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Drug Interactions with Antiretroviral Medications

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Module 3: Antiretroviral Therapy
Lesson 3: Drug Interactions with Antiretroviral Medications

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Overview

Successful antiretroviral therapy depends on attaining a therapeutic drug concentration that maximizes efficacy and minimizes toxicity.[1] Therefore, understanding drug interactions is an important component of providing effective and safe antiretroviral therapy. Drug interactions can be classified into 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 various biological, physiological, and chemical factors.[1] Pharmacokinetic studies 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.[1] Pharmacokinetic interactions can occur between concomitant use of antiretroviral and other medications during the absorption, metabolism, or elimination phases.

Table 1.

Pharmacokinetic Drug Interactions

Interaction	Comment
Absorption	Concurrent therapy or food ingestion results in increase or decrease in drug absorption, thereby increasing or decreasing bioavailability.
Distribution	Concurrent therapy leads to protein binding displacement, altering the activity of either drug.
Metabolism	Therapy induces or inhibits CYP450 enzymes, thereby increasing or decreasing drug concentration.
Excretion	Concurrent therapy results in

Interaction			Comment
	enhanced or decreased renal excretion of drug.		

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 metabolizing 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 the 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) and some other antiretrovirals. Certain antiretroviral agents, such as tenofovir alafenamide, rely on enzymes like P-glycoprotein (P-gp) for absorption in the gut, and thus may be affected by other medications that affect P-gp activity. 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 act 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 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 preinduction levels; this varies, 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. Drug interactions range from mild to severe (and even potentially fatal). 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 relatively 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. Medical providers should also be cautious when discontinuing boosters and changing HIV therapy to non-boosted regimens, as dose adjustments of concurrent medications may be needed following the regimen switch. Long-acting injectable antiretrovirals, such as intramuscular cabotegravir and rilpivirine, and subcutaneous lenacapavir, have 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. Interactions between antiretroviral medications and oral contraceptives can be found in the lesson HIV in Women.

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 other 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 select, 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, an excellent resource that addresses a broad array of drug interactions.

- Adult and Adolescent ARV Guidelines Drug-Drug Interactions (Overview Page)
    - 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
- Northeast Caribbean AIDS Education and Training Center Drug Interaction Mobile Apps
    - DHHS Guideline Drug Interaction App
        - Access via Apple App Store
        - Access via Google Play Store
    - Recreational and Narcotic Drug interaction App
        - Access via Apple App Store
        - Access via Google Play Store
    - Psychiatric Medication Drug interaction App
        - Access via Apple App Store
        - Access via Google Play Store
    - HCV Medication Drug interaction App
        - Access via Apple App Store
        - Access via Google Play Store

Acid Suppressive Therapy and Supplements

Medications used to treat dyspepsia, heartburn, and gastroesophageal reflux (GERD), including histamine-2 receptor antagonists (H2 blockers) and proton pump inhibitors (PPIs), 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 non-nucleoside reverse transcriptase inhibitor (NNRTI) doravirine is not impacted 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 antiretrovirals, most notably the integrase strand transfer inhibitors (INSTIs). Further, many multivitamins and other supplements may also contain polyvalent cations, including aluminum, calcium, iron, magnesium, selenium, and zinc. The INSTIs exert their action via binding to magnesium (an enzyme cofactor) in the active site of the HIV integrase enzyme. If an INSTI is coadministered with a polyvalent cation, including a divalent or trivalent metal cation, the INSTI and the polyvalent cation may chelate, which lowers the solubility of the INSTI and significantly reduces absorption of the INSTI.[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, acid-suppressive medications, and supplements that contain divalent cations.[2] The following summarizes some of key interactions and recommendations when taking antiretroviral medications with agents that lower gastrointestinal pH and with polyvalent cations.

Agents that Alter Gastrointestinal PH

Anatacids

- **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).
- **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.
- **INSTIs:** Coadministration of antacids or buffered medication can impact INSTIs if the medication has a polyvalent cation (see section below on Polyvalent Cations). Note that many antacids and sucralfate have polyvalent cations.

H2 blockers (H2 Receptor antagonists)

- **Atazanavir**: For treatment-naïve individuals 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 H2 blocker dose should not exceed a dose comparable to famotidine 40 mg twice daily. For antiretroviral treatment-experienced persons taking atazanavir, the H2 blockers can be administered according to the same schedule as for treatment-naïve persons, but the H2 blocker maximum dose should not exceed the equivalent of famotidine 20 mg twice daily. If the treatment-experienced person also takes 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 proton pump inhibitor dose 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 lower plasma rilpivirine levels to unacceptably low levels—omeprazole 20 mg has been shown to decrease 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.

