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Pharmacokinetics and pharmacodynamics of cytochrome P450 inhibitors for HIV treatment

Yuqing Gong[1], **Sanjana Haque**[1], **Pallabita Chowdhury**[1], **Theodore J. Cory**[2], **Sunitha Kodidela**[1], **Murali M. Yallapu**[1], **John M. Norwood**[3], and **Santosh Kumar**[1,*]

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN, 38163 USA

[2]Department of Clinical Pharmacy and Translational Science, College of Pharmacy, University of Tennessee Health Science Center, Memphis, TN 38163, USA

[3]Department of Infectious Disease, College of Medicine, University of Tennessee Health Science Center, Memphis, TN 38163, USA

Abstract

Introduction—Drugs used in HIV treatment; all protease inhibitors, some non-nucleoside reverse transcriptase inhibitors, and pharmacoenhancers ritonavir and cobicistat can inhibit cytochrome P450 (CYP) enzymes. CYP inhibition can cause clinically significant drug-drug interactions (DDI), leading to increased drug exposure and potential toxicity.

Areas covered—A complete understanding of pharmacodynamics and CYP-mediated DDI is crucial to prevent adverse side effects and to achieve optimal efficacy. We summarized the pharmacodynamics of all the CYP inhibitors used for HIV treatment, followed by a discussion of drug interactions between these CYP inhibitors and other drugs, and a discussion on the effect of CYP polymorphisms. We also discussed the potential advancements in improving the pharmacodynamics of these CYP inhibitors by using nanotechnology strategy.

Expert opinion—The drug-interactions in HIV patients receiving ARV drugs are complicated, especially when patients are on CYP inhibitors-based ART regimens. Therefore, evaluation of CYP-mediated drug interactions is necessary prior to prescribing ARV drugs to HIV subjects. To improve the treatment efficacy and minimize DDI, novel approaches such as nanotechnology may be the potential alternative approach. However, further studies with large cohort need to be conducted to provide strong evidence for the use of nano-formulated ARVs to effectively treat HIV patients.

[*]**Corresponding author:** Santosh Kumar, College of Pharmacy, University of Tennessee Health Science Center, 881 Madison Ave, Rm 456, Memphis, TN 38163, ksantosh@uthsc.edu.

Declaration of Interest

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1. Introduction

According to the UNAIDS, there were approximately 36.9 million people living with HIV/AIDS (PLWHA) worldwide in 2017 [1]. In 1987, the US FDA licensed the first antiretroviral drug (ARV) zidovudine (ZDV, also known as azidothymidine) [2]. ZDV works by inhibiting reverse transcriptase of HIV, slowing the replication of the virus and the progression of the disease. In the last two decades, the antiretroviral therapy (ART) has made a significant contribution to reduction in HIV/AIDS-related death and improved quality of life for PLWHA [3]. In 2018, there are more than 30 antiretroviral drugs (ARVs) approved for the treatment of HIV in the US [4]. According to the mechanism of action of ARVs, they are classified into six groups as follows: nucleoside reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), entry inhibitors (also known as CCR5 antagonist), and integrase strand transfer inhibitors (INSTIs) [5]. ARVs can be used as either a single regimen or the combination of 3-4 drugs [6]. In most of the cases, in order to achieve their highest efficacy, ARVs are used in combination regimens that can attack multiple stages of the HIV life cycle, and subsequently slow the disease progression of HIV.

Drugs used in HIV, especially drugs from the PIs, the NNRTIs, and the INSTIs classes are metabolized via the Cytochrome P450 (CYP) pathway [7, 8]. All the PIs are metabolized by CYP3A4, and almost all the PIs are inhibitors of CYP3A4. Other than PIs, Efavirenz (EFV) and etravirine (ETR) from the NNRTIs class also have the potential to inhibit CYP enzymes. EFV is metabolized by CYP2B6 but can inhibit CYP3A4. ETR is metabolized by CYP3A4, CYP2C9, and CYP2C19, and it is also an inhibitor of CYP2C9 and CYP2C19 [7, 8]. To minimize the first pass metabolism, pharmacokinetic enhancers (PK enhancers) ritonavir (RTV) and cobicistat (COBI) are used in ART regimen due to their ability to inhibit CYP3A4 leading to decreased doses and frequency of administration for ARVs which are substrates of CYP3A4. Table 1 provides a summary of CYP substrates, inhibitors, and inducers that are used in HIV treatment.

As CYP enzymes are responsible for the metabolism of 70%−80% drugs in clinical use [9], it is expected that CYP enzymes account for the majority of the variabilities in pharmacokinetics and pharmacodynamics for the ARVs which are substrates of CYP enzymes [10]. In fact, PLWHA are prone to drug interactions because of the use of multiple drugs in their ART regimens, as well as the use of other drugs for the treatment of coinfections and comorbidities, which are common in these patients [8]. It has been shown that most of the drug interactions of these ARVs are mediated by or due to the involvement of CYP enzymes [11]. Specifically, for those ARVs which can inhibit or induce the CYP enzymes, has a higher chance of interfering with the drug metabolism of other CYP substrates. In this review, we discussed the CYP inhibitors used in HIV treatment, including

the potent inhibitors RTV and COBI, and ARVs from the PI and NNRTI classes, which show inhibition for CYP enzymes. These CYP inhibitors can cause clinically significant drug-drug interactions (DDI) by inhibition of CYP enzymes, leading to increased drug exposure and potential toxicity [12]. We summarized the pharmacodynamics of all the CYP inhibitors used for HIV treatment, interactions between these CYP inhibitors and other non-ARV drugs, and the effect of CYP polymorphisms on the dynamics and interactions of these drugs. In the end, we also discussed the potential advancements in improving pharmacodynamics of these CYP inhibitors, using a novel nanotechnology strategy. A systematic literature search using PubMed, Google Scholar, ClinicalTrials.gov, and Drugs@FDA was performed using keywords such as ARV drug names, generic names combined with pharmacodynamics, DDI, and nanoformulation to obtain relevant literature.

2. Pharmacokinetics and pharmacodynamics of CYP inhibitors for HIV treatment

Among all the CYP inhibitors used for HIV treatment, RTV and COBI are the most potent CYP inhibitors of both CYP3A4 and CYP2D6 [12, 13]. In the regimen which does not contain PK enhancers, some ARVs can also act as a CYP inhibitor when it is given separately [7, 8]. PIs-including atazanavir (ATV), darunavir (DRV), fosamprenavir (FPV), lopinavir (LPV), saquinavir (SQV), indinavir (IDV), and nelfinavir (NFV) are intermediate/weak CYP3A4 inhibitors, while tipranavir (TPV) is a CYP2D6 inhibitor. EFV from the NNRTIs is a CYP3A4 inhibitor, while ETR from the same class is a CYP2C9 and CYP2C19 inhibitor [7, 8]. Moreover, RTV and COBI are using as a PK enhancing strategy to increase the systemic exposure of an ARV that increases the levels of ARV, which are being metabolized by CYP3A4 [12, 13]. The CYP inhibition potency for all the CYP inhibitors used in HIV treatment is shown in Table 2. In the following subsections, we categorized based on the inhibition potency of CYP enzymes.

2.1 Strong CYP inhibitors

2.1.1. Ritonavir (RTV) and RTV-boosted PIs

2.1.1.1 RTV: RTV was initially developed as a PI to combat HIV-1 [14]. During development, however, it was discovered to have weak antiretroviral capabilities, but to be a strong inhibitor of CYP3A4. Based on these findings, it was observed that administration of low doses of RTV could allow for decreased doses and administration times necessary for drugs, which were substrates of CYP3A4 [14]. It is available as a 100 mg tablet, in an oral solution, and in an oral powder [15]. It is also available co-formulated with lopinavir (LPV). Serious side effects can include hepatotoxicity, primarily observed through increased transaminase levels, pancreatitis, elongation of the PR-interval, and lipid abnormalities [15]. Currently, use of full-dose RTV as an ARV monotherapy is no longer recommended. RTV is only prescribed as a part of a therapeutic combination with ARVs to decrease HIV replication [15]. Table 3 lists the changes in PK parameters of the PIs in RTV-boosted PI regimens.

2.1.1.2 Lopinavir (LPV)/RTV: LPV is co-formulated with RTV as part of a tablet branded in the US as Kaletra [16]. Current guidelines recommend a dose of 800 mg of LPV

with 200 mg of RTV given either once or twice daily, in combination with 2 NRTIs. As the drug is primarily formulated as a 200 mg LPV/50mg RTV tablet, this recommended regimen requires taking 2-4 tablets daily. Once daily dosage is more common than twice daily due to ease for patients to take the regimen. However ,if there is a risk of LPV resistance developing, twice daily dosing is necessary [8]. The reported EC_{50} of LPV in the presence of human plasma has been reported at 0.18 μg/ml, well below the steady-state trough concentration of 9.8 μg/ml [16]. While the drug is generally well tolerated, the reported side effects include pancreatitis, liver damage, especially in individuals co-infected with hepatitis B or C, metabolic disturbances which can lead to diabetes, and increased lipid levels. Due to its co-formulation with RTV, concomitant therapy with Kaletra and drugs which are CYP3A4 substrates can result in increased concentrations of the other drugs [16]. Therefore, the dose of CY3A4 substrates should be administered cautiously when it is given along with the Kaletra.

