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**Pharmacogenomics of
Antiretroviral Drug
Metabolism and Transport**

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Abstract

Antiretroviral therapy has markedly reduced morbidity and mortality for persons living with human immunodeficiency virus (HIV). Individual tailoring of antiretroviral regimens has the potential to further improve the long-term management of HIV through the mitigation of treatment failure and drug-induced toxicities. While the mechanisms underlying anti-HIV drug adverse outcomes are multifactorial, the application of drug-specific pharmacogenomic knowledge is required in order to move toward the personalization of HIV therapy. Thus, detailed understanding of the metabolism and transport of antiretrovirals and the influence of genetics on these pathways is important. To this end, this review provides an up-to-date overview of the metabolism of anti-HIV therapeutics and the impact of genetic variation in drug metabolism and transport on the treatment of HIV. Future perspectives on and current challenges in pursuing personalized HIV treatment are also discussed.

1. INTRODUCTION

Human immunodeficiency virus (HIV) continues to be one of the greatest public health concerns worldwide. Although a cure for HIV infection has not been found, the advancement of antiretroviral therapy (ART) and pre- and postexposure prophylaxis is moving humanity ever closer to the total eradication of HIV by decreasing the risk of viral transmission. There are two major subtypes of HIV, namely HIV-1 and HIV-2, with HIV-1 being the most virulent and prevalent (1, 2). A 2019 report by the Joint United Nations Program on HIV/AIDS (UNAIDS) shows a significant global decrease in HIV-related mortality in the last decade, from an approximate 1.5 million in 2008 to 0.8 million in 2018 (3). Meanwhile, the number of new HIV infections per year continues to decline, though gradually (4). This decrease in new HIV infections is largely due to the development of more effective ART, which reduces the risk of the transmission of the virus between serodiscordant sexual partners by lowering the viral load of the infected partner to an undetectable level (5). Although ART has improved HIV outcomes, novel anti-HIV drugs are still needed to improve quality of life and further prevent viral transmission. This pursuit is not without challenges. Successful HIV treatment currently requires lifelong adherence to therapeutics, some of which are associated with adverse events such as dyslipidemia, hyperglycemia, hyperlactatemia, hepatotoxicity, and osteoporosis (6). Personalization of HIV treatment may help to abrogate these adverse effects (7).

1.1. Drug Metabolism

Drug metabolism refers to the biotransformation of a drug by metabolizing enzymes in a living organism. The enzymes involved in drug metabolism are expressed throughout the body but are predominantly present in the liver. During biotransformation, drugs can undergo modifications in which a functional group is introduced or revealed. This process is referred to as phase I metabolism. Phase II metabolism involves conjugation of a drug with a charged species such as glutathione, sulfate, or glucuronic acid (**Figure 1**). Drug oxidation and glucuronic acid conjugation, catalyzed by the cytochromes P450 (abbreviated as P450 when referring to a generic cytochrome P450 or the broad family; CYP is used when referring to a specific P450, e.g., CYP3A4) superfamily of enzymes and UDP-glucuronosyltransferases (UGTs), respectively, are central to the metabolism of a wide range of drugs, including many anti-HIV drugs (8, 9). The metabolites that are produced from these reactions are generally polar and therefore more readily excreted from the body than the drug itself (9, 10). As a result, drug metabolism plays an important role in governing therapeutic responses, including the duration and magnitude of a drug's pharmacological action. Additionally, drug metabolites can be more or less pharmacologically or toxicologically active than the parent drug (11–13). Beyond metabolizing enzymes, the therapeutic effects of a drug can also be regulated by drug transporters, which are cell membrane proteins that transport drugs into and out of the cell (**Figures 1 and 2**). Genetic variation in drug metabolism and transport can contribute to interindividual differences in treatment outcomes (7, 14). Thus, personalizing ART requires understanding and predicting the impact of genetics on drug metabolism and/or transport through the application of pharmacogenomics.

1.2. Pharmacogenomics

Pharmacogenomics, which is the study of how genetics influences a person's response to drugs, seeks to guide the rational selection and dosing of therapeutics. To this end, many of the analyses within pharmacogenomics are aimed at understanding the impact of single-nucleotide polymorphisms (SNPs) on drug metabolism and disposition. SNPs of particular interest are those that

