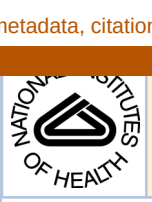

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Influence of Drug Transport Proteins on Pharmacokinetics and Drug Interactions of HIV Protease Inhibitors

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I. Introduction

Saquinavir was the first protease inhibitor introduced to the U.S. market in 1995 for the treatment of HIV/AIDS.[1] This class of life-saving antiretroviral agents has expanded to now include eight protease inhibitors that play an important role in the management of HIV infection.[2] Currently, the most frequently prescribed HIV protease inhibitors include lopinavir, atazanavir, darunavir and fosamprenavir, each of which is typically used in combination with one or more Nucleoside Reverse Transcriptase Inhibitor (NRTI) in Highly Active Antiretroviral Therapy (HAART) regimens.[3] In addition, more recent clinical data support the potential utility of HIV PI monotherapy in patients with prolonged viral suppression on HAART,[4] further illustrating the unique efficacy profile of these antiretroviral agents. The spectacular improvements in treatment success and life expectancy in patients with HIV infection can be attributed, in part, to the long-term suppression of HIV replication by antiretroviral regimens with acceptable side-effect profiles.[5] HIV protease inhibitors currently are key components of first-line therapy in both treatment-naive and -experienced patients. A major challenge in antiretroviral pharmacotherapy is the potential for gradual development of viral resistance. The introduction of 2nd generation protease inhibitors such as darunavir, which require at least four concomitant mutations in the viral genome for resistance development, has provided clinicians with superior drugs to counter the development of resistance.[6]

Physicochemical properties of the HIV protease inhibitors are summarized in Table 1. In general, HIV protease inhibitors are peptidomimetic, large molecular weight, and often poorly water soluble compounds. Consistent with their physicochemical properties, HIV protease inhibitors tend to be highly protein bound and extensively metabolized by cytochrome P450 (CYP) 3A4 (Table 2), with relatively short terminal elimination half-lives in plasma. Long-term therapeutic success can be maintained only when minimum trough concentrations of the HIV protease inhibitors are achieved.[4] Rapid elimination from plasma requires multiple daily doses of HIV protease inhibitors to maintain therapeutic concentrations, which complicates patient adherence to therapy. Ritonavir is a remarkably potent mechanism-based inhibitor of CYP3A4. Concomitant administration of a

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subtherapeutic dose (100-200 mg) of ritonavir as a pharmacokinetic booster ("enhancer") together with HIV protease inhibitors increases exposure of lopinavir, atazanavir and darunavir several-fold.[7] The use of ritonavir as a "boosting" agent was a major advance in HIV protease inhibitor-based therapy,[8,9] and has led to the development and marketing of once-daily dosage forms of HIV protease inhibitors, which has increased significantly patient adherence. In addition, the clinical use of ritonavir-boosted HIV protease inhibitors has improved the side-effect and toxicity profile of HAART regimens.[10] For example, the addition of ritonavir to atazanavir-based dosing regimens resulted in decreased incidence of lipoatrophy as compared to unboosted treatments.[11]

Although the clinical strategy of using ritonavir as a boosting agent has enhanced the success of HIV protease inhibitor-based antiretroviral regimens, it also has resulted in increased potential for drug-drug interactions (DDIs).[12] Drugs metabolized by CYP3A4 exhibit much longer elimination half-lives in ritonavir-treated patients as compared to other patients. Additional levels of complexity with respect to DDI potential are encountered in patients co-infected with *M. tuberculosis*, an infection that is increasing in prevalence in resource-limited countries.[13] Successful eradication of tuberculosis almost always requires administration of the very potent CYP3A4-inducer rifampicin, or the less potent but more expensive inducer rifabutin. These drugs reduce exposure to ritonavir-boosted HIV protease inhibitors.

This manuscript provides an updated review of the influence of drug transport proteins on the pharmacokinetics and DDIs of this important class of antiretroviral agents. Clearly, hepatic metabolism is an important step in the systemic elimination of HIV protease inhibitors. Drug transporters also play a key role in the oral bioavailability, hepatobiliary elimination and distribution of HIV protease inhibitors to target (lymphocytes) and peripheral (brain) tissues. ADME-relevant proteins that influence the pharmacokinetics of HIV protease inhibitors are discussed in section II. A critical review of the most important, clinically relevant DDIs involving HIV protease inhibitors is discussed in Section III. Sections IV and V focus on the role of transporters in mechanisms underlying side-effects associated with HIV protease inhibitors, and on the influence of HIV infection and disease on transporter expression and function, respectively. The recent approval of protease inhibitors for the treatment of hepatitis C has increased the number of patients who are exposed to this class of drugs, and emphasizes the importance of understanding factors that influence their pharmacokinetics and DDI potential.

II. The Impact of Transporters on Protease Inhibitor Pharmacokinetics/ Pharmacodynamics

Pharmacological and toxicological effects of protease inhibitors are determined by drug absorption and distribution which are influenced by transporter-mediated processes. Thus, identifying transport proteins that interact with protease inhibitors and understanding the magnitude of their contribution to overall drug disposition is critical. Although protease inhibitors are known to inhibit active transport processes, data regarding the ability of protease inhibitors, themselves, to act as substrates for uptake proteins remains controversial. Significant temperature-dependent uptake of ritonavir, saquinavir and nelfinavir into suspended rat hepatocytes, indicative of active uptake processes, has been reported.[14] In addition to evidence provided by limited *in vitro* studies, the physicochemical properties of protease inhibitors (e.g., molecular size, protein binding, lipophilicity) (see Table 1) also should be considered. Localization and orientation of membrane transporters in a generalized cell is illustrated in Figure 1. Transporters have been well characterized in the liver, kidney and, to a lesser extent, the brain and intestine. Unfortunately, one challenge in the field is that the expression, localization and functional activity of transport proteins at

target sites for viral transmission and sequestration, including the testicular system, female genital tract, lymphocytes and placenta are poorly characterized. However, this lapse in scientific knowledge is appreciated and studies in this area are ongoing. For an in depth discussion of the interactions between antiretroviral agents and transporters at these relevant organ systems see Kis et al, 2010.[15] The following discussion serves as an overview of solute carrier (SLCO) and ATP-binding cassette (ABC) membrane transport proteins involved in the uptake and efflux of protease inhibitors known to date.

A. Impact of SLCO Transporters on Protease Inhibitor Pharmacokinetics/ Pharmacodynamics

Transporter-mediated uptake, largely governed by members of the SLCO superfamily, may be rate limiting in the oral bioavailability and hepatobiliary clearance of drugs. The most prominent transporter interactions with protease inhibitors involve the organic anion transporting polypeptides (OATPs) and organic cation transporters (OCTs); the clinical relevance of these interactions has been well documented.

