J. Med. Toxicol. (2015) 11:326–341
DOI 10.1007/s13181-015-0465-0

REVIEW ARTICLE

A Review of the Toxicity of HIV Medications II: Interactions with Drugs and Complementary and Alternative Medicine Products

Andrew Stolbach · Karolina Paziana · Harry Heverling · Paul Pham

Published online: 3 June 2015

Abstract For many patients today, HIV has become a chronic disease. For those patients who have access to and adhere to lifelong antiretroviral (ARV) therapy, the potential for drug-drug interactions has become a real and life-threatening concern. It is known that most ARV drug interactions occur through the cytochrome P450 (CYP) pathway. Medications for comorbid medical conditions, holistic supplements, and illicit drugs can be affected by CYP inhibitors and inducers and have the potential to cause harm and toxicity. Protease inhibitors (PIs) tend to inhibit CYP3A4, while most non-nucleoside reverse transcriptase inhibitors (NNRTIs) tend to induce the enzyme. As such, failure to adjust the dose of co-administered medications, such as statins and steroids, may lead to serious complications including rhabdomyolysis and hypercortisolism, respectively. Similarly, gastric acid blockers can decrease several ARV absorption, and warfarin doses may need to be adjusted to maintain therapeutic concentrations. Illicit drugs such as methylenedioxymethamphetamine (MDMA, "ecstasy") in combination with PIs lead to increased toxicity, while the concomitant administration of sedative drugs such as midazolam and alprazolam in patients taking PIs can result in prolonged sedation, delayed recovery, and increased length of stay. Even supplements like St. John's Wort can alter PI concentrations. In theory, any drug that is metabolized by CYP has potential for a pharmacokinetic drug-drug interaction with all PIs, cobicistat, and most NNRTIs. When adding a new medication to an ARV regimen, use of a drug-drug interaction software and/or consultation with a clinical pharmacist/pharmacologist or HIV specialist is recommended.

Keywords Antiretroviral · Toxicity · Complementary medicine · Drug interactions · Drug-herb interactions

Previous presentation of data at meetings or in abstract form: No previous presentations of this data.

A. Stolbach · K. Paziana (✉) · H. Heverling
Department of Emergency Medicine, Johns Hopkins Department of Emergency Medicine, Johns Hopkins University School of Medicine, 1830 East Monument Street, Suite 6-100, Baltimore, MD 21287, USA
e-mail: kpazian1@jhmi.edu

P. Pham
Division of Infectious Diseases, Johns Hopkins University School of Medicine, 1830 East Monument Street, 4th floor, Baltimore, MD 21205, USA

Introduction

The success of antiretroviral (ARV) therapy has allowed individuals infected with HIV to suppress viral replication, preserve immune function, and reach similar life expectancies as non-infected individuals [1]. As a result, HIV is becoming manageable as a chronic disease in the setting of lifelong medication adherence. Having one chronic illness does not, however, preclude this population from the same growing burden of comorbidities seen in non-infected aging adults. In addition, the prevalence of the use of supplements or illicit drugs in this population is as high as any other. As such, HIV-infected individuals, and their providers alike, must be particularly mindful of the potential drug-drug interactions unique to this population.

The pharmacology and inherent toxicity of combinations of HIV medications were examined in a previous review [2]. Please refer to Tables 1, 2, 3, 4, and 5 for a summary of drugs included in each class. As previously discussed, many ARV drug interactions are mediated through cytochrome p450 (CYP), and to a lesser extent, p-glycoprotein (pgp), as these

Table 1 Common nucleoside reverse transcriptase inhibitors (NRTIs) and their route of metabolism and/or excretion

Nucleoside reverse transcriptase inhibitors	Metabolism/excretion
Abacavir	Alcohol dehydrogenase Glucuronidation Metabolite and parent drug undergo renal and hepatobiliary clearance
Didanosine	Renal elimination
Emtricitabine	Renal elimination
Lamivudine	Renal elimination
Stavudine	Renal elimination
Tenofovir	Renal elimination
Zidovudine	Glucuronidation Metabolite and parent drug undergo renal clearance

are the primary mechanisms of drug elimination. Similarly, many of the medications prescribed for common comorbid conditions compete for a shared pathway for elimination, resulting in either potential toxic drug accumulation or sub-therapeutic levels.

In a cross-sectional study of clinically significant drug-drug interactions in HIV-infected individuals on ARV medications, the use of more than five antiretroviral drugs and the use of non-raltegravir-based regimens were associated with an increased incidence of interactions. In most cases, the drug interaction did not cause morbidity, but did necessitate a dose adjustment of one of the patient's drugs. The HMG-Co-A reductase inhibitors were the non-ARV drugs most likely to require a dose adjustment. Dose adjustments were needed when the drugs were co-administered with either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). Phosphodiesterase inhibitors, calcium channel blockers, acid suppression medications, methadone, and fluticasone were also implicated [3].

Table 2 Common non-nucleoside reverse transcriptase inhibitors (NNRTIs) and their important interactions

Non-nucleoside reverse transcriptase inhibitors	Metabolism	Inducer of	Inhibitor of
Delavirdine	CYP3A4	–	CYP3A4
Efavirenz	CYP2B6 (major) CYP3A4 (minor)	CYP3A4	CYP2C9/19
Etravirine	CYP3A4 CYP2C9 CYP2C19	CYP3A4 (weak)	CYP2C9/19 (weak), pgp (weak)
Nevirapine	CYP3A4 CYP2B6	CYP3A4, CYP2B6	CYP3A4

CYP cytochrome p450 superfamily, *pgp* p-glycoprotein

Table 3 Common protease inhibitors (PIs) and their important interactions

Protease inhibitors	Metabolism	Inducer of	Inhibitor of
Amprenavir	CYP3A4	pgp	CYP3A4
Atazanavir	CYP3A4	–	CYP3A4, pgp
Darunavir	CYP3A4	–	CYP3A4
Fosamprenavir	CYP3A4	pgp	CYP3A4
Indinavir	CYP3A4	–	CYP3A4
Lopinavir	CYP3A4	UGT, CYP1A2	CYP3A4, CYP2D6
Nelfinavir	CYP2C19 (M8 metabolite via CYP3A4) CYP2D6	UGT, CYP1A2, CYP3A4, CYP2C9, pgp	CYP3A4
Ritonavir	CYP3A4, CYP2D6	CYP1A2	CYP3A4, CYP2D6
Saquinavir	CYP3A4	–	CYP3A4
Tipranavir	CYP3A4	CYP2C19, pgp	CYP3A4, CYP2D6

CYP cytochrome p450 superfamily, *pgp* p-glycoprotein, *UGT* uridine 5′-diphospho-glucuronosyltransferase, *M8 active metabolite* nelfinavir hydroxy-*t*-butylamide

This review examines the potential toxicities that all medical providers must consider before placing a patient currently taking ARV drugs on a new medication, whether for acute or chronic illness, and serves as a reference to help educate the HIV-infected population as to the potential harm of particular supplements or illicit drugs when combined with ARV drugs.

Materials and Methods

A comprehensive search of the PubMed, MEDLINE, and Google Scholar databases was conducted for articles related to ARV drugs and relevant interactions. PubMed Medical Subject Headings were used to search the controlled vocabulary thesaurus for indexing articles including clinical trials, meta-analyses, practice guidelines, and reviews. Textbooks of pharmacology and medical toxicology were also reviewed for references. The reference sections of pertinent articles/chapters were searched and cross-referenced to the findings

Table 4 Common entry inhibitors and their route of metabolism

Entry inhibitors	Metabolism
Enfuvirtide	Non-NADP- dependent hydrolysis
Maraviroc	CYP3A4 substrate

Table 5 Common integrase strand transfer inhibitors (INSTIs) and their route of metabolism

Integrase inhibitor	Metabolism
Raltegravir	Uridine diphosphate glycuronosyltransferase-mediated glucuronidation
Dolutegravir	UGT1A1-glucuronidation (major); CYP3A4 (minor) substrate
Elvitegravir	CYP3A4 substrate

from the electronic databases for any additional manuscripts and then compared to each other to identify duplicates. The following search terms were used either independently or in combination for all databases: drug toxicity, adverse drug reaction, HIV fusion inhibitors, HIV protease inhibitors, nucleoside reverse transcriptase inhibitor, non-nucleoside reverse transcriptase inhibitor, integrase inhibitor, anti-HIV agents, antiretroviral agents, CCR5 receptor blocker, nucleotide reverse transcriptase inhibitor, specific ARV drug names, drug interactions, common chronic illness medication names, names of frequently used recreational drugs, herbal, and complementary alternative medicine products.

One author gathered the articles matching the search criteria outlined, and all authors assessed each article for inclusion and exclusion criteria, quality as determined by internal validity, and extracted all data. Quality assessment for randomized, control studies included the following: methods for randomization, blinding, controls, and follow-up. Review articles and chapters were assessed for quality of included data. Observational and case studies were reviewed for measurement bias, confounding items, and statistical analysis.

Overview of Drug Metabolism and Efflux

Antiretroviral regimens typically consist of a combination of three drugs—two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) otherwise known as the "backbone" of the regimen, in addition to either a protease inhibitor (PI), non-nucleoside reverse transcriptase inhibitor (NNRTI), or an integrase strand transfer inhibitor (INSTI), or the "base". Most ARV drugs are metabolized via the CYP complex of proteins or are substrates for p-glycoprotein (pgp), as are many other commonly prescribed medications. Interference with CYP, pgp, or any other mechanism of drug elimination will result in unintended fluctuations in concentrations of both HIV and non-HIV drugs risking subtherapeutic dosing or toxicity.

Antiretroviral Therapy and Cytochrome P450

Cytochrome P450 belongs to a superfamily of enzymes containing a heme prosthetic group, which allows the compound to carry out enzymatic reactions including *N*-dealkylation, *O*-dealkylation, aromatic hydroxylation, *N*-oxidation, *S*-oxidation, deamination, and dehalogenation of substrates [4]. While over 50 CYP enzymes have been identified, approximately, a dozen are known to be important for drug metabolism, including CYP3A4.

