Published in final edited form as:

Pharmacogenomics. 2014 November ; 15(15): 1903–1930. doi:10.2217/pgs.14.147.

Pharmacogenomics of antimicrobial agents

Ar Kar Aung¹, David W Haas², Todd Hulgan², and Elizabeth J Phillips^{*,2,3}

¹Department of General Medicine & Infectious Diseases, The Alfred Hospital, Melbourne, Victoria, Australia

²Vanderbilt University School of Medicine, Nashville, TN, USA

³Institute for Immunology & Infectious Diseases, Murdoch University, Perth, Australia

Abstract

Antimicrobial efficacy and toxicity varies between individuals owing to multiple factors. Genetic variants that affect drug-metabolizing enzymes may influence antimicrobial pharmacokinetics and pharmacodynamics, thereby determining efficacy and/or toxicity. In addition, many severe immune-mediated reactions have been associated with HLA class I and class II genes. In the last two decades, understanding of pharmacogenomic factors that influence antimicrobial efficacy and toxicity has rapidly evolved, leading to translational success such as the routine use of *HLA-B*57:01* screening to prevent abacavir hypersensitivity reactions. This article examines recent advances in the field of antimicrobial pharmacogenomics that potentially affect treatment efficacy and toxicity, and challenges that exist between pharmacogenomic discovery and translation into clinical use.

Keywords

antibacterials; antifungals; antimalarials; antivirals; pharmacogenomics

Background

Sources of variation

Antimicrobial agents have dramatically reduced mortality and morbidity from communicable diseases [1,2]. Interindividual variability in treatment efficacy, effectiveness and toxicity is governed by complex relationships between host, microbe and drug factors (Figure 1) [3–5]. Within the human host, antimicrobial agents have distinct pharmacokinetic (PK; absorption, distribution, elimination and metabolism [ADME]) and pharmacodynamic (PD) profiles. Antimicrobials may be eliminated largely unchanged in stool or urine (e.g., vancomycin), or may undergo active metabolism. Drug metabolism is mediated by phase I

enzymes such as oxidative CYP450 (CYP) enzymes or phase II enzymes such as glutathione-*S*-transferases (GST) and UDP-glucuronosyltransferases (UGT), which produce pharmacologically active, inactive or reactive/toxic metabolites. In addition, disposition of many antimicrobials is affected by intestinal, hepatic and renal membrane transporters (Table 1) [6,7]. Individual differences in genes encoding ADME proteins may lead to variable expression and/or activity of these proteins leading to differences in drug exposure. However, whether this translates into clinically relevant differences in efficacy and toxicity depends on other antimicrobial properties such as the therapeutic window and host PD factors [8].

Adverse drug reactions (ADRs) to antimicrobials, as with other drugs, can be clinically and epidemiologically classified as either type A or type B reactions [10]. Type A reactions are related to intrinsic pharmacologic properties of a drug that tend to be predictable based on PK/PD parameters but affected by host ecology and pharmacogenomics (Figure 1). Type B reactions are predominantly allergic or immunologically mediated, which have been commonly classified according to Gell and Coombs (Table 2) [11]. Type I (IgE-mediated reactions, such as penicillin allergy) and type IV (delayed hypersensitivity, largely T-cell mediated) reactions are most relevant to antimicrobials. Recently these have been associated with variation in host MHC molecules and T-cell receptors, via hapten and nonhapten pathways [12]. Increasing evidence suggests that specific MHC class I *HLA-B* alleles in particular may predispose to severe T-cell mediated drug hypersensitivity [13].

Pharmacogenomics of antimicrobial agents have helped to define the pathophysiology of antimicrobial treatment response and toxicity, but full translation into clinical practice has not been realized. There are examples of antimicrobial drugs that have either not been further developed or withdrawn from the market due to severe toxicities. Preclinical prediction of such toxicity and pharmacogenomic variation would ultimately result in more efficient drug discovery and design, and safer and more efficacious therapies. This manuscript reviews advances in antimicrobial pharmacogenomics with emphasis on genetic factors that affect antimicrobial PK/PD, efficacy and toxicity. Microbe virulence/resistance factors and host immune responses are also important in understanding variable responses to infectious diseases (Figure 1), but are beyond the scope of this review.

Overview

Key genes that have been associated with variation in efficacy and toxicity of various antimicrobial classes/agents are summarized in Tables 3–5. The more recent and significant findings are discussed in detail below.

Antibacterial agents

Amoxicillin-clavulanate hepatotoxicity

Amoxicillin-clavulanate (AC) drug-induced liver injury (DILI) represents approximately 14% of all DILI cases [141] and is thought to be mainly due to the clavulanate component [142]. This affects approximately 1 in 1000 to 1 in 10,000 patients treated with AC [103]. Manifestations are heterogeneous, with a predominantly cholestatic pattern in up to 47% of

cases but hepatocellular and mixed patterns are also common [104,143]. Fulminant hepatic failure requiring transplantation is rare, and biochemical abnormalities usually resolve without long-term consequences. The mean age of onset for AC-DILI is between 55 and 65 years [104,105,143], with mean time to onset 2 weeks after initiation of treatment [104–106,143].

Mechanisms underlying AC-DILI are unclear although immunologic reactions due to drug hapten presentation via MHC molecules have been proposed [103]. Early studies in Europeans showed associations between *HLA-DRB1*15:01-DQB1*06:02* haplotype and increased risk of AC-DILI [103,105,106]. This finding was further supported by a recent genome-wide analysis study in individuals of Europeans descent that showed a strong association between AC-DILI and MHC class II SNP rs9274407, which correlated with rs3135388, a tag SNP of *HLA-DRB1*15:01-DQB1*06:02* ($p = 4.8 \times 10^{-14}$) [104]. Individuals with homozygous alleles for this haplotype may be at even higher risk (odds ratio [OR]: 35.54; relative risk [RR]: 8.68; $p < 1 \times 10^{-8}$) [106]. Independent associations were also observed for the MHC class I region, rs2523822, which correlated to *HLA-A*02:01* ($p = 1.8 \times 10^{-10}$) [104]. However, considering the population frequency of the *HLA-DRB1*15:01-DQB1*06:02* haplotype in northern Europeans and the relatively infrequent occurrence of AC-DILI, MHC associations are likely not the only factors responsible for this condition [106]. Interestingly, as opposed to cholestatic AC-DILI in northern Europeans, a recent Spanish study found that a hepatocellular pattern of AC-DILI predominated in southern Europeans, with statistically significant associations with MHC class I alleles *HLA-A*30:02* and *HLA-B*18:01* (OR: 6.7 and 2.9, respectively) [107]. These patients with hepatocellular injury were younger (mean age 54 years) and more likely to be males. Other data suggest that *HLA-DRB1*07* may be protective [105].

Flucloxacillin hepatotoxicity

The anti-staphylococcal β -lactam flucloxacillin is primarily associated with cholestatic hepatitis. Flucloxacillin DILI is rare (approximately 8.5 per 100,000) with onset between 1 to 45 days after initiation of therapy [144]. The DILIGEN study examined genome-wide associations in 51 cases of flucloxacillin DILI and 282 matched controls, and found the strongest association in the MHC region for rs2395029, corresponding to *HLA-B*57:01* ($p = 8.7 \times 10^{-33}$) [110]. Further analysis of flucloxacillin DILI cases and flucloxacillin-tolerant controls showed that *HLA-B*57:01* (rs2395029) was associated with an 80-fold increased risk for DILI (OR: 80.6; 95% CI: 22.8–284.9) [110].

The immunologic basis for *HLA-B*57:01* restricted activation of flucloxacillin-specific cytotoxic CD8⁺ T-cell clones has also been demonstrated *ex vivo*, with activation occurring in a labile pharmacological interaction (p-i) manner [145,146]. Similar to amoxicillin-clavulanate, very few patients who carry the implicated allele or allele pairing develop hepatitis. Therefore, routine *HLA-B*57:01* genotyping before prescribing flucloxacillin is currently not feasible as screening of almost 14,000 individuals would be required to prevent one case [268]. However, *HLA-B*57:01* genotyping may be used to implicate flucloxacillin as the cause of severe cholestasis when other causes are possible [147].

Proton pump inhibitors & *Helicobacter pylori* eradication

Proton pump inhibitors (PPIs) are combined with anti-bacterials to treat *H. pylori*-induced gastritis and peptic ulcer disease. They inhibit gastric acid secretion and raise intragastric pH, which makes *H. pylori* more susceptible to antimicrobial effects [148]. However, >20% of patients fail eradication therapy [149], likely owing to a combination of antimicrobial resistance and host factors.

All PPIs are extensively metabolized by CYP2C19 and CYP3A4, except for rabeprazole, which primarily undergoes nonenzymatic metabolism [150]. Plasma exposure differs between PPIs owing to different rates of CYP2C19 autoinhibition by metabolites. For example, omeprazole and esomeprazole metabolism by CYP2C19 produces sulfones, which in turn strongly inhibit CYP2C19, leading to nonlinear increases in area under the curve (AUC) with repeated administration [151]. *CYP2C19* polymorphisms that define genotypes/phenotypes are provided in Table 3 [152–154]. Intermediate metabolizer phenotypes are heterozygous for rapid and poor metabolizer alleles.

Recent meta-analyses suggest an effect of *CYP2C19* genotype on *H. pylori* eradication rates, particularly with omeprazole, but inconsistently with lansoprazole. Genotype status likely has no significant influence on eradication rates with rabeprazole and esomeprazole [49–51]. However, the choice of PPI and dosing strategy (twice daily versus once daily) may be important in overcoming the effect of *CYP2C19* genotype [51].

Aminoglycoside ototoxicity

All aminoglycosides can cause ototoxicity with bilateral high frequency sensorineural hearing loss, especially with prolonged treatment [124,125,155–157]. Several mitochondrial 12sRNA mutations (Table 5) have been associated with aminoglycoside-induced sensorineural deafness, especially a nucleotide A-to-G transition at position 1555 (1555A>G), although other factors such as cumulative dose and duration of therapy contribute [125,126,157]. In clinical practice, predisposing mitochondrial mutations are not routinely screened for before prolonged prescribing of aminoglycosides (e.g., for treatment of multidrug-resistant tuberculosis). However, a family history of hearing loss should be elicited and aminoglycosides used with caution in those with a positive history.

Linezolid toxicity

Linezolid, an oxazolidinone antimicrobial used to treat multiresistant Gram-positive infections, binds to the 23S ribosome and prevents 30S–50S fusion in bacteria. There is evidence that major toxicities with linezolid, including optic and peripheral neuropathies, myelosuppression and hyperlactatemia, are mediated through inhibition of mitochondrial protein synthesis and hence mitochondrial mutations may play a role in genetic predisposition to these toxicities [158–162].

Trimethoprim-sulfamethoxazole hypersensitivity in HIV patients

Trimethoprim-sulfamethoxazole (TMP-SMX) has been associated with hypersensitivity reactions of varying severity including generalized exanthem, drug reaction with eosinophilia, and systemic symptoms (DRESS)/drug-induced hypersensitivity reaction

(DIHS) and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN). Mild to moderate rash has been reported to affect up to 34% of HIV-infected patients with active HIV viremia [163]. Patients with HIV infection who develop TMP-SMX hypersensitivity in the setting of acute *Pneumocystis jiroveci* treatment and uncontrolled HIV-1 viremia will commonly tolerate TMP-SMX at lower prophylactic doses, and with subsequently suppressed HIV-1 replication on antiretroviral treatment, suggesting a role of immune activation. Although nearly 60% of HIV-infected patients who experienced mild to moderate reactions to TMP-SMX will tolerate the drug upon reintroduction [164], a Cochrane review showed that desensitization may result in fewer TMP-SMX discontinuations and side effects [165].

SMX is metabolized by both NAT1 and NAT2, and hypersensitivity reactions are thought to result from the formation of reactive hydroxylamine and nitroso metabolites [166]. *NAT2* slow acetylator genotype status (Table 3) was found at a higher frequency in HIV-positive patients with hypersensitivity to SMX than HIV-positive controls without such reaction (74 vs 56%; adjusted $p = 0.0003$; OR: 2.3) [71]. Interestingly, HIV-infected patients with *NAT2* slow acetylator genotypes may be protected from SMX hypersensitivity reactions by having concurrent gain of function mutations in *NAT1* (carrying *10 and *11 alleles; OR: 0.28; 95% CI: 0.081–0.978; $p = 0.046$) [64].

A study of 14 candidate genes in HIV-infected patients with SMX hypersensitivity (102 cases vs 318 controls) also found significant association with SNP rs76114 2T>G in *GCLC* (adjusted $p = 0.045$) [73]. Heterozygous (TG) and homozygous (GG) are at increased risk compared with TT genotype (OR: 2.2 and 3.3, respectively). *GCLC* is part of *GCL*, a rate-limiting enzyme for formation of glutathione, a key enzyme in phase II conjugation of toxic metabolites. However, no associations have been found for *HLA-DR*, *TNF*, *LTA* and *HSP1A1* gene polymorphisms with TMP/SMX hypersensitivity [167]. A more recent study proposes that SMX elucidates select immune responses through its binding and alteration of critical residues in the CDR2 β loop of a T-cell receptor that contains the domain V β 20-1, which was sequenced from SMX responsive T-cells from patients with hypersensitivity reactions [168].

Dapsone hypersensitivity syndrome

Dapsone has proven efficacy in the treatment of leprosy, and is used in prophylaxis for malaria and *P. jiroveci* infection among HIV-infected patients. Although combined formulation with chlorproguanil (Lapdap) was effective for treating uncomplicated falciparum malaria [169], it was withdrawn from the market in 2008 owing to risk of severe hemolysis in patients with G6PD deficiency, particularly with dapsone [170–172].

Dapsone hypersensitivity syndrome (DHS) is commonly reported among Asians. Patients with DHS often present with fever, lymphadenopathy, generalized rash and hepatitis [173]. It occurs at a mean duration of 28 days after administration and mortality can be up to 10% [173]. *HLA-B*13:01* was confirmed as a risk factor for DHS in a recent genome-wide study involving 872 Han Chinese patients treated for leprosy (39 DHS vs 833 controls; OR: 20.53; $p = 6.84 \times 10^{-25}$; localizing to SNP rs2844573) [108].

Antituberculous drugs

Isoniazid (INH), rifampicin, pyrazinamide and ethambutol remain the mainstay of treatment for drug-sensitive tuberculosis. However, of all the antituberculous drugs, only isoniazid pharmacogenomics have been extensively studied [60–63,65 – 67,72,174–182].

INH hepatotoxicity

INH can cause hepatotoxicity in 1–30% of patients and this risk increases with coadministration of rifampin [62,183]. INH DILI manifests within 3 months of drug administration and can present with gastrointestinal symptoms, transaminitis, cholestasis or even isolated jaundice in some cases. Mortality may reach 10% [62]. NAT2, CYP2E1, GSTM1 and GSTT1 are the extensively studied enzymes in INH DILI (see Figure 2 for INH metabolism).

NAT2

Several studies have examined the associations between genetic polymorphisms in NAT2 and the risk of hepatotoxicity across different ethnicities [60,62,65–67,174,176]. NAT2 polymorphisms that define its phenotypic acetylator status are shown in Table 3 [62,174]. Intermediate acetylators carry one fast and one slow acetylator allele. Three recent meta-analyses, which included different ethnic populations showed that slow acetylator genotypes were significantly associated with hepatotoxicity (range of OR: 1.93–4.69) [60,66,67], although the meta-analysis by Wang *et al.* showed no difference in DILI rates between intermediate and rapid acetylators [67]. Subgroup analyses further demonstrated that this risk extended to all ethnic groups except Caucasians, who were under-represented [60]. A study of efavirenz and rifampin-based regimens in an Ethiopian population coinfecting with HIV and TB (41 cases vs 160 controls) also showed increased risk of DILI with slow acetylator genotypes ($p = 0.039$), possibly resulting from three-way interactions between INH, rifampin and efavirenz [183].

A randomized, controlled trial involving 172 Japanese patients with tuberculosis compared the outcomes of pharmacogenomics-guided INH dosing regimens (2.5 mg/kg for slow acetylators, 5 mg/kg for intermediate acetylators and 7.5 mg/kg for fast acetylators) to a standard treatment regimen (5 mg/kg). This study found that pharmacogenomics-guided INH dosing was associated with lower treatment failure rates in rapid acetylators receiving higher doses (15 vs 38%; RR: 0.379; 0.097–0.776; $p = 0.015$) and lower risk of hepatotoxicity in slow acetylators receiving lower doses (0 vs 78%; RR: 4.5; 95% CI: 1.3–1.53) [65].