OATPs—OATPs, which are expressed in numerous organs and tissues including the intestine, liver, kidney, and placenta, mediate the sodium-independent bidirectional transport of diverse substrates including bile acids, bilirubin and xenobiotics.[16,17] OATPs interact with several protease inhibitors *in vitro*. OATP1A2, -1B1 and -1B3 expressed in *Xenopus laevis* oocytes mediate the uptake of lopinavir and saquinavir.[18-20] Darunavir transport via OATP1A2- and -1B1- also has been reported.[19,20] Lopinavir, atazanavir, darunavir, ritonavir and saquinavir inhibit OATP1B1- and -1B3-mediated CGamF accumulation in chinese hamster ovary (CHO) cells. Inhibition of OATP2B1-mediated transport of estrone 3-sulfate by atazanavir, lopinavir, tipranavir, nelfinavir indinavir, saquinavir, and ritonavir also has been shown in Caco-2 cells.[21,22] The clinical implications of these interactions are evident, for example, in the significant association between OATP1B1 521T>C polymorphisms and elevated lopinavir plasma concentrations.[19] Additionally, a recent pharmacogenetics study revealed that variability in lopinavir clearance was impacted by both genetic variants in OATP1B1 and ritonavir plasma concentrations.[23]

OCTs—OCTs, which are located predominantly in the kidneys and liver, are electrogenic uniporters that primarily transport small cations in a sodium-independent manner. Transport of uncharged and anionic compounds such as prostaglandins by OCTs has been described.[24] OCT1 and OCT3 are expressed at the sinusoidal membrane of liver tissue. OCT1 is expressed exclusively in the liver while OCT3 has a broader range of tissue distribution. Nelfinavir, ritonavir, indinavir, and saquinavir are reportedly potent inhibitors, but poor substrates, of OCT1- and OCT2-mediated transport.[25,26] Though the contribution of OCTs to protease inhibitor transport remains unclear, several nucleoside NRTIs are translocated by OCTs and often are co-administered with protease inhibitors, increasing the risk of DDIs.

B. The Impact of ABC Transporters on Protease Inhibitor Pharmacokinetics/ Pharmacodynamics

Members of the ABC transporter superfamily comprise one of the largest protein families with representatives in all living organisms. The structure and function of ABC transporters are relatively conserved across species. ABC transporters facilitate the transmembrane movement of substrates by utilizing the energy generated by ATP hydrolysis.[27] Mounting evidence suggests that ABC transport proteins confer drug resistance and alter protease inhibitor pharmacokinetics/pharmacodynamics by decreasing bioavailability, promoting sequestration at sanctuary sites, and decreasing accumulation in target organs and tissues.[28] This review focuses solely on ABC transporters clinically shown to impact the disposition of protease inhibitors.

P-gp—P-glycoprotein (P-gp; MDR1), which is expressed ubiquitously, protects cells from the accumulation of toxic drugs, metabolites, and endogenous compounds. P-gp exhibits broad substrate specificity, including protease inhibitors. Expression of P-gp in the intestine, brain and blood-testis barrier alters oral bioavailability and intracellular concentrations of protease inhibitors *in vivo*.[29-31] P-gp-mediated efflux of all currently marketed protease inhibitors has been demonstrated in several *in vitro* systems, including Caco-2 and MDCK-II cells.[32-36] Ritonavir, lopinavir and nelfinavir also inhibit P-gp-dependent efflux of calcein-AM in MDCK-II cells.[37] In addition to inhibition of P-gp transport, saquinavir and darunavir induce P-gp mRNA expression and activity *in vitro*. Induction by darunavir increased cellular resistance, as measured by growth inhibition assays in LS-180 cell lines [38].

BCRP—Breast cancer resistance protein (BCRP) is expressed in the liver, kidney, testis, GI tract and a many other tissues. BCRP is responsible for the extrusion of a broad range of both endogenous and exogenous compounds. Many protease inhibitors including lopinavir, nelfinavir, saquinavir, and ritonavir are effective inhibitors of BCRP-mediated transport, but appear to be poor substrates *in vitro*.[39-41] Although BCRP-mediated transport of protease inhibitors has not been elucidated, BCRP activity is known to alter systemic and tissue concentrations of a antiretroviral and in particular, protease inhibitors.[42] Consequently, the likelihood of DDIs between protease inhibitors and BCRP substrates remains a concern.

MRPs—To date, there are nine members of the multi-drug resistance-associated protein (MRP) transporter family. MRPs 1-5, all organic anion pumps, have been studied most extensively. MRP1 and MRP2 have similar substrate specificities; however, localization and tissue distribution differ. MRP1 is expressed widely and located in the basolateral membrane, while MRP2 is localized on the apical membrane and expression is restricted primarily to the liver, kidney, and intestine. MRP3 is expressed on the basolateral membrane of the liver, kidney and gastrointestinal tract.[29,43] Common MRP1, MRP2 and MRP4 substrates include glutathione conjugates and anionic drugs. Bilirubin glucuronide is a substrate for both MRP2 and MRP3.[44,45] MRP2-mediated transport of saquinavir, ritonavir, indinavir and lopinavir has been shown in stably transfected human MDCK-II cells.[32,46] Saquinavir, ritonavir and atazanavir potently inhibit MRP2-mediated biliary efflux of CDF in human hepatocytes.[47] In a panel of ABC transporter over-expressing cell lines, atazanavir, lopinavir and ritonavir inhibited MRP1 activity.[39] Furthermore, treatment with darunavir/ritonavir induced MRP1 protein expression in CD4 (+) T-cells from healthy human volunteers. MRP1-mediated efflux of carboxyfluorescein diacetate increased upon co-administration with efavirenz.[48] The contribution of MRPs to the transport of protease inhibitors remains unclear.

III. Drug-Drug Interactions Involving Transporters and HIV Protease Inhibitors

Numerous *in vitro* and *in vivo* studies have demonstrated that most HIV protease inhibitors interact with both CYP3A4 and P-gp, either as a substrate, inhibitor or inducer.[8,49,50] Given the dominant roles of these proteins in drug disposition, most clinical DDI studies have focused on the contribution of CYP3A4 and/or P-gp.[8] In addition to the CYP3A4-mediated inhibition of protease inhibitors by ritonavir, a beneficial DDI that is utilized chemically in HAART regimens, synergistic effects have been observed with other combination of HIV protease inhibitors. Dam and co-workers suggested that the synergistic inhibition of HIV-1 by a combination of saquinavir with lopinavir or atazanavir could be explained, at least in part, by enhanced inhibition of efflux mechanisms from target cells.[51] The complexity of HIV protease inhibitor-based treatment regimens, often in combination with non-

antiretroviral medication (e.g. anti-tuberculosis drugs), increases the potential for clinically significant DDIs (see www.hiv-druginteractions.org for a summary of risks and severity of antiretroviral DDIs). Unfortunately, details regarding the underlying mechanisms responsible for these DDIs are lacking, but clearly extend far beyond the involvement of CYP3A4 and P-gp. Clinically relevant changes in protease inhibitor concentrations often may be the net result of multiple DDIs that have opposite effects (e.g. concomitant induction and inhibition); the outcome frequently depends on the exact dose and regimens (e.g. etravirine and darunavir/ritonavir in Table 4).[52] Another reason for the lack of mechanistic information is that the relative roles of drug metabolizing enzymes and transporters in drug disposition and DDIs remain poorly understood. Table 4 provides a summary of clinically relevant DDIs involving HIV protease inhibitors and drug transporters; specific DDIs involving HIV protease inhibitors as 'victim' drugs (Table 4A), and those mediated by HIV protease inhibitors as 'perpetrator' drugs (Table 4B), are discussed below.