Cytochrome P450 interactions, however, can be complex. Any change in CYP activity, whether an increase (induction) or decrease (inhibition), can have a profound effect on the pharmacokinetics of the drugs using that metabolism pathway. Induction of CYP speeds up the complex's ability to metabolize its substrates and thus may dramatically decrease therapeutic concentrations of these medications. Alternatively, inhibition of the CYP enzyme slows substrate metabolism and delays excretion resulting in drug accumulation to possibly toxic concentrations. The clinical manifestations of CYP inhibition also depend on whether it is the drug or the metabolite of the drug (or both) that is the pharmacologically active compound. If the CYP substrate is the active pharmacological compound, then, slowing metabolism will prolong activity of the drug (e.g., midazolam). Alternatively, if the CYP substrate is an inactive intermediary that is biotransformed to an active compound, then, inhibiting CYP will decrease the clinical activity of the drug (e.g., clopidogrel).

Many ARV drugs are metabolized via CYP enzymes. Tables 2, 3, and 6 give examples of these CYP substrates, inducers, and inhibitors. While most PIs are CYP3A4 inhibitors, most NNRTIs are CYP3A4 inducers [5]. For example, ritonavir is a strong CYP3A4 and CYP2D6 inhibitor, and from the NNRTI class, efavirenz, etravirine, and nevirapine are CYP3A inducers. Knowing that ritonavir is a strong inhibitor allows practitioners to manipulate ARV drug regimes. For patients taking PI-based regimens, a low dose of ritonavir is frequently added as a second PI with the purpose of inhibiting the CYP metabolism of the main PI. This practice, known as "boosting," allows for a higher steady state concentration and prolonged half-life of the primary PI with fewer doses of medication and once daily dosing, thereby reducing the pill burden and improving adherence. Similarly, cobicistat, a CYP3A4 inhibitor without anti-HIV activity, inhibits elvitegravir (INSTI) metabolism and enhances its pharmacokinetic profile [6]. The same principle of inhibition applies to co-ingestion of HIV and non-HIV medications. For example, efavirenz decreases itraconazole concentrations by 39 % [7].

As always, there are exceptions to the rule. Delavirdine, an NNRTI and therefore expected to be a CYP inducer, is actually a strong CYP3A4 inhibitor. Similarly, rilpivirine is neither an inducer nor an inhibitor, but is a CYP3A4 substrate and therefore is subject to fluctuations in CYP metabolism secondary to co-ingested medications.

Although there is a plethora of literature regarding ARV drug-drug interactions, pharmacokinetic data from drug

Table 6 Common cytochrome p450 (CYP) inducers, inhibitors, and substrates, separated into ARV drugs and common chronic medication

Select CYP450 inducers, inhibitors, and substrates

	1A2	2C19	2D6	3A4
Inducers	Ritonavir	Ritonavir Efavirenz		Efavirenz (2B6>3A4), etravirine, nevirapine, ritonavir (high dose)
	Phenobarbital Phenytoin Rifampin	Carbamazepine Rifampin	Carbamazepine Phenobarbital Phenytoin Rifampin	Carbamazepine, dexamethasone phenytoin, phenobarbital, rifabutin, rifampin, rifapentine, St. John's wort
Inhibitors	Atazanavir	Etravirine	Ritonavir	Ritonavir, indinavir, nelfinavir, amprenavir, atazanavir, saquinavir, cobicistat, delavirdine
	Amiodarone	Ketoconazole Omeprazole	Amiodarone Quinidine Methadone	Azoles: fluconazole, posaconazole, ketoconazole, voriconazole, itraconazole Macrolides: clarithromycin, erythromycin Amiodarone, diltiazem, nefazodone, grapefruit juice, Seville orange juice
Substrates		Nelfinavir (2C19>3A4); etravirine		All PIs, elvitegravir, dolutegravir (UGT1A1>3A4), efavirenz (2B6>3A4), nevirapine, etravirine, delavirdine, rilpivirine, maraviroc
	Haloperidol Olanzapine Theophylline	Diazepam Phenytoin PPIs: lansoprazole, omeprazole pantoprazole Voriconazole	Carvedilol Codeine Metoprolol Tramadol	Macrolides: clarithromycin, erythromycin Benzodiazepines: alprazolam, midazolam, triazolam HMG-Co reductase inhibitors: simvastatin, lovastatin, atorvastatin Dihydropyridine Ca channel blockers: nifedipine, nisoldipine, felodipine Antiarrhythmics: bepridil, propafenone, amiodarone, flecainide Cyclosporine, ergotamine, irinotecan, pimozide

interaction studies are not always available. Clinicians must often rely on clinical judgment and are forced to predict drug interactions. Many significant drug-drug interactions, however, could be more reliably predicted if clinicians learned how to classify common drugs as substrates, inducers, or inhibitors of the CYP system and therefore envision their effect in conjunction with ARV medications.

Antiretroviral Therapy and P-Glycoprotein

Certain ARV medications can cause drug interactions through interference with membrane transport proteins that act as "pumps" to actively move molecules, such as drugs, across barriers. Membrane transporters exist in a variety of locations with specialized functions. Transport proteins in the intestines regulate absorption of orally delivered drugs into the body. Similarly, proteins in the heart and in the CNS affect drug delivery to those target organs respectively, while proteins in the kidney and liver modulate excretion. The best recognized of these membrane transport proteins is pgp, a member of the ATP-binding cassette (ABC) superfamily [8].

In general, PIs are substrates for pgp (with either inhibition or induction), while NNRTIs are not. For example, the PIs amprenavir, fosamprenavir, and tipranavir have been shown to induce pgp. Similar to ritonavir's boosting effect secondary to CYP inhibition, in animal models, ritonavir increased drug absorption via inhibition of pgp transport proteins in the GI tract [9]. As a result, the concentration of digoxin, a pgp substrate, was increased by 29 % with ritonavir co-administration. As always, however, there are exceptions to the rule. While expected to have no interaction with pgp substrates, certain NNRTIs (e.g., etravirine) act as inhibitors of pgp. On the whole, any interference with pgp may affect the final drug concentration to target organs.

Interactions Between HIV and Non-HIV Drugs

Drug-drug interactions between ARV drugs and other medications are common and often require dose adjustments. They also go frequently unrecognized if not managed by clinicians with clinical expertise in pharmacology.

In a review of outpatient HIV-infected individuals on ARV therapy, 27 % of patients had clinically significant drug-drug interactions. However, only 36 % of these were identified by physicians. The use of a PI-based regimen resulted in a sixfold increase in risk of any interaction. The most common drugs involved were CNS drugs (e.g., antidepressants), other ARVs, and statins [10]. A similar review looking at hospitalized HIV-infected patients on ARV therapy found 38 % of patients to have drug-drug interactions between HIV and non-HIV medications. There was no increase in length of stay associated with these drug-drug interactions. Atazanavir was the most commonly implicated ARV drug, and HMG-CoA reductase inhibitors were the most common non-ARV drugs associated with interactions. The most important risk factor associated with a drug-related problem was admission by a service other than infectious disease (odds ratio (OR) 3.83, 95 % confidence interval (CI) 1.08–13.54) [11]. Another review of hospitalized patients at Johns Hopkins Hospital revealed that medication errors and unrecognized drug-drug interactions remained high (29 %) on day 1, but the majority of errors were corrected by day 2. Common drug-drug interactions identified were the use of fluticasone or midazolam in patients already taking PIs and the use of proton pump inhibitors in patients taking atazanavir. Compared with patients admitted to the HIV/AIDS service, where patient medications are overseen by a clinical pharmacologist and an infectious disease physician, those admitted to surgical services were at increased risk of ARV medication errors (adjusted OR 3.10, 95 % CI 1.18–8.18) [12].

In theory, any drug metabolized by a CYP complex or transported by an efflux protein has the potential for a pharmacokinetic drug-drug interaction. When we consider that any drug that affects an organ could cause a pharmacodynamic interaction, the potential number of interactions is limitless. Outlined below are select clinically significant drug-drug interactions between HIV and non-HIV medications. Special emphasis is made on either commonly encountered drugs or medications with narrow therapeutic windows, making drug-drug interaction-induced fluctuations in concentrations a significant concern.

HMG-CoA Reductase Inhibitor Medications

HMG-CoA reductase inhibitors (statins) are widely prescribed for the treatment of hyperlipidemia. The most important adverse effect of statins is myotoxicity, ranging in severity from mild pain to life-threatening rhabdomyolysis. Simvastatin and lovastatin are exclusively metabolized by CYP3A, and because most PIs are potent inhibitors of CYP3A4, their concentrations are significantly increased when co-administered with a PI. As such, lovastatin and simvastatin are contraindicated in patients taking PIs. Furthermore, co-administration of simvastatin and boosted saquinavir resulted in a 31.59-fold increase in the area under the curve (AUC) of simvastatin [13, 14]. When this FDA-labeled contraindicated combination is not recognized and corrected, devastating consequences can result. One 70-year-old man, who was treated with a nelfinavir-based regimen, developed fatal rhabdomyolysis 1 month after starting simvastatin. He was previously on a stable dose of pravastatin with nelfinavir for 2 years without incident [15]. In kind, atorvastatin, a CYP3A4 substrate, when combined with a boosted lopinavir regimen has been noted to result in a 5.9-fold increase in statin concentration [16].

Although the co-administration of atorvastatin is not contraindicated with HIV protease inhibitors, it is important to

dose reduce atorvastatin. Pravastatin concentrations were increased by only 33 % with lopinavir/ritonavir co-administration [17]. In an observational study, this combination was well tolerated. The use of pravastatin, rosuvastatin, and atorvastatin with HIV protease inhibitors has been well tolerated and resulted in good virologic response [18]. Due to limited long-term clinical data, all patients taking both statins and PIs should be regularly monitored for myotoxicity and rhabdomyolysis, particularly with any dose changes.

Hormonal Contraceptive Medications

Hormonal contraceptives may contain an estrogen, progestin, or both and are primarily metabolized by CYP isoenzymes. Ethinyl estradiol undergoes oxidative metabolism by CYP3A4, CYP2C9, and other CYP isoforms [19] in addition to glucuronosyltransferases (UGTs) and pgp, which may also play a role [20]. Cytochrome p450 3A4 is also involved in the metabolism of the parent compound or active metabolites of the progestins: etonogestrel, levonorgestrel, medroxyprogesterone acetate, norelgestromin, norethindrone, norgestimate, and norgestrel. Although depot medroxyprogesterone acetate is a substrate for CYP3A4, the interaction appears to be clinically insignificant as the drug remains effective in patients taking CYP3A4 inducers.

