Drug Interactions with Antiretroviral Medications

Successful antiretroviral therapy depends on attaining a therapeutic drug concentration that maximizes efficacy and minimizes toxicity. Therefore, understanding drug interactions is important for clinicians in order to provide effective and safe antiretroviral therapy. Drug interactions can be classified into one of two general categories: those that alter pharmacodynamics (what medications do to the body) or those that alter pharmacokinetics (what the body does to medications).

- **Pharmacodynamics**: 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.

- **Pharmacokinetics**: Pharmacokinetics refers to the absorption, distribution, metabolism, and excretion of drugs in the body, which is often influenced by a variety of biological, physiological, and chemical factors. 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. Pharmacokinetic interactions can occur between concomitant use of antiretroviral and other medications during the absorption, metabolism, or elimination phases.

<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>
</tbody>
</table>
Types of Pharmacokinetic Interactions

This Topic Review will primarily focus on pharmacokinetic interactions that involve antiretroviral medications. Pharmacokinetic interactions can occur between concomitant use of antiretroviral and other medications during the absorption, metabolism, or elimination phases. 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.[1,2,3] There are many cytochrome P-450 proteins, but the most important for drug metabolism belong to the CYP1, CYP2, or CYP3 families.[3] Overall, the CYP3A enzyme has the greatest impact on drug metabolism of antiretroviral medications; this enzyme is abundant in both enterocytes of the small intestinal epithelium and hepatocytes (Figure 1).[3] Other enzymes in the cytochrome P-450 family, such as CYP1A2, 2C19, and 2D6, also play a key role. The uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzyme is an important mediator of pharmacokinetic interactions related to the metabolism of the integrase strand transfer inhibitors (INSTIs). 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 as 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 to 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. Interactions between antiretroviral medication and oral contraceptives can be found in the lesson HIV in Women. Drug interactions range from mild to severe (and even potentially fatal, requiring FDA labeling to prohibit coadministration). Medical providers who care for persons with HIV should always conduct a thorough medication history at each visit including prescription, over-the-counter, herbal, and recreational drugs, and consider potential interactions before prescribing any new medication. The highly potent INSTI anchor antiretroviral medications bictegravir and dolutegravir have few drug interactions.[4,5] In contrast, the pharmacologic boosters cobicistat and ritonavir frequently cause significant drug interactions, since they inhibit CYP3A and other transporters.
involved with the metabolism of many commonly used medications for general medical care. Long-acting injectable antiretrovirals, such as intramuscular cabotegravir and rilpivirine and subcutaneous lenacapavir, have drug-drug interactions that require special consideration, given the long half-lives of these drugs; clinicians should note that there exists potential for ongoing interactions for months after the last injection drugs are discontinued.

Resources for Drug Interactions Involving Antiretroviral Medications

For clinicians, it is impossible to know or memorize all of the potential drug interactions that can occur in people with HIV who are taking antiretroviral medications. Therefore, we strongly recommend utilizing drug interaction resources whenever a new medication is started in a person receiving antiretroviral therapy, as well as when starting antiretroviral therapy in a person who is already taking one or more medications. It is beyond the scope of this lesson to address all drug interactions that can occur with antiretroviral medications. For this reason, this lesson will highlight a number of clinically significant drug interactions to enhance clinician awareness of these interactions. The following list consists of (1) a series of antiretroviral medication drug interaction tables in the Adult and Adolescent ART Guidelines, and (2) the University of Liverpool HIV Drug Interaction checker, which is an excellent resource that addresses a broad array of drug interactions.

- **Adult and Adolescent ARV Guidelines Drug-Drug Interactions (Overview)**
  - **Protease Inhibitor (PI) Drug Interactions**
  - **Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) Drug Interactions**
  - **Nucleoside Reverse Transcriptase Inhibitor (NRTI) Drug Interactions**
  - **Integrase Strand Transfer Inhibitor (INSTI) Drug Interactions**
  - **CCR5 Antagonist Drug Interactions**
  - **HIV-1 gp120-Directed Attachment Inhibitors**
  - **Capsid Inhibitor Drug Interactions**
  - **Interactions between PIs and NNRTIs**
  - **Interactions between INSTIs and NNRTI or PI**
- **University of Liverpool: HIV Drug Interaction Checker**
Acid Suppressive Therapy

Medications used to treat dyspepsia, heartburn, and gastroesophageal reflux (GERD), including histamine-2 receptor antagonists (H2 blockers), and proton pump inhibitors, can alter gastric pH and potentially impact the absorption of certain antiretroviral medications.[6] Among the antiretroviral agents, atazanavir and rilpivirine are the most vulnerable to pharmacokinetic interactions with acid suppressing medications, since both of these agents require an acidic gastric pH for dissolution and absorption.[7,8,9] Unlike rilpivirine, the newer NNRTI doravirine is not affected by gastric pH or by acid suppressive therapy. In addition, other medications used to treat gastrointestinal symptoms, such as antacids and sucralfate, may contain polyvalent cations that can bind to and chelate certain integrase strand transfer inhibitors (INSTIs). The INSTIs exert their action via binding to magnesium in the active site of the HIV integrase enzyme, but if a polyvalent cation, including a divalent or trivalent metal cations, chelates with the INSTI, it can interfere with the INST binding to the integrase enzyme.[10,11] Medical providers can refer to the dosing recommendations in the drug interaction section of the Adult and Adolescent ART Guidelines when coadministering antiretroviral medications with antacids or acid-suppressive medications; the following summarizes some of these key recommendations:[2]

