A Pharmacogenomical perspective in HIV/AIDS Therapies

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Abstract

A Medical/ Health Care Provider, with specializations in Medicine (Family Medicine, Pediatrics, Psychiatry, Medicine,TB, STI, Sexual Medicine) ,
One among few Qualified HIV/AIDS Specialists/Physicians in India (HIV Medicine Fellowship (from School of Tropical Medicine Kolkata)
and credentialed globally as AAHIVM HIV Specialist™, (American Academy of HIV Medicine Specialist, USA -- an accredited US Body providing certification as HIV Specialist)
and recognized for the expertises in Counseling & Psychotherapy, Public Health Administration (M.Phil in Hospital & health care Admn), Management (HRM, Operations Management), Sociology, Psychology, & Training and Development,
Aiming- to pursue and strive for excellence in Int Medicine (including HIV Medicine) to be able to provide quality health care & attention to individuals with special needs (women , adolescents & children

Background

It has long been recognized 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 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.

For all major classes of drugs (ACE inhibitors, β-adrenoreceptor antagonists,selective serotonin reuptake inhibitors, tricyclic antidepressants, statins,and β-agonists) given at standard doses, a substantial proportion of patients do not respond, respond only partially, or experience adverse drug reactions (ADRs). Drug concentrations in plasma can vary more than 600-fold between two individuals of the same weight on the same drug dosage. This variation can be of genetic, physiological,pathophysiological, or environmental origin, but a drug's absorption,distribution and metabolism, and interactions with its target can be determined by genetic differences This is Pharmacogenomics,   which deals with the influence of genetic variation on drug response in patients by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity

Pharmacogenomics in medicine & clinical pharmacology :

The relationship between genetic determinants and drug response was established nearly 50 years ago, with the discovery that deficiency in glu cose-6-phosphate dehydrogenase (G6PD) results in hemolytic anemia following ingestion of primaquine In 1960, Evans and colleagues demonstrated inherited differences in isoniazid acetylation, resulting in 'slow inactivator' and 'rapid inactivator' phenotypes . More recent investigations have shown single nucleotide poly-morphisms (SNPs) in genes encoding important metabolizing enzymes (such as the cytochrome P450 enzyme superfamily) to be associated with clinical phenotypes of drug efficacy/toxicity. These and other ongoing studies are resulting in an increasing list of important associations touching nearly all medical specialties However, the utilization of pharmaco- genomics in day-to-day practice has lagged behind its potential, and most current therapeu- tic monitoring still relies upon the quantitation of drug and/or metabolites in the patient's blood. Fully integrating pharmacogenomic testing in clinical practice will require health practitioners to know the relationship between genotypes and clinical outcomes, and to have specific data that can be used to modify drug selection or dosage. The Human Genome Project has provided a critical tool for generating this information: a 'reference sequence' upon which DNA sequence variation can be cataloged and subsequently associated with different phenotypes. Despite the availability of the sequence data, our collec tive understanding of the form and scope of inter individual genetic variation is still in its infancy. While phenotypic associations with sequence variants in metabolizing enzymes have been established, it is believed that SNPs alone may not predict all phenotypes, and therefore certain drugs may require studies involving other aspects of genomic variation, to explain inter- individual variations in efficacy, metabolism, and/or toxicity.

Genetic Polymorphism
Analysis of the human genome indicates that there are several forms of genetic variation, including nucleotide deletions, insertions, inherited deficiency of the enzyme pseudocholinesterase, numerous examples of polymorphisms in genes encoding drug-metabolising enzymes, drug transporters and drug targets (enzymes, receptors) have oligonucleotide repeats and single nucleotide polymorphisms (SNPs) - stable, discrete, single-nucleotide substitutions that occur in $\geq 1\%$ of the population (lower-frequency variations are considered mutations--- been described.
Individual differences in human DNA sequence are predominantly the this information into clinical practice through the use of molecular diagnostics (genotyping) to identify patients at risk of idiosyncratic drug reactions. 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**
(table 3)

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. Other examples include CYP2C9 genotyping for avoidance of warfarin-related haemorrhage and CYP2D6 genotyping for optimisation of propafenone dosage.

However, numerous obstacles impede progress in the practical result of SNPs. These sequence alterations, which occur every 100-300 bases along the three-billion base pairs in the human genome, 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 toxic substances. All of the current PIs are substrates for the P-glycoprotein efflux pump in the small intestine, and polymorphisms in the multidrug transporter MDR1 gene encoding P-glycoprotein may have significant implications for protease inhibitor exposure, efficacy and toxicity Polymorphisms in drug transporters with potential relevance to antiretroviral therapy include P-glycoprotein (PIs, zidovudine, nevirapine) and organic anion transporters (OATs) (tenofovir)

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]. 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

