperbilirubinemia (Rodriguez-Novoa et al., 2007; Anderson et al., 2006; Rotger et al., 2005b).

Polymorphisms in apolipoproteins (APO) are associated with hyperlipidaemia and cardiovascular events in the general population. APO polymorphisms have been extensively studied regarding PI-associated metabolic and morphological abnormalities (Tarr et al., 2005; Fauvel et al., 2001; Foulkes et al., 2006; Guardiola et al., 2006).

4.1. Indinavir (IDV) and nelfinavir (NFV) plasma levels

P-gp and the multidrug-resistance-associated proteins MRP2 are known to play an important role in determining intracellular concentration of PIs. Anderson et al. investigated relationships among IDV pharmacokinetics and pharmacodynamics with polymorphisms in *CYP3A5*, *MDR1*, and *MRP2* genes. They found that genetically determined CYP3A5 expressors had 44% faster IDV oral clearance versus nonexpressors and that MRP2-24 C/T variant carriers had 24% faster IDV oral clearance (Anderson et al., 2006).

NFV is metabolized by cytochrome P-450 (CYP) CYP2C19 with some involvement by CYP3A and is a substrate for P-gp. Haas et al. (2005) reported that the polymorphisms CYP2C19 681G>A was significantly associated with plasma exposure to NFV and with reduced risk of virological failure.

These pilot observations, while providing a scientific basis for more rational utilization of NFV and IDV, need to be validated in additional studies.

4.2. Atazanavir (ATV) and indinavir (IDV) associated hyperbilirubinemia

ATV is among the most widely used PI due to its potency, low pill burden and favorable long-term tolerability. Unfortunately, hyper-

bilirubinemia may occur in a significant proportion of patients. Between 20% and 50% of patients exposed to ATV may develop hyperbilirubinemia that, in about 6% of cases, can be within the range of clinical jaundice (Busti et al., 2004). ATV, and to a lesser extent IDV, act as inhibitors of the UGT1A1, an enzyme responsible for bilirubin metabolism. Its inhibition leads to unconjugated hyperbilirubinemia and overt jaundice. Genetic polymorphisms of the UGT1A1 gene have an impact on enzyme activity. The most relevant genotypes for UGT1A1 are *6*6 (wild-type, homozygous for 6 thyamine–adenine repetitions), *7*7 (homozygous for 7 thyamine–adenine repetitions), and *6*7 (heterozygous). Studies across the world involving patients of different ethnicities treated with ATV or IDV demonstrated that the frequency and the severity of hyperbilirubinemia correlates with these polymorphisms, subjects with *7*7 genotype being at the highest risk of developing severe hyperbilirubinemia (Rodriguez-Novoa et al., 2007; Anderson et al., 2006; Rotger et al., 2005b). The underlying mechanism mimics that of Gilbert's syndrome (Monaghan et al., 1996).

A second mechanism has been shown to affect the risk of developing ATV-related unconjugated hyperbilirubinemia. ATV plasma levels are influenced by the drug transponder P-gp. It has been shown that genetic polymorphisms of MDR1 may influence ATV plasma concentrations since patients with MDR1 3435 C/C genotype are more likely to show greater ATV plasma levels (Rodriguez-Novoa et al., 2006). The risk of developing hyperbilirubinemia is also influenced by ATV exposure. It has been shown that bilirubin levels directly correlate with ATV plasma concentrations and the risk of severe hyperbilirubinemia is further increased in the presence of the UGT1A1-TA7 allele (Rodriguez-Novoa et al., 2007). Thus, genotyping for MDR1 3435 and UGT1A1 before ATV initiation could help to identify patients at risk of greater ATV plasma exposure and of severe hyperbilirubinemia.