Polyvalent Cations and Interaction with INSTIs

- **Bictegravir**: In general, if bictegravir (as a component of bictegravir-tenofovir alafenamide-emtricitabine) is used concomitantly with any polyvalent cation, bictegravir should be administered at least 2 hours before or 6 hours after the polyvalent cation. The one exception is that bictegravir can be taken with calcium and/or iron if taken together with food.
- **Cabotegravir**: This medication is available as an oral medication and as a long-acting injectable formulation; oral cabotegravir is sometimes used for an oral lead-in period before transitioning to the injectable formulation. Polyvalent cations should be taken 2 hours before or 4 hours after oral cabotegravir. Injectable cabotegravir is not affected by oral polyvalent cations.
- **Dolutegravir**: In general, dolutegravir should be administered at least 2 hours before or 6 hours after any polyvalent cation. Dolutegravir can be taken with calcium or iron, if taken together with food, based on a study in healthy volunteers. With dolutegravir-lamivudine, the recommendation is the same as dolutegravir alone. If dolutegravir-rilpivirine is used, it should be taken at least 4 hours before or 6 hours after the polyvalent cation.
- **Elvitegravir**: Elvitegravir is administered with boosted cobicistat, and it should be at least 2 hours before or 6 hours after any polyvalent cation.
- **Raltegravir**: Management interactions between raltegravir and polyvalent cations often depends on the formulation of raltegravir (400 mg BID versus 1200 mg daily of the HD formulation) and the specific supplement. Raltegravir (400 mg twice daily or 1200 mg once daily) should not be coadministered with aluminum- or magnesium-containing. Raltegravir 400 mg twice daily can be given with calcium and no dosing separation is required. The raltegravir 1200 mg once-daily dose is not recommended with calcium or magnesium.

Antimycobacterials

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

- **Azithromycin**: The macrolide azithromycin can be used with all antiretroviral medications without requiring 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.[12]
- **Clarithromycin**: Clarithromycin is a commonly used antimycobacterial for treating nontuberculous mycobacteria. An alternative to clarithromycin should be considered if used concomitantly with an NNRTI or a PI boosted with ritonavir or cobicistat.[12,13] For the treatment of *Mycobacterial avium* complex (MAC) infections, azithromycin can typically be substituted for clarithromycin without a loss of efficacy.[14,15] Clarithromycin can be used with the INSTIs bictegravir, dolutegravir, and raltegravir without requiring dose adjustments; clarithromycin can also be used at a standard dose with cobicistat-boosted elvitegravir if renal function is not impaired.[16]
- **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**: Rifabutin is a moderate inducer of CYP3A activity. No dosage adjustments are needed with the coadministration of rifabutin and either raltegravir or dolutegravir, but rifabutin should be avoided with bictegravir and with elvitegravir boosted with cobicistat.[16,17] Rifabutin should not be used with injectable cabotegravir and rilpivirine (due to decreased rilpivirine levels). Patients taking etravirine can use rifabutin without dose adjustment. When rifabutin is used 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; similarly, the once-daily oral rilpivirine dose should be increased from 25 mg to 50 mg.[13] The use of efavirenz with rifabutin requires a higher dose of rifabutin (450 to 600 mg per day).[13,18] In contrast, the rifabutin dose should be reduced to 150 mg daily when used with a ritonavir-boosted PI.[12] Rifabutin should be coadministered with tenofovir alafenamide with caution and with monitoring of antiretroviral efficacy using HIV RNA levels.[19] In addition, rifabutin should not be used concurrently with any cobicistat-boosted protease inhibitor or injectable lenacapavir.[12,20]
- **Rifampin**: The levels of PIs, NNRTIs, and INSTIs are significantly reduced with concurrent use of rifampin, which is a strong inducer of CYP3A activity.[17] The only antiretroviral anchor drugs that are recommended 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.[16,17] Efavirenz, at the standard 600 mg dose, can be used, but with close monitoring and possible therapeutic drug monitoring to ensure adequate efavirenz levels.[17,21] The regimen bictegravir-tenofovir alafenamide-emtricitabine should be avoided with rifampin due to reduced plasma concentrations of bictegravir.[17,22] Most NRTIs can be given in combination with rifampin, but tenofovir alafenamide should be used with caution and with monitoring for antiretroviral efficacy with HIV RNA levels.[17,19,23] Maraviroc can be used with rifampin, but the dose of maraviroc requires adjusting.[24] Rifampin should not be coadministered with the attachment inhibitor fostemsavir or the capsid inhibitor lenacapavir.[20,25]
- **Rifapentine**: Rifapentine, a moderate CYP3A inducer, can safely be used with efavirenz, raltegravir, and all NRTIs without dose adjustment; tenofovir alafenamide should be used with caution and with monitoring of antiretroviral efficacy with HIV RNA levels.[26,27] In addition, once-weekly rifapentine can be used in persons taking once-daily dolutegravir who have virologic suppression.[16,17]

