Drug Interactions with Antiretroviral Medications

Overview

Pharmacokinetic and pharmacodynamics principles are fundamental to achieving the optimal response to antiretroviral drug therapy: successful antiretroviral therapy depends on attaining a therapeutic drug concentration that maximizes efficacy and minimizes toxicity. Understanding drug interactions plays an important role for clinicians in providing effective and safe antiretroviral therapy. Drug interactions can be classified into one of two general categories: those that alter pharmacokinetics or those that alter pharmacodynamics. Pharmacokinetics involves the absorption, distribution, metabolism, and excretion of drugs in the body (Table 1), which is often influenced by a variety of biological, physiological, and chemical factors within each patient. Pharmacokinetic studies are used to define the steady-state concentration of a particular drug, taking into account dose, bioavailability, and clearance, as well as drug interactions that can alter the systemic concentration of coadministered medications. Pharmacodynamics describes the relationship of a drug and its effect on the body’s receptors, which can be affected by the number and affinity of receptors, drug concentration and genetics. In addition, genetic polymorphisms can influence the expression and availability of both receptor number and receptor affinity for a particular drug. Simplified, pharmacokinetics is what the body does to medication, and pharmacodynamics is what the medication does to the body. Pharmacokinetic interactions generally have greater clinical relevance. This Topic Review will primarily focus on pharmacokinetic interactions that involve antiretroviral medications.

Types of Pharmacokinetic interactions

Pharmacokinetic interactions can occur between antiretroviral and concomitant medications during the absorption, metabolism, or elimination phases and can involve several different mechanisms; however, most clinically significant interactions are mediated by the cytochrome P-450 system, a superfamily of microsomal, catalytic enzymes responsible for the metabolism of more than half of all drugs. Investigators have identified more than 50 cytochrome P-450 genes, but most of the cytochrome P-450 encoded proteins that play a significant role in drug metabolisms belong to the CYP1, CYP2, or CYP3 families. Overall, the CYP3A enzyme is the most important enzyme involved in drug metabolism of antiretroviral medications and this enzyme is abundant in both enterocytes of the small intestinal epithelium and hepatocytes (Figure 1). Other enzymes in the cytochrome P-450 family, such as CYP1A2, 2C19, and 2D6, also play a role. The uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzyme is an important mediator of pharmacokinetic interactions related to the metabolism of certain medication, including the integrase inhibitors dolutegravir and raltegravir. Drug therapy may affect enzyme activity in one of three major ways: (1) by inhibiting the activity of the enzyme, (2) by inducing the activity of the enzyme, or (3) by acting as a substrate for the enzyme. Some medications may act both as an inhibitor and an inducer of a particular enzyme, which can further complicate drug interactions.

Pharmacokinetic Inhibition
Drugs that inhibit enzymes (inhibitors) cause a decrease in the metabolism of other drugs that depend on the same enzyme, leading to increased drug levels of medications and potential drug toxicity (Figure 2). In the case of the cytochrome P-450 system of enzymes, inhibition of drug metabolism is usually rapid (based on drug half-life), with maximal effect occurring when the highest concentrations of the inhibiting drug are reached. Once the inhibitor is stopped, the effect of the inhibitor will typically dissipate after 3 to 5 half-lives.

Pharmacokinetic Induction

Drugs that induce enzymes (inducers) cause an increase in the clearance of drugs metabolized by the same enzyme, leading to decreased concentrations of the other drug(s) (Figure 3). The time to onset of induction is longer than the time for onset of inhibition and is based on the half-life of the inducing drug and the time required for new enzyme synthesis. As a general rule, the maximal effect of enzyme induction is apparent in 7 to 10 days, although for drugs with a relatively long half-life, the full effect of induction may take even longer. Upon discontinuation of the inducer, the effects of induction will last at least 3 to 5 half-lives plus the additional time for the induced enzyme to return to pre-induction levels; this will vary, but is likely to be approximately 7 to 10 additional days.

Drug Interactions in HIV Clinical Care

The most commonly encountered drug interactions in the context of HIV clinical care occur between antiretroviral therapies and medications used to manage common comorbidities. The following sections will address interactions between antiretroviral medications and several important therapeutic classes, including acid suppression medications, anticoagulants and antiplatelet agents, cardiac medications, anticonvulsants, medications used in the treatment of mental health and substance use disorders, and medications used in the management of hepatitis C and mycobacterial infections. Drug interactions are manifold and range from mild to severe (and even potentially fatal, requiring FDA labeling to prohibit co-administration). Medical providers who care for persons with HIV infection should always conduct a thorough medication history at each visit regarding the use of all medications, including prescription, over-the-counter, herbal, and recreational drugs, and consider potential interactions before prescribing a new medication. Among the highly potent anchor antiretroviral medications, the integrase strand transfer inhibitors (INSTIs) dolutegravir and raltegravir, have the fewest drug interactions.[4,5] The use of the pharmacologic boosters cobicistat and ritonavir frequently leads to significant drug interactions, since they inhibit CYP3A and other transporters involved with the metabolism of many commonly used medications for general medical care.

Resources for Drug Interactions Involving Antiretroviral Medications

There are several excellent resources available to help guide providers in the management of drug interactions involving antiretroviral medications. The following list of resources include sites with drug interaction tables:

- Department of Health and Human Services (HHS) Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV
- HIV Insite: Database of Antiretroviral Drug Interactions
- University of Liverpool: HIV Drug Interaction Checker
- Northeast/Caribbean AETC Antiretroviral Guides
Acid Suppressive Therapy

Alterations in gastric pH and symptoms of dyspepsia, heartburn, and gastroesophageal reflux (GERD) are common among persons living with HIV, and the medications used to treat these conditions, including antacids, histamine-2 receptor antagonists (H2 blockers), and proton pump inhibitors, can impact the absorption of coadministered antiretroviral medications.[6] Among the antiretroviral agents, atazanavir and rilpivirine are the most vulnerable to pharmacokinetic interactions with acid suppression medications, since both of these agents require an acidic gastric pH for dissolution and absorption.[7,8,9] The INSTIs, which exert their mechanism of action via binding to magnesium in the active site of the HIV integrase enzyme, generally have a lower risk of drug interactions, but are susceptible to drug interaction with divalent and trivalent metal cations, including antacids.[10,11] Medical providers can refer to the dosing recommendations in the drug interaction section of the Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV when coadministering antiretroviral medications and acid suppressors; the following summarizes some of these key recommendations:[2]