In conclusion, polymorphisms in genes encoding for UGT1A1 are strongly associated with the development of unconjugated hyperbilirubinemia during ATV and IDV treatment. The risk is further increased by polymorphisms in the *MDR1* gene associated with increased ATV plasma levels. The role of UGT1A1 alleles in determining hyperbilirubinemia in patients treated with ATV and IDV is among the best-established associations in pharmacogenetics of antiretrovirals. Prospective UGT1A1*28 genotyping and screening for MDR1 3435C>T polymorphism could be of value to identify subjects at highest risk of developing clinical jaundice upon ATV treatment.

4.3. PI-associated metabolic and morphological abnormalities

A relevant proportion of patients receiving PIs may develop either metabolic or morphological abnormalities or both (Safrin and Grunfeld, 1999). Metabolic abnormalities involve lipid and glucose metabolism and consist of hyperlipidaemia and insulin resistance or diabetes. Although its exact frequency is difficult to establish, hyperlipidaemia is very common in patients treated with antiretroviral therapy (Wohl et al., 2006). Up to 5% of patients treated with PI-containing HAART regimens may develop diabetes (Wand et al., 2007). PI-associated morphological abnormalities consist of visceral fat accumulation, subcutaneous accumulation of adipose tissue in the trunk and in the dorsocervical area also known as "buffalo hump". The exact prevalence of visceral fat accumulation differs widely between studies ranging from 20% to 70% (Carr et al., 1999). Morphological abnormalities have been shown to negatively affect quality of life and adherence to HAART (Santos et al., 2005). Moreover, both visceral fat accumulation and hyperlipidaemia increase the risk of cardiovascular disease.

Although only partly understood, the pathogenesis of PI-associated metabolic and morphological abnormalities is thought to be multi-factorial. It has been hypothesized that genetic factors could be associated with an increased risk of developing visceral fat accumulation and hyperlipidaemia since these conditions do not occur in all patients despite similar demographic and clinical characteristics (Lichtenstein et al., 2003).

In the general population, polymorphisms in APOC3 and APOE are associated with hyperlipidemia. For this reason Tarr et al. (2005) investigated the association of APOC3, APOE and TNF-alpha polymorphisms with the development of dyslipidaemia and lipodystrophy among patients participating in the Swiss HIV Cohort Study. They found that patients with all 3 variant alleles of APOC3 plus APOE genotypes other than $\varepsilon 2$, and $\varepsilon 4$ were at higher risk of developing severe hypertriglyceridaemia. An additional finding of this study was the association of lipoatrophy with all 3 variant alleles of APOC3 and TNF. The association between APOC3 polymorphisms and dyslipidaemia in patients treated with PI-based HAART was confirmed in a prospective study of 60 patients (Fauvel et al., 2001). Moreover, a large study involving 626 PI-treated patients of different ethnicities investigated APOC3 and APOA1 genotypes and their association with plasma lipids (Foulkes et al., 2006). In this study the development of hypertriglyceridaemia differed between racial/ethnic groups. Hispanics, but not Whites and Blacks with variations in the *APOC3* gene, appeared to be protected from the triglyceride-rising effect of PI treatment. Another study of 229 patients treated with PI showed that polymorphism in the *APOA5* gene is also associated with severe hyperlipidaemia (Guardiola et al., 2006). Finally, Arnedo et al. (2007) evaluated the contribution to dyslipidaemia of 20 selected single-nucleotide polymorphisms of 13 genes reported in the literature to be associated with plasma lipid levels like ABC transporter A1 (ABCA1), adrenergic receptor beta 2 (ADRB2), APOA5, APOC3, APOE, cholesteryl ester transfer protein (CETP), MDR1 and TNF in 438 ARV-treated patients. CETP is a plasma protein that facilitates the transport of colesteryl esters and triglycerides between lipoproteins. Mutations affecting CTEP functions have been linked to atherosclerosis. In the study from Arnedo et al. (2007), single-nucleotide polymorphisms of ABCA1, APOA5, APOC3, APOE, and CETP contributed to plasma triglyceride and high-density lipoprotein–cholesterol levels during ARV therapy.

Taken together these observations suggest that genetic factors may influence the development of lipid abnormalities during PI treatment and that genetic profiling may contribute to the identification of patients at risk for ARV-related dyslipidaemia.

