Pharmacogenetics of Anti-HIV Drugs

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Abstract

Pharmacogenetics holds promise in HIV treatment because of the complexity and potential toxicity of multidrug therapies that are prescribed for long periods. Thus far, few candidate genes have been examined for a limited number of allelic variants, but a number of confirmed associations have already emerged. A change in paradigm emerges from the availability of the HapMap, the wealth of data on less-common genetic polymorphisms, and new genotyping technology. This review presents a comprehensive analysis of the existing literature on pharmacogenetic determinants of antiretroviral drug exposure, drug toxicity, as well as genetic markers associated with the rate of disease progression. It is expected that larger-scale comprehensive genome approaches will profoundly change the landscape of knowledge in the future.

INTRODUCTION

Single-nucleotide polymorphism (SNP): pronounced "snip," a DNA sequence variation that arises when a single nucleotide (A, T, C, or G) in the genome sequence differs among members of the species

Cytochrome P450 (CYP): a superfamily of heme-binding proteins of which about a dozen are mainly responsible for oxidative drug metabolism in humans

Pharmacogenetics has been pursued in HIV therapeutics because of the prevalence of toxicity (1), the long-term nature of treatment, and the complexity inherent in multidrug therapy that could benefit from predictive tools to identify the drug combination most likely to be tolerated and effective. However, work thus far has been restricted to a few variants in a limited number of genes encoding metabolic enzymes and transporters and to a number of genes associated with drug toxicity. Moving from the current single candidate gene and single-nucleotide polymorphism (SNP) approach requires the effective use of novel genotyping technologies that allow a more thorough, cost effective genetic evaluation (2).

In addition to pharmacogenetics in a strict sense, genetic analysis holds promise in the study of HIV disease progression. This is of relevance for the understanding of pathogenesis and for vaccine development—through the investigation of mechanisms defining interindividual differences in susceptibility to HIV (3). A significant number of genetic markers of susceptibility to HIV can be considered in an approach to predicting disease progression.

Finally, pharmacogenetic data are increasingly used to predict the efficacy and safety of new compounds and to guide decision making in the discovery and development of new drugs (4). In some situations, a gene, and its encoded protein, appears biologically dispensable because its absence in humans is not associated with a recognizable phenotype. This scenario may define an attractive pharmacological target, as it is assumed that nature has already done the necessary proof-of-concept experiment (5). This reasoning greatly helped the development of CCR5 inhibitors—a new class of drugs in HIV therapeutics that targets a cellular coreceptor of HIV (6).

In this review we present current knowledge on candidate genes as well as future strategies to advance in the characterization of pharmacogenetics determinants of antiretroviral drug exposure, toxicity, and activity.

GENETIC DETERMINANTS OF PHARMACOKINETICS

As for most drugs, many factors contribute to pharmacokinetic variability of antiretroviral agents, including biological (e.g., sex, age, pregnancy, disease), environmental (e.g., drug-drug interactions, food, recreational drug intake), and genetic ones (polymorphisms and rare mutations), by affecting the expression and/or function of proteins that interact with drugs at various levels (7). Indirect evidence for the involvement of genetic factors came from population pharmacokinetic studies. Increased hepatic clearance found in patients of Caucasian origin versus African, Asian, or Hispanic patients suggested genetic differences in drug transporters or cytochrome P450 (CYP) genes (8, 9). Furthermore, it was observed that efavirenz pharmacokinetics exhibited large interpatient variability with more pronounced differences between than within individuals, also pointing at genetic rather than environmental influences (10). Below, we focus on the role of genetic polymorphisms in genes encoding metabolizing enzymes, transporters, and nuclear receptors involved in the transcriptional control of these proteins (**Table 1**). The nucleos(t)ide analogue reverse transcriptase

Table 1 Inherited differences in ADME of antiretroviral drugs. Only the most relevant associations are indicated. Compiled from http://www.hiv-pharmacogenomics.org

Gene or protein (*)	Allele or variant evaluated	Reported consequence for antiretroviral drugs
Metabolism		
CYP3A5	*CYP3A5*3* and *CYP3A5*6* (alleles associated with severely reduced enzyme expression due to aberrant spicing)	Higher saquinavir AUC and metabolite ratio. Reduction of oral indinavir clearance
CYP2C19	*CYP2C19*2* (null allele due to aberrant splicing; poor metabolizer phenotype results from homozygous condition)	Higher nelfinavir AUC and lower M8/nelfinavir AUC ratio, and less virological failure
CYP2B6	*CYP2B6*6*, **11*, **18*, **27*, **28*, **29* (alleles with diminished or lost function, associated with decreased expression or decreased function, protein truncation, or gene deletion)	Higher efavirenz and nevirapine AUC. Associated with increased neuropsychological toxicity
Transport		
P-glycoprotein (*MDR1*, *ABCB1*)	3435C>T (synonymous I1145I, in linkage disequilibrium with *ABCB1*_1236, and 2677). Limited data on 61A>G (N21D), 1199G>A (S400N), other variants, or on haplotypes	Controversial data with a number of reports indicating an association of 3435T with decreased transport function resulting in increased protease inhibitor exposure. Recent data indicates that this synonymous SNP results in altered codon usage for isoleucine, leading to a change in timing of cotranslational folding of the P-glycoprotein, and results in changes in substrate specificity (69)
MRP2 (ABCC2)	1249G>A (V417I)	Associated with risk of tenofovir-induced proximal tubulopathy in small study
MRP4 (ABCC4)	3724G>A (A1203A), 4131T>G, 669C>T (I223I)	Elevated zidovudine- and 3TC-triphosphate concentrations. Associated with risk of tenofovir-induced proximal tubulopathy (669C>T) in a small study
Protein binding		
α-1-acid glycoprotein *(ORM1)*	F1 and S protein variants of *ORM1*, which result from amino acid changes at two variant positions 20 and 156 (determined phenotypically)	Higher apparent clearance in F1F1 individuals as compared to SS for indinavir and, weakly, for lopinavir/ritonavir

inhibitors drugs (NRTI) are not metabolized as extensively by cytochromes P450 as are other antiretroviral agents, such as protease inhibitors (PI) or non-nucleoside reverse transcriptase inhibitors (NNRTI). Host–cell–mediated sequential enzymatic phosphorylation steps are required for activating the nucleotide- and nucleoside-analogue reverse-transcriptase inhibitors (11). There is, however, limited pharmacogenetic data on these pathways.