Given their CYP interactions, it is unsurprising that PIs such as efavirenz, nevirapine, and cobicistat cause fluctuations in the concentrations of hormonal contraceptives. This is true regardless of the route of administration, as the effect has been observed with tablets, implantable devices, and injectable hormones. A comprehensive review by Tseng et al. demonstrated how concentrations of transdermal or combined oral contraceptives might be reduced by ritonavir-boosted PIs [21]. In some cases, breakthrough pregnancies were reported in patients taking PIs concomitantly with estrogen-based contraceptives, making it imperative that barrier contraception is championed for these patients. On the other hand, estrogen and progestin components may be increased in the presence of certain *unboosted* PI regimens. For example, in patients taking atazanavir, the ethinyl estradiol AUC increases by 48 % and norethindrone increases by 110 %. Therefore, to decrease the risk of thromboembolism, the maximum ethinyl estradiol dose recommended in these patients is 30 mcg/day. However, with *boosted* atazanavir, ethinyl estradiol AUC *decreases* by 18 % requiring a minimum dose of 35 mcg/day to be effective [21].

Raltegravir, etravirine, rilpivirine, and maraviroc do not interact significantly with combination oral contraceptives. For patients taking PIs or NNRTIs, on the whole, depot medroxyprogesterone acetate and intrauterine devices do not appear to interact with ARV drugs and so are the preferred contraceptive methods [21].

Glucocorticoid Medications

The glucocorticoids triamcinolone, fluticasone, and budesonide are metabolized by CYP3A4. When co-administered with ritonavir, there are reports of each of these drugs accumulating and causing hypercortisolism, or Cushing's syndrome in its most severe form, and so should be avoided. Symptoms of hypercortisolism include weight gain and glucose intolerance, which often begin within weeks of starting co-administration. One review of the literature identified 25 cases of clinically significant adrenal suppression from fluticasone [22]. The use of both inhaled and intranasal steroids has been implicated with adrenal suppression when used in combination with ritonavir [23]. Another review identified 13 reports of Cushing's syndrome secondary to triamcinolone injection use in combination with ritonavir. Patients in the review had received a total of one or two doses of the medication, and symptoms usually began 2 or 3 weeks (range 4–42 days) after treatment [24]. In symptomatic patients, CYP3A4 inhibitors and corticosteroids should be stopped. Recovery may take months and may be monitored by obtaining cortisol assays and cosyntropin stimulation tests with the guidance of an endocrinology expert. Inhaled beclomethasone, on the other hand, is catabolized by pulmonary esterase and so is independent of the CYP isoenzymes, allowing for safe co-administration with ritonavir without significant threat of drug-drug interaction.

Acid-Reducing Medications

The ubiquity of H_2-antagonists or proton pump inhibitors increases the potential for adverse interactions. In most cases, the combination of an acid-reducing agent with an ARV drug results in a decrease in the concentration of the ARV drug because gastric acidity affects its dissolution and absorption. For example, an increase in gastric pH will result in reduced absorption of the NNRTIs rilpivirine and delavirdine and the PIs atazanavir and nelfinavir [25]. As an extreme example, in a healthy volunteer single-dose study, the combination of lansoprazole and atazanavir resulted in a 98 % decrease in atazanavir AUC [26].

Some of these drug-drug interactions can be managed by staggering the time of administration. For example, an ARV medication can be taken with food at least 2 h before or 10 h after an H_2 blocker. However, separating the timing of administration of rilpivirine with a proton pump inhibitor is not effective due to the near complete suppression of acid production [25]. Darunavir, etravirine, and other PIs, however, are not affected by gastric acid and so should be considered for patients where the use of a proton pump inhibitor cannot be avoided.

Antifungal Medications

Azole antifungals (e.g., fluconazole, ketoconazole, voriconazole, itraconazole, posaconazole) are generally considered to be inhibitors of CYP3A4. Ketoconazole and itraconazole specifically are substrates of CYP3A4. When co-administered with NNRTIs that induce CYP3A (e.g., efavirenz, nevirapine, etravirine), there is a significant decrease in the concentrations of the azoles. In contrast, there is an expected increase in azole concentrations when co-administered with PIs that inhibit CYP3A [7].

Fluconazole is predominantly renally excreted with minimal metabolism via CYP2D6 and 1A2. For this reason, fluconazole has minimal drug-drug interactions with ARV medications and is the preferred azole antifungal for the treatment of fluconazole-sensitive infections. Voriconazole is predominantly metabolized via CYP2C19 and to a lesser extent via CYP2C9 and 3A4. The co-administration of voriconazole with high-dose ritonavir (400 mg twice daily) has been reported to result in an 82 % decrease in voriconazole AUC. However, when given with low-dose ritonavir (100 mg twice daily), the voriconazole concentration only decreased by 39 %. When treating invasive aspergillosis, clinicians should consider using an additional antifungal until voriconazole concentrations are in the therapeutic range. Posaconazole, on the other hand, is an inhibitor of CYP3A4 and is metabolized via glucuronidation, and as such, PI concentrations may be increased with posaconazole co-administration. For example, atazanavir AUC was increased by 268 % when co-administered with posaconazole. Posaconazole concentrations may be decreased with inducers of glucuronidation (e.g., tipranavir/ritonavir). Posaconazole therapeutic drug monitoring is recommended when given with PIs or NNRTIs [7].

Nephrotoxic antifungals (e.g., amphotericin) should be used with caution in patients taking tenofovir due to the additive nephrotoxicity potential. Use of amphotericin lipid complex may be considered to decrease the nephrotoxicity potential in patients taking tenofovir.

Antimalarial Medications

Significant drug-drug interactions exist between certain antimalarial agents and PIs, with evidence for an even more potentiated effect with NNRTIs or boosted PI regimens. Quinine is metabolized by CYP3A4 to its active metabolite, 3-hydroxyquinine. When combined with ritonavir, a potent CYP inhibitor, quinine's AUC is increased approximately 3.4-fold. Understanding this, a 50 % dose reduction of quinine may be necessary to maintain effectiveness while decreasing the potential for cardiotoxicity [27].

Efavirenz, lopinavir/ritonavir, and atazanavir/ritonavir lowered atovaquone concentrations by 75, 74, and 46 %, respectively. Proguanil concentrations were also lowered by an estimated 40 %. The mechanism of lower atovaquone and proguanil exposure may be due to induction of glucuronidation and CYP2C19, respectively. Although the clinical significance of this interaction remains to be determined, an alternative antimalarial agent should be considered for patients already taking efavirenz or certain boosted PI regimens [28]. Chloroquine is predominantly excreted unchanged in the urine [29]. Antiretroviral drug-drug interaction is unlikely with PIs and NNRTIs. Primaquine is metabolized via CYP, possibly 3A4. In a rat study, primaquine serum concentrations were decreased by ritonavir co-administration at steady state [30]. This may be due to the mixed inhibition/induction of CYP3A4 by ritonavir. The clinical significance of this potential interaction is unknown, but there are no published reports of treatment failure when ritonavir is co-administered with primaquine.

Antitubercular Medications

Rifampin, rifapentine, and rifabutin are rifamycin antibiotics used in antitubercular drug regimens. Because of the frequent co-infection of HIV and tuberculosis, it is important to be aware of drug interactions between antitubercular and ARV drugs.

Rifampin is a potent inducer of glucuronidation, as well as many CYP isoforms including 3A4, 1A2, 2C9, 2C19, and 2D6. Co-administration of rifampin with a PI decreased PI concentrations by over 80 %s and so must be given with extreme caution. Rifabutin is structurally similar to rifampin but is only a moderate inducer and substrate of CYP3A4. When co-administered with a boosted PI regimen, rifabutin concentrations increase while PI concentrations decrease. Uveitis has been reported as a complication of supratherapeutic rifabutin concentrations [31]. Overall, rifabutin may be used as an alternative to rifampin with boosted PI co-administration; however, the dose will need to be decreased by 50 to 75 % to reduce toxicity. Rifampin's induction of glucuronidation also results in a decrease of the AUC of the INSTI, raltegravir, by 40 %. If rifampin and raltegravir are to be co-administered, an increase in the INSTI dose to 800 mg twice daily is required to maintain efficacy [32, 33].

When considering patients taking NNRTIs, there is an observed 26 % decrease in efavirenz concentration following rifampin administration; the clinical significance of which has been debated [34]. Subsequent work demonstrated that despite variable concentrations, the clinical efficacy is preserved when efavirenz and rifampin are given in combination [35].

Significant drug-drug interactions are unlikely with other first-line antitubercular agents since isoniazid undergoes acetylation, pyrazinamide undergoes non-CYP3A4 hepatic metabolism, and ethambutol is renally excreted. Limited data

are available in regard to capreomycin and cycloserine, but based on chemical structure and known metabolic pathways, significant drug-drug interaction is unlikely [36].

Anticoagulant and Antiplatelet Medications

Warfarin interactions with ARV drugs such as efavirenz, etravirine, or saquinavir are complex and difficult to predict given multiple confounding factors in maintaining a therapeutic international normalized ratio (INR). Warfarin is a racemic mixture of R-warfarin and S-warfarin. Both enantiomers are active, although S-warfarin is about five times as potent as R-warfarin. S-warfarin is primarily metabolized by CYP2C9 and R-warfarin by CYP1A2 and CYP3A4. When combined with ARV therapies including efavirenz, a CYP2C9 inhibitor, and nevirapine, a 2C9 inducer, warfarin doses may need to be adjusted to maintain a therapeutic INR. Saquinavir is not a 2C9 inhibitor, but there are reports of inhibited warfarin metabolism by saquinavir [37, 38]. This may be explained by inhibition of CYP3A4 by saquinavir. Regardless, close monitoring with frequent dose adjustments will likely be necessary.

Clopidogrel is an antiplatelet prodrug that is activated by CYP2C19 isoforms. Etravirine, an inhibitor of CYP2C19, may prevent biotransformation of clopidogrel into its active form, putting patients at risk of re-stenosis and other such sequelae. In addition, although the mechanism is not well understood, there is at least one report of a patient with diminished response to clopidogrel when co-administered with a PI [39].