Others

Table 3 summarizes other important genetic associations with INH DILI. The evidence for CYP2E1 polymorphisms has been conflicting [60, 62,174,177,184]. While some studies, including a meta-analysis, showed that **1A/*1A* genotype was associated with increased risk of INH DILI, particularly in combination with NAT2 slow acetylator status [61,66,177], other studies have not replicated the same findings [176,178], or significant association was found only in east Asians [60]. Variant CYP2E1*6 allele and **1A-*6 - *1D* haplotype were

also shown to be associated with increased risk of INH DILI [63] but *CYP2E1*1C* polymorphisms were not [179].

Associations between *GSTM1* null genotype and INH DILI were also shown in a recent meta-analysis [60] but such associations may be ethnicity specific [60,63,72]. *GSTT1* null genotype, on the other hand, was not associated with hepatotoxicity in different ethnic populations [60,62,175]. Other interesting associations with INH DILI include polymorphisms in minor variant allele A (AG or AA genotypes) of TNF- α gene in Korean patients [182], mitochondrial MnSOD 47T>C mutation in Taiwanese patients [72], absence of *HLA-DQA1*01:02* and presence of *HLA-DQB1*02:01* in Indian patients [181], and lack of association with genetic polymorphisms in *CES1*, 2 and 4 genes in Asians and Caucasians from Canada [180]. The relevance and practical applications of these findings remain uncertain.

INH peripheral neuropathy

Few studies have examined the risk of developing peripheral neuropathy with polymorphisms in enzymes involved in INH metabolism. Previous small studies showed that *NAT2* slow acetylators seemed to be at higher risk [62,68,69]. Genotyping of sural nerve biopsy samples in five Japanese patients with INH neuropathy found *NAT2* slow acetylator genotype status in all five, although no controls were included [70].

Antifungal agents

Voriconazole

Voriconazole undergoes elimination primarily by CYP2C19 (Table 3) and plasma voriconazole levels were found to be three-times higher in *CYP2C19* poor metabolizers and two-times higher in intermediate metabolizers compared with rapid metabolizers [52,185,186]. More recently younger age and gain-of-function alleles (*CYP2C19*17*) have been associated with subtherapeutic voriconazole concentrations suggesting higher dose requirements in some populations [187]. In those who lack CYP2C19 activity, secondary metabolism by CYP3A4 may become more important. Although *CYP3A4* polymorphisms do not influence voriconazole metabolism, coadministration with medications that inhibit CYP3A4 may lead to increased risk of toxicity [185,186]. Efflux pumps (MDR1/P-gp polymorphisms such as 3435C>T) may also play important roles in voriconazole elimination [52,186].

Hepatotoxicity is a complication of voriconazole treatment, possibly related to high trough plasma concentrations [188]. However, very little clinical pharmacogenomics data exist for correlations between *CYP2C19* genotypes and phenotypic manifestations of hepatotoxicity. A study by Levin *et al.* and also another small Japanese study of 29 patients found that hepatotoxicity (predominantly cholestasis followed by hepatitis patterns) was associated with high trough voriconazole concentrations but no discernible *CYP2C19* genotype association was noted [53,54]. Nevertheless, the latter study proposed pharmacogenomics guided initial dosing of voriconazole to attain favorable PK parameters [54]. A more recent study by Zonio *et al.* also found that genotypes did not influence voriconazole or metabolite levels, and hence toxicity significantly [57].

In addition, *CYP2C19* genotypes and polymorphisms in the PDE6 enzyme have been implicated in the development of visual side effects with voriconazole, although further studies are needed in this area [55,189].

Antimalarial agents

Malaria remains a major cause of mortality in many regions of the world. The WHO recommends four different artemisinin combination therapies for treatment of uncomplicated *Plasmodium falciparum* infection in adults (Table 6) [190], while primaquine remains the primary agent for eradicating intrahepatic hypnozoites of *Plasmodium vivax* and *Plasmodium ovale*. Major metabolic pathways for antimalarial agents include CYP2A6 for artesunate, CYP2B6 and CYP3A4 for other artemisinins, CYP2C8, CYP1A1 and CYP1B1 for amodiaquine, and CYP2C19 for biguanides [16]. However, pharmacogenomic associations with many antimalarial agents remain theoretical owing to lack of clinical studies in resource-limited settings.

Artemisinins

CYP2A6 plays a major role in metabolizing artesunate to its active anabolite, dihydroartemisinin [16,17], while CYP2B6, CYP1A1 and CYP1A2 play minor roles [19]. Compared to the reference *CYP2A6*1A* allele, approximately 40 gene variants exist, of which at least 13 demonstrate decreased metabolism and three no activity *in vivo* (selected genotypes are listed in Table 3) [191,192]. Variants with little or no enzyme activity may result in artesunate treatment failure and may contribute to emerging artemisinin resistance in Thailand. Clinical studies that correlate *CYP2A6* genotype with artemisinin combination therapy outcomes are needed [18–20]. An impact of *CYP2B6* polymorphisms on artemisinins metabolism remains theoretical, and was not shown in a study involving Cambodians and Tanzanians [44].

Amodiaquine

CYP2C8 converts amodiaquine (AQ) to the non-toxic moiety N-desethylamodiaquine. Quinoneimines (QNMs) are toxic metabolites more likely to be formed from AQ in the setting of *CYP2C8* slow metabolizer genotypes [17]. QNMs cause agranulocytosis and severe liver damage at an incidence of 1:2000 [14]. *In vivo* studies have shown that extrahepatic metabolism by CYP1A1 and CYP1B1 may also generate QNMs, further contributing to agranulocytosis [14,17]. The impact of *CYP2C8* polymorphisms on AQ efficacy and safety warrants further study [15,47,48].

Mefloquine

Mefloquine has a long elimination half-life (15–25 days) and is metabolized to inactive compounds by CYP3A4 [193]. Limited data suggest that P-gp/*ABCB1* polymorphisms (1236, 2777, 3435 CC, CG or GG > TT genotypes; OR: 6.3, 10.5 and 5.4, respectively) and 1236–2777–3435TTT haplotype ($p = 0.004$) are associated with neuropsychiatric side effects, particularly in white females [80,81]. Reduced efflux of mefloquine in neural tissues as a result of transporter polymorphisms may explain this association [16].

Biguanides

The biguanides, proguanil and chlorproguanil, are converted into active antimalarial metabolites, cycloguanil and procycloguanil, by CYP2C19 and less so by CYP3A4 [17]. A study in Gambian adults with uncomplicated malaria showed that ultrarapid metabolizers (*CYP2C19**17 homozygotes) had higher AUC and C_{max} values for these active metabolites [59]. However, other studies showed no association between *CYP2C19* polymorphisms and breakthrough parasitemia, treatment failure, *ex vivo* antimalarial activity or mild adverse events, possible reflecting compensatory metabolism by CYP3A4 (reviewed in [17]).

Other antimalarial agents

Primaquine-induced hemolysis has long been associated with G6PD deficiency, which is common in sub-Saharan Africans (~10–25%) [79]. Other potential associations include P-gp/*ABCB1* polymorphisms with quinine neurotoxicity, OCT-2-related pancreatic insulin secretion in quinine-induced hypoglycemia, *CYP3A5**3/*3 genotype with quinine hydroxylation, and ABC transporter polymorphisms with chloroquine neurotoxicity [16,17]. Pharmacogenomics of lumefantrine and newer agents such as tafenoquine, pyronaridine and piperazine warrant further study.

Antiviral agents

Hepatitis C antivirals

Hepatitis C virus (HCV) affects more than 150 million people worldwide and causes more than 350,000 deaths annually from HCV-related liver disease. The established standard of HCV treatment had been peg-IFN and ribavirin (RBV) combination therapy although contemporary treatment is now moving towards combination therapy with direct acting agents (DAA) and it is likely that in the near future combination DAA regimens that spare both peg-IFN and RBV will be the standard of care. Peg-IFN/RBV regimens are lengthy (24–72 weeks), poorly tolerated and have low response rates in HIV coinfecting patients, particularly with HCV genotype 1 disease. Newer direct acting antiviral agents such as the NS3/4A protease inhibitors boceprevir and telaprevir have been added to peg-IFN/RBV as triple therapy for the chronic HCV mono-infection with markedly improved efficacy, and data from HIV/HCV coinfecting patients are extremely encouraging.

In large genome-wide association studies, genetic polymorphisms in the *IL28B* gene (rs12979860 and rs8099917), which encodes *IL28B*, a IFN- λ 3, have been strongly associated with response to IFN-based HCV genotype 1 therapy, and spontaneous clearance of HCV [92–94] (Table 3). Neither SNP is in a coding region and it is thought that *IL28B* rs12979860CC and rs8099917TT genotypes are associated with low expression of IFN-stimulated genes, which leads to greater induction of these genes with IFN exposure and better treatment response. A functional variant TT/-G polymorphism in the CpG island upstream of *IL28B* has been shown to induce *IL28B* and IP-10 and may better predict HCV clearance than rs12979860 [95]. African-Americans are less likely to have favorable *IL28B* genotypes, which may contribute to their lower response rates to treatment. *IL28B* genotyping may be less predictive in HCV genotype 2 and 3 infections where treatment response rates are much higher than with HCV genotype 1.

For liver transplant patients reinfected with HCV genotype 1, studies have also associated sustained virologic response (SVR) and *IL28B* genotype of both the donor and recipient [194–196]. Emerging data in patients co-infected with HCV (genotype 1 and 4) and HIV-1 have also associated SVR with peg-IFN/ RBV with *IL28B* genotype, including previous non-responders to peg-IFN/RBV [197]. An additional study in Europeans with HCV genotype 1, and reproduced by a Japanese group, found that an unfavorable C2/C2 *HLA-C* genotype in combination with the two *IL28B* SNPs rs8099917 and rs12979860 increased the positive predictive value of nonresponse from 66 to 80% [198,199]. A dinucleotide frameshift variant in rs368234815 (TT or G) has been described, which generated IFNL4, and is in high linkage disequilibrium with rs12979860. The *IFN-γ* gene is largely inactive in human populations due to a frameshift mutation. It represents a paradox by which it exerts antiviral activity yet rs368234815 (G) allele carriers have impaired clearance of HCV and decreased response to HCV treatment [200–203]. Currently DAAs are extremely expensive and drug interactions with HCV/HIV coinfecting patients are complex. Triple therapy of IFN/ RBV with DAAs has been shown to significantly improve the response in nonresponder genotypes. In addition, however, there is evidence that patients with favorable *IL-28B* genotypes continue to have better efficacy and HCV virologic control even in IFN/RBV regimens in combination with DAAs and possibly IFN-free regimens, suggesting that *IL28B* genotype itself may impact viral kinetics [204].

Anemia has been reported in 30–50% of treatment-naïve patients receiving IFN/RBV treatment, with higher rates reported in combination with telaprevir and boceprevir. RBV-associated hemolysis is a major cause of anemia, which is more common in females, older patients, with higher RBV dose and lower baseline hemoglobin. Two variants in the *ITPA* gene (rs1127354 and rs7270101) have been associated with protection against anemia in patients receiving IFN/RBV [96–101]. These minor variant alleles were protective against anemia in patients with HCV genotype 2 and 3 and HIV/HCV coinfection treated with IFN/RBV. Similar protective effects were seen in HCV mono-infected patients treated with telaprevir/pegIFN/RBV. Prospective *ITPA* genotyping is not currently recommended, but could in the future be used with other PK and pharmacogenomic information to guide therapy.

Currently there are no definitive recommendations for *IL28B* genotyping prior to HCV treatment. *IL28B* genotype is currently the strongest available baseline predictor of HCV treatment response for IFN/RBV-containing regimens; however, it is not the only factor for consideration in treating the individual patient [205]. The greatest utility in an era when IFN-based regimens are still used would be to predict likelihood of SVR, which could lead to shortened treatment duration in patients predicted to have a favorable treatment response, or conversely to define which patients should initiate triple therapy, in HCV genotype 1 patients and HIV/HCV coinfecting patients with genotype 1 or 4. Given the high efficacy of new direct acting anti-HCV agents, with rapid movement toward IFN-sparing and RBV-sparing HCV treatment, the above issues may become less relevant over time.

Antiretroviral drugs

Over 25 antiretrovirals have been US FDA approved for combination antiretroviral therapy (ART). In addition, there are four fixed-dose combinations that provide single-tablet once-daily regimens. Recent HIV clinical trials and guidelines have endorsed test and treat strategies, treatment as prevention, and early ART initiation in attempts to reduce transmission and long-term morbidity. With patients remaining on the same ART regimen for >15 years, it is increasingly important to individualize ART to maximize efficacy, effectiveness and safety.

Nucleoside/tide reverse transcriptase inhibitors

The major treatment limiting toxicity of the guanosine analog, abacavir, is drug hypersensitivity syndrome (ABC HSR) that affected 5–8% of participants in clinical trials, and was well characterized during premarketing drug development [111,206]. In 2002, two groups independently discovered an association between ABC HSR and the HLA class I allele *HLA-B*57:01* [112,207,208]. Over the subsequent 6 years and through numerous translational hurdles, a randomized clinical trial confirmed the utility of *HLA-B*57:01* testing to prevent immunologically mediated (defined by ABC patch testing) ABC HSR [209,210]. Keys to translating *HLA-B*57:01* from discovery to guideline-supported implementation included the 100% negative-predictive value of *HLA-B*57:01* for ABC HSR, generalizability of this high predictive value across ethnic groups, the low number of tests needed to test to prevent each ABC HSR case, and the development of cost effective and quality assured laboratory technologies [13,113,211].

Tenofovir disoproxil fumarate is the prodrug of the nucleotide reverse transcriptase inhibitor, tenofovir. As many as 2% of those on long-term tenofovir develop significant declines in creatinine clearance, which is more likely with lower bodyweight, advanced age, pre-existing renal dysfunction, medical comorbidities, advanced HIV disease and concurrent nephrotoxic medications. Tenofovir nephrotoxicity can also manifest as proximal tubular dysfunction without evidence of impaired creatinine clearance. The mechanism of tenofovir renal toxicity has been postulated to reflect direct effects on tubular function or mitochondrial toxicity similar to the related nucleotide analogs, adefovir and cidofovir. Tenofovir is transported into renal proximal tubular cells by organic anion transporters hOAT1 and OAT3, and secreted into the tubular lumen by MRP4. Therefore pharmacogenomic studies of tenofovir toxicity have focused on these influx and efflux drug transporter genes, with inconsistent results (Table 3). Larger studies with more standardized definitions of renal toxicity may clarify the pharmacogenomic basis of tenofovir nephrotoxicity, as well as drug–drug interactions with tenofovir [82–91,212,213]. Drug transporters are also relevant to pre-exposure prophylaxis, as tenofovir may preferentially concentrate in rectal tissue following oral dosing based on mucosal transporter expression [214]. The newer prodrug of tenofovir, tenofovir alafenamide, concentrates in peripheral blood mononuclear cells resulting in lower plasma exposures at one tenth of the dose and potentially less renal toxicity [215].

Thymidine analogs (zidovudine/stavudine) & ‘D drugs’

Many thymidine analog-associated toxicities reflect mitochondrial toxicity mediated through inhibition of host DNA polymerase- γ . This includes lipoatrophy [133–135,216–218], a largely irreversible mitochondrial toxicity associated with stavudine (d4T) more so than with zidovudine, peripheral and other neuropathies (associated with the ‘D drugs’ d4T, didanosine [ddI] and zalcitabine [ddC]) [129,132,138–140,219,220], lactic acidosis [221–228] and metabolic disease [131,134,136,137,229]. Pharmacogenomic associations with these phenotypes are summarized (Table 5). Risk of lipoatrophy is associated with duration of treatment, female gender and lower body mass. Contemporary practice discourages the use of these agents, which has markedly reduced new cases, and WHO guidelines that currently recommend earlier initiation of ART exclude d4T from first-line therapy and suggest use of zidovudine only when tenofovir cannot be used. A recent study in d4T-treated patients from Malawi suggested that certain mtDNA haplogroups may protect against lipoatrophy [230].