Antacids and Buffered Medications

- **Atazanavir**: Coadministration 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).
- **Bictegravir**: If bictegravir (as a component of bictegravir-tenofovir alafenamide-emtricitabine) is used concomitantly with an aluminum- or magnesium-containing antacid, the bictegravir should be administered at least 2 hours before or 6 hours after the aluminum- or magnesium-containing antacid. Bictegravir can be taken with a calcium-containing antacid if both are taken together with food. Under fasting conditions, bictegravir should be taken at least 2 hours before or 6 hours after taking a calcium-containing antacid.
- **Cabotegravir**: This medication is available both as an oral medication and a long-acting injectable. Antacids that contain polyvalent cations should be taken 2 hours before or 4 hours after oral cabotegravir (which is sometimes used for an oral lead-in period before transitioning to the injectable formulation). Injectable cabotegravir is not affected by antacids that contain polyvalent cations.
- **Dolutegravir**: If dolutegravir is used concomitantly with an aluminum- or magnesium-containing antacid, sucralfate, or a laxative, dolutegravir should be administered at least 2 hours before or 6 hours after these medications. Dolutegravir can be taken with a calcium-containing antacid if they are taken together with food; under fasting conditions, dolutegravir should be taken at least 2 hours before or 6 hours after taking a calcium-containing antacid.
- **Elvitegravir**: Elvitegravir should be separated from antacid therapy (with any medication or supplement that contains polyvalent cations, such as magnesium, aluminum, or calcium) by at least 2 hours.
- **Raltegravir**: Raltegravir (400 mg twice daily or 1200 mg once 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 antacids.
- **Rilpivirine**: Caution should be given with the concomitant use of oral rilpivirine and antacids. If used together, the oral rilpivirine should be given at least 4 hours before or 2 hours after the antacid. There are no interactions with long-acting injectable rilpivirine and antacids.

H2 blockers (H2 Receptor 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 at 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. 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 with ritonavir
100 mg or cobicistat 150 mg. Unboosted atazanavir should not be coadministered with an H2 blocker.

- **INSTIs**: H2 blockers do not affect INSTI drug concentrations and no dose adjustment is necessary.
- **Rilpivirine**: Caution is recommended if using oral 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 oral rilpivirine.
  There are no interactions with long-acting injectable rilpivirine and H2 blockers.

### Proton Pump Inhibitors

- **Atazanavir**: For treatment-naïve patients, atazanavir (alone or boosted with ritonavir or cobicistat)
  should be taken at least 12 hours apart from the 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. There are no restrictions with the use of darunavir-
  cobicistat and proton pump inhibitors.

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

- **Rilpivirine**: Proton pump inhibitors taken with oral rilpivirine lowers plasma rilpivirine levels to
  unacceptably low levels—omeprazole 20 mg has been shown to lower rilpivirine levels by as much as
  40%. Accordingly, coadministration of oral rilpivirine or combinations containing oral rilpivirine with a
  proton pump inhibitor is contraindicated. There are no interactions with long-acting injectable
  rilpivirine and proton pump inhibitors.
Antimycobacterials

There are significant and well recognized interactions between antiretroviral therapy and medications used to treat regimens for mycobacterial infections, including active and latent *Mycobacteria tuberculosis*, as well as the nontuberculous mycobacteria (*Mycobacterium avium* complex [MAC]).