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.[16,17] Except for these medications, all other INSTIs, NNRTIs, and PIs should be avoided with rifapentine.[13] The recommendation to not coadminister rifapentine and tenofovir alafenamide is due to the possible lowering of tenofovir levels. Rifapentine is contraindicated for use with lenacapavir due to a potential lowering of lenacapavir levels.

Cardiovascular Medications

Hypertension affects approximately 25 to 35% of persons with HIV.[28,29,30,31,32] Although data are conflicting regarding the association between HIV, antiretroviral therapy, and hypertension,[31,33,34,35] 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.[36] 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.[12] 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) 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.[37] 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 a low potential for pharmacokinetic drug interactions with any of the antiretroviral therapies.[37]

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 the elimination of dofetilide.[38] 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.[39,40] Nevertheless, therapeutic drug monitoring of digoxin levels is recommended when 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.[20] 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.[41,42,43,44,45] This complication results from ritonavir-mediated inhibition of CYP3A4 enzymes, which increases the levels of certain corticosteroids 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.[46] 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.[47,48,49,50,51] 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.[52] Lenacapavir is a moderate inhibitor of CYP3A and can increase levels of any corticosteroid metabolized via CYP3A.[20]

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).[12,53] 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.[54] Systemic dexamethasone may also decrease levels of bictegravir, cobicistat-boosted elvitegravir, and lenacapavir.[16] Further, lenacapavir levels may decrease if a person is takes dexamethasone at a dose greater than 16 mg per day.[20]

Hepatitis C Treatments

When considering the 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.[55,56,57] It is important to note that antiretroviral medications are not a contraindication for HCV treatment. Three major classes of direct-acting antiviral medications are used to treat hepatitis C: NS3/4A protease inhibitors, NS5A inhibitors, and NS5B polymerase inhibitors.[58,59] In current clinical practice, treatment of HCV usually involves the use of a pangenotypic regimen, either glecaprevir-pibrentasvir, sofosbuvir-velpatasvir, or sofosbuvir-velpatasvir, voxilaprevir. The following provides key summary points for drug interactions between the pangenotypic 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.

- **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, 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 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. Coadministration 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, fostemsavir, and maraviroc. Experience of combining glecaprevir-pibrentasvir with lenacapavir is limited.
- **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 tenofovir levels.[60,61]. 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 sofosbuvir-velpatasvir. 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 of 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.[62] 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.[62,63] 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.[64] 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.[25] The capsid inhibitor, lenacapavir, also causes increased levels of simvastatin and lovastatin, so coadministration of these statins with lenacapavir should be avoided.[20]

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.[62] 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.[12,62] The same is likely true if combining atorvastatin with fostemsavir.[25] Since atorvastatin is considered a more potent statin, a low dose, with titration upward if needed, may be preferred over 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.[65,66] Some NNRTIs (efavirenz and etravirine) may decrease atorvastatin levels, necessitating higher dosing of atorvastatin, but should not exceed the recommended maximum dose.[13,64,67]

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.[12] 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).[63] 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 lovastatin.[68,69,70,71] 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.[64]

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.[12,72,73] 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.[74] Pitavastatin was used in the REPRIEVE trial—a study that compared pitavastatin 4 mg daily versus placebo in persons with HIV who had low-to-moderate risk of cardiovascular disease, and found a reduced risk of developing major cardiovascular events among those who took pitavastatin.[75] There are inadequate data regarding interactions between pitavastatin and the pharmacologic booster cobicistat, but, based on 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.[25]

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.[12,76] Therefore, when combining pravastatin and darunavir, pravastatin should be initiated at the lowest appropriate dose. 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.[77] 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.[12,16,25,78] The maximum recommended dose of rosuvastatin in persons taking ritonavir-boosted atazanavir or lopinavir is 10 mg daily.[12] No significant effect on rosuvastatin levels is expected with NNRTI therapy; lipid levels should be monitored, and the rosuvastatin dose adjusted as needed.[13]

Mental Health Medications

Persons with HIV have a high prevalence of coexisting mental health conditions.[79] In the process of managing these coexisting conditions, clinicians caring for persons with HIV often need to consider complex drug interactions between antiretroviral medications and medications used to treat depression, anxiety, or other mood disorders.[80,81] Several of the key interactions are discussed below.

