The Pharmacogenetics of Antiretroviral Therapy: A Review of Studies to Date

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Although the ever-expanding armamentarium of antiretroviral drugs has significantly decreased the morbidity and mortality due to human immunodeficiency virus infection, patients and clinicians are increasingly faced with the problems of inadequate or toxic response to therapy that may be genetically mediated. Significant evidence now exists that interindividual differences, such as efficacy of therapy, hypersensitivity reactions, and metabolic complications as a result of antiretroviral therapy, are in part genetically determined. This article reviews the significant studies published to date in the area of the pharmacogenetics of antiretroviral therapy and summarizes current trends, as well as areas where further research is needed.

Antiretroviral therapy for HIV infection has been available since the introduction and approval of zidovudine in 1986. At the time of writing, nearly 20 drugs in 4 classes and a number of immunomodulatory and other adjunctive agents are available for the treatment of HIV infection in the United States. The use of combinations of antiretroviral drugs to provide potent antiretroviral therapy (ART) has dramatically impacted the morbidity and mortality due to HIV infection and AIDS [1]. However, clinicians are increasingly faced with challenges in the selection and management of ART regimens, including the choice of most efficacious therapy, the avoidance of drug toxicity, and the impact of drug-drug interactions. Although the introduction of viral genotyping and combination-therapy pharmacokinetic data has provided some guidance, the investigation of host genetic factors that impact both the efficacy and toxicity of ART may also aid in selecting the best regimen for individual patients.

THE CONTEXT OF THE PROBLEM: PHARMACOGENETICS AND PHARMACOGENOMICS DEFINED

It is widely recognized that all classes of antiretroviral agents have multiple effects other than suppression of HIV replication and are associated with many adverse effects, some of which can be life threatening [2]. Until recently, however, it has been largely unclear why some patients experience these toxicities while others taking identical regimens do not. Furthermore, antiretroviral drugs do not always achieve the desired response; none of the many clinical studies of ART to date have demonstrated 100% response rates in terms of control of viral replication or CD4+ cell recovery. Multiple factors contribute to this phenomenon, including patient adherence to therapy, concurrent illnesses, and drug interactions, but complete response may still not be observed when these factors are controlled. Although many variables influence responses to ART, increasing evidence (table 1) points to a genetic basis for the observed variation in the effects of ART [19]. The toxicity of antiretrovirals also varies among individuals. Although some of this difference can be accounted for by age, nutritional status, comorbidities, concurrent medications, adherence to therapy, and stage of disease, genetic variation among hosts is also a plausible explanation [20]. Some adverse effects of antiretrovirals, particularly lipodystrophy syndromes and the mitochondrial toxicity induced by nucleoside reverse-transcriptase inhibitors (NRTIs), resemble genetically inherited disorders [21, 22]. It is logical, then, to hypothesize that genetic variation within loci for these disorders may predispose certain individuals toward toxicity associated with antiretroviral agents.

