The Impact of Human Genetic Variation on HIV Disease in the Era of HAART

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Abstract

Human genetic variation may directly or indirectly influence response to modern antiretroviral therapies for HIV. It is already known that some immunogenetic and other human genetic variations affect the natural history of HIV disease progression where individuals are untreated, but less information is available as to whether these differences are still relevant in the context of HAART. Antiretroviral therapy adds additional opportunities for human genetic contributions to affect variable prognosis – in particular for those genes which influence pharmacokinetics and/or adverse events. To date, the majority of studies investigating the influence of human genetic variation on HIV disease and treatment outcome have focused on single nucleotide polymorphisms or a small number of polymorphisms within a single gene. Reports to date have generally described small effect sizes, and have often been contradictory. Thus, while simple genetic markers relevant to HIV disease or treatment response have indeed been identified (e.g. CCR5Δ32 in the context of untreated HIV disease, or HLA-B*5701 allele on the abacavir hypersensitivity reaction in the context of HAART), it is more likely that HIV disease and treatment outcomes are influenced by a multitude of interacting genotypes and phenotypes, a hypothesis that will become increasingly possible to investigate as improvements in molecular and computational technologies are made. **(AIDS Reviews 2006;8:78-87)**

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Key words

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Introduction

A wide range of inter-individual variability is observed with respect to susceptibility to HIV-1 infection and subsequent rates of disease progression[1]. Although the median time from infection to AIDS diagnosis in the absence of antiretroviral treatment ranges from approximately five to 11 years, depending, in part, on age at seroconversion[2], there are individuals who progress to AIDS in as little as one year from infection ("fast progressors")[3,4], and others who remain asymptomatic, with essentially normal CD4 counts and low plasma viral loads for 20 years or more ("slow progressors")[5-7]. Historically, studies of multiply exposed yet uninfected individuals helped to identify factors which determine "natural" protection from HIV infection[8-12], while studies comparing characteristics of fast versus slow progressors led to the identification of factors which influence the natural course of HIV disease[13-16]. It is now known that host genetic factors significantly influence the risk of infection upon exposure to HIV[8-12], the rate of disease progression once infected[12,14-16], and the strength and diversity of the immune response[15,17,18].

The introduction of HAART in the mid-1990s revolutionized the treatment of HIV/AIDS, at least in areas of the world where antiretrovirals were made widely available. HAART resulted in reductions in plasma viral load to levels undetectable with sensitive assays, increases in CD4 counts, improvement of immune function, and most importantly, significantly prolonged survival[19-22].

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Despite the successes of HAART, however, many challenges and outstanding questions remain. For example, for reasons that remain incompletely understood, a small proportion of individuals fail to respond to HAART, despite apparently good adherence and no evidence of resistance mutations[23]. Among those who initially respond to HAART, subsequent virologic failure rates approach 20% in previously treatment-naive individuals[23] and 30-50% in previously treated individuals[23,24]. Even among those who maintain successful long-term responses, antiretroviral therapy represents a lifelong commitment. In order to maximize the long-term benefits of HAART, it is of importance to achieve a greater understanding of the factors, including genetic factors, which influence response to therapy.

This review will focus on those specific host genetic factors whose potential contributions to HIV clinical prognosis have been evaluated in the context of modern antiretroviral therapies. Human genetic polymorphisms will be classified into three broad categories based on the manner whereby the individual host factor may directly (or indirectly) influence therapeutic response. These categories are:

a) Previously-characterized immunogenetic parameters known to affect the natural history of HIV disease, but for which an effect has not yet been firmly established in the context of treated infection;
b) Genes influencing antiretroviral pharmacokinetics and thus potentially influencing therapy efficacy;
c) Genes implicated as risk factors for antiretroviral-associated adverse events.

For each of these categories, the evidence to date supporting (or not supporting) a potential role for these polymorphisms in the context of HAART will be summarized.