Objectives : Recent developments in the pharmacogenomics of antiretroviral drugs provide new prospects for predicting the efficacy of treatment and potential adverse effects. HIV/AIDS is a serious but treatable infectious disease, yet current treatment is limited by high rates of adverse drug reactions and development of resistance due to suboptimal drug concentrations in a significant proportion of patients. Antiretroviral therapy is especially suitable for pharmacogenomic investigation as both drug exposure and treatment response can be quantified and certain adverse effects can be assessed with validated measures. Additionally, there is increasing knowledge of the pharmacokinetics and dynamics of antiretroviral drugs, and some candidate genes implicated in the metabolism, transport and adverse effects have been identified. However, recent studies of the association of particular genes and their genetic variants with HIV management and adverse drug reactions have not provided unifying conclusions. This article reviews the significant studies published to date in the area of the pharmacogenomics of antiretroviral therapy and summarizes current trends, as well as areas where further research is needed

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. 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 .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.

Clinical Relevance of Genetic Polymorphism in the Treatment of HIV Infection

In the clinical setting, the use of poly pharmacy and combination therapy makes it difficult to establish the relationship, if any, between host- specific response factors and individual drugs, and greatly complicates the attempts to establish the broad clinical utility of screening for the relevant immunogenetic factors (HLA/immune response genes) and markers as an aid to drug selection. At the same time, poly pharmacy and pharmacogenetic factors (drug-metabolising enzyme and drug transporter and drug receptor genes 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.

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 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 CYP450 polymorphisms with potential relevance to antiretroviral therapy include CYP3A4 (PI), CYP3A5 (indinavir, 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.

 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.
Antiretroviral therapy for HIV infection has been available since the introduction and approval of zidovudine in 1986. Nearly 20 drugs in 5 classes and a number of immunomodulatory and other adjunctive agents are available for the treatment of HIV infection 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 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.

Methods/Study Design

Data Source   The scientific literature and eligible materials were surveyed related to the topic of. Pharmacogenomical perspective in HIV/AIDS Therapies

Data Selection: Building on this conceptual framework, the related studies and modeling works who met the selection criteria of being related to 'Pharmacogenomical perspective in HIV/AIDS Therapies'

Data Extraction: Reports were screened and information from eligible studies was abstracted and independently and synthesized

Study Design : A descriptive study on the of pharmacogenomical perspective in HIV/AIDS Therapies

comprising of cohort and retrospective studies .

Results/Findings

It has recently been shown that a CYP2B6 genetic variant predicts higher plasma efavirenz exposure and possibly increased central nervous system toxicity. A large number of studies on ABCB1 genetics with antiretrovirals have also been undertaken; however, as in other therapeutic areas, the data have been contradictory, and currently, no firm conclusions can be reached on the effect of ABCB1 variability as a determinant of efficacy. Indeed, this highlights the need for validation of initial association studies in pharmacogenetic research. By contrast, the clearest association between genetic variants and response relates to the hypersensitivity reaction that occurs with abacavir. The identification that the major histocompatibility complex haplotype 57.1 acts as a strong genetic predisposing factor can be regarded as a prime example of how fundamental research can be translated into a pharmacogenetic test. Nevirapine hypersensitivity has also been related to an HLA gene (HLA-DRB1*0101) but the predictive value does not appear to be sufficient to implement in clinical practice.

Role of host factors in response to Anti Retro Virals (ARVs)
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 Some adverse effects of antiretrovirals, particularly lipodystrophy syndromes and the mitochondrial toxicity induced by nucleoside reverse-transcriptase inhibitors (NRTIs), resemble genetically inherited disorders]. 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 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

Several studies examined a variety of issues related to host genetic characteristics and response to antiretroviral therapy. Five specific areas will be reviewed:
1. Genetic determinants of abacavir hypersensitivity
2. HLA type and viral mutations
3. Efavirenz response and race
4. P-glycoprotein genotype and response to therapy
5. Sex differences in saquinavir exposures
6. Other factors

Abacavir Hypersusceptibility

Abacavir hypersensitivity reactions (HSR) are known to occur in 4% to 5% of patients. The syndrome has been well characterized clinically, with most reactions occurring within the first 6 weeks of exposure to the drug. Underlying genetic causes for HSR have been of interest both to the manufacturer and the scientific community. The ability to better characterize those at greater risk for HSR would allow clinicians to avoid use in that population without denying an arguably potent and well-tolerated agent to patients in need.

Two important studies reported the first insights into the genetic basis underlying HSR. Simon Mallal and colleagues[1] from Perth, Australia, reported an association of the HLA-B*5701 ancestral haplotype with HSR. Studying 200 consecutive patients treated with abacavir, Mallal reported an overall 9% incidence of HSR. Several HLA allelic patterns were noted. HLA-B*5701 was present in 78% of those with HSR and in 2.3% of those who were abacavir-tolerant (odds ration [OR] = 117, $P < .0001$). The combination of HLA-DRB1*0701 -DQ3 was present in 72% and 3% of those with and without HSR, respectively (OR = 73). Combining the HLA-B*5701 and -DRB1*0701 yielded an odds ratio of 822.