Caution should be exercised when initiating direct Xa inhibitors or direct thrombin inhibitors for patients taking ARV medications, particularly as these drugs do not have reversal agents. Cytochrome 3A4 accounts for approximately 60 % of the metabolism of the factor Xa inhibitor, rivaroxaban. p-Glycoprotein is also known to be involved in the elimination of this anticoagulant. There is one reported case in the literature of gastrointestinal bleeding in a patient on darunavir/ritonavir with rivaroxaban, where rivaroxaban concentrations were found to be more than double what was expected based on his dose [40].

Apixaban is another factor Xa inhibitor that is both a CYP3A4 and pgp substrate. Although there are no reports of drug-drug interactions to date, one would expect supratherapeutic concentrations when co-administered with a PI and subtherapeutic concentrations with some NNRTIs (e.g., etravirine, efavirenz, nevirapine) [41].

The novel direct thrombin inhibitor, dabigatran etexilate, is a substrate of pgp; thus, concentrations are increased when taken concurrently with any strong pgp inhibitor (e.g., ketoconazole). Dabigatran etexilate is hydrolyzed to dabigatran by hepatic and plasma esterases and is also a gastrointestinal pgp substrate [42]. Significant drug-drug interaction only occurs when the interacting drug is present in the GI tract at the time that dabigatran is taken. When verapamil was given concomitantly with dabigatran, a significant increase in the concentration of dabigatran was observed. However, when verapamil was given 2 h after dabigatran (after dabigatran's absorption), no change in dabigatran concentrations occurred. Similarly, ritonavir, a strong pgp inhibitor, may increase dabigatran concentrations when co-administered. However, when dabigatran was given 2 h before ritonavir, no significant drug-drug interaction was observed [43]. Another recent case report demonstrated the safe administration of dabigatran with lopinavir/ritonavir by scheduling intake to be 1 h apart [44]. Since robust clinical data on PI administration with dabigatran is lacking, co-administration should only be considered with caution.

Neither heparins and enoxaparin nor the Xa inhibitor fondaparinux are substrates for CYP. These drugs are not expected to interact with ARV medications and thus may serve as appealing alternatives.

Cardiovascular Medications

Significant increases in concentrations of certain calcium channel blockers (e.g., diltiazem, amlodipine) have been reported in the literature when combined with ARV therapy, specifically PIs. Several PIs alone (e.g., atazanavir, lopinavir) have been associated with increased PR intervals [45]. Although the clinical significance remains to be determined, the manufacturer recommends close monitoring when combining these PIs with medications that can also prolong the PR interval (e.g., calcium channel blockers, beta-blockers, digoxin) especially in patients at higher risk for second and third degree block (e.g., structural heart disease, cardiomyopathy, ischemic heart disease) [17, 46].

Diltiazem is a non-dihydropyridine calcium channel blocker that is metabolized by CYP3A4 to its active metabolite *N*-desmethyldiltiazem. In healthy volunteers, co-administration of the PI atazanavir increased the median diltiazem AUC by 125 % and *N*-desmethyldiltiazem by 165 %. This significant rise in concentrations caused a reported increase in the subjects' PR intervals. The authors therefore recommended to start diltiazem at 50 % of the recommended dose and to titrate slowly [47].

Amlodipine, a dihydropyridine calcium channel blocker, was administered to healthy volunteers in combination with indinavir/ritonavir. The median amlodipine AUC was 89.8 % greater. Although these healthy volunteers did not develop any cardiovascular sequelae, this pharmacokinetic interaction may be of clinical significance for older patients with comorbid conditions [47].

Similarly, concentrations of the angiotensin-converting enzyme (ACE) inhibitors, captopril and enalapril, may be increased when taken with boosted PI regimens. Both are

substrates for CYP2D6 and 3A4, respectively: therefore, drug-drug interactions could be possible. Irbesartan, candesartan, and to a lesser extent losartan are metabolized via CYP2C9. Since PIs do not inhibit CYP2C9, significant drug-drug interactions are unlikely. To date, there are no reported drug-drug interactions between NNRTI and HIV protease inhibitors when co-administered with an ACE inhibitor or an angiotensin II receptor blocker (ARB). Lisinopril is not metabolized, but is primarily excreted unchanged in the urine, making it the preferred ACE inhibitor in HIV-infected patients treated with boosted PIs or NNRTIs.

Amiodarone is an antiarrhythmic agent used for control of both ventricular and atrial cardiac dysrhythmias. It is a major substrate of CYP3A4, where it is metabolized to its active form and so is susceptible to ARV drugs that modulate CYP function. Given its narrow therapeutic window, the risk of toxicity is significant with any fluctuations in concentration. There are reports of amiodarone toxicity in patients already on ARV medications that were recently started on the drug [48]. In the emergent setting (for example ventricular tachycardia), amiodarone should be administered if indicated, regardless of other medications. However, for patients in which amiodarone must be administered in conjunction with ARV therapy, the use of an INSTI (e.g., raltegravir, dolutegravir) is preferable over a PI. If a PI regimen must be used, low-dose amiodarone with close therapeutic drug monitoring and serial ECGs is recommended [49].

Lidocaine and procainamide are also major substrates of CYP3A4 and CYP2D6, respectively. Patients receiving these medications should similarly be monitored for signs of toxicity when used in conjunction with PIs or NNRTIs [49].

Antimigraine Medications

Ergotamine and dihydroergotamine are serotonin inhibitor vasoconstrictors used in migraine-abortive therapy. The ergot alkaloids are metabolized by CYP3A4. In the literature, there are reported cases of patients developing painful vasospasm, dubbed "ergotism," while taking ergot alkaloids concurrently with PIs. In some cases, patients on PIs have developed ergotism after only one dose of ergot medications, and as a result, these medications are considered contraindicated in patients taking PIs [50].

Limited data exist for any interaction between serotonin receptor agonist antimigraine drugs and ARVs. Since almotriptan, eletriptan, and naratriptan are CYP3A4 substrates, co-administration with boosted PIs may significantly increase the risk of severe vasoconstriction. These agents should be avoided in patients taking PIs. Consider the use of other serotonin receptor agonists that are not dependent on CYP3A4 metabolism (e.g., rizatriptan, sumatriptan, zolmitriptan).

Anticonvulsant Medications

Maintenance of appropriate anticonvulsant concentration is critical. Supratherapeutic concentrations may result in toxicity while subtherapeutic levels can precipitate breakthrough seizures. There are several significant interactions between anticonvulsants and ARV drugs in the medical literature.

Phenytoin is particularly important because of its ubiquitous administration and because it is both an inducer of CYP3A4 and a substrate of 2C9 and 2C19. In a pharmacokinetic study, a bi-directional drug-drug interaction was observed when lopinavir/ritonavir was co-administered with phenytoin. Lopinavir and phenytoin concentrations were reduced by 33 and 31 %, respectively. This study suggested that the lopinavir/ritonavir combination therapy might have CYP2C9 and 2C19 induction properties [51]. In a separate study of healthy volunteers, phenytoin administration decreased the mean lopinavir/ritonavir AUC by about one third. Similarly, carbamazepine, a CYP3A4 inducer and 3A4 and 2C9 substrate, was found to have a 45 % increase in its AUC when co-administered with darunavir/ritonavir. Interestingly, darunavir concentrations were not affected. This is likely due to the inhibitory effect of ritonavir outweighing the induction properties of carbamazepine on the metabolism of darunavir [52].

In contrast to phenytoin and carbamazepine, valproate is not an inducer of CYP3A4 and is only a minor substrate of 2A6, 2B6, 2C9, 2C19, 2E1, and 1A2. Lopinavir/ritonavir and efavirenz did not affect valproate concentrations. As expected, efavirenz concentrations were not significantly affected by valproic acid. Although lopinavir concentrations were 38 % higher, this did not reach statistical significance [53].

Lamotrigine, an anticonvulsant FDA-approved for control of seizures and mania, is metabolized via glucuronidation and is not a major CYP substrate. Since atazanavir is an inhibitor of glucuronidation, it is expected that lamotrigine concentrations should increase. However, by an unclear mechanism, addition of atazanavir/ritonavir to lamotrigine reduced lamotrigine AUC by 32 % [54]. A lamotrigine dose increase of 50 % should be considered in patients taking ritonavir/atazanavir [55].

Since enzyme induction by phenytoin takes 10–14 days to reach steady state, the standard loading doses of phenytoin should be used, especially in emergencies. In chronic use, clinicians should consider a dose increase for certain ARV/anticonvulsant combinations. For example, the lopinavir/ritonavir dose should be increased to 600/150 mg twice daily in patients taking phenytoin. Free phenytoin and carbamazepine concentrations should be closely monitored with appropriate dose adjustment with PI and NNRTI co-administration.

Levetiracetam does not undergo oxidative metabolism and is renally eliminated. Due to its broad spectrum, favorable side effect profile, and lack of drug-drug interactions, many experts

recommend levetiracetam in combination with NNRTI- and PI-based ARV regimens [56].

Antidepressant Medications

Potential for drug-drug interactions should not deter treatment of depression. Studies have shown that antiretroviral adherence is increased when depressed patients are treated with antidepressants [57].

Serotonin reuptake inhibitor (SSRI) antidepressants are generally preferred over tricyclic antidepressants (TCAs) due to their better safety profile [58, 59]. Although potential interactions between PIs and several SSRIs do exist, the dose of the SSRI can be titrated based on clinical assessment of antidepressant response. Co-administration of darunavir/ritonavir with paroxetine or sertraline has been reported to decrease concentrations of the SSRIs by 39 and 49 %, respectively [60]. On the other hand, no significant drug-drug interaction was noted between ritonavir and escitalopram [61]. Similarly, no significant change to fluoxetine concentrations was observed when given to patients taking ritonavir [62]. Despite these findings, however, there are reported cases in the literature of serotonin syndrome in patients treated with fluoxetine and PIs [63]. It is unclear if these reports of serotonin syndrome are higher than baseline rates among patients taking SSRIs.

Due to the potential for increased adverse drug reaction (e.g., sedation, anticholinergic side effect) with high TCA concentrations, close monitoring is recommended when TCAs are co-administered with PIs. Ritonavir increased desipramine concentrations by 145 % [64]. This interaction is likely due to inhibition of CYP2D6 by ritonavir. Other TCAs that are CYP2D6 substrates (e.g., amitriptyline, clomipramine, imipramine, nortriptyline) may also be increased with PI co-administration, but reports in the literature are limited. It is important to initiate TCAs at the lowest possible dose with close monitoring for adverse drug reactions when combined with PIs.

