Genetic, Ethnic, and Gender Differences in the Pharmacokinetics of Antiretroviral Agents

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Current HIV/AIDS Reports 2006, **3:**118–125
Current Science Inc. ISSN 1548-3568

Variable antiretroviral therapy (ART) drug response likely reflects the combined influence of environment, underlying disease, concurrent drugs, and genetics. Gender exerts modest or negligible effects on ART disposition, and it is expected to have limited clinical implication, although it should be accounted for in large population studies. Ethnic denominations have, with the notable exception of efavirenz, no clear influence on ART disposition. Exploration of genetic factors might offer a better comprehension to the largely unpredictable and unresolved variability in ART concentrations and related toxicity or treatment outcome. Despite the negative perception of genetic research among the general public, this type of investigation is now widely accepted by concerned parties: patients, relatives, and study volunteers.

Introduction

There is marked interindividual variation in plasma levels, efficacy, and in susceptibility to adverse effects of antiretroviral therapy (ART). Variable drug response may reflect the combined influence of exogenous factors (environment, underlying disease, concurrent drugs), as well as gender, ethnicity, and genetics. In this regard, variation in the genes that encode for proteins involved in the metabolism or disposition of ART is thought to represent a key determinant of their efficacy and toxicity. Genetic variation also underlies differences in treatment response that are ascribed to ethnicity. In this update, we describe advances in the understanding of pharmacogenetic factors relevant to ART, as well as gender and ethnic determinants of response. Finally, we will comment on specific research initiatives aiming at bringing genetic prediction to clinical use.

Gender and Pharmacokinetics

Sex or other sex-specific factors can influence ART pharmacokinetic profile, the incidence of adverse reactions, and treatment outcome [1••]. Differences in body weight, plasma volume, gastric emptying time, plasma protein levels, hepatic enzyme expression and activity, drug transporters function, excretion activity, or sex-specific conditions (pregnancy, hormonal therapy) may account for the gender variation in drug profiles [1••]. A few studies have explored, among other covariates, the influence of sex on the disposition parameters of ART in order to explain the large interpatient variability in the kinetic profile of these agents. Investigations of a sex-based effect on the pharmacokinetics of antiretroviral agents have provided inconsistent results between studies and among certain agents. These results are summarized in Table 1. A significant sex-effect was reported for indinavir in three population studies, which reported a decrease in apparent clearance in female compared with male patients after adjustment for body weight [2,3], as well as an increase in indinavir bioavailability in women [4]. Other investigators observed roughly similar pharmacokinetic parameters in women than in men [5]. In studies on saquinavir alone and saquinavir boosted by ritonavir, female patients had higher exposure, maximal, and trough concentrations of saquinavir and ritonavir [6,7] as well as a 50% reduction of clearance compared with male patients, after adjustment for body weight [8]. In contrast, no sex-related differences were reported in lopinavir [6,9], nelfinavir [10], amprenavir [11], and atazanavir (unpublished data) pharmacokinetic profiles.

Studies on the non-nucleoside reverse transcriptase inhibitors are not fully conclusive. Efavirenz was not shown to be influenced by sex in three studies [12,13•,14], whereas one investigation reported a small decrease in apparent clearance [15] and others reported a sustained increase in mean efavirenz concentrations in female compared with male patients [16,17]. No sex-related difference

in nevirapine elimination was reported by some authors [18,19], whereas two studies revealed a decrease in nevirapine clearance in females [14,20].

The nucleoside reverse transcriptase inhibitors didanosine, tenofovir, lamivudine, and zidovudine pharmacokinetic profiles were not found to be influenced by gender [18,20–22]. Interestingly, median intracellular concentrations of zidovudine triphosphate and lamivudine triphosphate were markedly increased in women compared with men without any other biologic explanation [21]. Finally, in the HIV-1 fusion inhibitor enfuvirtide, elimination was reported to be reduced in female compared with male patients [23].

Taken as a whole, these results suggest that, although of moderate clinical implication, the sex-based differences on the plasma and intracellular levels of antiretroviral agents should be accounted for in large population studies, in particular in the view of concomitant impacting factors such as other demographic covariates, comedications, or underlying diseases, ethnicity, and genetic differences. Additional data can be found in the registration files of the various drugs.