Antacids and Buffered Medications

- **Atazanavir**: Co-administration of atazanavir with antacids (or buffered medications) is acceptable as long as atazanavir (alone or boosted with ritonavir or cobicistat) is given at least 2 hours before, or at least 1 hour after the antacid (or buffered medication).
- **Rilpivirine**: Caution should be given with the concomitant use of rilpivirine and antacids. If used together, the antacid should be given at least 4 hours before or 2 hours after the rilpivirine dose.
- **Dolutegravir**: If dolutegravir is used concomitantly with a polyvalent cation acid reducer (sucralfate, cation-containing antacids or laxatives, or buffered medications), dolutegravir should be taken at least 2 hours before or 6 hours after medication that contains the polyvalent cation.
- **Elvitegravir**: Elvitegravir should be separated from antacid therapy by at least 2 hours.
- **Raltegravir**: Raltegravir (400 mg once daily or 1200 mg twice daily) should not be coadministered with any aluminum- or magnesium-containing antacid. Raltegravir 400 mg twice daily can be given with calcium-containing antacids and no dosing separation is required. The raltegravir 1200 mg once daily dose is not recommended with calcium-containing acids.

H2 blockers (H2 antagonists)

- **Atazanavir**: For treatment-naïve patients taking atazanavir 300 mg (boosted with either ritonavir 100 mg or cobicistat 150 mg) and an H2 blocker, the atazanavir plus booster should be taken with food and can be given a the same time or at least 10 hours after taking the H2 blocker. The dose of H2 blocker should not exceed a dose comparable to famotidine 40 mg twice daily. If unboosted atazanavir is used, atazanavir should be taken at least 2 hours before or at least 10 hours after taking an H2 blocker, and the dose should not exceed the equivalent of famotidine 20 mg twice daily; no single dose should exceed a dose comparable to famotidine 20 mg. For antiretroviral treatment-experienced patients taking atazanavir, the H2 blockers can be administered according to the same schedule as for treatment-naïve patients, but the maximum dose of the H2 blocker should not exceed the equivalent of famotidine 20 mg twice daily. If the treatment-experienced patient is also taking tenofovir DF, the atazanavir dose should be increased to 400 mg and given either with ritonavir 100 mg or cobicistat 150 mg. If the patient is protease-inhibitor experienced, they should not take unboosted atazanavir with an H2 blocker.
- **Rilpivirine**: Caution is recommended if using rilpivirine and an H2 blocker. If used together, the H2 blocker should be given at least 12 hours before or at least 4 hours after the dose of rilpivirine.
- **INSTI**: H2 blockers do not affect INSTI drug concentrations and no dose adjustment is necessary.

**Proton Pump Inhibitors**

- **Atazanavir**: In treatment-naïve patients, take atazanavir (alone or boosted with ritonavir or cobicistat) at least 12 hours apart from dose of proton pump inhibitor. When taken with atazanavir, the dose of the proton pump inhibitor should not exceed the equivalent of omeprazole 20 mg daily. Proton pump inhibitors are not recommended for use in patients taking unboosted atazanavir. In treatment-experienced patients taking a proton pump inhibitor, both boosted and unboosted atazanavir should be avoided.

- **Darunavir**: For patients taking ritonavir-boosted darunavir, the omeprazole dose (or omeprazole equivalent dose) should not exceed 40 mg daily.

- **Tipranavir**: The coadministration of proton pump inhibitors and tipranavir is not recommended.

- **Nelfinavir**: The protease inhibitor nelfinavir, while not used commonly in modern antiretroviral regimens, should also be avoided with proton pump inhibitors due to reduced nelfinavir concentrations.

- **Rilpivirine**: Proton pump inhibitors lower plasma rilpivirine levels to unacceptably low levels—omeprazole 20 mg has been shown to lower rilpivirine levels by as much as 40%. Co-administration of rilpivirine or combinations containing rilpivirine with a proton pump inhibitor is contraindicated.

- **INSTIs**: Proton pump inhibitors do not affect INSTI drug concentrations and no dose adjustment is necessary.

**HIV Insite: Database of Antiretroviral Drug Interactions**

- Interactions with Gastrointestinal Secretion and Motility
Oral Anticoagulants and Antiplatelet Therapy

Direct-Acting Oral Anticoagulant Medications

Among the commonly used direct-acting oral anticoagulant medications (DOACs)—apixaban, dabigatran, edoxaban, and rivaroxaban are eliminated either via CYP450 enzymes, P-glycoprotein, or both.\[12\] Therefore, potent cytochrome P-450 enzyme inhibition by protease inhibitors or pharmacologic enhancers (ritonavir or cobicistat) may lead to higher plasma drug concentrations of the DOAC and potentially increase the risk of bleeding.\[12,13\] In contrast, cytochrome P-450 enzyme induction by non-nucleoside reverse transcriptase inhibitors (NNRTIs) may lower the levels of the anticoagulant, which may lead to failure of the anticoagulant to prevent or treat thrombosis.\[12,14\] The Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV recommend avoiding concomitant use of most DOACs with ritonavir- or cobicistat- boosted PIs and with elvitegravir-cobicistat due to potential increases in the DOAC concentrations and potential risk of bleeding.\[13,15\] In general, the use of apixiban, betrixaban, edoxaban and rivaroxaban should be avoided in this setting. In some situations, medical providers may use dabigatran with ritonavir-boosted PI therapy, but the extent of the interaction when combining these medications is not known. Recent data evaluating the use of ritonavir 100 mg with dabigatran given 2 hours prior to ritonavir demonstrated that the dabigatran AUC was reduced by 29%; if these medications are used in combination, the dabigatran should be taken simultaneously with the ritonavir-boosted PI.\[12,13\] In a separate study, the use of dabigatran was evaluated with concurrent use of cobicistat 150 mg and the dabigatran AUC increased more than 2-fold; therefore, atazanavir-cobicistat, darunavir-cobicistat, and elvitegravir-cobicistat should not be used with dabigatran. Although the use of apixiban has not been studied to date with ritonavir or cobicistat containing regimens (including elvitegravir-cobicistat), the Antiretroviral Therapy guidelines state that coadministration is not recommend, but note that if coadministration is necessary, a 50% reduction in apixiban dose is required, with close monitoring for apixiban toxicity.\[13,15\]

