The Introduction of Pharmacogenetic Screening to HIV Clinical Practice – Potential Benefits and Challenges

a report by

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It has long been recognised that individuals vary in their susceptibility to diseases and in their response to drugs, but it is only in the last 50 years that progress has been made in elucidating the genetic basis of this phenomenon. The term 'pharmacogenetics' was coined by Friedrich Vogel in 1959 to denote the effects of polymorphisms within a particular human gene on the disposition and action of drugs. Since the discovery in the 1950s that the prolonged apnoea seen in some individuals after administration of succinylcholine (a muscle relaxant) was due to an inherited deficiency of the enzyme pseudocholinesterase,[1] numerous examples of polymorphisms in genes encoding drug-metabolising enzymes, drug transporters and drug targets (enzymes, receptors) have been described.[2,3] Recent years have seen the first steps in translating this information into clinical practice through the use of molecular diagnostics (genotyping) to identify patients at risk of idiosyncratic drug reactions.[4] However, most drug effects are determined by the interplay of multiple gene products, and polymorphisms in many genes may affect the response to a specific drug. Technological advances allowing the application of genome-wide approaches to identify the multiple genetic polymorphisms that affect a drug response (pharmacogenomics) hold out promise for the identification of disease-susceptibility genes and genetic markers for drug efficacy, thereby opening the way for personalised drug therapy.[5]

Clinical practice includes several notable examples of applied pharmacogenetics, although prospective genetic screening remains to be validated in randomised and adequately powered clinical trials. Licensing authorities currently recommend the investigation of pharmacogenetic associations, and genotyping information of relevance to drug safety is increasingly appearing in prescribing information. This particularly applies to drugs with narrow therapeutic indices, and several notable examples are presented by cytostatics, oral anticoagulants and antiarrhythmics metabolised by the polymorphic enzymes thiopurine S-methyltransferase (TPMT), cytochrome P450 (CYP) 2C9 and CYP2D6. Genetic polymorphism in these enzymes can variously result in abolished, reduced, altered or enhanced activity, which is expressed as four major phenotypes: poor metabolisers (lacking functional enzyme), intermediate metabolisers (heterozygous for a defective allele), fast metabolisers (homozygous for the functional allele) and ultra-rapid metabolisers (carrying >2 functional gene copies).[6] Genotyping for non-functional TPMT alleles is of value in identifying patients at risk of potentially life-threatening myelosuppression caused by thiopurines: in homozygous carriers of TPMT null mutations, 6-mercaptopurine and azathioprine doses have to be reduced 10-fold or more to avoid myelotoxicity.[7] Other examples include CYP2C9 genotyping for avoidance of warfarin-related haemorrhage and CYP2D6 genotyping for optimisation of propafenone dosage.[8,9]

However, numerous obstacles impede progress in the practical development of pharmacogenetics. Most clinically relevant genotype–phenotype associations are polygenic effects, and genome-wide studies require large sample sizes, involve complex statistical analyses and confer a significant risk of generating false-positive associations.

Genetic Polymorphism

Analysis of the human genome indicates that there are several forms of genetic variation, including nucleotide deletions, insertions, oligonucleotide repeats and single nucleotide polymorphisms (SNPs) – stable, discrete, single-nucleotide substitutions that occur in ≥1% of the population (lower-frequency variations are considered mutations).[10] Inter-individual differences in human DNA sequence are predominantly the result of SNPs. These sequence alterations, which occur every 100–300 bases along the three-billion base pairs in the human genome,[11] may have a variety of effects: non-synonymous SNPs within coding regions alter the amino acid sequence of the encoded protein; SNPs within the promoter region may affect the transcription of a gene; and SNPs within the 3' untranslated region following the coding sequence may affect the intracellular stability of the mRNA transcript. Moreover, not all individual changes in DNA sequence (genotype) have an effect on gene expression (phenotype). Most genes or groups of genes on a segment of a chromosome contain multiple SNPs that have been inherited together, and these polymorphisms therefore appear in specific blocks or patterns, known as haplotypes. The number of haplotypes for a gene or segment of a chromosome is generally considerably smaller than the total possible number of SNP combinations within that block. In addition to reducing

