CHAPTER

8

Pharmacogenomic Considerations in the Treatment of HIV Infection

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OUTLINE

INTRODUCTION

As of 2016, approximately 37 million people were infected with the human immunodeficiency virus (HIV), with two million new infections reported each year [1]. Once uniformly fatal, HIV has largely become a chronic manageable illness due to the advent and widespread use of potent combination antiretroviral therapy (cART). Indeed, AIDS-related deaths have dramatically fallen from their peak number in 2005 and millions of new cases are prevented due to the use of cART [2].

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Currently, there are 24 available antiretroviral (ARV) medications from six classes. These include nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors (EIs), and integrase strand inhibitors (INSTIs) [3]. Combination products and pharmacokinetic enhancers such as ritonavir and cobicistat are also available. The goal of cART, which must be administered throughout the course of a patient's life, is virologic suppression and maintenance, or reconstitution of immunologic function.

In simplest terms, the goal of antiretroviral therapy (ART) is to maximize therapeutic benefits while minimizing adverse events. Understanding variation in efficacy and toxicity of antiretroviral (ARV) drugs is evolving over time. Individualization of ARV therapy requires a holistic understanding of the drug, virus, and patient in terms of demography and pharmacogenetics. Testing for *HLA-B*57:01* and its association with abacavir hypersensitivity has been a success story and a notable example of pharmacogenetics-guided individualization of therapy [4]. Success of abacavir pharmacogenetic testing in routine clinical practice offers valuable insight for future implementation of pharmacogenetics as a tool to optimize antiretroviral pharmacotherapy (Table 8.1).

A number of factors, including drug interactions, age, gender, ethnicity, comorbidities such as hepatic or renal failure, pregnancy, and genetic differences can result in interpatient variability in ARV drug response [5]. Indeed, differences in genes that encode for drug targets, receptors, metabolizing enzymes, and drug transporters can contribute to variations in ARV efficacy and toxicity. Knowledge of interindividual pharmacogenetic differences has the potential to assist clinicians in individualizing ART to maximize therapeutic benefits. This chapter will discuss those ARV medications for which pharmacogenetic data are available.

NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS

Abacavir

Abacavir is an NRTI indicated for the treatment of HIV infection when used in conjunction with other ARVs [6]. It is commercially available as a single-dose formulation or in fixed-dose combinations with other ARVs that include lamivudine, zidovudine, and dolutegravir.

Although abacavir is generally safe, hypersensitivity reactions (HSRs) have been reported after initiation of treatment. These reactions occur in 5%–8% of patients treated with abacavir and typically manifest after 2–6 weeks of treatment [7,8]. The abacavir HSR is characterized by signs and symptoms in two or more of the following categories: fever; rash; gastrointestinal symptoms such nausea, vomiting, and diarrhea; constitutional symptoms such as myalgia, fatigue, and achiness; or respiratory symptoms such as dyspnea, cough, and pharyngitis. Upon developing the abacavir HSR, it is imperative that the drug be discontinued. Continuing abacavir in this setting can result in worsening of symptoms and rechallenge is contraindicated as it can result in severe, potentially fatal reactions [9,10]. Because symptoms of the abacavir HSR are nonspecific, they might be confused with other common conditions or infections. This issue was problematic in controlled double-blind trials leading to false positive diagnoses of the abacavir HSR in patients not receiving abacavir [11].

Shortly into the new millennium, an association was reported between the abacavir-induced HSR and the presence of the major histocompatibility complex (MHC) class I allele HLA-B*57:01 [12,13]. Since then, a number of additional studies have explored this association and observed similar findings [11,14,15]. The prevalence of the HLA-B allele varies among ethnicities. It is more commonly seen in Caucasians (6%–10%) compared

TABLE 8.1 Summary of Pharmacogenomics of Antiretroviral Medications

Drug	Genes	Effect	References
NUCLEOTIDE AND NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
Abacavir	*HLA-B*57:01*	Hypersensitivity reaction	[11,12,13]
Tenofovir	*ABCC4* 3463 A>G, *ABCC4* 4131T>G	Higher intracellular TFV concentrations	[31,34]
	ABCC2 24T	Higher urinary excretion	[35]
	ABCC10 SNPs (rs9349256 G>A, and rs2125739 C>T)	Renal tubular dysfunction	[36]
Zidovudine	*UGT2B7**1C	Higher AZT clearance	[42]
	ABCC4 G3724A	Higher intracellular AZT-TP concentrations	[43]
Lamivudine	*ABCC4* T4131G	Higher lamivudine-TP concentrations	[48]
NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS			
Efavirenz	*CYP2B6* 516TT, *CYP2B6* 516GT	Higher efavirenz concentration and CNS side effects	[53]
	CYP2B6 983TC		[53]
	CYP2B6 15582CT (rs4803419)		
Nevirapine	*CYP2B6* 516GT and TG	Lower nevirapine concentrations	[61]
	CYP2B6 516TT	Higher nevirapine concentrations	[62]
	ABCC10 (rs2125739)	Lower nevirapine concentrations	[63]
	ABCB1 3435CT	Less likelihood of hepatotoxicity	[64]
	*HLA-DRB1*01:01*, *HLA-DRB1*01:02*, *HLA-B*35*, and *HLA-Cw*04*	Adverse skin events	[65]
	*HLA-Cw*08*	Hepatic adverse events	
Etravirine	*CYP2C19*2*, *CYP2C9*3*	Reduced clearance of etravirine	[66]
PROTEASE INHIBITORS			
Atazanavir	*CYP3A5*1*	Higher clearance	[73]
	ABCB13435C→T homozygous	Severe hyperbilirubinemia	[74]
	PXR T63396T	Lower atazanavir concentrations	[76]
	UGT1A1(*28/*28 or *28/*37)	Jaundice	[37]
Lopinavir	*SLCO1B1*4*	Higher lopinavir clearance	[78]
	CYP3A and *ABCC2*	Lower lopinavir clearance	
	*SLCO1B1*521T→C	Higher plasma lopinavir concentrations	[79]
INTEGRASE STRAND TRANSFER INHIBITORS			
Raltegravir	*UGT1A1*28/*28*, *ABCG2* 421 CA/AA, *ABCB1* 4036 AG/GG	Higher raltegravir concentrations	[84]
Dolutegravir	*UGT1A1*(*28/*28,*28/*37,*1/*6,*1/*28, *1/*37,*28/*36, and *36/*37)	Lower dolutegravir clearance	[91]

to East Asian (1%–3%) or African populations (1%–2%). In fact, this allele is completely absent in certain ethnic groups such as Japanese individuals [16]. HLA-B allele status determines the susceptibility to hypersensitivity reactions but does not alter the pharmacokinetics or pharmacodynamics of abacavir in any of the studied ethnic groups.