Warfarin

Warfarin is metabolized via CYP2C9, and its’ use is complicated by a narrow therapeutic window, significant inter-patient variability, and major drug-drug and drug-food interactions.\[7\] Pharmacokinetic interactions between warfarin and antiretroviral medications are variable and often difficult to predict. Coadministration of PI, NNRTI, or cobicistat containing regimens is likely to alter warfarin levels. Therefore, close monitoring of the international normalized ratio (INR) is recommended whenever warfarin is combined with any of these antiretroviral medication. In addition, upon changing antiretroviral therapy in patients on a stable warfarin regimen, close INR monitoring is warranted. If reversal of warfarin anticoagulation is required, phytonadione (Vitamin K1) may be used. Raltegravir and dolutegravir are not extensively metabolized via CYP450 and thus are unlikely to cause significant drug interactions with warfarin.

Platelet Aggregate Inhibitors

The platelet aggregate inhibitors, such as clopidogrel, prasugrel, and ticagrelor, can interact with either PI or NNRTI antiretroviral medications due to overlapping metabolism via CYP34A and CYP2C19 enzymes.\[12\] These interactions are complex and the net effect can be difficult to predict. For example, PI-mediated inhibition of CYP34A may decrease metabolism of ticagrelor, thereby increasing drug levels, but at the same time, PIs can delay the conversion of prasugrel to its active metabolite, which may reduce the antiplatelet effect of prasugrel. Similarly, NNRTI-mediated inhibition of CYP2C19, particularly by efavirenz or etravirine, blocks the conversion of clopidogrel to its active metabolite, resulting in a decreased antiplatelet drug effect; clopidogrel should be avoided in individuals taking efavirenz or etravirine, but is considered acceptable in combination with rilpivirine or nevirapine.\[12\] The inhibition of CYP2C19 by NNRTIs does not appear to result in clinically relevant interactions with either prasugrel or ticagrelor, so these agents could be used in
patients taking any of the NNRTI medications.[12] These interactions can be difficult to predict and manage, especially in patients who are receiving both PI- and NNRTI-based therapies that interact with each of the medications in this class. An assay that measures platelet activation is available that may help measure the extent to which platelets are inhibited. Expert consultation is recommended.

**HIV Insite: Oral Anticoagulants Antiretroviral Drug Interactions**

- Interactions between Apixaban and Antiretroviral Medications
- Interactions between Dabigatran and Antiretroviral Medications
- Interactions between Rivaroxaban and Antiretroviral Medications
- Interactions between Warfarin and Antiretroviral Medications
- Interactions between Clopidogrel and Antiretroviral Medications
- Interactions between Ticagrelor and Antiretroviral Medications
HMG-CoA Reductase Inhibitors (Statins)

Dyslipidemia is prevalent among persons with chronic HIV infection and has been associated with traditional risk factors, HIV itself, and certain antiretroviral medications. The HMG-CoA reductase inhibitors, more commonly referred to as statins, are frequently used to treat lipid disorders in persons with HIV infection who are taking antiretroviral therapy. Statins have been associated with elevations of hepatic aminotransferase levels, as well as adverse effects on skeletal muscle abnormalities (ranging from mild muscle pain to fatal rhabdomyolysis) and these adverse effects are directly linked to statin concentration.\[16\] The key pharmacokinetic drug interactions between antiretroviral medications and statins occur with the statins that are metabolized through the CYP3A4 pathway (simvastatin, lovastatin, and atorvastatin) when taken concomitantly with the potent CYP3A inhibitors ritonavir or cobicistat.\[16\] Clinically important interactions also occur through induction of the CYP3A4 pathway by certain NNRTI medications, which do not cause adverse effects but can decrease statin efficacy.\[17\] It is important to recognize that antiretroviral medications may contribute independently to higher lipid levels; in most situations, switching to a different antiretroviral regimen with a more favorable lipid profile is preferable to initiating statin therapy as long as the new regimen can be expected to maintain virologic suppression.\[18,19\]

Simvastatin and Lovastatin

The use of simvastatin or lovastatin is contraindicated in patients receiving PI-containing or cobicistat-containing regimens due to significant increases in serum statin levels.\[13\] For example, when twice daily saquinavir (400 mg) boosted with ritonavir (400 mg) was combined with simvastatin, the AUC of simvastatin increased 32-fold (Figure 4).\[20\] As might be expected, the combination of various PIs with simvastatin has been associated with rhabdomyolysis and acute renal failure, and a similar response is expected with the use of lovastatin.\[21,22,23,24\] The use of simvastatin with efavirenz is also not recommended, though for the opposite reason that coadministration of efavirenz with simvastatin results in induction of statin metabolism and decreased lipid reducing effect.\[17\]

Pravastatin

Because pravastatin is not metabolized by CYP3A4, it is considered one of the safest statins for use in combination with antiretroviral medications, with the exception that pravastatin levels increase by about 80% when used concomitantly with darunavir.\[13,25\] Therefore, when combining pravastatin and darunavir, initiating pravastatin therapy at lowest doses is appropriate.