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Table 1: Contribution of Combined Individual Loci of 57.1 Haplotype to Susceptibility to Abacavir Hypersensitivity

HLA Type	Abacavir-hypersensitive (n=18)	Abacavir-tolerant (n=167)	Odds Ratio (95% CI)	P-value
HLA-B*5701	14 (78%)	4 (2%)	117 (29–481)	<0.0001
HLA-DR7, HLA-DQ3	13 (72%)	6 (3%)	73 (20–268)	<0.0001
HLA-B*5701; HLA-DR7, HLA-DQ3	13 (72%)	0 (0%)	822 (43–15675)	<0.0001

HLA: human leukocyte antigen; CI: confidence interval.
Reproduced from Winston et al. 2006.[81]

the number of variables that need to be examined for association with drug response, haplotypes provide a more accurate prediction of gene activity since they reflect the sum of the effects of individual SNPs.

Rationale for the Application of Pharmacogenetics to HIV Therapeutics

Since the introduction of zidovudine in 1987, more than 20 antiretroviral drugs targeting HIV reverse transcriptase, protease and viral entry have been licensed for the treatment of HIV/AIDS. The use of these agents is associated with considerable inter-individual variability in plasma drug exposure, antiretroviral efficacy and tolerability.[12] Factors affecting variability in plasma drug exposure include host genetics, underlying disease, patient compliance, co-medication and demographic factors such as age, gender and race. Host sources of variability in antiretroviral efficacy and tolerability include both immunogenetic factors (HLA/immune response genes) and pharmacogenetic factors (drug-metabolising enzyme and drug transporter and drug receptor genes).[13–15]

Pharmacogenetic Factors and Drug Response

Many antiretroviral agents have a predominant metabolic pathway and a narrow therapeutic index, and the HIV therapy area is particularly well suited to pharmacogenetic investigation. Important factors underlying the marked pharmacokinetic variability of antiretroviral drugs include their dependence on intracellular phosphorylation for generation of the active drug moiety (nucleoside reverse transcriptase inhibitors – NRTIs) and their role as substrates of genetically polymorphic drug-metabolising enzymes and transporters (protease inhibitors – PIs – and non-nucleoside reverse transcriptase inhibitors – NNRTIs). Prominent among this latter category are the phase I oxidative enzymes of the CYP450 family, phase II conjugative enzymes and drug transporters such as P-glycoprotein, the multidrug transporter multidrug resistance (MDR1) gene product.[3,13,16,17] Numerous genetic polymorphisms in the CYP450 family – most notably the CYP3A, CYP2C19/9 and CYP2D6 isoforms – influence drug metabolism, resulting in altered plasma drug exposure.[6,17] CYP450 polymorphisms with potential relevance to antiretroviral therapy include CYP3A4 (PI), CYP3A5 (indinavir, saquinavir), CYP2C19 (nelfinavir) and CYP2B6 (efavirenz, nevirapine).[14,18–22] Among the drug conjugation enzymes, polymorphisms in uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1), which catalyses drug–bilirubin conjugation reactions,[23] have implications for antiretroviral toxicity (atazanavir and indinavir).[19,24]

Transporter proteins – of which the best characterised are the adenosine triphosphate (ATP)-binding cassette proteins, which include P-glycoprotein (MDR1, ABC1) and the multidrug-resistance proteins (MRP-1–9) – have largely evolved to protect the host from potentially toxic substances. All of the current PIs are substrates for the P-glycoprotein efflux pump in the small intestine,[25] and polymorphisms in the multidrug transporter MDR1 gene encoding P-glycoprotein may have significant implications for protease inhibitor exposure, efficacy and toxicity.[26] Polymorphisms in drug transporters with potential relevance to antiretroviral therapy include P-glycoprotein (PIs, zidovudine, nevirapine) and organic anion transporters (OATs) (tenofovir).[22,25,27–29]

