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Perspectives on pharmacogenomics of antiretroviral medications and HIV-associated comorbidities

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Abstract

Purpose of review—To summarize current knowledge and provide perspective on relationships between human genetic variants, antiretroviral medications, and aging-related complications of HIV-1 infection.

Recent findings—Human genetic variants have been convincingly associated with interindividual variability in antiretroviral toxicities, drug disposition, and aging-associated complications in HIV-1 infection. Screening for *HLA-B*5701* to avoid abacavir hypersensitivity reactions has become a routine part of clinical care, and has markedly improved drug safety. There are well established pharmacogenetic associations with other agents (efavirenz, nevirapine, atazanavir, dolutegravir, and others), but this knowledge has yet to have substantial impact on HIV-1 clinical care. As metabolic complications including diabetes mellitus, dyslipidemia, osteoporosis, and cardiovascular disease are becoming an increasing concern among individuals who are aging with well controlled HIV-1 infection, human genetic variants that predispose to these complications also become more relevant in this population.

Summary—Pharmacogenetic knowledge has already had considerable impact on antiretroviral prescribing. With continued advances in the field of human genomics, the impact of pharmacogenomics on HIV-1 clinical care and research is likely to continue to grow in importance and scope.

Keywords

antiretroviral therapy; HIV-1; metabolic complications; pharmacogenetics; pharmacokinetics; toxicity

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Conflicts of interest

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INTRODUCTION

Pharmacogenomics may identify patients at increased risk for toxicity and/or reduced efficacy of antiretroviral therapy (ART). Genetic associations are also relevant to aging-related conditions in HIV [1]. Even with modern ART, life expectancy with HIV infection is somewhat shortened; whether this implies accelerated aging [2] remains controversial; moreover, clear genetic explanations for human longevity remain to emerge [3].

The field of human genomics has advanced from candidate gene studies to interrogating each individual's cumulative genetic background (see the article by McLaren and Fellay in this issue). This has largely involved genome-wide association studies (GWAS) covering common variants (allelic frequency >3%–5%), and increasingly exome sequencing studies that detect rare variants (allelic frequency >0.1%) [4,5]. An additional approach in both HIV-positive [6,7] and HIV-negative [8,9] populations has been to study single-nucleotide polymorphisms (SNPs) associated with outcomes in prior GWAS.

This article summarizes current knowledge and provides perspective on pharmacogenetics of ART. We consider toxicities, drug disposition, and aging-related complications in HIV-positive persons.

ASSOCIATIONS WITH SPECIFIC ANTIRETROVIRALS

Much is known regarding the genetics of drug absorption, distribution, metabolism, and elimination (ADME) [10], and polymorphisms in ADME genes are known to affect plasma and tissue drug exposure. Off-target adverse effects of some drugs also have genetic susceptibility markers. Guidelines regarding polymorphisms with sufficient evidence for clinical use are developed by the Clinical Pharmacogenetics Implementation Consortium (CPIC) [11].

Abacavir is widely prescribed, but can cause severe hypersensitivity reactions. In early trials, hypersensitivity affected approximately 5% of abacavir recipients. In 2002, *HLA-B*57:01* was reported to predispose to abacavir hypersensitivity [12,13]. A clinical trial of genetic testing ultimately showed that approximately 50% of *HLA-B*57:01*-positive individuals exposed to abacavir experience hypersensitivity, with negative predictive value of virtually 100% [14]. This association applies across populations [15]. Genetic testing to avoid abacavir hypersensitivity is cost-effective [16], and is now routinely used in developed countries. Among sub-Saharan black Africans, *HLA-B*57:01* is virtually absent [17], so genetic testing is not recommended.

Genetic testing has virtually eliminated abacavir hypersensitivity. Such success reflects severity and frequency of the phenotype, and the test's high negative predictive value. For the vast majority of other genetic associations, implications are far less clear.

Tenofovir disoproxil fumarate (TDF, the pro-drug of tenofovir) is well tolerated [18], but causes renal tubular dysfunction (Fanconi syndrome) with or without reduced creatinine clearance [18–20]. It appears that *SLC22A6* (solute carrier family 22 member 6) and *SLC22A7* mediate tenofovir entry into proximal tubule cells, with renal tubular secretion

mediated by *ABCC4* (ATP-binding cassette, subfamily C, member 4) and possibly *ABCC2*, although the latter's role has been refuted [21].

A French study implicated an *ABCC2* variant (1249G→A) [22]. A Japanese study also implicated *ABCC2* -24T→C (rs717620) and 1249 G→A (rs2273697) [23], whereas a Spanish study implicated *ABCC2* -24T→C and *ABCC10* variants [24]. Recent publications suggest other possible associations between *ABCC2* variants and either renal impairment [25] and/or plasma tenofovir concentrations [26]. Associations with creatinine clearance have been inconsistent [22,23]. A recent GWAS involving over 500 TDF recipients found no associations with change in creatinine clearance, but did not apply sensitive indices of tubular dysfunction [27]. Overall, evidence for genetic susceptibility to tenofovir renal toxicity is provocative but inconclusive [22,23].