2.1.1.3 Tipranavir (TPV)/RTV: TPV, a selective nonpeptidic PI, received its FDA approval in 2005 for the use in treatment-experienced patients and other PI-resistant HIV-1 strain [17]. TPV should always be co-administered with RTV to ensure optimum drug availability. TPV demonstrates antiviral activity against a wide range of HIV-1 isolates (EC_{50} = 0.03-0.07 μM) and HIV-2 (EC_{50} = 0.233-0.522 μM) [17]. The benefit of the combination was more pronounced in treatment-experienced patients receiving two active drugs with TPV/RTV and enfuvirtide combination [18]. Recommended dosage guideline is 500 mg TPV, co-administered with 200 mg RTV. TPV is one of the few effective and reasonably safe ART regimes available for children who have prior ART experience. Pediatric patients enrolled in a randomized, open-label trial who were on a TPV/RTV regimen from earlier ages, demonstrated long term safety, tolerability, and reasonable viral suppression level for up to 5 years [19].

2.1.2. Cobicistat (COBI) and COBI-boosted INSTIs

2.1.2.1 COBI: COBI is a well-known pharmacokinetic enhancer. It inhibits the most common ARV metabolizing enzyme, CYP3A4 in a better selective manner than RTV [20]. COBI does not have any anti-retroviral activity of its own, however, it efficiently increases total drug exposure of CYP substrates-based ARVs. COBI was initially FDA approved as a single tablet form in 2012. COBI is always co-administered with other ARVs, commonly with PIs, 150 mg tablet each time with food, and other ARVs if needed. Although COBI and RTV both act in a similar manner, they are not interchangeable in many cases due to lack of enough exposure data. As COBI itself is not an ARV, the activity and resistance development completely depend on the ARVs that are given with COBI. A randomized, double-blinded, active-controlled trial reported that the safety and efficacy of COBI co-administered with ATZ was comparable to that of RTV-boosted group [21].

2.1.2.2 Elvitegravir (EVG)/COBI: EVG binds to the integrase-viral DNA complex followed by interaction with the DNA and the magnesium ions in the integrase [22]. Currently, EVG only is available in multiple combinations with NRTIs and CYP3A inhibitors, which is considered a complete treatment regimen as a first-line therapy or in cases of resistance. It was first approved by FDA in 2012 as part of a combination drug, as

well as a single drug formulation, which was later retracted in 2017. While in combination, EVG shows 50% effective concentration (EC_{50}) ranging between 0.02 and 1.7 nM in in vitro system. EVG has antiviral activity against HIV-1 subtypes A-G and O (EC_{50} 0.1-1.3 nM) and HIV-2 (EC_{50} 0.53 nM). The safety and efficacy of EVG in combination with an RTV-boosted PI was compared with another INSTI in a multicenter, randomized, double-blinded, phase 3 study on 700 participants. It revealed that EVG has a similar effect as other INSTI. Moreover, EVG combination has a once daily dose, which is more convenient to adhere to the therapy [23]. Recommended dosage for EVG combination drug is one tablet once daily with food, considering body weight and creatinine level [22].

2.1.3. Distinctions between RTV and COBI—COBI was introduced to overcome the limitations of RTV as it selectively inhibits CYP3A4 and CYP2D6, with less off-target drug interaction potential [21, 24]. This is due to the limited effect of COBI on activation of pregnane X receptor (PXR), thus limited effect on other drug metabolizing enzymes [25]. Moreover, unlike RTV, COBI does not induce CYPs, which makes it less prone to DDI. Additionally, RTV itself has antiviral activity. Both drugs raise the serum creatinine level, however, COBI's effect is comparatively more pronounced [25]. In terms of the PIs-boosting activity, RTV and COBI have an equal effect on EVG, while RTV boosts TPV at relatively higher magnitude [26]. Switching from RTV- to COBI-boosted regimen should be observed closely because the enzyme-inducing property of both the drugs differs leading to potential differences in drug exposure. COBI-boosted formulations are shown to reduce pill burden and ensure same time dosing [27]. Conversely, the coformulated tablets may be too large for some patients, while RTV is available as an oral liquid. Overall, RTV and COBI both are effective ATV-boosters, however, dose adjustment and close monitoring are highly recommended while switching [27].

2.2. Intermediate CYP inhibitors

2.2.1 Fosamprenavir (FPV, prodrug of amprenavir)—FPV is administered as 1400 mg daily with RTV, either as a single 1400 mg dose, or a 700 mg twice daily dose [8, 28]. As with all other protease inhibitors, FPV/RTV must be coadministered with two NRTIs. Care must be taken for individuals with hepatic impairment, and doses are decreased based on their level of hepatic impairment. Compared to other PIs, FPV has a larger side effect profile [28]. Skin reactions and rashes, including Stevens-Johnson syndrome, have been reported with FPV, and it should not be administered in individuals with a sulfa allergy. Additionally, lipid elevation, metabolic disturbances, and gastrointestinal side effects can occur in individuals receiving FPV. Further, there are many drug-drug interactions, both with ARVs and other medications, including antiarrhythmics, anticonvulsants, many statins, and some oral contraceptives. Because of the high required dose, side effect profile, and drug-drug interactions, FPV is not commonly used for the treatment of HIV in the United States [28].

2.2.2 Indinavir (IDV)—IDV is another drug in this class, which was approved in the US in 1996. In vitro tests performed on lymphoblastic, monocytic, and peripheral blood lymphocytes demonstrated an IC_{95} (95% inhibitory concentration) ranged between 25-100 nM. A randomized, double-blinded study to evaluate the efficacy of IDV, zidovudine or the

combination showed improved CD4 cell count [29]. However, IDV is not currently recommended to be used in the USA due to the occurrence of severe drug-induced nephrotoxicity. 67% IDV-treated patients present asymptomatic crystalluria, 8% shows symptoms and 3% has nephrolithiasis [30]. IDV is still commercially available in capsule form with a recommended dosage of 800 mg every 8 hours, with water, 1-2 hours before/after a meal [31].

2.2.3 Nelfinavir (NFV)—NFV is a potent viral PI, preventing the cleavage of gag-pol polyprotein, leading to the formation of immature non-infectious viral particles [32]. NFV was first approved in the US in 1997 and is available as tablet and oral powder. EC_{50} of NFV against certain HIV-1 strains (RF and IIIB) ranges from 1-43 nM/L [33]. It is also effective against zidovudine-resistant HIV-1 strain (G910-6) with an EC_{50} of 60 nM/L. A study to evaluate the presence and efficacy of circulating NFV metabolites showed that NFV is the major chemical substance with two other metabolites. All of them are active against similar HIV-1 strains, although the efficacy level varies greatly between the metabolites [34]. An ART regimen of multiple-dose RTV in combination with two doses of NFV in a single-site, open-label, non-randomized clinical trial on PI-naïve HIV-infected patients, successfully demonstrated the combination as a potential dual PI-option in the mentioned group [35]. The adult dose of NFV is 1250 mg BD or 750 mg TID with a meal [32].

2.2.4 Darunavir (DRV)—DRV was initially approved in 2006. Its administration requires pharmacologic boosting, either with RTV or with COBI [36]. A co-formulated version with RTV does not exist, although a co-formulation with COBI (Prezcobix) does exist [37]. When administered with RTV, the recommended dose of DRV is 800 mg and RTV is 100 mg [36]. DRV/COBI consists of a single tablet of 800 mg DRV and 150 mg COBI [37]. Both of these combinations, coupled with 2 NRTIs are listed as recommended initial regimens in certain clinical situations in the current DHHS Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [8]. Based on pharmacokinetic studies, the drug should be administered after eating, as administration under a fasting state results in plasma concentrations 30% lower compared to administration after eating [38]. There have been no reports in differences in DRV pharmacokinetic profiles based on sex or ethnicity. DRV is, in general, well tolerated by patients. While in the ARTEMIS trial the vast majority of subjects reported an adverse event, only 28% had a grade 2-4 adverse event, with gastrointestinal adverse events being the most common. These adverse events were, however, less common than in the LPV comparator arm in the trial. Elevated liver enzymes and lipid panels also occur with relatively high frequency [39]. More recently, DRV was co-formulated with COBI, which showed a similar pharmacokinetic profile compared to DRV and RTV [40].

2.3. Weak CYP inhibitors

2.3.1 Atazanavir (ATV)—FDA first approved ATV in 2003. Unlike other PIs, ATV is a once-daily dose drug with minimal effect on the patient's lipid profile [41]. ATV is an azapeptide PI active against HIV-1, but ineffective against HIV-2. ATV shows an EC_{50} of 2-5 nM range against HIV-1 group M subtypes (A-D, AE, AG, F, G, and J) in in vitro system. A population pharmacokinetic model, including a mixed model of absorption,

suggested a significant difference in ATV pharmacokinetics, regimens, and virological failure between the patients experiencing unboosted ATV [42]. Accordingly, recommended dosing of ATV is 300 mg with RTV, a PI booster with food or only ATV 400 mg once daily with food. However, the prevalence of safety concerns and tolerability issues have been long-recognized [43]. ATV combinations commercially available are with COBI, lamivudine, and ZDV [41].