III.1. Mechanisms of HIV Protease Inhibitor DDIs: Drug Transporter Inhibition

As summarized in Table 3, HIV protease inhibitors are both substrates and potent inhibitors of some SLCO and ABC transport proteins, and typically behave as perpetrators when considering DDIs elicited by transporter inhibition. In addition, when more than two HIV protease inhibitors are combined, different protease inhibitors can act as the perpetrator and victim. This is illustrated by the effect of atazanavir on the pharmacokinetics of saquinavir when coadministered with ritonavir (see Table 4C).[53] Saturation and/or inhibition of efflux transporters modulating HIV protease inhibitor accumulation may explain this interaction.

The most well documented DDIs with respect to transporter inhibition involve HIV protease inhibitors and the disposition of well-known P-gp substrates including digoxin, fexofenadine and loperamide (see Table 4B). For example, single or multiple dose regimens with indinavir/ritonavir increased fexofenadine plasma AUC up to 5- and 4.2-fold, respectively.[54] The most pronounced effects on digoxin exposure were reported after 300 mg bid ritonavir or 400/100 mg lopinavir/ritonavir in combination with intravenous or oral digoxin doses of 0.5 mg.[55] Loperamide exposure was increased more than 3-fold in the presence of 600 mg ritonavir.[56] Case reports of elevated tacrolimus or sirolimus concentrations when combined with ritonavir-boosted amprenavir or darunavir also support pronounced P-gp inhibition.[57,58] HIV protease inhibitors appear to exhibit much less pronounced (up to 37% increase) effects on the plasma exposure of the NRTI and P-gp substrate tenofovir following co-administration of the disoproxil fumarate prodrug of tenofovir.[59] Minor increases in tenofovir plasma AUC values were observed (see Table 4B), which were attributed to inhibition of P-gp mediated intestinal efflux of the prodrug.[59,60]

Compared to ABC transporter-based DDIs, much less is known about the potential role of HIV protease inhibitors in DDIs associated with uptake transporters. Limited data suggest that hepatic uptake transporters of the *SLCO* family (specifically OATP1B1 and OATP1B3) are likely to play key roles in some DDIs involving HIV protease inhibitors. Shitara recently reviewed current clinical evidence demonstrating substantial alterations in the pharmacokinetics of OATP1B1 substrates (i.e. statins, repaglinide and bosentan) in combination with the OATP1B1 inhibitor cyclosporin A. These data revealed increases in the AUC of atorvastatin of up to 9-fold.[61] Pronounced increases in the AUC of the lipid-lowering drugs atorvastatin and rosuvastatin have been reported with coadministration of boosted lopinavir and tipranavir; OATP1B1 inhibition has been suggested as a likely mechanism to explain this interaction. [62] Moderately decreased exposure to the NRTI elvucitabine when combined with a single 300 mg ritonavir dose may be attributed to ritonavir-mediated inhibition of the intestinal uptake transporter.[63]

Finally, it is noteworthy that even though pronounced species differences exist,[47] several animal studies also support the role of transporters in mediating DDIs involving HIV protease inhibitors. For example, ritonavir enhanced darunavir absorption via P-gp inhibition in mouse *in situ* intestinal perfusions.[64]

III.2. Mechanisms of HIV Protease Inhibitor DDIs: Drug Transporter Induction

Data obtained in various *in vitro* models have shown that HIV protease inhibitors show affinity for the orphan nuclear receptor hPXR, activation of which is clearly linked to regulation of drug metabolizing enzymes as well as drug transporter expression.[65,66] Induction of drug metabolizing enzymes by HIV protease inhibitors is a common mechanism underlying clinically relevant protease inhibitor-associated DDIs.[67,68] Much less information is available with respect to the exact role of altered expression of drug transporters and changes in the pharmacokinetics of co-administered drugs relying on those drug transporters. Nevertheless, numerous examples in Table 5 illustrate that most drug transporters are susceptible to the inducing effects of HIV protease inhibitors. Clinically relevant DDIs that may be attributed, at least in part, to HIV protease inhibitor-mediated up-regulation of P-gp activity are included in Table 4B. For example, there is a 2-3-fold decrease in loperamide exposure when combined with tipranavir/ritonavir.[69] The latter protease inhibitor combination also significantly reduced exposure to the P-gp substrate digoxin, presumably through induction of P-gp, following concomitant doses of TPV/r.[70] It should be noted that the inducing effects of TPV predominate in contrast to ritonavir, which primarily inhibits P-gp when combined with loperamide or digoxin. The 25% reductions in fexofenadine Cmax and half-life (Table 4.B) when combined with nelfinavir for 1 week, may be explained by induction of intestinal P-gp and/or hepatic OATPs.[71] The reduced exposure to delaviridine also could be due to induction of P-gp by amprenavir [72]. The NNRTI etravirine can be combined with several boosted protease inhibitors, including darunavir, lopinavir and saquinavir;[73] however, when combined with tipranavir/ritonavir, the plasma exposure of etravirine is decreased by 76% (Table 4.B). As etravirine is not a P-gp, BCRP or MRP substrate,[74,75] induction of uptake transporters (e.g. OATPs) by tipranavir and/or ritonavir (in addition to induction of drug metabolizing enzymes) may contribute to this interaction.

Combined use of rifampicin, an anti-tuberculosis agent and potent inducer of drug metabolizing enzymes and transporters, with antiretroviral medication including HIV protease inhibitors is of high clinical relevance. As outlined in Table 4A, reductions in HIV protease inhibitor exposure when combined with rifampicin range from 75% to 89%, even in the presence of ritonavir as a boosting agent. When different LPV/r regimens combined with rifampicin were evaluated by la Porte et al., LPV/r combinations with higher ritonavir dose levels (i.e. LPV/r 400/400 > LPV/r 800/200) appeared to provide better compensation for the inducing effects of rifampicin.[76] This was especially reflected in the C_{min} concentrations achieved with the LPV/r 400/400 dose regimen, which tended to be comparable to the C_{min} concentrations achieved with the reference treatment of LPV/r 400/100 in the absence of rifampicin. Therefore, the use of rifabutin rather than rifampicin in the management of *M. Tuberculosis* infection in HIV positive patients on antiretroviral therapy is highly recommended.

IV. Transporter-mediated Processes Underlying Toxicity of HIV Protease Inhibitors

Both endogenous and exogenous (e.g. drugs) compounds are substrates for transporters. Interference of drugs with endogenous substrate transport may constitute a mechanism of drug-mediated toxicity. For example, interference of certain drugs (e.g. bosentan,

troglitazone) with hepatic bile salt transport has been implicated as one mechanism in the development of drug-induced cholestasis.[77] Several HIV protease inhibitors have been shown to interact with bile salt disposition in human and rat hepatocytes,[78] and this may explain, at least in part, the hepatotoxicity observed in some patients taking HIV protease inhibitors.[79] Rotger et al. quantified the effect of HIV protease inhibitor-containing antiretroviral therapy on the incidence of hyperbilirubinemia in 96 HIV-infected patients. Atazanavir and indinavir (but not lopinavir, saquinavir, ritonavir and nelfinavir) exhibited an increased incidence of elevated serum bilirubin concentrations.[80] Inhibition of the bilirubin conjugating enzyme UGT1A1 by these protease inhibitors has been proposed as a potential mechanism underlying this interaction. However, in vitro data generated by Campbell et al.[81] and Ye et al.[47] also support potent inhibition of OATP1B3, the bilirubin-transporter, by indinavir and atazanavir. As noted in Table 6, the altered lipid metabolism associated with HIV protease inhibitor-based therapy may be caused by inhibition of transport of the endogenous substrate palmitate.[82]