Efavirenz undergoes metabolism by CYP2B6, with minor involvement by CYP2A6, CYP3A [28], and UDP-glucuronosyltransferase (UGT) 2B7. Variants in *CYP2B6* predict increased plasma exposure, especially 516G→T (rs3745274) [29–31], 983T→C (rs28399499) [31,32], and 15582C→T (rs4803419) [31]. Greater mean plasma efavirenz exposure with African ancestry largely reflects increased frequency of *CYP2B6* 516G→T. *CYP2B6* 983T→C is less frequent than 516G→T, present only with African ancestry, and has a somewhat greater effect size than 516G→T [31]. *CYP2B6* 15582C→T is frequent with European and Asian ancestry, but its effect size is modest [31]. These *CYP2B6* variants in combination define efavirenz concentration strata across an approximately 10-fold range [31]. With *CYP2B6* slow metabolizer genotypes, efavirenz clearance depends more on minor pathways, such that *CYP2A6* (-48T→G, rs28399433) [33–35] and *UGT2B7* (735A→G, rs28365062) [33,35] associate with even greater efavirenz concentrations.

Efavirenz can cause central nervous system symptoms, which typically lessen with repeated dosing. Although there is concentration dependence, correlations between plasma efavirenz concentrations and symptoms are weak [36]. In fact, within 4 weeks after starting ART, central nervous system symptoms may not differ between efavirenz and placebo [37]. An analysis involving mostly Europeans suggested that combinations of *CYP2B6*, *CYP2A6*, and *CYP3A4* variants predicted likelihood of discontinuing efavirenz [38], but may have been confounded by population stratification. Overall, the role of genotyping for preventing efavirenz toxicity is unclear.

Individualized efavirenz dosing by *CYP2B6* genotype (reducing from 600 to 400 mg or 200 mg once daily) might decrease cost, perhaps side-effects, yet maintain efficacy [39]. In a recent clinical trial, universal dose reduction to 400 mg once daily did not increase overall risk for virologic failure [40], but it may be important to assure that efficacy is not reduced in the lowest extensive metabolizer stratum.

Nevirapine can cause severe immune-mediated liver and skin reactions in patients with higher CD4 T-cell counts. Likelihood of rash increases by 50% for each 20% decrease in plasma nevirapine clearance [41]. Nevirapine is metabolized by CYP2B6, and increased plasma exposure is associated with *CYP2B6* 516G→T [30,42,43], 983T→C [44], and 15582C→T [43].

Genetic susceptibility markers differ for nevirapine liver events and skin events without liver involvement. In a largely white cohort in Western Australia, *HLA-DRB1**01 : 01 and higher CD4 T-cell percentages predicted rash-associated liver events [45]. The closely related *HLA-DRB1**01 : 02 predicts liver events among black Africans [46], whereas studies from Sardinia and Japan implicated *HLA-Cw**08 [47,48]. For isolated skin events, Thai studies implicated *HLA-B**35 : 05 and *HLA-Cw**04 : 01 [49–51]. A large study involving cohorts of Asian, European, and African descent associated *HLA-B**35 and *HLA-Cw**04 with skin events, *CYP2B6* 516G→T with skin but not liver events, and *HLA-DRB1**01 with liver events in whites (an infrequent allele in blacks and rare in Asians) [52]. A recent study associated *HLA-C**04 : 01 with Stevens Johnson syndrome in Malawians [53[¶]].

The low negative predictive value of genetic testing for severe nevirapine reactions has precluded translation into clinical care [52]. Toxicity is best avoided by not initiating nevirapine at higher CD4+ T-cell counts. Patients already on ART with virologic control and high CD4 T cell counts may not be at increased risk if switched to nevirapine.

Etravirine is metabolized by *CYP2C19*, and *CYP2C19* loss-of-function variants predict somewhat increased plasma etravirine exposure [54]. The effect size is modest and clinical implications are unclear.

Atazanavir is metabolized by hepatic uridine diphosphate glucuronosyl-transferase (*UGT1A1*), which causes unconjugated bilirubin to increase. Although this does not reflect liver injury, atazanavir is sometimes not prescribed to avoid the possibility of jaundice. The magnitude of bilirubin increase with atazanavir is associated with a *UGT1A1* promoter (TA)_n repeat (rs8175317) that predicts reduced *UGT1A1* expression. Polymorphisms in *SLCO1B1* have been suggested to possibly also predispose to atazanavir hyperbilirubinemia [55,56], but a GWAS found no such association after controlling for *UGT1A1* rs887829 (in linkage with rs8175317) [57[¶]].