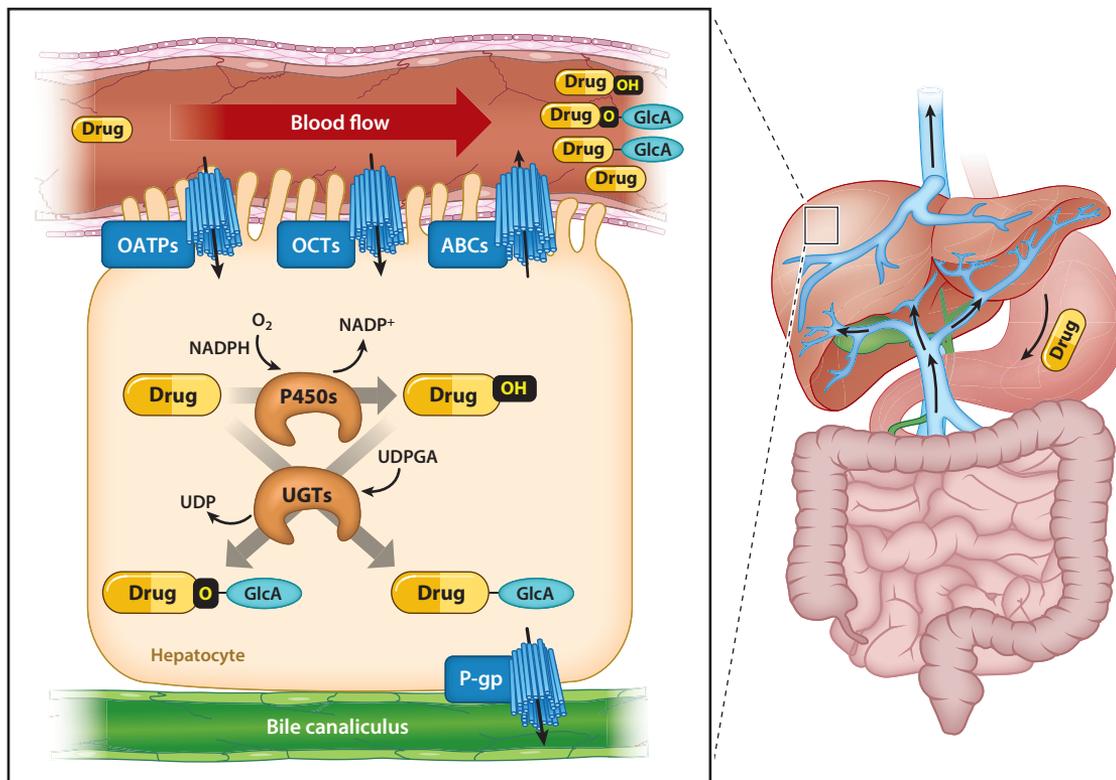


Figure 1

The first-pass metabolism of HIV drugs upon oral administration. After being swallowed, a drug is absorbed via the gut wall and intestine. The drug is actively transported [transporters discussed in this review are shown here: ATP-binding cassette transporters (ABCs), organic anion–transporting peptides (OATPs), organic cation transporters (OCTs), and P-glycoprotein (P-gp; a member of ABCs)] or passively diffuses into the cell, or both. From the gut wall and intestine, the drug enters the hepatic portal system. An abundance of drug-metabolizing enzymes are present in the intestine and liver. In the liver, drug metabolism occurs inside hepatocytes, where the drug undergoes modifications (e.g., oxidation by P450s) or conjugations [e.g., glucuronidation by UDP-glucuronosyltransferases (UGTs)]. The resulting metabolites are excreted into the bile canalculus or reenter the blood, after which they can be excreted by the kidneys.

impact the expression and/or activity of metabolizing enzymes and drug transporters and result in a change in drug efficacy and safety profiles (15). In order to standardize the annotation of these SNPs, pharmacogenomics employs a star nomenclature system (e.g., *CYP2B6**6) to denote genetic variants that are prevalent and may have clinical relevance. In this nomenclature system, *1 is typically assigned to the so-called wild-type allele. The impacts of several individual SNPs on the disposition of HIV drugs and/or clinical outcomes discussed in this review are summarized in **Table 1**. The goal of this review is to provide a comprehensive guide to the current knowledge of anti-HIV drug metabolism and transport pharmacogenomics with an eye toward leveraging these insights to inform the personalization of HIV treatment and prevention.

2. CLASSIFICATION OF HIV DRUGS

Based on the action of drugs on specific phases of the HIV life cycle (**Figure 2**), antiretroviral medications can be generally classified into four categories: entry inhibitors, reverse transcriptase

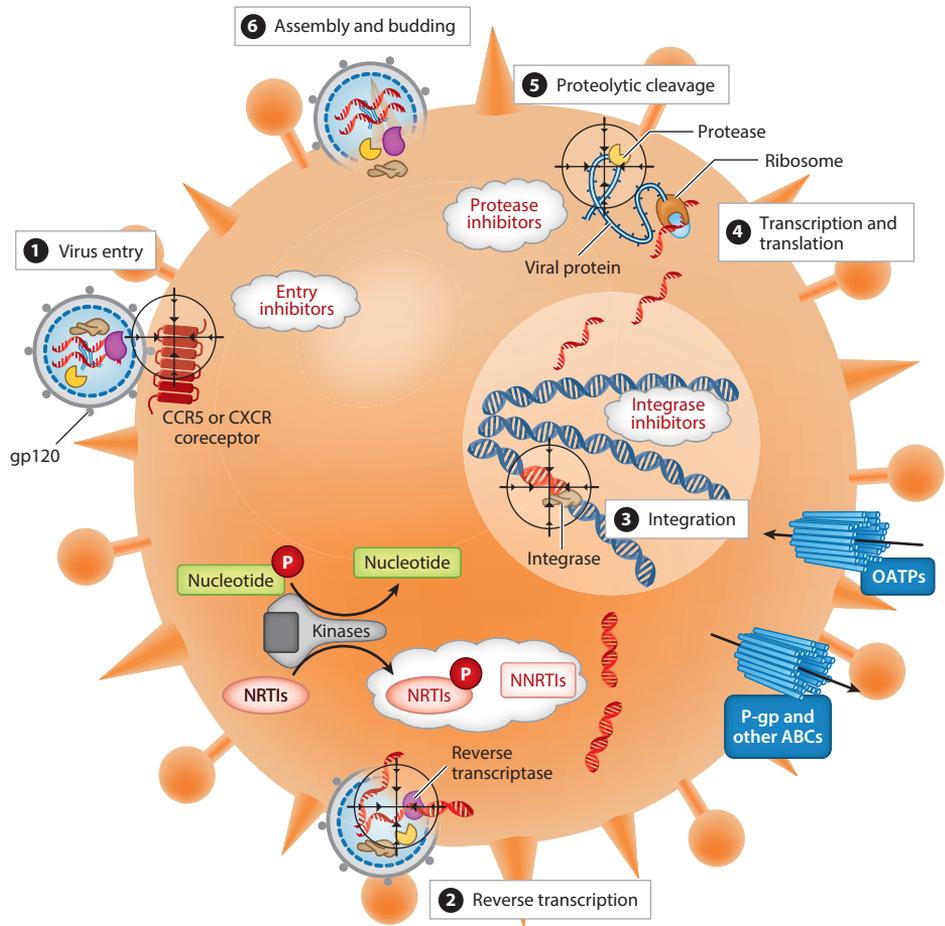


Figure 2

Life cycle of HIV-1 and action of antiretrovirals in CD4⁺ cells. The life cycle is initiated by the binding of viral envelope glycoprotein gp120 to the receptors on a CD4⁺ cell (process targeted by entry inhibitors) (①). Once inside the cell, HIV releases and uses reverse transcriptase to convert viral RNA into DNA [a process targeted by nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs); NRTIs must be phosphorylated by host kinases inside the cell in order to become pharmacologically active] (②). Subsequently, viral integrase catalyzes the incorporation of viral DNA into the host genome (a process targeted by integrase inhibitors) (③), which allows HIV to hijack host cellular machinery to produce long chains of viral proteins (④). Hydrolysis of these long chains of viral proteins by viral protease yields each individual component (a process targeted by protease inhibitors) (⑤) that is assembled into newly formed HIV progeny ready to bud off (⑥). An interplay between efflux and influx transporters, as well as simple diffusion, plays a role in the transport of HIV drugs in CD4⁺ cells.