Antipsychotics

Many antipsychotic medications are metabolized by CYP450, particularly CYP3A4, and antipsychotic medication levels 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 with medications that can prolong the 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 choose a different antiretroviral regimen that does not have interactions with quetiapine).[12,82,83] Drug 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 highlight concern with the 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 the 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.[12,84] Bictegravir, dolutegravir, and raltegravir do not appear to impact SSRI levels.[85] 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.[12]

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 not

metabolized via CYP-450; these include lorazepam, oxazepam and temazepam.[2,12] 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 are not recommended for concurrent use. In patients taking a PI, ritonavir, or cobicistat, the 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.[2,12]

Opioid Agonist Therapy

A substantial proportion of persons with HIV have a concomitant opioid use disorder. Thus, health care providers should become familiar with the pharmacologic interactions between antiretroviral medications and opioid agonist medications used for treating opioid use disorder.[86] 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 between methadone and the INSTIs dolutegravir, elvitegravir (boosted with cobicistat), raltegravir, or cabotegravir.[16,87,88,89] Although bictegravir coadministration with methadone has not yet been studied, no significant interaction is expected.[16] No dosage adjustments are recommended when using any of the INSTIs with methadone.[16]
- **Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)**: As a result of potent CYP34A induction by the NNRTI efavirenz, an increased methadone dose is often necessary for persons on methadone who are concomitantly taking efavirenz.[13,90] The likelihood of decreased methadone levels when coadministered with rilpivirine (oral or long-acting injectable) is lower than with efavirenz, but clinicians should monitor clinically for signs of decreased methadone levels if rilpivirine is used concomitantly.[13] No methadone dose adjustment is required for concurrent therapy with doravirine or etravirine.[13,87,91]
- **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.[12,92,93]

Buprenorphine and Buprenorphine-naloxone

- **Integrase Strand Transfer Inhibitors (INSTIs)**: Raltegravir does not appear to have any clinically significant interaction with buprenorphine or buprenorphine-naloxone.[16,86,87] Although cobicistat-boosted elvitegravir raises buprenorphine levels, no dose adjustment is necessary.[16,86] No significant interaction is expected if dolutegravir, bictegravir, or cabotegravir is coadministered with buprenorphine.[16]
- **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.[13,87]
- **Protease Inhibitors (PIs)**: Buprenorphine (and buprenorphine-naloxone) are metabolized by CYP3A4 and also undergo glucuronidation by the liver enzyme uridine diphosphate glucuronosyltransferase 1A1 (UGT1A1). The drug interactions with PIs are variable. No buprenorphine or buprenorphine-naloxone dosage adjustment is necessary for 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.[12,86,92,94] Buprenorphine should not be coadministered with unboosted atazanavir due to the risk of subtherapeutic atazanavir levels.[12,86]
- **Capsid Inhibitor**: The capsid inhibitor lenacapavir, which inhibits the CYP3A4 enzyme, may increase levels of buprenorphine.[20] If coadministering these agents, it is recommended to use the lowest feasible initial dose of buprenorphine and titrate to the desired effect.[20]

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.[95]

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.[16] The use of DOACs with regimens that contain elvitegravir-cobicistat can cause significant increases in the levels of apixaban, betrixaban, and dabigatran.[16]

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.[13,95] The most likely interactions to cause clinically significant lowering of the DOAC involve efavirenz, etravirine, or nevirapine combined with either apixaban or rivaroxaban.[13]

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.[12,95] 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.[12,16] In general, the use of apixaban, betrixaban, edoxaban and rivaroxaban should be avoided in this setting.[12] Dabigatran has the most data to guide us when it is necessary to coadminister DOACs with boosted-PI therapy; rivaroxaban should be avoided given the lack of data and potential risk for increased bleeding.

Interactions with Capsid Inhibitors

Lenacapavir, which inhibits cytochrome P-450 enzymes and, to a lesser degree, P-glycoprotein, may possibly raise levels of apixaban, dabigatran, edoxaban, and rivaroxaban.[20] No dose adjustment is recommended with apixaban, dabigatran, and edoxaban, but monitoring for adverse events, such as increased bleeding, is recommended.[20] Caution is urged with the use of lenacapavir and rivaroxaban, and the rivaroxaban dose may need to be adjusted.[20]

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.[12,95]
- **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.[12,16] 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.[96]

- **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.[97,98]

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 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, the use of modern NRTIs is unlikely to impact warfarin levels. Lenacapavir may increase warfarin levels and INR should be closely monitored.[20]