V. Influence of HIV Infection, Co-infection and Antiretroviral Therapy on Transporters: Implications for Protease Inhibitor Pharmacokinetics/ Pharmacodynamics

The effect of HIV infection on transporter expression and activity is not well understood. Effects of disease on P-gp mRNA expression and activity have been studied more extensively than other transport proteins. P-gp mRNA expression was decreased in leukocytes and PBMCs of SHIV infected macaques; changes in expression were more pronounced in animals receiving antiretroviral treatment that included indinavir. However, indinavir decreased P-gp expression, making it difficult to determine whether the disease state or indinavir itself were responsible for the observed effects;[83] similar findings have been reported in humans. Lucia and colleagues reported that P-gp function in peripheral blood lymphocytes, as measured by rhodamine-123 efflux, was decreased in HIV-infected patients. Separate clinical studies in patients with HIV infection relative to healthy volunteers support these findings, although expression of MRP1 in PBMCs was not altered.[84] Increased MRP-mediated efflux also has been reported in patients with primary HIV infection that strongly correlates with disease progression.[85] In contrast, a time-dependent significant *increase* in P-gp expression in PBMCs from HIV+ individuals has been reported.[86]

The influence of hepatitis C co-infection on transporter function, and the potential implications for antiretroviral therapy, has been the subject of recent investigations due to the increasing prevalence of co-infection. MRP4 protein expression is induced in patients with cholestasis and animals with common bile duct ligation. These changes may facilitate compensatory MRP4-mediated basolateral efflux of endogenous compounds such as bile acids.[87-90] MRP2 mRNA levels also are significantly decreased in human HCV-infected liver tissue relative to non-infected tissue.[91] In addition, significant reductions in OCT1 and OATP1B1 mRNA which correlated with hepatitis C progression also have been reported in humans.[92]

MRP1 expression in total human lymphocytes is unaffected by atazanavir treatment, but increased in human brain microvascular endothelial cells (HBMECs). P-gp expression, however, was increased in both total lymphocytes and HBMECs.[93] In human PBMCs, efavirenz-mediated induction of MRP1 and MRP6 mRNA has been reported. Tenofovir also was associated with a reduction in P-gp, MRP1, MRP5, and MRP6 mRNA expression in humans.[94]

Regulation of transporter expression by nuclear receptors such as PXR and CAR is now well-established. For example, induction of P-gp and MRP1 by ritonavir, and P-gp by saquinavir, both PXR agonists, has been reported.[95-97] Although a reduction in MRP1 protein expression in PBMCs of healthy volunteers following administration darunavir/ritonavir was observed, the clinically relevant consequences of these changes remain unclear.[48]

Evidence in the literature demonstrating a direct effect of HIV infection, coinfection and HAART therapy on transporter phenotype and function remains limited and controversial for a number of reasons. The contribution of HIV infection, underlying symptoms, co-infection and antiretroviral therapy to pathophysiological changes are multifactorial and difficult to distinguish. In addition, appropriate models to investigate the intricate relationships are limited. The effect of HIV infection and co-infection on transporter function is the subject of ongoing investigations.

VI. Conclusion

HIV protease inhibitors that interact with transport proteins are likely candidates for DDIs resulting in toxicity or the development of cellular resistance. Consequently, chemotherapeutic agents exhibit limited minimal interactions with transport proteins such as P-gp are preferred.[98] Conversely, therapeutic agents that competitively inhibit transporters governing efflux may increase victim drug concentrations in relevant organs and tissues (e.g. lymphocytes), thereby enhancing efficacy and decreasing pill burden. For example, Pluronic P85, an amphiphilic block copolymer and P-gp inhibitor, increases saquinavir and nelfinavir accumulation in MDCKII-MDR1 cells.[99] Modulation of transport function is particularly promising given the difficulty of antiretrovirals to penetrate sites of viral sequestration, such as the brain, which expresses a number of efflux transporters known to interact with protease inhibitors, including P-gp, BCRP and MRPs.[100-102] In addition to transporter interactions, HIV protease inhibitors may interact with cytochrome P450s, modify posttranscriptional regulation of nuclear receptors, and alter bile acid biosynthesis and metabolism. Gender, genetic polymorphisms and lifestyle choices such as smoking and alcohol consumption also must be taken into consideration when trying to predict the likelihood of drug-transporter interactions. Toxicity and efficacy associated with these interactions is undoubtedly multifactorial and remains difficult to predict. However clinicians, scientists and regulatory agencies are becoming increasingly aware of the importance of understanding the dynamics of these relationships and are working together to ensure the emergence of safe and efficacious chemotherapeutic treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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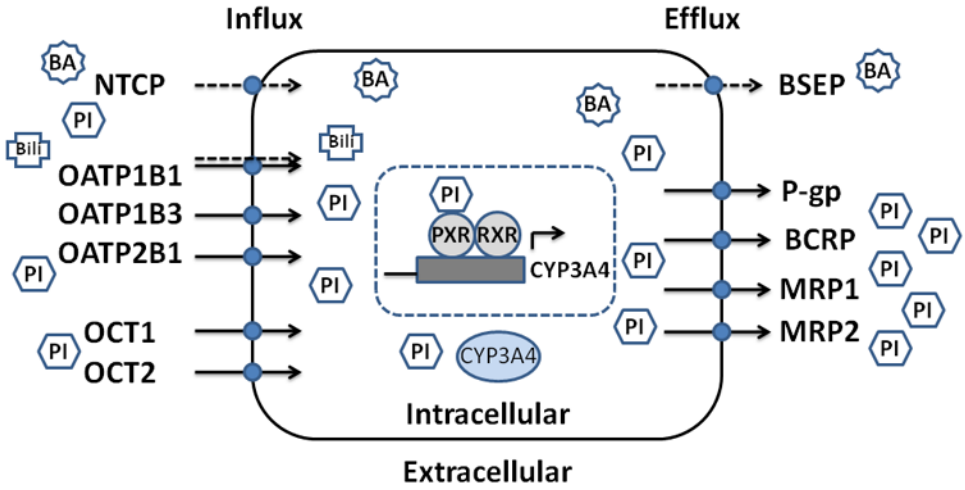

Figure 1.

Schematic depicting the localization of SLC and ABC transport proteins involved in the translocation of protease inhibitors at sites of absorption (intestine), excretion (liver, kidney) and at target sites (central nervous system, lymphatic system, placenta, blood-testis barrier, and female genital tract). Protease inhibitors (PI) are transported (denoted by solid lines) into cells by proteins of the SLC family (e.g., OATPs and OCTs) and transported out of cells by proteins of the ABC family (e.g., P-gp, BCRP, MRPs). The hepatic uptake and excretion of bile acids (BA), which is mediated by NTCP and BSEP, respectively, is inhibited (denoted by dashed lines) by protease inhibitors. The hepatic transport of bilirubin, which is mediated by OATP1B1, is inhibited (denoted by dashed line) by protease inhibitors. Protease inhibitors bind to pregnane X receptor (PXR), an orphan nuclear receptor, which forms a heterodimer with the retinoid X-receptor-α (RXR) and mediate the induction of Cytochrome P450 3A4 (CYP3A4).