Cytochrome P450

Allele: one of two or more alternate forms of a gene; can be characterized by a single SNP or by a haplotype

Approximately a dozen P450 isozymes of families *CYP1*, *CYP2*, and *CYP3* are collectively responsible for most Phase I biotransformations of drugs and other xenobiotics. Expression and function of these membrane-bound hemoproteins are highly variable both inter- and intraindividually, and thus are a major contributor to unpredictable drug/metabolite plasma concentrations and to unforeseen drug responses. Genetic polymorphisms in some cytochrome P450 genes have been studied intensely for more than 20 years, but more recently discovered examples are less completely studied and novel variants are continuously being described.

Classical P450 polymorphisms: CYP2D6, CYP2C19, CYP2C9. There are well-investigated P450 polymorphisms with established clinical implications for *CYPs 2D6*, *2C19*, and *2C9*. Multiple alleles with pronounced effects on gene expression or function, including alleles with low or absent expression or function and alleles with higher than normal activity (e.g., gene duplication in the case of *CYP2D6*), are common in certain populations. This leads to distinct phenotypes that affect the pharmacokinetics, efficacy, and toxicity of many drugs (12, 13). However, currently used HIV drugs are rarely substrates of these enzymes and their gene polymorphisms are apparently not of major importance.

An exception is the formation of nelfinavir hydroxy-t-butylamide (M8), a major and pharmacologically active metabolite of nelfinavir whose concentration varies according to *CYP2C19* genotype (14). Independent of ethnic background, a significant association was found between the *CYP2C19*2* null allele and nelfinavir plasma exposure, and patients with **2/*2* genotype had a ~36% higher AUC as compared with **1/*1* carriers and a significantly reduced M8/nelfinavir ratio (15) (**Table 1**). This was accompanied by a trend toward more favorable virologic response. The impact of 2C19 on nelfinavir kinetics needs further study, as it has not been reported in several other studies (16–18).

CYP3A subfamily. The *CYP3A* gene cluster on chromosome 7 encodes the 3A4, 3A5, 3A7 and 3A43 proteins, which collectively catalyze biotransformations of up to 50% of all currently used drugs and many other xenobiotics and endogenous compounds. CYP3A4 is the major form in adult liver and gut but CYP3A5 can make a significant contribution in individuals with low 3A4 levels, whereas 3A7 is primarily expressed in fetal liver and 3A43 may be a pseudogene (19). The strongly variable expression of CYP3A enzymes, both inter- and intraindividually, is due to multiple factors, including sex (20), age, hormone and health status, inducing or inhibitory drugs, and genetic factors. A common intronic SNP that defines the *CYP3A5*3* allele leads to erroneous splicing and almost complete loss of protein. Approximately 10% to 20% of Caucasians, but up to 50% or more of Africans, carry the wild-type allele (*1), thus enabling them to express active CYP3A5. The impact of this polymorphism on CYP3A-catalyzed biotransformations is, however, rather limited (21). Polymorphisms in *CYP3A4* include a promoter SNP (-392A>G, *CYP3A4*1B*) with

a controversial effect on expression, and many rarer variants with unclear phenotype (22, 23).

In an initial study with HIV patients receiving different PIs (nelfinavir, saquinavir, indinavir) and NNRTIs (nevirapine, efavirenz), *CYP3A4*1B* and the *CYP3A5*3* alleles were weakly associated with plasma efavirenz exposure (24), in agreement with a limited contribution of CYP3A to efavirenz metabolism (25). However, no such relationships were identified in several other studies (15–17, 26, 27). On one hand, although CYP3A participates in inactivation of nelfinavir, no pharmacogenetic impact on plasma levels was found (15–17). On the other hand, *CYP3A5* expressor genotype (carriers of *3A5*1*) was associated with moderate increases in oral clearance of saquinavir in HIV patients (28) and in healthy volunteers (29, 30). In a pilot study, genetically determined *CYP3A5* expressors also had faster indinavir oral clearance versus nonexpressors (31). Overall, owing to the inherent complexities, *CYP3A*-targeted pharmacogenetics appears to be of limited value, despite the importance of CYP3A enzymes for the metabolism of HIV drugs, in particular PIs and NNRTIs. A fact that further limits the ability of *CYP3A* pharmacogenetics to predict enzyme activity is that these enzymes are potently and irreversibly inhibited by almost all PI drugs (32).

Linkage disequilibrium: the more frequent association of alleles at two or more loci in a population than expected for independent markers

Haplotype: a collection of SNPs in one chromosome that tend to occur together (that is, are linked) in individuals

CYP2B6. This enzyme is encoded by the single active gene of the *CYP2B* subfamily. Average hepatic expression of CYP2B6 is an order of magnitude lower compared with CYP3A, but it plays a major role in the metabolism of some clinically used drugs. As for CYP3A4, induction by many drugs and environmental chemicals via the ligand-activated nuclear receptors CAR and PXR contributes to variable expression but in contrast to *CYP3A4* the *CYP2B6* gene is highly polymorphic, with over 70 identified SNPs in intronic, exonic, and promoter regions with extensive linkage disequilibrium causing complex haplotype structures (33–37). Allele frequencies vary strongly between very rare and common, with pronounced racial influences. The most frequent allele in all ethnic populations studied is *CYP2B6*6*, defined by two amino acid alterations, Q172H (c.516G>T) and K262R (c.785A>G). Functional data on the **6* allele have been controversial and may, in part, be substrate dependent. Recent evidence suggests that a combination of decreased liver expression (33, 38) and lower enzymatic turnover of the variant (39) leads to lower overall activity. Several of the rarer alleles show pronounced functional differences in vivo and/or in vitro with either higher or lower activity compared with the reference allele (36, 37, 39–41).

In vitro studies identified CYP2B6 as the enzyme responsible for the conversion of efavirenz into its major 8-hydroxylated and 8-, 14-dihydroxylated metabolites, with minor contribution by other isoforms, including CYP3A4/5 and CYP1A2 (25). Efavirenz is a potent agent recommended as initial therapy in regimens with two NRTIs, but patients with subtherapeutic plasma concentrations (<1 mg/l) more often develop resistance and treatment failure, whereas those with plasma concentrations more than 4 mg/l are at increased risk of CNS side effects (42, 43). Several recent clinical studies consistently found that HIV-infected patients homozygous for the 516T allele (a marker of allele *2B6*6*) had approximately two- to threefold higher median AUC values compared to those with only one or no T-allele (24, 26, 44, 45)

(**Table 1**). Although no metabolites had been analyzed in these patients, this agrees well with an approximately 60% decrease in the efavirenz 8-hydroxylation rate in liver microsomes from homozygous carriers of **6* compared with **1* (38).