In a large prospective multicenter study, PREDICT-1, the predictive power of HLA-B*57:01 (rs2395029) screening was tested by Mallal et al. [11] Out of 1956 HIV-infected patients from 19 countries, the prevalence of HLA-B*57:01 was 5.6%. The positive predictive power of HLA-B*57:01 was 47.9% (i.e., out of 100 people who are HLA-B*57:01 positive, 48 will develop the abacavir HSR). The negative predictive power was 100%, indicating that no subjects developed the abacavir HSR who were not HLA-B*57:01 positive [11]. As such, when a patient tests negative for HLA-B*57:01, they can safely be administered abacavir, as there is no chance they will develop the abacavir HSR. In those patients who test positive for HLA-B*57:01, abacavir should be withheld. To this end, HLA-B*57:01 screening has become the standard of care for all abacavir-naïve individuals before initiating therapy [17].

In 2008, the United States Food and Drug Administration (FDA) approved a change in the abacavir package insert that recommended HLA-B*57:01 screening for all patients prior to abacavir initiation, regardless of race or ethnicity [18]. Similar recommendations were made by the Department of Health and Human Services (DHHS) Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, the European Medicines Agency, and the Clinical Pharmacogenetics Implementation Consortium (CPIC). CPIC guidelines recommend that HLA-B*57:01 screening be performed in all abacavir-naïve individuals before initiating therapy. Noncarriers of this polymorphism can be initiated with abacavir therapy in recommended doses. Carriers of HLA-B*57:01 should not be prescribed abacavir except under exceptional circumstances when potential benefits outweigh the risks [16,19]. Medical records of HLA-B*57:01-positive patients should clearly indicate that the patient is allergic to abacavir to avoid future administration of the drug.

There are a number of reasons why HLA-B*57:01 screening has been successful. First, HIV care providers comprise a relatively small group of clinicians who are largely accessible through publications and conference presentations. This is not typically the case for larger groups of clinicians such as those treating patients with diabetes or cardiovascular disorders. Second, most HIV clinicians are already familiar with the use of genetic tests to interpret viral resistance panels; therefore, they may be more amenable to incorporating an additional genetic screening test into clinical practice. Third, the HLA-B*57:01 screening test is simple to interpret: if it is positive, abacavir should not be administered. In addition, because HLA testing for abacavir HSR does not involve complex dose adjustments or knowledge of multiple polymorphisms, its implementation is straightforward and easily adopted [20]. Although it depends on specific policies and plans, most third-party payers will cover HLA-B*57:01 screening for HIV-infected patients who may be starting abacavir therapy.

A study was carried out to assess the economic efficiency of prospective HLA-B*57:01 screening in ARV-naïve patients, using a 60-da decision tree model. Prospective HLA-B*5701 testing cost an additional US$17 per patient, and prevented 537 HSRs per 10,000 patients. Based on these results, the authors recommended that abacavir screening is economically viable and should become the standard of care [21]. Additional studies in the United States and other countries have also concluded that HLA-B*5701 screening is cost effective and should be performed as a part of standard care [14,22,23]. HLA-B*57:01 testing for the abacavir HSR represents an accessible, cost-effective example of successful implementation of pharmacogenetic testing in clinical practice.

Because HLA-B*5701 screening has a 100% negative predictive potential and is economically feasible (considering the high cost of treating a single case of abacavir HSR), it represents a widely accepted example of successful pharmacogenetic testing in clinical practice.

Tenofovir

Tenofovir disproxil fumarate (TDF) and tenofovir alafenamide are prodrugs of the NRTI tenofovir. Tenofovir is combined with other ARVs to treat patients with HIV. It is also used for pre- and post-HIV prophylaxis (PrEP and PEP, respectively) [24]. Tenofovir has a long intracellular half-life and is largely excreted unchanged in the urine by glomerular filtration and tubular secretion [25]. Although tenofovir is generally safe, it has been associated with increases in serum creatinine and modest reductions in creatinine clearance [24].

In a systematic review and metaanalysis, it has been reported that TDF-containing regimens significantly increased the risk of acute renal failure in a small number of patients (risk difference, 0.7%, 95% confidence interval [CI], 0.2–1.2). There was a trend toward greater degree of TDF-associated renal function loss in ARV-experienced patients compared to ART-naïve patients (Mean decrease in glomerular filtration rate (GFR), −2.50 vs. −5.15 mL/min; difference in TDF-associated renal function loss, 2.92 mL/min; 95% CI, 6.02 to −0.18 mL/min) [26]. Rarely, Fanconi Syndrome, which is characterized by loss of electrolytes, amino acids, glucose, and reduction in creatinine clearance, has been reported in patients receiving tenofovir (<0.1% incidence) [27]. Renal toxicity is observed more commonly when tenofovir is combined with other nephrotoxic agents or HIV-protease inhibitors. Long-term consequences such as bone demineralization due to calcium and phosphate wasting is a concern with tenofovir therapy [28].