2.3.2 Saquinavir (SQV)—SQV is available as single drug, in the form of tablets, capsules, and soft gelatin capsules. In vitro studies on acutely and chronically infected lymphoblastoid, monocytic cells, and peripheral blood lymphocytes demonstrated 50% and 90% inhibitory concentrations, namely IC_{50} and IC_{90} values in the range of 1-30 nM and 5-80 nM, respectively [44]. When administered in combination with reverse transcriptase inhibitors, SQV showed additive to synergistic in vitro effect, while with other PIs, SQV showed synergistic activity. In an open-label randomized clinical study in treatment-naïve, HIV-infected patient treated with SQV and other ARVs, showed decreased HIV RNA levels [45]. In general, it is recommended to always use SQV in the presence of RTV, which significantly inhibits the metabolism of SQV, thus increasing the drug availability [44]. SQV is a specific inhibitor of both HIV-1 and HIV-2 proteases. Some HIV-1 infected patients have reduced susceptibility to SQV, mostly due to the presence of multiple mutations in viral protease. Until now, there has been no report on resistance development in patients receiving SQV/RTV combination therapy [44]. General SQV (capsule/ tablet) dosage guideline for adults is 1000 mg twice daily, with a 100 mg RTV within 2 hours of a meal [44].

2.3.3 Efavirenz (EFV)—EFV was approved in the US in 1998, and now commercially available as tablet and capsule. It is commonly recommended as part of ART regimens [46]. EFV is used in combination with other NRTSs like lamivudine and ZDT or TFV in treatment-naïve HIV patients. It can also be used in combination with other retroviral drugs as post-exposure prophylactic agent to prevent HIV transmission. The recommended dosage of EFV is 600 mg, orally, once daily on empty stomach, preferably at bedtime. A 90-95% effective concentration of EFV in in vitro system (lymphoblastoid and monocytic cell lines, peripheral blood mononuclear cells) were between 1.7-25 nM. It has antiviral activity against most HIV-1 reverse transcriptase, but inactive against HIV-2. In vitro studies with HIV-1 isolates identified isolates with reduced susceptibility due to one or more amino acid substitutions in reverse transcriptase enzyme. Clinical isolates from patients failing treatment also showed amino acid substitutions. Reduced susceptibility was observed in the case of EFV alone or combination treatment with other NRTIs [46].

2.3.4 Etravirine (ETR)—ETR is a relatively newer addition to the FDA approved NNRTI drugs to be used in patients who have developed resistant against one NNRTI and other ARVs [47]. ETR blocks DNA and RNA-dependent viral polymerase activity by selectively binding to the reverse transcriptase enzyme. In patients with other NNRTI resistance, ETR is recommended to be prescribed in combination with both NRTIs and other ART regimens. General dosage guideline is to take 200 mg (two 100 mg tablets) twice daily following a meal. Currently, ETR is only available as a single drug regimen in tablet form. ETR exhibited appreciable activity (EC_{50} = 0.9-5.5 nM) against laboratory strains and

clinical isolates of HIV-1 in in vitro system. Developing resistance against ETR requires more than one substitution in reverse transcriptase enzyme [47]. In an open-label, partially blinded, randomized clinical trial on 199 patients assigned to ETR (400 mg and 800 mg twice daily) in presence of two optimized background ART showed a significant reduction in viral load as well as safety level compared to control [48]. Resistance against ETR may develop in case of multiple substitutions in reverse transcriptase enzyme, typically those which already shows resistance against other NNRTIs.

3. Drug-drug interactions involving CYP inhibitors in HIV treatment

CYP-mediated metabolism is the primary metabolic pathway for all PIs, all NNRTIs, and for few INSTIs. An understanding of the effect of the drug-drug interactions of those ARVs is crucial, especially for the CYP inhibitors. Since many other drugs on the market are CYP substrates, in the presence of a potent CYP inhibitor may cause a toxic drug accumulation. Therefore, numerous drugs should be avoided when using CYP inhibitors-based ARV regimens [10]. The below-mentioned class of drugs may have significant interactions with CYP inhibitors used in HIV treatment. Many of these drug-drug interactions require either decreased doses of the co-administered product, close monitoring, or avoid co-administration if needed. Table 4 summarized the most common CYP-mediated drug interactions between ARVs (CYP inhibitors) and other drugs.

3.1 Statins

Dyslipidemia is highly prevalent among PLWHA and it may increase the risk for cardiovascular disease [49]. Statins are commonly used drugs for treating hyperlipidemia for HIV patients. However, all the statins are CYP substrates, except pravastatin, which indicates that the potential drug-drug interactions between statins and CYP inhibitors need to be considered [50]. Among all the CYP inhibitors used in HIV therapy, almost all the PIs are potent CYP3A4 inhibitors except TPV and IDV. Therefore, the concentrations of the majority of statins are significantly increased when co-administrated with PIs. For example, when simvastatin, atorvastatin, and pravastatin were studied in the presence of SQV/RTV, the AUC of simvastatin and atorvastatin were increased by 3059% and 79%, respectively [51]. Significant drug interactions have also been reported between PIs and lovastatin [50]. Since CYP3A4 is the major metabolizing enzyme for simvastatin and lovastatin, simvastatin and lovastatin have the highest potency for drug-drug interaction with potent CYP3A4 inhibitors such as PIs, RTV-boosted ARV regimens, and COBI-boosted ARV regimens [8]. A recent review article summarized clinical efficacy trials until the year of 2016, suggesting that atorvastatin and pravastatin are safe for patients receiving PI-or NNRTIs-based therapies [52]. Rosuvastatin should be used with care in patients on ARV drug regimens containing PIs. The PI-based regimens are contraindicated for fluvastatin, simvastatin, and lovastatin. Other than PIs, some of the NNRTIs and INSTIs are CYP substrates or inhibitors, therefore, close monitoring and dose adjustments are often necessary for statins in patients receiving NNRTIs and INSTIs drug regimens [8].

3.2. Antituberculosis drugs

Although tuberculosis is a common disease even in immunocompetent population worldwide, it is one of the opportunistic and mortal diseases among PLWHA. People with HIV/TB coinfection has a much higher chance to develop to an active TB [53]. Rifampin and rifabutin are commonly used for the treatment of TB in PLWHA. However, both rifampin and rifabutin can induce CYP3A4, with rifampin as a potent CYP3A4 inducer [54]. Rifampin showed reduced AUC and C_{max} of EFV by 26% and 20%, respectively[46]. Rifampin also induces the metabolism of all PIs; more than 75% decrease of drug concentration was observed when co-administrated rifampin with PIs. PK enhancer RTV does not overcome this interaction and cause additional hepatotoxicity [8]. Therefore, rifampin is contraindicated with PIs, and rifabutin is a preferred regimen for the treatment of TB for people on PI-based regimens. In general, rifampin should be avoided in patients receiving PIs and NNRTIs. Some PIs and NNRTIs inhibit the metabolism of rifabutin significantly, causing a bidirectional drug interaction. Dose adjustments for rifabutin are needed when co-administered with PIs and NNRTIs [8].

3.3. Antifungal drugs

Antifungal drugs are commonly used for the treatment of oral candidiasis or cryptococcal meningitis among PLWHA [8]. Since antifungal drugs ketoconazole, fluconazole, miconazole, and itraconazole, are both CYP3A4 substrates and inhibitors, these antifungals have potential opportunities for CYP-mediated interactions with PIs, NNRTIS, INSTIs, and PK booster. Ketoconazole is the most potent CYP3A4 inhibitor among all the antifungals. Co-administration of ketoconazole with RTV/SQV led to an increased concentration of RTV and SQV by 62% and 94%, respectively [55], and an increased AUC of SQV by 190% [56]. Ketoconazole was also associated with a drug-drug interaction with amprenavir (active form of FPV). Co-administration of ketoconazole with amprenavir increased the AUC for both ketoconazole and amprenavir [57]. Additionally, because of the inhibition of CYP3A4, RTV and COBI demonstrated an increased level of ketoconazole and itraconazole, doses >200mg/day of ketoconazole or itraconazole is not recommended when using RTV- or COBI-boosted ARV regimens [15] [21].

3.4. Anticonvulsants

An increased risk of developing seizures was observed in HIV patients than in the general population [58]. Phenytoin, phenobarbital, and carbamazepine are commonly used drugs to control seizures. However, these drugs are metabolized by CYP enzymes and they induce CYP enzymes, which lead to CYP-mediated interactions with PIs, NNRTIS, some INSTIs, or PK enhancers. For example, co-administration of carbamazepine with IDV resulted in a failure of IDV therapy. Also, co-administration of phenytoin, phenobarbital, and carbamazepine with CYP inhibitors-based ARVs, caused increased plasma concentrations of anticonvulsants. Study showed an increased carbamazepine concentration concurrent with LPV/RTV [59]. RTV/SQV and EFV led to a 3-fold increase in plasma concentrations of carbamazepine. Similar interactions were also observed between NFV and carbamazepine [10]. In general, phenytoin, phenobarbital, and carbamazepine are not recommended when using PI- or NNRTI-based regimens. Co-administration of phenytoin, phenobarbital, and

carbamazepine with COBI-boosted PI regimen, LPV/RTV, ETR, and EVG/COBI are contraindicated [8].