Table 1

Physicochemical properties and *in vitro* cellular accumulation ratios of HIV Protease Inhibitors

	Amprenavir (APV) [Fosamprenavir]	Atazanavir (ATZ)	Darunavir (DRV)	Indinavir (IDV)	Lopinavir (LPV)	Nelfinavir (NLV)	Ritonavir (RTV)	Saquinavir (SQV)	Tipranavir (TPV)
pKa	1.9[#] [6.28][c]	4.3	14.2	6.2; 5.9, 3.7;	1.6	6.0, 11.1	2.8	1.1, 7.1; 7.0; 5.5[b]	7.8
Lipophilicity (Log P o/w) Log D (pH)	1.7; 3.3 or 4.2[b] [0.84][c]	4.25; 4.5[#]	1.8[#]	0.9; 2.9[#]	1.7	2.9; 6[#] 4.0 (pH 7.4); 4.1 (pH 6.0)	1.2; 5.2 3.9[#]	1.9; 4.1 (mesylate); 3.8[3]	6.9[#]
Solubility (μg/ml)	Mesylate: Aq: 190 pH 7.4: 60 pH 6.8: 190 [Calcium: Aq: 700] [c]	Aq: 4-5 mg/mL[#]	Ethanolate: Aq: 150[#]	Aq: 15[#] Sulfate: Aq: > 100 mg/ml pH 7.4: 70 pH 4.8: 300 pH 3.5: 60 mg/ml	Aq: very low	Mesylate: Aq: 4500 pH 7.4: very low pH 3.5: 500 pH 2.6: 4500	Aq: 1 pH 7.4: 5.3 pH 4: 6.9	Mesylate: Aq: 2220 pH 7.4: 36 pH 6.5: 73	Aq: insoluble
Intracellular Accumulation ratio's (*in vivo* in blood)[a]	3.2	1.2		0.29	1.55; 0.7-2.1	5.3	1.25; 1.7; 0.8-4.2	3.64; 4.9; 1.5-6.7	
References	103-105	22,53,106		103-105,107,108	103,109	103-105,109,110	53,103-105,109	1,53,103-105,109	

[#]Data obtained from Drugbank (http://drugbank.ca/drugs).

[a]When coadministered with ritonavir (except nelfinavir); ritonavir: coadministered with saquinavir.

[b]Conflicting results reported.

[c]Fosamprenavir.

Table 2

Key Pharmacokinetic Parameters of the HIV Protease Inhibitors.

Compound	Standard Dosing Level	Metabolism and Elimination	$t1/2_{\beta}$ (h)	Plasma Protein Binding (%)	Ritonavir Boosting effect	Oral Bioavailability (%); [unboosted]	DME interactions (based on boosted use in the clinic)	References
Amprenavir (from fosamprenavir)	700 mg b.i.d./r 100 mg b.i.d.	hepatic 3A4, 2D6 urine:14%; feces:75 %; (unchanged:1% urine; ND in feces)	7-12	90	C_{max}1.5 × ↑ AUC > 2× ↑ C_{trough} 4 × ↑	30-70	CYP3A	103,104
Atazanavir	300 mg q.d./r 100 mg q.d.	hepatic 3A4; Nonlinear (300-600 mg), 79% bile/13% urine; UD % dose in bile 20%, in urine 7%	6 (in HIV patients; 2 × ↓ in healthy volunteers)	86	C_{trough} 5 × ↑ AUC 3× ↑	68; pH dependent, AUC 1.7 × ↑ with food	CYP3A, UGT1A1	103,105
Darunavir	600-800 mg b.i.d./r 100 mg b.i.d.	Hepatic CYP3A4 Feces: 79.5%; urine: 13.9% Unchanged (unchanged: 41.2% in feces; 7.7 % in urine)	15	95 (AAG > ALB)	AUC 10 × ↑[a]	82 [37][b]	Inh.: CYP3A4, CYP2D6 Ind.: CYP2C9 CYP2C19	103,106,107
Indinavir	800 mg b.i.d./r 100 mg b.i.d.	hepatic CYP3A4; 19% and 83% recovered in urine and feces, respectively; Of this unchanged drugs accounted for 19.1% and 9.4% and in the urine and feces, respectively	2	61	AUC 2×↑[a] C_{min}> 4×↑[a]	60-65	CYP3A4 Weak 2D6 inhibitor	103,108
Lopinavir	400 mg b.i.d./r 100 mg b.i.d.	hepatic CYP3A4 10.4 % and 82% in urine and feces, respectively. Of this, 2.2 and 19.8% appeared unchanged in the urine and feces respectively	5-6	99	AUC 1.5 × ↑[a] C_{min}2 × ↑[a] C_{SS} 15-20 × ↑ [a]	Not established (increased AUC and Cmax under fed conditions however)	CYP3A4	103,109
Nelfinavir	635 mg b.i.d.	hepatic CYP3A4, 2C19, 2D6, 2C9 2% and 87% recovered in urine and feces, respectively. Of this, 22% and 1 % was unchanged in the urine and feces, respectively	1.8-3.4	99	AUC 2.5 × ↑[a] C_{max}1.4 × ↑[a]	> 78	CYP3A CYP2C19	103
Ritonavir	PI + 100 mg b.i.d.		3-5	99		66-75		
Saquinavir	1 g b.i.d./r 100 mg b.i.d.	hepatic CYP3A4	13	98		< 20 (Soft Gelatin Capsule)		
Tipranavir	500 mg b.i.d./r 200 mg b.i.d.							

r = ritonavir; SGC = soft gelatin capsule; UD = unchanged drug.

[a]Package insert based on calculated ratio of boosted to unboosted AUC0-∞.

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Table 3

A: HIV Protease Inhibitors as Inhibitors of ABC and SLCO Transporters.

ABC					SLC			
Protease Inhibitor	**Transporter**	**IC_{50}* or Ki** (μM)**	**System (Substrate)**	**Ref**	**Transporte r**	**IC_{50}* or Ki** (μM)**	**System (Substrate)**	**Ref**
Amprenavir	**P-gp**	23.1*	BBMEC (rhodamine 123)	110	**OATP1B1**	14.4*, 12.8**	CHO (CGamF)	21
	BCRP	181*	MDCKII (Pheophorbide A)	41	**OATP1B3**	19.1*, 13.1**	CHO (CGamF)	21
Atazanavir	**P-gp**	67.8*	MDCKII (Calcein-AM)	37	**OATP1B1**	1.7*, 1,5**	CHO (CGamF)	21
	BCRP	69.1*	MDCKII (Pheophorbide A)	41	**OATP1B3**	3*, 3**	CHO (CGamF)	21
					OATP2B1	2.2*	Caco-2 (E3S)	22
						3.6*	MDCKII (E3S)	22
Darunavir	**P-gp**	33*	Not reported	111	**OATP1B1**	3.5*, 3.1**	CHO (CGamF)	21
		>100*	MDCKII (Calcein-AM)	37	**OATP1B3**	4.8*, 3.3**	CHO (CGamF)	21
					OATP2B1	29*	Caco-2 (E3S)	22
						26*	MDCKII (E3S)	22
Indinavir	**P-gp**	54.6*	BBMEC (rhodamine 123)	110	**OATP1B1**	12.2*, 10.8**	CHO (CGamF)	21
		>100*	MDCKII (Calcein-AM)	37		5.84*	HeLa	112
					OATP1B3	12.3*, 8.5**	CHO (CGamF)	21
					OATP2B1	3.9*, 3**	Caco-2 (E3S)	21
					OCT1	37.6*	HEK293 (MPP)	25
						62*	HeLa (TEA)	26
Lopinavir	**P-gp**	10.3*	MDCKII (calcein-AM)	37	**OATP1B1**	0.5*,0.5**	CHO (CGamF)	21
	BCRP	7.66*	MDCKII (Pheophorbide A)	41	**OATP1B3**	2*, 1.4**	CHO (CGamF)	21
					OATP2B1	1.7*	Caco-2 (E3S)	22
						0.72*	MDCKII (E3S)	22
Nelfinavir	**P-gp**	1.7*	BBMEC (rhodamine 123)	110	**OATP1B1**	0.93*	HeLa (E217ßG)	112
		19.9*	MDCKII (calcein-AM)	37	**OATP2B1**	2.2*	Caco-2 (E3S)	22
	BCRP	13.5*	MDCKII (Pheophorbide A)	41		0.9*	MDCKII (E3S)	22
		12.5*	HEK293 (mitoxantrone)	40	**OCT1**	22*	HeLa (TEA)	26