In this study population, identification of the ancestral B*5701 haplotype could be expected to reduce HSR incidence from 9% to 2.5%. Mallal correctly observed that these findings require confirmation and may be specific to the Caucasoid population studied in Western Australia, and, most important, that testing for the HLA-B*5701 haplotype is in no way a substitute for the clinical evaluation and decision making of possible HSR. (Shortly after the meeting, Mallal and colleagues' work was published in *The Lancet* [2002;359:727-732], accompanied by an illuminating editorial by Telenti and associates.)

Seth Hetherington and the group from GlaxoSmithKline[2] reported on their initial analysis of 114 candidate genes. Further study is ongoing using whole genome scanning with mapping of single nucleotide polymorphisms (SNP) to elucidate HSR. Using a retrospective case-control method (N = 200) of matched patients with and without HSR, this group also noted the association with HLA-B*5701, though at a lower incidence (46%) than that reported by the Australian group. HSR was present in 85 patients, of whom 90% were male and 78% Caucasian. The difference in HLA-B*5701 expression between those with and without HSR remained highly statistically significant (P = .001). Other loci, including some in the promoter region of tumor necrosis factor-alpha (TNF-a), were noted to be statistically significantly more common in those with HSR.

The consistent finding of an association of HLA-B*5701 (and other genes) with HSR provides proof of principle that specific genes are associated with the occurrence of adverse drug reactions. These findings may be the most important example of the application of modern genetic techniques to the issue of drug safety. Both groups should be acknowledged for their contributions. Whether abacavir should best be studied and characterized by SNP mapping or the candidate gene approach is debatable. It is clear, however, that in the populations studied to date, a significant association exists between the ancestral HLA-B*5701 haplotype and HSR.

Several very important issues remain before the practitioner can reasonably apply HLA typing for HSR to the clinical arena. The generalizability of these findings to other genetically different populations must be determined. There is great genetic diversity, and we do not yet understand the associations (if any) of HSR in other populations. Even in the populations studied by Mallal and Hetherington, a significant percentage of patients with HSR did not have the putative haplotype, and the testing for HLA-B*5701 is not without its limitations. The adequacy of case definition is obviously critical in any case-control study. Misclassification errors in non-HLA-B*5701 controls, labeled as cases, would result in serious underestimation of the true sensitivity. *Finally, and most important, at this time the diagnosis and management of HSR remains a clinical, and not a laboratory, process. Testing for the 57.1 ancestral haplotype (HLA-B5701, DR7, DQ3) or the HLA-B5701 alone as studied by Mallal and Hetherington, respectively, should not be used to screen patients before initiating abacavir until further studies in different populations have been completed. Nor should testing be used as a means of diagnosing possible HSR.* Further definition of the full array of markers conferring susceptibility to HSR is needed. Until this is accomplished, there is little reason for clinicians to use HLA-B*5701 testing. One can be optimistic that the genetic basis underlying HSR will be determined, and will eventually allow a more individualized approach to use of this potent agent. Further work from both of these groups can be expected.

HLA Type and Viral Mutations

Host genetic factors that may interact with viral resistance mutations were the subject of an elegant poster by Moore and colleagues[3] from Simon Mallal's group. By way of background, it

is recognized that host cytotoxic T-lymphocyte (CTL) responses may select for viral mutations that allow the virus to escape those responses (so-called CTL escape mutations). On a population level, certain polymorphisms in the viral reverse transcriptase (RT) and protease domains are known to be specific to certain host HLA class I alleles. The authors proposed that these polymorphisms represent the effect of CTL escape mutations.

In this study, the investigators sought to link CTL escape mutations and specific host HLA alleles to amino acid substitutions in the viral RT and protease domains. A total of 492 patients were studied using viral mutations as the outcome, antiretroviral agents as covariates, and evaluating the effect of HLA alleles. They found that 57 residues in the RT and 33 in the protease domain were associated with specific HLA-A and -B alleles ($P < .05$). Similar to the specific amino acid substitutions that are recognized as drug resistance mutations, HLA mutations were site-specific. For example, the well-known T215Y mutation led to zidovudine resistance (OR = 3.7), as did the HLA-B7 allele (OR = 2.3). The mutation at codon 82 (V82A/T/F) that confers resistance to indinavir was associated with HLA-A2 (OR = 5.4).

This work confirms earlier pilot studies by Walker and colleagues[4] and Gao and coworkers.[5] While complex, these insights may help explain the observed variability in response among patients with drug resistance: Some patients with a specific complex of mutations may manifest different clinical responses from others with the same viral resistance pattern. CTL escape mutations may "predispose" to specific viral variants and an altered clinical response. Along with host factors affecting antiretroviral drug metabolism and exposures, characterization of CTL responses may provide insights into a patient's individual response to therapy. It is conceivable that a precise understanding of the host immune responses and consequent viral mutations will, in the future, allow a more individualized approach to therapy.