Sedative Hypnotics and Opioid Medications

Some of the most important drug-drug interactions for ARV medications involve sedatives because of the significant risks of either supratherapeutic or subtherapeutic concentrations. Drug accumulation may cause oversedation, hypoxia, and hypercapnia. Alternatively, decreased concentrations, as might be caused by CYP induction, could result in withdrawal in patients on a previously stable dose of an opioid or benzodiazepine.

Benzodiazepines are used as anxiolytics, anticonvulsants, and sleep aids. Although these drugs share a common mechanism of action, there are important differences in their metabolism and pharmacokinetics. Midazolam and alprazolam are metabolized by CYP3A4 [65, 66]. One study investigated the effect of co-administration of saquinavir, the weakest 3A4 inhibitor among the PIs, with oral and intravenous midazolam. The study reported a fivefold increase in the midazolam AUC and a more than double increase in midazolam's half-life. Sedation was, as expected, also increased [67]. Another retrospective cohort study looked at patients on ARV therapy receiving IV midazolam sedation for bronchoscopy. Both the length of hospitalization and the risk of prolonged sedation were significantly increased, with the sedation risk six times greater in those taking PIs than those who were not [68].

In a pharmacokinetic study of interactions involving alprazolam and the PI ritonavir, alprazolam concentrations were reported to have increased by 248 % with the initial dose; however, at steady state, alprazolam concentrations were decreased by 12 %. It is important to note that the study was conducted with high-dose ritonavir (500 mg twice daily), a known inducer of certain CYP3A4 substrates at steady state [69].

Diazepam, chlordiazepoxide, clonazepam, clorazepate, estazolam, and flurazepam are not pure CYP3A4 substrates. In addition to CYP3A4, other isoenzymes are involved in their metabolism. The presence of an inhibitor, such as ritonavir, could result in increased sedation, while the presence of an inducer, such as efavirenz, may result in decreased drug effect or withdrawal [70]. However, the magnitude of the drug-drug interactions between these benzodiazepines and PIs are not expected to be dramatic. Similarly, lorazepam, temazepam, and oxazepam are not metabolized exclusively via CYP3A4 and so are not expected to have significant interactions with boosted PIs.

Opioid-ARV drug interactions are tightly coupled to CYP modulation, where many are metabolized to their active form. Oxycodone is metabolized by CYP2D6 to the active metabolite oxymorphone. When pharmacokinetic study participants were co-administered oxycodone with lopinavir/ritonavir for 4 days, oxycodone concentrations were tripled and participants reported increased subjective feelings of opioid activity [71]. Hydrocodone is also metabolized by CYP2D6 to hydromorphone, which has 5.4-fold more opioid activity than the parent compound [72]. Inhibition of CYP by ritonavir should then theoretically lead to accumulation of the less potent parent compound with resultant risk for withdrawal symptoms or decreased analgesic effect [73].

Heroin (diacetylmorphine) is rapidly converted to morphine by plasma and liver esterases. Morphine is then glucuronidated to morphine-3-glucuronide and morphine-6-glucuronide (M6G). The latter is a renally eliminated metabolite with opioid agonist properties. Drugs that increase glucuronyltransferases (high-dose ritonavir, nelfinavir) may result in faster glucuronidation, but the clinical significance of this is unclear as both morphine and M6G itself have opioid activity.

Interactions between methadone and ARV drugs are extremely complex. Methadone is a racemic synthetic opioid that acts by binding the μ-opioid receptor, with the affinity for the R-enantiomer being 10 times higher than that for the S-enantiomer [74]. Methadone is a substrate of CYP2B6 and 2C19 and also of pgp, while the role of CYP3A4 remains debated [75, 76]. When methadone maintenance patients were started on NNRT Is such as efavirenz and nevirapine, methadone AUCs were observed to decrease to 55 and 63 %, respectively, precipitating withdrawal in nine out of 10 participants [77, 78]. As a result, methadone dose adjustments may be necessary in patients taking efavirenz or nevirapine, with dose increases typically initiated during the second week of co-administration. However, with administration of etravirine, the methadone AUC was slightly increased [79]. This could be potentially attributable to etravirine induction of CYP3A4 and concomitant inhibition of 2C19 [80].

The story is particularly more complicated in the scenario of concurrent PI and methadone administration. Ritonavir, a CYP inhibitor, would be expected to increase methadone concentrations. However, the opposite has been reported in multiple studies demonstrating a significantly reduced methadone AUC with administration of the boosted PI regimen of lopinavir/ritonavir. Ritonavir on its own, however, had no significant effect on methadone metabolism [81–83]. One study reported a decrease in R-methadone (active form) AUC by 16 % with administration of darunavir/ritonavir and noted withdrawal symptoms in four out of 16 patients [84]. It has been demonstrated that methadone metabolism by CYP3A4 is not stereoselective, while CYP2B6 metabolizes S more avidly than R, and vice versa for 2C19 [75]. The mechanism is unclear but it is possible that a complex interplay of enantiomer metabolism by these enzymes with possible involvement of pgp is responsible for this counterintuitive outcome.

Buprenorphine is a μ-opioid partial agonist metabolized by CYP3A4. The drug has a high affinity for opioid receptors and disappearance of clinical effects is more dependent on dissociation of the drug from the receptors than on metabolism or elimination [85]. Inhibition and induction of CYP3A4 affects buprenorphine concentration, but not necessarily its clinical effects. Co-administration of the inducer efavirenz with buprenorphine was associated with decreased buprenorphine AUC but not with withdrawal symptoms [86]. Nevirapine, which induces CYP3A4, affected neither buprenorphine concentration nor withdrawal symptoms [87]. However, increases in buprenorphine concentrations can result in increased sedation. Co-administration of atazanavir increased buprenorphine AUC by 93 %, causing clinical drowsiness in three of 10 patients [88].

Illicit and Commonly Misused Drugs

The potential for drug-drug reactions are not limited to prescription medications, as recreational drugs may interact with ARV therapy as well. Phenylethylamines and 3,4-methylenedioxy-*N*-methylamphetamine (MDMA, "ecstasy") are metabolized by CYP2D6 [89, 90]. Interference with CYP2D6 could prolong clinical effects and precipitate toxicity. One case report detailed the story of a 32-year-old male who suffered a fatal MDMA toxicity after using his typical dose of MDMA for the first time after starting ritonavir. He had a tonic-clonic seizure and severe tachycardia. On autopsy, the MDMA concentration was 10 times higher than expected [91].

The emergence of the synthetic cathinone derivatives ("bath salts") may also create potential interactions with ARV therapies. The metabolic pathways of these drugs are still being elucidated. There is a great deal of structural heterogeneity in this class, so it is likely that there are variations in metabolism as well. In vitro, methylenedioxypyrovalerone (MDPV) was metabolized by CYP 1A2, 2C19, and 2D6. It is possible that co-ingestion of a CYP2D6 inhibitor, such as ritonavir, may increase MDPV concentration but further study is required [92].

To date, there are no reported interactions between cocaine and ARV drugs. Cocaine hydrolysis by plasma cholinesterase is primarily responsible for the bulk (>50 %) of cocaine metabolism. *N*-demethylation to norcocaine by CYP3A4 accounts for <10 % of cocaine metabolism, so interactions with CYP inducers and inhibitors are unlikely to be clinically significant [93]. Norcocaine, however, may play an important role in cocaine hepatotoxicity. In patients with decreased plasma cholinesterase activity, cocaine metabolism is subsequently shunted down the *n*-demethylation pathway, creating more norcocaine—an active metabolite. Norcocaine accumulation has been linked to an increased risk of life-threatening hepatotoxicity [94, 95]. Given this, it is possible that CYP3A4 inducers (such as efavirenz) may predispose users to cocaine hepatotoxicity, particularly in patients with impaired cholinesterase activity, but this has not been reported.

Gamma hydroxybutyrate (GHB) undergoes first-pass hepatic metabolism [96]. One patient taking saquinavir/ritonavir experienced extreme sedation, myoclonus, and bradycardia after taking a small dose of GHB. These severe manifestations of GHB toxicity were thought to be due to CYP isoenzyme inhibition with resultant drug accumulation [97].

Ethanol is principally metabolized by alcohol dehydrogenase. Abacavir is unique among the antiretrovirals in its metabolism by alcohol dehydrogenase. Concomitant administration of ethanol with a single dose of abacavir resulted in a 41 % increase in the AUC of abacavir. Because abacavir is well tolerated at this concentration, this interaction is not considered clinically significant [98].

Tetrahydrocannabinol (THC) is an active compound, which is metabolized by CYP3A4 and 2C9 enzymes to active metabolites [99]. Antiretrovirals likely do not have an effect on THC pharmacokinetics. One randomized, placebo-controlled trial demonstrated that smoking THC cigarettes three times daily resulted in only a small and clinically insignificant decrease in nelfinavir concentration [100].

Phencyclidine is hepatically metabolized by CYP3A4 and a number of other CYP isoforms [101]. There are no published interactions between phencyclidine and ARV drugs, but theoretically, CYP3A4 inhibitors could result in increased concentrations of the drug.

Complementary and Alternative Medicine Products

Complementary and alternative medicine (CAM) products are ubiquitous and have the potential to also interact with ARV therapies. Separate studies suggested that nearly two thirds of HIV-infected people report using CAM [102]. One survey reported the most commonly used CAM products by HIV-infected individuals were multivitamins, followed by cod liver oil, and flax/flaxseed oil. These products do not have known or potential interactions with ARV therapies. However, the survey also identified several CAM products that had the potential for interaction with ARV medications including echinacea, garlic, kava, St. John's wort (SJW), aloe vera, cat's claw, DHEA, gingko, ginseng, licorice, milk thistle, red yeast, and high dose (>1 g) vitamin C. The top four drugs that resulted in a recommendation to stop therapy were echinacea, garlic, kava, and SJW [103].

Many CAM products have pharmacologically active compounds; however, lack of FDA regulation over these products results in inconsistent concentrations and unknown additives. The literature was reviewed for reports of interactions between ARV therapies and popular CAM products.