Our knowledge about contribution of genetic polymorphisms on morphologic abnormalities characterized by fat accumulation is more limited. Zanone Poma et al. (2008) examined the influence of genetic polymorphisms on the development of lipodystrophy. Regarding fat accumulation, adrenergic beta 2 receptor (ARbeta2) codon 27 CC genotype resulted protective, whereas ARbeta2 codon 16 A Agenotype resulted associated with increased risk. Asensi et al. (2008) examined cytokines polymorphisms and their association with lipodystrophic syndrome. They found that the polymorphic T allele of the (+3954 C/T) polymorphism of IL-1beta was less frequent in patients with lipodystrophic syndrome compared with those without (17.8% vs. 27.0%). These preliminary observations need to be confirmed in other studies.

Hyperlipidaemia has been associated not only with PI but also with EFV treatment. EFV plasma levels are influenced by the MDR1 C3435T polymorphism (Fellay et al., 2002). For this reason Alonso-Villaverde et al. (2005) investigated the effects of MDR1 polymorphisms on changes in HDL-cholesterol and in 59 HIV-infected patients initiating EFV-based HAART. Patients with MDR1 3435 TT genotype did not show a significant increase in HDL-cholesterol, whereas subjects with CT and TT genotypes showed an increase of 11.8% and 36.5%, respectively. However, the role of polymorphisms in the *MDR1* gene on lipid metabolism in patients in patients receiving EFV-based HAART needs to be further investigated.

Table 1
Summary of most relevant (established and putative) genetic determinants of antiretroviral drug pharmacokinetics and toxicity.

Drug, drug class	Gene, alllele(s)/polymorphism(s)	Reported associations	Additional findings and comments
Abacavir	HLA-B*5701	Increased risk of hypersensitivity reaction	Pharmacogenetic testing shown to be cost-effective. Pharmacogenetic testing before abacavir prescription recommended by all guidelines
TDF	ABCC2 (MRP2) 1249G>A	Increased risk of renal proximal tubulopathy	To be confirmed in other populations
3TC, ZDV	ABCC4 (MRP4) 3724G>A, 4131T>G	Higher intracellular exposure of the triphosphate metabolite	Uncertain clinical significance
NRTIs	TNFα 238G>A	Earlier onset of lipoatrophy	Negative findings reported by some authors
NRTIs	Mitochondrial DNA (haplogroup T)	Increased risk of peripheral neuropathy in some reports	Tissue-specific mitochondrial DNA depletion may also play a role in NRTI toxicity
NRTIs	HFE 845G>A	Reduced risk of peripheral neuropathy	Negative findings reported by some authors
NRTIs	CFTR 1717-1G>A, IVS8 5T SPINK-1 112C>T	Increased risk of pancreatitis	Reported also in the general population
NVP	HLA-DRB1*0101	Increased risk of hypersensitivity reaction and hepatotoxicity	CD4 cell percentage greater then 25% associated with increased risk
NVP	HLA-cw8	Increased risk of hypersensitivity reaction in some populations	
NVP, EFV	ABCB1 (MDR1) 3435C>T	Reduced risk of hepatotoxicity	
EFV	CYP2B6 516G>T, 983T>C	Greater plasma exposure and increased risk of CNS side effects	Reports of successful EFV dose individualization
EFV NVP	CYP2B6 516G>T, 983T>C	Greater plasma exposure	To be confirmed in other populations
EFV	MDR1 3435C>T	Reduced plasma exposure	Negative findings reported by some Authors
EFV	MDR1 3435C>T	Increase in HDL-cholesterol	To be confirmed in other populations
ATV, IDV	UGT1A1*28	Unconjugated hyperbilirubinemia and jaundice	
ATV	ABCB1 (MDR1) 3435C>T	Unconjugated hyperbilirubinemia and jaundice	Greater plasma levels
NFV	CYP2C19*2 (681G>A)	Higher drug exposure	To be confirmed in other populations
IDV	CYP3A5*3 (A6986G)	Faster oral clearance	To be confirmed in other populations
PIs	APOA5 –1131T>C, 64G>C	Increased risk of hyperlipidaemia	
PIs	APOC3 482C>T, 455C>T, 3238C>G	Increased risk of hyperlipidaemia	
PIs	APOE ε2 and ε3 haplotypes	Increased risk of hyperlipidaemia	
PIs	ABCA1 2962A>G CETP 279A>G	Increased risk of hyperlipidaemia	
RAL	UGT1A1*28/*28	Modestly higher plasma levels	Clinically not significant
MVC	CCR5 WT/Δ32	No effect on virological response	