Immunogenetic Factors and Drug Safety

Genetic factors have long been postulated to be important in drug hypersensitivity reactions, which can be regarded as inappropriate immune responses resulting in tissue damage from otherwise non-toxic agents. Investigation has largely focused on genes encoding for immune responsiveness, including major histocompatability complex (MHC), T-cell receptor and co-stimulatory molecules.[30] In the case of antiretroviral agents, evidence suggests that, in Caucasian populations, immunogenetic factors (human leukocyte antigen (HLA) haplotype) and/or immunological factors (CD4+ lymphocyte count) are important determinants of susceptibility to hypersensitivity reactions to abacavir and nevirapine.[31-35]

Clinical Relevance of Genetic Polymorphism in the Treatment of HIV Infection

In the clinical setting, the use of polypharmacy and combination therapy makes it difficult to establish the relationship, if any, between host-specific response factors and individual drugs, and greatly complicates attempts to establish the broad clinical utility of screening for the relevant markers as an aid to drug selection. At the same time, polypharmacy and combination therapy increase the risk of drug-specific adverse events. In contrast to host-specific response factors, the influence of host-specific toxicity factors for an individual drug are unlikely to be masked by the presence of co-administered agents.

Currently, the most promising application of pharmacogenetics to the field of HIV medicine, and one that readily lends itself to clinical investigation of its utility as a patient-management tool, is the identification of those individuals at greatest risk of genetically influenced drug toxicities. Potential genotypic–phenotypic correlations for drug-associated adverse events, or potential mechanisms for such events, have been elucidated for several antiretroviral agents, including nevirapine, atazanavir, efavirenz, tenofovir and abacavir.

Nevirapine-associated Hypersensitivity

Nevirapine-associated hypersensitivity, which is characterised by fever with rash or hepatitis during the first six weeks of treatment, affects an estimated 5% of HIV-infected patients.[34] Post-marketing surveillance indicates that nevirapine-associated hepatitis and rash are more common in women and those without HIV infection, as well as in men with CD4+ cell counts ≥400 cells/μl (odds ratio 3) and women with CD4+ counts ≥250 cells/μl (odds ratio 12).[36] Accordingly, high rates of nevirapine hypersensitivity are observed in HIV-negative individuals receiving nevirapine prophylactically.[37] Results from an Australian cohort study suggest that early hepatitis and hepatitis-associated rash with nevirapine have a strong immunogenetic basis, with HIV-infected patients exhibiting the HLA class II allele HLA-DRB1*0101 and CD4+ cell counts >25%

having a 17-fold increased risk of developing these symptoms.[35] This would suggest that HLA type may be a prerequisite, but is insufficient in itself, for development of nevirapine hypersensitivity, and that the reaction is attenuated by a low CD4+ cell count. Recent data from a Mediterranean (Sardinian) population indicate that the HLA class I allele HLA-Cw8-B14 is additionally associated with hypersensitivity to nevirapine.[38,39] Moreover, nevirapine-related hypersensitivity appears to be susceptible to MDR1 gene polymorphism, with MDR1 3435 CT or TT genotypes conferring a significantly lower risk of hepatotoxicity than the CC genotype.[40,41]