- **Azithromycin**: The macrolide azithromycin can be used with all antiretroviral medications without requiring any drug dosing adjustments. Atazanavir, with or without pharmacologic boosters, has a potential drug interaction that may elevate azithromycin levels, but this does not require any dose adjustment.[13]
- **Clarithromycin**: Clarithromycin is a commonly used antimycobacterial for treatment of nontuberculous mycobacteria. An alternative to clarithromycin should be considered if using with an NNRTI or a PI boosted with ritonavir or cobicistat.[13,14] For treatment of *Mycobacterial avium* complex (MAC) infections, azithromycin can typically be substituted for clarithromycin without a loss of efficacy.[15,16] Clarithromycin can be used with the INSTIs bictegravir, dolutegravir, and raltegravir without requiring any dose adjustments; clarithromycin can also be used at a standard dose with cobicistat-boosted elvitegravir if renal function is not impaired.[17]
- **Ethambutol**: There are no significant drug interactions involving ethambutol and antiretroviral medications.
- **Isoniazid**: There are no significant drug interactions involving isoniazid and antiretroviral medications.
- **Pyrazinamide**: There are no significant drug interactions involving pyrazinamide and antiretroviral medications.
- **Rifabutin**: No dosage adjustments are needed with the coadministration of rifabutin and either raltegravir or dolutegravir, but rifabutin should be avoided with regimens that contain bictegravir or elvitegravir boosted with cobicistat.[17,18] Patients taking etravirine can use rifabutin without dose adjustment. With some antiretroviral regimens, dose adjustment of the antiretroviral medication or rifabutin may be needed. For example, if doravirine is used with rifabutin, the doravirine dose should be increased from 100 mg once daily to 100 mg twice daily and the once daily rilpivirine dose should be increased from 25 mg to 50 mg.[14] Use of efavirenz with rifabutine requires a higher dose of rifabutin (450 to 600 mg per day).[14,19] In contrast, use of rifabutin with a ritonavir-boosted PI requires the rifabutin dose should be reduced to 150 mg daily.[13] Rifampin should not be coadministered with tenofovir alafenamide unless the benefit outweighs the risk. In addition, rifabutin should not be used concurrently with any cobicistat-boosted protease inhibitor, long-acting intramuscular rilpivirine, long-acting intramuscular cabotegravir, or injectable lenacapavir.
- **Rifampin**: The levels of PIs, NNRTIs, and INSTIs are significantly reduced with concurrent use of rifampin.[18] The only antiretroviral anchor drugs that are acceptable for use with rifampin are efavirenz, raltegravir, and dolutegravir; when using rifampin with raltegravir or dolutegravir, dose adjustments of the INSTIs are necessary, including doubling the dose of raltegravir from 400 mg twice daily to 800 mg twice daily and increasing dolutegravir from 50 mg once daily to 50 mg twice daily.[17,18] The regimen bictegravir-tenofovir alafenamide-emtricitabine should be avoided with rifampin due to reduced plasma concentrations of bictegravir.[18,20] Rifampin should not be coadministered with the attachment inhibitor fostemsavir or the capsid inhibitor lenacapavir.[21,22] Efavirenz, at the standard 600 mg dose, can be used, but with close monitoring and possibly to include therapeutic drug monitoring to ensure adequate efavirenz levels.[18,23] Most NRTIs can be given in combination with rifampin, but tenofovir alafenamide should be used with caution (only if the benefits outweigh the risks).[18,24] Maraviroc can be used with rifampin, but the dose of maraviroc requires adjusting.
- **Rifapentine**: Rifapentine can safely be used with efavirenz, and raltegravir, and all NRTIs (except for tenofovir alafenamide) without dose adjustment.[25,26] In addition, once-weekly rifapentine can be used in persons who are taking once-daily dolutegravir who have virologic suppression.[17,18] Rifapentine should not be used in persons taking twice-daily dolutegravir (e.g., individuals with integrase resistance mutations) and daily rifapentine should not be used in
persons taking once-daily or twice-daily dolutegravir.[17,18] Except for these medications, all other INSTIs, NNRTIs, and PIs should be avoided with rifapentine.[14] The recommendation to not coadminister rifapentine and tenofovir alafenamide is due to the possible lowering of tenofovir levels. Rifapentine is also contraindicated with lenacapavir due to a potential lowering of lenacapavir levels.
Cardiovascular Medications

Hypertension affects approximately 25 to 35% of persons with HIV.\cite{27,28,29,30,31} Although data are conflicting regarding the association between HIV, antiretroviral therapy, and hypertension,\cite{30,32,33,34} 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{35} 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 example, in 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 area under the curve (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. There are no significant interactions between the calcium channel blockers and INSTIs or doravirine.

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 for a person who requires a regimen with a pharmacologic booster. The NNRTIs have no significant impact on beta-blocker levels since beta-blockers are metabolized primarily by CYP2D6 and NNRTIs are inducers of CYP3A4.\cite{36} There are no significant interactions between beta-blockers and INSTIs.

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{36}

Antiarrhythmics

Drug levels of antiarrhythmic medications, 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 these cardiac medications, with the following exception: bictegravir and dolutegravir increase the serum drug concentration of dofetilide through inhibition of the renal cation transporter OCT2, which is primarily responsible for elimination of dofetilide.\cite{37} Bictegravir and dolutegravir should not be coadministered with dofetilide.

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 interaction with digoxin has been reported.\cite{38,39} Nevertheless, therapeutic drug monitoring of digoxin levels is recommended when any of these antiretroviral therapies are coadministered. Lenacapavir, which is a moderate inhibitor of CYP3A,
can increase digoxin levels and monitoring of digoxin therapeutic concentrations is recommended when these medications are used concomitantly.\[21\] No special monitoring is needed for concomitant INSTI or NNRTI if given with digoxin, since they have minimal effect on P-glycoprotein.
Corticosteroids

Significant potential pharmacokinetic drug interactions exist between antiretroviral therapy and corticosteroid treatment, including with non-oral formulations of corticosteroids. For example, serious complications, including adrenal suppression and Cushing's syndrome have been reported in patients receiving the pharmacokinetic booster ritonavir who were given inhaled or nasal preparations of fluticasone.[40, 41, 42, 43, 44] 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 involved intranasal or inhaled fluticasone, which is the most potent of the inhaled corticosteroids and also the most reliant on CYP3A4 metabolism, but complications have also been reported as a result of coadministering ritonavir with inhaled budesonide and mometasone.[45] Although most of the reports of serious drug interactions with corticosteroids have involved oral or inhaled corticosteroids, several reports have also described this complication with corticosteroids delivered through topical and injectable ocular preparations, as well as following intrabursal, intraarticular, and epidural injections.[46, 47, 48, 49, 50] 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.[51] Lenacapavir is a moderate 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.[51] Lenacapavir is a moderate inhibitor of CYP3A and it can increase levels of any corticosteroid metabolized via CYP3A.[21]