ABC genes: genes in the ATP-binding cassette (ABC) family that encode for transporter proteins responsible for carrying many types of drugs across cell membranes.
APO (apolipoproteins): lipid-binding proteins, divided in five major classes (A, B, C, D, E) and several sub-classes, are the constituents of the plasma lipoproteins.
CCR5 (chemokine receptor 5) gene: located on chromosome 3, encodes for the CCR5 protein, the chemokine receptor for the chemokines RANTES, MIP-1alpha and MIP-1beta.
CETP (cholesteryl ester transfer protein): plasma protein that facilitates the transport of cholesteryl esters and triglycerides between the lipoproteins.
CFTR (cystic fibrosis transmembrane conductance regulator): mutations in this gene are involved in a number of clinical conditions including cystic fibrosis, male infertility and idiopathic pancreatitis.
SPINK-1 (serine protease inhibitor, Kazal type 1): encodes for a trypsin inhibitor in the cytoplasm of pancreatic acinar cells.
CYP (cytochrome P450): a superfamily of heme-binding proteins responsible for oxidative metabolism of the majority of drugs.
HFE (hemochromatosis): hereditary hemochromatosis is a multisystem iron overload disorder cases due to mutations that in the HFE gene resulting in altered iron adsorption and transport.
HLA (human leukocyte antigen): group of genes resides on chromosome 6 that encodes cell-surface antigen-presenting proteins and many other genes.
MDR1 (multidrug-resistance 1) gene: gene (also called ABCB1) that encodes P-glycoprotein, the multidrug efflux pump transporter that eliminates many drugs from cells and tissues.
TNF (tumor necrosis factor): a cytokine involved in systemic inflammation and acute phase reactions.
UGT (uridine diphosphate-glucuronosyltransferase): a class of enzymes including UGT2B7, UGT1, and UGT1A1, an enzyme of the glucuronidation pathway that transforms small lipophilic molecules, such as steroids, bilirubin, hormones, and drugs, into water-soluble, excretable metabolites.

In summary, metabolic and morphological abnormalities may occur in a significant proportion of HAART-treated patients. Polymorphisms in genes encoding APOE, APOC3 and, possibly, in APOA5, MDR1, CETP have been associated with susceptibility to hyperlipidaemia in patients receiving PIs. The contribution of host genetic polymorphisms on the occurrence of fat accumulation is less well understood.

5. New drugs

Over the last few years new classes of drugs have been developed for patients failing or not tolerating their ARV regimen. Currently, there are licensed drugs from three new classes: enfuvirtide (fusion inhibitor), raltegravir (integrase inhibitor) and maraviroc (CCR5 antagonist).

Enfuvirtide (ENF) is a 36 amino acid peptide and is not metabolized by cytochrome P-450. Raltegravir (RAL) is mainly metabolized by UDP-glucuronosyltransferase 1A1 (UGT1A1). Maraviroc (MVC) is predominantly metabolized by CYP3A4 and CYP3A5. Currently, there are only limited data on the impact of host genetic polymorphisms on pharmacokinetics and pharmacodynamics of ENF, RAL and MVC.