inhibitors, integrase inhibitors, and protease inhibitors. A typical ART regimen consists of three drug components from at least two different classes (16). Due to the high mutation rate of HIV, no individual antiretroviral drug has been shown to have long-term therapeutic effects when administered alone. The combination of antiretrovirals overcomes drug resistance by suppressing the pools of potential resistance mutations. However, the nature of multidrug regimens and the necessity of long-term adherence to antiretrovirals present challenges in chronic management and

Table 1 The influence of genetic variation on antiretroviral drug exposure and clinical outcomes

Gene or protein	Drug affected	Alleles evaluated	Reported consequences (compared with wild type)
CYP3A5	Maraviroc	*2, *3, *6, and *7	41% higher plasma concentrations and 66% lower apparent clearance in homozygous dysfunctional groups (25)
CYP2C19	Etravirine	*2	8–38% decrease in intrinsic clearance (95)
	Nelfinavir		Rate of metabolism to hydroxy- <i>t</i> -butylamide metabolite decreases by 50%; no significant impact on efficacy or toxicity (134)
CYP2B6	Efavirenz	Loss-of-function alleles	Neuropsychiatric adverse events associated with decreased intrinsic clearance (88, 89)
	Nevirapine	<i>G516T</i>	Decreased intrinsic clearance; no clear association with adverse events (74)
UGT1A1	Dolutegravir	*6, *28, and other reduced-function alleles	Neuropsychiatric adverse events associated with decreased intrinsic clearance (125)
	Atazanavir	*6 and *28	Hyperbilirubinemia associated with decreased intrinsic clearance (140, 141)
	Indinavir		
	Raltegravir	*28	Decreased intrinsic clearance; no clear association with adverse events (111)
<i>HLA-B</i>	Abacavir	*5701	Strongly correlated with hypersensitivity (46)
OCT1	Lamivudine	<i>P283L</i> and <i>P341L</i>	Significantly decreased intrinsic clearance (56)
OCT2	Lamivudine	<i>T199I</i> , <i>T201M</i> , and <i>A270S</i>	
<i>ABCBI</i>	Nevirapine	<i>C3435T</i>	Decreased risk of hepatotoxicity (73)

often require pharmacovigilance to avoid potential drug–drug interactions and adverse reactions, especially in the presence of comorbidities.

2.1. Entry Inhibitors

HIV infection begins with viral particles anchoring on the surface of a host cell (e.g., helper T cell) by interacting with the surface CD4 glycoprotein. Once it binds to CD4, the viral envelope glycoprotein gp120 and the subunit gp41 engage one or both of the coreceptors CCR5 and CXCR4 and undergo conformation changes that lead to the fusion of the two membranes (17). Although it is an attractive target for anti-HIV intervention, the viral gp120 has remained elusive in the context of drug discovery due to its high degree of variability and limited access to the binding sites (18). For example, fostemsavir is currently being developed as an entry inhibitor that blocks the conformational change of gp120; however, due to the high variation in the amino acid sequence and the flexibility of gp120 of HIV-1, some HIV strains are naturally resistant to fostemsavir (19). Therefore, most entry inhibitors act by targeting the coreceptors CCR5 and/or CXCR4. Approved by the US Food and Drug Administration (FDA) in 2003, enfuvirtide was the first-in-class entry inhibitor used in combination therapy for the treatment of HIV. As a synthetic polypeptide, enfuvirtide mimics a conserved amino acid sequence of the envelope protein gp41, which serves as a key domain for the binding of the coreceptors, and therefore disrupts the fusion process. Enfuvirtide has not been found to be a substrate of P450s or UGTs (20). Additionally, since enfuvirtide is active extracellularly, cell membrane transport is unlikely to be important for its actions (21).

The second entry inhibitor, maraviroc, was approved by the FDA in 2007 and is a CCR5 antagonist that blocks the viral gp120 from interacting with the coreceptor. Maraviroc is principally metabolized by CYP3A5 and to a lesser extent by CYP3A4 (22). CYP3A4 and CYP3A5 share almost identical substrate specificity due to significant sequence homology (23); therefore, their distinct activities toward maraviroc are of interest. *N*-Dealkylation and mono- and di-oxygenation, as well as oxygenation followed by glucuronidation, were reported for maraviroc metabolism (22, 24). Meanwhile, an in vitro study using human liver microsomes indicated that the homozygous loss-of-function allele *CYP3A5**3/*3 had 79% less enzymatic activity compared to the wild-type homozygous *CYP3A5**1/*1 (22), while a clinical study observed 41% lower maraviroc plasma concentrations and 66% higher clearance in the homozygous wild-type group compared to the homozygous dysfunctional groups (*CYP3A5**2, *3, *6, and *7) (25). These results may partially explain clinically observed interindividual variation in maraviroc drug responses, suggesting that maraviroc may be underdosed in patients possessing homozygous *CYP3A5**1 alleles.

2.2. Reverse Transcriptase Inhibitors

Upon entering the cell, the HIV RNA genome is converted into DNA by reverse transcriptase (Figure 2). As an essential enzyme in viral replication, reverse transcriptase has been a primary target for anti-HIV therapeutics. Reverse transcriptase inhibitors are divided into subcategories of nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), each having distinctly different mechanisms of action. In addition to being used for the treatment of HIV, the combination of NRTIs emtricitabine and tenofovir disoproxil fumarate is prescribed for pre- and postexposure prophylaxis (26, 27). Therefore, understanding the metabolism and pharmacogenomics of these NRTIs is important to ensure their success in preventing HIV transmission.

2.2.1. Nucleoside/nucleotide reverse transcriptase inhibitors. NRTIs are analogs of naturally occurring nucleosides or nucleotides that lack a necessary hydroxyl for continuing polymerization. As a result, the incorporation of NRTIs into the nascent proviral DNA by reverse transcriptase prevents its elongation and thus terminates the DNA synthesis process. NRTIs are substrates of both viral reverse transcriptase and host cell DNA synthase; the former accounts for NRTI antiretroviral activity, while the latter contributes to drug toxicity.