Atorvastatin

Levels of atorvastatin can also be increased by ritonavir-boosted PIs and cobicistat-containing regimens, though the increases in drug levels are not as substantial as seen with simvastatin and lovastatin.\[16\] If atorvastatin is to be used in conjunction with a ritonavir-boosted PI and cobicistat-containing regimen, a low dose (20 mg or less of atorvastatin) should be used as initial therapy, since this dose is likely to provide the lipid-lowering effect equivalent to a dose 3 to 5 times higher if administered without a ritonavir-boosted PI or cobicistat-containing regimen.\[13,16\] Since atorvastatin is considered a more potent statin, this may be preferred to pravastatin in patients with known cardiovascular disease. Medical providers should be cautious not to exceed the recommended dosing of atorvastatin since there are case reports of rhabdomyolysis and acute renal failure associated with protease inhibitors and atorvastatin.\[26,27\] Some NNRTIs (efavirenz and etravirine) may decrease atorvastatin levels, necessitating higher dosing of atorvastatin, but not to exceed the recommended maximum dose.\[14,17,28\]

Rosuvastatin
Rosuvastatin is not a CYP3A4 substrate, but clinically relevant interactions with antiretroviral medications primarily occur through other transporters, specifically with OATP1B1 or BCRP.\[^{29}\] When co-administering rosuvastatin with PIs or cobicistat-containing regimens, rosuvastatin should be initiated at the lowest possible dose, with close observation for evidence of statin toxicity.\[^{30}\] The maximum recommended dose of rosuvastatin in persons taking ritonavir-boosted atazanavir or lopinavir is 10 mg daily.\[^{13}\] No significant effect on rosuvastatin levels is expected with NNRTI therapy; lipid levels should be monitored and rosuvastatin dose adjusted as needed.\[^{14}\]

### Pitavastatin

Recent studies indicate that no significant pharmacokinetic interactions occur between pitavastatin and efavirenz or ritonavir-boosted darunavir; thus pitavastatin may be safely coadministered with PIs and NNRTIs without dose adjustment.\[^{13,31,32}\] Furthermore, the efficacy of pitavastatin 4 mg daily was found to be superior to pravastatin 40 mg in reduction of LDL and other atherogenic lipid parameters.\[^{33}\] The large, international REPRIEVE study is currently evaluating whether pitavastatin is effective in the prevention of cardiovascular events in persons with HIV infection.\[^{34}\] There are inadequate data regarding interactions between pitavastatin and the pharmacologic booster cobicistat; however, based upon data with ritonavir boosted PIs it is unlikely to interact and should be considered safe to use in this setting.

### HIV Insite: Lipid-Lowering Agents and Antiretroviral Drug Interactions

- [Interactions between Lipid-Lowering Agents and Antiretrovirals](#)
Cardiovascular Medications

Hypertension affects approximately 25 to 35% of persons living with HIV infection.\cite{35,36,37,38,39} Although data are conflicting regarding the association of HIV, antiretroviral therapy, and hypertension,\cite{38,40,41,42} it is clear that important pharmacokinetic interactions exist between antiretroviral therapy and a number of cardiac medications used for control of blood pressure, rhythm, and rate.

Calcium Channel Blockers

Inhibition of the CYP4A, CYP2DG, and/or P-glycoprotein enzyme pathways by protease inhibitors and pharmacologic boosters (ritonavir and cobicistat) increases drug concentrations of calcium channel blockers.\cite{43} These cardiac medications can generally be used, but with caution, starting with low doses, adjusting the dose for appropriate clinical response, and monitoring with electrocardiograms. For patients taking boosted or unboosted atazanavir, the dose of diltiazem (a non-dihydropyridine calcium channel blocker) should be decreased by 50% since atazanavir significantly increases the AUC of diltiazem.\cite{13} Interactions between calcium channel blockers and NNRTIs are also possible, with efavirenz and nevirapine leading to decreased calcium channel blocker levels through induction of CYP34A enzymes; titration of the calcium channel blocker to achieve clinical efficacy is recommended.

Beta-Blockers

As with the calcium channel blockers, CYP enzyme inhibition by protease inhibitors and pharmacologic boosters (ritonavir and cobicistat), can be expected to increase levels of beta-blockers. It may be prudent to select a beta-blocker that is not metabolized through a CYP pathway (atenolol, labetalol, nadolol, or sotalol) in order to avoid these drug interactions. NNRTIs have no significant impact on beta-blocker levels since beta-blockers are metabolized primarily by CYP2D6 and NNRTIs are inducers of CYP34A.\cite{44}

Diuretics, ACE Inhibitors, and Angiotensin II Receptor Blockers

Diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin II receptor blockers (ARBs) are not involved in significant CYP450-mediated interactions and thus have low potential for pharmacokinetic drug interactions with any of the antiretroviral therapies.\cite{44}

Antiarrhythmics

Drug levels of antiarrhythmic medication, such as amiodarone, dofetilide, and flecainide, can increase with concomitant antiretroviral therapy that contains a PI or pharmacologic booster (ritonavir or cobicistat). The NNRTIs do not appear to impact antiarrhythmic therapy to a clinically significant degree. There are generally no significant class-wide interactions between INSTIs and cardiac medications, with one exception—dolutegravir increases the serum drug concentration of dofetilide through inhibition of the renal cation transporter OCT2, which is primarily responsible for elimination of dofetilide.\cite{45} Dolutegravir and dofetilide should not be coadministered.

Digoxin

Drug-induced inhibition of the efflux pump, P-glycoprotein, by ritonavir and other protease inhibitors can increase digoxin to toxic levels; cobicistat is also an inhibitor of P-glycoprotein, but no reports of interaction with digoxin have been reported.\cite{46,47} Nevertheless, therapeutic drug monitoring of digoxin levels is recommended when any of these antiretroviral therapies are coadministered. No special monitoring is needed for concomitant NNRTI and digoxin therapy, since they have minimal effect on P-glycoprotein.
HIV Insite: Database of Antiretroviral Drug Interactions

- Interactions between Cardiovascular Medications and Antiretrovirals
Anticonvulsants

Significant pharmacokinetic drug interactions occur with concomitant use of anticonvulsants and antiretroviral medications. Several anticonvulsant medications significantly lower antiretroviral drug levels, potentially leading to virologic failure. This is particularly a concern with older anticonvulsants, particularly phenobarbital, phenytoin, carbamazepine, and oxcarbazepine, since these medications act as potent inducers of CYP enzymes; these older anticonvulsants can lower levels of PIs, NNRTIs, INSTIs, and also the newer coformulated medications that contain tenofovir alafenamide. Due to these potentially significant drug interactions, many antiretroviral-anticonvulsant combinations are contraindicated. Accordingly, prior to using concomitant therapy with an older anticonvulsant and antiretroviral medications, careful review of interactions and recommendations should be performed.[2] Among possible options for use of an anticonvulsant medication in persons on antiretroviral therapy, levetiracetam is considered the antiepileptic of choice due to its broad spectrum of activity, minimal drug interactions (since it is not metabolized via any CYP450 pathway), and low side effect profile.[48] For patients who are not candidates for levetiracetam therapy and require a different anticonvulsant, raltegravir does not demonstrate any significant drug interactions with anticonvulsants and should be used as long as virologic resistance (proven or predicted) does not preclude its use.[48]

HIV Insite: Database of Antiretroviral Drug Interactions

- Interactions between Antiepileptics and Antiretrovirals
Medications Used to Treat Mental Disorders

In the United States, persons living with HIV have a high prevalence of coexisting mental health disorders.[49] In the process of managing these coexisting conditions, clinicians caring for persons living with HIV often need to manage complex drug interactions between antiretroviral medications and medications used to treat depression, anxiety, or other mood disorders.[50] Several of the key interactions are discussed below.