Tenofovir is transported (20%–30%) into renal epithelial cells via organic anionic transporters (OAT) OAT1 (solute carrier [*SLC*]*22A6*) and OAT3 (SLC*22A8*). It is then secreted into the tubular lumen through multidrug-resistant proteins (MRPs). MRP2 and MRP4, encoded by *ABCC2* and *ABCC4*, respectively, were associated with renal toxicity secondary to tenofovir in several reports [29–33]. In vitro studies suggest that tenofovir is secreted by MRP4. The reported association between MRP2 and tenofovir-induced renal tubulopathy is unclear [28]. One theory is that an unidentified factor secreted by MRP2 potentiates tenofovir-induced tubulopathy. An alternative proposal is that the ABCC2 haplotype may be in linkage disequilibrium with polymorphic genes that encode an unidentified factor that might play a role in tenofovir-induced tubulopathy [28].

Kiser et al. investigated the relationship between intracellular tenofovir concentrations and [34]genetic polymorphisms in ABCC2 and ABCC4. ABCC4 3463 A>G was significantly associated with 35% higher intracellular concentrations of tenofovir compared to the ABCC4 wild-type gene ($P = .04$) [31]. In another study by the same group of investigators, the relationship between single-nucleotide polymorphisms (SNPs) that encode for renal proximal tubule efflux transporters and tenofovir pharmacokinetics was assessed. Carriers of the ABCC4 3463G variant had renal clearance values 15% lower, and area under the concentration-versus-time curve (AUC) values 32% higher compared to wild-type patients ($P = .05$). In addition, urinary excretion of tenofovir was 19% higher in ABCC2 24T carriers compared to wild type ($P = .04$) [35]. In a recent study conducted in a Thai patient population, patients carrying the ABCC4 4131T>G variation (genotype TG or GG) had on average, 30% higher plasma tenofovir concentrations compared to patients carrying the TT genotype ($P = .072$), although this did not reach statistical significance. When a middose concentration of tenofovir >160 ng/mL was used as a cutoff for risk of renal toxicity, all patients with the ABCC4 4131T>G variation

(genotype TG or GG) had concentrations above this cutoff value and were potentially at higher risk for developing renal toxicity [34].

Pushpakom et al. [36] assessed the influence of ATP-binding cassette subfamily C member 10 (*ABCC10)* (which encodes for MRP7) genetic variants on kidney tubular dysfunction using ABCC10-transfected human embryonic kidney (HEK)293 cells and cluster of differentiation (CD)4+ cells of monocyte derived macrophages. Results from this in vitro study revealed that tenofovir is a substrate for MRP7, and two ABCC10 SNPs (rs9349256 G>A, and rs2125739 C>T) and their haplotypes were significantly associated with tubular dysfunction ($P < .05$). In addition, rs9349256 was associated with microglobinuria and urine phosphorus wasting ($P = .04$ and .02, respectively). Results from this study suggest that ABCC10 genetic variants may contribute to renal tubular toxicity with tenofovir. Further study in humans is necessary to confirm or refute these preclinical findings [36].

An observational study conducted in a cohort of 500 patients receiving tenofovir assessed the influence of genes previously reported to be associated with tenofovir renal toxicity; these included ABCC2 (rs2273697; G>A) and ABCC4 (rs899494 C>T). Neither of these genetic variants were significantly associated with rates of tenofovir discontinuation. Of note, the final cyclooxygenase analysis identified low body weight (<60 or 60–69 kg) as a risk for tenofovir discontinuation [37].

Tenofovir-induced tubulopathy and its long-term impact on bone health are concerns for individuals receiving this drug for PrEP, PEP, Hepatitis B, or as a part of cART. Although ABCC4 3463 A>G has been significantly associated with renal tubular toxicity in patients receiving tenofovir, development of this condition is generally slow in onset and can be monitored for by periodically assessing measures of renal function such as serum creatinine, blood urea nitrogen, electrolytes, and urine protein. The tenofovir manufacturer states that in patients with creatinine clearances (CrCl) 30–49 mL/min, tenofovir should be dosed at 300 mg every 48 h; in patients with CrCl 10–29 mL/min, tenofovir should be dosed at 300 mg every 72 or 96 h. In patients undergoing hemodialysis, tenofovir should be dosed 300 mg once weekly or after a total of 12 h of dialysis [38]. Currently, data are insufficient to support pharmacogenetic testing (i.e., ABCC4) to identify patients at risk for renal tubular toxicity with tenofovir. Until more data become available, clinicians are advised to carefully monitor renal function in patients receiving tenofovir and adjust tenofovir dosing if indicated.

Zidovudine

Zidovudine, also known as azidothymidine (AZT), was the first antiviral to be approved for the treatment of HIV. Although no longer a first-line agent, zidovudine is still used in combination with other ARVs for the treatment of HIV [39]. Zidovudine is an NRTI that undergoes intracellular phosphorylation reactions to eventually yield zidovudine-triphosphate (zidovudine-TP), which is the active moiety of the drug [40]. Zidovudine is largely renally eliminated as parent compound and inactive metabolites; it also undergoes glucuronidation primarily by uridine diphosphate glucuronosyltransferase (*UGT)2B7* [41]. Individuals with the UGT2B7 polymorphism UGT2B7*1C had a mean zidovudine clearance value that was 196% higher compared to individuals who did not possess the variant [42]. In a pharmacogenetic study of zidovudine, Anderson et al. observed elevated intracellular concentrations of zidovudine-TP in carriers of the *ABCC4* G3724A variant. There was a 49% increase in zidovudine-TP intracellular concentrations in individuals with at least one variant allele (AG or AA) compared to wild-type (GG) individuals ($P = .03$) [43]. Nonetheless, data are limited and there is still not a well-defined relationship between zidovudine-TP concentrations and efficacy or toxicity. As a result, pharmacogenetic testing for zidovudine is not currently indicated and any future role is highly unlikely.