Use of Corticosteroids Not Metabolized by CYP3A

To mitigate these drug interactions in patients taking ritonavir, cobicistat, or lenacapavir, 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, 52] Until further pharmacokinetic research is completed with other inhaled steroids, caution is recommended when any inhaled or intranasal corticosteroid 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 or boosting agents (ritonavir or cobicistat) As a consequence of reciprocal corticosteroid induction of the CYP3A4 enzyme pathway, dexamethasone may decrease levels of all 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.[53] Systemic dexamethasone may also decrease levels of bictegravir, and cobicistat-boosted elvitegravir, and lenacapavir.[17] Further, lenacapavir levels may be decreased if a person is taking dexamethasone at at dose greater than 16 mg per day.[21]
Hepatitis C Treatments

When considering treatment of hepatitis C virus (HCV) in persons with HIV coinfection, most individuals are taking antiretroviral therapy, which may pose a problem with drug interactions with HCV direct-acting antiviral medications.[54,55,56] It is important to note that antiretroviral medications are not a contraindication for HCV treatment. 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 4).[57,58] In current clinical practice, treatment of HCV treatment usually involves use of a pangenotypic regimen, either glecaprevir-pibrentasvir or sofosbuvir-velpatasvir. The following provides key summary points for drug interactions between HCV direct-acting antiviral medication regimens and HIV antiretroviral therapy. In general, INSTI-based antiretroviral therapy, without a pharmacokinetic booster, is a safe option in combination with HCV therapeutics.

- **Elbasvir-Grazoprevir**: The NS5A inhibitor elbasvir and the HCV NS3A/4A protease inhibitor grazoprevir are substrates for CYP3A and P-glycoprotein (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 is not recommended due to expected reductions in elbasvir and grazoprevir levels. The coadministration of elbasvir-grazoprevir is contraindicated with protease inhibitors (unboosted or boosted with cobicistat or ritonavir), or combinations with cobicistat-boosted elvitegravir due to the risk of hepatotoxicity from increased elbasvir and grazoprevir levels. Antiretroviral agents known to be safe and free of significant interactions with elbasvir-grazoprevir include: the NRTIs, non-cobicistat-boosted INSTIs, doravirine, rilpivirine, and maraviroc. Fostemsavir may increase grazoprevir levels, theoretically raising risk for hepatoxicity, so ideally this combination should be avoided.

- **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. Co-administration of glecaprevir-pibrentasvir with atazanavir (with or without ritonavir or cobicistat) is contraindicated because of increased glecaprevir and pibrentasvir levels, which has been associated with increased alanine aminotransferase (ALT) levels. In addition, although not contraindicated, it is recommended to avoid using glecaprevir-pibrentasvir with darunavir-cobicistat, darunavir boosted with ritonavir or lopinavir-ritonavir; this recommendation is because of the potential major increases in glecaprevir and pibrentasvir levels. Co-administration of glecaprevir-pibrentasvir with efavirenz or etravirine is not recommended because of substantial reductions in the levels of glecaprevir and pibrentasvir. Antiretroviral agents known to be safe and free of significant interactions with glecaprevir-pibrentasvir include: the NRTIs, non-cobicistat-boosted INSTIs, doravirine, rilpivirine, and maraviroc. Fostemsavir may increase grazoprevir levels, theoretically raising risk for hepatoxicity, so ideally this combination should be avoided.

- **Ledipasvir-Sofosbuvir**: The NS5A inhibitor ledipasvir is not metabolized by the cytochrome p450 system, but is a substrate of P-gp and BCRP. It also inhibits P-gp and BCRP activity (as does the NS5B polymerase inhibitor sofosbuvir). The inhibition of P-gp blocks hydrolysis of tenofovir, leading to increases in tenofovir levels when concomitantly given with tenofovir DF.[59] Therefore, ledipasvir-sofosbuvir should not be used in patients with HIV if they are taking tenofovir DF and the baseline creatinine clearance is less than 60 mL/min; if this option must be used in this scenario, monthly laboratory monitoring for renal toxicity is recommended during ledipasvir-sofosbuvir treatment. Co-administration with tenofovir alafenamide, however, is permissible. Small clinical studies, including two in individuals with HIV and HCV and one in individuals without those infections, showed that ledipasvir-sofosbuvir combined with tenofovir alafenamide does not lead to the same increase in tenofovir metabolite levels or renal risk, so most experts prefer tenofovir alafenamide over tenofovir DF if prescribing this HCV treatment regimen.[59,60] Co-administration of ledipasvir-sofosbuvir has also
been shown to be safe and acceptable with abacavir, emtricitabine (or lamivudine), bictegravir, dolutegravir, raltegravir, doravirine, and rilpivirine. Ledipasvir levels are decreased by efavirenz and increased by boosted atazanavir, but the clinical significance is unclear.