Inactive in their formulated forms, NRTIs must be phosphorylated (by kinases in host cells) to their pharmacologically active metabolites: nucleoside triphosphate analogs that inhibit HIV reverse transcription. This inhibition is achieved by competition with the natural reverse transcriptase substrates and incorporation into DNA, resulting in chain termination. The kinases that perform phosphorylation of NRTIs are less well understood from a drug metabolism perspective than are the classic metabolizing enzymes such as P450s and UGTs. This is in part attributable to the predominant biological role of these kinases in the phosphorylation of endogenous substrates, as opposed to the clearance of xenobiotics. Of note, the phosphorylation of NRTIs occurs within the target cell, and the presence of NRTIs in the plasma is not a robust marker of clinical efficacy or toxicity (28). However, the intracellular concentration of the phosphorylated metabolites has been demonstrated to serve as a better indicator of virologic effectiveness (29). NRTIs require sequential phosphorylation events to form a pharmacologically active nucleoside triphosphate analog, and multiple kinases have been observed to catalyze these phosphorylation steps (30) (summarized in Table 2). Thus, the activation of NRTIs is likely sensitive to a range of factors, including cell type-specific expression of the relevant kinases and disease states that impact kinase expression (28). Further, although currently unknown, genetic variation in

Table 2 Summary of proposed stepwise activation of NRTIs and the major enzymes for corresponding biotransformation

NRTI	Step 1		Step 2		Step 3		Step 4		Reference(s)
	Reaction	Enzyme	Reaction	Enzyme	Reaction	Enzyme	Reaction	Enzyme	
Zidovudine	Phs	TK1	Phs	TMPK	Phs	NDPK	NA	NA	23, 28
Tenofovir	Phs	AK2	Phs	PKM, PKLR, CKM	NA	NA	NA	NA	30
Emtricitabine	Phs	DCK	Phs	TK1	Phs	CMPK1, PGK1	NA	NA	42
Abacavir	Phs	AK	Dea	ADAL1	Phs	GUK1	Phs	NA ^a	45, 46
Didanosine	Phs	C5NT	Amn	ADSS, ASL	Phs	AK	Phs	NDPK	50
Lamivudine	Phs	DCK	Phs	U/CMPK	Phs	PGK, NDPK	NA	NA	54, 55
Stavudine	Phs	TK	Phs	TMPK	Phs	NDPK	NA	NA	59

^aVarious enzymes are involved, and the principal enzymes have not been well characterized.

Abbreviations: ADAL1, adenosine deaminase-like protein 1; ADSS, adenylosuccinate synthetase; AK, adenosine kinase; AK2, adenylate kinase 2; Amn, amination; ASL, adenylosuccinate lyase; C5NT, cytosolic 5'-nucleotidase; CKM, creatine kinase muscle; CMPK1, cytidine monophosphate kinase 1; DCK, deoxycytidine kinase; Dea, deamination; GUK1, guanylate kinase 1; NA, not available; NDPK, nucleoside-diphosphate kinase; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; PGK, 3-phosphoglycerate kinase; PGK1, phosphoglycerate kinase 1; Phs, phosphorylation; PKLR, pyruvate kinase liver and blood cell; PKM, pyruvate kinase muscle; TK, thymidine kinase; TK1, thymidine kinase 1; TMPK, thymidylate kinase; U/CMPK, uridine/cytidine monophosphate kinase.

NRTI-phosphorylating kinases may alter drug response (31). This uncertainty represents an important knowledge gap, since differential ability to activate NRTIs could explain interindividual variability in treatment outcomes that cannot be attributed to adherence alone.

Zidovudine was the first antiretroviral medication for HIV and was approved by the FDA in 1987. Zidovudine undergoes three phosphorylation steps to form the active triphosphate, with the second phosphorylation being rate limiting (32). As a thymidine analog, the first phosphorylation to monophosphate is primarily catalyzed by thymidine kinase 1 (23); the monophosphate is then phosphorylated to diphosphate by thymidylate kinases, followed by the final phosphorylation by nucleoside-diphosphate kinases to produce the active triphosphate metabolite (28). Zidovudine is also subject to glucuronidation by UGT2B7 (33), which accounts for approximately 75% of the elimination of the drug via renal excretion (34). Induction of UGTs by rifampin significantly increases the oral clearance of zidovudine (35). In addition, the reduction of the 3'-azido to 3'-amino group results in the formation of 3'-amino-3'-deoxythymidine, which is highly toxic for human bone marrow cells (36). Interestingly, P450 enzymes were suggested to be involved in 3'-amino-3'-deoxythymidine formation, though the contribution of specific isozymes remains unknown (37).

Approved in 2001 by the FDA for treatment of HIV as well as in 2008 for hepatitis B, tenofovir (administered as tenofovir alafenamide or tenofovir disoproxil fumarate) is widely prescribed to treat HIV infections. In addition, tenofovir is prescribed for HIV pre- and post-exposure prophylaxis. In its original form, which contains a phosphonate group, tenofovir is highly hydrophilic and does not readily diffuse through cell membranes. To improve its bioavailability, tenofovir is prescribed as prodrugs tenofovir disoproxil fumarate or tenofovir alafenamide, which are hydrolyzed by esterases to release tenofovir. As an NRTI, tenofovir must be phosphorylated to its pharmacologically active tenofovir-diphosphate metabolite. Unlike other NRTIs, tenofovir contains a pseudophosphate group (phosphonate), and therefore only two phosphorylation steps are required to form the pharmacologically active triphosphate (tenofovir-diphosphate). Several kinases have been found to phosphorylate tenofovir in a cell/tissue-specific manner (30). In peripheral blood

mononuclear cells and vaginal tissue, the first phosphorylation is carried out by adenylate kinase 2, while the second phosphorylation is catalyzed by either pyruvate kinase muscle or pyruvate kinase liver/red blood cell (30). In colonic tissue, the first phosphorylation is also catalyzed by adenylate kinase 2, but the second phosphorylation is catalyzed primarily by muscle creatine kinase (30). Of note, while these pyruvate and creatine kinases are named for the cells and tissues in which they were first identified and found to be active, they are expressed in a range of cells and/or tissues. Genetic variation has been found in these kinases (30, 38, 39), but the influence of these polymorphisms on phosphorylation of NRTIs remains largely unexplored. Genetic variants of these kinases have been studied in a cohort of 505 individuals from the United States, Thailand, and South Africa (39). In that study, 19 of the 505 subjects (~4%) carried at least one kinase variant that is predicted (using *in silico* tools) to be deleterious, which could result in low or no tenofovir activation. Further *in vitro* assays using recombinant enzymes confirmed decreased activity toward tenofovir phosphorylation by certain naturally occurring adenylate kinase 2 variants such as K28R, T194I, V19G, A55V, and K62E compared to the wild type (39), indicating that genetics may impact tenofovir activation. Apart from phosphorylation, tenofovir undergoes minimal hepatic metabolism and is primarily cleared in the unchanged form, via renal excretion (40). In addition, tenofovir and tenofovir disoproxil fumarate have been shown to inhibit CYP2C9 and CYP2E1 (41).