Lamivudine

Lamivudine is an NRTI that is used in combination with other ARV agents for the treatment of HIV infection. Lamivudine undergoes rapid oral absorption and is largely excreted in the urine (approximately 70%) as unchanged drug [44]. Lamivudine is a substrate for three types of organic cation transporters (OCT), OCT1 (SLC22A1), OCT2 (SLC22A2), and OCT3 (SLC22A3); it is also transported by breast cancer resistance protein (BCRP) (ATP-binding cassette subfamily G member 2 [*ABCG2*]). Lamivudine-triphosphate (lamivudine-TP) is transported by MRP4 (ABCC4) [42]. Genetic polymorphisms in the genes encoding for these transporters could potentially impact the disposition and pharmacodynamics of lamivudine and/or lamivudine-TP [45–47]. Carriers of the ABCC4 T4131G variant allele had 20% higher lamivudine-TP concentrations compared to wild-type individuals ($P = .004$) [48]. When healthy volunteers were administered 100 mg of lamivudine, the observed difference in lamivudine AUC for various *ABCG2* genotypes was not significant ($P = .85$) [49].

Lamivudine pharmacogenetic data are minimal and do not predict a future role for pharmacogenetic testing with this drug in the future. Moreover, lamivudine has a wide safety margin and dosage adjustments made secondary to pharmacogenetic testing would be unlikely to yield clinically relevant benefits.

NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS

Efavirenz

Efavirenz is an NNRTI with a long terminal elimination half-life of 36–100 h. It is used in combination with other classes of drugs such as NRTIs. The usual recommended adult dose of efavirenz is 600 mg once daily [50]. Plasma concentrations of efavirenz vary widely among individuals and higher plasma concentrations (>4 μg/mL) are associated with central nervous system (CNS) side effects. CNS disturbances with efavirenz include dizziness, and vivid dreams including nightmares, insomnia, and, less frequently, hallucinations. These symptoms are usually mild to moderate in severity, and tend to progressively subside over weeks. Nonetheless, approximately 20% of patients discontinue efavirenz due to persistent adverse CNS effects [51,52].

Efavirenz is metabolized predominantly by cytochrome P450 family 2 subfamily B member 6 (*CYP2B6*) and cytochrome P450 family 3 subfamily A member 4 (*CYP3A4*), and its plasma concentrations are impacted by CYP2B6 genetic polymorphisms, specifically rs3745274 (c.516 G>T) and rs28399499 (c.983 T>C) [53]. Median efavirenz concentrations in individuals with the CYP2B6 516TT genotype, which has been associated with decreased CYP2B6 catalytic activity compared to the wild type, were at least five times higher than both the CYP2B6 516GT and 516GG genotype groups (heterozygous and homozygous wild type, respectively). The median efavirenz concentration for CYP2B6 516GT genotype was 1.2 times higher than that for the 516GG genotype. Out of CYP2B6 polymorphisms, CYP2B6 516GT is the most common (21%–38% allele frequency) [54]. This allele is more common in Sub-Saharan Africans (35%–42%) compared to Caucasians (23%–27%) and Asians (15%–18%), which may explain higher efavirenz plasma concentrations in people of African origin [51]. Kwara et al. reported that median efavirenz concentrations in CYP2B6516TT patients were at least five times higher than those with CYP2B6516GT ($P < .001$) and CYP2B6516GG ($P < .001$) genotypes. Other CYP2B6 polymorphisms, which may be associated with increased efavirenz exposure, are CYP2B6 983TC and CYP2B6 15,582CT (rs4803419) [54]. Swart et al. reported the impact of genotype on the plasma levels of efavirenz in 301 South African HIV patients.

Results of a multivariate regression analysis in their study showed that, CYP2B6516 *G>T* and *983T>C* SNPs were the two most significant predictors of efavirenz plasma concentration above 4 μg/mL ($P < .006$), which has previously been associated with efavirenz-associated CNS toxicity [52]. The *NR1I2239-1089T>C* SNP played a minor role ($P = .011$) in explaining variability in efavirenz plasma concentrations [55].

ENCORE1 was a noninferiority trial in HIV-1-infected antiretroviral-naïve adults in 38 clinical sites across 13 countries. ENCORE1 subjects were randomized to receive tenofovir and emtricitabine with either a reduced daily dose (400 mg) or a standard dose (600 mg) of efavirenz. This trial showed that efavirenz 400 mg was noninferior to 600 mg in terms of viral growth suppression and $CD4^+$ cell counts, although CNS adverse effects were lower in the efavirenz 400 mg group. HIV-RNA < 200 copies/mL at week 48 of treatment was achieved in 94% of 321 subjects in the efavirenz 400 mg group compared to 92% of 309 subjects in the efavirenz 600 mg group (difference: 1.85; 95% CI: −2.1 to 5.79). $CD4^+$ cell counts were significantly higher in the efavirenz 400 mg group compared to the efavirenz 600 mg group (mean difference: 28 cells/μL; 95% CI: 8 to 48, $P = .01$). Adverse events in the efavirenz 400 mg group were reported in 37% of subjects compared to 47% of subjects in the efavirenz 600 mg group (difference: −10.5; 95% CI: −18.2 to −2.8, $P = .08$) [56].

Ribaudo et al. assessed the relation between CYP2B6 genotypes and plasma efavirenz concentrations after treatment discontinuation in 152 subjects. Plasma efavirenz concentrations were predicted to exceed the estimated protein binding–adjusted 95% inhibitory concentration (IC_{95}) for wild-type HIV virus (46.7 ng/mL) for a median of 5.8 days (interquartile range [IQR]: 4.4–8.3 days), 7.0 days (IQR: 5.0–8.0 days), and 14 days (IQR: 11.1–21.1 days) in CYP2B6 516GG (homozygous wild type), GT (heterozygous mutant) and TT (homozygous mutant) genotypes, respectively ($P < .001$). This is potentially problematic in CYP2B6 516TT individuals who simultaneously discontinue an efavirenz-containing cART regimen. If coadministered medications (NRTIs and/or PIs) with short half-lives are discontinued at the same time as efavirenz, efavirenz plasma concentrations (>46.7 ng/mL) would be expected to persist after the other medications are eliminated; thereby resulting in virtual monotherapy with efavirenz. Such a scenario could place patients at risk for the development of HIV-resistance mutations and virologic failure. The authors recommended that NRTIs and PIs with shorter half-lives be continued for a period of time after discontinuation of efavirenz in carriers of CYP2B6 516TT. This study highlights the potential role for CYP2B6 genotyping when efavirenz-containing cART regimens are discontinued [53].