- **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. In persons receiving tenofovir DF, the sofosbuvir component may increase levels of tenofovir.[61,62]

- **Sofosbuvir-Velpatasvir**: The NS5A inhibitor velpatasvir is metabolized predominantly by CYP2B6, CYP2C8, and CYP3A4 enzymes. The NNRTI medications efavirenz and etravirine should not be administered concurrently with velpatasvir. In persons receiving tenofovir DF, the sofosbuvir component may increase levels of tenofovir.[61,62]. As with ledipasvir-sofosbuvir, coadministration of sofosbuvir-velpatasvir with tenofovir DF can lead to an increase in levels of tenofovir. If sofosbuvir-velpatasvir must be used in conjunction with tenofovir DF and the individual has a baseline creatinine clearance below 60 mL/min or is also taking a boosted protease inhibitor, monthly laboratory monitoring should be implemented during HCV treatment to assess for renal side effects. Alternatively, most experts would favor switching tenofovir DF to tenofovir alafenamide, which does not carry the same risk, and/or switching the boosted protease inhibitor to another option (such as dolutegravir or bictegravir), prior to initiating velpatasvir-sofosbuvir. No significant issues are expected when combining velpatasvir-sofosbuvir with tenofovir alafenamide, abacavir, INSTIs, rilpivirine, doravirine, boosted atazanavir, or boosted darunavir (unless the boosted PI is in a regimen with tenofovir DF).

- **Sofosbuvir-Velpatasvir-Voxilaprevir**: All drug interactions that are of concern with sofosbuvir-velpatasvir are also of concern with sofosbuvir-velpatasvir-voxilaprevir. The combination sofosbuvir-velpatasvir-voxilaprevir with either efavirenz or etravirine should be avoided. Use of sofosbuvir-velpatasvir-voxilaprevir with tenofovir DF will likely cause increases in tenofovir levels. The coadministration of sofosbuvir-velpatasvir-voxilaprevir with either atazanavir or lopinavir would likely increase voxilaprevir levels and thus is not recommended. Fostemsavir may increase voxilaprevir levels, though the clinical significance has not been determined.
HMG-CoA Reductase Inhibitors (Statins)

The HMG-CoA reductase inhibitors, more commonly referred to as statins, are frequently used to treat lipid disorders in persons with HIV who are taking antiretroviral therapy. Statins have been associated with elevations of hepatic aminotransferase levels, as well as adverse effects on skeletal muscle (ranging from mild muscle pain to fatal rhabdomyolysis) and these adverse effects are directly linked to statin concentration.[63] 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.[63,64] 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.[65] The attachment inhibitor fostemsavir may possibly raise levels of all statins, so the lowest possible statin dose should be used, with clinical monitoring for statin side effects.[22] The capsid inhibitor, lenacapavir, also causes increased levels of simvastatin and lovastatin, so coadministration of these statins with lenacapavir should be avoided.[21] 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.[66,67]

Atorvastatin

Levels of atorvastatin can 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.[63] If atorvastatin is to be used in conjunction with a ritonavir-boosted PI or 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 than if administered without a ritonavir-boosted PI or cobicistat-containing regimen.[13,63] The same is likely true if combining atorvastatin with fostemsavir.[22] Since atorvastatin is considered a more potent statin, a low dose, with titration upward if needed, may be preferred over using pravastatin, especially 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.[68,69] Some NNRTIs (efavirenz and etravirine) may decrease atorvastatin levels, necessitating higher dosing of atorvastatin, but should not exceed the recommended maximum dose.[14,65,70]

Lovastatin and Simvastatin

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 5).[64] 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.[71,72,73,74] 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.[65]

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.[13,75,76] Furthermore, the efficacy of pitavastatin 4 mg daily was found to be superior to pravastatin 40 mg in reduction of low-density lipoprotein (LDL) and other atherogenic lipid parameters.[77] There are inadequate data regarding interactions between pitavastatin and the pharmacologic booster cobicistat, but based upon data with ritonavir-boosted PIs, it is unlikely to interact and
should be considered safe to use in this setting. Fostemsavir can potentially raise pitavastatin levels; the combination is not contraindicated, but if coadministered, the lowest starting dose of pitavastatin should be used with slow titration up if needed, with monitoring for side effects.[22]

**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, 78] Therefore, when combining pravastatin and darunavir, initiating pravastatin therapy at the lowest dose that is appropriate. It should be noted, though, that pravastatin is one of the least potent statins, so many clinicians prefer to use a low dose of a more potent agent, such as rosuvastatin or atorvastatin, as opposed to a standard dose of pravastatin.