Non-nucleoside reverse transcriptase inhibitors

The non-nucleoside reverse transcriptase inhibitors efavirenz and nevirapine have been extensively prescribed for HIV-1 infection worldwide. Efavirenz is metabolized primarily by hepatic CYP2B6, with minor contributions by CYP2A6 and CYP3A4/5 [231,232], and direct *N*-glucuronidation by UGT2B7 [231,233]. At least three *CYP2B6* loss-of-function polymorphisms have been consistently associated with increased plasma efavirenz exposure, 516G>T (rs3745274, *CYP2B6**6, *7, *9 and *13) [24–29], 983T>C (rs28399499, *CYP2B6**16 and *18) [29–32] and 15582C>T (rs4803419, *CYP2B6**1C, *13B and *15A) [29] (Table 3). Greater mean plasma efavirenz trough concentrations with African ancestry than with European ancestry are largely explained by differing frequencies of *CYP2B6* 516G>T. The effect of *CYP2B6* 983T>C on efavirenz concentrations (per C allele) is somewhat greater than that of 516G>T [29], but its frequency is far less and appears to be found only with African ancestry. The effect of *CYP2B6* 15582C>T (per allele) is less than that of 516G>T [29], but its frequency is high with European and Asian ancestry. These three polymorphisms stratify patients into ten plasma trough concentration subgroups across an approximately tenfold range of medians [29]. These polymorphisms explain approximately 35% of inter-individual variability in efavirenz trough concentrations [29]. The top three strata (*CYP2B6* slow metabolizer genotypes) are defined by 516T/T homozygosity, dual 516G/T-983C/T heterozygosity and 983C/C homozygosity. With *CYP2B6* slow metabolizer genotypes, even greater plasma efavirenz concentrations are associated with polymorphisms in minor pathway genes *CYP2A6* (-48T>G, rs28399433) [21,22,234] and possibly *UGT2B7* (homozygosity for 735A>G, rs28365062) [22,23].

While genetic predictors of increased plasma efavirenz exposure are well established, associations between plasma efavirenz concentrations and CNS side effects have been less consistent, reported in some studies [26,235–239] but not others [240–242]. Such inconsistency may relate to inconsistent definitions of CNS toxicity and attenuation of efavirenz CNS symptoms with repeated dosing [237]. In the only double-blinded, placebo-controlled study to specifically assess efavirenz CNS symptoms, efavirenz was significantly

associated with increased CNS symptoms within the first week of treatment, but at week 4 and beyond CNS symptoms did not differ between efavirenz and placebo recipients [237].

Precision efavirenz dosing guided by genetic testing might decrease side effects and drug cost. With *CYP2B6* intermediate or slow extensive metabolizer genotypes, efavirenz could likely decrease from the usual 600 mg daily dose to 400 mg in intermediate metabolizers, and 200 mg in slow metabolizers, without reducing virologic responses [243]. It is reassuring that the lowest *CYP2B6* extensive metabolizer genotype stratum is not at increased risk for virologic failure with 600 mg once-daily efavirenz dosing [244]. By contrast, universal efavirenz dose reduction without genetic screening, as studied in ENCORE1 [245], might increase risk for virologic failure in the lowest *CYP2B6* extensive metabolizer genotype stratum.

ADRs with nevirapine are primarily immune mediated, occur within the first 2 months of therapy, and affect the liver and/or skin. These include mild to moderate skin rash or, less commonly, severe cutaneous adverse reactions such as SJS/TEN or DRESS/DIHS. In a clinical trial from South Africa, in which participants with lower plasma HIV-1 RNA concentrations (i.e., higher CD4⁺ T-cell counts) were stratified to receive nevirapine-containing regimens, 17% of nevirapine recipients experienced grade 3 or 4 liver toxicity, and two died of hepatic failure [246]. Inactivation of nevirapine occurs primarily through hepatic CYP2B6, less so through CYP3A and other isoforms; nevirapine induces its own metabolism (i.e., autoinduction). As with efavirenz, increased plasma nevirapine exposure has been associated with *CYP2B6* loss-of-function variants including 516G>T [26,38,39,247–249], 983T>C [40] and 15582C>T [39]. An association has been reported between nevirapine pharmacokinetics and rash, with 50% increased likelihood of rash for every 20% decrease in plasma nevirapine clearance [250].

Genetic variants that confer increased risk for nevirapine hepatic events differ for those associated with cutaneous events without liver involvement. A seminal study from western Australia implicated *HLA-DRB1*01:01* (HLA class II) and CD4% ≥ 25 with rash-associated hepatic events in a largely Caucasian cohort [251]. A relationship was later reported between *HLA-DRB1*01:02* and nevirapine-associated hepatic events (rash status unknown) in a largely black African cohort [120]. By contrast, studies in Sardinia and Japan implicated *HLA-Cw*08* in hepatotoxicity [116,252]. Regarding nevirapine-associated cutaneous events, studies in Thailand implicated *HLA-Cw*04:01* and *HLA-B*35:05* (HLA class I) [115,121,253]. In a large, retrospective, case-controlled pharmacogenomic study that separately considered severe cutaneous and hepatic adverse events, and separately considered cohorts of Asian, European and African descent [122], cutaneous events were associated with *HLA-Cw*04*, especially among black subjects and Asians, and with *HLA-B*35* among Asians. The *CYP2B6* loss-of-function variant 516G>T was also associated with cutaneous but not hepatic adverse events. Hepatic adverse events were associated with *HLA-DRB1*01* among white subjects, but this allele was infrequent among black subjects and rare among Asians. More recently, SJS/TEN has been associated with *HLA-C*04:01* in a Malawian cohort [123]. Although immune-mediated nevirapine ADRs cannot be reliably predicted by class I or class II HLA associations, implicated HLA alleles may share peptide binding characteristics [254]. The impact of CD4⁺ T-cell count is expected to be greater

with HLA class II mediated hepatic events than HLA class I mediated cutaneous events. This is supported by *in vitro* studies showing that nevirapine-specific CD8⁺ T-cell responses and depletion of CD8⁺ T cells more markedly abrogate nevirapine-specific IFN- γ output than CD4⁺ T-cell depletion [117]. In addition, recent data suggest that high CD4%/count may not significantly increase risk of toxicity when virologically suppressed HIV-positive patients on combination antiretroviral therapy switch to nevirapine-based regimens [255–257]. Data are limited regarding pharmacogenetics of the newer non-nucleoside reverse transcriptase inhibitors, efavirenz and rilpivirine. Loss-of-function *CYP2C19* variants are associated with greater plasma efavirenz exposure [58], but implications for efavirenz prescribing are not known.

Protease inhibitors

Pharmacogenomics relationships have been proposed for many HIV-1 protease inhibitors, but results have been inconsistent and clear efficacy relationships have not been established (Table 3) [41,258–260]. CYP3A4 primarily metabolizes many HIV-1 protease inhibitors, and most also inhibit CYP3A. The potent CYP3A inhibitor ritonavir is frequently used as a PK enhancer to increase exposure of other CYP3A substrate protease inhibitors. Ritonavir and other protease inhibitors are also substrates for the efflux transporter P-gp, and for other drug transporters such as OATP1A2, OATP1B1 and OATP1B3, and somewhat higher lopinavir plasma exposure has been consistently associated with *SCLCO1B1* 521T>C [261,262]. Synthetic PK enhancers lacking antiretroviral activity such as cobicistat have been developed to boost elvitegravir (integrase inhibitor) and HIV protease inhibitors.

Protease inhibitors have been associated with metabolic disturbances, including ritonavir with hypertriglyceridemia. Genetic variants associated with hyperlipidemia in HIV-negative populations appear to be over-represented in patients with hyperlipidemia on protease inhibitor therapy (Table 5) [263,264].

Both atazanavir and indinavir inhibit plasma bilirubin clearance by competing for binding to UGT1A1, resulting in unconjugated hyperbilirubinemia. The magnitude of hyperbilirubinemia is associated with a promoter polymorphism in *UGT1A1* (*UGT1A1**28), that is significantly associated with reduced bilirubin-conjugating activity and unconjugated hyperbilirubinemia [74]. Approximately 6% of patients develop clinically apparent jaundice and studies have suggested a correlation between *UGT1A1* polymorphisms and atazanavir treatment discontinuation [76]. Bilirubin uptake into hepatocytes is also facilitated by OATP1B1 and OATP1B3, and *SLCO1B1* polymorphisms may contribute to unconjugated hyperbilirubinemia with atazanavir [265,266]. A recent genome-wide association study showed that atazanavir-associated hyperbilirubinemia was most strongly associated with *UGT1A1* rs887829 (which is in almost complete linkage with *UGT1A1**28), but with no polymorphisms beyond *UGT1A1* [75].

Future perspective

Pharmacogenomic discoveries have contributed to understanding of pathogenesis of infections, host–pathogen interactions, and efficacy and toxicities of antimicrobial agents [3]. Translational successes such as *HLA-B**57:01 screening to prevent ABC HSR, and *IL28*

genotyping prior to HCV treatment, provide encouragement that pharmacogenomics can improve safety, efficacy and effectiveness of antimicrobials. Other associations, such as *HLA-B*13:01* screening in Han Chinese for dapsone hypersensitivity syndrome, may become standard of care as more data become available [65,108]. However, major challenges remain on many fronts, including for HIV, tuberculosis and malaria, where continued pharmacogenomic studies are warranted given the huge epidemiological burdens worldwide [17].

In the future, pharmacogenomic studies of well-phenotyped populations, coupled with newer quality-assured technologies such as high-throughput deep sequencing, will facilitate understanding of interactions between host, drug, and pathogen genetic signatures that are important in determining the pathogenesis, efficacy and toxicity of antimicrobial treatment. Research advances in type A and type B reactions will improve prediction of interactions between drugs and their targets, as well as predisposing MHC genotypes leading to more efficient drug design and development [47,203,204]. Pharmacogenomic-guided stratification and dosing has the potential to increase power and improve outcomes of clinical studies [267]. The field of pharmacogenomics will likely continue to evolve. For antimicrobial agents, this will have downstream benefits not only for improved understanding of immunopathogenesis of antimicrobial efficacy and toxicity and host–pathogen interactions, but also translation into safer, more efficacious and cost-effective applications.

Acknowledgments

This work was supported in part by: AI103348 to E Phillips (NIH), APP1064524 to E Phillips (NHMRC – Australia), Australian Centre for HIV and Hepatitis Virology Research (E Phillips), MH95621 to T Hulgán (NIH) and AI077505 to D Haas (NIH).

References

Papers of special note have been highlighted as:

- of interest;
- of considerable interest

1. Lim SS, Vos T, Flaxman AD, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2013; 380(9859):2224–2260. [PubMed: 23245609]
2. Yang G, Wang Y, Zeng Y, et al. Rapid health transition in China, 1990–2010: findings from the Global Burden of Disease Study 2010. *Lancet*. 2013; 381(9882):1987–2015. [PubMed: 23746901]
3. Davison DB, Barrett JF. Antibiotics and pharmacogenomics. *Pharmacogenomics*. 2003; 4(5):657–665. [PubMed: 12943472]
4. McNicholl JM, Downer MV, Udhayakumar V, Alper CA, Swerdlow DL. Host-pathogen interactions in emerging and re-emerging infectious diseases: a genomic perspective of tuberculosis, malaria, human immunodeficiency virus infection, hepatitis B, and cholera. *Annu Rev Public Health*. 2000; 21(1):15–46. [PubMed: 10884944]
5. Tan SL, Ganji G, Paepers B, Proll S, Katze MG. Systems biology and the host response to viral infection. *Nat Biotechnol*. 2007; 25(12):1383–1389. [PubMed: 18066032]
6. Ho RH, Kim RB. Transporters and drug therapy: Implications for drug disposition and disease. *Clin Pharmacol Ther*. 2005; 78(3):260–277. [PubMed: 16153397]

7. Minuesa G, Huber-Ruano I, Pastor-Anglada M, Koepsell H, Clotet B, Martinez-Picado J. Drug uptake transporters in antiretroviral therapy. *Pharmacol Ther.* 2011; 132(3):268–279. [PubMed: 21816170]
8. Attar M, Lee VH. Pharmacogenomic considerations in drug delivery. *Pharmacogenomics.* 2003; 4(4):443–461. [PubMed: 12831323]
9. Pavlos R, Phillips EJ. Individualization of antiretroviral therapy. *Pharmacogenomics Personal Med.* 2012; 5:1.
10. Wedi B. Definitions and mechanisms of drug hypersensitivity. *Expert Rev Clin Pharmacol.* 2010; 3(4):539–551. [PubMed: 22111682]
11. Johansson S, Hourihane JB, Bousquet J, et al. A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy.* 2001; 56(9):813–824. [PubMed: 11551246]
12. Posadas S, Pichler W. Delayed drug hypersensitivity reactions – new concepts. *Clin Exp Allergy.* 2007; 37(7):989–999. [PubMed: 17581192]
13. Pavlos R, Mallal S, Phillips E. HLA and pharmacogenetics of drug hypersensitivity. *Pharmacogenomics.* 2012; 13(11):1285–1306. [PubMed: 22920398]
14. Gil JP. Amodiaquine pharmacogenetics. *Pharmacogenomics.* 2008; 9(10):1385–1390. [PubMed: 18855526]
15. Cavaco I, Piedade R, Msellem M, Bjorkman A, Gil J. Cytochrome 1A1 and 1B1 gene diversity in the Zanzibar islands. *Trop Med Int Health.* 2012; 17(7):854–857. [PubMed: 22594779]
16. Piedade R, Gil JP. The pharmacogenetics of antimalaria artemisinin combination therapy. *Expert Opin Drug Metabol Toxicol.* 2011; 7(10):1185–1200.
17. Kerb R, Fux R, Mörike K, et al. Pharmacogenetics of antimalarial drugs: effect on metabolism and transport. *Lancet Infect Dis.* 2009; 9(12):760–774. [PubMed: 19926036]
18. Phompradit P, Muhamad P, Cheoyman A, Na-Bangchang K. Preliminary investigation of the contribution of *CYP2A6*, *CYP2B6*, and *UGT1A9* polymorphisms on artesunate-mefloquine treatment response in Burmese patients with *Plasmodium falciparum* malaria. *Am J Trop Med Hyg.* 2014; 91(2):361–366. [PubMed: 24891466]
19. Roederer MW, McLeod H, Juliano JJ. Can pharmacogenomics improve malaria drug policy? *Bull World Health Organ.* 2011; 89(11):838–845. [PubMed: 22084530]
20. Noedl H, Socheat D, Satimai W. Artemisinin-resistant malaria in Asia. *N Engl J Med.* 2009; 361(5):540–541. [PubMed: 19641219]
21. di Iulio J, Fayet A, Arab-Alameddine M, et al. *In vivo* analysis of efavirenz metabolism in individuals with impaired CYP2A6 function. *Pharmacogenet Genomics.* 2009; 19(4):300–309. [PubMed: 19238117]
22. Haas DW, Kwara A, Richardson DM, et al. Secondary metabolism pathway polymorphisms and plasma efavirenz concentrations in HIV-infected adults with *CYP2B6* slow metabolizer genotypes. *J Antimicrob Chemother.* 2014; 69(8):2175–2182. [PubMed: 24729586]
23. Kwara A, Lartey M, Sagoe KW, Kenu E, Court MH. *CYP2B6*, *CYP2A6* and *UGT2B7* genetic polymorphisms are predictors of efavirenz mid-dose concentration in HIV-infected patients. *AIDS.* 2009; 23(16):2101–2106. [PubMed: 19779319]
24. Haas DW, Ribaud HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS.* 2004; 18(18):2391–2400. [PubMed: 15622315]
25. Tsuchiya K, Gatanaga H, Tachikawa N, et al. Homozygous *CYP2B6**6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. *Biochem Biophys Res Commun.* 2004; 319(4):1322–1326. [PubMed: 15194512]
26. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. *Pharmacogenet Genomics.* 2005; 15(1):1–5. [PubMed: 15864119]
27. Haas DW, Smeaton LM, Shafer RW, et al. Pharmacogenetics of long-term responses to antiretroviral regimens containing efavirenz and/or nelfinavir: an Adult AIDS Clinical Trials Group Study. *J Infect Dis.* 2005; 192(11):1931–1942. [PubMed: 16267764]