Ethnicity-related Differences in Pharmacokinetics

Geographic patterns of genetic variation indicate that geographic structuring of interindividual variation in drug concentration and response may occur [24••]. This is the basis for investigating whether ethnic, racial, or ancestry factors influence ART. Unfortunately, most of the available studies rarely include more than 25% of non-whites in the analysis. A better representation of the various ethnic groups is clearly needed (Table 1).

Several studies on efavirenz have revealed ethnic-related differences in the clearance or bioavailability and of the plasma concentrations of this drug. A population meta-analysis of 16 phase I studies revealed a decrease in efavirenz apparent clearance in blacks and Asians compared with that of whites [15]. Two subsequent population analyses of efavirenz in a cohort of 235 [12] and 398 [13•] individuals with HIV infection showed a modest but significant increase in bioavailability and a decrease in apparent clearance in the black and Hispanic subpopulations versus whites. Similarly, a clear increase in bioavailability in Asians versus whites with no effect on clearance or volume of distribution was reported in a cohort of 178 patients [25]. Blacks and Hispanics were reported to present double maximal concentrations and drug exposure compared with whites in a cohort of 190 patients as well [26•] and similar increases in mean efavirenz plasma concentrations were observed in blacks and in Asians [16]. An important genetic component to these ethnic differences is discussed below. A few analyses of nevirapine kinetics did not report any ethnic differences in elimination [18,20].

Several population pharmacokinetic studies have investigated the influence of ethnicity to explain the large interindividual variability in the plasma levels of protease inhibitors. No ethnicity-based difference in the pharmacokinetic parameters of indinavir [3,4], nelfinavir [10], saquinavir [8], lopinavir [9], and atazanavir (unpublished data) are reported. A study on amprenavir did not report any influence of ethnicity on its elimination [11]. Another cross-study analysis of three single-dose studies in 83 HIV-positive and -negative individuals explored the relationship between amprenavir, α1-glycoprotein (AAG) level in plasma and ethnicity [27]. The authors found that mean concentrations of AAG were 17% lower in black individuals compared with whites and that a significant inverse linear relationship was found between AAG concentration and amprenavir apparent clearance. The observed differences in amprenavir elimination might partially reflect a contribution of ethnicity-associated genotypic-differences in AAG concentrations [28,29]. The same relationship between ethnicity, AAG concentrations and clearance are also observed for indinavir and lopinavir (unpublished data). No differences in zidovudine and lamivudine kinetics were observed between whites and other populations [21].

Thus, except for efavirenz, no clear influence of an ethnic component on ART disposition has been evidenced. It has been suggested that the commonly used ethnic labels might be insufficient and inaccurate representations of actual genetic clusters and that the drug-metabolizing profiles differ significantly among the different clusters [24••]. Exploration of genetic-related factors might offer a better comprehension to the largely unpredictable and unresolved variability in antiretroviral agents' concentrations and related toxicity or treatment outcome. However, Ioannidis et al. [30] emphasized that although allelic frequency may vary across ethnic groups, the specific effect of a functional variant allele was conserved.

Genetic Variation in Genes Involved in the Pharmacokinetics of Antiretroviral Agents

Genetic variation in drug-metabolizing enzymes

Drug metabolism can be divided in two phases: phase I, that may occur by oxidation, reduction or hydrolysis, and phase II, where drugs are conjugated with polar-endogenous compounds that will facilitate their elimination from the body. Cytochrome (CYP) P450 is a group of heme-containing enzymes responsible for the majority of phase I metabolism. Five CYP enzymes (CYP3A4, CYP3A5, CYP2C19, CYP2D6, and CYP2B6) are involved in the metabolism of ART. Genetic polymorphism may result in poor metabolizer phenotype due to gene deletion, to mutations creating an alternative splice site, or a premature stop codon that results in nonexpressed, nonfunctional truncated proteins. At the other side of the spectrum, there are individuals presenting ultra-rapid metabolizer phenotypes due to a phenomenon of gene duplication. A significant number of nonsynonymous (amino acid-changing) variants alter enzyme function. The frequency of these genetics variants differs among ethnic groups [24••] (Table 2).