**Rosuvastatin**

Rosuvastatin is not a CYP3A4 substrate, but clinically relevant interactions with antiretroviral medications primarily occur through other transporters, specifically with OATP1B1 or BCRP.[79] When coadministering rosuvastatin with PIs (boosted with cobicistat or ritonavir), cobicistat-boosted elvitegravir, or fostemsavir, rosuvastatin should be initiated at the lowest possible dose, with close observation for evidence of statin toxicity.[13, 17, 22, 80] 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]
Mental Health Medications

Persons with HIV have a high prevalence of coexisting mental health conditions.[81] In the process of managing these coexisting conditions, clinicians caring for persons with HIV often need to manage complex drug interactions between antiretroviral medications and medications used to treat depression, anxiety, or other mood disorders.[82] 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. Thus, drug interactions and recommendations should be closely checked when initiating an antipsychotic medication, especially in those medications that can prolong QTc. Similarly, drug interactions should be closely examined in a person on an antipsychotic who is starting a new antiretroviral regimen. For example, in a patient already taking any boosted PI, the lowest possible dose of quetiapine should be used; if a patient is already 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 (or preferably a different antiretroviral regimen is chosen that does not have interactions with quetiapine).[13,83,84] Dut 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. Since most of the medications in NNRTI class decrease antipsychotic drug concentrations, primarily due to induction of CYP34A and CYP2D6 enzymes, caution is advised with coadministration of these agents; the use of rilpivirine or doravirine is less likely to lead to significant interactions with antipsychotic medications.

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.[13,85] Bictegravir, dolutegravir, and raltegravir do not appear to impact SSRi levels.[86] Doravirine and rilpivirine are also considered safe in combination with SSRIs, as are the non-boosted INSTIs and NRTIs.

Tricyclic Antidepressants (TCAs)

Protease inhibitors, ritonavir, and cobicistat have also been shown to increase levels of tricyclic antidepressants and trazodone. 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, or cobicistat, 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, boosting agents (ritonavir and cobicistat), so these benzodiazepines and antiretroviral medications so these are not recommended for concurrent use. In patients taking a PI, ritonavir, cobicistat, use of triazolam or midazolam is contraindicated, with the exception that midazolam can be used with caution in these patients when given parenterally as a single-dose, pre-procedural medication in a monitored setting.[2,13]
Opioid Agonist Therapy

A substantial proportion of persons with HIV have a concomitant opioid use disorder. Thus, HIV medical care providers should become familiar with the pharmacologic interactions between antiretroviral medications and opioid agonist medications used for the treatment of opioid use disorder.\[87\] Key interactions between antiretroviral therapies, methadone, buprenorphine, and buprenorphine-naloxone will be addressed here.

Methadone

- **Integrase Strand Transfer Inhibitors (INSTIs):** There are no significant pharmacokinetic interactions that have been between methadone and the INSTIs dolutegravir, elvitegravir (boosted with cobicistat), or raltegravir.\[87,88,89,90\] Although bictegravir coadministration with methadone has not yet been studied, no significant interaction is expected. There are no dosage adjustments recommended when using any of the INSTIs with methadone.\[17\]

- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs):** As a result of potent CYP34A induction by the NNRTIs efavirenz and nevirapine, an increased methadone dose is often necessary in persons on methadone who are concomitantly taking efavirenz or nevirapine; no methadone dose adjustment is required for concurrent therapy with the other NRTIs— doravirine, etravirine, or rilpivirine.\[88,91,92,93\]

- **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.\[94,95\]

Buprenorphine and Buprenorphine-naloxone

- **Integrase Strand Transfer Inhibitors (INSTIs):** Raltegravir does not appear to have any clinically significant interaction with buprenorphine or buprenorphine-naloxone.\[87,88\] Although cobicistat-boosted elvitegravir raises buprenorphine levels, no dose adjustment is necessary.\[87\] Although dolutegravir and bictegravir coadministration with buprenorphine or buprenorphine-naloxone have not been studied, no significant interaction is expected.

- **Non-Nucleoside 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.\[88\]

- **Protease Inhibitors (PIs):** Buprenorphine (and buprenorphine-naloxone) are metabolized by CYP3A4 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 ritonavir-boosted darunavir, but lower doses of buprenorphine may be needed in patients taking ritonavir-boosted atazanavir (since atazanavir inhibits both CYP3A4 and UGT1A1) or any cobicistat-boosted PI.\[87,94,96\] Buprenorphine should not be coadministered with unboosted atazanavir due to the risk of subtherapeutic atazanavir levels.\[13,87\]

- **Capsid Inhibitor:** The capsid inhibitor lenacapavir, which inhibits the CYP3A4 enzyme, may increase levels of buprenorphine. If coadministering these agents, it is recommended to use the lowest feasible initial dose of buprenorphine and titrate to desired effect.\[21\]
**Oral Anticoagulants and Antiplatelet Therapy**

**Direct-Acting Oral Anticoagulant Medications**

The commonly used direct-acting oral anticoagulant medications (DOACs)—apixaban, dabigatran, edoxaban, and rivaroxaban—are eliminated either via CYP450 enzymes, P-glycoprotein, or both.[97]

**Interactions with INSTIs**

Drug interactions with DOACs and the non-boosted INSTIs bictegravir, cabotegravir, dolutegravir, and raltegravir are not significant and no dose adjustments are required.[17] The use of DOACs with regimens that contain elvitegravir-cobicistat can cause significant increases in the levels of apixaban, betrixaban, and dabigatran.[17]