28. Rodriguez-Novoa S, Barreiro P, Rendon A, Jimenez-Nacher I, Gonzalez-Lahoz J, Soriano V. Influence of 516G>T polymorphisms at the gene encoding the CYP450-2B6 isoenzyme on efavirenz plasma concentrations in HIV-infected subjects. *Clin Infect Dis*. 2005; 40(9):1358–1361. [PubMed: 15825040]
29. Holzinger ER, Grady B, Ritchie MD, et al. Genome-wide association study of plasma efavirenz pharmacokinetics in AIDS Clinical Trials Group protocols implicates several *CYP2B6* variants. *Pharmacogenet Genomics*. 2012; 22(12):858–867. [PubMed: 23080225]
30. Wyen C, Hendra H, Vogel M, et al. Impact of *CYP2B6* 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. *J Antimicrob Chemo*. 2008; 61(4):914–918.
31. Wang J, Sonnerborg A, Rane A, et al. Identification of a novel specific *CYP2B6* allele in Africans causing impaired metabolism of the HIV drug efavirenz. *Pharmacogenet Genomics*. 2006; 16(3): 191–198. [PubMed: 16495778]
32. Ribaud HJ, Liu H, Schwab M, et al. Effect of *CYP2B6*, *ABCB1*, and *CYP3A5* polymorphisms on efavirenz pharmacokinetics and treatment response: an AIDS Clinical Trials Group study. *J Infect Dis*. 2010; 202(5):717–722. [PubMed: 20662624]
33. Gounden V, Van Niekerk C, Snyman T, George JA. Presence of the *CYP2B6* 516 G> T polymorphism, increased plasma efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther*. 2010; 7:32. [PubMed: 20723261]
34. Sánchez Martín A, Cabrera Figueroa S, Cruz Guerrero R, Hurtado LP, Hurlé ADG, Carracedo Álvarez Á. Impact of pharmacogenetics on CNS side effects related to efavirenz. *Pharmacogenomics*. 2013; 14(10):1167–1178. [PubMed: 23859571]
35. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6* 6 and* 26. *Clin Infect Dis*. 2007; 45(9):1230–1237. [PubMed: 17918089]
36. Gatanaga H, Oka S. Successful genotype-tailored treatment with small-dose efavirenz. *AIDS*. 2009; 23(3):433–434. [PubMed: 19188761]
37. Tsuchiya K, Gatanaga H, Tachikawa N, et al. Homozygous *CYP2B6**6 (Q172H and K262R) correlates with high plasma efavirenz concentrations in HIV-1 patients treated with standard efavirenz-containing regimens. *Biochem Biophys Res Commun*. 2004; 319(4):1322–1326. [PubMed: 15194512]
38. Penzak SR, Kabuye G, Mugenyi P, et al. Cytochrome P450 2B6 (CYP2B6) G516T influences nevirapine plasma concentrations in HIV-infected patients in Uganda. *HIV Med*. 2007; 8(2):86–91. [PubMed: 17352764]
39. Bertrand J, Chou M, Richardson DM, et al. Multiple genetic variants predict steady-state nevirapine clearance in HIV-infected Cambodians. *Pharmacogenet Genomics*. 2012; 22(12):868–876. [PubMed: 23104099]
40. Vardhanabhuti S, Acosta EP, Ribaud HJ, et al. Clinical and genetic determinants of plasma nevirapine exposure following an intrapartum dose to prevent mother-to-child HIV transmission. *J Infect Dis*. 2013; 208(4):662–671. [PubMed: 23687222]
41. Colombo S, Soranzo N, Rotger M, et al. Influence of *ABCB1*, *ABCC1*, *ABCC2*, and *ABCG2* haplotypes on the cellular exposure of nevirapine *in vivo*. *Pharmacogenet Genomics*. 2005; 15(9): 599–608. [PubMed: 16041239]
42. Saitoh A, Fletcher CV, Brundage R, et al. Efavirenz pharmacokinetics in HIV-1-infected children are associated with *CYP2B6*-G516T polymorphism. *J Acquir Immune Defic Syndr*. 2007; 45(3): 280–285. [PubMed: 17356468]
43. Yuan J, Guo S, Hall D, et al. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. *AIDS*. 2011; 25(10): 1271–1280. [PubMed: 21505298]
44. Hodel EMS, Csajka C, Arie F, et al. Effect of single nucleotide polymorphisms in cytochrome p450 isoenzyme and N-acetyltransferase 2 genes on the metabolism of artemisinin-based combination therapies in malaria patients from Cambodia and Tanzania. *Antimicrob Agents Chemother*. 2013; 57(2):950–958. [PubMed: 23229480]

45. Bains RK. African variation at cytochrome P450 genes: evolutionary aspects and the implications for the treatment of infectious diseases. *Evol Med Public Health*. 2013; 2013(1):118–134. [PubMed: 24481193]
46. Paganotti GM, Gallo BC, Verra F, et al. Human genetic variation is associated with *Plasmodium falciparum* drug resistance. *J Infect Dis*. 2011; 204(11):1772–1778. [PubMed: 21998472]
47. Parikh S, Ouedraogo J, Goldstein J, Rosenthal P, Kroetz D. Amodiaquine metabolism is impaired by common polymorphisms in *CYP2C8*: implications for malaria treatment in Africa. *Clin Pharmacol Ther*. 2007; 82(2):197–203. [PubMed: 17361129]
48. Adjei GO, Kristensen K, Goka BQ, et al. Effect of concomitant artesunate administration and cytochrome P4502C8 polymorphisms on the pharmacokinetics of amodiaquine in Ghanaian children with uncomplicated malaria. *Antimicrob Agents Chemother*. 2008; 52(12):4400–4406. [PubMed: 18779360]
49. Padol S, Yuan Y, Thabane M, Padol IT, Hunt RH. The effect of *CYP2C19* polymorphisms on *H. pylori* eradication rate in dual and triple first-line PPI therapies: a meta-analysis. *Am J Gastroenterol*. 2006; 101(7):1467–1475. [PubMed: 16863547]
50. Zhao F, Wang J, Yang Y, et al. Effect of *CYP2C19* genetic polymorphisms on the efficacy of proton pump inhibitor-based triple therapy for *Helicobacter pylori* eradication: a meta-analysis. *Helicobacter*. 2008; 13(6):532–541. [PubMed: 19166419]
51. Tang HL, Li Y, Hu YF, Xie HG, Zhai SD. Effects of *CYP2C19* loss-of-function variants on the eradication of *H. pylori* infection in patients treated with proton pump inhibitor-based triple therapy regimens: a meta-analysis of randomized clinical trials. *PLoS ONE*. 2013; 8(4):e62162. [PubMed: 23646118]
52. Meletiadis J, Chanock S, Walsh TJ. Defining targets for investigating the pharmacogenomics of adverse drug reactions to antifungal agents. *Pharmacogenomics*. 2008; 9(5):561–584. [PubMed: 18466103]
53. Levin MD, den Hollander JG, van der Holt B, et al. Hepatotoxicity of oral and intravenous voriconazole in relation to cytochrome P450 polymorphisms. *J Antimicrob Chemother*. 2007; 60(5):1104–1107. [PubMed: 17827141]
54. Matsumoto K, Ikawa K, Abematsu K, et al. Correlation between voriconazole trough plasma concentration and hepatotoxicity in patients with different *CYP2C19* genotypes. *Int J antimicrob agents*. 2009; 34(1):91–94. [PubMed: 19261446]
55. Hariprasad SM, Mieler WF, Holz ER, et al. Determination of vitreous, aqueous, and plasma concentration of orally administered voriconazole in humans. *Arch Ophthalmol*. 2004; 122(1):42–47. [PubMed: 14718293]
56. Scholz I, Oberwittler H, Riedel KD, et al. Pharmacokinetics, metabolism and bioavailability of the triazole antifungal agent voriconazole in relation to *CYP2C19* genotype. *Br J Clin Pharmacol*. 2009; 68(6):906–915. [PubMed: 20002085]
57. Zonios D, Yamazaki H, Murayama N, et al. Voriconazole metabolism, toxicity, and the effect of cytochrome P450 2C19 genotype. *J Infect Dis*. 2014; 209(12):1941–1948. [PubMed: 24403552]
58. Kakuda, T.; Nijs, S.; van Hoecke, G., et al. Pharmacokinetics of etravirine According to *CYP2C9* and *CYP2C19* metabolizer status: a meta-analysis of Phase I trials. Presented at: 20th Conference on Retroviruses and Opportunistic Infections; Atlanta, GA, USA. 3–6 March 2013;
59. Janha RE, Sisay-Joof F, Hamid-Adiamoh M, et al. Effects of genetic variation at the *CYP2C19/CYP2C9* locus on pharmacokinetics of chlorcycloguanil in adult Gambians. *Pharmacogenomics*. 2009; 10(9):1423–1431. [PubMed: 19761366]
60. Cai Y, Yi J, Zhou C, Shen X. Pharmacogenetic study of drug-metabolising enzyme polymorphisms on the risk of anti-tuberculosis drug-induced liver injury: a metaanalysis. *PLoS ONE*. 2012; 7(10):e47769. [PubMed: 23082213]
61. Huang YS, Chern HD, Su WJ, et al. Cytochrome P450 2E1 genotype and the susceptibility to antituberculosis drug-induced hepatitis. *Hepatology*. 2003; 37(4):924–930. [PubMed: 12668988]
62. Roy PD, Majumder M, Roy B. Pharmacogenomics of anti-TB drugs-related hepatotoxicity. *Pharmacogenomics*. 2008; 9(3):311–321. [PubMed: 18303967]

63. Roy B, Ghosh SK, Sutradhar D, Sikdar N, Mazumder S, Barman S. Predisposition of antituberculosis drug induced hepatotoxicity by cytochrome P450 2E1 genotype and haplotype in pediatric patients. *J Gastroenterol Hepatol*. 2006; 21(4):784–786. [PubMed: 16677176]
64. Wang D, Para MF, Koletar SL, Sadee W. Human *N*-acetyltransferase 1 (NAT1)*10 and *11 alleles increase protein expression via distinct mechanisms and associate with sulfamethoxazole-induced hypersensitivity. *Pharmacogenet Genomics*. 2011; 21(10):652–664. [PubMed: 21878835]
65. Azuma J, Ohno M, Kubota R, et al. NAT2 genotype guided regimen reduces isoniazid-induced liver injury and early treatment failure in the 6-month four-drug standard treatment of tuberculosis: a randomized controlled trial for pharmacogenetics-based therapy. *Eur J Clin Pharmacol*. 2012; 1–11. A randomized controlled trial showing *NAT2* genotype based isoniazid dosing may improve outcomes in patients treated for tuberculosis. Slow acetylators who received lower isoniazid dosing (2.5 mg/kg) had less hepatotoxicity and fast acetylators who received higher dosing (7.5 mg/kg) had less treatment failure.
66. Sun F, Chen Y, Xiang Y, Zhan S. Drug-metabolising enzyme polymorphisms and predisposition to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2008; 12(9): 994–1002. [PubMed: 18713495]
67. Wang P, Xie S, Hao Q, Zhang C, Jiang B. *NAT2* polymorphisms and susceptibility to anti-tuberculosis drug-induced liver injury: a meta-analysis. *Int J Tuberc Lung Dis*. 2012; 16(5):589–595. [PubMed: 22409928]
68. Nebert DW. Polymorphisms in drug-metabolizing enzymes: what is their clinical relevance and why do they exist? *Am J Hum Genetics*. 1997; 60(2):265–271. [PubMed: 9012398]
69. Goel U, Bajaj S, Gupta O, Dwivedi N, Dubey A. Isoniazid induced neuropathy in slow versus rapid acetylators: an electrophysiological study. *J Assoc Phys India*. 1992; 40(10):671–672.
70. Yamamoto M, Sobue G, Mukoyama M, Matsuoka Y, Mitsuma T. Demonstration of slow acetylator genotype of *N*-acetyltransferase in isoniazid neuropathy using an archival hematoxylin and eosin section of a sural nerve biopsy specimen. *J Neurol Sci*. 1996; 135(1):51–54. [PubMed: 8926496]
71. Pirmohamed M, Alfirevic A, Vilar J, et al. Association analysis of drug metabolizing enzyme gene polymorphisms in HIV-positive patients with co-trimoxazole hypersensitivity. *Pharmacogenet Genomics*. 2000; 10(8):705–713.
72. Huang YS, Su WJ, Huang YH, et al. Genetic polymorphisms of manganese superoxide dismutase, NAD(P)H: quinone oxidoreductase, glutathione S transferase M1 and T1, and the susceptibility to drug-induced liver injury. *J Hepatol*. 2007; 47(1):128–134. [PubMed: 17400324]
73. Wang D, Curtis A, Papp AC, Koletar SL, Para MF. Polymorphism in glutamate cysteine ligase catalytic subunit (GCLC) is associated with sulfamethoxazole-induced hypersensitivity in HIV/AIDS patients. *BMC Med Genomics*. 2012; 5(1):32. [PubMed: 22824134]
74. Rodríguez-Nóvoa S, Martín-Carbonero L, Barreiro P, et al. Genetic factors influencing atazanavir plasma concentrations and the risk of severe hyperbilirubinemia. *AIDS*. 2007; 21(1):41–46. [PubMed: 17148966]
75. Johnson DH, Venuto C, Ritchie MD, et al. Genomewide association study of atazanavir pharmacokinetics and hyperbilirubinemia in AIDS Clinical Trials Group protocol A5202. *Pharmacogenet Genomics*. 2014; 24(4):195–203. [PubMed: 24557078]
76. Lubomirov R, Colombo S, di Iulio J, et al. Association of pharmacogenetic markers with premature discontinuation of first-line anti-HIV therapy: an observational cohort study. *J Infect Dis*. 2011; 203(2):246–257. [PubMed: 21288825]
77. Ribaud HJ, Daar ES, Tierney C, et al. Impact of UGT1A1 gilbert variant on discontinuation of ritonavir-boosted atazanavir in AIDS Clinical Trials Group Study A5202. *J Infect Dis*. 2013; 207(3):420–425. [PubMed: 23148286]
78. Lankisch TO, Behrens G, Ehmer U, et al. Gilbert's syndrome and hyperbilirubinemia in protease inhibitor therapy – an extended haplotype of genetic variants increases risk in indinavir treatment. *J Hepatol*. 2009; 50(5):1010–1018. [PubMed: 19303655]
79. Cappellini MD, Fiorelli G. Glucose-6-phosphate dehydrogenase deficiency. *Lancet*. 2008; 371(9606):64–74. [PubMed: 18177777]

80. Toovey S. Mefloquine neurotoxicity: a literature review. *Travel Med Infect Dis.* 2009; 7(1):2–6. [PubMed: 19174293]
81. Aarnoudse AL, van Schaik RH, Dieleman J, et al. *MDR1* gene polymorphisms are associated with neuropsychiatric adverse effects of mefloquine. *Clin Pharmacol Ther.* 2006; 80(4):367–374. [PubMed: 17015054]
82. Mandíková J, Volková M, Pávek P, et al. Interactions with selected drug renal transporters and transporter-mediated cytotoxicity in antiviral agents from the group of acyclic nucleoside phosphonates. *Toxicology.* 2013; 311(3):135–146. [PubMed: 23856525]
83. Pushpakom SP, Liptrott NJ, Rodríguez-Nóvoa S, et al. Genetic variants of *ABCC10*, a novel tenofovir transporter, are associated with kidney tubular dysfunction. *J Infect Dis.* 2011; 204(1): 145–153. [PubMed: 21628669]
84. Kohler JJ, Hosseini SH, Green E, et al. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. *Lab invest.* 2011; 91(6):852–858. [PubMed: 21403643]
85. Rodríguez-Novoa S, Labarga P, Soriano V. Pharmacogenetics of tenofovir treatment. *Pharmacogenomics.* 2009; 10(10):1675–1685. [PubMed: 19842939]
86. Lebrecht D, Venhoff AC, Kirschner J, Wiech T, Venhoff N, Walker UA. Mitochondrial tubulopathy in tenofovir disoproxil fumarate-treated rats. *J Acquir Immune Defic Syndr.* 2009; 51(3):258–263. [PubMed: 19582894]
87. Rodríguez-Nóvoa S, Labarga P, Soriano V, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. *Clin Infect Dis.* 2009; 48(11):e108–e116. [PubMed: 19400747]
88. Kiser JJ, Aquilante CL, Anderson PL, King TM, Carten ML, Fletcher CV. Clinical and genetic determinants of intracellular tenofovir diphosphate concentrations in HIV-infected patients. *J Acquir Immune Defic Syndr.* 2008; 47(3):298–303. [PubMed: 18398970]
89. Uwai Y, Ida H, Tsuji Y, Katsura T, Inui KI. Renal transport of adefovir, cidofovir, and tenofovir by SLC22A family members (hOAT1, hOAT3, and hOCT2). *Pharm Res.* 2007; 24(4):811–815. [PubMed: 17372702]
90. Izzedine H, Hulot JS, Villard E, et al. Association between *ABCC2* gene haplotypes and tenofovir-induced proximal tubulopathy. *J Infect Dis.* 2006; 194(11):1481–1491. [PubMed: 17083032]
91. Ray AS, Cihlar T, Robinson KL, et al. Mechanism of active renal tubular efflux of tenofovir. *Antimicrob Agents Chemother.* 2006; 50(10):3297–3304. [PubMed: 17005808]
92. Suppiah V, Moldovan M, Ahlenstiel G, et al. *IL28B* is associated with response to chronic hepatitis C interferon- α and ribavirin therapy. *Nat Genet.* 2009; 41(10):1100–1104. [PubMed: 19749758]
93. Ge D, Fellay J, Thompson AJ, et al. Genetic variation in *IL28B* predicts hepatitis C treatment-induced viral clearance. *Nature.* 2009; 461(7262):399–401. [PubMed: 19684573]
94. Rauch A, Kutalik Z, Descombes P, et al. Genetic variation in *IL28B* is associated with chronic hepatitis C and treatment failure: a genome-wide association study. *Gastroenterology.* 2010; 138(4):1338–1345. 1345.e1–7. [PubMed: 20060832]
95. Bibert S, Roger T, Calandra T, et al. *IL28B* expression depends on a novel TT/-G polymorphism which improves HCV clearance prediction. *J Exp Med.* 2013; 210(6):1109–1116. [PubMed: 23712427]
96. Fellay J, Thompson AJ, Ge D, et al. *ITPA* gene variants protect against anaemia in patients treated for chronic hepatitis C. *Nature.* 2010; 464(7287):405–408. [PubMed: 20173735]
97. Thompson AJ, Fellay J, Patel K, et al. Variants in the *ITPA* gene protect against ribavirin-induced hemolytic anemia and decrease the need for ribavirin dose reduction. *Gastroenterology.* 2010; 139(4):1181–1189. [PubMed: 20547162]
98. Sakamoto N, Tanaka Y, Nakagawa M, et al. *ITPA* gene variant protects against anemia induced by pegylated interferon- α and ribavirin therapy for Japanese patients with chronic hepatitis C. *Hepatol Res.* 2010; 40(11):1063–1071. [PubMed: 20977565]
99. Hitomi Y, Cirulli ET, Fellay J, et al. Inosine triphosphate protects against ribavirin-induced adenosine triphosphate loss by adenylosuccinate synthase function. *Gastroenterology.* 2011; 140(4):1314–1321. [PubMed: 21199653]