Antipsychotics

Many antipsychotic medications are metabolized by CYP450, in particular CYP3A4, and thus levels of antipsychotic medications may increase when used concurrently with cobicistat- or ritonavir-containing regimens. Several case reports have highlighted clinically significant adverse effects resulting from combining quetiapine and ritonavir-boosted PI regimens. Thus, when initiating quetiapine in a patient already taking any PI, including ritonavir or cobicistat as a booster, the lowest possible dose of quetiapine should be used; if a patient is taking quetiapine and is starting antiretroviral therapy with a regimen that includes PIs, ritonavir, or cobicistat, the quetiapine dose should be reduced to approximately one-sixth of the current dose to avoid toxicity.[13, 51, 52] Similar interactions may occur when cobicistat- or ritonavir-containing antiretroviral regimens are combined with older antipsychotics, such as perphenazine and thioridazine, as well as with some of the newer agents, such as risperidone and lurasidone. Recent label updates to cobicistat and protease inhibitors demonstrate concern with concomitant use of these agents with lurasidone. Thus, medical providers should exert caution and carefully evaluate potential drug interactions when using antipsychotics and antiretroviral regimens that contain a PI, ritonavir, or cobicistat, especially when making changes to either regimen. The NNRTI class, due to induction of CYP enzymes, primarily with CYP34A and CYP2D6, decrease antipsychotic drug concentrations, so caution is advised with coadministration of these agents.

Selective Serotonin Reuptake Inhibitors (SSRIs)

Similar to the interactions noted between antiretroviral medications and antipsychotics, selective serotonin reuptake inhibitors (SSRIs) may also interact with pharmacologic boosters (cobicistat and ritonavir), PIs, and NNRTIs. In general, most SSRIs are safe with concurrent antiretroviral therapy; nonetheless, the effects of coadministration are variable and treatment should be titrated to response. For example, lopinavir-ritonavir raises paroxetine levels, darunavir given with ritonavir lowers paroxetine levels, and efavirenz does not significantly impact paroxetine levels.[13, 53] Raltegravir does not appear to affect SSRI levels; dolutegravir has not been adequately studied, but it is not likely to affect SSRI levels.

Tricyclic Antidepressants (TCAs)

Protease inhibitors, ritonavir, and cobicistat have also been shown to increase levels of tricyclic antidepressants and trazodone; due to toxicity risk, trazodone is contraindicated in patients taking ritonavir-boosted saquinavir.[13, 50, 53] When using TCAs or trazodone concurrently with other protease inhibitors or cobicistat, the lowest possible starting dose of the TCA or trazodone should be used and then titrated for clinical effect.[13]

Benzodiazepines

Benzodiazepines are commonly used for acute anxiety and are extensively used in anesthesia as sedative hypnotics. The use of benzodiazepines in the setting of antiretroviral therapy is complicated because benzodiazepines are metabolized via several different pathways and thus drug interactions are not always predictable. In patients taking a PI, ritonavir, cobicistat, or an NNRTI, the safest benzodiazepines to use are those that are not metabolized via CYP-450; these include lorazepam,
oxazepam and temazepam.[2,13] Drug concentrations of other benzodiazepines such as alprazolam, clonazepam, and diazepam are likely to be increased by PIs, ritonavir, cobicistat, and NNRTIs so should not be used concurrently, with the exception that clonazepam appears to be safe in combination with NNRTIs. Chronic administration of midazolam (oral or parenteral) is contraindicated in patients taking a PI, ritonavir, cobicistat, or a NNRTI, but midazolam can be used with caution in these patients when given parenterally as a single-dose, pre-procedural medication.[2,13]

HIV Insite: Database of Antiretroviral Drug Interactions

- Interactions between Antidepressants and Antiretrovirals
- Interactions between Antipsychotics and Antiretrovirals
- Interactions between Sedative Hypnotics and Antiretrovirals
Medications Used to Treat Opioid Dependence

A substantial proportion of persons living with HIV infection have an opioid use disorder. Thus, HIV clinical care providers should become familiar with the pharmacologic interactions between antiretroviral medications and medications used for the treatment of opioid use disorder.[54] This has become more complex with the introduction of several new antiretroviral and antiviral therapies for HIV and HCV, respectively, and with the increasing use of buprenorphine-based therapies to treat substance use disorders. Key interactions between antiretroviral therapies, methadone, buprenorphine, and buprenorphine-naloxone will be addressed here; interactions involving direct-acting antivirals to treat hepatitis C virus will be addressed in the next section.

Methadone

- **Protease Inhibitors**: Although PIs generally inhibit CYP enzymes and increase plasma concentrations of drugs metabolized through CYP pathways, all ritonavir-boosted protease inhibitors have the potential to reduce methadone exposure, possibly through induction of CYP2B6 or through other mechanisms; therefore, methadone dose adjustment may be necessary to avoid precipitating opiate withdrawal.[55,56]

- **Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)**: As a result of potent CYP34A induction by select NNRTIs, an increased methadone dose is often necessary in patients who are taking efavirenz or nevirapine; no methadone dose adjustment is required for concurrent therapy with either etravirine or rilpivirine.[57,58,59,60]

- **Integrase Strand Transfer Inhibitors (INSTIs)**: There are no significant pharmacokinetic interactions between methadone and raltegravir, dolutegravir, or cobicistat-boosted elvitegravir.[54,59,61]