Atazanavir- and Indinavir-related Hyperbilirubinaemia and Jaundice

Unconjugated hyperbilirubinaemia affects ~20–50% of atazanavir- and 5–25% of indinavir-treated patients, and ~6% of patients show overt clinical jaundice.[42,43] This effect is attributable to competitive inhibition by atazanavir and indinavir of uridine diphosphate glucuronosyl transferase 1A1 (UGT1A1)-mediated bilirubin conjugation and clearance.[44] This adverse metabolic event is much more common in the 5–10% of the population with Gilbert's syndrome, who have an underlying genetic defect in bilirubin conjugation. Gilbert's syndrome is caused by a polymorphism in the promoter TATA region of the gene encoding UGT1A1, with the UGT1A1*28 allele resulting in reduced enzyme activity and asymptomatic hyperbilirubinaemia.[19,24,45] In these patients, the incidence of atazanavir- or indinavir-associated hyperbilirubinaemia varies according to UGT1A1 promoter genotype, ranging from ~15% in those with the wild-type allele to 90% in those homozygous for the UGT1A1*28 allele; this latter group is more likely to experience bilirubin levels within the clinical jaundice range (>2.5mg/dl).[19] It is unclear, however, whether this drug-associated hyperbilirubinaemia is linked exclusively to functional polymorphism in UGT1A1: UGT1A1*28 forms part of a haplotype of four UGT1A variants (UGT1A1*28, UGT1A3-66C, UGT1A7-57G and UGT1A7129K/131K) spanning three genes at the UGT1A gene locus that predisposes to hyperbilirubinaemia with atazanavir.[46] In addition, a polymorphism in the MDR1 gene (3435C>T) appears to result in increased plasma atazanavir exposure and elevated plasma bilirubin levels.[29]

Efavirenz-related Neurotoxicity

Efavirenz is extensively metabolised by CYP2B6,[47] a genetically polymorphic enzyme,[48] and displays marked inter-individual and inter-racial variability in both its pharmacokinetics and incidence of neurotoxicity.[49,50] The CYP2B6 516G>T polymorphism – which occurs more frequently in African-Americans than in Caucasians (20% versus 3%, respectively, have the 516T/T genotype)[51] – is associated with increased plasma efavirenz exposure and a higher incidence of adverse central nervous system (CNS) effects during initial treatment.[18,51,52] In addition, individuals homozygous for the CYP2B6*6 allele, which contains both the 516G>T and 785A>G polymorphisms, show significantly higher plasma efavirenz levels than heterozygous individuals or those without the CYP2B6*6 allele.[53] Likewise, the CYP2B6*16 allele, which contains the 983T>C and 785A>G polymorphisms, is associated with elevated plasma efavirenz levels.[54]

Nucleoside Reverse Transcriptase Inhibitor-related Lipodystrophy and Peripheral Neuropathy

Lipodystrophy (subcutaneous fat wasting) and peripheral neuropathy are manifestations of mitochondrial toxicity associated with NRTIs, most notably the thymidine analogues stavudine, zidovudine and didanosine.[55]

Table 2: Factors Favouring Implementation of Pharmacogenetic Testing in Clinical Practice

• Ready availability of a rapid, low-cost pharmacogenetic test
• High predictive value
• Ease of incorporation into routine patient management
• Identification of clinical parameters that determine usefulness
• Clinical outcome affects the wellbeing of patients

The risk and subsequent severity of NRTI-related lipodystrophy is affected by host factors such as age, race (it is more common in Caucasians) and level of immune competence, suggesting a possible underlying genetic mechanism.[56] In Caucasians, susceptibility to NRTI-associated lipodystrophy has been linked to a promoter polymorphism in the tumour necrosis factor (TNF)-α gene (TNF-238A).[57,58] This may represent an important pathophysiological association, as TNF appears to regulate mitochondrial apoptosis.[59] Also in Caucasians, susceptibility to stavudine- and didanosine-related peripheral neuropathy has been associated with polymorphisms in the mitochondrial genome, in particular with the mitochondrial haplogroup T.[60]

Ritonavir-associated Hyperglyceridaemia

The use of protease inhibitors, in particular ritonavir, in HIV-infected patients is frequently associated with atherogenic lipid abnormalities, including increased plasma triglyceride, high-density-lipoprotein cholesterol and apolipoprotein B levels,[61] and there is marked racial variability in susceptibility to antiretroviral drug-induced hyperglyceridaemia.[62] Polymorphism in the genes encoding apolipoproteins E and C3 (APOE, APOC3) and the promoter region of the TNF-α gene have been linked to development of dyslipidaemia with protease inhibitors. The presence of variant APOC3 (455 T/C, 482 C/T, SstI) and APOE (ε2, ε4) alleles has been associated with increased risk of severe hyperglyceridaemia in Caucasian patients on protease inhibitor-containing highly active antiretroviral therapy (HAART) regimens,[63,64] whereas variant APOC3 (455 T/C, 482 C/T, Intron 1 G/C) alleles appear to confer protection against hypertriglyceridaemia in Hispanic patients.[62]

