ART Drug-Drug Interactions

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Purpose of this Resource

The New York State Department of Health (NYSDOH) AIDS Institute (AI) developed this reference for clinicians who manage the care of patients with HIV to accomplish the following:

- Provide a central source of information on drug-drug interactions involving antiretroviral (ARV) medications.
- Assist healthcare providers in preventing or managing drug-drug interactions that could have a negative or dangerous effect on patient health.
- Balance the risks and benefits of noted drug-drug interactions to identify those that should or must be avoided and those that can be managed to alleviate adverse outcomes.

The NYSDOH AI Medical Care Criteria Committee offers guidance on the interactions between ARV agents and medications commonly used in the management of comorbid conditions seen in care settings, based on a comprehensive review of available clinical trial data.

This guideline supports the NYSDOH Ending the Epidemic Initiative by providing a tool for clinicians to use in safely prescribing antiretroviral therapy (ART). ART initiation is now recommended for all patients diagnosed with HIV to improve the health of the patient, optimize virologic suppression, and reduce transmission of HIV (see NYSDOH AI guideline When to Initiate ART). This reference supports proper management of ART.

Scope: This resource does not provide an exhaustive survey of all possible interactions between ARVs and other medications. The focus is on those interactions most commonly encountered. Several robust free online resources are available to check specific drug-drug interactions, including the following:

- University of Liverpool HIV Drug Interaction Checker
- UCSF HIV InSite Database of Antiretroviral Drug Interactions
- WebMD Drug Interaction Checker
- AIDSinfo Drug–Drug Interactions

Consultation with an experienced HIV care provider is also recommended when assistance is needed in choosing an ART regimen for a patient who has multiple comorbidities and may have multiple drug–drug interactions. For help locating an experienced HIV care provider, contact the Clinical Education Initiative at 866-637-2342.

Identifying Drug-Drug Interactions

Individuals with HIV have a greatly increased risk of exposure to polypharmacy, especially as the population ages [Edelman, et al. 2013; Gleason, et al. 2013]. The use of several concomitant medications can have unintended consequences, including increased risk of drug-drug interactions and associated adverse events such as fatigue, nausea, and weight gain or loss. Drug-drug interactions may also decrease virologic control of HIV, increasing the risk of drug resistance and HIV-associated symptoms. Multiple factors may be associated with polypharmacy in patients. Physicians should be mindful of potential drug–drug interactions as a possible mechanism for new symptoms or unexpected medical events [Davies and O'Mahony 2015].

Drug–drug interactions can occur regardless of age or disease state. Any of the following potential risk factors for polypharmacy may signal the need to update a patient’s medication list and evaluate the potential for drug–drug interactions:

- Longstanding illness, chronic conditions, or disability [Walckiers, et al. 2015; Zingmond, et al. 2017].
- Age older than 50 years: Comorbidities commonly seen in an aging population, such as hypertension, chronic obstructive pulmonary disease, and diabetes mellitus, are increasingly prevalent in patients with HIV [Gleason, et al. 2013]. As people age, more diseases develop, which increases the risk of polypharmacy. Further, age-related physiologic changes may alter drug response in older patients [Gujjarlamudi 2016].
• Treatment provided by more than 1 care provider (including specialty providers) and limited communication between providers.
• Filling prescriptions at multiple pharmacies.
• Recent hospitalization: Hospitalization may be the result of adverse reactions caused by drug-drug interactions, or interactions may result during transitions of care or because of medication changes for formulary decisions [Mixon, et al. 2015; Walckiers, et al. 2015].

→ KEY POINT

• People with HIV may experience a greater number of comorbid conditions as they age. Treatment of multiple comorbid conditions increases the risk of polypharmacy and associated drug-drug interactions.

**Beneficial Concomitant Drug Use**

Drug-drug interactions are most commonly thought of as having a negative effect on a patient’s quality of life, but beneficial drug-drug interactions may also occur. Beneficial concomitant drug use can work in multiple ways [Trevor, et al. 2015].

**Pharmacodynamic synergy:** The most common positive outcome of drug-drug interactions is pharmacodynamic synergy, which is the combination of 2 or more drugs in which the shared effect is greater than the effect of either agent used alone.

Examples of this type of interaction include the combined use of antiretroviral (ARV) agents from multiple classes to manage a patient’s HIV infection. Combining agents with multiple mechanisms of action suppresses replication of the virus to a greater extent and for a longer period than use of a single agent and reduces the risk of resistance to any single ARV. The use of multiple pharmaceutical agents to treat 1 medical condition is also beneficial for a number of the comorbidities that people with HIV may develop, including hypertension, diabetes, chronic obstructive pulmonary disease, or some psychological disorders.