Buprenorphine and Buprenorphine-naloxone

- **Protease Inhibitors (PIs)**: Buprenorphine (and buprenorphine-naloxone) are metabolized by CYP34A and also undergo glucuronidation by UGT1A1. The drug interactions with PIs are variable. No buprenorphine or buprenorphine-naloxone dosage adjustment is necessary in patients taking darunavir-ritonavir, but lower doses of buprenorphine may be needed in patients taking atazanavir plus ritonavir (since atazanavir inhibits both CYP34A and UGT1A1) or any cobicistat-boosted PI.[54,55,62] Buprenorphine should not be coadministered with unboosted atazanavir due to the risk of subtherapeutic atazanavir levels.[13,54]

- **Nonnucleoside Reverse Transcriptase Inhibitors (NNRTIs)**: No dose adjustments are necessary when buprenorphine or buprenorphine-naloxone is used concurrently with NNRTIs, but efavirenz has been demonstrated to lower buprenorphine levels so monitoring for withdrawal is recommended.[59]

- **Integrase Strand Transfer Inhibitors (INSTIs)**: Raltegravir and dolutegravir do not appear to have any clinically significant interaction with buprenorphine or buprenorphine-naloxone.[59] Although cobicistat-boosted elvitegravir raises buprenorphine levels, no dose adjustment is necessary.[54]

HIV Insite: Database of Antiretroviral Drug Interactions

- Interactions between Methadone and Antiretrovirals
- Interactions between Buprenorphine and Antiretrovirals
Corticosteroids

The risk of significant pharmacokinetic drug interactions between antiretroviral therapy and corticosteroid treatment was first identified in patients taking the inhaled or nasal preparation of the corticosteroid, fluticasone. Multiple subsequent reports have documented iatrogenic severe adrenal suppression and Cushing’s syndrome in patients (children and adults) concomitantly receiving a corticosteroid and a ritonavir-boosted antiretroviral regimen.\[63,64,65,66,67\] This complication results from ritonavir-mediated inhibition of CYP3A4 enzymes, which increases the levels of certain corticosteroids that are also metabolized via CYP3A enzymes. Most cases of ritonavir-associated adrenal suppression have involved fluticasone, but other corticosteroids, such as budesonide and mometasone, were subsequently also identified with this unfavorable interaction.\[68\] Most of these cases have involved oral or inhaled corticosteroids, but recent reports have also described this complication with corticosteroids delivered through topical and injectable ocular preparations, as well as following intrabursal, intraarticular, and epidural injections.\[69,70,71,72,73\] A similar drug interaction between cobicistat, also a potent inhibitor of CYP3A4, and fluticasone has been documented and it is expected that cobicistat will have similar effects as ritonavir on the metabolism of other steroids.\[74\]

Use of Corticosteroids Not Metabolized by CYP3A

To mitigate these drug interactions in patients taking ritonavir or cobicistat, clinicians should consider using a corticosteroid other than fluticasone or budesonide, such as inhaled or nasal beclomethasone (which is not metabolized by the CYP3A4 enzyme and, thus, does not produce the same interaction).\[13,75\] Until further pharmacokinetic research is completed with other inhaled steroids, caution is recommended when any inhaled or nasal steroid other than beclomethasone is used concomitantly with ritonavir or cobicistat. Injectable forms of methylprednisolone, prednisolone, and triamcinolone should also be avoided in patients taking antiretroviral regimens containing PIs, ritonavir, or cobicistat. As a consequence of reciprocal corticosteroid induction of the CYP3A4 enzyme pathway, dexamethasone may decrease levels of NNRTIs and compromise virologic efficacy; rilpivirine is most affected by this interaction, so more than a single dose of dexamethasone is contraindicated in patients taking rilpivirine.\[76\]

HIV Insite: Database of Antiretroviral Drug Interactions

- Interactions between Antiinflammatories and Antiretrovirals
Direct-Acting Antiviral Agents for Treatment of Hepatitis C

Most persons coinfected with HCV and HIV are taking multi-drug antiretroviral therapy, which may pose a problem with drug interactions when initiating therapy with HCV medications.\[77,78,79\]

There are three major classes of direct-acting antiviral medications used to treat hepatitis C: NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors (Figure 5).\[80,81\] The following provides key summary points for drug interaction between HCV direct-acting antiviral medication regimens and HIV antiretroviral therapy. Although ribavirin is not considered a direct-acting antiviral medication, information is included on ribavirin since it is used in some regimen combinations to treat HCV and it has the potential to cause adverse effects due to drug interactions with HIV antiretroviral medications.