Pharmacogenetics is the study of the influence of genetic polymorphisms within a particular human gene on the response to pharmacotherapy. The first phase of the human genome project is now complete and has revealed that interindividual variation in human genetic sequences is quite common [23].
Table 1. A synopsis of findings from pharmacogenetic studies of the efficacy of antiretroviral therapy, to date.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Locus</th>
<th>Polymorphism</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>[3]</td>
<td>HLA-B</td>
<td>HLA-B*5701</td>
<td>Strong association between HLA-B*5701/HLA-DR7/HLA-DQ3 haplotype and abacavir hypersensitivity</td>
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<tr>
<td></td>
<td>HLA-DR</td>
<td>HLA-DR7</td>
<td></td>
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<tr>
<td></td>
<td>HLA-DQ</td>
<td>HLA-DQ3</td>
<td></td>
</tr>
<tr>
<td>[4]</td>
<td>HLA-B</td>
<td>HLA-B*5701</td>
<td>55% sensitivity for abacavir hypersensitivity</td>
</tr>
<tr>
<td>[5]</td>
<td>MDR1</td>
<td>3435 C/T</td>
<td>Greater increase in CD4 cell count after 6 months of PI therapy among TT genotypes</td>
</tr>
<tr>
<td>[6]</td>
<td>MDR1</td>
<td>3435 C/T</td>
<td>No correlation between genotype and CD4 cell count recovery or virus load at 6 months in PI- and non-PI-based regimens</td>
</tr>
<tr>
<td>[7]</td>
<td>MDR1</td>
<td>3435 C/T</td>
<td>No association between genotype and phase 1 or phase 2 viral decay after 2 weeks of ritonavir monotherapy</td>
</tr>
<tr>
<td>[8]</td>
<td>SREBP-1c</td>
<td>3322 C/G</td>
<td>Higher total cholesterol and triglyceride levels after starting PI therapy in persons with C haplotypes</td>
</tr>
<tr>
<td>[9]</td>
<td>SREBP-1c</td>
<td>3322 C/G</td>
<td>No association with hyperlipidemia</td>
</tr>
<tr>
<td>[10]</td>
<td>TNF-α</td>
<td>-238G/A, -308G/A</td>
<td>Increased incidence of lipodystrophy among -238A haplotypes; No association with -308 polymorphism</td>
</tr>
<tr>
<td>[11]</td>
<td>TNF-α</td>
<td>-238G/A, -308G/A</td>
<td>More rapid progression to peripheral fat wasting among -238 AA compared to GG; No association with fat redistribution and TNFA -308 or TNFB -250 polymorphisms</td>
</tr>
<tr>
<td>[12]</td>
<td>UGT1A1</td>
<td>A(TA)/TAA</td>
<td>7/7 genotype significant predictor of hyperbilirubinemia after starting atazanavir therapy</td>
</tr>
<tr>
<td>[13]</td>
<td>CCR5</td>
<td>Δ32 deletion</td>
<td>Increased likelihood of virus load of &lt;400 copies/mL</td>
</tr>
<tr>
<td>[14]</td>
<td>CCR5</td>
<td>Δ32 deletion</td>
<td>Predictor of achieving a virus load of &lt;500 copies/mL and an increase in CD4 cell count of &gt;50 cells/μL with PI therapy</td>
</tr>
<tr>
<td>[15]</td>
<td>CCR5</td>
<td>Δ32 deletion</td>
<td>No association with virologic response to PI therapy</td>
</tr>
<tr>
<td>[16]</td>
<td>CCR5</td>
<td>Δ32 deletion</td>
<td>No significant association with greater virus load reduction after PI therapy</td>
</tr>
<tr>
<td>[17]</td>
<td>CCR5</td>
<td>Δ32 deletion</td>
<td>No association with time to virologic failure (virus load, &gt;400 copies/mL) or immunological failure (lower CD4 cell count than at baseline)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>208 G/T, 303 A/G, 627 C/T, 676 A/G, 927 C/T</td>
<td></td>
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<tr>
<td>[18]</td>
<td>CCR5</td>
<td>Δ32 deletion</td>
<td>No association between CCR5 or CXCR1 genotype and time to immunologic or virologic failure</td>
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<tr>
<td></td>
<td>CXCR1</td>
<td>T280M, V249I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MDR1</td>
<td>3435 C/T</td>
<td>No association between MDR1 genotype and development of PI resistance mutations</td>
</tr>
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NOTE. CCR5, CC-chemokine receptor 5; CXCR1, chemokine (C-X3-C) receptor 1; HSPA1L, heat-shock protein 70 homolog; MDR1, multidrug resistance transporter 1; SREBP-1c, sterol regulatory element binding protein 1c; PI, protease inhibitor; UGT1A1, uridine diphosphate-glucuronosyltransferase 1A1.