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) . This transporter serves as an efflux pump for numerous compounds and has been associated with resistance to chemotherapeutic agents in multiple tumor types PGP may also limit intestinal absorption, intracellular retention, and CNS penetration of PIs Increased intracellular PI levels within lymphocytes may also be linked to decreased *MDR1* expression]. 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 . 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 This may have significant implications for PI use in patients of certain African ethnic backgrounds

The Swiss HIV Cohort Study first reported that immunological response to PI-based ART is linked to *MDR1* 3435 genotype . 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; $n = 43$) 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-naive, western Canadian, white patients treated with either double- or triple-combination therapy, unless heterozygotes were excluded from the analysis 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

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-naive 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 Consistent definitions of the syndrome, which comprises fat loss and gain associated with hyperlipidemia and hypertriglyceridemia, are becoming established 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 lipoprotein lipase, fatty acid synthase, peroxisome proliferator-activated receptor *(PPARγ)*, and glucokinase, thereby playing an important role in cholesterol, triglyceride, and glucose metabolism , and *SREBP-1c* adipocyte expression has been linked to lipoatrophy in HIV-infected patients Moreover, indinavir decreases *SRBP-1c* expression and nuclear localization while promoting apoptosis of adipocytes]. TNF-α is a cytokine involved in adipocyte lipid metabolism, differentiation, and apoptosis (reviewed in 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]. Functional polymorphisms at positions -308 and -238 within the TNF-α promoter have been linked to TNF-α production (reviewed in

Two trials have investigated the role of single-nucleotide polymorphisms in treatment-related metabolic side effects of ART. Miserez et al. 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 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 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]. 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)*]. This enzyme catalyzes the glucuronidation of bilirubin as well as multiple exogenous compounds as a component of phase II drug metabolism]. A variable number of TA repeats within the promoter of the *UGT1A1* gene have been described in world populations, although either 6 (A(TA)$_6$TAA) or 7 (A(TA)$_7$TAA) repeats predominate in most groups . 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) *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* .

The *UGT1A1* 7/7 genotype has been associated with hyperbilirubinemia in 353 participants treated with atazanavir in phase I trials 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 association studies should be performed in populations from other regions as the drug becomes more commonly used

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 CXCR4 and CCR5 are the major HIV-1 coreceptors, although several other chemokine receptors (including CX_3CR1) have been identified as coreceptors for certain HIV strains. Each of these are have been shown to possess allelic polymorphisms, often with differences in interpopulation frequencies – 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. Other SNPs within the *CCR5* promoter have been described which have been linked to propensity toward HIV infection and progression]. A C-to-T change at amino acid 280 (T280M) of the CX_3CR1 sequence has been liked to a more rapid progression to AIDS], although analysis in various populations has not upheld this association 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 . 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 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 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 *CCR532* 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 No association was found between the presence *CX3CR1* T280M or *CCR532* 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.

Efavirenz Response and Race

Do antiretroviral response rates differ by race? Interest in this important question has grown as the existence of racial differences in drug-metabolizing enzyme systems and cellular efflux pumps has become better characterized. The study of clinical outcomes and race is complex. Social and economic factors, including access to care, must be considered in any attempt to evaluate racial differences in response to therapy. So, too, must the definition of race: Substantial intermixing of the races during the past centuries has resulted in differences in the genotypic and phenotypic definition of race. Research into possible racial differences in response to therapy has been hampered by a history of underrepresentation of minorities in clinical trials.

Wegner and colleagues from the US Military HIV Research Program described poor outcomes among blacks treated with an efavirenz-containing highly active antiretroviral therapy (HAART) regimen. Among a group of 56 blacks and 43 whites, the median time to virologic failure was 1400 days for whites and only 422 days for blacks (OR = 2.42; 95% CI, 1.35-4.57; P = .0027). A group of patients treated with nelfinavir (n = 172) or indinavir (n = 102) was used as a comparison, but time to failure did not differ by race in either of these treatment groups, thus suggesting that regimen adherence was not the likely explanation. Given the unimpeded access to care in the military services, this, too, was believed unlikely to explain the differences observed. Efavirenz is metabolized through the 2D6 isoenzyme system, and although no substantial differences in 2D6 expression between blacks and whites have previously been described, this is a possible explanation of the virologic findings. These authors characterized expression of 2D6 in their study population, and while differences were noted, they did not correlate with outcome. Unfortunately, plasma efavirenz levels were not measured, preventing the investigators from offering an explanation for their observation.