Immunogenetic parameters known to affect the natural history of HIV disease: a role in the era of HAART?

Chemokine receptor polymorphisms and the natural history of HIV disease progression

In the mid-1990s, the identification of the human chemokine receptors CXCR4[25] and CCR5[26-29] as coreceptors for HIV entry into CD4+ cells led to the discovery that genetic variation among chemokine receptor genes could directly influence susceptibility to HIV infection, as well as the subsequent rate of disease progression. The best-studied example of the contribution of chemokine receptor variation to HIV disease is CCR5Δ32, a naturally-occurring 32 base-pair deletion in the gene encoding CCR5[11]. Individuals homozygous for CCR5Δ32 do not express CCR5 and are thus naturally "resistant" to HIV infection[11,30-33], although exceptions have been documented where CCR5Δ32/Δ32 individuals have been infected with CXCR4-using HIV variants[34,35]. Individuals heterozygous for CCR5Δ32 express CCR5 at significantly reduced levels on the cell-surface[36]. Although these individuals are equally as susceptible to HIV infection as CCR5 wild-type individuals, they progress to AIDS at a significantly slower rate after infection than those lacking this mutation[30-32,37-39]. Polymorphisms in the promoter region of CCR5, presumably affecting expression of the receptor, have also been shown to influence HIV disease progression[40-44], as have variations in genes encoding the natural chemokine ligands of CCR5[45,46].

Despite these correlations, CCR5 genetics may at most account for only a small proportion of observed variation in HIV disease progression on a population basis. In fact, several naturally-occurring polymorphisms in other minor HIV coreceptors have been reported, including a V62I mutation in the CCR2 gene, which has been shown to confer a protective effect with respect to progression to AIDS[47,48], although not in all studies[49]. The fact that the V62I mutation is in complete linkage disequilibrium with the aforementioned CCR5 promoter polymorphisms[48] may explain this association. More recently, two common, single nucleotide polymorphisms in the CX3CR1 receptor, a minor coreceptor for HIV-1[50], have been identified[51]. HIV-infected individuals homozygous for the CX3CR1 249I and 280M amino acid substitutions progressed to AIDS and death more rapidly than those with other haplotypes[51,52]; however, this observation has been somewhat controversial[53].

No polymorphisms relevant to HIV transmission or pathogenesis have been reported in the highly conserved CXCR4 gene (encoding the major coreceptor for T-cell-tropic, syncytium-inducing strains of HIV), although a polymorphism has been reported in the 3' untranslated region of the gene encoding its natural chemokine ligand, stromal cell-derived factor (SDF)-1[54]. It has been postulated that the SDF-1 3'α mutation may upregulate SDF-1 expression and thus potentially increase its ability to act as a competitive inhibitor for HIV binding to CXCR4-expressing cells[14]. However, the clinical relevance of SDF-1 3'α to untreated HIV disease progression is not clear, and reports have

ranged from a protective effect[54] to no effect[47] to a detrimental effect[55] of this mutation on progression to AIDS.

Chemokine receptor polymorphisms and their relevance in context of HAART

Because of the significant effect of HAART on the natural history of HIV disease, human genetic polymorphisms influencing untreated HIV clinical outcomes may, in the context of HAART, exert a proportionally smaller effect. It is of importance, therefore, to re-evaluate the relative contributions of known genetic determinants of untreated HIV disease in the context of HAART outcomes, as it is not known what residual effects, if any, these factors may contribute above and beyond the effects of treatment[56].

CCR5Δ32

Studies investigating whether the CCR5Δ32 mutation retains any protective effect during treatment with HAART have reported conflicting results. The heterozygous CCR5wt/Δ32 genotype has been significantly associated with an increased likelihood of plasma virus suppression[57-59], improved short-term CD4 responses[59,60], as well as improved six- and 12-month virologic responses to HAART in one study of patients with advanced disease[61]. In contrast, other studies have reported no significant correlation between CCR5Δ32 and HAART response[62-66]. To date, the majority of these studies have been limited to the evaluation of the effect of CCR5Δ32 on shorter-term (< 2-year) clinical outcomes.