CAM Products Thought to Interact with ARV Therapy

Hypericum perforatum, or SJW, is a CAM product often used for depression. Compounds in SJW are known inducers of CYP3A4 and pgp [104]. Ideally, the "active" components of SJW would be isolated from the components that are most likely to cause drug interactions. Unfortunately, hyperforin, the compound in SJW that induces CYP3A4, is also the compound purported to have the greatest beneficial activity [105]. As such, SJW is thought to decrease the concentration of ARV medications that are CYP3A4 substrates (e.g., PIs, nevirapine, rilpivirine) by way of CYP induction. In a population that was co-administered SJW and nevirapine, concentrations of the NNRTI were significantly decreased. Similarly, co-administration of SJW with indinavir in healthy volunteers reduced the AUC of the PI by 57 % [106].

Echinacea is believed by some to have general immunologic stimulant properties. However, there is limited data that the use of echinacea may induce an increase in viral load [107]. Extracts of *Echinacea angustifolia* have been shown to be in vitro CYP3A4 inhibitors [108]. *Echinacea purpurea*, on the other hand, was demonstrated to induce CYP3A4 metabolism of darunavir but without effect on overall darunavir or ritonavir pharmacokinetics. The results of the study were not clinically significant [109]. In a similar study, the use of echinacea did not effect etravirine concentrations in HIV-infected individuals [110].

Garlic is prized for its anti-hyperlipidemic and antioxidant properties. Components of garlic may induce intestinal CYP3A4 or pgp. However, pharmacokinetic studies with saquinavir and ritonavir failed to show statistically significant declines in PI concentration. [107].

Ginseng may also induce CYP3A activity in the liver and possibly the GI tract [111]. One case report described a patient with a history of HIV and chronic hepatitis C on raltegravir and lopinavir/ritonavir admitted for transaminitis, jaundice, and evidence of liver failure after starting ginseng. The authors noted a clinical improvement in symptoms and lab data with cessation of the CAM product [112].

Another case report discusses a patient taking efavirenz with sudden virologic failure after starting gingko. Serial ARV concentrations were taken on plasma samples dating back 2 years and found a steady decrease in plasma efavirenz concentrations over that time period. The patient had been taking gingko for several months. The authors attributed the ARV decline and viral load increase to CYP3A4 or pgp induction by gingko. Because of the variability in efavirenz concentrations, conclusive evidence was lacking [113].

One single case report described significant increases in the concentrations atazanavir, ritonavir, and saquinavir in a patient that took cat's claw for 2 months [114]. Kava (*Piper methysticum*), another CAM product, is used as a minor sedative. The plant product produces significant inhibition of CYP2E1, but not of CYP3A4, so interaction with ARV medication is unlikely. However, concern for direct hepatotoxicity from kava should limit its use in HIV-infected patients [115].

CAM Products Unlikely to Interact with ARV Therapy

Aloe is sometimes consumed for digestive health and general well-being. Its juice is known to be a minor CYP3A4 and 2D6 inhibitor, but does not affect ARV metabolism [116]. Similarly, licorice is thought by some to have antiviral properties. This *Glycyrrhiza glabra* root extract, however, may induce CYP3A4 and pgp. There are no reports of interactions with ARV therapies, but more study is needed [117].

Red yeast rice is fermented rice taken for digestive and general well-being. It is thought to inhibit CYP1A2 and 2C19; however, no ARV interactions have been reported to

date [118]. Similarly, the administration of milk thistle (*Silymarin marianum*), taken to help treat liver disease and prevent hepatotoxicity via antioxidant properties, has not been shown to significantly affect darunavir-ritonavir concentrations [119].

Goldenseal root (*Hydrastis canadensis*) is a CAM product purported to improve immune function, which is of particular interest for the HIV-infected population. Goldenseal inhibits CYP3A4 but did not affect indinavir pharmacokinetics in one study [120]. And while high-dose vitamin C increased drug metabolism in animal models, its use has not been associated with any effects on indinavir pharmacokinetics in healthy volunteers [121].

Conclusion

The emergence of effective, lifelong ARV therapy has allowed HIV to be managed as a chronic disease. Many ARV drugs are substrates, inducers, or inhibitors of the CYP family of isoenzymes and of pgp, as are many generally prescribed medicines, illicit drugs, and CAM products. As patients taking ARV therapy continue to age, they are susceptible to the same chronic diseases and acute illnesses as any non-HIV-infected population; however, they are at a higher risk for drug interaction with the initiation of many new medical therapies.

Many patients on ARV therapy also take additional medications, supplements, and illicit drugs. Most ARV regimens include an INSTI, PI, or NNRTI. PIs tend to inhibit CYP3A4, while NNRTIs (nevirapine, efavirenz, etravirine) often induce the enzyme. INSTIs (e.g., dolutegravir, raltegravir) neither inhibit nor induce CYP3A4. Not surprisingly, CYP modulation comprises the most important drug-drug interactions. While ARV drug interactions with statins may be the most common, interactions with medications like midazolam (prolonged sedation) and fluticasone (hypercortisolism) may be more clinically significant.

ARV drug interactions are complicated, involving multiple metabolic pathways and enzymes, and are not easily predicted. For example, when considering the opioid class, methadone concentrations are decreased when combined with efavirenz and nevirapine, but morphine and heroin are usually unaffected. In addition, buprenorphine concentrations may be decreased, but the clinical effect is insignificant due to receptor affinity. However, with understanding of the effect that the drug class in question may have on CYP or pgp, better insight may be gained into the possible expected outcome on concentration of both the ARV therapy and the concurrent medication.

Clinicians should use caution when starting new medications in any patients taking ARV therapies. A healthy respect for the influence of CYP modulation is necessary, as misadministration or inappropriate prescription of medications may have a devastating effect on the patient's viral control and/or may induce drug toxicity. If the clinician is unsure about the possible interaction between an ARV drug and a new medication, consultation with a drug-drug interaction database, clinical pharmacologist/pharmacist, or HIV specialist is recommended. HIV-infected individuals, and their providers alike, must be particularly mindful of the potential complications of new drug use (prescribed, over the counter and illicit) and the susceptibility of this population for unique drug-drug interactions.

Conflict of Interest Andrew Stolbach owns stock in Gilead Pharmaceuticals. Paul Pham served on an advisory board for Janssen Pharmaceuticals last year. Paul Pham also performs consulting work for MADAP (Maryland AIDS Drug Assistance Program).

External Funding None

References

1. Thompson MA, Aberg JA, Hoy JF et al (2012) Antiretroviral treatment of adult HIV infection: 2012 recommendations of the international antiviral society-USA panel. JAMA 308(4):387
2. Margolis AM, Heverling H, Pham PA, Stolbach A (2014) A review of the toxicity of HIV medications. J Med Toxicol 10(1):26–39
3. Patel N, Abdelsayed S, Veve M, Miller CD (2011) Predictors of clinically significant drug-drug interactions among patients treated with nonnucleoside reverse transcriptase inhibitor-, protease inhibitor-, and raltegravir-based antiretroviral regimens. Ann Pharmacother 45(3):317–324
4. Gonzalez FJ, Coughtrie M, Tukey RH (2011) Drug metabolism. In: Brunton LL, Chabner BA, Knollmann BC (eds) Goodman & Gilman's the pharmacological basis of therapeutics, 12e. McGraw-Hill, New York, Chapter 6
5. Pham PA, Flexner CW (2009) HIV infections and AIDS. In: Waldman SA, Terzic A (eds) Pharmacology and therapeutics: principles to practice. Saunders/Elsevier, Philadelphia, Chapter 84
6. Parienti JJ, Bangsberg DR, Verdon R, Gardner EM (2009) Better adherence with once-daily antiretroviral regimens: a meta-analysis. Clin Infect Dis 48(4):484–488
7. Hughes CA (2010) Interactions between antifungal and antiretroviral agents. J Expert Opin Drug Saf 9(5):723–42
8. Hediger MA, Romero MF, Peng JB, Rolfs A, Takanaga H, Bruford EA (2004) The ABCs of solute carriers: physiological, pathological and therapeutic implications of human membrane transport proteins. Pflugers Arch 447(5):465–468
9. Fukushima K, Kobuchi S, Mizuhara K, Aoyama H, Takada K, Sugioka N (2013) Time-dependent interaction of ritonavir in chronic use: the power balance between inhibition and induction of P-glycoprotein and cytochrome P450 3A. J Pharmaceut Sci 102(6): 2044–2055
10. Evans-Jones JG, Cottle LE, Back DJ et al (2010) Recognition of risk for clinically significant drug interactions among HIV-infected patients receiving antiretroviral therapy. Clin Infect Dis 50(10):1419–21
11. Mok S, Minson Q (2008) Drug-related problems in hospitalized patients with HIV infection. Am J Health Syst Pharm 65(1):55–9
12. Yehia BR1, Mehta JM, Ciuffetelli D (2012) Antiretroviral medication errors remain high but are quickly corrected among hospitalized HIV-infected adults. Clin Infect Dis 55(4):593–9