The vast majority of this variation is due to single nucleotide polymorphisms (SNPs) at discrete nucleotide positions. Nucleotide insertions and deletions and oligonucleotide repeats constitute most of the remainder. These variations in genetic sequence can have a variety of effects. Nonsynonymous SNPs occur within coding regions and change the amino acid sequence of the encoded protein. synonymous SNPs do not produce amino acid changes. polymorphisms in the promoter region may influence the level of transcription of a gene, whereas those in the 3′ untranslated region following the coding sequence may affect the intracellular stability of the mRNA gene transcript. Intronic SNPs may alter the encoded protein by affecting intron splicing. However, variations at any of these sites often have no effect on gene expression.

Nearly all studies to date linking genetic data to antiretroviral response have involved a pharmacogenetic approach. Typically, investigators have relied on in vitro and animal data to provide educated guesses in selecting a target gene in which to identify common human polymorphisms and subsequently explore the association between these polymorphisms and clinical pharmacological responses. In other, less common instances, clinically important polymorphisms in target genes have been identified through human DNA resequencing and genome-wide screening methods.

Pharmacogenomics addresses the combined effect of multiple genes—the makeup of an individual’s entire genome—on the response to ART. The additive effect of interindividual genetic variation in loci encoding metabolic enzymes, drug
transporters, cell surface markers, and cellular growth and differentiation factors among other gene products may play a significant role in the variability of response and toxicity of a number of agents, including antiretroviral drugs. Although a few studies have analyzed the effect of multiple genes on a single outcome of ART, this approach to genotype-phenotype associations generally will require the advancement of currently available technologies for efficient genome-wide screening and statistical analysis before comprehensive associations between genetic makeup and the overall response to antiretrovirals can be definitively drawn.

**HLA HAPLOTYPE AND ABACAVIR HYPERSENSITIVITY**

The strongest genotype association to date in HIV therapeutics links certain HLA alleles to the development of abacavir hypersensitivity. At times life-threatening, systemic hypersensitivity reactions have occurred in ~5% of patients treated with the NRTI abacavir [24, 25]. The potential heritability of this drug reaction was suggested by a higher incidence of abacavir hypersensitivity in white populations than in those of African descent and by a report of hypersensitivity in 2 family members exposed to abacavir [25–28]. Genome-wide screening of hypersensitivity cases and evidence that drug allergy responses are mediated by human leukocyte antigens points toward the major histocompatibility complex (MHC) as a putative region of genetic susceptibility [4, 29, 30]. One of the most variable regions of our genome, the human MHC comprises >200 different loci encoding proteins determining innate and acquired immune responses, including complement factors, chaperonins and inflammatory cytokines, and components of MHC I and II receptors [4, 31, 32]. Variation within MHC loci probably arose before the evolution of vertebrates and has led to the formation of ancestral haplotypes (i.e., MHC alleles that are inherited in blocks; figure 1) [4, 32].

The first study that reported an association between MHC alleles and antiretroviral hypersensitivity assessed 200 HIV-positive, Western Australian participants treated with abacavir, 88% of whom were white [3]. Abacavir hypersensitivity developed in 18 patients (9%) in the cohort within the first 6 weeks of therapy; all affected patients were white. The HLA-B^*5701 allele was overrepresented among the abacavir-hypersensitive participants, with a frequency of 78%, compared with a frequency of 2% among abacavir-tolerant participants. Moreover, the combination of the HLA-B^*5701, HLA-DR7, and HLA-DQ3 alleles was present in 72% of those with abacavir hypersensitivity and in none of the abacavir-tolerant participants, producing a positive predictive value of 100% and a negative predictive value of 97% for the use of the ancestral HLA-B^*5701/HLA-DR/HLA-DQ3 haplotype to predict abacavir hypersensitivity. Despite these compelling findings, the investigators emphasize that genotypic studies should not influence the decision of whether to rechallenge with abacavir in patients with a possible hypersensitivity reaction, and they recommend further studies to investigate the association between HLA subtype and abacavir hypersensitivity in populations from other regions.