**Pharmacokinetic boosting:** Another positive drug-drug interaction results from use of a potent enzyme inhibitor to allow higher bioavailability of a second agent. This effect is commonly achieved in HIV therapy through pharmacokinetic boosting with ritonavir and cobicistat. Boosting makes possible once-daily dosing or lower dosing of ARVs, which may decrease adverse events caused by higher or more frequent dosing of the active agent. In turn, adherence may be improved by reduced pill burden. Similarly, use of a potent inhibitor of a drug transporter allows for reduced dosing or frequency of the second active agent. An example is the use of probenecid, an organic anion transporter inhibitor, to decrease the elimination of penicillins, such as penicillin, ampicillin, or nafcillin. This increases the clinical activity and efficacy of these agents.

In the current era of HIV treatment, it is well established that, when used as prescribed, 3-drug antiretroviral therapy (ART) regimens effectively suppress viral load over the long term. Ongoing research attempts to simplify ART regimens in an effort to reduce the number of ARVs that a patient must take long-term, thus reducing any long-term adverse effects or drug-drug interactions [Boswell, et al. 2018; Orkin, et al. 2018; Wandeler, et al. 2018]. However, simplifying a patient’s ART regimen can have unintended or unrecognized consequences. For instance, a switch from a boosted ART regimen that includes ritonavir or cobicistat to an unboosted regimen removes a cytochrome P450 (CYP) isoenzyme inhibitor, which may reduce concentrations of drugs that had previously been boosted, and reduce the therapeutic effects of any such concomitantly administered agents. Similarly, when switching from an unboosted regimen to a boosted regimen, a CYP inhibitor is added, which may increase the therapeutic effects or toxicities of other medications.

As a result, when new adverse events occur, a patient or clinician may attribute them to the new ART regimen, even if they are simply the result of a loss or addition of CYP inhibition. It is important to consider the effect of such simplification strategies on concentrations of all of a patient’s concomitantly administered medications. Doing so may prevent the addition of more medications to manage adverse events that could otherwise have been expected or avoided. For example, if ritonavir-boosted darunavir (which inhibits various CYP enzymes) is replaced with dolutegravir (which is not known to be an inhibitor of CYP enzymes), then a low dose of a psychotropic medication known to be a substrate of any of these enzymes may have to be increased to maintain therapeutic effect.
KEY POINT

• When simplifying ART regimens, it is important to identify the potential effects that a loss (or gain) of CYP inhibition may have on every drug (not just ARVs) that an individual is taking.

Risks of Concomitant Drug Use

Combining drugs that have multiple mechanisms of action to achieve a similar therapeutic endpoint introduces the risk of additive adverse events. Although this is not seen when combining ARVs to suppress HIV viral load, it can be seen when combining antihypertensive agents (which may cause hypotension) or antidiabetic drugs (which may lead to additive hypoglycemia). In addition, an additive effect may result from medications with overlapping adverse event profiles. A historic example is the use of zidovudine with other drugs that cause bone marrow suppression, including ribavirin or ganciclovir [Aulitzky, et al. 1988; Sim, et al. 1998].

Potent inhibitors: The use of potent inhibitors of metabolizing enzymes or drug transport proteins, such as protease inhibitors, may also lead to negative clinical outcomes (e.g., toxicities). Pharmacokinetic boosting, which is described as a potential beneficial drug-drug interaction in the section Beneficial Concomitant Drug Use, above, can have adverse outcomes if boosting leads to an undesired increase in the level of a concomitantly administered drug. When patients experience adverse events, they are more likely to discontinue medications. Adverse events also increase the number of patient visits to healthcare providers and may lead to prescription of additional medications to treat the adverse symptoms caused by the original medication, thus perpetuating the cycle of polypharmacy.

Potent inducers: The use of potent inducers of metabolizing enzymes or drug transport proteins, such as efavirenz or nevirapine, also has the potential to result in negative clinical outcomes. By increasing the metabolism or elimination of pharmacotherapeutic agents, reduced concentrations of these drugs are available to exert the expected therapeutic effect. Reducing ARVs to subtherapeutic levels can compromise viral suppression and increase the potential for resistance mutations. When simplifying ART by removing strong inducers of CYP isoenzymes, clinicians should remember that the loss of CYP induction may also affect all concomitant medications that a patient is taking, not just the ARVs.