ABC					SLC			
Protease Inhibitor	**Transporter**	**IC_{50}* or Ki** (μM)**	**System (Substrate)**	**Ref**	**Transporte r**	**IC_{50}* or Ki** (μM)**	**System (Substrate)**	**Ref**
						7*	HEK293 (MPP)	25
					OCT2	13*	HEK293 (MPP)	25
Ritonavir	**P-gp**	3.8*	Caco-2 (digoxin)	102	**OATP1B1**	0.71*	HeLa (E217ßG)	112
		5*	Caco-2 (digoxin)	113		0.78**	HEK293 (pitavastatin)	116
		6.7*	Caco-2 (rhodamine 123)	114		1.6*, 1.4**	CHO (CGamF)	21
		26.4*	BBMEC (rhodamine 123)	110	**OATP1B3**	3.6*, 2.5**	CHO (CGamF)	21
		28.2*	MDCKII (digoxin)	115	**OATP2B1**	6.3*, 4.8**	Caco-2 (E3S)	21
		39.6*	MDCKII (calcein-AM)	37		0.93*	Caco-2 (E3S)	22
	BCRP	19.5*	HEK293 (mitoxantrone)	40		2.2*	MDCKII (E3S)	22
					OATP1A2	<10*	HeLa (fexaofenadine)	117
						5.2*	HeLa (TEA)	26
					OCT1	14*	HEK (MPP)	25
						25*	HEK (MPP)	25
					OCT2	13.9*	HeLa (TEA)	118
					MATE1	15.4*	HeLa (metformin)	118
Saquinavir	**P-gp**	1.4*	BBMEC (rhodamine 123)	110	**OATP1B1**	1.23*	HeLa (E217ßG)	112
	BCRP	27.4*	MDCKII (Pheophorbide A)	41		2.1*, 1.8**	CHO (CGamF)	21
		19.5*	HEK293 (mitoxantrone)	40		1.59**	HEK293 (pitavastatin)	116
					OATP1B3	4.1*, 2.8**	CHO (CGamF)	21
					OATP1A2	<10	HeLa (Fexofenadine)	117
					OATP2B1	5.3*, 4**	Caco-2 (E3S)	21
						3.5*	Caco-2 (E3S)	22
						4.6*	MDCKII (E3S)	22
					OCT1	8.3*	HeLa (TEA)	26
						37*	HEK293 (MPP)	25
Tipranavir					**OATP2B1**	0.77*	Caco-2 (E3S)	22
						0.88*	MDCKII (E3S)	22

ABC					SLC			
Protease Inhibitor	**Transporter**	**IC_{50}* or Ki** (μM)**	**System (Substrate)**	**Ref**	**Transporte r**	**IC_{50}* or Ki** (μM)**	**System (Substrate)**	**Ref**

CGamF, cholylglycylamidofluorescein; E3S, estrone 3-sulfate; MPP, 1-methyl-4-phenylpyridinium; TEA, tetraethylammonium; E217βG, estradiol-17β-glucuronide.

Table 3.B: HIV Protease Inhibitors as Substrates of ABC and SLCO Transporters.

	ABC				SLCO			
Protease Inhibitor	**Transporter**	**K_m* (μM) or ER (PI dose)****	**In vitro System**	**Ref**	**Transporter**	**K_m* (μM) or ER (PI dose)****	**In vitro System**	**Ref**
Amprenavir	P-gp	47* 24.2 (10 μM)**	High Five membranes MDCKII-MDR1	110 119				
Atazanavir								
Darunavir								
Indinavir	P-gp	0.47* 2.1*	High Five membranes High Five membranes High Five membranes	120 110				
Lopinavir								
Nelfinavir	P-gp	3.6*	High Five membranes	110				
Ritonavir	P-gp	0.8*	LLC-PK1	121				
Saquinavir	P-gp	1.4* 14.5* 15.4*	High Five membranes LLC-PK1 Caco-2	110 121 122	OATP1A2	36.4*	Oocytes	18
Tipranavir								

ER, efflux ratio (B-A/A-B).

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Table 4

Summary of Clinically Relevant Drug-Drug Interactions Involving HIV Protease Inhibitors with evidence for a role of drug transporters in mediating the interactions.

A. Protease Inhibitor as victim drug				
Transport Protein	**Perpetrator Drug (Inhibitor/Inducer)**	**Victim Protease Inhibitor**	**Clinical Exposure changes**	**In Vitro Studies**
MDR1 (ABCB1, P-gp)	Rifampicin 600 mg qd	Most HIV PI	Plasma AUC 5.6 × ↓ (APV) Plasma AUC significantly ↓ (ATV) Plasma AUC 9.1 × ↓ (IDV) Plasma AUC 5.6 × ↓ (NFV) Plasma AUC 2.9 × ↓ (RTV) Plasma AUC 6.3 × ↓ (SQV) (possibly partly attributable to intestinal P-gp induction)[123]	HIV PI are (poor) P-gp substrates, but exact role of intestinal efflux transporters in their absorption unclear. [31,39,124,125]
	Rifampicin 600 mg qd	LPV/r 800/200 mg qd 400/400 mg qd	Plasma AUC 4 × ↓ (LPV/r)[76]	LPV is an ABCB1 (but not ABCC2) substrate[36]
	Rifampicin 600 mg qd	ATV/r 300/100 mg qd	Plasma AUC 6.7 × ↓ (ATV) and 2.9 × ↓ (RTV) (possibly partly attributable to intestinal P-gp induction; evaluated in three patients only) [126]	ATV and RTV are (poor) P-gp substrates.[39]
MDR1 (ABCB1, P-gp)	Rifabutin	APV IDV NFV SQV	Inductive effects on HIV PI PK is less pronounced (1.2-1.7 × ↓) than for rifampicin.[123,127]	cfr. above
MDR1 (ABCB1, P-gp)	SJW, Ginkgo and other herbal medicines	Several HIV PI	Reduced exposure, potentially leading to therapy failure (exact contribution of efflux transporters versus drug metabolizing enzymes not clear)[128]	see Table 3, illustrating that HIV PI are substrates for efflux transporters
MDR1 (ABCB1, P-gp)	Ketoconazole 200 bid	DRV/r 400/100 bid	Plasma DRV AUC 1.4 × ↑[129]	DRV is a P-gp substrate, even though RTV co-administration limits the role of P-gp. [64,130]
MDR1 (ABCB1, P-gp)	Ketoconazole 200-400 qd	SQV/r 400/400 bid	Plasma SQV AUC 1.4 × ↑[131]	Ketoconazole inhibits P-gp-mediated SQV transport across Caco-2 monolayers.[132]
MDR1 (ABCB1, P-gp)	Etravirine	FPV700/r100 bid IDV800 tid TPV500/r200 bid ATV400 qd SQV1200 single	Plasma APV AUC 1.7 × ↑ Plasma IDV AUC 1.5 × ↓ Plasma TPV AUC 1.2 × ↑ Plasma ATV AUC 1.2 × ↓ Plasma SQV AUC 1.5 × ↓[73]	Etravirine has been shown to be a potent BCRP inhibitor and inducer *in vitro,* however PI are not BCRP substrates;[40] etravirine shows no significant P-gp inhibition, but modest induction of P-gp and MRP3 [75]
OATP1B? (SLCO1B)	Rifabutin 150 mg qod	DRV/r 600/100 mg bid	DRV plasma AUC 1.6 × ↑ RTV plasma AUC 1.7 × ↑ Mechanism unknown but possibility of SLCO inhibition has been suggested.[133]	No data available on effect of rifabutin on OATP activity
"× ↑": fold increase; "× ↓" fold decrease; "*AAAXXX*/r*xxx*" = XXX mg of AAA as a primary HIV protease inhibitor, combined with xxx mg ritonavir as a booster				