A retrospective analysis of 85 North American patients with a history of abacavir hypersensitivity and 115 control subjects with ≥6 weeks of exposure to abacavir without hypersensitivity has also been performed [4]. Genotypes for 114 polymorphisms within 12 gene families identified through a genome-wide screen were determined, and an association was also found between HLA-B^*5701 and hypersensitivity to abacavir. Although the authors determined that the presence of HLA-B^*5701 was the most significant predictor of abacavir hypersensitivity, only a slight prevalence of HLA-B^*5701 was found among cases (sensitivity, 55%). This decreased to 33% when the presence of both HLA-B^*5701 and HLA-DR7 was analyzed. Moreover, the frequency of HLA-B^*5701 was only 46% when analysis was restricted to hypersensitivity cases confirmed by drug rechallenge. Of note, none of the black participants (9 in the hypersensitivity case group and 18 in the control group) possessed the HLA-B^*5701 allele.

The authors of the North American study attributed the lower sensitivity of HLA-B allele to a predictor of abacavir hypersensitivity to ethnic differences among various white populations in the world. Differences in identification of abacavir-susceptible cases between the 2 studies, however, is a more likely explanation of the disparate predictive values. Moreover, the Australian investigators used an ancestral HLA haplotype analysis that provided a stronger association than HLA-B allele analysis alone. It is clear, however, that the HLA-B^*5701 haplotype does not independently account for all genetic susceptibility to abacavir hypersensitivity, because both studies include hypersensitive cases that do not possess these alleles. Additional studies that involve populations from other regions should be performed to establish the presence of certain HLA alleles as important predictors of abacavir hypersensitivity and potentially decrease the incidence of this life-threatening drug reaction.

**DRUG TRANSPORTERS AND RESPONSE TO ART**

Protease inhibitors (PIs) are substrates for the ATP-binding cassette transporter gene (ABCB1), a multidrug-resistance transporter also referred to as MDR1 and P-glycoprotein (PGP) [33–36]. This transporter serves as an efflux pump for numerous compounds and has been associated with resistance to chemotherapeutic agents in multiple tumor types [37, 38]. PGP may also limit intestinal absorption, intracellular retention, and CNS penetration of PIs [33, 35, 39]. Increased intracellular PI levels within lymphocytes may also be linked to decreased MDR1 expression [40, 41]. A single synonymous C to T change
at base pair 3435 in exon 26 alters \( MDR1 \) activity such that homozygotes for the variant allele (3435 TT) have decreased expression of PGP and increased intestinal absorption and intracellular retention of PGP substrates, although these functional changes may be attributed to other closely linked, nearby nonsynonymous and noncoding region polymorphisms with the gene [42–46]. The frequency of this polymorphism varies markedly among different world ethnic populations, and PGP may be more highly expressed in African individuals, in whom the \( MDR1 \) 3435 C allele is more common [47–50]. This may have significant implications for PI use in patients of certain African ethnic backgrounds [50].

The Swiss HIV Cohort Study first reported that immunological response to PI-based ART is linked to \( MDR1 \) 3435 genotype [5]. Among 96 patients—some with PI experience—treated with regimens including nelfinavir and efavirenz, those heterozygous for the rare allele (\( MDR1 \) 3435 T/T) had significantly greater increases in absolute CD4 lymphocyte count over a 6-month period than did those with C/T or C/C genotypes. Moreover, \( MDR1 \) 3435 T/T was second only to HIV virus load at baseline as the strongest predictor of immunologic response. There was no significant difference in time to or duration of undetectable HIV virus load attributable to \( MDR1 \) genotype. Those with T/T genotypes had lower median plasma nelfinavir concentrations, which likely reflected decreased \( MDR1 \) efflux pump activity and retention of the drug in intracellular compartments. Genetic variation at relevant cytochrome P450 isoenzyme loci did not explain differences in plasma nelfinavir concentrations.