In a recent large study investigating the effect of CCR5Δ32 on short- and long-term treatment responses in > 1000 HIV-infected individuals initiating HAART, individuals heterozygous for the CCR5Δ32 deletion experienced significantly more rapid initial suppression of plasma HIV-RNA below 400 copies/ml, an observation which remained significant after adjustment for baseline sociodemographic and clinical parameters[67]. However, there was no observed association between CCR5Δ32 and the subsequent duration of viral suppression, or immunologic response as measured by the time to a decline of CD4 count to below pretreatment levels. A trend toward improved > 5-year survival post-HAART in CCR5wt/Δ32 individuals was observed; however, this association did not remain significant after controlling for antiretroviral prescription refill percentage[67] (a surrogate of adherence), suggesting that the observed association was likely due to a residual "natural history effect" driven by nonadherent individuals in the cohort.

Taken together, these results suggest that any protective effect conferred by CCR5Δ32 in the context of HAART may not be clinically significant on an individual patient management basis. These results also emphasize the need to include data on therapy adherence in studies evaluating the effects of potential prognostic markers on treatment response, and may partially explain the contrasting reports on the relevance of CCR5Δ32 to treatment outcomes thus far. Currently available data, therefore, do not support the utility of the CCR5Δ32 genotype as an independent clinical prognostic marker for HAART response; however the potential clinical utility of CCR5 genotypes evaluated in context with other host factors[46,68] remains to be determined.

CX3CR1

There have been a relatively small number of studies investigating the relevance of other chemokine receptor and/or ligand polymorphisms in the context of HAART. A study of 461 antiretroviral-naive individuals initiating HAART reported a statistically significant trend to earlier immunologic failure in individuals with the CX3CR1 I249 polymorphism[69]. Similarly, HIV-infected children participating in randomized clinical trials of mono and dual therapy also showed a significant independent association of CX3CR1 I249 with more rapid virologic and immunologic disease progression, even after adjustment for baseline CD4 count and viral load[70]. Somewhat in contrast, a study of 169 individuals reported improved CD4 responses after one year of HAART among individuals with the homozygous CX3CR1 280M genotype, although no association was reported with variation at codon 249[65]. Although available data suggest that polymorphisms in CX3CR1 may be useful prognostic indicators of HIV clinical status, further studies will be required in order to confirm this observation and clarify the mechanism whereby these polymorphisms contribute to HIV disease progression in the context of untreated as well as treated infection.

Other chemokine receptor and/or ligand polymorphisms

Limited studies of the CCR2-64I polymorphism have reported no association of CCR2-64I with short-term virologic and immunologic responses to combination therapy[57,64,65], although a recent study reports a more

favorable viral-load response in individuals carrying CCR2-64I[66]. Similarly, some evidence suggests that polymorphisms in the CCR5 promoter region do not significantly influence response to HAART[63,66], although one study reported that CCR5 promoter genotype, evaluated in combination with both CCR5Δ32 and CCR2 genotypes, were predictive of short-term viral-load response to antiretroviral therapy[71]. An earlier study reported an association between the homozygous SDF-1 3'α variant and more rapid disease progression while undergoing nucleoside therapy[72]. More recently, however, this SDF-1 3'α allele has been linked to increased likelihood of plasma viral suppression to undetectable levels after initiation of HAART[65], although in one study this did not achieve statistical significance[57]. Similarly, significant associations between SDF1-3'α and improved CD4 responses following HAART initiation have also been reported[65,66].

Overall, studies to date appear to indicate that host chemokine genetic factors may contribute to disease progression and treatment response in the context of HAART, although in most cases this contribution is likely to be small and potentially confounded by a "natural history" effect in those with partial or complete nonadherence. Further research will be needed in order to determine the potential clinical utility of host chemokine receptor genotyping in the HAART era.