B. Protease Inhibitor as Perpetrator Drug				
Transport Protein	**Victim Drug**	**Protease Inhibitor as Perpetrator Drug (Inhibitor/Inducer)**	**Clinical Exposure Changes**	***In Vitro* Studies**
MDR1	Tenofovir (TFV) disoproxil fumarate (TDF)	ATV/r, DRV/r, LPV/r, SQV/r	Plasma TFV AUC 1.1-1.4 × ↑ in combination with ATV/r, DRV/r, LPV/r, SQV/r.[59,134]	• Efflux Ratio (ER) of TDF across MDCK-MDR1 is 34 (control); ER is significantly reduced to 4.3 (NFV), 4.4 (LPV, RTV); 16 (ATV); 22 (SQV); 24 (APV);[59] • Limited interaction of HIV PI with transporters involved in TFV disposition in the kidney (hOAT1/3, MRP4).[135]
MDR1	Fexofenadine 120 mg	LPV/r RTV	AUC 2.2 × ↑ (single RTV 100) AUC 4.0 × ↑ (single LPV/r 400/100) AUC 2.9 × ↑ (steady-state LPV/r 400/100)[136]	• RTV IC_{50} = 5.4 μM for P-gp-mediated fexofenadine transport across Caco-2[137] • LPV and RTV are P-gp inhibitors (Table 3) and inducers (Table 7) • RTV causes net induction (rather than inhibition) of P-gp *in vivo* in rats – based on CsA oral BA [138] • Largest change for IDV may be explained by P-gp being an inhibitor but not an inducer
	Fexofenadine 60 mg	RTV 200 tid – 400 bid	AUC 2.8 × ↑ (acute RTV) AUC 1.4 × ↑ (steady-state RTV)[139]	
	Fexofenadine 60 mg	IDV/r 800/100 bid	AUC 5.0 × ↑ (single dose IDV/r) AUC 4.2 × ↑ (steady-state IDV/r)[54]	
MDR1	Digoxin 0.4 mg oral	RTV200; 14d	Plasma AUC 1.2 × ↑[140]	• RTV blocks P-gp activity (Table 3) • RTV (>5μM) enhances digoxin (0.1μM) accumulation in RBE4 cells[141]
	Digoxin 0.5 mg iv	RTV300 bid	Plasma AUC 1.9 × ↑, V_d 1.8 × ↑, Cl_{renal} 1.5 × ↓, $Cl_{non\text{-}renal}$ 2× ↓[142]	
	Digoxin 0.4mg qd	DRV600/r100 bid	Plasma AUC 1.4 × ↑[106]	• DRV and RTV block P-gp (Table 3)
	Digoxin 0.5 mg (oral)	SQV1,000/r10 0 bid	Plasma AUC 1.5 × ↑[143]	• SQV (>10μM) and RTV (>5μM) enhance digoxin (0.1μM) accumulation in RBE4 cells[141]
	Digoxin 0.25 mg (oral)	TPV/r	Plasma AUC 1.9 × ↑ after first dose Plasma AUC unchanged and Cmax 1.5 × ↑ at steady-state[70]	See Table 5
	Digoxin 0.5 mg (oral)	LPV400/r100 bid (14 d)	Plasma AUC 1.8 × ↑[55]	See Table 3
MDR1	Loperamide	TPV750(/r200)	Plasma AUC 2-3 × ↓: in vivo intestinal P-gp induction, also in presence of RTV as inhibitor [69]	See Table 5
		RTV200	Plasma AUC 2.2 × ↑: in vivo intestinal P-gp inhibition;[69] no effect on brain PD (loperamide)	See Table 3
		RTV600	Plasma AUC 3.2 × ↑: in vivo intestinal P-gp inhibition[56]	See Table 3

B. Protease Inhibitor as Perpetrator Drug				
Transport Protein	**Victim Drug**	**Protease Inhibitor as Perpetrator Drug (Inhibitor/Inducer)**	**Clinical Exposure Changes**	***In Vitro* Studies**
MDR1	Delaveridine	APV600 bid	possibly partly due to intestinal P-gp induction[72]	See Table 5
MDR1	Tacrolimus Sirolimus	APV/r	Case report in HIV-infected patient indicates increased tacrolimus/sirolimus half-life and trough levels, attributed to CYP and/or P-gp inhibition by APV/r[57]	See Table 3
	Tacrolimus	DRV/r	Case report: HIV-infected kidney-transplant patient required a tacrolimus dose equal to 3.5% of usual dose.[58]	See Table 3
	Sildenafil	DRV/r 400/100 bid	Plasma AUC 4 × ↑: possibly due to P-gp inhibition (or OATP inhibition)[144]	See Table 3
	Ketoconazole 200 bid	DRV/r 400/100 bid	Plasma AUC 3.1 × ↑: possibly due to P-gp inhibition (or OATP inhibition)[133]	See Table 3
	Ketoconazole 200 qd	RTV	Plasma AUC 3.4 × ↑: possibly due to P-gp inhibition (or OATP inhibition)[145]	See Table 3
	Ketoconazole 200 single dose	LPV/r 400/100 bid	Plasma AUC 3.0 × ↑: possibly due to P-gp inhibition (or OATP inhibition)[109]	See Table 3
	Ketoconazole 200 qd	FPV/r 700/100 bid	Plasma AUC 2.7 × ↑: possibly due to P-gp inhibition (or OATP inhibition) [104]	See Table 3
OATP/BCRP	Atorvastatin	LPV/r TPV/r SQV/r (400/400 bid) DRV/r (300/100 bid)	AUC 5.9 × ↑(LPV/r) AUC 9.4 × ↑ TPV/r [62] AUC 3.4 × ↑(SQV/r) [146]AUC 4.0 × ↑ (DRV/r)[62,147]	• Atorvastatin is an OATP1B1 and BCRP substrate [148,149] • HIV PI are OATP and BCRP inhibitors[41,150,151]
OATP1B1/BCRP	Rosuvastatin	TPV/r LPV/r ATV/r	AUC 1.4× ↑ (TPV/r)[62] AUC 2.1× ↑(LPV/r); $t_{1/2}$ not affected [134] AUC 3.1× ↑(APV/r) [152]	• Rosuvastatin is an OATP1B1 and BCRP substrate [148,149] • LPV, TPV, ATV and RTV are OATP and BCRP inhibitors [41,150,151]
OATP1B1 MRP2	Pravastatin 40 mg qd	DRV/r 600/100bid	Plasma AUC 1.8 × ↑[106]	See Table 3[153]
OATP/MDR1	Fexofenadine	NLF 1250 bid (1wk)	Fexofenadine C_{max} 1.3 × ↓, $t_{1/2}$ 1.3 × ↓; possibly due to intestinal P-gp and hepatic OATP induction[71]	See Table 5
OATP2B1?	Elvucitabine 20 mg	RTV 300 (single dose)	Elvucitabine AUC 1.3× ↓ and C_{max} 1.7 × ↓; possibly due to inhibition of intestinal influx transporters [63]	See Table 3 for effect of RTV on OATP activity
Uptake transporters?	Etravirine	DRV/r (600/100 bid)	100 bid: plasma AUC 1.6 × ↓ 200 bid: plasma AUC 1.8 × ↑[52,154]	Etravirine is not a substrate for P-gp, BCRP or MRP1-3. [75]. The role of uptake transporters has not been investigated.
	Etravirine	TPV/r (500/200 bid)	Plasma AUC 4.2 × ↓[73]	See Table 5