Table 1. Sex- and ethnicity-related differences in the pharmacokinetics of antiretroviral agents

Drug	Gender (women vs men)	Study	Ethnicity (% of patients in each ethnic group)		Study
PIs					
Lopinavir	No difference in CL, AUC, C_{max} and C_{trough}	[6,9]	White (75) Black (14) Asian (9)	No difference in CL	[9]
			White (90) Black (6) Asian (9) Hispanic (8)	Lower mean AAG in black, Asian, and Hispanic. Inverse relationship between AAG and CL	UD
Indinavir	Decrease in CL Increase in F	[2–4]	White (82–92) Black (5–9) Asian (1–5)	No difference in CL	[3,4]
	Lower C_{min}		White (90) Black (6) Asian (9) Hispanic (8)	Lower mean AAG in black, Asian, and Hispanic. Inverse relationship between AAG and CL	UD
	No difference in concentrations	[5]			
Nelfinavir	No difference in CL	[10]	White (78) Black (12) Asian (2)	No difference in CL	[10]
Amprenavir	No difference in CL,V	[11]	White (66) Other (34)	No difference in CL,V	[11]
			White (59) Black (40)	Lower mean AAG in black. Inverse relationship between AAG and CL	[27]
Saquinavir	Decrease in CL, higher AUC, C_{max}, and C_{trough}	[6–8]	White (52) Black (27) Hispanic (17) Asian (2)	No difference in CL	[8]
Ritonavir	Decrease in CL, higher AUC, C_{max}, and C_{trough}	[6,7]			
Atazanavir	No difference CL	UD	White (86) African (9) Asian (3)	No difference in CL	UD

AAG—α1-glycoprotein; AUC—area under the concentration-time curve; C_{av}—average concentration; CL—clearance; C_{max}—maximal concentration; C_{min}—minimal concentration; C_{ss}—concentration at steady-state; C_{trough}—trough concentration; F—bioavailability; NNRTI—non-nucleoside reverse transcriptase inhibitor; NRTI—nucleoside transcriptase inhibitor; PI—protease inhibitor; UD—unpublished data; V—volume of distribution.

CYP3A4 and CYP3A5 are responsible for the metabolism of 50% of therapeutic drugs. Both are polymorphic: 20 different alleles are described for CYP3A4 and 11 for CYP3A5 (Table 2). Studies performed to evaluate the effect of *CYP3A4*1B*, *CYP3A5*3*, and *CYP3A5*6* on the pharmacokinetics of nelfinavir [31••,32••], efavirenz [26•,31••,32••], and saquinavir [33,34] indicate no influence on nelfinavir and efavirenz pharmacokinetics. In contrast, CYP3A5*3 has been associated with the urinary metabolic ratio of saquinavir to its hydroxy metabolites in healthy individuals [33,34]. Differences in levels of CYP3A expression appear more relevant to ART metabolism than specific genetic variants [35].

CYP2D6 is the most polymorphic of all CYP enzymes with 58 alleles described (Table 2). A study published by Fellay et al. [31••] analyzed the association between CYP2D6 genetic variations and plasma levels of nelfinavir and efavirenz in treatment-naïve individuals with HIV infection. Individuals homozygous or heterozygous for a loss-of-function CYP2D6 allele had higher median plasma concentrations of both drugs. However, CYP2D6 is not thought to participate significantly to the metabolism of these drugs, and the results await confirmation.

There are 21 different alleles described for CYP2C19. A recent study demonstrated that nelfinavir exposure was significantly higher in treatment-naïve individuals with GA or AA genotypes at position 681 in CYP2C19 (ie, *CYP2C19*2*) compared with the common allele. The same study showed a trend toward decreased virologic failure in individuals with the GA genotype. Genotypic differences are also observed among ethnic groups because 2% to 3% of whites and 4% of blacks have the poor metabolizer phenotype versus 10% to 25% of Asians [36].

CYP2B6 is also polymorphic (21 alleles described) particularly in blacks. Different studies have shown that 516G>T single nucleotide polymorphism (SNP) in exon

Table 1. Sex- and ethnicity-related differences in the pharmacokinetics of antiretroviral agents