The 516T variant was also associated with increased CNS side effects after one week of exposure to efavirenz, but interestingly, the commonly observed development of tolerance abolished this difference after 24 weeks of treatment despite persistently higher plasma levels, indicating that additional factors play a role for CNS side effects (24). The authors speculated that modulation of CYP2B6 expressed in brain neurons and astrocytes (46) could have intracranial effects not detectable by measurement of plasma concentrations. However, *CYP2B6* genotype was not predictive for virologic failure, indicating a wider therapeutic window for efavirenz than previously anticipated (24). Based on these results, the authors suggested that *CYP2B6* genotyping may be used to identify patients that could be treated with lower doses without compromising efficacy (15). In another study, the same researchers investigated the consequences of treatment discontinuation on efavirenz plasma concentrations (47). Efavirenz was present in plasma of HIV-infected patients with the homozygous 516T variant for up to 21 days after treatment interruption, thus potentially increasing the risk for selection of drug-resistant HIV. Because efavirenz exerts its anti-HIV effect within infected blood cells, it is important to know whether differences in plasma concentrations are transferred into that compartment. Rotger et al. (44) measured drug levels in both compartments and confirmed the association between the 516T variant and higher intracellular exposure for PBMCs. In homozygous individuals, the plasma and PBMC concentrations were threefold and 2.3-fold higher, respectively, as compared with individuals lacking the allele.

The NNRTI nevirapine is metabolized to four hydroxylated products by CYP3A4/5 (2- and 12-OH-NVP) and CYP2B6 (3- and 8-OH-NVP). Patients with the 516TT genotype had a significant 1.7-fold increase in plasma AUC compared with 516GG patients (44). A similar difference found in HIV patients from Uganda confirmed this prominent role of CYP2B6 in NVP elimination (48).

A comprehensive study that included testing for all known functional variants of *CYP2B6* using a multiplex MALDI-TOF mass spectrometric assay (49) demonstrated that the ability of *CYP2B6* genotyping to predict unexpectedly high efavirenz plasma levels is significantly enhanced by including the rarer loss-of-function alleles (39) (**Figure 1**). Of particular relevance, in addition to allele **6*, is **18* (983T>C, I328T), a variant that showed extremely low expression in recombinant systems and was found at frequencies of ~4%–10% in various populations of African descent and in Turks, but not in White Europeans or Asians (36, 41, 50). The study also showed that sequencing of *CYP2B6* in outliers is advisable, as exemplified by the finding of novel loss-of-function alleles *27 and *28, which helped to explain high EFV plasma AUC in **6/*27* and **6/*28* compound heterozygotes. Analysis of *CYP2B6* gene deletion/duplication in this population also allowed the identification of a partial deletion of *CYP2B6* (exons 1–4), resulting in a *CYP2B7/B6* hybrid (allele *29) (51).

A number of variants that increase enzyme expression or activity have been described. The *4 allele (K262R) was associated with increased bupropion clearance in vivo (52) and with decreased EFV drug levels (39). The latter study also identified

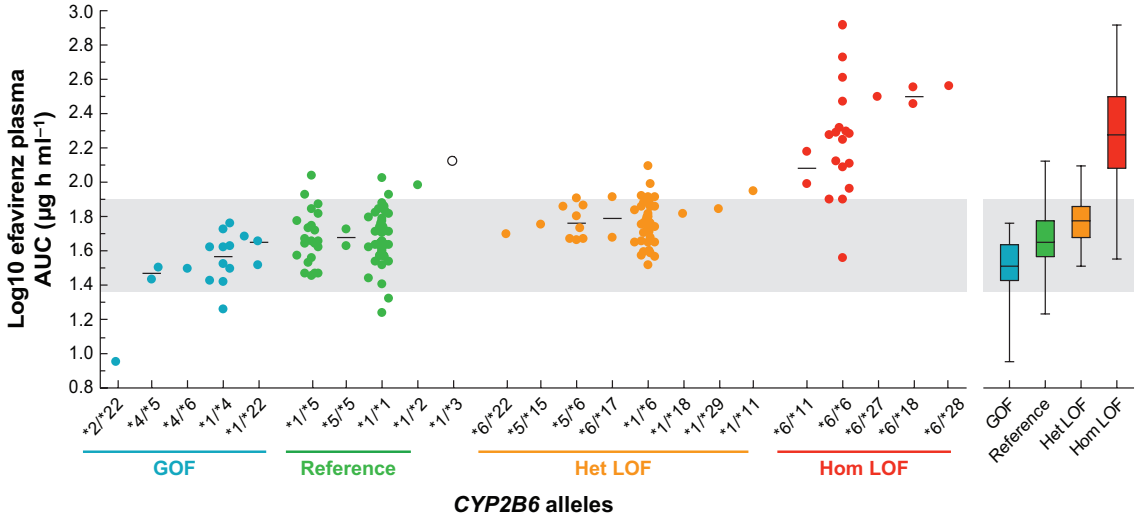

Figure 1

Influence of *CYP2B6* alleles on efavirenz plasma exposure (Log10 efavirenz area under the curve, AUC). Reference = alleles not associated with changes in CYP2B6 function and efavirenz metabolism; GOF, gain of function alleles; LOF, loss/diminished function alleles; Het, heterozygous; Hom, homozygous. Function of allele *2B6*3* (not colored) has not been defined. The gray interval represents the thresholds of 85 mg h/ml and 25 mg h/ml above and below of which AUC values deviate from the normality distribution. Horizontal lines represent median values. Updated from References 39, 51.

the variant -82T>C (*22), which increases expression via a complex rearrangement of the transcriptional machinery at the *CYP2B6* core promoter (37), in a patient with very low EFV concentration (39) (**Figure 1**).

Transporters

Drug transporters expressed in tissues such as the intestine, liver, kidney, and brain play an important role in the absorption, distribution, and excretion of many drugs in clinical use. There are two major types of drug transporters: uptake and efflux transporters. Uptake transporters act by facilitating the translocation of drugs into cells, whereas efflux transporters function to export drugs from the intracellular to the extracellular milieu. Most efflux transporters tend to be members of the adenosine triphosphate (ATP)-binding cassette (ABC) superfamily of proteins that use energy derived from ATP hydrolysis to mediate substrate translocation across biologic membranes. Included in this class of transporters are multidrug resistance protein 1 (ABCB1/MDR1), the multidrug resistance-associated protein (MRP) family, and the breast cancer resistance protein (BCRP). There is now increasing evidence to suggest that genetic heterogeneity in drug transporters not only contributes to the observed interindividual variation in drug disposition but also to the drug response. Numerous polymorphisms have been identified in transporters important to drug disposition

(53, 54). Other than for *ABCB1*, there are limited data on the role of transporter polymorphism and antiretroviral drug exposure (**Table 1**).