Tenofovir-related Renal Proximal Tubulopathy

Renal proximal tubulopathy – manifest as acidosis, glycosuria and proteinuria – has been described during long-term tenofovir therapy in HIV-infected patients.[65] This renal cytotoxicity has been associated with a polymorphism (1249G>A) in the ABCC2 gene encoding the MRP2 transporter.[66] ABCC2 haplotype also appears to influence susceptibility to tenofovir-induced renal proximal tubulopathy, with CATC functioning as a predisposing haplotype and CGAC as a protective haplotype.[66] In addition, tenofovir (in common with adefovir and cidofovir) is a substrate of the renal OAT-1.[67] The R50H genetic variant of OAT-1, which appears to be confined to Africans, shows substantially enhanced binding with tenofovir,[68] suggesting that those individuals carrying the R50H polymorphism in OAT-1 have altered tenofovir handling.

Abacavir-related Hypersensitivity

Abacavir therapy is limited by idiosyncratic hypersensitivity reactions characterised by fever, rash and gastrointestinal symptoms that usually appear within the first six weeks of treatment.[69] These affect ~8% of patients,[32] although symptoms are non-specific and can be difficult to distinguish from those of concomitant viral illness and/or similar reactions to concomitant antiretrovirals, other drugs or inflammatory disease.[70] The

2–3% false-positive rate for diagnosis of clinical hypersensitivity to abacavir[71–73] means that the true incidence is closer to 5%. The syndrome is reversed on abacavir discontinuation, but abacavir rechallenge can result in rapid onset of life-threatening hypotension.[74] A genetic component of the syndrome was originally suggested by reports of a familial association[75] and a lower incidence in men and individuals of African origin.[76] In Caucasians, abacavir hypersensitivity has been linked with HLA markers, with the HLA-B*5701 allele being most strongly implicated.[31,77,78] Recombinant mapping of other alleles on the 57.1 ancestral haplotype, as well as the presence of HLA-B*5701 in abacavir-tolerant individuals, suggests that HLA-B*5701 is necessary but not sufficient by itself for causing abacavir hypersensitivity.[32,79] Estimates of the sensitivity of HLA-B*5701 as a predictor of abacavir hypersensitivity in this ethnic group range from 48 to 94%.[32,78,80] In contrast, the association between HLA-B*5701 genotype and abacavir hypersensitivity appears to be appreciably weaker in individuals of African origin,[33,78] although, as with the variable strength of association noted in Caucasians, it is currently unclear whether this is a true effect or a consequence of the difficulty of accurate clinical phenotyping. A retrospective analysis of 595 cases of suspected abacavir hypersensitivity indicated that no combination of markers offered superior predictive sensitivity or specificity to HLA-B*5701 alone (50% and 98%, respectively) among Caucasians.[78] However, early studies have been limited by their retrospective design, as well as by problems in defining precisely the phenotype of the abacavir hypersensitivity reaction. Results from an Australian cohort indicated that the HLA-B*5701, HLA-DR7 and HLA-DQ3 haplotype had a positive predictive value of 100% and a negative predictive value of 97% for abacavir hypersensitivity (see *Table 1*).[31,81] Recombinant haplotype mapping has also implicated a variant allele within the heat-shock protein family (Hsp70 Hom M493T), which is carried on the ancestral 57.1 haplotype, as being important in abacavir hypersensitivity,[32] with the HLA-B*5701 and Hsp70 Hom M493T combination occurring in >90% of the abacavir-hypersensitivity patients compared with fewer than 0.4% of abacavir-tolerant individuals.[32]

> Pharmacogenetic associations are typically derived from small or stratified population samples, and their applicability to the broader population and diverse ethnic groups is unclear.