3.5. Ergot alkaloids

Co-administration of CYP inhibitors with ergot alkaloid agents can develop ergot toxicity and increase the risk for ergotism or cause life-threatening side effects [60]. For example, a potent inhibition of ergot metabolism was observed even at prescribed doses of PIs and developed ergotism on an HIV-positive man in the United States [61]. A recent study from Belgium also reported a severe drug-drug interaction of ergotamine co-administered with DRV, abacavir, and lamivudine, causing fetal ischemia on an HIV-positive woman [62]. Additionally, there are total of 22 clinical ergotism cases reported in Thailand in HIV-infected patients from 2011 to 2013 [63]. This report summarized the severe clinical consequences caused by co-administration of RTV-boosted ARVs with ergot alkaloid agents and brought global attention to the potential of causing life-threatening drug-drug interactions by ergotamine and strong CYP3A4 inhibitors. CYP inhibitors used for HIV therapy include all PIs, EFV from NNRTIs, and PK enhancers are contraindicated with concomitant use of ergot alkaloid agents [64]. Thus, alternative agents 5-HT agonists (triptans) can be prescribed for PLWHA to treat a migraine type headache [15].

3.6. Other CYP substrates

Due to the CYP inhibition of PIs, some NNRTIs, and RTV- or COBI- boosted ARVs, it is expected that potential drug-drug interactions between these ARVs and other CYP substrates will occur [10]. Other than the drugs that are mentioned above, CYP-mediated drug interactions of PIs, NNRTIs, INSTIs, and PK boosters occur with numerous other non-ARV drugs. For examples, the macrolide antibiotics erythromycin and clarithoromycin show increased concentration of SQV and amprenavir, while RTV can increase the concentration of clarithromycin. Co-administration of oral contraceptives with PIs and NNRTIs also cause significant DDI. The AUC and C_{max} of ethinyl estradiol are reduced if patient is taking RTV and NFV daily. Since acid reducer cimetidine and omeprazole are inhibitors of CYP3A4, they cause potential adverse DDI with PIs and NNRTIs. Increased concentrations of the immunosuppressant tacrolimus were observed due to the inhibition of CYP3A4 by NFV. SQV also increased the concentration of ciclosporin, due to the CYP3A4 inhibition [10].

4. Polymorphism of CYP enzymes affecting pharmacodynamics of CYP inhibitors used in HIV treatment

Other than CYP-mediated DDI mentioned above, another major challenge posed by the CYP inhibitors is the inter-ethnic and inter-individual differences in expression and activity of CYP enzymes due to polymorphisms [65]. In fact, single nucleotide polymorphisms (SNP) cause approximately 60% inter-individual dependent difference in drug response [66, 67]. CYP3A4, the most common drug-metabolizing enzyme, responsible for metabolism of PIs and secondary metabolizer of several other ARVs, has at least 19 CYP3A4 variants and a number of sub-variants [68]. For example, CYP3A4*1B −392A>G and CYP3A4 671-202C>T reduce EFV clearance, whereas the CYP3A4*22 SNP is associated with decreased clearance of RTV-boosted LPV. This is more prevalent in the Caucasian

population and virtually absent within East Asian population [69]. In addition, CYP3A5*3 6986A>G, commonly found within the Caucasian population, is significantly associated with LPV/RTV monotherapy failure in general population [70, 71]. Although, when the study was performed specifically on Caucasians, there was potentially no decrease in the efficacy of these two drugs [71].

CYP2B6, involved in metabolism of few ARV drugs (e.g. EFV and nevirapine are substrates and inducers, RTV is an inducer) is highly polymorphic in nature [72]. Certain SNPs e.g. the 516G>T variant of CYP2B6*6 reduces the enzyme expression resulting into differences in plasma concentration and neuropsychological toxicity of EFV in adult HIV patients [73]. Similarly, 516G>T plays a significant role in EFV concentrations, especially in children older than 10 years [74]. Moreover, higher EFV plasma levels and CNS-related complications are observed in patients deficient in CYP2B6 516T allele [75]. 516G>T variant is most common in the South Asian population, while least frequently observed in East Asians [69]. Studies have also shown the presence of CYP2B6*18 variant in the African population, which produces non-functional protein, leading to increased nevirapine and EFV plasma exposure [76]. Drug monitoring is recommended for clinicians when prescribing EFV and NFV, and pharmacogenetics-based dosing should be done if possible. For CYP2B6 poor metabolizer SNPs, dose reduction or drug replacement is needed.

Other CYPs like CYP2C9 and CYP2C19 show polymorphisms, which influence the metabolism of ARVs such as ETR, TPV, NFV, and DLV. Presence of CYP2C9*3 variant leads to reduced ETR clearance, while CYP2C19*2 is related to decreased NFV clearance in Black, Caucasian, and Hispanic populations [69]. HIV-positive alcohol abusers with CYP2C9*3 genotype are also at a higher risk of developing ARV-associated hepatotoxicity, particularly, if NFV is prescribed [77]. A study on voriconazole co-administered with an RTV-boosted ATV regimen demonstrated that both extensive and poor metabolizers have a modest reduction in ATV exposure [78]. Similarly, factors like gender, age, and diet can also influence the expression/activity of CYP enzymes leading to inter-individual differences in drug response [79].

5. Research and development to improve pharmacodynamics and to overcome DDI of CYP inhibitors

Researchers are developing new delivery methods to improve pharmacodynamics of ARVs and to overcome DDI [80]. One of the promising methods to achieve this is the use of nanotechnology using polymer-based nanoparticles. Nanoparticles could be used to improve drug delivery because they are generally taken up by cells efficiently [81]. Therapeutic drugs can be encapsulated in the core of nanoparticles and provide targeted delivery of drugs at the site of action, bypass transporters and metabolic enzymes, and cross the BBB [82, 83]. For example, in the clinic, EVG is recommended with a co-administration of a PK enhancer COBI for better efficacy [22]. However, co-administration of EVG with COBI is relatively expensive and may also cause DDI [84]. An improved delivery method of EVG can, not only improve drug concentration in viral reservoirs but also eliminate the use of COBI and thus reduce the cost and minimize the potential of CYP-mediated DDI. Recently, Kumar and

Yallapu groups developed a PLGA nanoformulation loaded with EVG, which increased the level of the drug by 2-fold compared to drug alone in macrophages [84]. This EVG nanoformulation also showed an improved viral suppression in HIV-infected primary macrophages. They hypothesized that this high bioavailability of EVG in nanoparticles is due to the protection of nanoparticles from EVG metabolic enzyme CYP3A4.

Nanoformulation of other CYP inhibitors used for HIV treatment has also been developed. For example, ATV suffers from poor water solubility and rapid first-pass metabolism by CYP3A4 causing reduction in bioavailability by 60% [85]. With this regard, ATV was nanoformulated to improve the bioavailability. , in Compared to plain drug, the nanoformulated ATV showed significant enhanced improvement of C_{max} and AUC_{0-24} by 1.1- and 2.9-fold, respectively [86]. Another example is DRV, a CYP inhibitor from the PIs. DRV has poor oral bioavailability (37%), metabolizes in the liver by CYP enzymes, and may lead to liver diseases and skin rashes [87, 88]. Desai *et al.* demonstrated that solid lipid nanoparticles loaded DRV has 4-fold increased permeability than DRV plain drug [89]. Similar these nanoparticles also enhanced AUC by 2.50- and 2.51-fold upon intra-gastric and intra-duodenal administration, respectively. Further, higher accumulation of DRV was also found in the brain (1.5-fold and 3.5-fold for plain drug and nanoparticles, respectively) and even in the spleen, which serves as the main reservoir for HIV replication. Low accumulation of nanoparticles loaded DRV in the liver suggests the ability of these nanoparticles to bypass first-pass liver metabolism, prolonging circulation of the drug [89]. Similar attempt to improve oral bioavailability of DRV/RTV was made by Augustine *et al*, where the authors generated nanoparticles and microencapsulated them within calcium alginate/chitosan film to enhance their stability in pH-sensitive gastric conditions and sustain the release of drugs in the small intestine. Investigators were able to increase oral bioavailability of the drugs by 2-fold by encapsulating the nanoparticles versus plain drugs [90].

6. Conclusion

ARVs belonging to different classes are combined due to their ability to act at different stages of HIV life cycle. Most of the ARVs are metabolized by CYP pathway, and majority of them are either CYP inhibitors or inducers, and few possess both the activities. This can lead to both pharmacokinetics and pharmacodynamics interactions which can complicate the treatment of HIV infection. Acquisition of the knowledge of CYP-mediated drug interactions will help healthcare providers to manage patients on ART regimens more efficiently. When prescribing or switching one or more ARVs during HIV therapy, clinicians should be diligent about potential pharmacokinetics and pharmacodynamics drug-drug interactions to avoid drug resistance and adverse effects.