A subsequent Italian study investigated the association between \( MDR1 \) genotype and response to ART. One hundred thirty-five white patients naive to ART were treated with 2 NRTIs plus either 1 PI (\( n = 106 \)) or 1 non-NRTI (NNRTI; \( n = 43 \)) [6]. No significant correlation between \( MDR1 \) genotype and ART response at 3 or 6 months was found in either cohort. A separate group also found that \( MDR1 \) 3435 genotype did not significantly influence time to virologic or immunologic failure after a median duration of follow-up of 40 months among ART-naïve, western Canadian, white patients treated with either double- or triple-combination therapy, unless heterozygotes were excluded from the analysis [18]. This group also found no association between \( MDR1 \) 3435 genotype and development of PI resistance mutations. Finally, analysis of phase I viral decay among North American patients treated with ritonavir for 2 weeks failed to show an association with \( MDR1 \) genotype [7].

These conflicting results may be explained by several factors. Adherence was not assessed in the Swiss study, and the response attributed to \( MDR1 \) genotype may have been due to higher rates of medical compliance occurring by chance in the T/T genotype group. Moreover, the patient cohorts differed with respect to antiretroviral experience among the studies. The Swiss study analyzed patients with prior ART experience, whereas the others were restricted to ART-naïve patients. \( MDR1 \) genotype, therefore, might be more predictive of immunological response to treatment intensification with PIs than to initial therapy. Finally, none of these studies assessed the correlation between response to ART and polymorphisms other than the \( MDR1 \) 3435C-T change or at other loci that may more significantly affect response to PIs.

### INFLAMMATORY CYTOKINES, ADIPOCYTE DIFFERENTIATION FACTORS, AND METABOLIC EFFECTS OF ART

Among the multiple adverse metabolic effects of ART is lipodystrophy syndrome [51–62]. Consistent definitions of the syndrome, which comprises fat loss and gain associated with hyperlipidemia and hypertriglyceridemia, are becoming established [63, 64]. Although the pathogenic mechanisms of ART-associated fat redistribution are complex and not yet defined, preliminary data suggest that inflammatory cytokines and transcription factors that influence adipocyte differentiation, maturation, and apoptosis may be involved in the development of these metabolic effects.

Steroid receptor element–binding protein 1c (\( SREBP-1c \) or \( SREBF1 \), also referred to as “adipocyte determination and differentiation factor 1,” or “ADD-1”) is an important candidate gene for metabolic adverse events associated with HIV infection and treatment. Activated by insulin, \( SREBP-1c \) regulates lipo-
protein lipase, fatty acid synthase, peroxisome proliferator-activated receptor (PPARγ), and glucokinase, thereby playing an important role in cholesterol, triglyceride, and glucose metabolism [65], and SREBP-1c adipocyte expression has been linked to lipoatrophy in HIV-infected patients [66]. Moreover, indinavir decreases SRBP-1c expression and nuclear localization while promoting apoptosis of adipocytes [67, 68]. TNF-α is a cytokine involved in adipocyte lipid metabolism, differentiation, and apoptosis (reviewed in [69]). TNF-α expression has been shown to be 2.9-fold higher in peripheral adipocytes obtained from lipoatrophic HIV-infected patients than in those obtained from uninfected control subjects [66]. Functional polymorphisms at positions -308 and -238 within the TNF-α promoter have been linked to TNF-α production (reviewed in [70]).

Two trials have investigated the role of single-nucleotide polymorphisms in treatment-related metabolic side effects of ART. Miserrez et al. [8] examined a cohort of 67 Swiss HIV-1–infected participants with total cholesterol levels, absolute CD4 cell counts, and HIV-1 RNA loads available before and 6 months after they began receiving a PI-based regimen. This cohort and a control group of 2727 subjects accrued from population studies were assessed for the previously undescribed C to G polymorphism at nucleotide position 3322 in SREBP-1c. Those with SREBP-1c 3322 C haplotypes experienced a median increase in the total cholesterol level of 26.4%, whereas those who were homozygous for 3322G had a median increase in the total cholesterol level of 10.6% (P = .0314). Similar trends were found with respect to serum triglyceride measurements. A subsequent North American study of 355 patients treated with stavudine, lamivudine, and either lopinavir-ritonavir or ritonavir found no difference in changes in the total cholesterol or triglyceride level among SREBP-1c 3322 genotypes at 48 weeks of treatment [9]. Several differences between the 2 studies may explain the disparate outcomes. Nonfasting cholesterol and triglyceride levels were obtained in the North American study, making comparison with lipid profiles obtained in the Swiss study difficult. Moreover, the North American cohort was more racially diverse, which may obscure associations with other undefined polymorphisms highly linked to the SREBP-1c 3322 SNP that have functional significance for lipid changes after the initiation of ART.