This author contacted scientific personnel from the manufacturer of efavirenz, to try to uncover more data speaking to this question. Their analysis of 170 black subjects in the registrational trial, DMP 006, showed no racial disparity in response, with no significant difference from whites in the proportion with virologic failure (HIV-1 RNA > 50 copies/mL) or virologic success (HIV-1 RNA < 50 copies/mL) in either intention-to-treat or on-treatment analyses (Laura Besson, written personal communication, February 27, 2002). These conflicting observations mirror those previously reported on the possible relationship between efavirenz plasma levels and central nervous system toxicity, as discussed in this author's report from the 41st ICAAC. In both instances a larger dataset analysis by Bristol-Myers Squibb seemed to refute findings of independent investigators. Further genetic characterization is necessary to explore the presence and significance of any racial or ethnic differences in therapeutic outcomes.

P-glycoprotein Genotype and Response to Therapy

At the 41st ICAAC, Telenti [ ] presented evidence that P-glycoprotein (P-gp) genotype (and expression) affected the immunologic outcomes of antiretroviral therapy. At this meeting, Dong and colleagues from the British Columbia Centre for Excellence in HIV/AIDS presented data suggesting that no such relationship exists between P-gp genotype and time to virologic or immunologic failure. In a retrospective analysis of 510 patients, this group found that roughly equal numbers of subjects had genotypes corresponding to normal, over-, or underexpression of P-gp. P-gp is responsible for efflux of protease inhibitors (PIs) from lymphocytes and other

cellular compartments (brain, genital tract, gut, bone marrow), and overexpression of P-gp should therefore result in greater removal of drug from the intracellular space and diminished virologic and immunologic response.

What accounts for the difference between the Telenti report and this from the British Columbia group? No clear answers emerge at this time. The relative homo- or heterogeneity of the studied population may account for some differences. Given the known correlation between intracellular drug concentration and P-gp expression for several chemotherapeutic agents, it seems likely that PIs, known substrates for P-gp, will be similarly affected. Ongoing studies by leading groups at Vanderbilt University in Nashville, Tennessee, and David Back's group in Liverpool, United Kingdom, should provide clarity in the near future.

Sex Differences in Saquinavir Exposures

The relationship between sex differences and drug exposures in patients with HIV has been poorly studied. Brundage and colleagues from the ACTG 359 pharmacology group reported on the difference in saquinavir exposure between men and women enrolled in this salvage trial. ACTG 359 was a complex study, further complicated by unanticipated drug-drug interactions that led to poor virologic outcomes. Patients failing previous PI-based HAART were treated with a saquinavir-based regimen, paired either with ritonavir or nelfinavir. In addition, patients received delavirdine with or without adefovir. The pharmacology substudy included 186 patients, and data on saquinavir levels from 1022 samples were available for analysis. Saquinavir and delavirdine exposures (AUC) were markedly diminished in those randomized to the adefovir arm, for reasons that remain poorly understood. Exposures were also reduced among males, those with higher body weight, and those with higher baseline plasma HIV-1 RNA levels. There were significant differences in saquinavir clearance, bioavailability, and half-life among those treated with ritonavir as opposed to nelfinavir. The addition of adefovir to the regimen further increased saquinavir clearance, resulting in lower exposures. Among women, however, saquinavir exposure (AUC) was increased by 50% due to reduced clearance, and the plasma half-life was increased to 6.1 hours, which was 50% to 100% longer than the mean for the ritonavir- or nelfinavir-treated groups.

This study confirms previous observations of the influence of sex on saquinavir exposure. As clinicians are aware, antiretroviral dosages for adults are rarely individualized, with the exception of those for stavudine and didanosine. Further study of dose adjustment by weight and sex is obviously needed..

The Resurrection of Saquinavir Hard-Gel Capsules

The original *Invirase* formulation of saquinavir comprised hard-gel capsules (HGC) that were troubled by poor bioavailability and large pill burden. The manufacturer, Roche, subsequently developed the *Fortovase* soft-gel capsule (SGC) formulation which has enhanced bioavailability but also significant gastrointestinal toxicity. The near-routine use of ritonavir as a pharmacokinetic enhancer for saquinavir has brought about a re-evaluation of the HGC.

Kurowski and colleagues reported the results of a crossover study comparing the 2 saquinavir formulations in 24 HIV-seronegative adults. Both formulations were dosed at 1000-mg twice daily with ritonavir 100-mg twice daily. All pharmacokinetic parameters ($C_{max\ 12}$, $C_{max\ 24}$, $C_{min\ 12}$, $C_{min\ 24}$, and AUC) favored the HGC, which were also better tolerated. This is important information, and should allow the clinician to use the better tolerated HGC with ritonavir. Previous studies have demonstrated a close correlation between saquinavir exposures in HIV-

seronegative and HIV-infected individuals, further enhancing the clinical application of these findings for this drug combination.