**Interactions with NNRTIs**

Cytochrome P-450 enzyme induction by certain NNRTIs may lower the levels of some DAOACs, which may lead to failure of the anticoagulant to prevent or treat thrombosis.[14,97] The most likely interactions to cause clinically significant lowering of the DOAC involve efavirenz, etravirine, or nevirapine combined with either apixaban or rivaroxaban.[14]

**Interactions with Boosting Agents**

Potent cytochrome P-450 enzyme inhibition by PIs or pharmacologic boosters (ritonavir or cobicistat) may lead to higher plasma drug concentrations of the DOACs and potentially increase the risk of bleeding.[13,97] Thus, the concomitant use of most DOACs with ritonavir- or cobicistat-boosted PIs (and with elvitegravir-cobicistat) should be avoided due to potential increases in the DOAC concentrations and potential risk of bleeding.[13,17] In general, the use of apixaban, betrixaban, edoxaban and rivaroxaban should be avoided in this setting. If coadministration of DOACs with boosted-PI therapy is necessary, dabigatran has the most data to guide use, and rivaroxaban should be avoided given the paucity of data and potential risk for increased bleeding.

**Interactions with Capsid Inhibitor**

Lenacapavir, which inhibits cytochrome P-450 enzymes and, to a lesser degree, P-glycoprotein, may possibly raise levels of apixaban, dabigatran, edoxaban, and rivaroxaban. No dose adjustment is recommended with apixaban, dabigatran, and edoxaban, but monitoring for adverse events, such as increased bleeding, is recommended.[21] Caution is urged with the use of lenacapavir and rivaroxaban and the rivaroxaban dose may need to be adjusted.[21]

**Studies with DOAC-Antiretroviral Medication Interactions**

The following summarizes several studies related to DOAC-antiretroviral drug interactions.

- **Dabigatran and Ritonavir**: 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.[13,97]
- **Dabigatran and Cobicistat**: 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.
- **Apixaban and Boosting Agents**: In general, the coadministration of apixaban with ritonavir- or
cobicistat-containing regimens (including elvitegravir-cobicistat) should be avoided, but note that if coadministration is necessary, a 50% reduction in apixaban dose is required, with close monitoring for apixaban toxicity.\textsuperscript{[13,17]} In a small retrospective case series using reduced-dose apixaban with either ritonavir- or cobicistat-boosted antiretroviral therapy, all 6 patients tolerated the combination of DOAC with antiretroviral therapy.\textsuperscript{[98]}

- **Rivaroxaban and Boosting Agents:** Rivaroxaban also has not been adequately studied to date with ritonavir- or cobicistat-containing regimens, but case reports have documented increased bleeding risk when rivaroxaban was combined with ritonavir.\textsuperscript{[99,100]}

**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.\textsuperscript{[7]} Pharmacokinetic interactions between warfarin and antiretroviral medications are variable and often difficult to predict. Coadministration of warfarin with an antiretroviral regimen that contains a PI, NNRTI, or cobicistat 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 medications. 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. Bictegravir, cabotegravir, dolutegravir, and raltegravir are not extensively metabolized via CYP450 and thus are unlikely to cause significant drug interactions with warfarin. In addition, use of modern NRTIs is unlikely to impact warfarin levels. Lenacapavir may increase levels of warfarin and INR should be closely monitored and the dose of warfarin adjusted accordingly.\textsuperscript{[21]}

**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.\textsuperscript{[97]} These interactions are complex, and the net effect can be difficult to predict and manage, especially in persons who are receiving both PI- and NNRTI-based therapies. An assay that measures platelet activation is available that may help measure the extent to which platelets are inhibited. Expert consultation is recommended.

- **Interactions with PIs:** The inhibition of CYP34A via PIs 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.
- **Interactions with NNRTIs:** The 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 dolutegravir or rilpivirine.\textsuperscript{[97]} 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.\textsuperscript{[97]}

\textsuperscript{[13,17]} \textsuperscript{[98]} \textsuperscript{[99,100]} \textsuperscript{[21]}
Phosphodiesterase Type 5 (PDE5) Inhibitors

Phosphodiesterase type 5 (PDE5) inhibitors are frequently prescribed in men with HIV for symptoms of erectile dysfunction, sometimes for benign prostatic hypertrophy, and rarely for pulmonary artery hypertension. Pharmacokinetic interactions between antiretroviral therapies and the PDE5 inhibitors—avanafil, sildenafil, tadalafil, and vardenafil—are well recognized.[101, 102] The major drug interactions with antiretroviral therapy medications and PDE5 inhibitors involve pharmacologic boosters and PIs and cobicistat-boosted elvitegravir. In general, significant drug interactions with PDE5 inhibitors do not occur with NRTIs, NNTIs, unboosted INSTIs.