In a retrospective study involving 191 Spanish patients receiving efavirenz 600 mg daily, doses were reduced in 31(16%) subjects. In subjects with the CYP2B6 516TT genotype, the efavirenz dose was reduced to 200 mg. The dose reduction resulted in decreased CNS adverse effects, effective virological control, and an average cost savings of 43,539 Euros per year [57]. Shackman et al. studied the cost-effectiveness of CYP2B6 genotyping in guiding efavirenz dosing in ART-naïve patients in the United States; the investigators used the widely published Cost-Effectiveness of Preventing AIDS complications (CEPAC) microsimulation model. In this model, genotyping strategy was compared to the current standard of care in a simulated cohort of patients receiving efavirenz-based ART as their initial regimen. This simulation study showed that CYP2B6 genotyping reduced lifetime treatment cost and marginally increased quality-of-life years (QUALYs) compared to standard care. This held true even if lowering efavirenz doses resulted in suboptimal control of HIV replication. Differences in QUALYs between the groups were negligible, suggesting that genotyping is a preferable option that results in a cost-effectiveness threshold of $100,000/QALY [58].

Next to abacavir, efavirenz has the strongest data supporting the use of pharmacogenetic testing to optimize therapy. CYP2B6 genotyping appears to be a cost-effective approach to improving efficacy—especially during efavirenz discontinuation—while reducing CNS-mediated adverse effects.

Nevirapine

Nevirapine is an NNRTI indicated for use in combination with other ARV agents for the treatment of HIV-1 infection [59]. Nevirapine is metabolized by CYP2B6 into 3- and 8-hydroxynevirapine, and CYP3A4 into 2- and 12-hydroxynevirapine [60].

In a study by Schipani and coworkers, pharmacogenetic data was integrated into a population pharmacokinetic (PopPK) model for optimizing nevirapine dosing. The PopPK model was developed with 406 nevirapine concentrations from 275 patients receiving nevirapine for 4 weeks or more. Inclusion of CYP2B6 genetic data improved the model fit and the change in objective function value (OFV) was −27.8, which was significant ($P < .001$). The 516TT genotype was associated with a 37% reduction in nevirapine clearance compared to wild type. The 516GT genotype was associated with a 15% decrease in clearance compared to patients expressing wild-type CYP2B6. The impact of 983T>C was also significant ($\Delta OFV = -9.4$, i.e., $P < .005$), with heterozygotes for this allele having a 40% lower clearance compared to wild type [61]. A study by Penzak et al. reported the impact of genetic polymorphisms of CYP2B6 G516T on nevirapine plasma trough concentrations in 23 HIV-infected patients from Uganda. genotypes at position 516 were expressed by 57%, 26%, and 17% of patients, respectively. The median nevirapine concentration for carriers of the variant allele (TT) was 7607 ng/mL compared to 4181 and 5559 ng/mL for individuals carrying the GG and GT alleles, respectively [62]. Of note, nevirapine trough concentrations were above the [62]target level for therapeutic efficacy (3000 ng/mL) in all three CYP2B6 genotype groups.

An in vitro study showed that the ABCC10 (which encodes for MRP7) expressing HEK cell lines C17 and C18 had significantly lower nevirapine accumulation compared with parental HEK 293 cells that did not express ABCC10. This nevirapine transport process was reversed by the MRP7 inhibitor cepharanthine, thereby confirming the role of MRP7 as a nevirapine transporter. These data were corroborated in a clinical pharmacokinetic and pharmacogenetic analysis in 163 HIV-infected patients of the German Competence Network for HIV/AIDS. Patients who were homozygous for the ABCC10 variant C allele of rs2125739 showed significantly lower nevirapine plasma concentrations compared to those with the heterozygous genotype (4212 vs. 5931 ng/mL; $P = .004$), respectively [63].

A case control study investigated the relationship between ATP-binding cassette subfamily B member 1*(ABCB1),* CYP2B6, and CYP3A4 genotypes and hepatotoxicity with nevirapine or efavirenz containing regimens. Of 201 subjects receiving nevirapine therapy, 14 experienced severe hepatotoxicity. Univariate analysis showed that ABCB1 (formerly MDR1) 3435 C→T polymorphism was associated with reduced likelihood of hepatotoxicity (OR, 0.25; 95% CI, 0.09–0.76). Independently the following genetic polymorphisms did not significantly impact the likelihood of hepatotoxicity: CYP2B6 1459CrT, CYB2B6 516GrT, and CYP3A4 -392ArG ($P > .1$). Multifactorial dimensionality reduction analysis showed an interaction between ABCB1 3435C→T and CYP2B6 1459C→T, which predicted hepatotoxicity status correctly 74% of the time ($P < 0$ 0.001). Similarly, hepatotoxicity risk was predicted by an interaction between ABCB1 C3435T and hepatitis B surface antigen (HBsAg) positivity with 82% accuracy ($P < .001$). The favorable association between ABCB1 3435T and reduced likelihood of hepatotoxicity was lost in the presence of HBsAg positivity [64].

Nevirapine has also been reported to cause immune-mediated skin and liver toxicity in

subjects with higher CD4+ cell counts. Human leukocyte antigen (HLA)-*DRB1∗01:01* and higher CD4+ T-cell percentages predicted rash-associated liver events in white patients, whereas HLA-DRB*1*01:02* predicted liver events among Black Africans. In patients from Sardinia and Japan HLA-*Cw*08* was associated with liver events. Studies from Thailand implicated HLA-B**35:05* and HLA-*Cw*04:01* with isolated skin events. HLA-B**35* and HLA-*Cw*04* were associated with skin events in a large cohort study that included subjects of African, Asian, and European descent. Unlike HLA-B*57:01 testing for abacavir HSR, HLA genetic polymorphism testing for nevirapine had a low negative prediction value for these adverse reactions, thus making these tests impractical in clinical practice [65].