7. Expert opinion

Because of the combination of multiple drugs in ART regimen, the CYP-mediated DDI occurrence in a specific patient is complex and hard to predict even with the information provided on package inserts. The CYP inhibitors used in HIV treatment, which we discussed here, can cause clinically significant DDI by inhibition of CYP enzymes, leading to

increased drug exposure and potential toxicity. There is a need to know the factors that contribute to CYP-mediated DDI to avoid unpredictable interactions and consequent toxicity. Moreover, this complexity is also indicated by the polymorphism of CYP enzymes and individual differences of CYP activities. A pharmacogenetics evaluation for PLWHA is needed to determine whether the patient has fast or poor metabolizer for CYP enzymes. It is important to consider all these factors while prescribing ARV drugs, which are metabolized by CYP pathway, to HIV patient who also receives other drugs for the treatment of other conditions such as opportunistic infections. If several drugs are competing for the same metabolic pathways and drug interactions are hard to predict, clinicians need to titrate drug dose based on clinical response. Patient monitoring is critical to avoid their toxicity when CYP substrates are prescribed to patients who are on CYP inhibitors-based ARV regimens.

Recently, nanoformulation of ARVs is under development to overcome the limitations and side effects of current HIV treatment [80]. As we mentioned before, nanoparticles could be used as an effective delivery system of EVG in HIV-infected monocytes, perhaps bypassing CYP3A4 and eliminating the use of COBI [84]. Although only few nanoparticles loaded ARVs/molecules have reached to the clinical trials for HIV treatment, nanomedicine may provide a new approach for delivery of ARVs on a safe and efficient base for long-term therapy [80]. However, it was found that few nanoparticles itself may involve in drug metabolism and inhibit/induce some CYP enzymes [91]. Thus, in order to move forward to clinical use, one should consciously select a nanoparticle which doesn't affect CYP induction/inhibition. Also, several aspects including long-term adverse reactions, systemic toxicities, accumulation of nanomaterials, and their interactions with plasma proteins need to be studied before moving to clinical use.

In addition, the influence of drug transporters should also be considered because drug transporter expression is also influenced by ARVs, which can lead to DDI [92]. The solute carrier (SLC) and ATP-binding cassette (ABC) transporters superfamily may limit the oral bioavailability of PIs, causing opposing effects [93]. Changes in the expression of drug transporters are also related to toxicity and efficacy of ARV drugs and the influence of drug transporters on ARVs was reviewed by Griffin *et al.* [93].

Overall, ARV drug interactions are complicated, especially when patients are on CYP-inhibitors-based ART regimens. Therefore, it is necessary for clinicians to consider CYP-mediated drug interactions while prescribing co-medications to patients receiving ARV therapy as inappropriate prescription may cause drug toxicity and/or fail to achieve viral control. If the clinician is unsure about the possible interactions, titration of drug dose based on a clinical response is needed.

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References

Papers of special note have been highlighted as:

* of interest

** of considerable interest to readers.

1. UNAIDS fact sheet 2018 [cited 2018 11/20] Available from: http://www.unaids.org/en/resources/fact-sheet
2. Lange J, Ananworanich J. The discovery and development of antiretroviral agents. Antivir Ther. 2014;19(Suppl 3):5–14. [PubMed: 25310317]
3. Mayer KH, Venkatesh KK. Antiretroviral therapy as HIV prevention: status and prospects. American journal of public health. 2010;100(10):1867–1876. doi: 10.2105/AJPH.2009.184796. [PubMed: 20724682]

*4. FDA. Antiretroviral drugs used in the treatment of HIV infection 2018 [cited 2018 11/20] Available from: https://www.fda.gov/forpatients/illness/hivaids/treatment/ucm118915.htm*Listed all the FDA-approved medicines used in the treatment of HIV infection (updated on April 12, 2018)

5. De Clercq E Antiretroviral drugs. Current Opinion in Pharmacology. 2010 2010/10/01/;10(5):507–515. doi: 10.1016/j.coph.2010.04.011. [PubMed: 20471318]
6. De Clercq E Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. International Journal of Antimicrobial Agents. 2009 2009/04/01/;33(4):307–320. doi: 10.1016/j.ijantimicag.2008.10.010. [PubMed: 19108994]
7. Stolbach A, Paziana K, Heverling H, et al. A Review of the Toxicity of HIV Medications II: Interactions with Drugs and Complementary and Alternative Medicine Products. Journal of medical toxicology : official journal of the American College of Medical Toxicology. 2015;11(3):326–341. doi: 10.1007/s13181-015-0465-0. [PubMed: 26036354]

8. DHHS. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. Available at http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf. Key paper on explaining the enzymes that metabolize or are induced or inhibited by ARVs. Key paper on summerizing the CYP-mediated drug interactions of ARVs.

9. Zanger UM, Schwab M. Cytochrome P450 enzymes in drug metabolism: Regulation of gene expression, enzyme activities, and impact of genetic variation. Pharmacology & Therapeutics. 2013 2013/04/01/;138(1):103–141. doi: 10.1016/j.pharmthera.2012.12.007. [PubMed: 23333322]

**10. Walubo A The role of cytochrome P450 in antiretroviral drug interactions. Expert opinion on drug metabolism & toxicology. 2007;3(4):583–598. [PubMed: 17696808] ** Key paper on summerizing the CYP-mediated drug interactions of ARVs.

11. Dooley KE, Charles F, Andrade AS. Drug Interactions Involving Combination Antiretroviral Therapy and Other Anti-Infective Agents: Repercussions for Resource-Limited Countries. The Journal of Infectious Diseases. 2008;198(7):948–961. doi: 10.1086/591459. [PubMed: 18713054]
12. Granfors MT, Wang J-S, Kajosaari LI, et al. Differential Inhibition of Cytochrome P450 3A4, 3A5 and 3A7 by Five Human Immunodeficiency Virus (HIV) Protease Inhibitors in vitro. Basic & clinical pharmacology & toxicology. 2006 2006/01/01;98(1):79–85. doi: 10.1111/j.1742-7843.2006.pto_249.x. [PubMed: 16433896]
13. Hossain MA, Tran T, Chen T, et al. Inhibition of human cytochromes P450 in vitro by ritonavir and cobicistat. Journal of Pharmacy and Pharmacology. 2017 2017/12/01;69(12):1786–1793. doi: 10.1111/jphp.12820. [PubMed: 28960344]
14. Merry C, Barry MG, Mulcahy F, et al. Saquinavir pharmacokinetics alone and in combination with ritonavir in HIV-infected patients. AIDS. 1997 3 15;11(4):F29–33. [PubMed: 9084785]
15. Norvir (R) [Package insert] Abbvie Inc., North Chicago, IL; 2017.
16. Kaletra (R) [Package insert] Abbvie Inc, North Chicago, IL; 2015.
17. Aptivus (R) [Package insert] Boehringer Ingelheim, Ingelheim am Rhein, Germany, 2018.
18. Orman JS, Perry CM. Tipranavir. Drugs. 2008 2008/07/01;68(10):1435–1463. doi: 10.2165/00003495-200868100-00006. [PubMed: 18578560]

*19. Salazar JC, Cahn P, Della Negra M, et al. Efficacy and Safety of Tipranavir Coadministered with Ritonavir in HIV-1-Infected Children and Adolescents: 5 Years of Experience. The Pediatric

Infectious Disease Journal. 2014;33(4):396–400. doi: 10.1097/inf.0000000000000038. [PubMed: 23995585] * Recommended ARV regimen for children living with HIV.

*20. Larson KB, Wang K, Delille C, et al. Pharmacokinetic Enhancers in HIV Therapeutics. Clinical Pharmacokinetics. 2014 2014/10/01;53(10):865–872. doi: 10.1007/s40262-014-0167-9. [PubMed: 25164142] * The use of PK enhancers in HIV therapy.

21. Tybost (R) [Package insert] Gilead Sciences, Inc, Foster City, CA, 2018.

22. Genvoya (R) [Package insert] Gilead Sciences, Inc, Foster City, CA, 2015.

23. Molina J-M, LaMarca A, Andrade-Villanueva J, et al. Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study. The Lancet Infectious Diseases. 2012 2012/01/01/;12(1):27–35. doi: 10.1016/S1473-3099(11)70249-3. [PubMed: 22015077]

24. Deeks ED. Cobicistat: A Review of Its Use as a Pharmacokinetic Enhancer of Atazanavir and Darunavir in Patients with HIV-1 Infection. Drugs. 2014 2014/02/01;74(2):195–206. doi: 10.1007/s40265-013-0160-x. [PubMed: 24343782]

25. Marzolini C, Back D, Gibbons S, et al. Cobicistat versus ritonavir boosting and differences in the drug–drug interaction profiles with co-medications. Journal of Antimicrobial Chemotherapy. 2016;71(7):1755–1758. doi: 10.1093/jac/dkw032. [PubMed: 26945713]

26. Ramanathan S, Custodio JM, Wei X, et al. Pharmacokinetics of Co-Formulated Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate After Switch From Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in Healthy Subjects. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2016;72(3):281–288. doi: 10.1097/qai.0000000000000959. [PubMed: 26885802]

27. Tseng A, Hughes CA, Wu J, et al. Cobicistat Versus Ritonavir: Similar Pharmacokinetic Enhancers But Some Important Differences. The Annals of pharmacotherapy. 2017;51(11):1008–1022. doi: 10.1177/1060028017717018. [PubMed: 28627229]