Atazanavir Plus Efavirenz

Atazanavir, the once-daily PI in the late stages of clinical development, was studied when coadministered with efavirenz. An interaction between these agents was anticipated because of the known CYP 3A4 induction effect of efavirenz. Preston and colleagues studied 31 HIV-seronegative subjects and demonstrated a profound decrease in atazanavir exposures (C_{min}, C_{max}, and AUC) caused by efavirenz. The plasma half-life of atazanavir was also reduced from 7.0 to 5.1 hours. It seems clear that atazanavir at the standard 400-mg dose cannot be administered with efavirenz, and probably not with nevirapine either.

However, in an adjacent poster, O'Mara and colleagues reported the pharmacokinetic profile of atazanavir when boosted with ritonavir (200 mg) and dosed with concomitant efavirenz in 20 HIV-seronegative subjects. The induction effect of efavirenz was completely offset by the ritonavir. Atazanavir exposures increased 2.2-fold for the C_{max}, 3.4-fold for the AUC, and nearly 8-fold for the C_{min}. Work is under way to determine the effect of a 100-mg dose of ritonavir, but presumably atazanavir exposures will be adequate, at least for wild-type virus.

An important issue is whether the increased atazanavir exposures will result in higher rates of toxicity. This is of special concern for the hyperbilirubinemia that can complicate atazanavir therapy. It is known that higher atazanavir C_{min} and AUC levels are associated with elevations in serum bilirubin to > 2.5 mg/dL. The extent to which increased rates of clinically significant hyperbilirubinemia (related to the Gilbert's genotype) will occur is unknown. Similarly, the virtual absence of hyperlipidemia seen in atazanavir-treated individuals may be eroded by the concomitant use of ritonavir. Further work is needed to answer these clinically important questions.

Once-Daily Lopinavir/Ritonavir

Coformulated lopinavir/ritonavir has been a powerful addition to the PI class. In a pilot study reported by Bertz and colleagues treatment-naive patients were randomly assigned to receive lopinavir/ritonavir at the usual 400 mg/100 mg twice-daily dose or at a 800 mg/200 mg once-daily dose, each combined with stavudine and lamivudine.

Virologic and immunologic outcomes were similar. Pharmacokinetic studies showed that the C_{trough} was 56% lower in the once-daily group, and the variability of C_{trough} was also greater, by approximately 2-fold. Neither C_{max} or AUC was significantly different between the dosage groups.

These findings have prompted a larger trial by the manufacturer, Abbott Laboratories. If this confirms these pilot findings in a larger patient population, the use of once-daily lopinavir/ritonavir may be appropriate in certain subsets of patients, such as treatment-naive or PI-naive patients in whom wild-type virus is expected. It would be premature for clinicians to adopt the strategy of once-daily lopinavir/ritonavir at this time.

Study Limitations : Much more work needs to be done to define the genetic factors determining response to antiretroviral agents. These studies need to be sufficiently powered and utilize a modern genotyping strategy. Most importantly, the phenotype needs to be carefully characterized.. Some of these issues are now being tackled, but studies need to be sufficiently powered and the phenotype carefully characterized.

Despite many advances in genomic studies of anti retrovirals, the clinical application of pharmacogenomics remains in its infancy. This is mainly due to the fact that very few clear relationships between host genotype and patient outcomes have been identified. Two areas are expected to have great impact on antiretroviral therapy:

- Polymorphisms associated with metabolism and transport, such as CYP enzymes and membrane transporters;
- Genetic factors responsible for certain adverse effect, such as *HLA-B*5701* for abacavir hypersensitivity.

The use of a diagnostic kit has been recently approved by the US FDA for the screening of common polymorphisms in *CYP2D6* and *CYP2C19* in psychiatric patients to guide their treatment. It seems reasonable to anticipate that in HIV medicine similar diagnostic tools would be developed and found to affect clinical out-comes, particularly for *CYP2B6* polymorphisms that involve in efavirenz disposition. In addition, the high correlation between *HLA-B*5701* and abacavir hypersensitivity may lead to wide-spread testing to optimize abacavir-containing treatment.

It has been increasingly recognized that genetic difference among ethnic/minority groups is an important determinant in disease risk, progress, prognosis and patients' responses to treatment. In recent years, the research on pharmacogenomic differences among ethnic minorities has broadened to include a larger range of targets, such as multiple metabolizing enzymes, drug transporters and receptors.[49] Increasing evidence suggests that drug metabolism alone does not account for the observed inter-racial variability in drug disposition or response, but other processes, including drug transport, are also important determinants as well. Among the drug transporters shown to play a key role in drug disposition, P-gp encoded by the *ABCB1* gene is one of the most extensively studied. The wild-type alleles (CC) of the *ABCB1* gene at the 3435 C>T locus are more prevalent in the African□American population than in Caucasians and Hispanics. Such racial differences in the *ABCB1* polymorphisms may contribute to previously recognized racial differences in the clinical response to antiretrovirals. In the near future, pharmacogenomics may have the most immediate application in HIV therapy with respect to race/ethnicity and sex-related differences in pharmacokinetics and pharmacodynamics. A growing body of literature has highlighted the different distribution of genetic variants among ethnic groups. As most pharmacogenomic findings are related to the older antiretrovirals, which have been increasingly used in sub-Saharan Africa, African patients should theoretically benefit more from these findings. This is, however, not the current situation in resource-limited settings, mainly due to the lack of full-scale confirming genomic studies. In addition, several studies suggest pharmacokinetic and response differences between men and women, which have prompted more detailed investigations in women to determine if dosing adjustment by gender is warranted.