Emtricitabine is used in combination for HIV treatment and prevention. Emtricitabine undergoes three phosphorylation steps to form the active metabolite, emtricitabine-triphosphate. In peripheral blood mononuclear cells, the first and second phosphorylations are catalyzed by deoxycytidine kinase and thymidine kinase 1, respectively, whereas the final phosphorylation is carried out by both cytidine monophosphate kinase 1 and phosphoglycerate kinase 1 (42). A quantitative reverse transcriptase PCR assay indicated that the abundance of cytidine monophosphate kinase 1 messenger RNA (mRNA) was eightfold greater in colon tissue than in vaginal tissue, whereas phosphoglycerate kinase 1 mRNA abundance is fourfold greater in vaginal than colonic tissue, which could result in differential formation of the active emtricitabine-triphosphate in these tissues (43). A genetic study of 498 HIV-uninfected participants reported that 44 of the 498 individuals (9%) carried at least one variant of a kinase involved in phosphorylation of emtricitabine (42). Emtricitabine has not been found to undergo significant metabolism by P450s or UGTs (24). However, it is both a substrate and an inhibitor of ATP-binding cassette transporter (ABC) C1 (44).

Abacavir was approved by the FDA in 1998 for the treatment of HIV. Unlike most NRTIs, abacavir activation involves four metabolic reactions. Adenosine kinases carry out the formation of abacavir monophosphate, which undergoes deamination by adenosine deaminase-like protein 1 (45) to form carbovir monophosphate; the second phosphorylation is catalyzed by guanylate kinase 1, followed by the conversion to triphosphate by a number of kinases, including creatine kinases, pyruvate kinases, nucleoside diphosphate kinases, phosphoglycerate kinases, and phosphoenolpyruvate carboxykinase (46). Interestingly, abacavir diphosphate and triphosphate are not detectable within cells (47), which suggests that deamination of abacavir monophosphate to carbovir monophosphate is necessary for the subsequent phosphorylation. Besides intracellular phosphorylation, abacavir is also subject to hepatic metabolism, including oxidation catalyzed by alcohol dehydrogenases and glucuronidation by UGTs (48); however, the contribution of individual enzymes within these families to abacavir metabolism has not been fully characterized. The pharmacogenetic study of abacavir is almost exclusively focused on the human leukocyte antigen B (*HLA-B*) gene. The variant allele *HLA-B*5701* is strongly correlated with abacavir hypersensitivity, which is clinically observed in 5–8% of patients during the first 6 weeks of abacavir treatment (46). A double-blind, randomized study with 1,956 patients showed that prospective screening of the *HLA-B*5701* allele could prevent abacavir hypersensitivity (49).

In 1991, didanosine became the second FDA-approved HIV medication. Phosphorylation of didanosine to didanosine-monophosphate is carried out by cytosolic 5'-nucleotidases. Didanosine-monophosphate is then converted to dideoxy adenosine monophosphate by the synergistic action of adenylosuccinate synthetase and adenylosuccinate lyase (50). The second and third phosphorylations of dideoxy adenosine monophosphate to dideoxy adenosine diphosphate and dideoxy adenosine triphosphate may be carried out by adenylate kinases (51, 52). Didanosine is not subject to hepatic metabolism, and no inhibitory effect on P450s has been demonstrated (53).

Lamivudine is an NRTI that was approved by the FDA in 1995. Deoxycytidine kinase carries out the first phosphorylation of lamivudine to lamivudine-monophosphate (54). Uridine/cytidine monophosphate kinase catalyzes the phosphorylation of lamivudine-monophosphate to lamivudine-diphosphate (54), whereas both 3-phosphoglycerate kinase and nucleoside diphosphate kinases catalyze the third phosphorylation step to generate the active lamivudine-triphosphate (55). Lamivudine is mostly excreted unchanged and undergoes minimal hepatic metabolism (28). On the other hand, drug transporters involved in renal excretion have an important impact on the clearance of lamivudine. A transport kinetics study using oocytes expressing organic cation transporter (OCT)1 and OCT2 suggested that, compared to the wild type, the intrinsic clearance of lamivudine decreased significantly in the presence of OCT1 variants P283L and P341L and OCT2 variants T199I, T201M, and A270S (56). These variants are all commonly found in Asian populations (57). Further *in vivo* study is required to evaluate the impact of drug transporter pharmacogenetics on lamivudine disposition.

Stavudine has relatively high toxicity compared to other NRTIs, which has limited the use of this drug (58). Stavudine is metabolized intracellularly to mono-, di-, and triphosphate metabolites sequentially by thymidine kinases, thymidylate kinases, and nucleoside diphosphate kinases (59). Interestingly, as a 2',3'-didehydro-2',3'-dideoxy analog of thymidine, stavudine has only 0.17% affinity toward thymidine kinases compared to that of thymidine (60), and the intracellular accumulation of stavudine triphosphate may be associated with adverse reactions such as lipodystrophy (61). Similar to tenofovir, emtricitabine, and lamivudine, stavudine is not susceptible to hepatic metabolism, and limited study has been carried out on its interactions with these metabolizing enzymes.