Challenges for Translating Pharmacogenetic Research into Routine Patient Management

The application of pharmacogenetics to clinical practice is complicated by the lack, in most instances, of a robust and uniform correlation between single polymorphisms and plasma drug exposure, drug efficacy and/or tolerability. Factors determining the successful implementation of pharmacogenetic testing in clinical practice are summarised in *Table 2*. Pharmacogenetic associations are typically derived from small or stratified population samples, and their applicability to the broader population and diverse ethnic groups is unclear. The sensitivity and specificity of a pharmacogenetic association is likely to vary from study to study because of these factors, raising uncertainty about the clinical utility of routinely screening for the marker in question. Despite the previously described established associations between specific polymorphisms and drug safety outcomes, most come with challenges for their potential implementation as patient-management tools.

HLA-DRB1*0101 Screening for Nevirapine Hypersensitivity

The presence of the HLA class II allele HLA-DRB1*0101 in conjunction with CD4+ cell count >25% has been associated with a markedly increased (17-fold) risk of nevirapine-related hepatitis and rash in Caucasian patients, suggesting that this allele may serve as an immunogenetic marker for nevirapine hypersensitivity.[35] However, the recent identification of a different allelic marker (HLA-Cw8) in at least some populations[38,39] may complicate efforts to establish the utility of a universal prognostic marker.

UGT1A1*28 Screening for Atazanavir-/Indinavir-related Hyperbilirubinaemia and Jaundice

Prospective UGT1A1*28 genotyping has been proposed for identifying patients at risk of atazanavir/indinavir-related hyperbilirubinaemia and jaundice.[19] However, the influence of the P-glycoprotein 3435C>T polymorphism on plasma atazanavir exposure and plasma bilirubin levels[29] introduces a potential second mechanism that requires separate assessment.

CYP2B6 Genotyping for Efavirenz-related Neurotoxicity

The high degree of overlap between CYP2B6 genotypes and the multiplicity of factors affecting efavirenz exposure are likely to limit the value of CYP2B6 genotyping in identifying patients at risk of efavirenz-related neurotoxicity.[82]

MRP2 Genotyping for Tenofovir-related Renal Proximal Tubulopathy

The practical value of screening for the 1249G>A polymorphism in the MRP2 transporter as a means of identifying patients at risk of tenofovir-related renal tubulopathy is uncertain, given the relatively low sensitivity of this marker (41% of cases versus 17% of tolerant controls).[66] Additionally, the potential for a racially stratified second pathophysiological mechanism (hOAT-1 transport) underlying tenofovir-mediated renal cytotoxicity may complicate matters.[66,68]

HLA-B*5701 Screening for Predisposition to Abacavir Hypersensitivity

HLA-B*5701 is the most extensively studied pharmacogenetic marker in HIV therapeutics, and HLA-B*5701 screening for predisposition to abacavir hypersensitivity is currently the most clinically promising pharmacogenetic intervention for improving patient safety. Observational findings suggest that prospective HLA-B*5701 genotyping and subsequent avoidance of abacavir use in HLA-B*5701-positive patients can reduce the incidence of hypersensitivity reactions to less than 2% in Caucasian populations.[83–85] Moreover, HLA-B*5701 genotyping appears to be a cost-effective strategy in this population: results based on a meta-analysis of three cohorts showed that to prevent one case of hypersensitivity, eight HLA-B*5701-positive patients would be denied abacavir and that, to identify them, 48 patients would require testing.[80] HIV clinics in some centres now routinely screen patients for HLA-B*5701,[86] although the benefits of universal screening, particularly in non-Caucasian populations, are unclear: preliminary evidence suggests that the predictive sensitivity of the HLA-B*5701 test is appreciably lower in Hispanic and Black than in Caucasian populations,[78] although this may be an artefact of case ascertainment. For prospective HLA-B*5701 screening to realise its full potential, it will be necessary to establish the degree of association in non-Caucasians using