Neither CYP2B6 nor HLA testing is feasible for widespread clinical implementation. Moreover, CYP2B6 genotyping, although associated with nevirapine exposure is not expected to inform nevirapine dosing or improve the safety profile of the drug. Currently, CD4+ counts are measured to determine the risk of hepatic events prior to nevirapine initiation. Women with CD4+ counts >250 cells/mm^3 should not receive nevirapine, as they were shown to have a 12-fold higher risk of symptomatic hepatic events compared to women with CD4+ counts <250 cells/mm^3. Similarly, an increased risk of hepatic adverse events was found in men with CD4+ counts >400 cells/mm^3 [64]. Baseline and frequent monitoring of CD4+ cell counts can help to identify patients at potential risk for hepatic toxicity and guide prescribing decisions.

Etravirine

Etravirine is an NNRTI that is used to treat ARV-experienced HIV-infected patients who harbor resistance mutations to other NNRTIs. It is dosed at 200 mg twice daily [66]. Etravirine is primarily metabolized by CYP3A, CYP2C9, and CYP2C19 [67]. A study was conducted to assess the impact of genetic polymorphisms on the key enzymes involved in etravirine metabolism. Compared to the wild type (CYP2C19*1), carriers of CYP2C19*2 showed a 23% reduction in etravirine clearance ($P = .003$), which explained 5% of the variability in clearance. Similarly, carriers of CYP2C9*3, showed a 21% (95% CI: –6.8–48.3%) reduction in clearance, but the effect was not significant. Pharmacogenetic testing with etravirine is not supported based on the limited data that are currently available.

PROTEASE INHIBITORS

Atazanavir

Atazanavir is indicated in combination with other antiretroviral agents for the treatment of HIV infection [68]. Although no longer recommended for first-line treatment, atazanavir is still a widely used protease inhibitor with long-term efficacy data, low pill burden, and an acceptable tolerability profile. Atazanavir is typically administered as a 300-mg dose boosted with a pharmacokinetic enhancer such as ritonavir or cobicistat. Depending upon a patient's ARV-treatment status (naïve vs. experienced) and ability to tolerate ritonavir, atazanavir may also be given as a single 400-mg dose without a pharmacokinetic enhancer, or in combination with cobicistat. Plasma atazanavir concentrations are markedly higher with boosted regimens compared to 400-mg unboosted regimens [68–70]. Atazanavir is metabolized by CYP3A and is also an inhibitor of CYP3A and UGT1A1, the enzyme responsible for conjugating bilirubin in the liver. As an inhibitor of UGT1A1, atazanavir produces grade 3 hyperbilirubinaemia (>2.5 × upper limit of normal [ULN]) in 40% of treated subjects and grade 4 (>5 × ULN) in 4%–8% of HIV-infected patients taking the drug. Plasma indirect (unconjugated) bilirubin increases from baseline in virtually every patient who takes atazanavir [71]. Although bilirubin increases with atazanavir can result in a jaundiced appearance in some patients, this effect is largely cosmetic in nature [72].

In a study to assess the population pharmacokinetics and pharmacogenetics of ritonavir-boosted atazanavir, 272 atazanavir concentrations from 35 patients were analyzed. Subjects with at least one copy of the (functional) CYP3A5*1 allele (n = 12) had 42% higher atazanavir oral clearance compared to those who did not have at least one CYP3A5*1 allele ($P < .01$) [73]. The influence of ABCB1 polymorphisms were also assessed for their influence of atazanavir disposition. ABCB1 genotypes were found to correlate with the risk of developing severe hyperbilirubinemia in a study of 74 HIV-infected patients. The risk was 24% in subjects with ABCB1 wild-type alleles, but close to zero in patients who were homozygous for the 3435C→T polymorphism. It was proposed that subjects carrying these polymorphic alleles had reduced P-glycoprotein (P-gp)-mediated cellular efflux, thereby leading to elevated intracellular, and lower plasma-drug concentrations [74]. A reduction in plasma concentrations would then explain reduced UGT1A1 inhibition by atazanavir and a lower risk of atazanavir-induced hyperbilirubinemia.

Pharmacogenetic-guided dosing of unboosted atazanavir was assessed for its impact on plasma atazanavir concentrations. Eighty subjects were randomized to receive standard-dose atazanavir (400 mg once daily) or pharmacogenetic-guided atazanavir (400 mg once daily or 200 mg twice daily). Genetic polymorphisms in pregnane X receptor (*PXR*), ABCB1, and SLCO1B1 were assessed. PXR is a nuclear receptor that regulates the expression of several genes involved in drug metabolism and transport. ABCB1and SLC01B encode for P-gp and organic-anion-transporting polypeptide (OATP) 1B1, respectively. Patients were classified into two groups based on their genetic profiles. The groups were labeled as "most favorable" and "least favorable." The "most favorable" group received atazanavir 400 mg once daily and the "least favorable" group received 200 mg twice daily. The geometric mean trough concentration after weeks 4–12 of atazanavir treatment was significantly higher ($P < .001$) in the pharmacogenetic-guided treatment arm (253 ng/mL [150–542]) compared to the standard-dose treatment arm (111 ng/mL [64–190]) [75]. These results are interesting, and suggest that certain patients may benefit from receiving atazanavir 200 mg twice daily versus 400 mg once daily. However, identifying such patients would require pharmacogenetic testing for atazanavir, which is not widely available. Moreover, it would be easier to give patients a boosted atazanavir regimen, which does not require pharmacogenetic testing and yields atazanavir trough concentrations in excess of unboosted regimens (including 200 mg twice daily).