Platelet Aggregate Inhibitors

The platelet aggregate inhibitors, such as clopidogrel, prasugrel, ticagrelor, and vorapaxar, can interact with PI or NNRTI antiretroviral medications due to overlapping metabolism via CYP34A and CYP2C19 enzymes.[95] These interactions are complex, and the net effect can be difficult to predict and manage, especially in persons 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 the metabolism of ticagrelor or vorapaxar, thereby significantly increasing ticagrelor and vorapaxar drug levels. Use of any PI with ticagrelor or vorapaxar is contraindicated. Use of any boosted PI with clopidogrel is not recommended due to lowering of the clopidogrel active [12]metabolite by 69%.[12] Although levels of the active prasugrel metabolite are also decreased when used with a boosted PI, this effect is less than with clopidogrel and no dose adjustment is needed.
- **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 doravirine or rilpivirine.[95] 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 NNRTI medications.[95]

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.[99,100] The major drug interactions with antiretroviral therapy medications and PDE5 inhibitors involve pharmacologic boosters, PIs, and cobicistat-boosted elvitegravir. In general, significant drug interactions with PDE5 inhibitors do not occur with NRTIs, NNTIs, or 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 PDE5 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 a specific duration (the threshold dose and duration 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 PDE5 inhibitor levels 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.[8,99,100,101] For persons taking lenacapavir, the levels of PDE5 inhibitors are increased, and dose adjustment may be needed with avanafil, sildenafil, and vardenafil.[20]
- **Use of PDE5 Inhibitors for Benign Prostatic Hypertrophy**: The PDE5 inhibitor tadalafil is the only PDE5 inhibitor recommended for treating benign prostatic hypertrophy. When using tadalafil with a protease inhibitor, the maximum daily dose of tadalafil is 2.5 mg per day.[12]
- **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), is contraindicated with most HIV medications that inhibit CYP3A4 because the PDE5 inhibitors may reach dangerous levels.[12] 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.[12,16]

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.[102] 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.[103,104] Medical providers should use caution with this combination and limit the metformin dose to no more than 1 gram per day.[16] Less pronounced effects on metformin concentrations were seen with bictegravir coadministration, so the recommendation is to monitor for adverse events from metformin (generally no dose reduction is required with metformin-bictegravir coadministration).[16] None of the other INSTIs, or other classes of antiretrovirals, have demonstrated a significant drug interaction with metformin.[16]

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.

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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% 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.

Source: Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352:2211-21.
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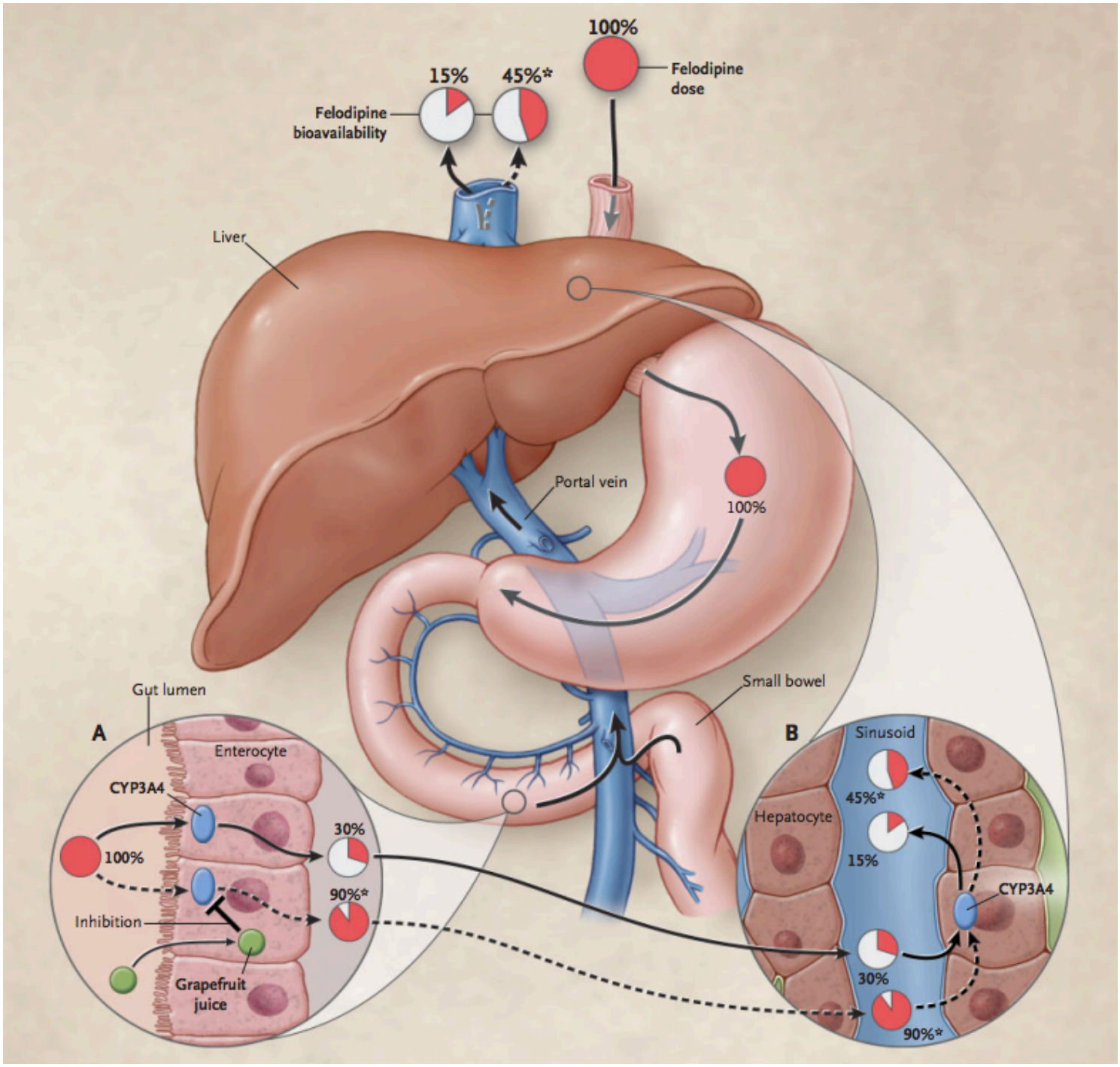
100%
Felodipine dose
15%
45%*
Felodipine bioavailability
Liver
Portal vein
100%
Small bowel
Gut lumen
A
Enterocyte
CYP3A4
100%
30%
90%*
Inhibition
Grapefruit juice
B
Sinusoid
45%*
Hepatocyte
15%
CYP3A4
30%
90%*