Conclusions

This is just the beginning of the genomic era of antiretroviral therapy. Despite current limited applications, it is likely that new findings from pharmacogenomic studies will facilitate therapy individualization and achieve better treatment outcomes in HIV-infected patients. The ability to predict efficacy and toxicity during antiretroviral therapy for HIV would be of obvious advantage Drug treatment in HIV disease is characterized by variable responses, in terms of

both efficacy and toxicity. Both genetic and environmental factors are important determinants of this variability, although the relative contributions are unclear and likely to vary with different drugs. Many of the antiretrovirals (NNRTIs /PIs) are metabolized by polymorphically expressed enzymes (cytochrome P450, CYP450; glucuronyl transferase, GT) and/or transported by drug transporters (ABC and SLC families). Initial studies of antiretroviral efficacy have therefore focused on these genes. In pharmacokinetics and efficacy studies, issues are complicated by multiple loci effects (driven by the large number of proteins contributing to disposition) and heterogeneity in both study populations and the virus (ie, the target)

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 (Table 2). Although data are not yet available, areas of current pharmacogenetic investigation include efficacy of NRTI therapy; neurotoxic and hematotoxic responses to NRTIs; allergic, hepatotoxic, and neurologic responses to NNRTIs; 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. **So we can conclude over here as :**

- Most pharmacogenomic studies on the association of gene polymorphisms and response to antiretrovirals do not meet methodological criteria, such as sufficient sample size. Therefore, most results should be considered as preliminary.
- Recent interests have centered on *CYP2B6*, *CYP3A5*, membrane transporter genes and immunogenetic factors. With few exceptions, most findings are inconclusive and need to be confirmed in larger more extensive future studies.
- The *CYP2B6* genotypes appear to be associated with efavirenz disposition.
- The *HLA-B*5701* and UGT1A1 genotypes can be used to predict abacavir hypersensitivity and atazanavir-induced hyperbilirubinemia in certain populations.
- Few studies have been carried out in resource-limited settings that could provide the large sample size to determine effects of certain genotypes.

Future Perspectives :

Pharmacogenomics will provide a powerful tool to investigate variable responses to antiretroviral therapy. Therapeutic management of HIV infection has been characterized by

substantially differing response rates and adverse effects. To date, few antiretrovirals appear to have a clear genotype-phenotype correlation. However, such correlations have been demonstrated for *CYP2B6* and efavirenz disposition, *HLA-B*5701* and abacavir hypersensitivity, and UGT1A1 and atazanavir hyperbilirubinemia. More work is needed to explore the relationship of polymorphisms, particularly at membrane transporters, and subsequent pharmacokinetic and response outcomes. The clinical implications of pharmacogenomic advances should be interpreted with caution until further confirmation is available.

Pharmacogenomics will also provide the foundation for antiretroviral treatment individualization based on race/ethnicity and gender. The completion of the Human Genome Project has dramatically increased the potential of pharmacogenomics to individualize antiretroviral therapy based on genetic constitution. It has been proposed that the current therapeutic drug monitoring of therapy guided by viral genotyping and phenotyping will be significantly enhanced by incorporation of host genomics. The impacts of pharmacogenomics on the following will be the focus for future studies:

- Dosage adjustment of antiretrovirals in clinical practice based on patients' genetic make-up, and testing for polymorphisms as a means to optimize treatment;
- Potential need for local guidelines to address ethnic variation, particularly in resource-limited settings;
- Research priority based upon current pharmacogenomic knowledge.

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Table 1. A synopsis of findings from pharmacogenetic studies of the efficacy of antiretroviral therapy, to date