100. Clark P, Aghemo A, Degaspero E, et al. Inosine triphosphatase deficiency helps predict anaemia, anaemia management and response in chronic hepatitis C therapy. *J Viral Hepat.* 2013; 20(12): 858–866. [PubMed: 24304455]
101. Rallón NI, Morello J, Labarga P, et al. Impact of inosine triphosphatase gene variants on the risk of anemia in HIV/ hepatitis C virus-coinfected patients treated for chronic hepatitis C. *Clin Infect Dis.* 2011; 53(12):1291–1295. [PubMed: 22028438]
102. Whirl-Carrillo M, McDonagh E, Hebert J, et al. Pharmacogenomics knowledge for personalized medicine. *Clin Pharmacol Ther.* 2012; 92(4):414–417. [PubMed: 22992668]
103. Hautekeete ML, Horsmans Y, van Waeyenberge C, et al. HLA association of amoxicillin-clavulanate-induced hepatitis. *Gastroenterology.* 1999; 117(5):1181–1186. [PubMed: 10535882]
104. Lucena MI, Molokhia M, Shen Y, et al. Susceptibility to amoxicillin-clavulanate-induced liver injury is influenced by multiple HLA class I and II alleles. *Gastroenterology.* 2011; 141(1):338–347. [PubMed: 21570397]
105. Donaldson PT, Daly AK, Henderson J, et al. Human leucocyte antigen class II genotype in susceptibility and resistance to co-amoxiclav-induced liver injury. *J Hepatol.* 2010; 53(6):1049–1053. [PubMed: 20800921]
106. O'Donohue J, Oien K, Donaldson P, et al. Co-amoxiclav jaundice: clinical and histological features and HLA class II association. *Gut.* 2000; 47(5):717–720. [PubMed: 11034591]
107. Stephens C, López-Nevot MÁ, Ruiz-Cabello F, et al. HLA alleles influence the clinical signature of amoxicillin-clavulanate hepatotoxicity. *PLoS ONE.* 2013; 8(7):e68111. Describes a previously unnoticed unique genotype–phenotype correlation between hepatocellular pattern of liver injury and HLA class I alleles *A*30:02* and *B*18:01* in a cohort of Spanish patients who had amoxicillin-clavulanate drug-induced liver injury. This association may be race specific as opposed to previously described associations with class II alleles *HLA-DRB1*15:01-DQB1*06:02*, which showed a predominantly cholestatic picture. [PubMed: 23874514]
108. Zhang FR, Liu H, Irwanto A, et al. *HLA-B*13:01* and the dapsone hypersensitivity syndrome. *N Engl J Med.* 2013; 369(17):1620–1628. Key article that showed strong association between *HLA-B*13:01* and dapsone hypersensitivity syndrome in Han Chinese treated for leprosy. The presence of *HLA-B*13:01* increases the risk of dapsone hypersensitivity (odds ratio: 20.53) with sensitivity, specificity and negative predictive value of the test being 85.5, 85.7 and 99.8%, respectively. This test may become part of routine clinical practice before initiating dapsone therapy. [PubMed: 24152261]
109. Wang H, Yan L, Zhang G, et al. Association between *HLA-B*1301* and dapsone-induced hypersensitivity reactions among leprosy patients in China. *J Invest Dermatol.* 2013; 133(11): 2642–2644. [PubMed: 23604100]
110. Daly AK, Donaldson PT, Bhatnagar P, et al. *HLA-B*5701* genotype is a major determinant of drug-induced liver injury due to flucloxacillin. *Nat Genet.* 2009; 41(7):816–819. [PubMed: 19483685]
111. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet.* 2002; 359(9312):1121–1122. [PubMed: 11943262]
112. Mallal S, Nolan D, Witt C, et al. Association between presence of *HLA-B* 5701*, *HLA-DR7*, and *HLA-DQ3* and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet.* 2002; 359(9308):727–732. [PubMed: 11888582]
113. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-B* 5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis.* 2008; 46(7):1111–1118. [PubMed: 18444831]
114. Martin AM, Nolan D, James I, et al. Predisposition to nevirapine hypersensitivity associated with *HLA-DRB1*0101* and abrogated by low CD4 T-cell counts. *AIDS.* 2005; 19(1):97–99. [PubMed: 15627041]
115. Chantarangsu S, Mushiroda T, Mahasirimongkol S, et al. Genome-wide association study identifies variations in 6p21.3 associated with nevirapine-induced rash. *Clin Infect Dis.* 2011; 53(4):341–348. [PubMed: 21810746]

116. Gatanaga H, Yazaki H, Tanuma J, et al. *HLA-Cw8* primarily associated with hypersensitivity to nevirapine. *AIDS*. 2007; 21(2):264–265. [PubMed: 17197830]
117. Keane NM, Pavlos RK, McKinnon E, et al. HLA class I restricted CD8⁺ and Class II restricted CD4⁺ T cells are implicated in the pathogenesis of nevirapine hypersensitivity. *AIDS*. 2014; 500:14–00302. Highlights that nevirapine hypersensitivity reactions can occur in genetically predisposed infants <6 months of age with much the same clinical phenotype (fever, rash, eosinophilia and hepatitis) and class I HLA associations as adults with demonstrable nevirapine specific CD8⁺ T-cell responses.
118. Littera R, Carcassi C, Masala A, et al. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. *AIDS*. 2006; 20(12):1621–1626. [PubMed: 16868443]
119. Gao S, Gui XE, Liang K, Liu Z, Hu J, Dong B. HLA-dependent hypersensitivity reaction to nevirapine in Chinese Han HIV-infected patients. *AIDS Res Hum Retroviruses*. 2012; 28(6): 540–543. [PubMed: 21902584]
120. Phillips E, Bartlett JA, Sanne I, et al. Associations between *HLA-DRB1*0102*, *HLA-B*5801*, and hepatotoxicity during initiation of nevirapine-containing regimens in South Africa. *J AIDS*. 2013; 62(2):e55–e57.
121. Chantarangsu S, Mushirola T, Mahasirimongkol S, et al. *HLA-B*3505* allele is a strong predictor for nevirapine-induced skin adverse drug reactions in HIV-infected Thai patients. *Pharmacogenet Genomics*. 2009; 19(2):139–146. [PubMed: 19104471]
122. Yuan J, Guo S, Hall D, et al. Toxicogenomics of nevirapine-associated cutaneous and hepatic adverse events among populations of African, Asian, and European descent. *AIDS*. 2011; 25(10): 1271–1280. [PubMed: 21505298]
123. Carr DF, Chaponda M, Jorgensen AL, et al. Association of human leukocyte antigen alleles and nevirapine hypersensitivity in a Malawian HIV-infected population. *Clin Infect Dis*. 2013; 56(9): 1330–1339. Shows that the risk of developing Stevens–Johnson syndrome/toxic epidermal necrolysis from nevirapine treatment is associated with *HLA-C*04:01* in a Malawian cohort. [PubMed: 23362284]
124. Fischel-Ghodsian N. Genetic factors in aminoglycoside toxicity. *Pharmacogenomics*. 2005; 6(1): 27–36. [PubMed: 15723603]
125. Guan MX. Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity. *Mitochondrion*. 2011; 11(2):237–245. [PubMed: 21047563]
126. Pacheu-Grau D, Gómez-Durán A, Montoya J, Ruiz-Pesini E. Influence of mtDNA genetic variation on antibiotic therapy. *Pharmacogenomics*. 2010; 11(9):1185–1187. [PubMed: 20860455]
127. Prezant TR, Agopian JV, Bohlman MC, et al. Mitochondrial ribosomal RNA mutation associated with both antibiotic-induced and non-syndromic deafness. *Nat Genet*. 1993; 4(3):289–294. [PubMed: 7689389]
128. Carson J, Cerda J, Chae JH, Hirano M, Maggiore P. Severe lactic acidosis associated with linezolid use in a patient with the mitochondrial DNA A2706G polymorphism. *Pharmacotherapy*. 2007; 27(5):771–774. [PubMed: 17461714]
129. Holzinger ER, Hulgán T, Ellis RJ, et al. Mitochondrial DNA variation and HIV-associated sensory neuropathy in CHARTER. *J Neurovirol*. 2012; 18(6):511–520. [PubMed: 23073667]
130. Canter JA, Robbins GK, Selph D, et al. African mitochondrial DNA subhaplogroups and peripheral neuropathy during antiretroviral therapy. *J Infect Dis*. 2010; 201(11):1703–1707. [PubMed: 20402593]
131. Sinxadi PZ, Dave JA, Samuels DC, et al. Mitochondrial genomics and antiretroviral therapy-associated metabolic complications in HIV-infected black South Africans: a pilot study. *AIDS Res Hum Retroviruses*. 2013; 29(7):1031–1039. [PubMed: 23428049]
132. Kampira E, Kumwenda J, van Oosterhout JJ, Dandara C. Mitochondrial DNA subhaplogroups L0a2 and L2a modify susceptibility to peripheral neuropathy in Malawian adults on stavudine containing highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2013; 63(5):647–652. [PubMed: 23614993]

133. De Luca A, Nasi M, Di Giambenedetto S, et al. Mitochondrial DNA haplogroups and incidence of lipodystrophy in HIV-infected patients on long-term antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2012; 59(2):113–120. [PubMed: 22245716]
134. Hulan T, Haubrich R, Riddler SA, et al. European mitochondrial DNA haplogroups and metabolic changes during antiretroviral therapy in AIDS Clinical Trials Group Study A5142. *AIDS*. 2011; 25(1):37–47. [PubMed: 20871389]
135. Hendrickson SL, Kingsley LA, Ruiz-Pesini E, et al. Mitochondrial DNA haplogroups influence lipodystrophy after highly active anti-retroviral therapy. *J Acquir Immune Defic Syndr*. 2009; 51(2):111–116. [PubMed: 19339895]
136. Micheloud D, Berenguer J, Guzmán-Fulgencio M, et al. European mitochondrial DNA haplogroups and metabolic disorders in HIV/HCV-coinfected patients on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2011; 58(4):371–378. [PubMed: 21792063]
137. Hulan T, Stein JH, Cotter BR, et al. Mitochondrial DNA variation and changes in adiponectin and endothelial function in HIV-infected adults after antiretroviral therapy initiation. *AIDS Res Hum Retroviruses*. 2013; 29(10):1293–1299. [PubMed: 23944767]
138. Canter J, Haas D, Kallianpur A, et al. The mitochondrial pharmacogenomics of haplogroup T: *MTND2*^{LHON4917G}* and antiretroviral therapy-associated peripheral neuropathy. *Pharmacogenomics J*. 2007; 8(1):71–77. [PubMed: 17684475]
139. Hulan T, Haas DW, Haines JL, et al. Mitochondrial haplogroups and peripheral neuropathy during antiretroviral therapy: an adult AIDS clinical trials group study. *AIDS*. 2005; 19(13):1341–1349. [PubMed: 16103764]
140. Hendrickson SL, Jabs DA, Van Natta M, Lewis RA, Wallace DC, O'Brien SJ. Mitochondrial haplogroups are associated with risk of neuroretinal disorder in HIV-positive patients. *J Acquir Immune Defic Syndr*. 2010; 53(4):451–455. [PubMed: 20098332]
141. Andrade RJ, Lucena MI, Fernández MC, et al. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology*. 2005; 129(2):512–521. [PubMed: 16083708]
142. Stricker B, Van Den Broek J, Keuning J, et al. Cholestatic hepatitis due to antibacterial combination of amoxicillin and clavulanic acid (augmentin). *Digest Dis Sci*. 1989; 34(10):1576–1580. [PubMed: 2791808]
143. Lucena MI, Andrade RJ, Fernández MC, et al. Determinants of the clinical expression of amoxicillin-clavulanate hepatotoxicity: a prospective series from Spain. *Hepatology*. 2006; 44(4):850–856. [PubMed: 17006920]
144. Russmann S, Kaye JA, Jick SS, Jick H. Risk of cholestatic liver disease associated with flucloxacillin and flucloxacillin prescribing habits in the UK: cohort study using data from the UK General Practice Research Database. *Br J Clin Pharmacol*. 2005; 60(1):76–82. [PubMed: 15963097]
145. Monshi MM, Faulkner L, Gibson A, et al. Human leukocyte antigen *HLA-B*57:01* restricted activation of drug-specific T cells provides the immunological basis for flucloxacillin-induced liver injury. *Hepatology*. 2013; 57(2):727–739. [PubMed: 22987284]
146. Willemin N, Adam J, Fontana S, Krähenbühl S, Pichler WJ, Yerly D. HLA haplotype determines hapten or pi T cell reactivity to flucloxacillin. *J Immunol*. 2013; 190(10):4956–4964. Shows that flucloxacillin was presented to CD8⁺ T cells by HLA molecules in two distinct manners: a stable hapten and a labile manner. In *HLA-B*57:01* [+] individuals, labile p-i based T-cell reactivity was observed. [PubMed: 23596311]
147. Becquemont L, Alfievic A, Amstutz U, et al. Practical recommendations for pharmacogenomics-based prescription: 2010 ESF–UB Conference on Pharmacogenetics and pharmacogenomics. *Pharmacogenomics*. 2011; 12(1):113–124. [PubMed: 21174626]
148. Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. *Pharmacogenomics*. 2011; 12(6):873–888. [PubMed: 21692617]
149. Suzuki H, Nishizawa T, Hibi T. *Helicobacter pylori* eradication therapy. *Future Microbiol*. 2010; 5(4):639–648. [PubMed: 20353303]