The relationship between TNF-α promoter polymorphisms and the risk of fat redistribution syndromes has also been explored. A case-control study compared TNF-α promoter genotypes among 61 cases of HIV-infected, British, white patients with lipodystrophy (defined as physician-confirmed lipoatrophy of the extremities or face and/or abdominal or dorsocervical fat accumulation) to 2 control groups: 31 HIV-infected study participants with exposure to PIs but without lipodystrophy, and 239 healthy, HIV-negative volunteers [10]. The frequency of TNF-α–238 GG, GA, and AA genotypes were similar between the lipodystrophy case group and the HIV-negative control subjects. Among the HIV-infected control subjects without lipodystrophy, however, there was an absence of -238 A alleles; 100% of this group possessed the -238 GG genotype, suggesting that the -238 A allele predisposes HIV-infected patients to lipodystrophy. A subsequent study of Western Australians demonstrated a similar association between the TNF-α–238 polymorphism and progression to lipoatrophy [11]. Among 191 white participants, TNF-α–238 GA genotype was associated with a more rapid progression to peripheral fat wasting than was the homozygous wild-type genotype, TNF-α–238 GG. The TNF-α–238 A allele was found to be independent of age and prior ART history as a predictor of lipoatrophy. Although the specific antiretroviral regimens used in the Australian study are not available, the similar results of these 2 studies support the need for further investigations of TNF-α polymorphisms as a risk factor for ART-associated lipodystrophy.

**PHASE II DRUG METABOLISM AND PI-INDUCED HYPERBILIRUBINEMIA**

Atazanavir is a newly approved PI indicated for the treatment of HIV infection. Early clinical trials indicate that the drug is associated with hyperbilirubinemia in 20%–48% of patients, as a result of inhibition of uridine diphosphate-glucuronosyltransferase 1A1 (UGT1A1) [71, 72]. This enzyme catalyzes the glucuronidation of bilirubin as well as multiple exogenous compounds as a component of phase II drug metabolism [73]. A variable number of TA repeats within the promoter of the UGT1A1 gene have been described in world populations, although either 6 (A(TA) 6TAA) or 7 (A(TA) 7TAA) repeats predominate in most groups [74]. An increased number of TA repeats has been associated with decreased UGT1A1 activity, and individuals homozygous for 7 repeats (the 7/7 genotype) have chronic hyperbilirubinemia (Gilbert syndrome) [75–77]. UGT1A1 is important in the elimination of several drugs, and among patients treated for solid tumors, the 7/7 genotype has been shown to predict toxicity with irinotecan, a substrate of UGT1A1 [78].

The UGT1A1 7/7 genotype has been associated with hyperbilirubinemia in 353 participants treated with atazanavir in phase I trials [12]. In patients achieving therapeutic serum atazanavir concentrations, the 7/7 genotype was highly predictive of total serum bilirubin elevations of >2.5 mg/dL. Although the UGT1A1 promoter genotype appears to be a significant predictor of atazanavir-induced hyperbilirubinemia, the clinical utility of this pharmacogenetic association is unclear. The lack of significant clinical toxicity associated with atazanavir hyperbilirubinemia probably does not justify genetic testing before administration of therapy, although further genotype associa-
CHEMOKINE RECEPTORS AND RESPONSE TO ART