**Use of PDE5 for Erectile Dysfunction:** The use of PDE5 inhibitors with PIs and/or pharmacologic boosters (ritonavir or cobicistat) typically causes an increase in the level of the PDE-5 inhibitor medications, which can potentially result in priapism, hypotension, and other adverse effects; in these situations, it is recommended to use lower doses of the PDE5 inhibitor, monitoring for adverse effects, and to not exceed a threshold dose over certain time period (the threshold dose and time period vary depending on the recommended dose and half-life of the PDE5 inhibitor). Similarly, the capsid inhibitor lenacapavir, which inhibits CYP3A4, may increase PDE5 inhibitor levels and require lower doses and enhanced monitoring. In contrast, etravirine and efavirenz lower levels of PDE5 levels of inhibitor and may necessitate dose increases for the PDE5 inhibitors sildenafil, tadalafil, and vardenafil; rilpivirine has been studied with sildenafil and tadalafil, and no dose adjustment appears to be necessary with either combination.[8, 101, 102, 103] For persons taking lenacapavir, the

**Use of PDE5 Inhibitors for Benign Prostatic Hypertrophy:** The PDE5 inhibitor tadalafil is the only PDE5 inhibitor recommended for treatment of benign prostatic hypertrophy. When using tadalafil with a protease inhibitor, the maximum daily dose of tadalafil is 2.5 mg per day.[13]

**Use of PDE5 Inhibitors for Pulmonary Arterial Hypertension (PAH):** Use of high-doses of the PDE5 inhibitors, such as doses used to treat pulmonary arterial hypertension (PAH), are contraindicated with most HIV medications that inhibit CYP3A4 because the PDE5 inhibitors may reach dangerous levels.[13] Sildenafil for PAH is contraindicated with all PIs and pharmacologic boosters (ritonavir or cobicistat). In a person receiving a PI or cobicistat-boosted elvitegravir, tadalafil can be initiated at a dose of 20 mg once daily and increased to 40 mg once daily based on tolerability.[13, 17]
**Miscellaneous Interactions**

**Alpha Adrenergic Blockers**

Tamsulosin and other alpha adrenergic receptor antagonists (prazosin, alfuzosin, doxazosin, and terazosin), which may be used for benign prostatic hypertrophy (BPH) or hypertension, are metabolized by CYP3A4 and, to a lesser degree, by CYP2D6. Therefore, antiretroviral medications that affect these pathways can affect the drug levels; this includes boosted PIs, cobicistat-boosted elvitegravir, and lenacapavir. Increased levels of the alpha adrenergic blockers can lead to orthostatic hypotension and other adverse effects, so starting with the lowest feasible dose and monitoring for side effects is recommended when coadministering these agents.

**Anticonvulsant Medications**

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, such as 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, tenofovir alafenamide, the attachment inhibitor fostemsavir, long-acting injectable cabotegravir and rilpivirine, and long-acting injectable lenacapavir. Due to these potentially significant drug interactions, many antiretroviral-anticonvulsant combinations are contraindicated. Accordingly, prior to using concomitant therapy with 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.[12] For patients who are not candidates for levetiracetam therapy and require a different anticonvulsant, expert consultation is recommended.

**Metformin**

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.[104, 105] Medical providers should use caution with this combination and limit the metformin dose to no more than 1 gram per day.[17] Less pronounced effects on metformin concentrations were seen with bictegravir coadministration, so the recommendation is to monitor for adverse events from metformin.[17] None of the other INSTIs, or other classes of antiretrovirals, have demonstrated a significant drug interaction with metformin.

**St. John’s Wort**

The herbal medication St. John’s Wort is contraindicated with a number of antiretroviral medications. Because of induction effects on CYP3A4 and P-gp, it should not be coadministered with protease inhibitors, NNRTIs, INSTIs, maraviroc, or fostemsavir. The low-hyperforin formulations of St. John’s Wort may be safer and less likely to interact, but have not been studied in combination with antiretroviral medications.
Summary Points

- Effective antiretroviral therapy depends on attaining a therapeutic serum drug concentration that maximizes efficacy and minimizes toxicity.
- Excellent online resources are available to help clinicians manage drug interactions.
- 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 best option for avoiding 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 and should not be considered interchangeable. Cobicistat has also been less studied than ritonavir.
- The capsid inhibitor lenacapavir has significant inhibition of CYP3A and may cause significant drug interactions.
- Any changes to a drug regimen require careful consideration of potential drug interactions.
Citations

   [PubMed Abstract] -

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18. Panel on Opportunistic Infections in Adults and Adolescents with HIV. Guidelines for the prevention and treatment of opportunistic infections in adults and adolescents with HIV: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America Mycobacterium tuberculosis infection and disease. Last updated September 27, 2019. [HIV.gov] -


References


**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% of the administered dose enters the portal vein (solid line). Subsequently, CYP3A enzymes in the liver further metabolize the drug so that only 15% 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
Figure 3 CYP 450 Induction

Source: Illustration by John J. Faragon, PharmD
Figure 4 Classes of Direct-Acting Antiviral Medications Used to Treat HCV

Note that all medications in gray boxes have been discontinued and are no longer manufactured in the United States.
Figure 5 Ritonavir-Boosted Saquinavir Interactions with Statins

Table 1.

**Pharmacokinetic Drug Interactions**

<table>
<thead>
<tr>
<th>Interaction</th>
<th>Comment</th>
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</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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</tbody>
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