28. Lexiva (R) [Package insert] GlaxoSmithKline, Research Triangle Park, NC; 2009.

29. Lewi DS, Suleiman JM, Uip DE, et al. Randomized, double-blind trial comparing indinavir alone, zidovudine alone and indinavir plus zidovudine in antiretroviral therapy-naive HIV-infected individuals with CD4 cell counts between 50 and 250/mm3. Revista do Instituto de Medicina Tropical de São Paulo. 2000;42(1):27–36. [PubMed: 10742724]

30. Fogo AB, Lusco MA, Najafian B, et al. AJKD Atlas of Renal Pathology: Indinavir Nephrotoxicity. Am J Kidney Dis. 2017 2017/01//;69(1):e3. doi: 10.1053/j.ajkd.2016.11.004 eng. [PubMed: 28007196]

31. Crixivan (R) [Package insert] Merck, Kenilworth, NJ; 2018.

32. Viracept (R) [Package insert] Pfizer, New York City, NY, 2016.

33. Pai VB, Nahata MC. Nelfinavir Mesylate: A Protease Inhibitor. Annals of Pharmacotherapy. 1999 1999/03/01;33(3):325–339. doi: 10.1345/aph.18089. [PubMed: 10200859]

34. Zhang KE, Wu E, Patick AK, et al. Circulating metabolites of the human immunodeficiency virus protease inhibitor nelfinavir in humans: structural identification, levels in plasma, and antiviral activities. Antimicrobial agents and chemotherapy. 2001;45(4):1086–1093. doi: 10.1128/AAC.45.4.1086-1093.2001. [PubMed: 11257019]

35. Raines CP, Flexner C, Sun E, et al. Safety, tolerability, and antiretroviral effects of ritonavir-nelfinavir combination therapy administered for 48 weeks. Journal of acquired immune deficiency syndromes (1999). 2000;25(4):322–328. [PubMed: 11114832]

36. Prezista (R) [Package insert] Janssen Therapeutics, Inc, Titusville, NJ, 2016.

37. Prezcobix (R) [Package insert] Janssen Therapeutics, Inc, Titusville, NJ, 2018.

38. Kakuda TN, Brochot A, Tomaka FL, et al. Pharmacokinetics and pharmacodynamics of boosted once-daily darunavir. J Antimicrob Chemother. 2014 10;69(10):2591–605. doi: 10.1093/jac/dku193. [PubMed: 24951533]

39. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naive patients in the ARTEMIS trial. HIV Med. 2013 1;14(1):49–59. doi: 10.1111/j.1468-1293.2012.01060.x.

40. Kakuda TN, Van De Casteele T, Petrovic R, et al. Bioequivalence of a darunavir/cobicistat fixed-dose combination tablet versus single agents and food effect in healthy volunteers. Antivir Ther. 2014;19(6):597–606. doi: 10.3851/IMP2814. [PubMed: 24964392]

41. Reyataz (R) [Package insert] Bristol-Myers Squibb Company, Princeton, NJ, 2018.

42. Goutelle S, Baudry T, Gagnieu M-C, et al. Pharmacokinetic-pharmacodynamic modeling of unboosted Atazanavir in a cohort of stable HIV-infected patients. Antimicrobial agents and chemotherapy. 2013;57(1):517–523. doi: 10.1128/AAC.01822-12. [PubMed: 23147727]

43. Cihlar T, Fordyce M. Current status and prospects of HIV treatment. Current Opinion in Virology. 2016 2016/06/01/;18:50–56. doi: 10.1016/j.coviro.2016.03.004. [PubMed: 27023283]

44. Invirase (R) [Package insert] Roche, Basel, Switzerland, 2018.

45. ClinicalTrials.gov. A Randomized, Parallel Arm, Comparative, Open Label, Multicenter Study of the Activity and Safety of Two Formulations of Saquinavir in Combination With Other Antiretroviral Drugs 2005 Available from: https://clinicaltrials.gov/ct2/show/NCT00002162

46. Sustiva (R) [Package insert] Bristol-Myers Squibb Pharma Company, New York City, NY, 2016. Recommended ARV for people starting HIV treatment.

47. Intelence (R) [Package insert] Janssen Products,Titusville NJ, 2008.

48. Nadler JP, Berger DS, Blick G, et al. Efficacy and safety of etravirine (TMC125) in patients with highly resistant HIV-1: primary 24-week analysis. AIDS (London, England). 2007;21(6):F1–10. Recommended ARV for people with highly resistant HIV-1.

49. Grunfeld C. Dyslipidemia and its Treatment in HIV Infection. Topics in HIV medicine : a publication of the International AIDS Society, USA. 2010 Aug-Sep;18(3):112–118.

50. Neuvonen PJ, Backman JT, Niemi M. Pharmacokinetic Comparison of the Potential Over-the-Counter Statins Simvastatin, Lovastatin, Fluvastatin and Pravastatin. Clinical Pharmacokinetics. 2008 2008/07/01;47(7):463–474. doi: 10.2165/00003088-200847070-00003. [PubMed: 18563955]

51. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. Aids. 2002;16(4):569–577. [PubMed: 11873000]

**52. Chastain DB, Stover KR, Riche DM. Evidence-based review of statin use in patients with HIV on antiretroviral therapy. Journal of clinical & translational endocrinology. 2017;8:6–14. doi: 10.1016/j.jcte.2017.01.004. [PubMed: 29067253] ** A comprehensive review covered clinical trials published form 1940 to November 2016 on the use of statins in HIV patients reciving ARVs.

53. CDC. TB and HIV Coinfection 2018 Available from: https://www.cdc.gov/tb/topic/basics/tbhivcoinfection.htm

54. Chen J, Raymond K. Roles of rifampicin in drug-drug interactions: underlying molecular mechanisms involving the nuclear pregnane X receptor. Annals of clinical microbiology and antimicrobials. 2006;5:3–3. doi: 10.1186/1476-0711-5-3. [PubMed: 16480505]

55. Khaliq Y, Gallicano K, Venance S, et al. Effect of ketoconazole on ritonavir and saquinavir concentrations in plasma and cerebrospinal fluid from patients infected with human immunodeficiency virus. Clinical Pharmacology & Therapeutics. 2000;68(6):637–646. doi: doi: 10.1067/mcp.2000.112363. [PubMed: 11180024]

56. Grub S, Bryson H, Goggin T, et al. The interaction of saquinavir (soft gelatin capsule) with ketoconazole, erythromycin and rifampicin: comparison of the effect in healthy volunteers and in HIV-infected patients. European journal of clinical pharmacology. 2001;57(2):115–121. [PubMed: 11417442]

57. Polk RE, Crouch MA, Israel DS, et al. Pharmacokinetic Interaction between Ketoconazole and Amprenavir after Single Doses in Healthy Men. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 1999;19(12):1378–1384. doi: doi:10.1592/phco.19.18.1378.30905.

58. Siddiqi O, Birbeck GL. Safe Treatment of Seizures in the Setting of HIV/AIDS. Current treatment options in neurology. 2013;15(4):529–543. doi: 10.1007/s11940-013-0237-6. [PubMed: 23657845]

59. Bates DE, Herman RJ. Carbamazepine toxicity induced by lopinavir/ritonavir and nelfinavir. Annals of Pharmacotherapy. 2006;40(6):1190–1195. [PubMed: 16720703]