large-scale, well-powered prospective studies in geographically and ethnically diverse HIV-patient populations. These data will hopefully be provided by the European Prospective Randomised Evaluation of DNA Screening In a Clinical Trial (PREDICT-1) (Study CNA106030; clinicaltrials.gov ID NCT00340080) and the US Study of Hypersensitivity to Abacavir and Pharmacogenetic Evaluation (SHAPE) (Study ABC107442, clinicaltrials.gov ID NCT00373945) trials, which are now completed and due to report later this year. PREDICT-1 is a randomised, double-blind study designed to assess the impact of HLA-B*5701 screening on the incidence of abacavir hypersensitivity in ~2,000 abacavir-naïve adults with HIV infection. Hypersensitivity rates, with and without case refinement by epicutaneous abacavir patch testing,[87,88] will be compared between two groups of patients with a pre-existing clinical need for *de novo* abacavir therapy: a non-screening (current standard-of-care) arm whose HLA-B*5701 status was evaluated retrospectively at study end and a prospective genetic screening arm in which subjects testing positive for carriage of HLA-B*5701 were excluded from receiving abacavir in the study. Investigators and patients remained blinded to which arm patients receiving abacavir were randomised. As such, it is the first controlled, blinded, randomised prospective study undertaken with the statistical power to determine the clinical utility of screening for a specific pharmacogenetic marker.

SHAPE is a retrospective case-control study designed to evaluate the performance characteristics of HLA-B*5701 as a marker for abacavir hypersensitivity in Caucasian and African-Americans, using epicutaneous patch testing as a tool of case refinement. The study will include approximately 600 HIV-infected adults (approximately 200 with suspected or patch-test-confirmed abacavir hypersensitivity and approximately 200 abacavir-tolerant controls for each racial group), and will estimate the sensitivity/specificity of the HLA-B*5701 marker in each ethnic group.

The feasibility of widespread application of HLA-B*5701 genotyping in the clinical setting will depend not only on the outcomes of the PREDICT-1 and SHAPE studies, but will also be materially assisted by the development and introduction of validated high-throughput screening methods for HLA-B*5701, such as sequence-specific amplification or flow cytometry.[89,90]

Conclusions

Pharmacogenetics provides scope for a more informed and individualised treatment approach to HIV, using information about host genetic variability to optimise antiretroviral drug efficacy, safety and longevity of therapy. This is likely to become an increasingly important area of study as the diversity of the treatment population expands and pharmacogenetic research in developing countries adds to the state of knowledge. Moreover, the field of pharmacogenetics is likely to provide further insight into our understanding of the pathophysiology and evolution of disease. However, success in translating pharmacogenetic knowledge into clinical practice has been limited to date, and a number of factors complicate attempts to establish the applicability and utility of pharmacogenetics in the general patient population. Of the various pharmacogenetic associations noted in the field of HIV therapeutics, those relating to drug-specific adverse events are the most clear-cut and convincing. However, even here, confounding factors reflecting the polygenic nature of the event, the use of small or stratified sample populations, and the moderate and/or variable levels of pharmacogenetic association typically reported have impeded progress in implementing standard-of-care genetic screening for identifying patients at risk of antiretroviral drug toxicity. Realisation of the full potential of pharmacogenetics in the clinic will require attention to appropriate phenotypic definitions, completion of large-scale, well-controlled prospective studies and the introduction of novel laboratory technologies. Such studies are currently underway to investigate the utility of HLA-B*5701 as a genetic marker for predisposition to abacavir hypersensitivity, and this will be the first pharmacogenetic association for which definitive data applicable to routine clinical practice will be available. However, there are other pharmacogenetic associations, particularly those relating to drug safety, in HIV and other therapy fields that would similarly benefit from a rigorous investigation of genotype-guided drug selection. ■

Realisation of the full potential of pharmacogenetics in the clinic will require attention to appropriate phenotypic definitions, completion of large-scale, well-controlled prospective studies and the introduction of novel laboratory technologies.

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