5.1. Raltegravir (RAL) pharmacokinetics

RAL belongs to the class of HIV integrase inhibitors, a new class of antiretroviral drugs that target the life cycle of HIV by blocking incorporation of the proviral HIV DNA into the host cell DNA. RAL is metabolized by glucuronidation via UDP-glucuronosyltransferase 1A1 (UGT1A1). Since UGT1A1*28/*28 genotype is associated with decreased activity of UGT1A1, Wenning et al. (2009) performed a case–control study in 30 subjects with a UGT1A1*28/*28 genotype and 27 UGT1A1*1/*1 control subjects treated with RAL. RAL plasma concentrations were modestly higher in individuals with the UGT1A1*28/*28 genotype than in those with the UGT1A1*1/*1 genotype but this increase was not clinically significant. The authors concluded that no dose adjustment of RAL was required for individuals with the UGT1A1*28/*28 genotype.

5.2. Maraviroc (MVC) and chemokine receptor 5 (CCR5) polymorphism

MVC is an oral chemokine receptor 5 (CCR5) antagonist that interferes with viral–cellular interactions at the entry process (Westby and van der Ryst, 2005). Considering the mechanism of action, this drug will be effective only in a subpopulation of HIV-1-infected people, those harboring viruses with selective tropism for the CCR5 receptor. The best-characterized human polymorphisms observed in the CCR5 chemokine receptor gene are the Δ32 deletion. Δ32 deletion is associated with an absence of cell surface-expressed CCR5 molecule. Subjects that are homozygous for this mutation (Δ32/Δ32) are highly resistant to HIV infection (Liu et al., 1996; Samson et al., 1996). Subjects that are heterozygous for this mutation (WT/Δ32) often show slower disease progression (Eugen-Olsen et al., 1997). To determine whether polymorphisms in the *CCR5* gene could impact virological response to MVC-based HAART Sanders et al. (2007) genotyped for the CCR5Δ32 mutation 982 patients within the MOTIVATE 1 and 2 studies. Overall, within the study population there were 76 (7.8%) CCR5Δ32 heterozygotes (WT/Δ32). All CCR5Δ32 heterozygotes were Caucasians. There was no statistically significant difference in baseline viral load by CCR5Δ32 genotype. Moreover, when stratified by CCR5Δ32 genotype, the virological response at week 24 was similar between the WT/WT and WT/Δ32. Thus, there was no evidence of a treatment–genotype interaction. In conclusion, genetic variation in the CCR5 chemokine receptor gene does not seem to affect virological response to MVC-based regimens.

6. Summary of potential implications for clinical practice

Since the introduction of new drugs and of drugs of new classes, the virological efficacy of antiretroviral therapy for adherent HIV-infected patients has increased significantly. However, drug toxicity nowadays represents a major obstacle to treatment success in a relevant proportion of patients. Host genetic factors are believed to play a major role in the predisposition to drug toxicity. The association between host genetic factors and increased risk of ABC HRS is, to date, the best example of the clinical utility of pharmacogenetic screening in HIV medicine. HLA-B*5701 testing has already entered routine clinical practice as the standard of care before ABC prescription (DHHS, 2008; Gazzard, 2008; Hammer et al., 2008). A second well-established association is the role of CYP2B6 alleles in EFV pharmacokinetics and toxicity and CYP2B6 genotyping has been proposed for the individualization of EFV dose in attempt to reduce SNS side effects. The association of UGT1A1 and MDR1 polymorphisms in ATV-associated hyperbilirubinemia is also a well-established pharmacogenetic association and genotyping for UGT1A1 before ATV treatment has been proposed for the individuation of subjects at risk for severe hyperbilirubinemia. Moreover, consistent data support the notion that the presence of the HLA class II allele HLA-DRB*0101 is associated with an increased risk of NVP-associated hepatotoxicity, and that the risk is attenuated by low CD4 cell count. Finally, preliminary observations suggest an association between host genetic variants and HAART-associated peripheral neuropathy, hyperlipidaemia, lipodystrophy, NRTI-related pancreatitis and TDF-associated renal proximal tubulopathy.

Hopefully, in future the next ARV therapy could increasingly benefit from genotype-guided drug choice, toward the ultimate goal of a personalized HAART (Table 1).

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