60. Liegl CA, McGrath MA. Ergotism: Case Report and Review of the Literature. The International journal of angiology : official publication of the International College of Angiology, Inc. 2016;25(5):e8–e11. doi: 10.1055/s-0034-1376397.
61. Baldwin ZK, Ceraldi CC. Ergotism associated with HIV antiviral protease inhibitor therapy. Journal of Vascular Surgery. 2003;37(3):676–678. doi: 10.1067/mva.2003.80. [PubMed: 12618710]
62. Petit E, Schoonheydt K, Meert P, et al. Drug-Drug Interaction of Ergotamine with a Combination of Darunavir, Abacavir, and Lamivudine Causing a Fatal Vasospastic Ischemia. Case Reports in Emergency Medicine. 2018;2018:4. doi: 10.1155/2018/4107450.
63. Avihingsanon A, Ramautarsing RA, Suwanpimolkul G, et al. Ergotism in Thailand caused by increased access to antiretroviral drugs: a global warning. Topics in antiviral medicine. 2016;21(5): 165–168.
64. Fröhlich G, Kaplan V, Amann-Vesti B. Holy fire in an HIV-positive man: a case of 21st-century ergotism. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne. 2010;182(4):378–380. doi: 10.1503/cmaj.091362.
65. Zhou S-F, Liu J-P, Chowbay B. Polymorphism of human cytochrome P450 enzymes and its clinical impact. Drug Metabolism Reviews. 2009 2009/05/01;41(2):89–295. doi: 10.1080/03602530902843483. [PubMed: 19514967]
66. Swart M, Mpeta B, Wonkam A, et al. Cytochrome P450 pharmacogenetics in African populations: implications for public health AU - Dandara, Collet. Expert Opinion on Drug Metabolism & Toxicology. 2014 2014/06/01;10(6):769–785. doi: 10.1517/17425255.2014.894020. [PubMed: 24588448]
67. Kodidela S, Pradhan SC, Dubashi B, et al. Influence of dihydrofolate reductase gene polymorphisms rs408626 (−317A>G) and rs442767 (−680C>A) on the outcome of methotrexate-based maintenance therapy in South Indian patients with acute lymphoblastic leukemia. European Journal of Clinical Pharmacology. 2015 2015/11/01;71(11):1349–1358. doi: 10.1007/s00228-015-1930-z. [PubMed: 26335211]
68. Owen A, Siccardi M, Olagunju A, et al. Class-specific relative genetic contribution for key antiretroviral drugs. Journal of Antimicrobial Chemotherapy. 2015;70(11):3074–3079. doi: 10.1093/jac/dkv207. [PubMed: 26221018]
69. Neary M, Owen A. Pharmacogenetic considerations for HIV treatment in different ethnicities: an update. Expert opinion on drug metabolism & toxicology. 2017 2017/11//;13(11):1169–1181. doi: 10.1080/17425255.2017.1391214 eng. [PubMed: 28994310]
70. Thompson EE, Kuttab-Boulos H, Witonsky D, et al. CYP3A variation and the evolution of salt-sensitivity variants. American journal of human genetics. 2004;75(6):1059–1069. doi: 10.1086/426406. [PubMed: 15492926]
71. Berno G, Zaccarelli M, Gori C, et al. Analysis of single-nucleotide polymorphisms (SNPs) in human CYP3A4 and CYP3A5 genes: potential implications for the metabolism of HIV drugs. BMC medical genetics. 2014;15:76–76. doi: 10.1186/1471-2350-15-76. [PubMed: 24986243]
72. Rotger M, Colombo S, Furrer H, et al. Influence of CYP2B6 polymorphism on plasma and intracellular concentrations and toxicity of efavirenz and nevirapine in HIV-infected patients. Pharmacogenetics and genomics. 2005;15(1):1–5. [PubMed: 15864119]
73. Hofmann MH, Blievernicht JK, Klein K, et al. Aberrant Splicing Caused by Single Nucleotide Polymorphism c.516G>T [Q172H], a Marker of CYP2B6*6, Is Responsible for Decreased Expression and Activity of CYP2B6 in Liver. Journal of Pharmacology and Experimental Therapeutics. 2008;325(1):284–292. doi: 10.1124/jpet.107.133306. [PubMed: 18171905]
74. Liu X, Ma Q, Zhao Y, et al. Impact of Single Nucleotide Polymorphisms on Plasma Concentrations of Efavirenz and Lopinavir/Ritonavir in Chinese Children Infected with the Human Immunodeficiency Virus. Pharmacotherapy. 2017;37(9):1073–1080. doi: 10.1002/phar.1988. [PubMed: 28718515]
75. Gallien S, Journot V, Loriot MA, et al. Cytochrome 2B6 polymorphism and efavirenz-induced central nervous system symptoms : a substudy of the ANRS ALIZE trial. HIV Medicine. 2017 2017/09/01;18(8):537–545. doi: 10.1111/hiv.12488. [PubMed: 28145050]

76. Wyen C, Hendra H, Vogel M, et al. Impact of CYP2B6 983T>C polymorphism on non-nucleoside reverse transcriptase inhibitor plasma concentrations in HIV-infected patients. The Journal of antimicrobial chemotherapy. 2008;61(4):914–918. doi: 10.1093/jac/dkn029. [PubMed: 18281305]
77. Singh H, Lata S, Nema V, et al. CYP1A1m1 and CYP2C9*2 and *3 polymorphism and risk to develop ARV-associated hepatotoxicity and its severity. APMIS. 2017 2017/06/01;125(6):523–535. doi: 10.1111/apm.12683. [PubMed: 28370504]
78. Zhu L, Brüggemann RJ, Uy J, et al. CYP2C19 Genotype–Dependent Pharmacokinetic Drug Interaction Between Voriconazole and Ritonavir-Boosted Atazanavir in Healthy Subjects. The Journal of Clinical Pharmacology. 2017 2017/02/01;57(2):235–246. doi: 10.1002/jcph.798. [PubMed: 27432796]
79. Lakhman SS, Ma Q, Morse GD. Pharmacogenomics of CYP3A: considerations for HIV treatment. Pharmacogenomics. 2009;10(8):1323–1339. doi: 10.2217/pgs.09.53. [PubMed: 19663676]
80. Roy U, Rodríguez J, Barber P, et al. The potential of HIV-1 nanotherapeutics: from in vitro studies to clinical trials. Nanomedicine (London, England). 2015;10(24):3597–3609. doi: 10.2217/nnm.15.160.
81. Suri SS, Fenniri H, Singh B. Nanotechnology-based drug delivery systems [journal article]. Journal of Occupational Medicine and Toxicology. 2007;2(1):16. doi: 10.1186/1745-6673-2-16. [PubMed: 18053152]
82. Roy U, Rodriguez J, Barber P, et al. The potential of HIV-1 nanotherapeutics: from in vitro studies to clinical trials. Nanomedicine. 2015;10(24):3597–609. doi: 10.2217/nnm.15.160. [PubMed: 26400459]
83. Edagwa BJ, Zhou T, McMillan JM, et al. Development of HIV reservoir targeted long acting nanoformulated antiretroviral therapies. Current medicinal chemistry. 2014;21(36):4186–98. [PubMed: 25174930]
84. Gong Y, Chowdhury P, Midde NM, et al. Novel elvitegravir nanoformulation approach to suppress the viral load in HIV-infected macrophages. Biochemistry and biophysics reports. 2017;12:214–219. [PubMed: 29214223]
85. Fukushima K, Terasaka S, Haraya K, et al. Pharmaceutical approach to HIV protease inhibitor atazanavir for bioavailability enhancement based on solid dispersion system. Biological and Pharmaceutical Bulletin. 2007;30(4):733–738. [PubMed: 17409512]
86. Singh G, Pai RS. Atazanavir-loaded Eudragit RL 100 nanoparticles to improve oral bioavailability: optimization and in vitro/in vivo appraisal. Drug delivery. 2016;23(2):532–539. [PubMed: 24963752]
87. McKeage K, Perry CM, Keam SJ. Darunavir. Drugs. 2009;69(4):477–503. [PubMed: 19323590]
88. Haubrich R, Berger D, Chiliade P, et al. Week 24 efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients. Aids. 2007;21(6):F11–F18. [PubMed: 17413685]
89. Desai J, Thakkar H. Darunavir-Loaded Lipid Nanoparticles for Targeting to HIV Reservoirs. AAPS PharmSciTech. 2018;19(2):648–660. [PubMed: 28948564]
90. Augustine R, Ashkenazi DL, Arzi RS, et al. Nanoparticle-in-microparticle oral drug delivery system of a clinically relevant darunavir/ritonavir antiretroviral combination. Acta biomaterialia. 2018.
91. Ong CE, Pung YF, Chieng JY. The current understanding of the interactions between nanoparticles and cytochrome P450 enzymes – a literature-based review AU - Pan, Yan. Xenobiotica; the fate of foreign compounds in biological systems. 2018:1–14. doi: 10.1080/00498254.2018.1503360.
92. Alam C, Whyte-Allman S-K, Omeragic A, et al. Role and modulation of drug transporters in HIV-1 therapy. Advanced Drug Delivery Reviews. 2016 2016/08/01/;103:121–143. doi: 10.1016/j.addr.2016.05.001. [PubMed: 27181050]
93. Griffin L, Annaert P, Brouwer KLR. Influence of drug transport proteins on the pharmacokinetics and drug interactions of HIV protease inhibitors. Journal of pharmaceutical sciences. 2011;100(9):3636–3654. doi: 10.1002/jps.22655. [PubMed: 21698598]
94. Wyen C, Fuhr U, Frank D, et al. Effect of an Antiretroviral Regimen Containing Ritonavir Boosted Lopinavir on Intestinal and Hepatic CYP3A, CYP2D6 and P-glycoprotein in HIV-infected Patients. Clinical Pharmacology & Therapeutics. 2008 2008/07/01;84(1):75–82. doi: 10.1038/sj.clpt.6100452. [PubMed: 18183034]

95. Eagling VA, Back DJ, Barry MG. Differential inhibition of cytochrome P450 isoforms by the protease inhibitors, ritonavir, saquinavir and indinavir. British journal of clinical pharmacology. 1997;44(2):190–194. doi: 10.1046/j.1365-2125.1997.00644.x. [PubMed: 9278209]

96. Rittweger M, Arastéh K. Clinical Pharmacokinetics of Darunavir. Clinical Pharmacokinetics. 2007 2007/09/01;46(9):739–756. doi: 10.2165/00003088-200746090-00002. [PubMed: 17713972]

97. Busti AJ, Hall RG II, Margolis DM. Atazanavir for the Treatment of Human Immunodeficiency Virus Infection. Pharmacotherapy: The Journal of Human Pharmacology and Drug Therapy. 2004;24(12):1732–1747. doi: doi:10.1592/phco.24.17.1732.52347.