Drug	Gender (women vs men)	Study	Ethnicity (% of patients in each ethnic group)		Study
NNRTI					
Efavirenz	No difference in CL, V, F	[12,13•,14]	White (57–82) Black (16–32) Hispanic (5–11) Asian (2)	AUC, C_{max} and C_{av} greater in black, Hispanic, and Asian. Decrease in CL, F in black and Asian.	[12,13•,15, 16,26•]
	Decrease in CL, increase in C_{av}	[15–17]	White (75) Black (15) Asian (7) Hispanic (4)	Increase in F in Asian. No difference in CL,V	[25]
Nevirapine	No difference in CL and V	[18,19]	White (82–89) Black (6-19) Hispanic (10)	No difference in CL, V	[18,20]
	Decrease in CL	[14]	Asian (2–3)		
NRTI					
Tenofovir	No difference in CL	[22]			
Didanosine	No difference in CL, V, F	[20]	White (81) Black (9) Hispanic (10)	No difference in CL, V, F	[20,25]
Lamivudine	No difference in CL, plasma C_{ss}	[18,21]	White (70) Black (21)	No difference in CL	[21]
Lamivudine triphosphate	Higher median intracellular concentration	[21]			
Zidovudine	No difference in CL, V, F, C_{ss}	[21]	White (70) Black (21)	No difference in CL	[21]
Zidovudine triphosphate	Higher median intracellular concentration	[21]			
Fusion inhibitor					
Enfuvirtide	Decrease in CL	[23]			

AAG—α1-glycoprotein; AUC—area under the concentration-time curve; C_{av}—average concentration; CL—clearance; C_{max}—maximal concentration; C_{min}—minimal concentration; C_{ss}—concentration at steady-state; C_{trough}—trough concentration; F—bioavailability; NNRTI—non-nucleoside reverse transcriptase inhibitor; NRTI—nucleoside transcriptase inhibitor; PI—protease inhibitor; UD—unpublished data; V—volume of distribution.

4 (marker for *CYP2B6*6* with a high allelic frequency in blacks) is significantly associated with high plasma levels of non-nucleoside reverse transcriptase inhibitors (efavirenz and nevirapine) [26,37,38•,39•]. In addition, the 983T>C SNP in exon 7 (marker for *CYP2B6*16* and **18* [only found among blacks]) has also been associated with high efavirenz plasma levels [40••,41]. Efavirenz concentrations are more profoundly altered in individuals carrying two copies of loss-of-function alleles: generally one copy of *CYP2B6*6* with a second copy including alleles **11* and **18* or new alleles, such as M198T and R378stop [42].

Genetic variation in drug transporters

Drug transporters play also an important role in the disposition of ART. There are two major types: uptake and efflux transporters. P-glycoprotein, the gene product of *ABCB1/MDR1*, an efflux transporter, has received the greatest attention in terms of identification of genetics variants. Protease inhibitors are substrates of this transporter.

Screening of the entire *ABCB1* coding region identified a synonymous SNP in exon 26 (ie, 3435C>T) possibly associated with altered protein expression and mRNA stability, although the particular SNP does not change the encoded amino acid (isoleucine) [43,44]. The allelic frequency of this SNP also differs among ethnic groups being more common in whites and Asians (~ 0.5) than in blacks (0.10) [45]. Different studies attempting to define associations between this SNP and other ABCB1 variants, and the pharmacokinetics of several protease inhibitors and efavirenz have resulted in conflicting and controversial findings [31••,32••,46•].

The members of the multidrug resistance-associated (MRP) protein family are efflux transporters that have the potential to affect the disposition of ART. Colombo et al. [46•] evaluated the effect of different genetic variants in *ABCC1* and *ABCC2* (the genes coding for MRP1 and MRP2) on cellular levels of nelfinavir indicating no influence of these variants. MRP4 and MRP5 are involved in the transport of adefovir and different

Table 2. Frequency of functionally relevant alleles and ethnic differences for selected metabolizing enzyme, transporter, and nuclear receptor alleles