Genes that affect pharmacokinetics of antiretroviral agents

The second broad category of human genes that may affect HAART response includes those genetic parameters which are likely of little relevance in context of untreated HIV infection, but likely are of direct relevance in the context of antiretroviral treatment. These include polymorphisms in genes which regulate drug absorption, distribution, metabolism and excretion. A wide range of variability in the pharmacokinetics of antiretroviral agents is observed between individuals, and this variability may be attributed in part to differences in host genetics[73]. Although clinical treatment outcomes are undeniably influenced by variation in antiretroviral metabolism, an in-depth summary of all human genetic polymorphisms implicated in antiretroviral-associated pharmacokinetic variation to date is beyond the scope of this review (for an excellent review on this subject please see Rodriguez-Novoa, et al.[73]). Rather, the following section will focus mainly on specific genes involved in antiretroviral pharmacokinetics which have been investigated in the context of longitudinal HAART outcomes.

MDR-1

The human multidrug resistance (MDR)-1 gene is implicated in the development of resistance to a variety of chemotherapeutic agents[74,75]. MDR-1 encodes the P-glycoprotein (P-gp) membrane efflux transporter, which is expressed on a variety of cell types including CD4+ lymphocytes[76]. P-gp possesses a broad substrate specificity[77-81] that includes HIV protease inhibitors (PI)[82,83]. A single, synonymous C3435T polymorphism in exon 26 of MDR-1 affects membrane expression and activity of P-gp[84], an observation which may have consequences for the bioavailability of PI in different body compartments[73,85], and thus potential consequences for treatment response. However, reports to date regarding the effect of MDR-1 C3435T on antiretroviral pharmacokinetics have yielded conflicting results. Indeed, in some studies, the homozygous MDR-1 C3435T polymorphism has been associated with significantly reduced P-gp expression and activity in the gastrointestinal tract[84], reduced P-gp function and expression in immune cells[86,87], significantly reduced plasma levels[87] and significantly increased intracellular concentrations[88,89] of the PI nelfinavir. However, other studies report no association between MDR-1 C3435T and P-gp mRNA expression in peripheral blood lymphocytes (PBL)[90]. Yet others report no association between the MDR-1 C3435T and pharmacokinetics of various compounds[91-93].

Based on the conflicting data surrounding the effect of the MDR-1 C3435T polymorphism on antiretroviral pharmacokinetics, it is not surprising that no clear consensus has yet emerged regarding associations of MDR-1 C3435T to treatment response. Since Fellay, et al. reported a significant association between the homozygous 3435T/T genotype and improved CD4 response to PI-containing regimens[87], there has been a number of studies attempting to address this issue, the majority of which have failed to support this observation. A recent study of 384 antiretroviral-naive individuals randomized to receive two nucleoside analogs plus efavirenz and/or nevirapine reported a decreased likelihood of virologic failure as well as a decreased emergence of efavirenz-resistant virus in individuals with the homozygous 3435T/T genotype receiving efavirenz[94]. Similarly, a previous study of 461 antiretroviral-naive individuals initiating first HAART reported a trend to earlier virologic failure in those individuals with the MDR-1 3435C/C genotype[69], although no correlation between MDR-1 genotype and development of PI-resistance mutations was observed in a small study

subset[69]. Other smaller studies have reported no correlation between MDR-1 C3435T polymorphism and initial virologic and/or immunologic response to combination therapy among previously antiretroviral-naive individuals[92,95,96] as well as individuals with previous antiretroviral exposure[88,92]. Recently, HIV-1 infected children with the heterozygous MDR-1 3435C/T genotype had higher plasma nelfinavir levels and improved virologic responses to HAART when compared to those with the 3435C/C genotype[97].