150. Horn J. Review article: relationship between the metabolism and efficacy of proton pump inhibitors – focus on rabeprazole. *Aliment Pharmacol Ther.* 2004; 20(S6):11–19. [PubMed: 15496214]
151. Andersson T, Röhss K, Bredberg E, Hassan-Alin M. Pharmacokinetics and pharmacodynamics of esomeprazole, the S-isomer of omeprazole. *Aliment Pharmacol Ther.* 2001; 15(10):1563–1569. [PubMed: 11563995]
152. Li WPA, Girard T, Farndon P, Cooley C, Lithgow J. Pharmacogenetics of *CYP2C19*: functional and clinical implications of a new variant *CYP2C19*17*. *Br J Clin Pharmacol.* 2010; 69(3):222–230. [PubMed: 20233192]
153. Zanger UM, Turpeinen M, Klein K, Schwab M. Functional pharmacogenetics/genomics of human cytochromes P450 involved in drug biotransformation. *Anal Bioanal Chem.* 2008; 392(6):1093–1108. [PubMed: 18695978]
154. Bertilsson L. Geographical/interracial differences in polymorphic drug oxidation. *Clin Pharmacokinet.* 1995; 29(3):192–209. [PubMed: 8521680]
155. Guthrie O. Aminoglycoside induced ototoxicity. *Toxicology.* 2008; 249(2–3):91–96. [PubMed: 18514377]
156. Selimoglu E. Aminoglycoside-induced ototoxicity. *Curr Pharm Des.* 2007; 13(1):119–126. [PubMed: 17266591]
157. Xie J, Talaska AE, Schacht J. New developments in aminoglycoside therapy and ototoxicity. *Hear Res.* 2011; 281(1):28–37. [PubMed: 21640178]
158. Pacheu-Grau D, Gómez-Durán A, Iglesias E, López-Gallardo E, Montoya J, Ruiz-Pesini E. Mitochondrial antibiograms in personalized medicine. *Hum Mol Genet.* 2013; 22(6):1132–1139. [PubMed: 23223015]
159. Garrabou G, Soriano A, López S, et al. Reversible inhibition of mitochondrial protein synthesis during linezolid-related hyperlactatemia. *Antimicrob Agents Chemother.* 2007; 51(3):962–967. [PubMed: 17194826]
160. McKee E, Ferguson M, Bentley A, Marks T. Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. *Antimicrob Agents Chemother.* 2006; 50(6):2042–2049. [PubMed: 16723564]
161. De Vriese AS, Van Coster R, Smet J, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. *Clin Infect Dis.* 2006; 42(8):1111–1117. [PubMed: 16575728]
162. Soriano A, Miró O, Mensa J. Mitochondrial toxicity associated with linezolid. *N Engl J Med.* 2005; 353(21):2305–2306. [PubMed: 16306535]
163. Jaffe H, Ammann A, Abrams D, Lewis B, Golden J. Complications of co-trimoxazole in treatment of AIDS-associated *Pneumocystis carinii* pneumonia in homosexual men. *Lancet.* 1983; 322(8359):1109–1111. [PubMed: 6138645]
164. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for *Pneumocystis carinii* pneumonia prophylaxis in human immunodeficiency virus-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis.* 2001; 184(8):992–997. [PubMed: 11574913]
165. Lin D, Li W, Rieder M. Cotrimoxazole for prophylaxis or treatment of opportunistic infections of HIV/AIDS in patients with previous history of hypersensitivity to cotrimoxazole. *Cochrane Database Syst Rev.* 2007; 2:1–15.
166. Tilles SA. Practical issues in the management of hypersensitivity reactions: sulfonamides. *South Med J.* 2001; 94(8):817–824. [PubMed: 11549195]
167. Alfievic A, Vilar FJ, Alsou M, et al. *TNF*, *LTA*, *HSPAIL* and *HLA-DR* gene polymorphisms in HIV-positive patients with hypersensitivity to cotrimoxazole. *Pharmacogenomics.* 2009; 10(4):531–540. [PubMed: 19374512]
168. Watkins S, Pichler WJ. Sulfamethoxazole Induces a switch mechanism in T cell receptors containing TCRV β 20–1, altering pHLA recognition. *PLoS ONE.* 2013; 8(10):e76211. [PubMed: 24116097]
169. Bukirwa H, Garner P, Critchley J. Chlorproguanil–dapson for treating uncomplicated malaria. *Cochrane Database Syst Rev.* 2004; 4:CD004387. [PubMed: 15495106]

170. Fanello CI, Karema C, Avellino P, et al. High risk of severe anaemia after chlorproguanil-dapsone+ artesunate antimalarial treatment in patients with G6PD (A-) deficiency. *PLoS ONE*. 2008; 3(12):e4031. [PubMed: 19112496]
171. Premji Z, Umeh RE, Owusu-Agyei S, et al. Chlorproguanil–dapsone–artesunate versus artemether–lumefantrine: a randomized, double-blind Phase III trial in African children and adolescents with uncomplicated *Plasmodium falciparum* malaria. *PLoS ONE*. 2009; 4(8):e6682. [PubMed: 19690618]
172. Luzzatto L. The rise and fall of the antimalarial Lapdap: a lesson in pharmacogenetics. *Lancet*. 2010; 376(9742):739–741. [PubMed: 20599264]
173. Lorenz M, Wozel G, Schmitt J. Hypersensitivity reactions to dapsone: a systematic review. *Acta Derm Venereol*. 2012; 92(2):194–199. [PubMed: 22307940]
174. Ramachandran G, Swaminathan S. Role of pharmacogenomics in the treatment of tuberculosis: a review. *Pharmacogenomics Personal Med*. 2012; 5:89–98.
175. Monteiro T, El-Jaick K, Jeoviano-Silva A, et al. The roles of *GSTM1* and *GSTT1* null genotypes and other predictors in anti-tuberculosis drug-induced liver injury. *J Clin Pharm Ther*. 2012; 37(6):712–718. [PubMed: 22845549]
176. Kim SH, Kim SH, Bahn JW, et al. Genetic polymorphisms of drug-metabolizing enzymes and anti-TB drug-induced hepatitis. *Pharmacogenomics*. 2009; 10(11):1767–1779. [PubMed: 19891553]
177. Vuilleumier N, Rossier MF, Chiappe A, et al. *CYP2E1* genotype and isoniazid-induced hepatotoxicity in patients treated for latent tuberculosis. *Eur J Clin Pharmacol*. 2006; 62(6):423–429. [PubMed: 16770646]
178. Cho HJ, Koh WJ, Ryu YJ, et al. Genetic polymorphisms of *NAT2* and *CYP2E1* associated with antituberculosis drug-induced hepatotoxicity in Korean patients with pulmonary tuberculosis. *Tuberculosis*. 2007; 87(6):551–556. [PubMed: 17950035]
179. Yamada S, Tang M, Richardson K, et al. Genetic variations of *NAT2* and *CYP2E1* and isoniazid hepatotoxicity in a diverse population. *Pharmacogenomics*. 2009; 10(9):1433–1445. [PubMed: 19761367]
180. Yamada S, Richardson K, Tang M, et al. Genetic variation in carboxylesterase genes and susceptibility to isoniazid-induced hepatotoxicity. *Pharmacogenomics*. 2010; 10(6):524–536.
181. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. *Am J Respir Crit Care Med*. 2002; 166(7):916–919. [PubMed: 12359646]
182. Kim SH, Kim SH, Yoon HJ, et al. TNF- α genetic polymorphism -308G/A and antituberculosis drug-induced hepatitis. *Liver*. 2012; 32(5):809–814.
183. Yimer G, Ueda N, Habtewold A, et al. Pharmacogenetic and pharmacokinetic biomarker for efavirenz based ARV and rifampicin based anti-TB drug induced liver injury in TB-HIV infected patients. *PLoS ONE*. 2011; 6(12):e27810. [PubMed: 22162992]
184. Tang S, Lv X, Zhang Y, et al. Cytochrome P450 2E1 gene polymorphisms/haplotypes and anti-tuberculosis drug-induced hepatitis in a Chinese cohort. *PLoS ONE*. 2013; 8(2):e57526. [PubMed: 23460870]
185. Mikus G, Schöwel V, Drzewinska M, et al. Potent cytochrome P450 2C19 genotype-related interaction between voriconazole and the cytochrome P450 3A4 inhibitor ritonavir. *Clin Pharmacol Ther*. 2006; 80(2):126–135. [PubMed: 16890574]
186. Mikus G, Scholz IM, Weiss J. Pharmacogenomics of the triazole antifungal agent voriconazole. *Pharmacogenomics*. 2011; 12(6):861–872. [PubMed: 21692616]
187. Hicks JK, Crews KR, Flynn P, et al. Voriconazole plasma concentrations in immunocompromised pediatric patients vary by *CYP2C19* diplotypes. *Pharmacogenomics*. 2014; 15(8):1065–1078. [PubMed: 25084200]
188. Suzuki Y, Tokimatsu I, Sato Y, et al. Association of sustained high plasma trough concentration of voriconazole with the incidence of hepatotoxicity. *Clin Chim Acta*. 2013; 424:119–122. [PubMed: 23747486]
189. Laties AM, Zrenner E. Viagra® (sildenafil citrate) and ophthalmology. *Prog Retin Eye Res*. 2002; 21(5):485–506. [PubMed: 12207947]

190. WHO. Guidelines for the treatment of malaria. 2006. www.who.int/malaria/publications/atoz/9789241547925/en/
191. Di YM, Chow VDW, Yang LP, Zhou SF. Structure, function, regulation and polymorphism of human cytochrome P450 2A6. *Curr Drug Metabol.* 2009; 10(7):754–780.
192. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation. *Pharmacol Ther.* 2013; 138(1): 103–141. [PubMed: 23333322]
193. Aweeka FT, German PI. Clinical pharmacology of artemisinin-based combination therapies. *Clin Pharmacokinet.* 2008; 47(2):91–102. [PubMed: 18193915]
194. Coto-Llerena M, Pérez-del-Pulgar S, Crespo G, et al. Donor and recipient IL28B polymorphisms in HCV-infected patients undergoing antiviral therapy before and after liver transplantation. *Am J Transplant.* 2011; 11(5):1051–1057. [PubMed: 21466653]
195. Charlton MR, Thompson A, Veldt BJ, et al. Interleukin-28B polymorphisms are associated with histological recurrence and treatment response following liver transplantation in patients with hepatitis C virus infection. *Hepatology.* 2011; 53(1):317–324. [PubMed: 21254179]
196. Fukuhara T, Taketomi A, Motomura T, et al. Variants in IL28B in liver recipients and donors correlate with response to Peg-interferon and ribavirin therapy for recurrent hepatitis C. *Gastroenterology.* 2010; 139(5):1577–1585. 1585.e1–3. [PubMed: 20708617]
197. Rallón NI, Soriano V, Naggie S, et al. IL28B gene polymorphisms and viral kinetics in HIV/ hepatitis C virus-coinfected patients treated with pegylated interferon and ribavirin. *AIDS.* 2011; 25(8):1025–1033. [PubMed: 21505315]
198. Suppiah V, Gaudieri S, Armstrong NJ, et al. *IL28B*, *HLA-C*, and *KIR* variants additively predict response to therapy in chronic hepatitis C virus infection in a European Cohort: a cross-sectional study. *PLoS Med.* 2011; 8(9):e1001092. [PubMed: 21931540]
199. Nozawa Y, Umemura T, Joshita S, et al. *KIR*, *HLA*, and *IL28B* variant predict response to antiviral therapy in genotype 1 chronic hepatitis C patients in Japan. *PLoS ONE.* 2013; 8(12):e83381. [PubMed: 24349500]
200. Prokunina-Olsson L, Muchmore B, Tang W, et al. A variant upstream of IFNL3 (*IL28B*) creating a new interferon gene IFNL4 is associated with impaired clearance of hepatitis C virus. *Nat Genet.* 2013; 45(2):164–171. Describes a newly discovered dinucleotide variant rs469415590 (TT or G) which is upstream of the *IL28B* gene, which is in complete linkage disequilibrium with rs12979860, is more strongly associated with hepatitis C virus clearance in individuals of African ancestry and maybe a better predictor than *IL28B* genotypes. This *IFNL4* genotypic variant also provides comparable information to treatment outcomes in Europeans and Asians. [PubMed: 23291588]
201. Amanzada A, Kopp W, Spengler U, Ramadori G, Mihm S. Interferon- λ 4 (IFNL4) transcript expression in human liver tissue samples. *PLoS ONE.* 2013; 8(12):e84026. [PubMed: 24376784]
202. Franco S, Aparicio E, Parera M, Clotet B, Tural C, Martinez MA. *IFNL4* rs469415590 variant is a better predictor than *IFNL3* (*IL28B*) rs12979860 of pegylated interferon-alpha/ribavirin therapy failure in hepatitis C virus/ HIV-1 coinfecting patients. *AIDS.* 2013; 28(1):133–136. [PubMed: 24072198]
203. Hamming OJ, Terczy ska-Dyla E, Vieyres G, et al. Interferon lambda 4 signals via the IFN λ receptor to regulate antiviral activity against HCV and coronaviruses. *EMBO J.* 2013; 32(23): 3055–3065. [PubMed: 24169568]
204. Kamal SM. Pharmacogenetics of hepatitis C: transition from interferon-based therapies to direct-acting antiviral agents. *Hepat Med.* 2014; 6:61. [PubMed: 25114601]
205. Muir AJ, Gong L, Johnson SG, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *IFNL3* (*IL28B*) genotype and PEG interferon- α -based regimens. *Clin Pharmacol Ther.* 2013; 95(2):141–146. [PubMed: 24096968]
206. Symonds W, Cutrell A, Edwards M, et al. Risk factor analysis of hypersensitivity reactions to abacavir. *Clin Ther.* 2002; 24(4):565–573. [PubMed: 12017401]
207. Aboulker J, Babiker A, Campagnucci A, et al. Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not

- previously been treated: the PENTA 5 randomised trial. *Lancet*. 2002; 359(9308):733–740. [PubMed: 11888583]
208. Martin AM, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by *HLA-B*5701* and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci USA*. 2004; 101(12): 4180–4185. [PubMed: 15024131]
 209. Phillips EJ, Wong GA, Kaul R, et al. Clinical and immunogenetic correlates of abacavir hypersensitivity. *AIDS*. 2005; 19(9):979–981. [PubMed: 15905681]
 210. Mallal S, Phillips E, Carosi G, et al. *HLA-B*5701* screening for hypersensitivity to abacavir. *N Engl J Med*. 2008; 358(6):568–579. [PubMed: 18256392]
 211. Phillips E, Mallal S. Successful translation of pharmacogenetics into the clinic. *Mol Diagn Ther*. 2009; 13(1):1–9. [PubMed: 19351209]
 212. Kis O, Zastre JA, Hoque MT, Walmsley SL, Bendayan R. Role of drug efflux and uptake transporters in atazanavir intestinal permeability and drug–drug interactions. *Pharm Res*. 2012; 1–15.
 213. Moss DM, San Kwan W, Liptrott NJ, et al. Raltegravir is a substrate for *SLC22A6*: a putative mechanism for the interaction between raltegravir and tenofovir. *Antimicrob Agents Chemother*. 2011; 55(2):879–887. [PubMed: 21078936]
 214. Nicol MR, Fedoriw Y, Mathews M, et al. Expression of six drug transporters in vaginal, cervical, and colorectal tissues: implications for drug disposition in HIV prevention. *J Clin Pharmacol*. 2014; 54(5):574–583.
 215. Ruane P, Dejesus E, Berger D, et al. Antiviral activity, safety, and pharmacokinetics/pharmacodynamics of tenofovir alafenamide (TAF) as 10-day monotherapy in HIV-1-positive adults. *J Acquir Immune Defic Syndr*. 2013; 63(4):449–455. [PubMed: 23807155]
 216. Ortiz M, Poloni ES, Furrer H, et al. No longitudinal mitochondrial DNA sequence changes in HIV-infected individuals with and without lipoatrophy. *J Infect Dis*. 2011; 203(5):620–624. [PubMed: 21227914]
 217. Nasi M, Guaraldi G, Orlando G, et al. Mitochondrial DNA haplogroups and highly active antiretroviral therapy-related lipodystrophy. *Clin Infect Dis*. 2008; 47(7):962–968. [PubMed: 18752438]
 218. Hulgan T, Tebas P, Canter JA, et al. Hemochromatosis gene polymorphisms, mitochondrial haplogroups, and peripheral lipoatrophy during antiretroviral therapy. *J Infect Dis*. 2008; 197(6): 858–866. [PubMed: 18419350]
 219. Kallianpur AR, Hulgan T, Canter JA, et al. Hemochromatosis (HFE) gene mutations and peripheral neuropathy during antiretroviral therapy. *AIDS*. 2006; 20(11):1503–1513. [PubMed: 16847405]
 220. Hulgan T, Hughes M, Sun X, et al. Oxidant stress and peripheral neuropathy during antiretroviral therapy: an AIDS clinical trials group study. *J Acquir Immune Defic Syndr*. 2006; 42(4):450–454. [PubMed: 16791116]
 221. Wester CW, Eden SK, Shepherd BE, et al. Risk factors for symptomatic hyperlactatemia and lactic acidosis among combination antiretroviral therapy-treated adults in Botswana: results from a clinical trial. *AIDS Res Hum Retroviruses*. 2012; 28(8):759–765. [PubMed: 22540188]
 222. Leung GP. Iatrogenic mitochondrial pathologies: a recent lesson from nucleoside/nucleotide reverse transcriptase inhibitors. *Adv Exp Med Biol*. 2012; 942:347–369. [PubMed: 22399431]
 223. Arenas-Pinto A, Weller I, Ekong R, et al. Common inherited mitochondrial DNA mutations and nucleoside reverse transcriptase inhibitor-induced severe hyperlactataemia in HIV-infected adults: an exploratory study. *Antiviral Ther*. 2012; 17(2):275–282.
 224. Feeney E, Chazallon C, O'Brien N, et al. Hyperlactataemia in HIV-infected subjects initiating antiretroviral therapy in a large randomized study (a substudy of the INITIO trial). *HIV Med*. 2011; 12(10):602–609. [PubMed: 21599820]
 225. Matthews LT, Giddy J, Ghebremichael M, et al. A risk-factor guided approach to reducing lactic acidosis and hyperlactatemia in patients on antiretroviral therapy. *PLoS ONE*. 2011; 6(4):e18736. [PubMed: 21494566]
 226. Fielder J, Rambiki K. Occurrence of stavudine-induced lactic acidosis in 3 members of an African family. *J Int Assoc Phys AIDS Care*. 2010; 9(4):236–239.