Gene*	Alleles with altered function (total no. of known alleles)	Ethnicity differences in frequency of altered functional alleles (≥ 1.5-fold)	Altered function alleles only described in one ethnic group	Effect on ART
CYP3A4	11 (20)	**1B, *11*	W: **2, *8, *12, *13, *17* A: **4, *5, *6, *18*	Studied in EFV and NFV. Possible effect of **1B* on EFV plasma AUC.
CYP3A5	6 (11)	**3, *6*	W: **10* B: **7, *8* A: **9*	Studied in EFV, NFV, and SQV. Possible effect of **3* on EFV plasma AUC. Relevance of **3* on SQV metabolism.
CYP2D6	29 (58)	**2xn, *3, *4, *6, *9, *10, *12, *17, *29, *35, *36*	W: **7, *8, *11, *13, *15, *16, *19, *20, *31* B: **40, *42* A: **14, *18, *21, *44*	Studied in EFV and NFV. Controversial relevance.
CYP2C19	11 (21)	**2, *3, *4, *17*	W: **6, *7,*8* B: **9, *10, *12* A: **5*	Studied in EFV and NFV. Possible effect of **2* on NFV plasma AUC.
CYP2B6	14 (25)	**5, *6, *7, *22*	W: **8, *11, *12, *14, *15* B: **16, *18, *19, *20, *21*	Studied in NFV, EFV, and NVP. Influences EFV and NVP plasma and intracellular AUC.
ABCB1†	3435C>T (in linkage disequilibrium with 1236C>T, 2677G>T and IVS26+80T>C)	Allelic frequency of 3435 T higher in whites and Asians than in blacks	—	Studied in EFV, NFV, LPV, RTV, and IDV. Controversial effect
PXR	3 (8)	**3*	W: **4* B: **2*	None reported
CAR	Different single nucleotide polymorphisms described but no allele assignment (unknown impact on function)	—	Only in Asians (unknown impact on function)	None reported

*For more detailed information: www.hiv-pharmacogenomics.org and http://www.imm.ki.se/cypalleles/.
†Limited information available on other transporters.
A—Asians; ART—antiretroviral therapy; B—blacks; EFV—efavirenz; IDV—indinavir; LPV—lopinavir; NFV—nelfinavir, NVP—nevirapine; RTV—ritonavir; SQV—saquinavir; W—whites.

nucleoside reverse transcriptase inhibitors, such as azidothymidine, lamivudine, zalcitabine, and stavudine [47]. Numerous genetics variants have been identified for *ABCC4* and *ABCC5* (the genes coding for MRP4 and MRP5, respectively) [48], although their effect on ART is yet to be evaluated.

Regulation of drug-metabolizing enzymes and drug transporters

CYP enzymes and drug transporters present wide interindividual variability in expression and function that cannot be completely explained by drug interactions and/or genetic variation, suggesting that transcriptional regulators may contribute to these differences. Pregnane X receptor (PXR) and constitutive androstane receptor (CAR) are members of the nuclear receptor superfamily that, once activated by ligands, can regulate the transcription of different target genes [49]. Genetic polymorphisms have been described for *PXR* and *CAR* present at low allelic frequency (≤ 3%) in the general population except for P27S (79C>T) (*PXR*2*) that is highly frequent in blacks (0.22) [50,51]. Their effect on ART is yet to be evaluated.

Genetic variations in AAG

AAG, also called orosomucoid (ORM), is a small acute-phase glycoprotein that extensively binds the protease inhibitors. Protein-binding may affect ART activity by decreasing the amount of free drug capable to exert an effect. Two proteins (ORM1 and ORM2) encoded by two functional genes (*ORM1* and *ORM2*) exist. AAG concentration is higher in whites than in

blacks or Asians [28,29]. *ORM2* is monomorphic in most populations whereas *ORM1* is polymorphic with three alleles described: *ORM1*F1, ORM1*F2,* and *ORM1*S*. *ORM1*F1* and **S* are observed worldwide, whereas **F2* is rare. The influence of ORM concentrations as well as genetic variants in the pharmacokinetics of ART has been recently evaluated by Colombo et al. [52]. ORM concentrations influenced indinavir apparent clearance (CL_{app}) and to a less extent lopinavir CL_{app}. Indinavir CL_{app} was significantly higher in individuals **F1*F1* and **F1*S* than **S*S*.

Conclusions

The number of genetic association studies is growing rapidly. A number of recommendations for optimal design of genetic association studies and for conducting of clinical trials and for cohort studies are presented elsewhere [53]. Evaluation and integration of genetic data for clinical use will be facilitated by initiatives such as the Adult AIDS Clinical Trials Group Protocol A5128 [54••], and the GENOMICS protocol ("Collection and use of blood for genetic and other related analyses") sponsored by the National Institutes for Allergy and Infectious Disease. Both protocols establish the conditions to storing DNA for studies that were not planned when informed consent was provided, and for future analyses. The GENOMICS protocol aims at providing genetic data to the Community Programs for Clinical Research on AIDS, with a particular interest in people of color, women, and injection drug users. Despite the negative perception of genetic research among the general public, recent studies indicate that this type of investigation is widely accepted by concerned parties: patients, relatives, and healthy study volunteers [55••].

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