- **Daclatasvir**: The NS5A inhibitor daclatasvir is a substrate of CYP3A. When daclatasvir is given with a CYP3A inhibitor, the levels of daclatasvir can increase, particularly with strong inhibitors of CYP3A. The dose of daclatasvir should therefore be reduced to 30 mg when used with either ritonavir-boosted atazanavir or lopinavir-ritonavir. In contrast, when used with efavirenz, a CYP3A inducer, the dose of daclatasvir should be increased to 90 mg daily.
- **Elbasvir-Grazoprevir**: The NS5A inhibitor elbasvir and the HCV NS3A/4A protease inhibitor grazoprevir are substrates for CYP3A and P-gp. Thus, use of strong CYP3A inducers or inhibitors can impact levels of elbasvir and grazoprevir. Elbasvir-grazoprevir is contraindicated for use with efavirenz due to marked reductions in elbasvir and grazoprevir; the coadministration of elbasvir-grazoprevir with etravirine or nevirapine is not recommended due to expected reductions in elbasvir and grazoprevir levels. The coadministration of elbasvir-grazoprevir is contraindicated with protease inhibitors (unboosted and boosted with cobicistat or ritonavir), elvitegravir-cobicistat-tenofovir DF-emtricitabine, or elvitegravir-cobicistat-tenofovir alafenamide-emtricitabine due to the risk of hepatotoxicity from increased elbasvir and grazoprevir levels.
- **Glecaprevir-Pibrentasvir**: The medications glecaprevir (NS3/4A protease inhibitor) and pibrentasvir (NS5A inhibitors) both have the potential to inhibit P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and organic anion transporting polypeptide (OATP) 1B1/3. In addition, both glecaprevir and pibrentasvir are weak inhibitors of CYP3A4, CYP1A2 and uridine glucuronosyltransferase (UGT) 1A1. Coadministration of glecaprevir-pibrentasvir with atazanavir (with or without ritonavir or cobicistat) is contraindicated because of increased glecaprevir and pibrentasvir levels. In addition, although not contraindicated, it is not recommended to use glecaprevir-pibrentasvir with darunavir-cobicistat, darunavir boosted with ritonavir, lopinavir-ritonavir, or tipranavir boosted with ritonavir due to potential increases in glecaprevir and pibrentasvir levels. Coadministration of glecaprevir-pibrentasvir with either efavirenz, nevirapine, or etravirine is not recommended because of substantial reductions in the levels of glecaprevir and pibrentasvir.
- **Ledipasvir-Sofosbuvir**: The NS5A inhibitor ledipasvir is not metabolized by the cytochrome p450 system, but is a substrate of p-glycoprotein. Ledipasvir increases tenofovir levels 1.3- to 2.6-fold when concomitantly given with either rilpivirine or efavirenz. Although ledipasvir administered concomitantly with tenofovir and an HIV protease inhibitor has not been studied, there is concern that tenofovir levels may increase substantially with this combination. Because of this concern and lack of data, the use of ledipasvir with ritonavir-boosted (or cobicistat-boosted) HIV protease inhibitors should, if possible, be avoided. If coadministration is needed, then close monitoring for tenofovir DF-associated toxicity should occur. Coadministration of ledipasvir-sofosbuvir with cobicistat-elvitegravir-tenofovir DF-emtricitabine or tipranavir is not recommended. Ledipasvir-sofosbuvir should not be used in patients with HIV infection if they are taking tenofovir DF and the baseline creatinine clearance is less than 60 mL/min.
- **Ombitasvir-Paritaprevir-Ritonavir**: The major concern for drug interaction with this regimen is the significant p450 inhibition generated by ritonavir. This combination regimen should not be used with efavirenz, rilpivirine, darunavir, or lopinavir-ritonavir.
- **Dasabuvir-Ombitasvir-Paritaprevir-Ritonavir**: The major concern for drug interaction
with this regimen is the significant p450 inhibition generated by ritonavir. This combination regimen should not be used with efavirenz, rilpivirine, darunavir, or lopinavir-ritonavir.

- **Ribavirin**: Significant and serious toxic drug interactions can occur with the simultaneous use of ribavirin and certain HIV nucleoside reverse transcriptase inhibitors. The use of ribavirin with didanosine is strictly contraindicated due to a marked increase in intracellular didanosine levels, which may cause hepatic failure, pancreatitis, and lactic acidosis. This can also occur with stavudine or zidovudine. Thus, simultaneous use of ribavirin with either didanosine, stavudine, or zidovudine should be avoided. Concurrent use of ribavirin and zidovudine should also be avoided because of additive hematologic toxicity and increased risk of severe anemia with this combination.

- **Simeprevir**: This NS34A HCV protease inhibitor has complex interactions with antiretroviral medications because it is a substrate and an inhibitor of CYP3A4 and p-glycoprotein. In addition, simeprevir inhibits the OATP1B1/3 drug transporter. Simeprevir should not be used concomitantly with any of the following medications: efavirenz, etravirine, nevirapine, any HIV protease inhibitors, or any regimen that contains cobicistat. Simeprevir can be used with reverse transcriptase inhibitors and with rilpivirine, dolutegravir, and raltegravir; if used with maraviroc, the dose of maraviroc should be decreased to 150 mg twice daily.

- **Sofosbuvir**: This NS5B polymerase inhibitor is rapidly converted to a dominant circulating metabolite (GS-331007). Sofosbuvir is not metabolized by the cytochrome p450 system, but is a substrate of p-glycoprotein. The only significant interaction with antiretroviral medications occurs with the p-glycoprotein inducer tipranavir, which may decrease levels of sofosbuvir and the GS-331007 metabolite. Accordingly sofosbuvir should not be used concomitantly with tipranavir, but it can be used with all other antiretrovirals.

- **Velpatasvir**: The NS5A inhibitor velpatasvir is metabolized predominantly by CYP2B6, CYP2C8, and CYP3A4 enzymes. The NNRTI medication efavirenz significantly lowers velpatasvir levels and efavirenz should not be administered concurrently with velpatasvir. Similarly, ritonavir-boosted tipranavir lowers velpatasvir levels coadministration of these medications should be avoided.

**Northeast/Caribbean AETC Drug Interaction Guide**

- [NECA AETC Clinical Support Tools](#)

**Antiretroviral Therapy Guidelines**

- [Concomitant Use of Selected Antiretroviral Drugs and Hepatitis C Virus Direct-Acting Antiviral Drugs for Treatment of HCV in Adults with HIV](#)
Antimycobacterial Medications

The interaction of antiretroviral therapy and medications used in treatment regimens for mycobacterial infections (including active and latent mycobacterial tuberculosis as well as *Mycobacterium avium* complex, or MAC) is well recognized. Rifampin significantly reduces the levels of protease inhibitors, NNRTIs, and INSTIs; the only acceptable antiretroviral anchor drugs that are acceptable for use with rifampin are efavirenz and raltegravir; even when using these medications, adjustments are necessary, including close monitoring of efavirenz (possibly to include therapeutic drug monitoring to ensure adequate efavirenz levels) and doubling the dose of raltegravir from 400 mg twice daily to 800 mg twice daily. Among the NRTIs, tenofovir alafenamide is not recommended in combination with rifampin due to the induction effect of rifampin on P-glycoprotein.[82] In some antiretroviral regimens, rifabutin can be used as an alternative to rifampin, with careful dose adjustments as needed. For example, while receiving a ritonavir-boosted PI, a patient with tuberculosis or another mycobacterial infection can take rifabutin at a reduced dosage of 150 mg daily or 300 mg three times weekly. Patients taking nevirapine or etravirine (without a ritonavir-boosted PI) can use rifabutin without dose adjustment; patients taking efavirenz will require higher doses of rifabutin, and patients taking rilpivirine will require a doubling of the rilpivirine dose to 50 mg daily.[14, 84] Rifabutin can be safely coadministered to patients taking raltegravir or dolutegravir without any dose adjustments.[15] Providers should also be aware that rifabutin should not be used concurrently with tenofovir alafenamide, since tenofovir levels can be reduced significantly. Clarithromycin, which is another commonly used antimycobacterial agent, should be avoided with most antiretroviral medications, with the exception of raltegravir and dolutegravir; clarithromycin can also be used with cobicistat-boosted elvitegravir as long as the clarithromycin dose is reduced by 50% and renal function is not impaired.[15] For treatment of *Mycobacterial avium* complex (MAC) infections, azithromycin can typically be substituted for clarithromycin without a loss of efficacy.[85, 86]