Antiretroviral therapy (ART): combination therapy, generally co-administration of three or more drugs, is also referred to as potent ART or highly active ART (HAART)

Owing to its broad substrate specificity, P-glycoprotein (P-gp), the gene product of *ABCB1*, has received the greatest attention in terms of identification and characterization of SNPs. P-gp is found on the canalicular domain of hepatocytes, the apical surface of proximal tubular cells in the kidney, the brush border surface of enterocytes, the epithelium of the brain choroid plexus, as well as the luminal surface of blood capillaries in the brain, the placenta, the ovaries, the testes, and, of relevance to HIV therapy, in CD56+, CD8+, and CD4+ lymphocytes (55–57). Expression of P-gp at the level of the blood-brain barrier has shown to be critical for limiting the CNS entry of many drugs. Supportive evidence was obtained from animal models (58, 59). P-gp has been shown to be particularly relevant to HIV therapy, as PIs have been shown to be substrates of this transporter (60).

Screening of the entire *MDR1* coding region identified a synonymous SNP in exon 26 (i.e., 3435C>T) associated with altered protein expression, although the SNP does not change the encoded amino acid (Ile) (61). In the same study, P-gp expression in duodenal biopsy samples among healthy Caucasians with the homozygous T allele (variant) was noted to be decreased when compared to those with the C allele (common). Subjects with the variant allele were also shown to have increased digoxin plasma concentrations after oral administration, suggesting greater drug absorption in individuals with low intestinal P-gp levels. The first study exploring associations between SNPs in *ABCB1* and antiretroviral pharmacokinetic parameters was performed by Fellay et al. (16). The authors examined the influence of 3435C>T on the median concentrations of nelfinavir and efavirenz in the treatment of naïve HIV-infected patients. Patients with the variant allele were shown to have lower nelfinavir and efavirenz levels compared to the wild type. Subsequent studies attempting to define associations between this same polymorphism in exon 26 and another in exon 21 (i.e., 2677G>T/A) and the pharmacokinetics of several PIs and efavirenz have resulted in conflicting and controversial findings (15, 17, 24, 26, 62–64) (**Table 1**).

In addition to drug levels, SNPs in *MDR1* may also alter the physiological protective role of P-gp and therefore influence disease (60). Fellay et al. found a relationship between expression of P-gp in peripheral blood mononuclear cells (PBMC) of HIV-infected patients and CD4 lymphocyte response to treatment (16). Patients with the 3435T allele in exon 26 had a significantly greater rise in CD4 cell count 6 months after starting antiretroviral therapy (ART). It was hypothesized that this benefit associated with the T allele could result from an enhanced HIV protease inhibitor penetration into CD4 cells. Three additional studies have reported a better virological outcome associated with the 3435T allele (15, 17, 65). However, other studies reported no virological or immunological effects associated with the study allele (66–68).

Recent data may provide the response to the elusive role of *ABCB1* 3435C>T. This synonymous SNP represents a rare codon usage for isoleucine that leads to a change in timing of cotranslational folding of the P-glycoprotein and results in changes in substrate specificity (69). This novel mechanism explains to a large extent the controversial results or the lack of association of this variant directly, or through linkage disequilibrium, with causal variants or with changes in mRNA expression. In

the larger scope of genetics, it opens the Pandora's Box of biological consequences of silent polymorphisms (70).

Nuclear Receptors

Absorption, distribution, metabolism, and excretion (ADME): encompasses the disposition of a drug within the body

The drug detoxification system of the vertebrate liver has evolved as a chemical defense system against endogenous and exogenous (e.g., herbal) toxins. The constitutive and tissue-selective expression of the numerous Phase I and Phase II enzyme and transporter genes is orchestrated by a complex interplay of liver-enriched and basic transcription factors with the gene regulatory sequences (71). Additional regulatory networks enable the organism to react in a coordinated response to toxic stimuli and to effectively eliminate even highly lipophilic substances from the cell. Focal points of these gene regulatory networks are nuclear receptors that function as ligand-activated transcription factors for numerous, coordinately regulated target genes. The orphan nuclear receptors PXR (pregnane X receptor, NR1I2) and CAR (constitutive androstane receptor, NR1I3) are sensors for myriads of drugs and other xenobiotics and toxic byproducts derived from endogenous metabolism. Following heterodimerization with RXR (retinoid X receptor) they increase the transcription of multiple target genes that are involved in drug clearance, i.e., Phase I and Phase II enzymes and transporters that enhance elimination of the chemicals (72, 73). It is well-known from clinical studies and from studies with human primary hepatocytes that not only the constitutive expression of detoxification genes but also their inducibility is highly variable among individuals, in part, owing to genetic polymorphisms in nuclear receptor and transcription factor genes (74). At least CYP3A4, CYP2B6, and P-gp, but probably many other enzymes and transporters, are inducible by efavirenz, nevirapine, and ritonavir and a number of drugs often coadministered to HIV-positive patients, such as the antituberculosis drug rifampicin. PXR and CAR have been shown to mediate the induction to various extents (75–77). Polymorphisms in these nuclear receptor genes thus contribute to interindividual variation in drug clearance and could possibly modulate the severity of certain drug-drug interactions (78).

More than 50 genetic variants of PXR and CAR are known to date, but their functional consequences have not yet been well explored. Investigation of genotype-phenotype relationships has been hampered by the lack of good antibodies and by the occurrence of numerous splice variants with unknown significance. Nevertheless, some rare variants of PXR were shown to have functional deficiencies in in vitro test systems, (79) and a few common variants have been associated with functional changes in vivo, including a promoter variant (-25385C>T) that was correlated with increased inducibility of CYP3A4 by rifampicin (80). At the present time, the assessment of variants in nuclear receptor and other transcription factor genes remains a challenge in the field of antiretroviral drug therapy.

Comprehensive Analysis of ADME Pathways

Moving from single gene candidates to a comprehensive analysis of ADME (absorption, distribution, metabolism, and excretion) pathways for various antiretroviral

drugs is now possible (81). The strategy uses HapMap data to define common human variation, enriched by proven or predicted functional SNPs. The HapMap project (shorthand for the Haplotype Mapping Project) (82) characterizes patterns of association among different gene variants—the patterns of linkage disequilibrium across the genome—to select a minimal set of variants that capture most of the diversity of the human genome. These polymorphisms are called tagging single-nucleotide polymorphisms (tSNPs) because they "tag" other polymorphisms, which then do not need to be genotyped (82, 83).