The earliest studies exploring heritability of response to ART examined variation in HIV coreceptor alleles CCR5 and CXCR4. Although expression of HIV primary receptor CD4 is necessary for HIV infection via interaction with viral gp120, the presence of coreceptors that facilitate fusion of the viral envelope with the cell membrane are also required [reviewed in [79, 80]]. CXCR4 and CCR5 are the major HIV-1 coreceptors, although several other chemokine receptors (including CX3CR1) have been identified as coreceptors for certain HIV strains. Each of these have been shown to possess allelic polymorphisms, often with differences in interpopulation frequencies [81–84]. For CCR5, the best-characterized polymorphism is a 32 base pair deletion within the promoter region (CCR5 Δ32), which is common among white persons and has been associated with decreased susceptibility to HIV infection and disease progression [85–90]. Other SNPs within the CCR5 promoter have been described which have been linked to propensity toward HIV infection and progression [91–94]. A C-to-T change at amino acid 280 (T280M) of the CX3CR1 sequence has been linked to a more rapid progression to AIDS [95, 96], although analysis in various populations has not upheld this association [97, 98].

Studies exploring secondary HIV receptor polymorphisms and response to ART have yielded mixed results. A positive association between the CCR5 Δ32 deletion and virologic and immunologic responses to PI-based regimens has been shown among white and French HIV-infected patients [13, 14]. Other investigators have failed to find associations between response to ART and CCR5 genotype. Studies of 147 Swedish and 307 North Americans patients found no significant correlations between CCR5 Δ32 and response to ART [15, 16]. The largest and longest-term CCR5 genotype association study to date examined virologic and immunologic response to ART in 405 patients from British Columbia who were observed for 40 months. No association between time to virologic failure or immunologic failure and CCR5 promoter polymorphisms was found [17]. Of note, >40% of the participants in this study experienced virologic failure over the 40 month follow-up period, and some participants (<25%) were initially treated with only 2 antiretroviral agents, reflecting the time of initiation of the study and the long-term follow-up period. A genomic analysis investigating the independent and combined effects of CX3CR1 T280M and V249I, as well as CCR5 Δ32 polymorphisms, on the efficacy of ART has been performed in a cohort of 461 western Canadian patients treated with 2 NRTIs, either with or without a PI [18]. No association was found between the presence CX3CR1 T280M or CCR5 Δ32 alleles and response to ART.

Comparisons of studies investigating secondary HIV receptor polymorphisms and response to therapy are problematic, because the analyses differ in terms of treatment outcomes, ART regimens, disease state at the time of therapy, and patient backgrounds. Despite this, the existing pharmacogenetic studies in
this area have yielded mixed results, and the clinical value of the CCR5 polymorphisms are currently limited to prediction of the natural course of HIV disease and susceptibility to infection rather than response to ART.

CONCLUSIONS AND FUTURE APPLICATIONS

Clearly, significant inroads have been made in defining the heritability of responses to antiretroviral medications. Although a few important and consistent genotype-phenotype associations have been established in the areas of abacavir hypersensitivity and ART-induced fat redistribution, most HIV pharmacogenetic studies to date have had conflicting or inconsistent results. Moreover, the study of the impact of human genetic variation upon interindividual responses to ART continues to be complicated by several factors. The functional impact of these genetic polymorphisms is unexplained in most cases. Although there are many examples of variation in antiretroviral pharmacokinetics resulting from certain SNPs, these have yet to be linked to specific alterations in the pharmacodynamics of these drugs. More importantly, these polymorphisms do not act independently to influence drug response in most cases, and it will require great advances in genomic technologies and our understanding of the complexity of the human genome before we can define how alleles act in concert to influence the response to drug therapy.

In the meantime, clinical decision-making regarding the choice of ART grows more complex as our available therapies expand. It is important, then, that current genotype associations are confirmed in larger populations in the world and that target genes of interest continue to be identified and associations established between these genes and response to ART to help guide our decisions when prescribing antiretrovirals (figure 2). Although data are not yet available, areas of current pharmacogenetic investigation include efficacy of NRTI therapy; neurotoxic and hematotoxic responses to NRTIs; allergic, hepatoxic and hematotoxic responses to NRTIs; and likelihood of response to fusion inhibitors. As these data accumulate, we may be able to prospectively increase the chance of treatment success while avoiding toxicity as personalized HIV therapy evolves.

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