Inconsistent relationships have been reported between *UGT1A1* polymorphisms and all-cause atazanavir discontinuation [38,58]. If negative predictive value for bilirubin-related discontinuation is ultimately shown to be high, *UGT1A1* genotyping in clinical practice may have a role.

Lopinavir, used in second-line ART in developing countries, is co-formulated with low-dose ritonavir as a pharmacokinetic enhancer. Several groups have associated a *SLCO1B1* 521T→C (rs4149056) with increased plasma lopinavir exposure [59–62]. This variant is infrequent with European ancestry and rare or absent among Africans, and its effect on lopinavir exposure is modest. It therefore has no clear implications for lopinavir prescribing.

Dolutegravir is conjugated by *UGT1A1*. Homozygosity for the *UGT1A1* promoter variant correlates with approximately 50% greater plasma dolutegravir concentrations [63], judged not clinically significant. However, such information might be useful in patients receiving concomitant drugs that increase (atazanavir) or decrease (darunavir) dolutegravir exposure, or when underlying integrase inhibitor resistance suggests the need for higher daily doses.

METABOLIC AND AGING-RELATED DISORDERS

Metabolic complications are of increasing concern as individuals with well controlled HIV-1 infection age [64]. The pathogenesis of these complications depends on factors well recorded in the general population (e.g., smoking, hypertension, drug use, obesity), HIV-specific effects (e.g., effects of immunosuppression, residual immune activation on ART), and ART toxicity [2]. Genetic predisposition to these conditions has been characterized by GWAS meta-analyses in the general population, with sample sizes often exceeding 10 000 subjects [65,66], and more recently by exome sequencing studies [67,68].

Dyslipidemia

In reports from the Swiss HIV Cohort Study [69], genetic effect sizes for dyslipidemia equaled or exceeded effects of ART regimen or other nongenetic risk factors. Egaña *et al.* [70] assessed 192 candidate GWAS-derived SNPs in 727 patients starting ART and found age-dependent genetic associations with HDL and LDL cholesterol levels.

Three large studies in the general population failed to identify associations of mitochondrial DNA (mtDNA) polymorphisms with aging-related and metabolic traits including BMI, hypertension, diabetes, hypercholesterolemia, and frailty [71–73]. Nonetheless, a study of 171 HIV-positive South Africans identified an association between hypertriglyceridemia during ART and an African mtDNA variant [74].

Diabetes mellitus

In a Swiss HIV Cohort Study analysis, GWAS-derived SNPs were validated in HIV-positive whites with new-onset diabetes [6]. A recent study [75] extended these findings to HIV-positive women in the United States, including 591 African Americans, 49 of whom developed diabetes during ART.

Cardiovascular risk

The largest cardiovascular-genetic study in HIV was published in 2013 [7]. An international collaboration involving 24 observational studies assessed gene variants and coronary artery disease (CAD) in HIV-positive whites including 571 cases and 1304 controls [7]. Effect size for genetic risk, present in 25% of the cohort, was smaller than that for smoking, approximated that of established CAD risk factors (hypertension, diabetes, hypercholesterolemia) and certain adverse ART exposures, and was independent of family history.

In 2010, a GWAS involving 177 HIV-positive white males associated *RYR3* variants with carotid intimal media thickness (cIMT) [76]. This was later replicated in 244 HIV-positive males [77] and extended to 1213 HIV-positive women of white, black, and Hispanic descent [78]. Of note, SNPs associated with CAD in GWAS in the general population [65] differ from those associated with cIMT or carotid plaque [79]. A preliminary study involving 39 HIV-positive individuals suggested an association between a mtDNA SNP and changes in endothelial function with ART [80].

Bone health

GWAS meta-analyses in the general population have associated 56 SNPs with bone mineral density and 14 SNPs with fracture [81]. An ongoing Swiss HIV Cohort Study analysis is comparing HIV-positive patients with and without low trauma fractures (Junier, unpublished). Guidi *et al.* [82] replicated, in 664 white HIV-positive patients, a SNP previously associated with OH-25 vitamin D serum levels, and found that the effect of seasonality on vitamin D levels exceeded the effect of other variables (e.g., BMI, type of ART) including genetic background.

Body fat changes including obesity

Candidate SNPs have been associated with lipoatrophy and lipodystrophy in HIV-positive adults, but have not reliably replicated [83,84]. Egaña *et al.* [85] recently applied dual-energy X-ray absorptiometry at baseline and 12 months of ART to 89 HIV-positive persons, and associated one candidate SNP with limb fat loss and two SNPs with trunk fat gain. Pushpakom *et al.* [86], genotyping SNPs in seven candidate nuclear receptor genes in 124 ART-treated patients with lipodystrophy and 56 controls, suggested associations with *RXR α* SNPs. Vilades *et al.* [87], comparing 240 HIV-positive patients with lipodystrophy and 318 controls, reported associations between candidate SNPs in the lipopolysaccharide signaling pathway, suggesting a link between HIV-associated bacterial translocation, immune activation, and body fat redistribution.