Because of the limitations of single-gene approaches, there has been increasing interest in establishing the basis for a more comprehensive approach using comprehensive sets of SNPs (84), or assessing complete ADME pathways (81). Reconstitution of ADME pathways is a key step in establishing a frame of plausibility to select genes for study. For a given drug or drug class, the ADME proteins and their encoding genes can be classified according to their proven/proposed (existing evidence), putative (inferred evidence; e.g., from metabolites), or potential (rational basis; e.g., nuclear receptors and regulatory networks) role in transport, metabolism, and excretion. Overall, 175 ADME genes can be proposed as potentially relevant to current ART (81).

A second step is the analysis of genetic variation with integrated data from the literature or from predictive bioinformatics tools to establish the functionality of candidate SNPs. Proven/proposed functional polymorphisms represent the subset of SNPs for which there is experimental evidence for a functional effect of the substitution. Putative SNPs are defined by bioinformatic tools by using programs such as FastSNP (85) or TAMAL (86) that score the likelihood of a functional effect according to predefined algorithms. These proven or putative functional SNPs will enrich a background of common human genetic variation as described by utilizing the data from the human HapMap. Progress in our understanding of the characteristics that define a SNP as functional will continue to evolve and should be incorporated into future definitions of the minimum set of SNPs that characterize a gene. An estimate for the Caucasian population includes 188 proven and 664 putative functional variants in ADME genes that can be proposed for the study of current antiretroviral drugs (**Table 2**). In addition, common variation in these genes is captured by 2444 HapMap tSNPs (**Table 2**). Overall, genetic variation can be captured by an average of 19 SNPs per candidate gene. As above, the resulting ranking of biological plausibility (i.e., proven, putative) can be used in the evaluation of results emanating from genetic association studies in sequential or in joint analysis.

TOXICOGENETICS

The analysis of pharmacogenetic determinants of toxicity has been successful for the unequivocal identification of the genetic basis of hypersensitivity reactions to the NRTI abacavir, in the understanding of the genetic basis of PI-induced hyperlipidemia, and in defining associations of several PIs and unconjugated hyperbilirubinemia in the context of Gilbert's syndrome. In addition, there is some,

Table 2 Genetic variation in ADME pathways of anti-HIV drugs. Updated from Reference 81

Gene class (#)	SNP type			Total SNPs (SNPs/gene)
	Pr-fSNP	Pu-fSNP	Tag-SNP	
Drug metabolism				
CYPs (18)	49	84	113	246 (14)
FMOs (6)	3	51	58	112 (19)
ADHs (7)	3	31	75	109 (16)
ALDHs (19)	2	76	220	298 (16)
UGTs (16)	23	35	59	117 (8)
SULTs (14)	15	43	137	195 (14)
Transporters				
ABCs (10)	31	70	328	429 (43)
SLCs (37)	32	142	702	876 (24)
Other				
PBPs (3)	2	7	15	24 (8)
NRs (25)	25	86	475	586 (24)
PHOs (15)	3	27	234	264 (18)
PDZs (5)	0	12	28	40 (8)
Total (175)	**188**	**664**	**2444**	**3296 (19)**

This set does not include genes involved in phosphorylation, mitochondrial genes, mitochondrial transporters, or genes implicated in abacavir metabolism (alcohol and aldehyde dehydrogenases). CYPs, cytochrome P450 enzymes; FMOs, flavin-containing monooxygenase; ADHs, alcohol dehydrogenases; ALDHs, aldehyde dehydrogenases; UGTs, UDP glucuronosyltransferases; SULTs, sulfotransferases; ABCs, ATP-binding cassette transporters; SLCs, solute carrier transporters; PBPs, plasma binding proteins; NRs, nuclear receptors; PHOs, enzymes involved in the anabolic phosphorylation steps of the NRTIs; PDZs, PDZ-domain containing proteins; Pr-fSNP, proven/proposed functional polymorphism; Pu-fSNP, putative functional polymorphism; Tag-SNP, HapMap tagging SNP.

albeit sparse, information on the genetic basis for other recognized adverse effects of ART (**Table 3**).

Drug Hypersensitivity Syndromes

The pathogenesis of a number of multisystem drug hypersensitivity reactions involves major histocompatibility complex (MHC)-restricted presentation of drug or drug metabolites to MHC molecules and/or haptenation to endogenous proteins prior to T cell presentation (87–89). Genetic loci within the MHC are determinants of hypersensitivity reactions to abacavir and to nevirapine. Only a subset of individuals exposed to abacavir develop hypersensitivity, typically within 6 weeks of initiating therapy, and those individuals who do not develop the syndrome within this time frame remain at low risk despite ongoing therapy (90). Non-Caucasian racial origin also decreases risk of abacavir hypersensitivity, and familial predisposition has also been reported (91). Specific MHC alleles are strongly associated with risk of abacavir

Table 3 Toxicogenetics of antiretroviral drugs. Only the most relevant associations are indicated. Compiled from http://www.hiv-pharmacogenomics.org

Gene or protein (*)	Allele or variant evaluated	Reported consequence for antiretroviral drugs
HLA-B	*HLA-B*57.1* haplotype (defined by the presence of *HLAB*5701*, *HLA-DR7*, and *HLA-DQ3*)	Hypersensitivity reaction to abacavir
HLA-C	*HLA-Cw8*	Hypersensitivity reaction to nevirapine
HLA-DR	*HLA-DRB1*0101*	High negative predictive value of hypersensitivity reactions to nevirapine (fever, rash, hepatitis)
TNFα	-238G/A *TNF-α* promoter polymorphism	Earlier onset of lipoatrophy
UGT1A1	*UGT1A1*28*, promoter region (insertion at TATA box associated with reduction in bilirubin-conjugating activity)	Gilbert's syndrome. Hyperbilirubinemia, increased levels of bilirubin in presence of atazanavir or indinavir
APOC3, *APOE*	*APOC3* -482 C>T, -455 T>C, 3238 C>G. *APOE* ε2 and ε3 haplotypes	Increased risk of hypertriglyceridemia associated with use of ritonavir. Including analysis of variants of APOA5, CETP, and ABCA1 may improve prediction and also help in identifying individuals at risk for low HDL-cholesterol
SPINK1, *CFTR*	Multiple variants associated with cystic fibrosis and pancreatitis	Susceptibility to pancreatitis
Mitochondrial DNA	Tissue-specific mitochondrial DNA depletion may represent a toxic effect of NRTI therapy on mitochondrial DNA synthesis. Possibility for accumulation of mutations in mtDNA due to gamma polymerase damage due to nucleoside analogue reverse transcriptase inhibitors	Certain human mtDNA haplotypes (haplotype T) may increase susceptibility to peripheral neuropathy. Depletion and mutation of mtDNA likely associated with lipodystrophy

hypersensitivity (92, 93). The *HLA-B*5701* allele has an independent positive predictive value of greater than 70% and a negative predictive value of >90% in Caucasians, suggesting that prospective testing for susceptibility to this syndrome may represent a useful clinical test in some populations (94).