The cytochrome P450 system

The cytochromes-P450 (CYP) are a superfamily of heme-containing enzymes present in the liver and gut wall which are involved in the metabolism of a diverse range of compounds, which include all presently available PI as well as nonnucleoside reverse transcriptase inhibitors (NNRTI)[98]. The CYP3A isoenzyme of the CYP system (comprising major isoforms CYP3A4 and CYP3A5) is the chief metabolizer of all currently available PI and NNRTI[98,100]. In addition, the NNRTI nevirapine and efavirenz are metabolized by the CYP2B6 isoenzyme[99], while other PI, including nelfinavir, are metabolized by CYP2C19[100]. Other CYP isoenzymes also likely play a role in antiretroviral metabolism[101]. The genes encoding the individual CYP isoenzymes exhibit a relatively high level of polymorphism, and the elucidation of the effects of CYP polymorphism on antiretroviral pharmacokinetics is currently an intense area of focus[73].

Data on the effects of CYP polymorphisms on clinical HAART responses is also emerging. The CYP2B6 G516T polymorphism has been associated with increased plasma[94,102] and intracellular[102] concentrations of efavirenz, as well as increased plasma concentrations of nevirapine[102], although this mutation did not influence treatment outcomes in 384 previously antiretroviral-naive individuals initiating nevirapine-containing therapy[94]. In the same study group, the CYP2C19 G681A polymorphism was associated with increased plasma nelfinavir levels as well as a trend toward decreased virologic failure in individuals receiving nelfinavir[94].

Currently available evidence is not sufficient to draw firm conclusions regarding the effects of MDR-1 and/or CYP polymorphisms on antiretroviral treatment response. The lack of consistency among reports to date is perhaps not surprising given the fact that a single nucleotide polymorphism in a single human gene, however relevant, can realistically only account for a small portion of the interindividual differences in observed pharmacokinetic profiles and treatment responses. This is especially true in the case of a polymorphism such as MDR-1 C3435T, a synonymous substitution that does not affect the amino acid sequence of the protein and thus most likely confers a protective effect indirectly, possibly through linkage with polymorphisms at other sites. In fact, the MDR-1 C3435T polymorphism is known to be in linkage disequilibrium with the MDR-1 G2677T substitution in exon 21[103], among others[104-106], and thus it has been suggested that MDR-1 haplotype analysis may be superior to analysis of single nucleotide polymorphisms (SNP) in predicting pharmacokinetics[104] and treatment response. However, a recent study taking into consideration both the MDR-1 G2677T and C3435T reported no association between combined MDR-1 genotype and virologic or immunologic response to therapy in the first 48 weeks of treatment[96], while another independent study reported no improvement over single-SNP predictive values when haplotypic analysis of MDR-1 was used[89]. It remains to be determined whether comprehensive CYP polymorphism analysis will be superior to evaluation of SNP in predicting pharmacokinetic profiles. Realistically, as the contribution of individual SNP to antiretroviral pharmacokinetics is likely to be minor, definitive conclusions regarding the influence of genetic variability on HAART clinical outcomes will therefore require larger studies with greater power to detect significant associations[107].

Emerging toxicities of HAART: human genes as risk factors for antiretroviral-associated adverse events

Despite the unprecedented benefits associated with HAART, emerging toxicities associated with long-term antiretroviral therapy represent major challenges to treatment success, due in large part to their implications for medication adherence. Adverse effects include, but are not limited to, lipid abnormalities and other metabolic effects[108-113], as well as side effects due to mitochondrial[114], cardiovascular[110,115], renal[116], hepatic[117,118] and other[119,120] toxicities. As the nature and severity of adverse reactions to antiretroviral agents varies among individuals, it is likely that genetic variation plays at least some role in mediating adverse reactions to HAART[121].