Locus	Polymorphism	Effect
HLA-B	HLA-B*5701	Strong association between *HLA-B*5701/ HLA-DR7/ HLA-DQ3* haplotype and abacavir hypersensitivity
HLA-DR	HLA-DR7	
HLA-DQ	HLA-DQ3	
HLA-B	HLA-B*5701	55% sensitivity for abacavir hypersensitivity
MDR1	3435 C/T	Greater increase in CD4 cell count after 6 months of PI therapy among *TT* genotypes
MDR1	3435 C/T	No correlation between genotype and CD4 cell count recovery or virus load at 6 months in PI- and non-PI-based regimens
MDR1	3435 C/T	No association between genotype and phase 1 or phase 2 viral decay after 2 weeks of ritonavir monotherapy
SREBP-1c	3322 C/G	Higher total cholesterol and triglyceride levels after starting PI therapy in persons with *C* haplotypes
	3322 C/G	No association with hyperlipidemia
SREBP-1c	-238G/A	Increased incidence of lipodystrophy among -238A haplotypes
TNF-.	-308G/A	No association with -308 polymorphism
	-238G/A	More rapid progression to peripheral fat wasting among -238 *AA* compared to *GG*
TNF-.	-308G/A -250	No association with fat redistribution and TNFA -308 or *TNFB* -250 polymorphisms
TNFB	G/C	7/7 genotype significant predictor of hyperbilirubinemia after starting atazanavir therapy
UGT1A1	A(TA)6TA A	Increased likelihood of virus load q1400 copies/mL
CCR5	A(TA)7TA A	Predictor of achieving a virus load of 500 copies/mL and an increase in CD4 cell count of 150 cells/ L with PI therapy
CCR5	32 deletion	No association with virologic response to PI therapy
CCR5	32 deletion	No significant association with greater virus load reduction after PI therapy
CCR5		No association with time to virologic failure (virus load,1400 copies/mL) or immunological failure (lower CD4 cell count than at baseline)
CCR5	32 deletion 32 deletion 32 deletion	
CCR5	208 G/T, 303 A/G, 627 C/T, 676 A/G, 927 C/T	No association between *CCR5* or *CX3CR1* genotype and time to immunologic or virologic failure
CX3CR1	32 deletion	No association between *MDR1* genotype and development of PI resistance mutations
MDR1	T280M, V249I 3435 C/T	

Table 2 : . Potential future role of patient genetic information in the personalization of HIV therapy. NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.
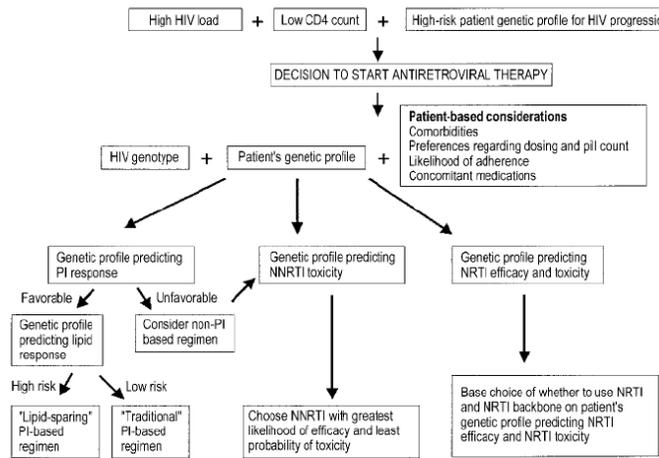
Table : 3

PERSONALIZED PILLS

The US Food & Drug Administration (FDA) has recommended genetic analysis tests before prescribing certain drugs. Most of these are chemotherapeutic drugs , as they alter cell processes and can destroy living cell too., which can cause Adverse side effects .

DRUG	USE	GENE VARIANTS & SIDE EFFECTS
Abacavir	Anti viral drug used in HIV management (ART -Anti Retro viral Therapy –NRTI – Nucleoside Reverse Transcriptase Inhibitor)	Those with HLA-B*5701 gene are at great risk for hypersensitivity – respiratory distress, fatigue, gastrointestinal upset , fever and 'rash'
Atrovastatin	Lipid lowering agent , used in ischemic stroke, dyslipidemia	COQ2 gene variations are associated with intolerance –myalgia and other muscular disorders
Azathioprine	Immunosuppressant	TPMT genetic polymorphism can lead to drug toxicity
Carbamezipine	Anti epileptic drug	HLA- B*1502 senstivity test will help avoid 'Stevens Johnson Syndrome
Cetuximab	Monoclonal antibody used in colorectal cancer	Will not work in those with KRASgene mutation .
Clopidogrel	Anti platelet agent	Haemorrhage in those with CYP2C19 gene variant
Dasatanib	Gastro intestinal tumor	Gastro intestinal upsets, dizziness , works best with BCR-ABL gene
Imatinib	Leukaemia and lung cancer	Neurtopenia , works best in those with BCR and ABL-1 genes
Ininotecan	Solid tumor	Those with UGTIA1variants need greater dosage.
Panitumumab	Monoclonal antibody used in colorectal cancer	Hypomagnesemia tendency , tendency to bleed, works best in those with non-mutated KRAS gene.
Rasburicase	Hyperuricemia and tumor lysis	G6PD enzyme deficiency causes hemolysis
Trastuzumab	Breast cancer , ovarian cancer	Works well for those with HER2 protein , could affect heart working
Valproic Acid	Anticonvulsant	Loss of bone density , lowers blood ammonia to fatal levels in those with urea cycle disorders and CPS1gene variants
Warfarin	Anticoagulant	Myelosuppressive and fluid retention in those with VKORCI-CYP2C9 polymorphism