13. Fichtenbaum CJ, Gerber JG, Rosenkranz SL et al (2002) Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 16(4):569–77
14. Chauvin B, Drouot S, Barrail-Tran A, Taburet AM (2013) Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. Clin Pharmacokinet 52(10):815–31
15. Hare CB, Vu MP, Grunfeld C et al (2002) Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. Clin Infect Dis 35(10):111–2
16. Carr R, Andre A, Bertz R et al. Concomitant administration of ABT-378/ritonavir results in a clinically important pharmacokinetic interaction with atorvastatin but not pravastatin. In: 40th ICAAC, Toronto, Canada; 2000. Abstract 1644.
17. Potential for Kaletra to affect other drugs. In: Kaletra FDA label. http://www.rxabbvie.com/pdf/kaletratabpi.pdf. Accessed 19 Nov 2014.
18. Calza L, Manfredi R, Colangeli V, Pocaterra D, Pavoni M, Chiodo F (2008) Rosuvastatin, pravastatin, and atorvastatin for the treatment of hypercholesterolaemia in HIV-infected patients receiving protease inhibitors. Curr HIV Res 6(6):572–578
19. Wang B, Sanchez RI, Franklin RB et al (2004) The involvement of CYP3A4 and CYP2C9 in the metabolism of 17 alpha-ethinylestradiol. Drug Metab Dispos 32(11):1209–12
20. Zhang H, Cui D, Wang B et al (2007) Pharmacokinetic drug interactions involving 17 alpha-ethinylestradiol: a new look at an old drug. Clin Pharmacokinet 46(2):133–57
21. Tseng A, Hills-Nieminen C (2013) Drug interactions between antiretrovirals and hormonal contraceptives. Expert Opin Drug Metab Toxicol 9(5):559–572
22. Foisy MM, Yakiwchuk EMK, Chiu I, Singh AE (2008) Adrenal suppression and Cushing's syndrome secondary to an interaction between ritonavir and fluticasone: a review of the literature. HIV Med 9(6):389–396
23. Blondin MC, Beauregard H, Serri O (2013) Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract 19(6): 138–41
24. Song Y, Schroeder JR, Bush LM (2013) Iatrogenic Cushing syndrome and secondary adrenal insufficiency related to concomitant triamcinolone and ritonavir administration: A case report and review. J Int Assoc Provid AIDS Care. ePub ahead of print.
25. Falcon RW, Kakuda TN (2008) Drug interactions between HIV protease inhibitors and acid-reducing agents. Clin Pharmacokinet 47(2):75–89
26. Tomilo DL, Smith PF, Ogundele AB et al (2006) Inhibition of atazanavir oral absorption by lansoprazole gastric acid suppression in healthy volunteers. Pharmacotherapy 26:341–6
27. Soyinka JO, Onyeji CO, Owolabi AR et al (2010) Pharmacokinetic interactions between ritonavir and quinine in healthy volunteers following concurrent administration. Br J Clin Pharmacol 69(3): 262–70
28. Van Luin, Matthijsa,b,c; Van der Ende et al. (2010) Lower atovaquone/proguanil concentrations in patients taking efavirenz, lopinavir/ritonavir or atazanavir/ritonavir. Research Letters. AIDS 24(8):1223-1226.
29. Khoo S, Back D, Winstanley P (2005) The potential for interactions between antimalarial and antiretroviral drugs. Aids 19(10):995–1005
30. Louisa M, Soetikno V, Setiabudy R, Suyatna FD (2012) Co-administration of ritonavir and primaquine decreases plasma concentration of primaquine: single-and multiple-dose study in the rats. Acta medica Indonesiana 44(4):273–279
31. Saran BR, Maquire AM, Nichols C et al (1994) Hypopyon uveitis in patients with acquired immunodeficiency syndrome treated for systemic Mycobacterium avium complex infection with rifabutin. Arch Ophthalmol 112:1159–1165
32. Sterling TR, Pham PA, Chaisson RE (2010) HIV infection-related tuberculosis: clinical manifestations and treatment. Clin Infect Dis 50(3):223–30
33. Sousa M, Pozniak A, Boffito M (2008) Pharmacokinetics and pharmacodynamics of drug interactions involving rifampin, rifabutin, and antimalarial drugs. J Antimicrob Chemother 62(5):872–878
34. López-Cortés LF, Ruiz-Valderas R, Viciana P et al (2002) Pharmacokinetic interactions between efavirenz and rifampin in HIV-infected patients with tuberculosis. Clin Pharmacokinet 41(9):681–690
35. Friedland G, Khoo S, Jack C, Lalloo U (2006) Administration of efavirenz (600 mg/day) with rifampicin results in highly variable levels but excellent clinical outcomes in patients treated for tuberculosis and HIV. J Antimicrob Chemother 58(6):1299–1302
36. CDC. Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis. 2013. Available from URL: http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm. Accessed 19 Nov 2014.
37. Darlington MR (1997) Hypoprothrombinemia during concomitant therapy with warfarin and saquinavir. Ann Pharmacother 31:647
38. Liedtke MD (2010) Drug interactions with antiretrovirals and warfarin. Exp Opin Drug Saf 9(2):215–23
39. Metzger NL (2013) A patient with HIV and tuberculosis with diminished clopidogrel response. Int J STD AIDS 25(7):532–534
40. Lakatos B, Stoeckle M, Elzi L, Battegay M, Marzolini C (2014) Gastrointestinal bleeding associated with rivaroxaban administration in a treated patient infected with human immunodeficiency virus. Swiss Med Wkly 144:13906
41. Skeik N, Rumery K, Rodriguez G (2014) The new era of anticoagulation. Ann Vasc Surg 28(2):503–514
42. Hellwig T, Gulseth M (2013) Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants what do they mean for patients with atrial fibrillation? Ann Pharmacother 47(11): 1478–87
43. Gordon LA, Hadigan C, McManus M et al. Influence of separated and concomitant administration of ritonavir on the anticoagulant effect of dabigatran etexilate in healthy volunteers. 15th International Workshop on Clinical Pharmacology of HIV and Hepaitis Therapy, Washington DC: 2014.
44. Barco S, Coppens M, van den Dool EJ, van de Kerkhof D, Stroobants AK, Middeldorp S (2014) Successful co-administration of dabigatran etexilate and protease inhibitors ritonavir/lopinavir in a patient with atrial fibrillation. Thromb Haemost 112(4):836–8
45. Soliman EZ, Lundgren JD, Roediger MP (2011) Boosted protease inhibitors and the electrocardiographic measures of QT and PR durations. AIDS (London, England) 25(3):367
46. Established and other potentially significant drug interactions. In: Reyetaz FDA label. http://hivdb.stanford.edu/pages/linksPages/ATV_PI.pdf. Accessed 19 Nov 2014.
47. Glesby MJ1, Aberg JA, Kendall MA (2005) Adult AIDS clinical trials group A5159 protocol team. Pharmacokinetic interactions between indinavir plus ritonavir and calcium channel blockers. Clin Pharmacol Ther 78(2):143–53
48. Naccarato M, Yoong D, la Porte C, Fong I (2013) Amiodarone and concurrent antiretroviral therapy: a case report and review of the literature. Antivir Ther 19(4):329–39
49. Thummel KE, Shen DD, Isoherranen N. Design and optimization of dosage regimens: pharmacokinetic data. In: Brunton LL, Chabner BA, Knollmann BC. editors. Goodman & Gilman's The pharmacological basis of therapeutics, 12e. New York: McGraw-Hill; 2011. Appendix II.
50. Baldwin ZK, Ceraldi CC (2003) Ergotism associated with HIV antiviral protease inhibitor therapy. J Vasc Surg 37(3):676–8

51. Lim ML, Min SS, Eron JJ et al (2004) Coadministration of lopinavir/ritonavir and phenytoin results in two-way drug interaction through cytochrome P-450 induction. J Acquir Immune Defic Syndr 36:1034–1040
52. Wong MC, Suite ND, Labar DR (1990) Seizures in human immunodeficiency virus infection. Arch Neurol 47:640–642
53. DiCenzo R, Peterson D, Cruttenden K et al (2004) Effects of valproic acid coadministration on plasma efavirenz and lopinavir concentrations in human immunodeficiency virus-infected adults. Antimicrob Agents Chemother 48:4328–31
54. Burger DM, Huisman A, Van Ewijk N et al (2008) The effect of atazanavir and atazanavir/ritonavir on UDP-glucuronosyltransferase using lamotrigine as a phenotypic probe. Clin Pharmacol Ther 84:698–703
55. Birbeck GL, French JA, Perucca E et al (2012) Quality Standards Subcommittee of the American Academy of Neurology; Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. Antiepileptic drug selection for people with HIV/AIDS: evidence-based guidelines from the ILAE and AAN. Epilepsia 53(1):207–14
56. Siddiqi O1, Birbeck GL (2013) Safe treatment of seizures in the setting of HIV/AIDS. Curr Treat Options Neurol 15(4):529–43
57. Yun LW, Maravi M, Kobayashi JS, Barton PL, Davidson AJ (2005) Antidepressant treatment improves adherence to antiretroviral therapy among depressed HIV-infected patients. JAIDS J Acq Immune Def Synd 38(4):432–438
58. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK (2008) Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. Ann Intern Med 149(10):725–733
59. Treisman, G. J., & Angelino, A. F. (2004). The psychiatry of AIDS: a guide to diagnosis and treatment. JHU Press.
60. Established and other potentially significant drug interactions. In: Prezista FDA label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021976s021lbl.pdf. Accessed 19 Nov 2014.
61. Gutierrez MM, Rosenberg J, Abramowitz W (2003) An evaluation of the potential for pharmacokinetic interaction between escitalopram and the cytochrome P450 3A4 inhibitor ritonavir. Clin Ther 25(4):1200–10
62. Ouellet D, Hsu A, Qian J et al (1998) Effect of fluoxetine on pharmacokinetics of ritonavir. Antimicrob Agents Chemother 42(12): 3107–12
63. DeSilva KE, Le Flore DB, Marston BJ, Rimland D (2001) Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. Aids 15(10):1281–85
64. Established and other potentially significant drug interactions. In: Prezista FDA label. http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020945s033lbl.pdf. Accessed 19 Nov 2014.
65. Kronback T, Mathys D, Umeno M, Gonzalez FJ, Meyer UA (1989) Oxidation of midazolam and triazolam by human liver cytochrome P450IIIa4. Mol Pharmacol 36(1):89–96
66. Venkatakrishnan K, Greenblatt DJ, von Moltke LL, Shader RI (1998) Alprazolam is another substrate for human cytochrome P450-3A isoforms. J Clin Psychopharmacol 18(3): 256
67. Palkama VJ, Ahonen J, Neuvonen PJ, Olkkola KT (1999) Effect of saquinavir on the pharmacokinetics and pharmacodynamics of oral and intravenous midazolam. Clin Pharmacol Ther 66(1):33–39
68. Hsu AJ, Carson KA, Yung R, Pham PA (2012) Severe prolonged sedation associated with coadministration of protease inhibitors and intravenous midazolam during bronchoscopy. Pharmacotherapy 32(6):538–45
69. Greenblatt D, Moltke L, Harmatz J et al (2000) Alprazolam–ritonavir interaction: implications for product labeling. Clin Pharmacol Ther 67(4):335–341
70. Dresser GK, Spence JD, Bailey DG (2000) Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition. Clin Pharmacokinet 38(1):41–57
71. Nieminen TH, Hagelberg NM, Saari TI et al (2010) Oxycodone concentrations are greatly increased by the concomitant use of ritonavir or lopinavir/ritonavir. Eur J Clin Pharmacol 66(10):977–985
72. Navani DM, Yoburn BC (2013) In vivo activity of norhydrocodone: an active metabolite of hydrocodone. J Pharm Exp Therapeut 347(2):497–505
73. Wynn GH, Cozza KL, Zapor MJ et al (2005) Med-psych drug–drug interactions update: antiretrovirals, part III: antiretrovirals and drugs of abuse. Psychosomatics 46:79–87
74. Somogyi AA1, Barratt DT, Ali RL, Coller JK (2014) Pharmacogenomics of methadone maintenance treatment. Pharmacogenomics 15(7):1007–27
75. Gerber JG, Rhodes RJ, Gal J (2004) Stereoselective metabolism of methadone N-demethylation by cytochrome P4502B6 and 2C19. Chirality 16(1):36–44
76. Iribarne C, Berthou F, Baird S et al (1996) Involvement of cytochrome P450 3A4 enzyme in the N-demethylation of methadone in human liver microsomes. Chem Res Toxicol 9(2):365–373
77. McCance-Katz EF, Gourevitch MN, Arnsten J et al (2002) Modified directly observed therapy (MDOT) for injection drug users with HIV disease. Am J Addict 11(4):271–278
78. Arroyo E, Valenzuela B, Portilla J et al (2007) Pharmacokinetics of methadone in human-immunodeficiency-virus-infected patients receiving nevirapine once daily. Eur J Clin Pharmacol 63:669–675
79. Scholler-Gyure M, van den Brink W, Kakuda TN et al (2008) Pharmacokinetic and pharmacodynamic study of the concomitant administration of methadone and TMC125 in HIV-negative volunteers. J Clin Pharmacol 48:322–329
80. Gruber VA, McCance-Katz EF (2010) Methadone, buprenorphine, and street drug interactions with antiretroviral medications. Curr HIV/AIDS Rep 7(3):152–60
81. Bertz R, Hsu A, Lam W et al. Pharmacokinetic interactions between Kaletra and other non-HIV drugs. In: Program and abstracts of the 5th International Congress on drug therapy in HIV infection (Glasgow, Scotland). Gardiner-Caldwell Group. UK: Macclesfield; 2000. Abstract 438.
82. Clarke S, Mulcahy F, Bergin C et al (2002) Absence of opioid withdrawal symptoms in patients receiving methadone and the protease inhibitor lopinavir/ritonavir. Clin Infect Dis 34:1143–5
83. McCance-Katz EF, Rainey P, Friedland G, Jatlow P (2003) The protease inhibitor lopinavir/ritonavir may produce opiate withdrawal in methadone-maintained patients. Clin Infect Dis 37:476–482
84. Sekar V1, Tomaka F, Lefebvre E (2011) Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenance therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol 51(2):271–8
85. Yaksh TL, Wallace MS (2011) Opioids, analgesia, and pain management. In: Brunton LL, Chabner BA, Knollmann BC (eds) Goodman & Gilman's the pharmacological basis of therapeutics, 12e. McGraw-Hill, New York, Chapter 18
86. McCance-Katz EF, Moody DE, Morse G et al (2006) Interactions between buprenorphine and antiretrovirals I: non-nucleoside reverse transcriptase inhibitors I: efavirenz and delavirdine. Clin Infect Dis 43(4):224–34
87. McCance-Katz EF, Moody DE, Morse E et al (2010) Lack of clinically significant drug interactions between nevirapine and buprenorphine. Am J Addict 19:30–37
88. McCance-Katz EF, Moody DE, Morse GD et al (2007) Interaction between buprenorphine and atazanavir or atazanavir/ritonavir. Drug Alcohol Depend 91:269–278