Antiretroviral hypersensitivity reactions

The highly polymorphic human leukocyte antigen (HLA) region plays a significant role in the immune control

of HIV. Genetic variation within the HLA region influences the natural course of HIV disease progression through allele frequency mediated effects[122-125], as well as through allele-specific effects[126-132]. At present, it is not known whether HLA alleles associated with differential prognosis during untreated infection are also associated with clinical treatment outcomes. One recent report suggests that specific HLA polymorphisms may influence CD4 response following initiation of HAART[133], although others have observed no correlation between specific HLA class I alletes and HAART outcome[134].

The HLA region is known to contain specific genetic risk factors for HAART-associated adverse events. Specifically, the HLA-B*5701 allele (and its associated ancestral haplotype) is associated with an up to tenfold increased risk of a dramatic and potentially life-threatening hypersensitivity reaction to the nucleoside analog reverse transcriptase inhibitor (NRTI) abacavir[135,136]. However, the strength of this association may vary based on ethnicity[137], and variation at other loci may also contribute to the hypersensitive phenotype[138]. Due to the clinical implications of this reaction, studies have begun to evaluate the clinical utility of skin "patch-testing" for abacavir hypersensitivity[139,140], and it is likely that genetic screening programs for HLA-B*5701 will be useful in the clinical setting[140-143].

The HLA region has also been implicated in a hypersensitivity reaction to the NNRTI nevirapine, which is characterized by hepatic toxicity as well as fever and rash[118]. This reaction occurs in approximately 5% of exposed individuals, although it has been observed more frequently and severely in individuals with higher CD4 counts[144,145]. A recent analysis of 235 individuals in the Western Australian HIV cohort identified the HLA class II allele DRB1*0101 as a genetic risk factor for hepatic/systemic nevirapine-associated hypersensitivity reactions, although this association was only significant in individuals with a higher CD4+ T-cell percentage (> 25%)[146]. Of note, absolute CD4 count was not a significant risk factor when observed in combination with DRB1*0101, and no HLA associations were detected for isolated rash in the absence of hepatic toxicity[146]. Taken together, these data suggest that the combination of CD4 status and expression of HLA-DRB1*0101 influences the occurrence of nevirapine hypersensitivity, an observation that is consistent with a CD4 T-cell-dependent immune response to nevirapine-specific antigens[146]. Prospective screening for HLA-DRB1*0101, aimed at decreasing or eliminating incidence of the nevirapine-induced adverse events may also be of clinical utility[143].

Lipid-associated adverse events

Naturally-occurring genetic variants have been implicated as potential risk factors for a variety of lipid-associated toxicities. Single-nucleotide polymorphisms at positions –308 and –238 within the promoter region of tumor necrosis factor-alpha (TNF-α), a cytokine involved in adipocyte lipid metabolism and other functions[147], have been linked to differential TNF-α production[148] and have been hypothesized to play a role in treatment-related lipid abnormalities. Some studies support an association between the TNF-α –G238A allele (but not differences at position –308) and an increased risk of lipodystrophy[149,150], although this association was not confirmed in a larger study[151]. Variant alleles in other genes involved in adipocyte metabolism, namely apolipoprotein C-III (ApoC3) and apolipoprotein E (ApoE), have been shown to contribute to an unfavorable lipid profile in HIV-infected patients receiving ritonavir[151,152], although a recent study reports that differences in the influence of ApoC3 on the development of PI-related hypertriglyceridemia may be heavily influenced by ethnicity[153]. In addition, the MDR-1 3435C allele has been associated with significant elevations of HDL-cholesterol in patients receiving efavirenz[154].

Protease inhibitor-induced unconjugated hyperbilirubinemia and associated jaundice

The HIV PI atazanavir and indinavir have been associated with asymptomatic unconjugated hyperbilirubinemia in up to > 40% of individuals receiving these agents[155-157], an adverse event associated with the development of clinical jaundice in some individuals[158]. A polymorphism in the promoter region of the gene encoding the bilirubin-specific isoform of the enzyme UDP-glucuronosyltransferase (UGT-1A1), the enzyme responsible for conjugating and clearing bilirubin from plasma, has recently been implicated as a risk factor for PI-associated hyperbilirubinemia[157]. In this study, 67% of individuals homozygous for the UGT1A1*28 allele receiving atazanavir or indinavir had ≥ 2 episodes of hyperbilirubinemia in the jaundice range, compared to 7% of individuals lacking this genotype[157], again supporting a potential role for genetic screening for specific allelic variants prior to initiation of antiretroviral therapy.