2.2.2. Nonnucleoside/nucleotide reverse transcriptase inhibitors. Unlike NRTIs, NNRTIs are chemically distinct from nucleotides/nucleosides, do not get incorporated into DNA, and therefore do not require intracellular activation via phosphorylation. The NNRTI binding pocket is located on the p66 subunit of HIV-1 reverse transcriptase, which is approximately 10 Å from the active site for DNA polymerization (62, 63). Generally, NNRTIs bind to the allosteric site of HIV-1 reverse transcriptase and induce a conformational change, inhibiting catalysis. As such, NNRTIs act as noncompetitive inhibitors in contrast to the competitive inhibition by NRTIs (62). Although HIV-2 reverse transcriptase shares significant homology with HIV-1 reverse transcriptase, most NNRTIs are inactive toward HIV-2, primarily due to HIV-2 lacking the Tyr181 and Tyr188 residues that are required for binding (64).

The first-in-class NNRTI nevirapine was approved by the FDA in 1996 as a first-line medication for HIV infections. In some settings, nevirapine is prescribed as a single dose to prevent mother-to-child transmission of HIV (65). Despite its efficacy, nevirapine can have side effects, including severe skin rash and hepatotoxicity, and as such, nevirapine carries an FDA black box warning (66). Pharmacovigilance of the plasma nevirapine concentration is warranted for patients with compromised livers (67). Several studies suggest that biotransformation of nevirapine to 12-hydroxy-nevirapine is likely to underlie nevirapine-induced toxicity (68–70). In addition to 12-hydroxy-nevirapine, other monooxygenated metabolites have been identified, including 2-, 3-,

and 8-hydroxy-nevirapine (71). Nevirapine is primarily metabolized by CYP3A4, CYP2D6, and CYP2B6 and to a lesser extent by CYP3A5, giving rise to the above monooxygenated metabolites. A phenotyping study using cDNA-expressed P450s demonstrated that the formation of 2- and 3-hydroxy-nevirapine was exclusively catalyzed by the CYP3A subfamily (CYP3A4 and CYP3A5) and CYP2B6, respectively, whereas formation of 8- and 12-hydroxy-nevirapine was likely mediated by multiple P450s (72). All four monooxygenated metabolites can be further glucuronidated in subsequent phase II metabolism, which accounts for 80% of the elimination of nevirapine (71). Besides hepatic metabolizing enzymes, several clinical studies have shown that ABCs are involved in the hepatotoxicity of nevirapine-containing regimens (73–75). Specifically, homozygosity for the loss-of-function *ABCB1* 3435C>T SNP is associated with a decreased risk of hepatotoxicity (73). In addition, the *CYP2B6* 516G>T variant affects nevirapine clearance: Those with the homozygous *CYP2B6* 516TT genotype exhibit an estimated nevirapine clearance of 1.86 L/h compared to that of 2.62 L/h and 2.95 L/h for heterozygous *CYP2B6* 516GT and homozygous *CYP2B6* 516GG, respectively (74).

Since being approved by the FDA in 1998, efavirenz has been one of the most widely used antiretroviral drugs. Efavirenz is primarily metabolized by CYP2B6 to 8-hydroxy-efavirenz and 8,14-dihydroxy-efavirenz. CYP2A6 catalyzes the formation of 7-hydroxy-efavirenz. The 8-hydroxy-efavirenz metabolite is the predominant P450-dependent metabolite of efavirenz (76, 77). As with nevirapine, chronic use of efavirenz has been associated with hepatotoxicity, resulting in approximately 10% of patients discontinuing treatment due to intolerable side effects (78). It has been suggested that efavirenz induces hepatic cell death, but a study using primary human hepatocytes demonstrated that 8-hydroxy-efavirenz stimulates cell death via activation of c-Jun N-terminal kinase and Bcl-2-interacting mediator of cell death (79). Neurotoxicity resulting in cognitive and mood disorders has also been reported for efavirenz-containing regimens (80–83). A study using primary neurons found that efavirenz and its metabolites 7- and 8-hydroxy-efavirenz induce dendritic spine injury in a concentration-dependent manner (84). Notably, 8-hydroxy-efavirenz produced at least an order of magnitude more damage to the neurons than the parent efavirenz or the other monooxygenated metabolite 7-hydroxy-efavirenz. Compartmentalization of efavirenz metabolites was revealed by studying the bodily fluid of patients on an efavirenz-based regimen (77). In this study, 8-hydroxy-efavirenz was detected in blood plasma, seminal plasma, and cerebrospinal fluid, whereas 7-hydroxy-efavirenz and 8,14-dihydroxyefavirenz were only found in blood and seminal plasma, and none of the metabolites were found to exhibit pharmacologic activity toward HIV-1. Besides P450-mediated metabolism, efavirenz is glucuronidated by UGT2B7 to form efavirenz-*N*-glucuronide (85). The formation of secondary metabolites such as efavirenz-7-*O*-glucuronide and efavirenz-8-*O*-glucuronide (these metabolites represent oxidation of efavirenz to the 7- or 8-hydroxy-efavirenz metabolite, followed by glucuronidation) is carried out by several UGT isoforms (86). Interestingly, in vivo, a decrease in the levels of oxygenated metabolites and a commensurate increase in the levels of efavirenz-*N*-glucuronide were observed for *CYP2B6* loss-of-function alleles (47, 87). In the context of efavirenz-mediated toxicity, Clinical Pharmacogenetics Implementation Consortium guidelines for *CYP2B6* and efavirenz suggest an increased risk of adverse effects for carriers of decreased-function variant alleles (88). A clinical study has suggested an a priori 35% dosage reduction in patients carrying homozygous *CYP2B6**6 variant alleles, which are prevalent among people of African origin (89).

Unfortunately, the chronic use of first-generation NNRTIs such as nevirapine and efavirenz has led to the emergence of drug-resistant viral strains, which often results in treatment failure (90, 91). The second-generation NNRTI etravirine was approved by the FDA in 2008 and has proven resilient toward resistant viral strains (92). A structural study demonstrated that the potency of etravirine against drug-resistant mutations was due to torsional flexibility of the diarylpyrimidine

structure of etravirine that can bind to reverse transcriptase in multiple conformations (92). Therefore, etravirine has been suggested for treatment-experienced patients who have developed drug resistance to nevirapine and efavirenz (93). In an in vitro study using complementary DNA (cDNA)-expressed P450s and inhibition assays, etravirine was found to be primarily metabolized by CYP2C19 and CYP3A4/5 and to a lesser extent by CYP2B6 and CYP2C9 (94). In addition, assays performed using human liver microsomes that were genotyped as homozygous for the loss-of-function *CYP2C19*2* allele indicated a 75–100% decrease in the formation of oxygenated metabolites of etravirine (94). Similarly, a clinical study showed that carriers of the *CYP2C19*2* variant allele (both homozygous and heterozygous) had 8–38% less clearance compared to the wild type (95). Although etravirine has been shown to induce CYP3A4/5 via pregnane X receptor-mediated modulation in vitro (94, 96), no clinically significant etravirine-mediated drug-drug interactions have been observed, and therefore dosage adjustment is generally not required (97).