Figure 2 CYP 450 Inhibition

Source: Illustration by John J. Faragon, PharmD

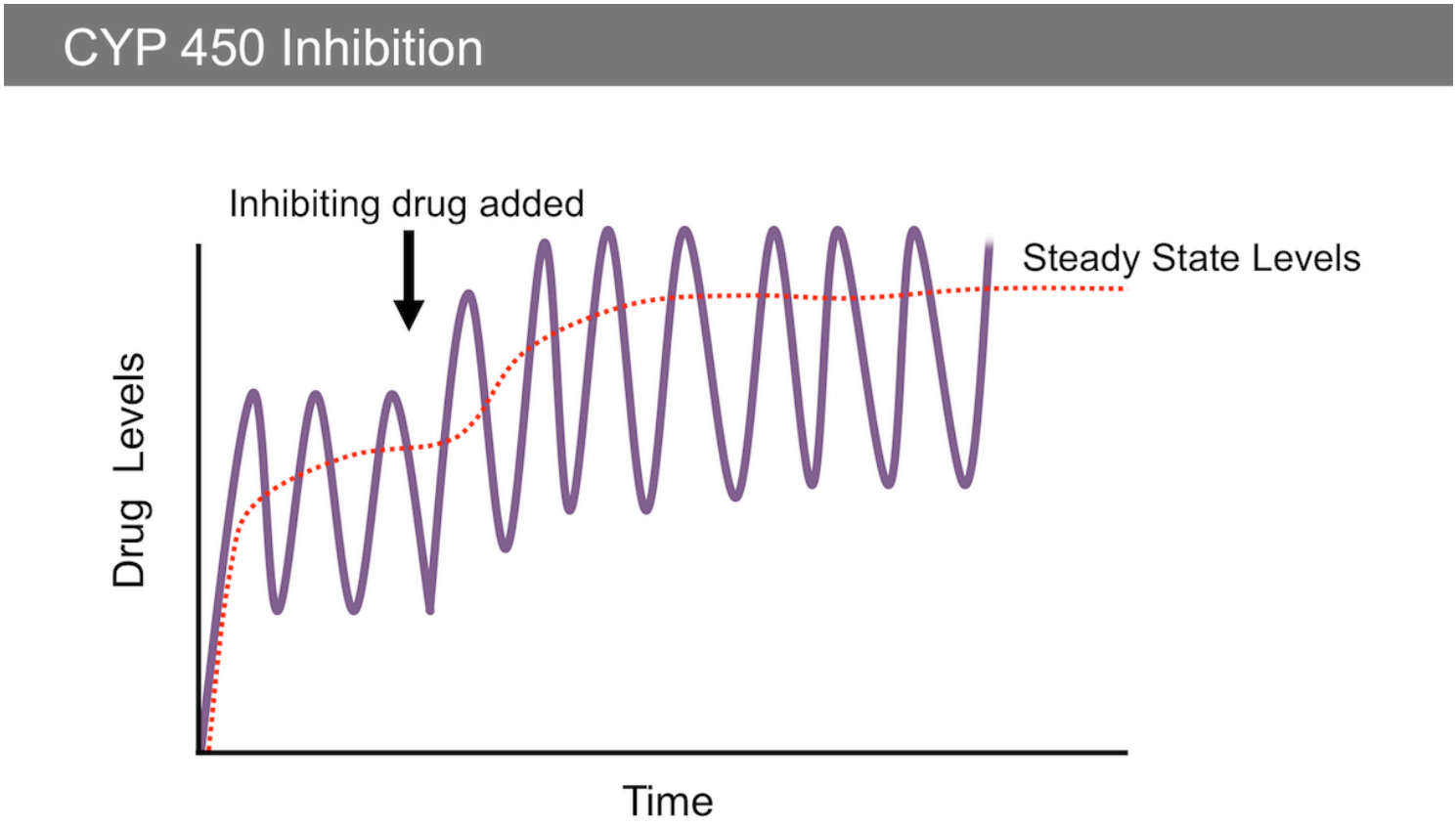

Figure 3 CYP 450 Induction

Source: Illustration by John J. Faragon, PharmD

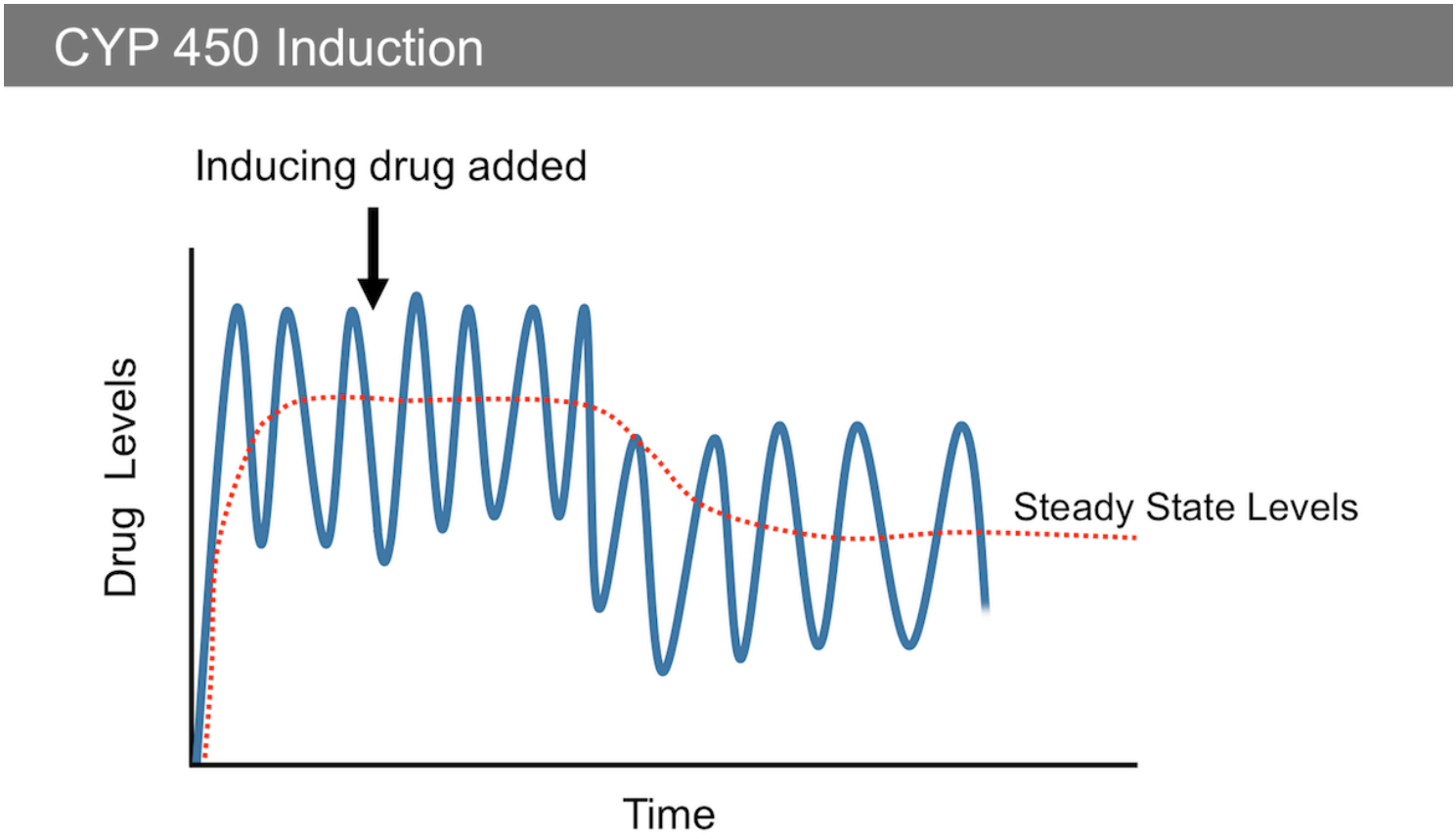

Figure 4 Ritonavir-Boosted Saquinavir Interactions with Statins