HIV Insite: Database of Antiretroviral Drug Interactions

- [Interactions between Antibiotics (including Antimycobacterials) and Antiretrovirals](#)
- [Interactions with Azithromycin and Antiretrovirals](#)
- [Interactions with Clarithromycin and Antiretrovirals](#)
- [Interactions with Isoniazid and Antiretrovirals](#)
- [Interactions with Rifabutin and Antiretrovirals](#)
- [Interactions with Rifampin and Antiretrovirals](#)
- [Interactions with Rifapentine and Antiretrovirals](#)
Phosphodiesterase type 5 (PDE-5) inhibitors are frequently prescribed in men living with HIV for symptoms of erectile dysfunction; pharmacokinetic interactions between antiretroviral therapies and the PDE-5 inhibitors—avanafil, sildenafil, tadalafil, and vardenafil—are well recognized.\cite{87,88} Protease inhibitors and pharmacologic boosters (ritonavir and cobicistat) generally increase the levels of PDE-5 inhibitor medications, which can result in priapism, hypotension, and other adverse effects. In contrast, etravirine and efavirenz lower levels of PDE-5 levels and may necessitate dose increases for the PDE-5 inhibitors sildenafil, tadalafil, and vardenafil; rilpivirine has been studied with sildenafil and tadalafil, and no dose adjustment appears to be necessary with either combination.\cite{8,87,88,89,90} Due to lack of data, coadministration of antiretroviral therapies from any class and avanafil is not recommended. Before treating men with HIV infection with a PDE-5 inhibitor, medical providers should consider evaluation for testosterone deficiency, since high rates of hypogonadism have been reported across many studies of men with HIV infection.\cite{90,91} Both the 2013 HIV primary care guidelines and the Endocrine Society Clinical Practice Guidelines recommend testing for testosterone deficiency in adult men with HIV infection who have decreased libido, erectile dysfunction, or other signs of androgen deficiency; if testosterone therapy is warranted and symptoms of sexual dysfunction resolve with testosterone therapy, treatment with a PDE-5 inhibitor is not warranted.\cite{92,93}

**HIV Insite: PDE-5 and Antiretroviral Drug Interactions**

- Interactions with Avanafil and Antiretrovirals
- Interactions with Sildenafil and Antiretrovirals
- Interactions with Tadalafil and Antiretrovirals
- Interactions with Vardenafil and Antiretrovirals
Miscellaneous Interactions

The use of metformin with concurrent dolutegravir therapy results in a roughly 2-fold increase in metformin levels, likely due to the inhibition of organic cation transporter 2 (OCT2) by dolutegravir.[94,95] Providers should use caution with this combination and limit the metformin dose to no more than 1 gram per day).[15] None of the other INSTIs, or other classes of antiretrovirals, have demonstrated a significant drug interaction with metformin.

HIV Insite: Metformin and Antiretroviral Drug Interactions

- Interactions between Metformin and Antiretrovirals
Summary Points

- Effective, antiretroviral therapy depends on attaining a therapeutic serum drug concentration that maximizes efficacy and minimizes toxicity.
- Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the antiretroviral and/or the interacting drugs.
- The most common mechanisms involve absorption or interactions mediated by the CYP and UGT1A1 enzymes, which can increase or decrease serum drug levels.
- Regimens containing protease inhibitors and/or cobicistat generally confer the greatest risk of drug interactions, whereas regimens containing integrase inhibitors (without cobicistat) are generally the “cleanest” and confer the lowest risk of drug interactions.
- Ritonavir and cobicistat are both pharmacologic enhancers (boosters) that are potent inhibitors of CYP3A4; however, they may have different effects on other CYP and UGT enzymes or other transporters so should not be considered interchangeable. Cobicistat has also been less studied.
- Any changes to a drug regimen require careful consideration of potential drug interactions.
- Excellent online resources are available to help clinicians manage drug interactions.
Citations


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Figures

Figure 1 First-Pass Metabolism after Oral Administration of a Drug and Its Interaction with Grapefruit Juice

Figure legend from article: CYP3A enzymes (e.g., CYP3A4) present in enterocytes of the intestinal epithelium extensively metabolize felodipine during its absorption, and on average only 30 percent of the administered dose enters the portal vein (solid line). Subsequently, CYP3A enzymes in the liver further metabolize the drug so that only 15 percent of the dose is bioavailable and finally reaches the systemic circulation and is able to exert its effects. Grapefruit juice selectively inhibits CYP3A in the enterocyte, with the net result being an increase in the oral bioavailability of felodipine by a factor of three, denoted by the asterisks and the dashed lines.

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Figure 2 CYP 450 Inhibition

Source: Illustration by John J. Faragon, PharmD
CYP 450 Induction

Source: Illustration by John J. Faragon, PharmD
Figure 4 Ritonavir-Boosted Saquinavir Interactions with Statins

Figure 5 Classes of Direct-Acting Antiviral Medications Used to Treat HCV

Note that among these direct-acting antiviral medications, boceprevir and telaprevir are no longer manufactured in the United States.
<table>
<thead>
<tr>
<th>Interaction</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorption</td>
<td>Concurrent therapy or food ingestion results in increase or decrease in drug absorption, thereby increasing or decreasing bioavailability.</td>
</tr>
<tr>
<td>Distribution</td>
<td>Concurrent therapy leads to protein binding displacement, altering the activity of either drug.</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Therapy induces or inhibits CYP450 enzymes, thereby increasing or decreasing drug concentration.</td>
</tr>
<tr>
<td>Excretion</td>
<td>Concurrent therapy results in enhanced or decreased renal excretion of drug.</td>
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