Rilpivirine is another second-generation NNRTI and a diarylpyrimidine derivative that provides the advantage of flexible binding to the HIV-1 viral reverse transcriptase. Rilpivirine was approved by the FDA in 2011 for the treatment of HIV infection. An in vitro study using a panel of cDNA-expressed P450s and UGTs indicated that rilpivirine was primarily metabolized by CYP3A4 and CYP3A5, leading to the formation of mono- and dioxygenated metabolites, whereas glucuronidation was mostly carried out by UGT1A1 and UGT1A4 to form rilpivirine-*O*-glucuronide (oxidation followed by glucuronidation) and rilpivirine-*N*-glucuronide (direct glucuronidation), respectively (98). A population pharmacokinetics study in 249 adult HIV-positive patients suggested minimal impact of genetic variance in CYP3A4, CYP3A5, CYP2C19, UGT1A1, or UGT1A4 on rilpivirine clearance, likely due to the multiple metabolic pathways involved (99). Although no significant drug-drug interactions have been reported, rilpivirine has been shown to significantly inhibit P-glycoprotein, organic anion-transporting peptides 1B1 and 1B3, and CYP3A4, CYP2C19, and CYP2B6 while inducing the mRNA expression of CYP3A4 and UGT1A3 (100). Therefore, further investigations are warranted on the potential interactions of rilpivirine with substrates of these transporters and metabolizing enzymes.

Doravirine was approved by the FDA in 2018 for treatment-naïve patients and has shown non-inferiority as well as an improved safety profile compared to the standard-of-care regimens (101, 102). An in vivo study involving healthy human volunteers suggested that doravirine is primarily metabolized by CYP3A4 and CYP3A5 (103). Doravirine has not been found to exhibit inhibition toward major P450s, UGTs, or P-glycoprotein (101), while several clinical investigations have indicated that it has a low propensity for causing drug-drug interactions (104, 105). Therefore, doravirine has the potential to become a preferred drug in its class and is currently being investigated in treatment-experienced patients (101).

2.3. Integrase Inhibitors

Integrase is one of three viral enzymes (the other two being protease and reverse transcriptase) essential to HIV replication, and it is an excellent therapeutic target since there is no equivalent enzyme within host cells; therefore, the inhibition of viral integrase does not interfere with normal cell functions (106). After reverse transcription, the viral DNA is integrated into the host DNA by integrase, enabling the transcription of viral DNA to produce viral proteins (**Figure 2**). As such, blocking the function of integrase can halt the retroviral replication process and terminate the viral life cycle. Integrase inhibitors generally act by chelating Mg^{2+} , a critical cofactor for viral DNA binding in the integrase active site, thereby preventing integrase from interacting with the viral DNA (107). Four integrase inhibitors—raltegravir, elvitegravir, dolutegravir, and bictegravir—have been approved by the FDA to treat HIV infections. Of note, due to the high barrier to

resistance and tolerability of drugs in this class, particularly dolutegravir, the 2018 World Health Organization recommendations suggest administering dolutegravir in combination with a two-NRTI backbone as the preferred first-line HIV treatment regimen (108).

The first-in-class integrase inhibitor raltegravir received FDA approval in 2007, and despite its inconvenient twice-daily dosing schedule, it has proven effective against drug-resistant HIV-1 infection when the standard-of-care regimen has failed (109). Based on a study conducted with healthy volunteers, raltegravir is primarily metabolized by UGT1A1; this represents a major route of elimination (110). Although clinically significant drug-drug interactions have not been reported for raltegravir, caution should be exercised when it is coadministered with strong UGT1A1 inhibitors or inducers. The *UGT1A1*28* genetic variant can have a significant impact on raltegravir metabolism: Patients carrying homozygous *UGT1A1*28* variant alleles were found to have greater raltegravir plasma concentrations when compared to wild type (111). However, no correlation between this pharmacokinetic effect and treatment outcomes has been established.

In 2008, elvitegravir became the second integrase inhibitor approved by the FDA as a part of a fixed-dose combination (elvitegravir/cobicistat/emtricitabine/tenofovir). Elvitegravir is rapidly metabolized by CYP3A subfamily enzymes, resulting in an average half-life of 3.5 h after a single dose (112). As such, elvitegravir is prescribed with pharmacokinetic boosters such as cobicistat and ritonavir, which inhibit the human CYP3A subfamily, resulting in higher plasma concentrations and a longer half-life of elvitegravir than can be achieved with lower doses (113). For example, when 100 mg of elvitegravir was coadministered twice daily with 100 mg of ritonavir, a 20-fold increase in AUC and a threefold increase of half-life to 9.5 h were observed, compared to twice-daily administration of 100 mg of elvitegravir alone (112). Due to the success of such pharmacokinetic boosting, pharmacokinetic boosters are now broadly utilized in HIV treatment; this strategy has been applied to nearly all protease inhibitors (114–116). Despite the benefits, an altered metabolic profile resulting from concomitant use of pharmacokinetic boosters also represents a challenge for dose adjustment of other coadministered drugs in order to avoid drug-drug interactions. Serious and sometimes fatal drug-drug interactions have been reported with the administration of pharmacokinetic boosters (117–119). Therefore, evaluation of potential drug-drug interactions is warranted for the treatment of HIV-associated comorbidities under boosted antiretroviral regimens. However, most NRTIs are not subject to P450-mediated metabolism and therefore are generally not affected when coadministered with pharmacokinetic boosters (120).