Source: Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS. 2002;16:569-77. Reproduced with permission from Lippincott Williams & Wilkins

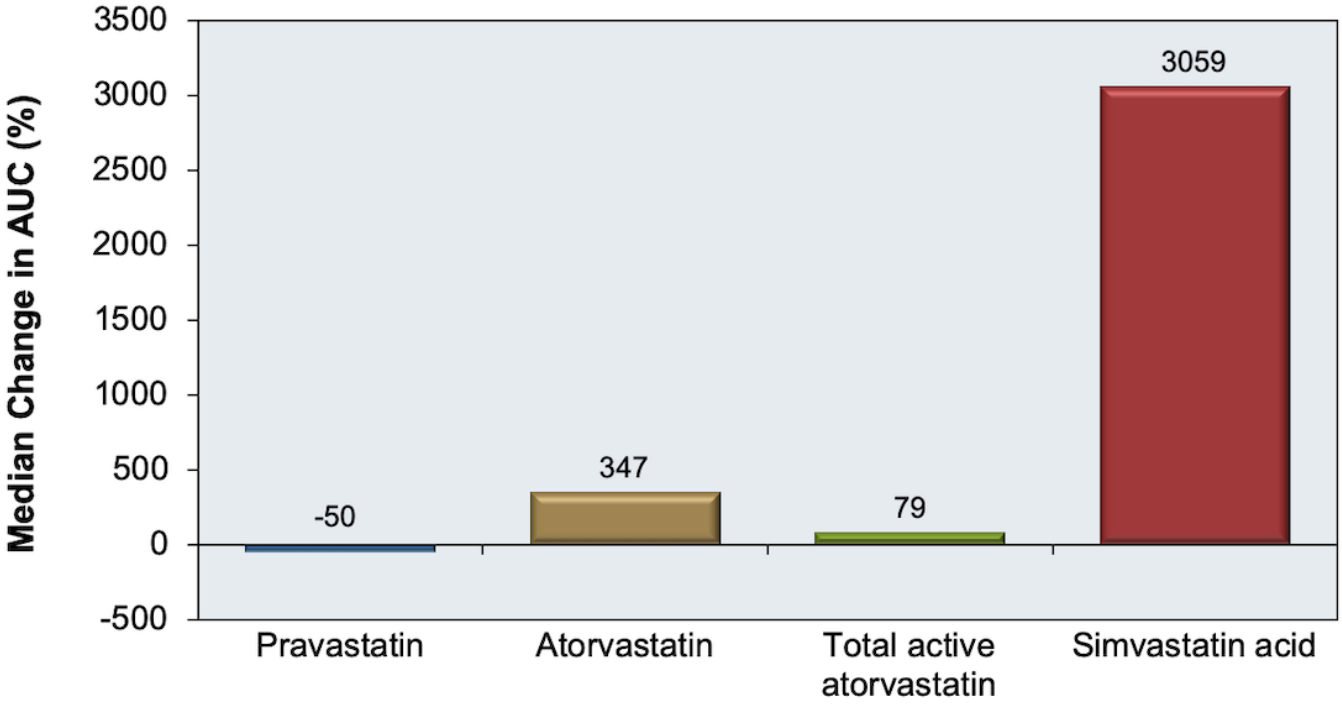

Table 1.

Pharmacokinetic Drug Interactions

Interaction	Comment
Absorption	Concurrent therapy or food ingestion results in increase or decrease in drug absorption, thereby increasing or decreasing bioavailability.
Distribution	Concurrent therapy leads to protein binding displacement, altering the activity of either drug.
Metabolism	Therapy induces or inhibits CYP450 enzymes, thereby increasing or decreasing drug concentration.
Excretion	Concurrent therapy results in enhanced or decreased renal excretion of drug.