227. Thoden J, Lebrecht D, Venhoff N, Neumann J, Müller K, Walker UA. Highly active antiretroviral HIV therapy-associated fatal lactic acidosis: quantitative and qualitative mitochondrial DNA lesions with mitochondrial dysfunction in multiple organs. *AIDS*. 2008; 22(9):1093–1094. [PubMed: 18520357]
228. Wester CW, Okezie OA, Thomas AM, et al. Higher-than-expected rates of lactic acidosis among highly active antiretroviral therapy-treated women in Botswana: preliminary results from a large randomized clinical trial. *J Acquir Immune Defic Syndr*. 2007; 46(3):318–322. [PubMed: 18090299]
229. Kallianpur AR, Hulan T. Pharmacogenetics of nucleoside reverse-transcriptase inhibitor-associated peripheral neuropathy. *Pharmacogenomics*. 2009; 10(4):623–637. [PubMed: 19374518]
230. Kampira E, Kumwenda J, Van Oosterhout JJ, Dandara C. Mitochondrial subhaplogroups and differential risk of stavudine-induced lipodystrophy in Malawian HIV/AIDS patients. *Pharmacogenomics*. 2013; 14(16):1999–2004. [PubMed: 24279854]
231. Ward BA, Gorski JC, Jones DR, Hall SD, Flockhart DA, Desta Z. The cytochrome P450 2B6 (CYP2B6) is the main catalyst of efavirenz primary and secondary metabolism: implication for HIV/AIDS therapy and utility of efavirenz as a substrate marker of CYP2B6 catalytic activity. *J Pharmacol Exp Ther*. 2003; 306(1):287–300. [PubMed: 12676886]
232. Riska P, Lamson M, MacGregor T, et al. Disposition and biotransformation of the antiretroviral drug nevirapine in humans. *Drug Metab Dispos*. 1999; 27(8):895–901. [PubMed: 10421616]
233. Belanger AS, Caron P, Harvey M, Zimmerman PA, Mehlotra RK, Guillemette C. Glucuronidation of the antiretroviral drug efavirenz by UGT2B7 and an *in vitro* investigation of drug–drug interaction with zidovudine. *Drug Metab Dispos*. 2009; 37(9):1793–1796. [PubMed: 19487252]
234. Kwara A, Lartey M, Sagoe KW, Rzek NL, Court MH. CYP2B6 (c.516G→T) and CYP2A6 (*9B and/or *17) polymorphisms are independent predictors of efavirenz plasma concentrations in HIV-infected patients. *Br J Clin Pharmacol*. 2009; 67(4):427–436. [PubMed: 19371316]
235. Gutierrez F, Navarro A, Padilla S, et al. Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring. *Clin Infect Dis*. 2005; 41(11):1648–1653. [PubMed: 16267739]
236. Gounden V, van Niekerk C, Snyman T, George JA. Presence of the CYP2B6 516G> T polymorphism, increased plasma efavirenz concentrations and early neuropsychiatric side effects in South African HIV-infected patients. *AIDS Res Ther*. 2010; 7:32. [PubMed: 20723261]
237. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med*. 2005; 143(10):714–721. [PubMed: 16287792]
238. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS*. 2001; 15(1):71–75. [PubMed: 11192870]
239. Gallego L, Barreiro P, del Rio R, et al. Analyzing sleep abnormalities in HIV-infected patients treated with efavirenz. *Clin Infect Dis*. 2004; 38(3):430–432. [PubMed: 14727217]
240. Read TR, Carey D, Mallon P, et al. Efavirenz plasma concentrations did not predict cessation of therapy due to neuropsychiatric symptoms in a large randomized trial. *AIDS*. 2009; 23(16):2222–2223. [PubMed: 19773634]
241. Takahashi M, Ibe S, Kudaka Y, et al. No observable correlation between central nervous system side effects and EFV plasma concentrations in Japanese HIV type 1-infected patients treated with EFV containing HAART. *AIDS Res Hum Retroviruses*. 2007; 23(8):983–987. [PubMed: 17725414]
242. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence. *J Acquir Immune Defic Syndr*. 2005; 38(5):560–565. [PubMed: 15793366]
243. Gatanaga H, Hayashida T, Tsuchiya K, et al. Successful efavirenz dose reduction in HIV type 1-infected individuals with cytochrome P450 2B6 *6 and *26. *Clin Infect Dis*. 2007; 45(9):1230–1237. [PubMed: 17918089]

244. Haas DW, Severe P, Juste MAJ, Pape JW, Fitzgerald DW. Functional *CYP2B6* variants and virologic response to an efavirenz-containing regimen in Port-au-Prince, Haiti. *J Antimicrob Chemo*. 2014; 69(8):2187–2190.
245. Puls, R. Group tES. A daily dose of 400mg efavirenz (EFV) is non-inferior to the standard 600mg dose: week 48 data from the ENCORE1 study, a randomised, double-blind, placebo controlled, non-inferiority trial. Presented at: 7th IAS Conference on HIV Pathogenesis, Treatment and Prevention; Kuala Lumpur, Malaysia. 30 June–3 July 2013; Abstract WELBB01
246. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis*. 2005; 191(6):825–829. [PubMed: 15717255]
247. Uttayamakul S, Likanonsakul S, Manosuthi W, et al. Effects of *CYP2B6* G516T polymorphisms on plasma efavirenz and nevirapine levels when co-administered with rifampicin in HIV/TB co-infected Thai adults. *AIDS Res Ther*. 2010; 7:8. [PubMed: 20338069]
248. Ramachandran G, Ramesh K, Hemanth Kumar AK, et al. Association of high T allele frequency of *CYP2B6* G516T polymorphism among ethnic south Indian HIV-infected patients with elevated plasma efavirenz and nevirapine. *J Antimicrob Chemother*. 2009; 63(4):841–843. [PubMed: 19218571]
249. Saitoh A, Sarles E, Capparelli E, et al. *CYP2B6* genetic variants are associated with nevirapine pharmacokinetics and clinical response in HIV-1-infected children. *AIDS*. 2007; 21(16):2191–2199. [PubMed: 18090046]
250. Dong BJ, Zheng Y, Hughes MD, et al. Nevirapine pharmacokinetics and risk of rash and hepatitis among HIV-infected sub-Saharan African women. *AIDS*. 2012; 26(7):833–841. [PubMed: 22301417]
251. Martin AM, Nolan D, James I, et al. Predisposition to nevirapine hypersensitivity associated with *HLA-DRB1*0101* and abrogated by low CD4 T-cell counts. *AIDS*. 2005; 19(1):97–99. [PubMed: 15627041]
252. Littera R, Carcassi C, Masala A, et al. HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. *AIDS*. 2006; 20(12):1621–1626. [PubMed: 16868443]
253. Likanonsakul S, Rattanatham T, Feangvad S, et al. *HLA-Cw*04* allele associated with nevirapine-induced rash in HIV-infected Thai patients. *AIDS Res Ther*. 2009; 6:22. [PubMed: 19845952]
254. Pavlos, R.; Rive, C.; McKinnon, E., et al. Specific binding characteristics of HLA alleles associated with nevirapine hypersensitivity. Presented at: Conference on Retroviruses and Opportunistic Infections; Boston, MA, USA. 3–6 March 2014; Abstract 804
255. Antela A, Ocampo A, Gómez R, et al. Liver toxicity after switching or simplifying to nevirapine-based therapy is not related to CD4 cell counts: results of the TOSCANA study. *HIV Clin Trials*. 2010; 11(1):11–17. [PubMed: 20400407]
256. Wit FW, Kesselring AM, Gras L, et al. Discontinuation of nevirapine because of hypersensitivity reactions in patients with prior treatment experience, compared with treatment-naïve patients: the ATHENA cohort study. *Clin Infect Dis*. 2008; 46(6):933–940. [PubMed: 18271750]
257. Kesselring AM, Wit FW, Sabin CA, et al. Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy. *AIDS*. 2009; 23(13):1689–1699. [PubMed: 19487907]
258. Lubomirov R, di Iulio J, Fayet A, et al. ADME pharmacogenetics: investigation of the pharmacokinetics of the antiretroviral agent lopinavir coformulated with ritonavir. *Pharmacogenet*. 2010; 20(4):217–230.
259. Bertrand J, Treluyer JM, Panhard X, et al. Influence of pharmacogenetics on indinavir disposition and short-term response in HIV patients initiating HAART. *Eur J Clin Pharmacol*. 2009; 65(7): 667–678. [PubMed: 19440701]
260. Elens L, Yombi JC, Lison D, Wallemacq P, Vandercam B, Haufroid V. Association between *ABCC2* polymorphism and lopinavir accumulation in peripheral blood mononuclear cells of HIV-infected patients. *Pharmacogenomics*. 2009; 10(10):1589–1597. [PubMed: 19842932]
261. Hartkoorn RC, San Kwan W, Shallcross V, et al. HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by *SLCO1B1* polymorphisms. *Pharmacogenet Genomics*. 2010; 20(2):112–120. [PubMed: 20051929]

262. Kohlrausch FB, De Cássia Estrela R, Barroso PF, Suarez-Kurtz G. The impact of *SLCO1B1* polymorphisms on the plasma concentration of lopinavir and ritonavir in HIV-infected men. *Br J Clin Pharmacol*. 2010; 69(1):95–98. [PubMed: 20078617]
263. Arnedo M, Taffe P, Sahli R, et al. Contribution of 20 single nucleotide polymorphisms of 13 genes to dyslipidemia associated with antiretroviral therapy. *Pharmacogenet Genomics*. 2007; 17(9):755–764. [PubMed: 17700364]
264. Tarr PE, Rotger M, Telenti A. Dyslipidemia in HIV-infected individuals: from pharmacogenetics to pharmacogenomics. *Pharmacogenomics*. 2010; 11(4):587–594. [PubMed: 20350140]
265. Kile DA, MaWhinney S, Aquilante CL, Rower JE, Castillo-Mancilla JR, Anderson PL. A population pharmacokinetic–pharmacogenetic analysis of atazanavir. *AIDS Res Hum Retroviruses*. 2012; 28(10):1227–1234. [PubMed: 22394315]
266. Annaert P, Ye Z, Stieger B, Augustijns P. Interaction of HIV protease inhibitors with OATP1B1, 1B3, and 2B1. *Xenobiotica*. 2010; 40(3):163–176. [PubMed: 20102298]
267. Burt T, Dhillon S. Pharmacogenomics in early-phase clinical development. *Pharmacogenomics*. 2013; 14(9):1085–1097. [PubMed: 23837482]
268. Phillips EJ, Mallal SA. Pharmacogenetics of drug hypersensitivity. *Pharmacogenomics*. 2010; 11(7):973–987. [PubMed: 20602616]

Executive summary

Pathogenesis of antimicrobial efficacy & toxicity, & pharmacogenomics associations

- Efficacy of antimicrobial agents and their toxicities, both type A and/or type B reactions, are affected by pharmacokinetic (PK) and pharmacodynamic (PD) profiles of individual agents, which are in turn influenced by absorption, distribution, metabolism and elimination (ADME) enzymes, and by immunologic interactions between MHC peptides, drug molecules and T cells. Some toxicities result from mitochondrial dysfunction.
- Polymorphisms in ADME genes such as CYPs, N-acetyl transferases (NATs), glutathione-S-transferase (GSTs), UDP-glucuronosyltransferases (UGTs), P-gp/multidrug resistance protein (MDRs) and organic anion transporters (OATs)/organic cation transporters (OCTs) may influence gene expression, further influencing the antimicrobial effectiveness or risk of toxicities (mainly type A reactions). Examples of implicated antimicrobials include antimalarial drugs, isoniazid, sulfamethoxazole, voriconazole, HIV agents (tenofovir, efavirenz and protease inhibitors), and proton pump inhibitors for *Helicobacter pylori* treatment.
- Polymorphisms in HLA genes influence risk of type B hypersensitivity reactions. Multiple MHC class I genes have been implicated in high-risk associations. Associations include *HLA-DRB1*15:01-DQB1*06:02*, *HLA-A*30:02* and *HLA-B*18:01* with amoxicillin-clavulanic acid; *HLA-B*57:01* with abacavir and flucloxacillin; *HLA-B*13:01* with dapsone; and multiple class I and II HLA alleles with nevirapine hypersensitivity phenotypes.
- Mitochondrial gene mutations may increase risk for toxicity with antimicrobial agents. Examples include 12sRNA mutations with aminoglycoside ototoxicity; linezolid-induced neurotoxicities and myelotoxicities; and peripheral neuropathy and lipoatrophy with thymidine analogs.
- Other key pharmacogenomics associations also exist (e.g., *IL28B* polymorphisms and hepatitis C treatment response), which have been relevant to treatment outcome.

Clinical practice & future role of antimicrobial pharmacogenomics

- Although many antimicrobial pharmacogenomic discoveries have been made, few have translated into clinical practice. Major hurdles still exist, and clinical studies are needed in many settings.
- Technological advances may improve our understanding of interactions between host, drug and pathogen genetic signatures and may better explain pathogenesis, individualize medical therapy, and result in safer and more efficacious antimicrobial therapy.

Figure 1. Complex relationships between various drug, pathogen and host factors affecting antimicrobial treatment outcome

ADR: Adverse drug reaction; PD: Pharmacogenomics; PK: Pharmacokinetics

Modified and reproduced with written permission from *Pharmacogenomics and Personalized Medicine* [9].

Figure 2. Isoniazid metabolic pathways

GST: Gluthathione-S-transferase; NAT: *N*-acetyl transferase.

Table 1

Drug uptake transporters and their interactions with antimicrobial agents.

Family	Member	Tissue distribution	Cellular localization	Antimicrobial substrates	Important roles
SLCO	OATP2B1	Liver, intestine, placenta	Basolateral	Benzylpenicillin	CNS distribution
	OATP1B1	Liver	Basolateral	Benzylpenicillin, rifampin	Hepatic uptake
	OATP1B3	Liver	Basolateral	Rifampin	Hepatic uptake
SLC22	OAT1	Kidney, brain	Basolateral	Cidofovir, acyclovir, tetracycline	Renal uptake
	OAT3	Kidney, brain	Basolateral	Valacyclovir, tetracycline	Renal uptake
	OAT4	Kidney, placenta	Apical	Tetracycline	Renal secretion
	OCT1	Liver, brain, small intestine	Basolateral	Quinine	Hepatic/renal uptake
ABCB	MDR1 (P-gp)	Kidney, liver, brain, small intestine	Apical	Erythromycin, protease inhibitors, voriconazole, mefloquine, quinine, chloroquine	Oral absorption, renal secretion, biliary excretion, CNS distribution
ABCC	MRP2	Liver, kidney, small intestine	Apical	Ampicillin, ceftriaxone, tenofovir	Biliary excretion, renal secretion

ABC: Adenosine triphosphate-binding cassette; MDR: Multidrug resistance protein; MRP: Multidrug resistance-associated protein; OCT: Organic cation transporter; OAT: Organic anion transporter; OATP: Organic anionic transporting polypeptide.

Reproduced with permission from [6], *Clinical Pharmacology and Therapeutics*, Macmillian Publishers Ltd © (2005)

Table 2

Gell and Coombs classification for hypersensitivity reactions.