A cost-effectiveness study concluded that pretreatment screening of HLA-B*5701 in Caucasian (and Hispanic) populations would be a cost-effective use of health-care resources (95). The relevance of the study's findings to populations where carriage of the HLA-B*5701 allele is at a significantly lower frequency (such as many Asian and African populations) is less certain (96). These questions are currently being addressed by large-scale prospective international studies, such as PREDICT-1 and SHAPE (96a). There are practical considerations influencing the widespread implementation of a pharmacogenetic approach to abacavir prescription because analysis is more complex than the analysis of a simple SNPs. HLA-B*5701 diagnostic methods need high-resolution typing assays to resolve HLA alleles within the B17 serological family (e.g., HLA-B*5701, HLA-B*5702, HLA-B*5703, and HLA-B*5801) (97).

Nevirapine hypersensitivity—manifesting as potentially life-threatening hepatotoxicity with or without rash—is also a result of genetic factors. This syndrome is similar to abacavir hypersensitivity in that susceptible individuals develop symptoms within 6 weeks, whereas continuing therapy beyond this period is not associated with increased risk (98). The protective effect of low CD4 T cell count in the case of nevirapine hypersensitivity (98, 99) is consistent with a CD4 T cell–dependent immune response to nevirapine-specific antigens and participation of HLA Class II alleles (100). Human cases involving combinations of hepatitis, fever, or rash have been associated with an interaction between HLA-DRB1*0101 and the number of CD4 cells, whereas no associations were detected for isolated rash (100). More recently, two reports have described the association of the MHC allele HLA-Cw8 and hypersensitivity reactions in Sardinia and in Japan (101, 102) (**Table 3**).

Lipid Disorders

In considering the pharmacogenetics of ART-related dyslipidemia, it may be useful to evaluate factors that may influence lipid metabolism in the general population and may therefore potentiate ART-related dyslipidemia. Initial work identified the role of *APOE* and *APOC3* variants as risk factors for hyperlipoproteinemia (predominantly hypertriglycerdemia) (103–105). In addition, there is a deleterious gene-drug interaction resulting in a high risk for extreme hypertriglyceridemia when ritonavir is prescribed to individuals with an unfavorable genetic profile. A recent analysis of selected allelic variants of 13 genes proposed in the literature as influencing plasma lipid levels in the general population validated five genes as contributing to ART-associated dyslipidemia (106).

The most favorable and unfavorable *APOE/APOC3/APOA5/CETP/ABCA1* genotype resulted in median triglyceride levels of 2.6 and 4.1 mmol/l, respectively, when patients were exposed to ritonavir. In contrast, the triglyceride levels for individuals with the most favorable and unfavorable genotype were 1.4 and 2.3 mmol/l, respectively, in the absence of ritonavir exposure. The most favorable and unfavorable CETP/APOA5 genotype resulted in median HDL-cholesterol levels of 1.5 and 1.17 mmol/l with NNRTI-ART, and of 1.25 and 1.11 mmol/l with other ART combinations, respectively. No genotype was significantly associated with non-HDL cholesterol levels. Thus, the contribution of any single SNP on lipid levels was modest. However, the magnitude of the genetic effects on dyslipidemia became apparent in the multigene analysis. A theoretical strategy of selecting the initial ART according to the results of genotyping would have the potential to reduce the number of patients with sustained hypertriglyceridemia by 30% and possibly even more for individuals with unfavorable genotypes (**Figure 2**).

Lipodystrophy and Mitochondrial Disorders

Lipodystrophy has been described in 25%–50% of ART-treated patients. The cumulative exposure to ART has been identified as the major risk factor in multiple studies. However, lipodystrophy affects some but not all patients despite similar ART

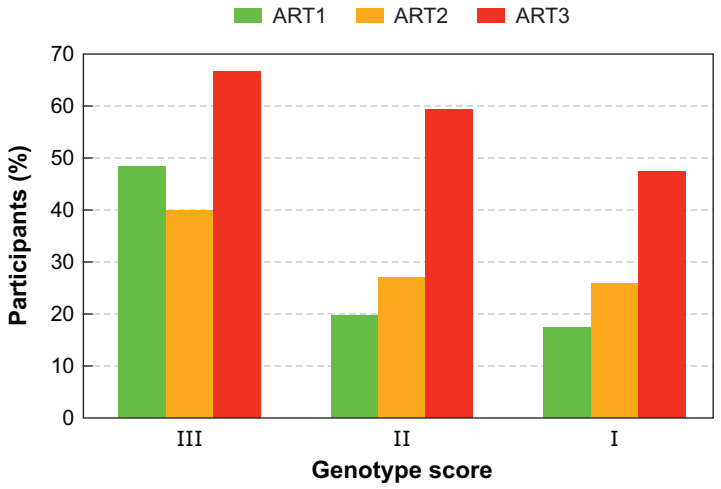

Figure 2

Cumulative *ABCA1/APOA5/APOC3/APOE/CETP* genotype score and antiretroviral drug combination (ART) group on the observed proportion of patients (%) with sustained hypertriglyceridemia. ART group 1: NRTI ART or nevirapine-containing ART; group 2: single protease inhibitor or efavirenz-containing ART; group 3: ritonavir-containing ART. Cross-tabulation of three genotype scores and three ART groups generates nine genotype score-by-ART group categories that define the risk of hyperlipidemia. Adapted from Reference 106.

exposure, which suggests that genetic factors may be involved. A functional promoter polymorphism in *TNF-α* (-238A) has been associated with a more rapid onset of lipoatrophy in some (107, 108) but not all studies (105). The functional correlates of this effect have not been characterized, although higher TNF-α levels are described among individuals carrying the -238A *TNF-α* promoter variant (107, 108).