98. Hsu A, Granneman GR, Bertz RJ. Ritonavir. Clinical Pharmacokinetics. 1998 1998/10/01;35(4): 275–291. doi: 10.2165/00003088-199835040-00002. [PubMed: 9812178]

99. Schöller-Gyüre M, Kakuda TN, Raoof A, et al. Clinical Pharmacokinetics and Pharmacodynamics of Etravirine. Clinical Pharmacokinetics. 2009 2009/09/01;48(9):561–574. doi: 10.2165/10895940-000000000-00000. [PubMed: 19725591]

100. Petruschke RA, Zeldin RK. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. Journal of Antimicrobial Chemotherapy. 2004;53(1):4–9. doi: 10.1093/jac/dkh029. [PubMed: 14657084]

101. Sabo JP, Norris SH, Johnson P, et al. Pharmacokinetic Characterization of Different Dose Combinations of Coadministered Tipranavir and Ritonavir in Healthy Volunteers AU - MacGregor, Thomas R. HIV Clinical Trials. 2004 2004/12/01;5(6):371–382. doi: 10.1310/RRX7-49ME-27V7-MWWV. [PubMed: 15682350]

102. Kurowski M, Kaeser B, Sawyer A, et al. Low-dose ritonavir moderately enhances nelfinavir exposure. Clinical Pharmacology & Therapeutics. 2002 2002/08/01;72(2):123–132. doi: 10.1067/mcp.2002.126178. [PubMed: 12189359]

Article Highlights

- Most of the drugs used in HIV such as protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), integrase strand transfer inhibitors (INSTIs), and pharmacokinetics enhancers (PK enhancers) are metabolized by cytochrome P450 (CYP) pathway.
- PK enhancers, all PIs, and some NNRTIs are also CYP inhibitors, which are expected to have a higher chance of interfering with drug metabolism causing unexpected pharmacodynamic changes and drug-drug interactions. Among all the CYP inhibitors used for HIV treatment, RTV and COBI are the most potent CYP inhibitors of both CYP3A4 and CYP2D6.
- The drug groups most implicated in CYP-mediated interactions with CYP inhibitors-based antiretroviral therapy (ART) include: statins, anti-TB drugs, antifungals, and anticonvulsants.
- Acquisition of the knowledge of CYP-mediated drug-drug interactions will help clinicians to manage patients on ART regimens more efficiently.
- To improve the treatment efficacy and minimize the drug-drug interactions, novel approaches which can bypass CYP metabolism may be the potential alternative future direction.

Table 1:

CYP substrates, inhibitors, and inducers that are used in HIV treatment

ARV drugs by drug class	CYP substrate	CYP inhibitor	CYP inducer
Protease inhibitors			
Atazanavir (ATV)	3A4	3A4, 2C8 (weak)	
Darunavir (DRV)	3A4	3A4	2C9
Fosamprenavir (FPV)	3A4	3A4	3A4 (weak)
Lopinavir (LPV)	3A4	3A4 (weak)	
Saquinavir (SQV)	3A4	3A4	
Tipranavir (TPV)	3A4	3A4, 2D6 (weak)	3A4, 1A2, 2C19
Indinavir (IDV)	3A4	3A4	
Nelfinavir (NFV)	3A4, 2C19	3A4	
Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)			
Efavirenz (EFV)	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19
Etravirine (ETR)	3A4, 2C9, 2C19	2C9, 2C19	3A4
Delavirdine (DLV)	3A4		3A4, 2D6, 2C9, 2C19
Nevirapine (NVP)	3A4, 2B6		3A4, 2B6
Rilpivirine (RPV)	3A4		
Integrase strand transfer inhibitors (INSTIs)			
Bictegravir (BIC)	3A4		
Dolutegravir (DTG)	3A4 (minor)		
Elvitegravir (EVG)	3A4		2C9
CCR5 Antagonist			
Maraviroc	3A4		
PK Enhancers (Boosters)			
Cobicistat (COBI)	3A4	3A4, 2D6	
Ritonavir (RTV)	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19

Table 2:

CYP inhibition potency of drugs used in HIV treatment

Drugs used in HIV treatment	IC_{50} in microsomes (μM)	K_i in microsomes (μM)	Inhibition potency
CYP3A4 inhibitors			
Ritonavir (RTV) [12, 13]	0.015	0.017-0.03	Strong
Cobicistat (COBI) [13]	0.036	-	Strong
Fosamprenavir (FPV)/Amprenavir [12]	0.38	0.11	intermediate
Lopinavir (LPV)/RTV [94]	-	-	Strong
Tipranavir (TPV)/RTV [8]	-	-	Strong
Indinavir (IDV) [12, 13, 95]	0.4 −0.9	0.24	intermediate
Nelfinavir (NFV) [12]	1.90, 0.30	0.30	intermediate
Darunavir (DRV) [96]	-	0.4	intermediate
Squainavir (SQV) [12, 95]	2.14	0.76	weak
Atazanavir (ATV) [97]	-	2.35	weak
Efavirenz (EFV) [8]	-	-	weak
CYP2D6 inhibitors			
Ritonavir (RTV) [13, 98]	6.4	-	Strong, but less extent than CYP3A4 inhibition.
Cobicistat (COBI) [13]	6.5	-	
Tipranavir (TPV)/RTV [8]	-	-	
Lopinavir (LPV)/RTV [94]	-	-	
CYP2C9 inhibitors			
Etravirine (ETR) [99]	0.58	-	weak
CYP2C19 inhibitors			
Etravirine (ETR)[99]	-	-	weak

IC_{50} values shows the concentration producing 50% inhibition of control enzyme

K_i values shows inhibition rate constant. – Data not available

Table 3:

Changes in pharmacokinetics parameters of the PIs in RTV-boosted PI regimens

	RTV boosting effect	
Protease inhibitors	**Concentration (C_{min}/C_{max}/C_{ss})**	**Area under curve (AUC)**
Atazanavir (ATV)[93]	C_{min} ↑ ~5 fold	↑ ~3 fold
Darunavir (DRV) [93]	-	↑ ~10 fold
Fosamprenavir (FPV)/Amprenavir [93]	C_{max} ↑ ~1.5 fold C_{min} ↑ ~4 fold	↑ >2 fold
Lopinavir (LPV) [93]	C_{min}↑ ~2 fold C_{ss} ↑ ~15-20 fold	↑ ~1.5 fold
Saquinavir (SQV)[100]	C_{min}↑ ~18 fold C_{max} ↑ ~7 fold	↑ ~16 fold
Tipranavir (TPV)[101]	C_{ssmin}↑ ~20 fold C_{ssmax} ↑ ~3 fold	↑ 4-13 -fold
Indinavir (IDV) [93]	C_{min} ↑ ~1.4 fold	↑ ~2 fold
Nelfinavir (NFV)[102]	C_{12h}↑ 30-90% C_{max} ↑ ~20%	↑ 20-40%

– Data not available

Table 4:

Drug-drug interactions between ARVs (CYP inhibitors) and other drugs

Class of drugs	ARVs	Outcomes (ARV drug levels)	Outcomes (co-administered drug levels)	Dosing Recommendation	Ref
Lipid-lowering (Statins)	All PIs, EVG/COBI	No effect	↑ simvastatin, ↑ lovastatin, ↑ fluvastatin, ↑ atorvastatin possible ↑ rosuvastatin possible	Do not co-administer simvastatin, lovastatin, fluvastatin with PIs and EVG/COBI; Dose adjustments for atorvastatin and rosuvastatin may be necessary.	[8, 50, 51] [52]
	EFV, ETR	No effect	↑ fluvastatin possible	Dose adjustments for fluvastatin may be necessary.	[8]
Anti-TB (Rifampin, rifabutin)	All PIs, EFV, ETR, EVG/COBI	↓ ARV levels when co-administered with rifampin.	No effect	Do not co-administer rifampin with PIs, EFV, ETR, and EVG/COBI. Rifabutin is a preferred regimen after dose-adjustment.	[8, 46]
Antifungals (Ketoconazole, itraconazole)	All PIs, PI/RTV, PI/COBI, EVG/COBI	↑ PIs,	↑ ketoconazole, ↑ itraconazole	Dose adjustments are needed. Doses >200mg/day of ketoconazole or itraconazole is not recommended.	[15] [21] [55] [56]
Anticonvulsants (Phenytoin, phenobarbital, carbamazepine)	PI/RTV, PI/COBI, EFV, ETR, EVG/COBI	↓ ARV levels	↑ carbamazepine with PI/RTV and PI/COBI	Do not co-administer phenytoin, phenobarbital and carbamazepine with PI/RTV, PI/COBI, ETR, and EVG/COBI. Monitor anticonvulsants and EFV concentrations for dose adjustments.	[8] [59] [10]
Ergot alkaloids	PI/RTV, PI/COBI, EFV, ETR, EVG/COBI	No effect	↑ ergotamine effects	Do not co-administer. Use alternative agents: 5-HT agonists (“triptans”).	[15] [64]

ARVs- Antiretroviral drugs; PIs, -Protease inhibtors; EVG-Elvitegravir; EFV-Efavirenz; COBI-Cobicistat; ETR- Etravirine; RTV- Ritonavir.