Raltegravir and elvitegravir have overlapping and modest genetic barriers for resistance (121), which has spurred interest in the development of second-generation integrase inhibitors, one of which—dolutegravir—was approved by the FDA in 2013. Unlike twice-daily raltegravir, dolutegravir is dosed once daily and, unlike elvitegravir, does not require pharmacokinetic boosting (122). Dolutegravir is extensively metabolized by UGT1A1 to the inactive dolutegravir-*O*-glucuronide metabolite and to a lesser extent by CYP3A4-mediated oxidation (123). Decreased oral clearance was observed among carriers of *UGT1A1* reduced-function alleles (124). Neuropsychiatric adverse events were more often observed for patients carrying *UGT1A1*6* and/or *UGT1A1*28* reduced-function alleles than those with normal alleles (125). In addition, a clinical study reported potential drug-drug interactions with abacavir, which is likely due to the competition between dolutegravir and abacavir for UGT1A1 (126). Thus, further investigation of potential interactions of dolutegravir with other UGT1A1 substrates is warranted.

Bictegravir, the newest addition to the integrase inhibitors family, was approved by the FDA in 2018. Bictegravir is currently only available as part of a bictegravir/emtricitabine/tenofovir alafenamide combination tablet (127). Similar to dolutegravir, bictegravir is metabolized by CYP3As and UGT1A1 (128). More information on drug-drug interactions, the influence of pharmacogenomics, and metabolite profiles of bictegravir is expected in future studies.

2.4. Protease Inhibitors

After the integration of viral DNA into the host genome, transcription of viral DNA produces polyproteins that are inactive until cleaved by viral protease into individual functional parts (**Figure 2**). Inhibition of the viral protease prevents the maturation of viral particles and blocks the infectivity of nascent virions (129). Generally, protease inhibitors resemble the tetrahedral intermediate of the substrate and competitively bind to the protease active site to disable its enzymatic function (130). However, due to the high mutation rate of HIV, the protease active site can change rapidly to block accessibility to protease inhibitors, rendering them ineffective.

To date, nine protease inhibitors have been approved by the FDA for HIV treatment, including saquinavir, indinavir, ritonavir, nelfinavir, amprenavir, lopinavir, atazanavir, tipranavir, and darunavir. Except for tipranavir, all protease inhibitors are peptidomimetics and share a common feature: a chiral secondary hydroxyl group that makes critical contact with the protease catalytic Asp25/25' residues (131). Most protease inhibitors are primarily metabolized by the CYP3A subfamily during phase I metabolism, except for nelfinavir, which is metabolized primarily by CYP2C19 (132). Biotransformation of nelfinavir by CYP2C19 leads to the formation of an active hydroxy-*t*-butylamide metabolite with antiretroviral activities similar to the parent nelfinavir (133). The rate of metabolism of nelfinavir to the hydroxy-*t*-butylamide metabolite is decreased by 50% in patients carrying the *CYP2C19**2 loss-of-function allele as compared to wild type, but no significant changes in efficacy or toxicities due to this genetic variation were found (134). The oral bioavailability of protease inhibitors is generally low (<68%), with a median half-life of approximately 6 h (135); thus, a frequent dosing schedule is required. To overcome their short half-lives, concomitant use of pharmacokinetic boosters that selectively inhibit CYP3A4 activity has made once-daily dosing possible for protease inhibitors (136). While the protease inhibitor ritonavir is often used as a booster due to its potent CYP3A4 inhibition, another commonly used booster, cobicistat, does not have antiretroviral activity (137). Despite the similarities between ritonavir and cobicistat, switching the boosters should be systematically reviewed to anticipate proper dosage adjustment (138). Concurrent administration of protease inhibitors with CYP3A4 inducers is often problematic in that the resulting decrease of protease inhibitor plasma concentrations often leads to reduced efficacy and the development of drug resistance (129). In addition to being substrates of CYP3A4, all protease inhibitors also inhibit CYP3A and other P450 enzymes with varying degrees of potency (24, 129). This often results in altered pharmacokinetic profiles of other coadministered drugs such as ethinyl estradiol and statins (129, 139). Therefore, caution should be exercised when coadministering protease inhibitors with drugs that are known substrates of the corresponding P450 enzymes.

In addition to phase I metabolism, several protease inhibitors undergo glucuronidation during phase II metabolism. Of note, atazanavir and indinavir reportedly induce hyperbilirubinemia among patients with Gilbert's syndrome carrying *UGT1A1**28 and/or *UGT1A1**6 alleles, which ultimately leads to the discontinuation of this treatment in this subpopulation (140, 141).

Most protease inhibitors are substrates of drug transporters, such as multidrug resistance proteins (e.g., P-glycoprotein) (142) and organic anion-transporting polypeptides (143), which affects their intracellular accumulation at the site of viral replication. Significant interindividual variation in protease inhibitor plasma concentrations can be attributed in part to genetic polymorphisms in genes that encode these drug transporters (144). For example, overexpression of P-glycoprotein has been associated with the accelerated acquisition of drug resistance (145). Targeted inhibition of P-glycoprotein has been shown to increase the penetration of HIV protease inhibitors into sanctuary sites, e.g., the brain and testes (146). Overall, pharmacogenomic factors that modulate metabolism and active transport can have significant implications for the disposition and distribution of protease inhibitors and thereby influence their pharmacokinetic and safety profiles.

3. CONCLUSION AND FUTURE CONSIDERATIONS

Understanding the metabolism of HIV drugs can provide important insights into the mechanisms that govern interindividual variability in treatment outcomes. The application of pharmacogenomic insights has the potential to inform the personalization of HIV treatment and the rational selection and dosing of drugs. Further, as next-generation ARTs are developed to address important issues such as end-organ disease, drug-drug interactions, and adherence, the abundance of existing knowledge of anti-HIV drug metabolism and transport can be leveraged to facilitate the development of new drugs. The impact of genetics on susceptibility to drug-drug interactions at the level of drug metabolism and transport is largely unexplored. Research in this area is required in order to mitigate and better predict adverse outcomes due to drug-drug interactions involving HIV therapies. Primary challenges and barriers to broadscale implementation of pharmacogenomics for use in individualizing HIV treatment include difficulties in performing testing as part of routine clinical practice, a lack of the clinical data required to solidify gene-drug associations, and the expense of genetic tests. If these factors can be overcome, an exciting new era of personalized HIV therapy could be on the horizon.

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