Siccardi et al. analyzed 3 pregnane X receptor (*PXR*) SNPs in relation to unboosted atazanavir trough concentrations in two cohorts. The 3 PXR SNPs were 44,477T→C, 63,396C→T and 69,789A→G. In cohort A, which included 47 white subjects, median C_{trough} was lower for T63396T individuals compared to the other two groups (C63396T or C63396C) (34 ng/mL [IQR, 25–63 ng/mL] vs. 152 ng/mL IQR, 47–388 ng/mL; $P = .001$). The PXR T63396T genotype was associated with atazanavir trough concentrations below the recommended threshold for efficacy in atazanavir-naïve patients (150 ng/mL) with an odds ratio of 18 (95% CI, 2.1–153.9; $P = .008$) [76].

Lubomirov assessed a number of UGT1A1 genetic polymorphisms to assess their impact on premature discontinuation of first-line ARV therapy containing ritonavir-boosted atazanavir. Thirty of 121 patients receiving ritonavir-boosted atazanavir discontinued treatment during the first year of treatment. Homozygosity for reduced function alleles (*28/*28 or *28/*37) was associated with treatment discontinuation risk (adjusted hazard ratio [HR_2] = 9.13, 95% CI: 0.77–5.03) [37]. These data suggest that knowledge of UGT1A1 polymorphisms may inform atazanavir prescribing decisions. Nonetheless, in patients who do not develop noticeable (or cosmetically unacceptable) jaundice, the risk of atazanavir discontinuation is minimal regardless of UGT1A1

genotype. For individuals carrying two copies of reduced function alleles (i.e., homozygous mutants), risk of discontinuation is higher. In heterozygous or homozygous wild-type subjects, risk of atazanavir discontinuation due to hyperbilirubinemia is lower [71]. When UGT1A1 pharmacogenetic information is available prior to atazanavir initiation, patients should be warned about the risks of hyperbilirubinemia according to their genotype.

A simulation study was conducted to determine the cost-effectiveness of UGT1A1 pharmacogenetic testing when choosing a protease inhibitor-containing regimen. The simulation revealed that UGT1A1 testing was not cost-effective in most of the tested scenarios, except when patients were lost to follow-up due to hyperbilirubinemia. In other words, the cost of testing outweighed any potential benefits [77]. Unless further studies confirm the cost effectiveness of UGT1A1 testing to address atazanavir-associated hyperbilirubinemia, it is unlikely to have a role in routine clinical practice.

Lopinavir

Lopinavir undergoes extensive presystemic metabolism by CYP3A. As such, it is co-formulated with the CYP3A inhibitor and pharmacokinetic booster, ritonavir [78]. In a study to assess genetic polymorphisms in the genes that encode for enzymes and transporters involved in lopinavir disposition, the roles of SLCO1B1, ABCB2, and CYP3A were explored. SLCO1B1 encodes for the uptake transporter OATP1B1 and ABCC2 and CYP3A encode for MRP2 and CYP3A, respectively. Overall, only 5% of variation in clearance could be explained by genetic variants; however, in a small subset of patients, these genetic variants had significant impact. Individuals homozygous for SLCO1B1*4 (3%) had a mean lopinavir clearance of 12.6 L/h compared with 5.5 L/h in the reference population ($P < .01$). Patients with multiple variants (13%) of SLCO1B1, CYP3A, and ABCC2 had a mean lopinavir clearance of 3.7 L/h which was significantly lower compared to the reference population ($P < .01$) [78].

The role of SLCO1B1388A→G, 463C→A and 521T→C genetic variants on the disposition of lopinavir were studied. A trend toward increasing concentrations of lopinavir from TT to TC to CC genotypes was observed. It has been proposed that the 521T→C polymorphism is associated with reduced OATP1B1 activity in vivo, resulting in decreased uptake into hepatocytes and higher plasma concentrations of substrates, including lopinavir. There is uncertainty surrounding this interpretation, because there is extensive overlap in plasma lopinavir concentrations across the three 521T→C genotypes, and one of the variants (521CC) was only present in 5% of patients [79].

Genetic polymorphisms appear to explain lopinavir pharmacokinetics in a small subset of the population, but extensive data from large studies are lacking. This, plus the fact that the Department of Health and Human Services (DHHS) no longer recommends lopinavir/ritonavir as a first-line ARV agent to treat ARV-naïve patients [80], strongly suggests that there is not a role for lopinavir/ritonavir pharmacogenetic testing in the future.

INTEGRASE STRAND TRANSFER INHIBITORS

Raltegravir

Raltegravir is the first-in-class integrase strand transfer inhibitor (INSTI), an HIV-1 specific enzyme that is required for viral replication [81]. It is metabolized primarily by UGT1A1 with UGT1A3 and UGT1A9 playing minor roles [82]. Raltegravir is not a substrate of CYP enzymes, but is transported by P-gp and BCRP [83]. Combined data from a cohort study and two clinical trials were analyzed to determine the influence of SNPs in UGT1A, UGT2B, and nuclear receptors

on raltegravir plasma concentrations. In total, 544 raltegravir plasma concentrations from 145 HIV-infected patients and 19 healthy volunteers were analyzed. Higher plasma raltegravir concentrations were observed in one subject who was homozygous for UGT1A9*3; this association reached study-wide significance ($P = .0004$), whereas none of the other SNPs reached study-wide significance [84].

In a study to investigate the role of UGT1A1*28/*28 on plasma raltegravir concentrations, 30 subjects with UGT1A1*28/*28 (homozygous mutant) genotypes and 27 matched subjects with UGT1A1*1/*1 (homozygous wild-type) genotypes were enrolled. UGT1A1*28 homozygotes had a mean AUC from time zero to infinity ($AUC_{0-\infty}$) that was approximately 40% higher than their comparators (geometric mean ratio [GMR]: 1.41; 90% CI, 0.96–2.09). The magnitude of this increase was modest and the CI included 1.0; therefore, the results are not deemed statistically or clinically significant [85].