Defects in either the quantity or quality of mitochondrial DNA (mtDNA) have been associated with lipodystrophy, neuropathy, lactic acidosis, and the associated complex metabolic disorders. In contrast to the nuclear genome, mtDNA may undergo quantitative and qualitative changes over an individual's lifetime and may be influenced directly by environmental factors (109). The effects are likely to be tissue-specific rather than general, reflecting the differing requirements of tissues for cellular energy and the differing availability of energy substrates. The putative mechanism that is invoked to explain mitochondrial toxicity of ART (and, most prominently, for the NRTI class), includes the inhibition of the gamma polymerase, the only enzyme that replicates mtDNA. Inhibition of gamma polymerase leads to depletion of mtDNA and inhibition of the transcription of proteins encoded by mtDNA, all of which represent enzymes of the electron transport system, which is involved in oxidative phosphorylation. Initiation of ART has triggered bilateral optic atrophy and blindness in HIV-infected individuals with unrecognized mitochondrial disorders, such as Leber's hereditary optic neuropathy (109–113). Underlying human variation

of mtDNA, represented by common haplotypes, has been associated with differences in susceptibility to ART-related neuropathy (114) (**Table 3**). In addition, the possible accumulation of mtDNA mutations during aging leads to mitochondrial dysfunction. Knockin mtDNA mutator mice that expressed an exonuclease-deficient gamma polymerase developed a three- to fivefold increase in mtDNA mutations and deletions (115). These mice presented subcutaneous fat loss, weight loss, osteoporosis, anemia, and cardiomegaly. Overall, accumulation of mutations and reduction of mtDNA quantity associated with ART and against a background of aging would be a plausible mechanism explaining the complex features of lipodystrophy and associated metabolic syndrome. Detailed analysis of the mtDNA genome may help identify individuals at risk of toxicity.

Unconjugated Hyperbilirubinemia

Unconjugated hyperbilirubinemia is an adverse effect of therapy containing indinavir (IDV) or atazanavir (ATV) (116, 117). Unconjugated bilirubin enters the hepatocyte by passive diffusion and may be facilitated through the human organic transporting polypeptide 1B1 (OATP1B1) encoded by *SLCO1B1* (118–120). Once in the hepatocyte, bilirubin is conjugated with glucuronic acid by the microsomal enzyme UDP-glucuronosyltransferase 1A1 (UGT1A1) and excreted in the bile by MRP2 (ABCC2) (121). A polymorphism in the promoter TATA element of the gene encoding UGT1A1 (allele *UGT1A1*28*) decreases transcriptional activity and it is responsible for the unconjugated hyperbilirubinemia observed in the context of Gilbert's syndrome (122, 123) (**Table 3**), and is associated with the occurrence of jaundice upon initiation of PIs IDV and ATV (124, 125). Nonsynonymous polymorphisms in *SLCO1B1* have been associated with differences in the function of the transporter in vitro (126–128) and in vivo (129–133).

The additive effect of the genes described above will influence the rates of hyperbilirubinemia upon introduction of drugs such as ATV (125, 134). There are ethnical/racial differences in the frequency of both *UGT1A1* and *OATP1B1* variants, such that hyperbilirubinemia may occur more frequently for individuals of African and less frequently for individuals of Japanese origin. The theoretical advantage of genotyping for *SLCO1B1* and *UGT1A1*28* before initiation of ART would be a reduction of bilirubin determinations in the jaundice range from 22% to 5.0% (134).

Neurotoxicity of Efavirenz

As described above, efavirenz and nevirapine are metabolized by CYP2B6. The best-studied allele, *2B6*6* (516 G>T and 785 A>G), is a pharmacogenetic marker of efavirenz neuropsychological toxicity. This allele is associated with adverse neuropsychological scores during the first 12 weeks after initiation of efavirenz therapy (24), although the symptoms of toxicity decrease thereafter (135). Genotyping can also identify individuals at risk for late or persistent neuropsychological toxicity while on long-term efavirenz-containing therapy (136). In the latter setting, the presence of

the variant allele was two to three times more frequent among individuals describing sleep or mood disorders or fatigue.

Epistasis: the interaction between genes at two or more loci

Pancreatitis

Drug-induced pancreatitis in individuals with advanced HIV infection/AIDS has been attributed to use of pentamidine, trimethoprim-sulfamethoxazole, or didanosine (137). Drugs may be contributing to pancreatitis by potentiating other toxic agents, through a genetic predisposition, or by their action on a pancreas that was already diseased. *CFTR* (cystic fibrosis transmembrane conductance regulator) mutations are associated with pancreatitis (138, 139). *SPINK1* (serine protease inhibitor kazal-1), which encodes a trypsin inhibitor in the cytoplasm of pancreatic acinar cells, is also a genetic risk factor for pancreatitis (140). Frossard et al. evaluated the frequency of *CFTR* and *SPINK1* mutations in HIV-positive patients with clinical pancreatitis or asymptomatic elevation of serum pancreatic enzymes (141). Among 51 patients presenting with hyperamylasemia, there were 13 carriers of *CFTR* or *SPINK1* polymorphisms (12.7%). Four of ten (40%) patients with clinical acute pancreatitis had *CFTR* or *SPINK1* mutations.

GENETICS OF HIV SUSCEPTIBILITY

The rate of HIV disease progression reflects the influence of the genetic diversity of the virus as well as variation in host factors (142). Dominant host factors identified to date include diversity in MHC Class I and alleles of chemokine, chemokine receptor, and cytokine genes. MHC homozygosity, as well as specific HLA Class I alleles, are well-documented modifiers of infection (**Table 4**). The most relevant alleles associated with protection are *HLA-B*27* and *B*57*. In contrast, *HLA-B*35Px*, *B*37*, *B*53*, *B*56*, *B*58*, and *A1-B8-DR3* have been associated with rapid progression (143, 144). Epistatic interactions between certain KIR (3DS1) and HLA-B alleles delay disease progression (145). Following the discovery of the CCR5 Δ32 deletion, conferring a high level of resistance to HIV infection (146–148), extensive research has addressed the contribution of additional variants in the CCR5-CCR2 locus. Variants of the CCR5 promoter region include a human haplotype HHE that is associated with rapid disease progression (149, 150). In contrast, haplotypes carrying the CCR2 64I allele are associated with a favorable prognosis (151), and possibly with some degree of protection from infection. Duplication at the locus encoding the chemokine CCL3L1 leads to a gene-dose effect that, alone or in association with genetic variants determining CCR5 expression or function, is proposed to modify the rate of disease progression (152). Various cytokine variants have been reported to influence the course of HIV-1 disease through more general effects on HIV-1 pathogenesis and inflammatory homeostasis (142). Variants in cellular host factors, and in antiviral innate defense modifying HIV-1 susceptibility have effects in the range of those of well-documented variants such as those in the CCR5/CCR2 region (153–155). However, the contribution of any genetic variant is limited and any genetic prediction must account for the influence of multiple alleles (154, 156, 157).