“× ↑”: fold increase; “× ↓” fold decrease; “*AAAXXX*/**r***xxx*” = XXX mg of AAA as a primary HIV protease inhibitor, combined with xxx mg ritonavir as a booster

Table 5

***In vitro* Induction Data With HIV Protease Inhibitors**

Transporter	HIV PI	Model System (marker): Effect (conc)	Reference
MDR1	APV	T84 (0.1μM digoxin ER): ER doubled (10μM; 72h) T84 (mRNA): 5× ↑ (10μM; 72h) LS180 (mRNA): 17× ↑ (10μM; 96h)	96,156
	ATV	LS180V (protein): 2.5× ↑ (30 μM, 3 d) LS180V (Rh123 uptake): 55%↓ (30 μM, 3 d) hCMEC/D3 cells (protein): 2.5× ↑ (10 μM; 3d) LS180 (mRNA): 5× ↑ (10μM; 96h)	96,157,158
	DRV	LS180 (mRNA): 3.8× ↑ (10μM; 1wk)	34
	IDV	No significant P-gp induction	96,157,158
	LPV	LS-180V (protein/mRNA): 3× ↑ (30 μM 72h) LS-180V (Rh123 uptake): 50%↓ (30 μM 72h) LS180 (mRNA): 12× ↑ (10μM; 96h)	96,157-159
	NFV	Cultured Hepatocytes (mRNA): 4-6× ↑ (10-25 μM) Cytotrophoblast culture (Rh123 uptake): 23% ↓ (3 μg/ml; 24h) LS180 (mRNA): EC50 = 1.2 μM (96h); LS180 (mRNA): 7× ↑ (10μM; 96h)	67,96,160
	RTV	Human hepatocytes (mRNA): 9-10× ↑ (10-25 μM) LS-180V cells (protein): 6× ↑ (1-100 μM; 3d) LS-180V (Rh123 uptake): 50%↓ (>10 μM; 3d) hCMEC/D3 cells (protein): 2× ↑ (10 μM; 3d) LS180 (mRNA): EC50 = 1.7 μM (96h); LS180 (mRNA): 12× ↑ (10μM; 96h)	67,96,97,158,161
	SQV	LS180 (mRNA): 5.7× ↑ (10μM; 1wk) Cytotrophoblast culture (protein): 2× ↑ (1 μg/ml; 24h) Cytotrophoblast culture (Rh123 uptake): 18% ↓ (1 μg/ml; 24h) LS180 (mRNA): 5× ↑ (10μM; 96h)	34,96,160
	TPV	LS180 (mRNA): 10× ↑ (10μM; 96h)	96
MRP1	RTV	LS-180V cells (protein): 3× ↑ (1-100 μM; 3d) LS-180V (CBF uptake): 30% ↓ (30 μM; 3d)	97
	SQV	LS180 (mRNA): 2.3× ↑ (10μM; 1wk)	34
MRP2	NFV	Human hepatocytes (mRNA): 2-4× ↑ (10-25 μM)	67
	RTV	Human hepatocytes (mRNA): 5-6× ↑ (10-25 μM)	67
	SQV	LS180 (mRNA): 4.5× ↑ (10μM; 1wk)	34
MRP3	SQV	LS180 (mRNA): 2× ↑ (10μM; 1wk)	34
MRP4	SQV	LS180 (mRNA): 1.8× ↑ (10μM; 1wk)	34
MRP5	SQV	LS180 (mRNA): 3.8× ↑ (10μM; 1wk)	34
BCRP	NFV	Human hepatocytes (mRNA): < 2× ↑ (10-25 μM)	67

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Transporter	HIV PI	Model System (marker): Effect (conc)	Reference
	RTV	Human hepatocytes (mRNA): 2-3× ↑ (10-25 μM)	67
	SQV	LS180 (mRNA): 4.1× ↑ (10μM; 1wk)	34
OATP1B1	NFV	Hepatocytes (mRNA): 2-3× ↑ (10-25 μM)	67
	RTV	Hepatocytes (mRNA): 2× ↑ (10-25 μM)	67
	SQV	LS180 (mRNA): 4.6× ↑ (10μM; 1wk)	34
OATP1B3	NFV	Human hepatocytes (mRNA): 2-5× ↑ (10-25 μM)	67
	RTV	Human hepatocytes (mRNA): 3-4× ↑ (10-25 μM)	67
OATP2B1	DRV	LS180 (mRNA): 1.9× ↑ (10μM; 1wk)	34
	SQV	LS180 (mRNA): 1.8× ↑ (10μM; 1wk)	34

ER, Efflux ratio (B-A/A-B).

Table 6

Clinically Relevant Examples of Transporter-mediated Interactions Between HIV Protease Inhibitors and Endogenous Compounds.

Endogenous Compound	Transport Protein	Protease Inhibitor	In Vitro Studies	Clinical Relevance
Bile salts	NTCP BSEP	RTV, SQV	Inhibition of bile acid transport [78]	Increased serum bile acids; Increased hepatocyte bile acids; Increased risk for hepatotoxicity
Palmitate	CD36 and CPT1 fatty acid transporters	LPV/r and DRV/r (not ATV/r)	Inhibition of palmitate uptake in cultured skeletal muscle cells (myotubes)[82]	Dyslipidaemia, insulin resistance
Bilirubin	OATP1B1	ATV, IDV	Potent inhibition of OATP1B activity by HIV protease inhibitors causing increased incidence of hyperbilirubinemia and jaundice[47,81]	Increased serum bilirubin levels associated with the use of specific protease inhibitors.[80]

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