Tsuchiya et al. investigated the impact of ABCB1 (P-gp) and ABCG2 (BCRP) polymorphisms on peak (2–4 h post-dose) and trough (predose) plasma concentrations of raltegravir in Japanese patients. Thirty-one trough and 41 peak concentrations were collected in 20 patients. All patients were receiving raltegravir 400 mg twice daily as part of cART. Raltegravir trough concentrations were not impacted by any of the ABCB1 or ABCG2 polymorphisms. Conversely, significantly higher mean peak raltegravir concentrations were observed in carriers of ABCB1 4036 AG/GG versus AA (3466 ± 3174 ng/mL vs. 1628 ± 1878 ng/mL; $P = .03$). None of the other ABCB1 polymorphisms (1236 C>T, 2677 G>T/A, or 3435 C>T) significantly impacted raltegravir peak concentrations. Plasma concentrations of raltegravir were also noted to be higher in carriers of ABCG2 421 CA/AA versus ABCG2 421CC (3576 ± 3488 vs. 1702 ± 1572 ng/mL; $P = .03$) [86]. Increased peak raltegravir concentrations were postulated to be due to reduced intestinal expression of P-gp and BCRP in individuals with ABCB1 4036 AG/GG and ABCG2 421 CA/AA genotypes (heterozygous and homozygous variant alleles, respectively). Because raltegravir peak concentrations have not been shown to be associated with efficacy or a particular toxicity, the clinical relevance of these findings appears minimal.

Dolutegravir

Dolutegravir is an integrase strand transfer inhibitor (INSTI) indicated in combination with other antiretroviral agents for the treatment of HIV-1 infection [87]. dolutegravir has a terminal elimination half-life of 12 h and can be given as a part of a once-daily single-dose regimen without pharmacokinetic boosting [88]. Dolutegravir is predominantly metabolized by UGT1A1, with CYP3A4 playing a minor role [89].

To assess the impact of UGT1A1 polymorphisms on the disposition of dolutegravir, pooled data from nine Phase I and II clinical studies was assessed in 89 subjects receiving dolutegravir 50 mg daily. Subjects were categorized as having low (*28/*28 and *28/*37), reduced (*1/*6, *1/*28, *1/*37, *28/*36, and *36/*37) or normal (*1/*1 and *1/*36) UGT1A1 activity. In subjects harboring low-activity UGT1A1 polymorphisms, dolutegravir oral clearance was 32% less compared to subjects with normal UGT1A1 function (GMR: 0.68; 92% CI: 0.54–0.86). When grouped together, subjects with low and reduced UGT1A1 activity had a geometric mean oral clearance that was 23.5% lower compared to subjects with normal UGT1A1 function (GMR: 0.77 [92% CI: 0.66–0.89]) [90]. Despite the observed increase in dolutegravir exposure in patients with low and reduced UGT1A1 activity, the increase was modest and not clinically significant based on accumulated safety data [91]. Therefore, dolutegravir dose adjustments are not necessary based on UGT1A1 polymorphisms.

CONCLUSION

Completion of the human genome project at the turn of the 21st century represented a significant achievement that was made possible via collective international efforts. At that time, it was predicted that in 20 years pharmacogenetic testing would be embraced as the standard of practice for managing a number of diseases [92]. However, nearly two decades later, pharmacogenetic testing is only employed routinely for a small number of medications. This is likely due to the presence of barriers that limit the translation of pharmacogenetic knowledge into clinical practice. These barriers include test-related barriers, knowledge barriers, evidence barriers, and ethical, legal, and social implications [93,94]. In addition, polymorphic genes that have been studied in the setting of HIV are associated with mild–moderate pharmacokinetic changes that do not warrant a change in therapy or dosing. Recently, several genome-wide association studies (GWAS) were conducted to search for novel genetic factors and pathways involved in HIV infection, replication, pathogenesis, and treatment [95]. Most of these studies have centered on virologic response and disease progression. A shift from GWAS to whole-genome sequencing (WGS), along with continued classical candidate gene approaches is poised to allow for the identification of novel genetic variations that impact antiretroviral drug response.

Successful implementation of HLA-B*57:01 testing offers valuable information that can be applied to other medications. HLA-B*57:01 screening was backed by a prospective, double-blind randomized clinical trial (PREDICT-1) that clearly demonstrated the benefit of genetic testing. The clinical interpretation of this test is straightforward, thus making it easy for clinicians to implement into routine practice. Furthermore, the cost-effectiveness of abacavir pharmacogenetic testing also assisted in its widespread implementation.

Another ARV agent for which pharmacogenetic testing may have a future role is efavirenz. Pharmacogenetic testing with efavirenz may improve safety and tolerability of this drug by allowing certain patients to receive doses below the recommended 600 mg. This approach has been shown to potentially result in cost savings. Barriers to the widespread acceptance of pharmacogenetic testing with efavirenz include availability of low-cost testing, turnaround time of tests, lack of education or knowledge of clinicians, and questions surrounding reimbursement.

Much information has been learned regarding pharmacogenetic testing with ARV medications. Despite improvements in ARV treatment over the past 35 years, challenges remain when attempting to optimize therapy in HIV-infected patients. Many antiretroviral agents are metabolized by CYP enzymes, which are susceptible to modulation by coadministered medications. As such, the phenomenon of phenoconversion may result in genotypic extensive metabolizers being converted to phenotypic-poor metabolizers. A similar phenomenon may occur with P-gp-transported medications. As such, the impact of phenoconversion secondary to drug interactions must be taken into account along with pharmacogenetics in HIV-infected patients receiving cART. Indeed, pharmacogenetic testing ± therapeutic drug monitoring of ARV therapy may prove helpful in managing unique populations such as children, pregnant females, those with organ dysfunction, and those on multiple interacting medications.

Inherent barriers to pharmacogenetic testing with ARV medications remain. However, previous success of genetic testing with abacavir, and the need to continually improve the efficacy and safety of ARV medications, indicate that this is a ripe area for continued research. Education of clinicians and development of cost-effective testing are also key factors that must be addressed as part of any pharmacogenetic testing program.

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