Table 4 Predictors of susceptibility to HIV and disease progression. Only the most relevant associations are indicated. Compiled from http://www.hiv-pharmacogenomics.org

Gene or protein (*)	Allele or variant evaluated	Reported consequence for HIV susceptibility
CCR5-CCR2 locus. Chemokine receptors; coreceptor of HIV-1 (CCR5)	*CCR5 Δ32*, *CCR5 303T>A*, *CCR5 P1*, *CCR2 V64I*, and derived haplotypes	Protection (*CCR5 Δ32*, *CCR5 303T>A*, *CCR2 V64I*) or progression (*CCR5 P1*)
HLA MHC, acquired immunity	*HLA A*, *B*, C homozygosity, or selected *HLA B* and *HLA* C alleles	*HLA-B*27* and *B*57* are associated with protection. In contrast, *HLA-B*35Px*, *B*37*, *B*53*, *B*56*, *B*58*, and *A1-B8-DR3* have been associated with rapid progression
KIR innate immunity, regulation of NK cell response	Specific *KIR-HLA* associations	Epistatic interactions between certain *KIR* (*3DS1*) and *HLA-B* alleles delay disease progression
CXCL12 (SDF-1) ligand of CXCR4	3′UTR *SDF1-3′A*	Neutral or progression
TSG101 vacuolar protein sorting, required for HIV-1 budding	Various haplotypes of promoter: *-183T>C* and intronic *181A>C*	Protection or progression depending on haplotype
CCL5 (RANTES) ligand of CCR5	Various haplotypes of promoter: *-403G>A*, *-28C>G* and intronic *In1.1T>C*	Protection or progression depending on haplotype
IL-10 antiinflammatory cytokine	Promoter *-592C>A*	Progression
CCL3L1 (MIP1αP), ligand of CCR5	Variable gene copy number	Progression associated with low-copy number
CX3CR1, fractalkine receptor, minor HIV-1 coreceptor	T280M	Progression
APOBEC3G, intrinsic immunity; HIV-1 cDNA hypermutation, *Cul5* (Cullin5)	*APOBEC3G* H186R or expression polymorphism. Various *Cul5*haplotypes	Progression. Some haplotypes of *Cul5* may have additive effect with *APOBEC3G* H186R. HIV-1 viral infectivity factor (Vif) suppresses Apobec3 activity through the Cullin 5-Elongin B-Elongin C E3 ubiquitin ligase complex
RNF39, ring finger protein 39, and *ZNRD1*, zinc ribbon domain containing 1	Seven polymorphisms located in and near these genes. Identified through genome-wide analysis	Protection. Explains 5.8% of the variation in disease evolution
PPIA, prolyl isomerase A or cyclophilin A, incorporated into the virion	Regulatory SNPs associated with differential nuclear protein-binding efficiencies in a gel shift assay	Progression
CCL3 (MIP1α) ligand of CCR5	Intronic *459C>T*	Progression

There is great interest to go beyond single-gene studies to more comprehensive approaches. The Center for HIV/AIDS Vaccine Immunology (CHAVI, **http://www.chavi.org**) has launched whole genome studies investigating the control of the earlier phases of infection, focusing on viral set point (3). The first study has been successfully completed (157a). This first genome-wide study of host determinants of viral control identifies major effect gene variants. In addition, the study emphasizes the central role of the MHC region in HIV-1 restriction, estimates the contribution of HLA against all genome influences, and opens up new perspectives in the understanding of its mode of action.

A second initiative, the HIV Elite Controller Study (**http://www.massgeneral.org/aids/hiv_elite_controllers.asp**), will apply genomic techniques to the investigation of HIV-1-infected people who have been able to maintain viral loads at or below the limits of detection. Analysis of data from whole-genome association studies remains a critical challenge because of the unprecedented quantity of genomic information (158).

CONCLUSIONS AND PERSPECTIVES

HIV infection and treatment represents an important field for application and validation of pharmacogenetic knowledge. The field has excellent patient cohorts and well-developed structures for clinical trials that could allow pharmacogenetic investigations. Overall, 5 genes involved in metabolism, 5 genes involving drug transporters, 23 genes involved in toxicity and treatment response, and 50 genes involved in HIV susceptibility and disease progression have been evaluated with more or less detail in the recent years (**http://www.hiv-pharmacogenomics.org**).

Large-scale approaches are expected to rapidly modify the landscape of knowledge. For pharmacogenetics, in a strict sense, this represents the use of ADME arrays in studies with well-defined pharmacokinetic, pharmacodynamic, or toxicity study endpoints (phenotypes) (81). Pharmacogenetic data can be integrated in population pharmacokinetic modeling. On a larger scale, HIV disease is currently approached by using whole-genome association analysis (3). The proof of concept and the validity of the whole-genome approaches are provided by recent publications on whole-genome association analysis in inflammatory bowel disease, diabetes, and leukemia (159–161). Follow-up studies of candidate genes and gene variants will be needed to assess their functional role in vitro (3). In vivo validation studies should be performed with well-defined study phenotypes, study design, and adequate power.

SUMMARY POINTS

1. Pharmacogenetics holds promise in HIV treatment because of the complexity and potential toxicity of multidrug therapies that are prescribed for long periods.

2. Available pharmacogenetic data includes information on a limited number of genes and genetic variants. Thus far, 70 genes involved in metabolism, drug transport, toxicity, and HIV susceptibility and disease progression have been evaluated.
3. The best-established associations include the role of *CYP2B6* alleles and efavirenz (and nevirapine) pharmacokinetics and possibly toxicity, the association of HLAB*5701 and abacavir hypersensitivity reactions, and the interaction of some protease inhibitors with UGT1A1 in Gilbert's syndrome.
4. An approach using SNPs from the HapMap, enriched by functional polymorphisms of candidate genes, may allow the high-throughput screening of ADME (absorption, distribution, metabolism, and excretion) pathways of antiretroviral drugs.
5. The low allelic frequency of proven and putative functional SNPs underscores the need for appropriate high-throughput technology to interrogate multiple positions simultaneously.
6. Exploratory studies analyzing a large number of candidate genes and genetic variants represent a step toward in vitro analysis of the biological plausibility.

DISCLOSURE STATEMENT

U. Zanger is a named coinventor of a pending patent application directed to the detection of specific *CYP2B6* polymorphisms for diagnostic purposes and is entitled to share in any net income derived from licensing these patent rights under standard academic institutional policies. A. Telenti declares no conflict of interest.

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Errata

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