Mitochondrial toxicity

The NRTI stavudine (d4T) and didanosine (ddI) are known to cause peripheral neuropathy, a common

manifestation of NRTI-associated mitochondrial toxicity[114]. Hulgan, et al. reported that among 137 Caucasian individuals randomized to receive d4T and ddI, 21% of those who developed peripheral neuropathy exhibited a specific mitochondrial genotype (haplotype "T"), compared to 4.5% of control subjects, an observation which remained statistically significant after adjusting for demographic, clinical, and treatment parameters[159], indicating that naturally occurring genetic variation within the human mitochondrial genome may also contribute to HAART-associated adverse events.

Concluding remarks

Evidence from clinical trials and observational, population-based studies conducted since the introduction of combination antiretroviral therapy indicate that genetic variation likely remains a relevant parameter in today's era of HAART, although in general, the contribution of individual genetic polymorphisms to treatment outcome is likely to be small and thus difficult to consistently detect. Available evidence suggests that immunogenetic parameters previously associated with untreated HIV/AIDS outcomes may still exert a small but measurable residual effect on HIV clinical prognosis in the context of antiretroviral treatment, and that variation in genes involved in antiretroviral metabolism and transport also likely contribute to treatment outcome. In neither case, however, is the strength of the association large enough (or evidence conclusive enough) to justify the incorporation of chemokine receptor, MDR-1 or CYP genotypes into HIV clinical practice at the present time. The most compelling evidence supporting the potential incorporation of human genetic screening as a clinical management tool lies in the area of genetic risk factors for HAART-associated adverse events – namely, the recommendation and initiation of HLA-B*5701 screening procedures prior to the administration of abacavir-containing regimens in order to reduce the incidence of associated hypersensitivity reactions[140-143]. Further analysis of large, observational cohort studies will increase our power to detect significant genetic associations in cases where the prevalence of polymorphisms is low and the magnitude of individual effects is small[107].

The impact of human genetic variation on HIV pathogenesis and treatment response is a complex, multifactorial phenomenon. To date, the majority of studies investigating the influence of human genetic variation on HIV disease and treatment outcomes have focused on SNP or, at most, combinations of a small number of polymorphisms within a single gene, and thus it is perhaps not surprising that reports to date have been somewhat controversial. Although simple genetic markers relevant to HIV disease and treatment response have indeed been identified (as evidenced by the effect of CCR5Δ32 on untreated HIV disease progression and the HLA-B*5701 allele on abacavir hypersensitivity reaction), it is more likely that HIV disease and treatment outcome are influenced by a multitude of interacting genotypes and phenotypes[160]. Improvements in DNA sequencing technologies[161], computer processing and bioinformatics will result in increasing potential to generate, store and manipulate large sets of sequence data, while an improved understanding of the results of the human genome[162] and HapMap[163] projects will facilitate the analysis of complex genotypic profiles on disease outcome. In fact, an increasing number of studies indicate that analysis of combined host genetic profiles (when compared to single markers alone) may be superior in predicting HIV clinical outcome in the context of untreated infection[13,46,68,164-166]. Thus, it remains to be determined whether host genetic profiling may be of relevance in predicting response to HAART on a population basis, and more importantly, whether there will ever be enough evidence to justify the incorporation of comprehensive host-genetic profiling into individual HIV clinical practice. The future of HIV research will therefore undoubtedly include a focus on the role of human immunogenetic and pharmacogenetic variation on HIV disease progression in the context of modern and future combination antiretroviral therapies.

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