89. Wynn GH, Cozza KL, Zapor MJ, Wortmann GW, Armstrong SC (2005) Med-psych drug–drug interactions update: antiretrovirals, part III: antiretrovirals and drugs of abuse. Psychosomatics 46(1):79
90. Tucker GT, Lennard MS, Ellis SW et al (1994) The demethylenation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). Biochem Pharmacol 47(7):1151–56
91. Henry JA, Hill IR (1998) Fatal interaction between ritonavir and MDMA. Lancet 352(9142):1751–1752
92. Meyer MR, Du P, Schuster F, Maurer HH (2010) Studies on the metabolism of the α-pyrrolidinophenone designer drug methylenedioxy-pyrovalerone (MDPV) in rat and human urine and human liver microsomes using GC-MS and LC-high resolution MS and its detectability in urine by GC-MS. J Mass Spectrom 45(12):1426–1442
93. Inaba T, Stewart DJ, Kalow W (1978) Metabolism of cocaine in man. Clin Pharmacol Ther 23(5):547–552
94. Hoffman RS, Henry GC, Howland MA, Weisman RS, Weil L, Goldfrank LR (1992) Association between life-threatening cocaine toxicity and plasma cholinesterase activity. Ann Emerg Med 21(3): 247–253
95. Ndikum-Moffor FM, Schoeb TR, Roberts SM (1998) Liver toxicity from norcocaine nitroxide, an N-oxidative metabolite of cocaine. J Pharmacol Exp Ther 284(1):413–419
96. Lettieri JT, Fung HL (1976) Absorption and first pass metabolism of 14C-gamma-hydroxybutyric acid. Res Commun Chem Pathol Pharmacol 13(3):425–437
97. Harrington RD, Woodward JA, Hooton TM, Horn JR (1999) Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 159(18):2221–2224
98. McDowell JA, Chittick GE, Pilati-Stevens C, Edwards KD, Stein DS (2000) Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus–infected adults. Antimicrob Agents Chemother 44(6):1686–1690
99. Bornheim LM, Lasker JM, Raucy JL (1992) Human hepatic microsomal metabolism of delta 1-tetrahydrocannabinol. Drug Metab Dispos 20(2):241–246
100. Kosel BW, Aweeka FT, Benowitz NL et al (2002) The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS 16(4):543–550
101. Laurenzana EM, Owens SM (1997) Metabolism of phencyclidine by human liver microsomes. Drug Metab Dispos 25(5):557–563
102. Littlewood RA, Vanable PA (2008) Complementary and alternative medicine use among HIV-positive people: research synthesis and implications for HIV care. AIDS Care 20(8):1002–1018
103. Ladenheim D, Horn O, Werneke U et al (2008) Potential health risks of complementary alternative medicines in HIV patients. HIV Med 9(8):653–9
104. Mannel M (2004) Drug interactions with St John's wort: mechanisms and clinical implications. Drug Saf 27(11):773–797
105. Hafner V, Jäger M, Matthée AK et al (2010) Effect of simultaneous induction and inhibition of CYP3A by St John's Wort and ritonavir on CYP3A activity. Clin Pharmacol Ther 87(2):191–6
106. Piscitelli SC, Burstein AH, Chaitt D, Alfaro RM, Falloon J (2000) Indinavir concentrations and St John's wort. Lancet 355(9203):547–8
107. Lee LS, Andrade AS, Flexner C (2006) Interactions between natural health products and antiretroviral drugs: pharmacokinetic and pharmacodynamic effects. Clin Infect Dis 43(8):1052–9
108. Budzinski JW, Foster BC, Vandenhoek S, Arnason JT (2000) An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7(4):273–282
109. Molto J, Valle M, Miranda C et al (2011) Herb-drug Interaction between echinacea purpurea and darunavir-ritonavir in HIV-infected patients. Antimicrob Agents Chemother 55(1):326–330
110. Moltó J, Valle M, Miranda C, Cedeño S, Negredo E, Clotet B (2012) Herb-drug interaction between Echinacea purpurea and etravirine in HIV-infected patients. Antimicrob Agents Chemother 56(10):5328–31
111. Malati CY1, Robertson SM, Hunt JD (2012) Influence of Panax ginseng on cytochrome P450 (CYP)3A and P-glycoprotein (P-gp) activity in healthy participants. J Clin Pharmacol 52(6):932–9
112. Mateo-Carrasco H, Gálvez-Contreras MC, Fernández-Ginés FD, Nguyen TV (2012) Elevated liver enzymes resulting from an interaction between raltegravir and Panax ginseng: a case report and brief review. Drug Metabol Drug Interact 27(3):171–5
113. Wiegman DJ, Brinkman K, Franssen EJ (2009) Interaction of Ginkgo biloba with efavirenz. AIDS 23(9):1184–5
114. López Galera RM, Ribera Pascuet E, Esteban Mur JI, Montoro Ronsano JB, Juárez Giménez JC (2008) Interaction between cat's claw and protease inhibitors atazanavir, ritonavir and saquinavir. Eur J Clin Pharmacol 64(12):1235–6
115. Gurley BJ, Gardner SF, Hubbard MA et al (2005) In vivo effects of goldenseal, kava kava, black cohosh, and valerian on human cytochrome P450 1A2, 2D6, 2E1, and 3A4/5 phenotypes. Clin Pharmacol Ther 77(5):415–26
116. Djuv A, Nilsen OG (2012) Aloe vera juice: IC_{50} and dual mechanistic inhibition of CYP3A4 and CYP2D6. Phytother Res 26(3): 445–51
117. Hou YC, Lin SP, Chao PD (2012) Liquorice reduced cyclosporine bioavailability by activating P-glycoprotein and CYP 3A. Food Chem 135(4):2307–12
118. Chen CH, Uang YS, Wang ST, Yang JC, Lin CJ (2012) Interaction between red yeast rice and CYP450 enzymes/P-Glycoprotein and its implication for the clinical. Evid Based Complement Alternat Med 2012:127043
119. Moltó J, Valle M, Miranda C, Cedeño S, Negredo E, Clotet B (2012) Effect of milk thistle on the pharmacokinetics of darunavir-ritonavir in HIV-infected patients. Antimicrob Agents Chemother 56(6): 2837–41
120. Sandhu RS, Prescilla RP, Simonelli TM, Edwards DJ (2003) Influence of goldenseal root on the pharmacokinetics of indinavir. J Clin Pharmacol 43(11):1283–88
121. Slain D, Amsden JR, Khakoo RA, Fisher MA, Lalka D, Hobbs GR (2005) Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. Pharmacotherapy 25:165–70