As thymidine analogue prescribing has declined, attention has shifted from lipoatrophy to obesity and abdominal fat accumulation [88]. Over 40 GWAS SNPs have been reliably associated with obesity in the general population [89], and interactions with diet and lifestyle factors have been suggested. For example, favorable genetic background may protect against weight gain despite consuming soft drinks [8] and limited physical activity [9]. These findings set the stage to translate knowledge from studies in the general population to obesity in HIV-positive persons, including interactions with HIV-related factors [88].

Neurocognitive dysfunction

Candidate gene variants have been associated with HIV-associated neurocognitive impairment, but few findings have been replicated (reviewed in [90]). Levine *et al.* [91] in 2012 reported the first GWAS of HIV-associated neurocognitive impairment and dementia, done in 1287 Multicenter AIDS Cohort Study participants. No previously reported SNPs were replicated and no novel associations were identified.

The *APOE4* allele has been associated with an increased risk of Alzheimer disease, HIV-associated disease progression, and dyslipidemia. A potential role for *APOE4* genotype in HIV-associated neurocognitive disorder (HAND) remains controversial. Morgan *et al.* [92] evaluated *APOE4* and HAND in 466 CHARTER study participants (mean age, 44 years). No association of *APOE4* with HAND was found and no interaction with age or other factors including nadir CD4 T-cell count and CSF HIV-1 RNA level.

HUMAN GENETIC TESTING IN HIV CLINICAL PRACTICE

A common perception is that genetic information is mainly useful for deterministic tests, such as *HLA-B*5701* screening to avoid abacavir hypersensitivity. Here test interpretation is straightforward and prevents a severe event. However, like 'traditional' nongenetic risk factors for cardiovascular events, genetic associations are more often of a qualitative or quantitative nature. Such information may be summarized in genetic scores, which associate with moderate severity phenotypes, for example, multiple genetic variants jointly affecting cardiovascular risk [6,7,65].

Another consideration is that the effect size of genetic background may be similar to certain ART exposures and risk factors in the general population. Genotype may contribute to risk stratification for conditions such as diabetes [6] or cardiovascular events [7] comparable with information gained by history (smoking, ART regimen), physical examination (blood pressure, body mass index), or routine laboratory values (cholesterol level) [93].

Finally, interest in analyzing any single gene or any particular antiretroviral drug is limited to research settings. In contrast, clinically useful genotyping in routine HIV practice (in addition to *HLA-B*5701*) almost certainly will involve assessing multiple gene variants reported to predict all ART toxicities and metabolic complications that have robust published genetic associations. This is the aim of an ongoing prospective study involving HIV-positive patients starting ART in Switzerland (McLaren, Swiss HIV Cohort Study, unpublished). The best validated SNPs typically are those identified in large cohort studies, often relying on multiinstitutional efforts and longitudinal data analysis.

Rapid technical progress and decreasing cost are also making it increasingly feasible for individuals to have their personal genome analyzed. In 2013, however, the FDA ordered that a personal genome testing company, 23andme, stopped direct marketing of genome-wide genotyping to the general public. This was because of questions about the validation of genome-wide genotype data, consequences of potentially inaccurate results, and donor consent and protection of privacy [94,95]. Nonetheless, once regulatory issues are addressed and genotyping costs continue to drop, millions of people may ultimately have their genomes analyzed [96].

CONCLUSION

Human genetic variants associate with ART toxicities, drug disposition, and aging-related complications in HIV-1 infection. Knowledge of pharmacogenetic associations will likely increasingly impact prescribing well beyond *HLA-B*5701* testing to avoid abacavir hypersensitivity. With continued collaborative multicohort genotyping efforts, advances in genomics and decreasing genotyping cost, the impact of pharmacogenomics on HIV care and research will grow in importance and scope.

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KEY POINTS

- Among individuals treated for HIV-1 infection, human genetic variants have been convincingly shown to be associated with interindividual variability in toxicity and/or drug disposition with many antiretroviral medications.
- As metabolic complications such as diabetes mellitus, dyslipidemia, osteoporosis, and cardiovascular disease become a growing concern among individuals who are aging with well controlled HIV-1 infection, human genetic variants that predispose to these complications will also become increasingly relevant in this population.
- Human genetic variants have been shown to affect almost every class of drugs that are approved for treating HIV-1 infection, including nucleoside/tide reverse transcriptase inhibitors, nonnucleoside reverse transcriptase inhibitors, protease inhibitors, and integrase inhibitors.