Classification	Effector response	Immunopathologic mechanisms	Clinical features	Time of onset	Examples of associated antimicrobials
Type I, immediate	IgE	Mast cell/basophil degranulation and histamine release	Urticaria, angioedema, anaphylaxis	Immediate (<30 min) after exposure	β -lactams, fluoroquinolones
Type II, cytotoxic	IgM, IgG, complement	FcR-dependent cell destruction	Cytopenias, nephritis	1–2 weeks after exposure [†]	β -lactams, quinine
Type III, immune complex	IgM, IgG, complement	Immune complex deposition in organs	Serum sickness, vasculitis	1–2 weeks after exposure [†]	Penicillin, cefactor (serum-sickness like reaction)
Type IV, delayed	T lymphocytes				
IVa	Th-1	Cell-mediated immunity, monocytes, macrophages, IFN- γ	Contact dermatitis	A few days to weeks after exposure [‡]	Neomycin
IVb	Th-2	Eosinophilic inflammation, IL-4, IL-5	DRESS	2–6 weeks after exposure [‡]	Nevirapine, vancomycin, sulfa antimicrobials, dapsone
IVc	CTL	CD4/CD8 ⁺ T cells, perforin, granzymes	SJS/TEN	4 days to 1 month after exposure [‡]	Nevirapine, sulfa antimicrobials, β -lactams
IVd	T lymphocytes	Neutrophils, IL-8	AGEP	Within 1 week of exposure [‡]	Aminopenicillins, pristinamycin, hydroxychloroquine, sulfa antimicrobials, fluoroquinolones, terbinafine

[†] Shorter duration of onset with pre-formed antibodies.

[‡] Shorter duration of onset with pre-sensitized T cells.

AGEP: Acute generalized exanthematous pustulosis; CTL: Cytotoxic T-lymphocytes; DRESS: Drug rash, eosinophilia and systemic symptoms; Ig: Immunoglobulin; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis; Th: T helper.

Table 3

Genetic associations (excluding HLA) with antimicrobial agent pharmacokinetics and pharmacodynamics.

Genes	Allele	Phenotype	Drugs	Phenotypic associations	Level of evidence [†]	Selected references
<i>CYP1A1</i>	rs1048943, 2454A>G with rs4646903, 3798T>C (e.g., *2B)	EM	Amodiaquine	Neutropenia with <i>CYP1A1</i> /EM genotypes	4	[14,15]
	rs1048943, 2454A>G (e.g., *2C)	EM				
<i>CYP1B1</i>	Reference (*1)	EM	Amodiaquine	Neutropenia with <i>CYP1B1</i> /EM genotypes	4	[15]
	rs10012, 142C>G with rs1056827, 355G>T (e.g., *2)	EM				
	rs10012, 142C>G, rs1056827, 355G>T with rs1056836, 4326C>G (e.g., *6)	SM				
		SM				
<i>CYP2A6</i>	rs1801272, 1799T>A (e.g., *2)	SM	Artesunate	Increased treatment failure with <i>CYP2A6</i> SM or null genotypes	4	[16–18]
	rs5031016, 6558T>C (e.g., *7)	SM		Possible contribution to apparent 'artemisinin resistance' in southeast Asia with <i>CYP2A6</i> SM genotypes	NA	[19,20]
	rs28399433, 48T>G (e.g., *9)	SM	Efavirenz	Increased plasma exposure with <i>CYP2A6</i> SM genotypes	1b	[21–23]
	rs28399454, 5065G>A (e.g., *17)	SM				
	*4A to *4H	Null				
<i>CYP2B6</i>	rs3745274, 516G>T (e.g., *6)	SM	Efavirenz	Increased plasma exposure with <i>CYP2B6</i> SM genotypes	1b	[24–32]
	rs28399499, 983T>C (e.g., *18)	SM		Increased CNS side effects with <i>CYP2B6</i> SM genotypes	2b	[33–37]
	rs4803419, 15582C>T (e.g., *1C)	SM	Nevirapine	Increased plasma exposure with <i>CYP2B6</i> SM genotypes	1b	[30,38–42]
	rs3745274, 516G>T (e.g., *6)	SM		Increased skin toxicity with <i>CYP2B6</i> SM genotypes	1b	[43]
	rs28399499, 983T>C (e.g., *18)	SM	Artemisinins	Increased treatment failure with <i>CYP2B6</i> SM genotypes (theoretical)	4	[17–18,44]
<i>CYP2C8</i>	rs4803419, 15582C>T (e.g., *1C)	SM				
	rs3745274, 516G>T (e.g., *6)	SM				
<i>CYP2C8</i>	rs11572103, 805A>T (e.g., *2)	SM	Chloroquine	Increased resistance with <i>CYP2C8</i> *2 and <i>CYP2C8</i> *3	3	[45,46]

Genes	Allele	Phenotype	Drugs	Phenotypic associations	Level of evidence [†]	Selected references
<i>CYP2C19</i>	rs11572080, 416G>A and rs10509681, 1196A>G (e.g., *3)	SM	Amodiaquine	Increased resistance with <i>CYP2C8</i> *2 and <i>CYP2C8</i> *3	4	[45,47,48]
				Hepatotoxicity and agranulocytosis with <i>CYP2C8</i> *2 and <i>CYP2C8</i> *3	4	[14,17,47,48]
				Increased minor abdominal pain with <i>CYP2C8</i> *2	3	[47]
				Increased <i>Helicobacter pylori</i> eradication with <i>CYP2C19</i> SM genotypes	2a	[49–51]
<i>CYP2E1</i>	rs4986893, 626G>A (e.g., *3)	SM	Voriconazole	Increased plasma exposure with <i>CYP2C19</i> SM genotypes	1b	[52–56]
	rs17885098, 99C>T with rs3758581, 991A>G (e.g., *17)	UM		Increased visual side effects and hepatotoxicity with <i>CYP2C19</i> SM genotypes	3	[52–57]
			Etravirine	Increased plasma exposure with <i>CYP2C19</i> SM genotypes	3	[58]
			Nelfinavir	Increased plasma exposure with <i>CYP2C19</i> SM genotypes	1b	[27]
			Biguanides	Increased plasma exposure with <i>CYP2C19</i> UM genotypes	3	[59]
<i>CYP2E1</i>	Reference (*1A)	EM	Isoniazid	Increased hepatotoxicity with <i>CYP2E1</i> *1A/*1A genotype	2b	[60,61]
	rs72559710, 1132G>A (e.g., *2)	SM		Increased hepatotoxicity with <i>CYP2E1</i> *1A-*6-*1D haplotype	3	[62,63]
<i>NAT1</i>	rs3813867, -1293G>C, rs2031920, -1053C>T with 7632T>A (e.g., *5A)					
	rs3813867, -1293G>C and rs2031920, -1053C>T (e.g., *5B)					
<i>NAT1</i>	(*10)	FA	Sulfamethoxazole	Decreased hypersensitivity reactions in HIV-infected patients with <i>NAT1</i> FA genotypes	3	[64]
	*11	FA				
<i>NAT2</i>	*4	FA	Isoniazid	Increased hepatotoxicity with <i>NAT2</i> SA genotypes	2b	[60,65–70]
	*5	SA		Increased tuberculosis treatment failure with <i>NAT2</i> FA genotypes	2b	[65]
	*6	SA	Sulfamethoxazole	Increased hypersensitivity reactions in HIV-infected patients with <i>NAT2</i> SA genotypes	3	[71]
	*7	SA				

Genes	Allele	Phenotype	Drugs	Phenotypic associations	Level of evidence [†]	Selected references
	*I2 *I3	SA SA				
<i>GSTM1</i>	*0	Null	Isoniazid	Increased hepatotoxicity with <i>GSTM1</i> null genotype	2b	[60,62,72]
<i>GCLC</i>	rs761142T>G		Sulfamethoxazole	Increased hypersensitivity in HIV-infected patients with rs761142T>G allele	3	[73]
<i>UGT1A1</i>	*28, rs887829	–	Atazanavir	Increased unconjugated hyperbilirubinemia with <i>UGT1A1</i> SM genotypes	1b	[74,75]
				Increased drug discontinuation <i>UGT1A1</i> SM genotypes	2b	[76,77]
			Indinavir	Increased unconjugated hyperbilirubinemia with <i>UGT1A1</i> SM genotypes	1b	[78]
<i>G6PD</i>	Deficiency		Dapsone Primaquine	Increased hemolytic anemia Increased hemolytic anemia	1b 1b	[79] [79]
<i>ABCB1</i>	3435C>T and others		Many	Associations reported but none consistently replicated	2b	[52,80,81]
<i>OAT1, OAT3, ABCC2, ABCC4</i>			Tenofovir	Increased renal tubulopathy	2b	[82–91]
<i>IL28B</i>	rs12979860C>T rs8099917T>G		Pegylated interferon	Increased hepatitis C virologic response with rs12979860 CC genotype, rs8099917 TT genotype	1a	[92–95]
<i>ITPA</i>	rs1127354A rs7270101 C		Ribavirin	Decreased anemia with hepatitis C treatment with rs1127354 A and rs7270101 C genotypes	1b	[96–101]
<i>PDE6</i>			Voriconazole	Increased visual side effects	4	[52]

[†] Levels of evidence (PharmGKB [102]): Level 1a = Annotation for a variant-drug combination in a Clinical Pharmacogenetics Implementation Consortium (CPIC) or medical society-endorsed pharmacogenomics guideline, or implemented at a Pharmacogenomics Research Network (PGRN) site, or in another major health system; Level 1b = Annotation for a variant-drug combination in which the preponderance of evidence shows an association. This association must be replicated in more than one cohort with significant p-values and preferably with a strong effect size; Level 2a = Annotation for a variant-drug combination that qualifies for level 2b, in which the variant is within a Very Important Pharmacogene (VIP) as defined by PharmGKB where their functional significance is more likely known; Level 2b = Annotation for a variant-drug combination with moderate evidence of an association. This association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small; Level 3 = Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination

evaluated in multiple studies but lacking clear evidence of an association; Level 4 = Annotation based on a case report, nonsignificant study, *in vitro*, molecular or functional assay evidence only EM: Extensive metabolizer; FA: Fast acetylator; NA: Not applicable; SA: Slow acetylator; SM: Slow metabolizer; UM: Ultrarapid metabolizer.

Table 4

MHC class I and II polymorphism associations with hypersensitivity reactions to antimicrobials.

HLA associations	Population studied	Antimicrobial hypersensitivity	Level of Evidence [†]	Selected references
<i>HLA-DRB1*15:01–DQB1*06:02</i> and <i>HLA-A*02:01</i>	White Europeans and Americans	AC-DILI, predominant cholestatic/mixed pattern	1b	[103–106]
<i>HLA-DRB1*07</i> and <i>HLA-A1</i>	Northern Europeans	Protective from AC-DILI	3	[105]
<i>HLA-A*30:02</i> and <i>HLA-B*18:01</i>	Spanish	AC-DILI, predominant hepatocellular injury	3	[107]
<i>HLA-B*13:01</i>	Han Chinese	Dapsone hypersensitivity syndrome	1b	[108,109]
<i>HLA-B*57:01</i>	European	Flucloxacillin DILI	1b	[110]
	All races	Abacavir hypersensitivity syndrome	1a	[111–113]
<i>HLA-DRB1*01</i> , <i>HLA-DRB1*01:01</i>	Australian, European, white	Nevirapine hepatotoxicity phenotype (abrogated by low CD4 count for <i>HLA-DRB1*01:01</i>)	1b	[43,114]
<i>HLA-DRB1*01:02</i>	White, European South African	Nevirapine hepatotoxicity phenotype	2b	[40,115]
<i>HLA-Cw*8</i> or <i>HLA-Cw*8-B*14</i> haplotype	Italian, Japanese	Nevirapine DIHS/DRESS (cutaneous phenotype)	2b	[43,116–119]
<i>HLA-Cw*4</i>	Han Chinese, white, black, southeast Asians		1b	[77,115,120–122]
<i>HLA-C*04:01</i>	White, southeast Asians		2b	
<i>HLA-B*35</i>	Southeast Asian, whites		1b	
<i>HLA-B*35:05</i>	Asian, southeast Asians		1b	
<i>HLA-B*35/Cw*4</i>			2b	
<i>HLA-B*35:01</i>	Australian		2b	
<i>HLA-C*04:01</i>	Malawians	Nevirapine SJS/TEN	3	[123]

[†] Levels of evidence (PharmGKB [102]): Level 1a = Annotation for a variant-drug combination in a Clinical Pharmacogenetics Implementation Consortium (CPIC) or medical society-endorsed pharmacogenomics guideline, or implemented at a Pharmacogenomics Research Network (PGRN) site, or in another major health system; Level 1b = Annotation for a variant-drug combination in which the preponderance of evidence shows an association. This association must be replicated in more than one cohort with significant p-values and preferably with a strong effect size; Level 2a = Annotation for a variant-drug combination that qualifies for level 2b, in which the variant is within a Very Important Pharmacogene (VIP) as defined by PharmGKB where their functional significance is more likely known; Level 2b = Annotation for a variant-drug combination with moderate evidence of an association. This association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small; Level 3 = Annotation for a variant-drug combination based on a single significant (not yet replicated) study or annotation for a variant-drug combination evaluated in multiple studies but lacking clear evidence of an association; Level 4 = Annotation based on a case report, nonsignificant study, *in vitro*, molecular or functional assay evidence only.

AC: Amoxicillin-clavulanate; DIHS: Drug-induced hypersensitivity syndrome; DILI: Drug-induced liver injury; DRESS: Drug rash with eosinophilia and systemic symptoms; SJS: Stevens–Johnson syndrome; TEN: Toxic epidermal necrolysis.

Table 5

Mitochondrial DNA polymorphism associations with antimicrobial toxicities.

Mitochondrial gene mutations	Population studied	Associated phenotypes [†]	Level of Evidence [‡]	Selected references
12sRNA mutations: 1555A>G, 1494C>T, 1095T>C, ET961Cn, 961T> G, 961T> C	Various (note: prevalence of 1555A>G mutation in the white population is 1 in 500)	Aminoglycoside ototoxicity	1b	[124–127]
16s rRNA mutation: A2706G	Case report	Lactic acidosis with linezolid	3	[128]
Haplogroups				
L1 c	Non-Hispanic black North American	Peripheral neuropathy	3	[129,130]
L3e1	Black South African	Hypertriglyceridemia	3	[131]
L0a2, L2a	African (Malawian)	Peripheral neuropathy	3	[132]
W, I, T, H, K	European (Italians) and/or non-Hispanic white North American	Lipoatrophy/ lipodystrophy	3	[133–135]
H, clade HV, U	European (Spanish) and/or non-Hispanic white North American	Insulin resistance	3	[136,137]
I	European and/or non-Hispanic white North American	Dyslipidemia	3	[134]
Clade JT, T, H, clade HV	European (Spanish)	Atherogenic risk	3	[136]
T	Non-Hispanic white North American	Peripheral neuropathy	3	[138,139]
J, H3, U5a	Non-Hispanic white North American	Neuroretinal disorders	3	[140]

[†] Associated phenotypes with antiretroviral therapy for haplogroups.

[‡] Levels of evidence (PharmGKB [102]): Level 1a = Annotation for a variant–drug combination in a Clinical Pharmacogenetics Implementation Consortium (CPIC) or medical society-endorsed pharmacogenomics guideline, or implemented at a Pharmacogenomics Research Network (PGRN) site, or in another major health system; Level 1b = Annotation for a variant–drug combination in which the preponderance of evidence shows an association. This association must be replicated in more than one cohort with significant p-values and preferably with a strong effect size; Level 2a = Annotation for a variant–drug combination that qualifies for level 2b, in which the variant is within a Very Important Pharmacogene (VIP) as defined by PharmGKB where their functional significance is more likely known; Level 2b = Annotation for a variant–drug combination with moderate evidence of an association. This association must be replicated, but there may be some studies that do not show statistical significance, and/or the effect size may be small; Level 3 = Annotation for a variant–drug combination based on a single significant (not yet replicated) study or annotation for a variant–drug combination evaluated in multiple studies but lacking clear evidence of an association; Level 4 = Annotation based on a case report, nonsignificant study, *in vitro*, molecular or functional assay evidence only.

Table 6

WHO recommended options for artemisinin combination therapy for treatment of *Plasmodium falciparum* malaria.

Regimen	Artemisinin	Partner long-acting drug
AL	Artemether	Lumefantrine
AS+AQ	Artesunate	Amodiaquine
AS+MQ	Artesunate	Mefloquine
AS+SP	Artesunate	Sulfadoxine and pyrimethamine

AL: Artemether and lumefantrine; AS: Artemisinins; AQ: Amodiaquine; MQ: Mefloquine; SP: Sulfadoxine and pyrimethamine Data taken from [190].