For example, if efavirenz (which induces various CYP enzymes) is replaced with dolutegravir (which is not known to be an inhibitor of CYP enzymes) in a patient who was previously taking high doses of a methadone (which is a substrate of several CYP enzymes), then the dose of methadone may have to be decreased to maintain the same therapeutic effect that was seen while the patient was taking efavirenz, but without precipitating overdose.

Clinical Considerations and Prevention of Medication-Related Adverse Events

Box 1: Medication Review and Prescribing Checklist

At each clinical visit, ask patients about the following:

- Current medication list, including prescription medications, over-the-counter medications, supplements, and herbal preparation (see discussion below).
- Any changes in medications or dosages since the last visit and medication review.
- Current medical conditions being treated or that require treatment.
- Previous medical conditions that have been resolved to check for medications that should be discontinued.

When prescribing new medications or renewing a prescription, always:

- Identify the new drug’s potential to cause adverse events and current or future drug-drug interactions.
- Identify any potential interactions between an existing prescription medication and any new medications on the patient’s list.
- Inform patients about the potential for drug-drug interactions and/or side effects when taking ARVs that interact with commonly available over-the-counter medications, including nasal steroids, mineral supplements, antacids, or proton pump inhibitors.
In reviewing medications, note all current prescription and over-the-counter medications (i.e., oral, inhalers, eye drops, eardrops, throat lozenges, suppositories, and topical medications), injectable drugs (including biologic agents and vaccines), complementary products (i.e., vitamins, supplements, and herbal products), and social and recreational drug use.

Clinicians can take several additional steps to prevent or alleviate unnecessary adverse events, such as encouraging patients to avoid seeing multiple prescribers, to avoid filling their prescriptions at multiple pharmacies, and to keep each of their healthcare providers informed of treatment decisions made by other specialists [Lehnbom, et al. 2014; Lavan, et al. 2016]. Prescribers are encouraged to work closely with clinical pharmacists and, in settings where this is possible, to consider collaborative drug therapy management agreements with these pharmacists [McBane, et al. 2015].

Healthcare providers can assist patients in structuring detailed medication lists to be readily available in case of emergencies. This list should include the patient’s:

- Medication allergies and intolerances.
- Prescription drugs.
- Pharmacy and contact information.
- Over-the-counter drugs and vitamins.
- Herbal or supplemental products.

With the help of their care providers, patients can update their medication list at each medical appointment to ensure its accuracy [Rose, et al. 2017]. For each medication listed, the following information should be included [McBane, et al. 2015]:

- Name of medication.
- Appropriate dosing.
- Indication for each medication, including those taken “as needed.”
- How and when each medication should be taken.
- How long each medication will be taken.
- What foods, beverages, or medications to avoid while taking each medication.
- Adverse events a medication may cause.
- Special monitoring a medication may require.

Electronic health records have streamlined the process of prescribing and dispensing medications and may even flag the potential for new therapeutic duplication, adverse drug reactions, or drug-drug interactions. Unfortunately, clinical decision support (CDS) systems, which aim to alert clinicians to therapeutic duplications, inappropriate dosages, or drug-drug interactions, are not without their drawbacks. Busy clinicians who receive more notifications than they can attend to may ignore important alerts [Wright, et al. 2018]. Such “alert fatigue” can potentially compromise patient safety. Efforts to further refine and/or customize the information detailed in these CDS alerts are ongoing. However, clinicians should be aware of the risks associated with alert fatigue when utilizing electronic health records or prescribing systems.

Electronic health records are not a replacement for direct review of a patient’s current medications or other drugs being taken. Care providers using electronic health records are at risk of missing important drug information if they fall victim to alert fatigue [Zahabi, et al. 2015].

The New York Medicaid Electronic Health Records Incentive Program is currently available to support care providers in improving interoperability and patient access to health information.

⇒ KEY POINT

- Clinicians utilizing electronic prescribing systems should be aware of the risks associated with “alert fatigue,” including the potential to miss drug-drug interaction alerts.

**Medication therapy management (MTM) model:** The MTM model was created in collaboration with 11 national pharmacy organizations and offers a useful approach to assessing and managing patient health concerns when disciplines work separately to care for a single patient. Centers for Medicaid and Medicare Services (CMS) must participate in MTM programs, and the goals of these programs are to optimize therapeutic outcomes through improved medication use, to reduce the risk of adverse drug events and drug-drug interactions, and to improve medication adherence. The CMS website provides more information on requirements and services. Core elements of the MTM model include [American Pharmacists Association 2018]:
• Medication therapy review, which is a systematic process of collecting patient-specific information to assess medication therapies in order to identify a prioritized list of medication-related problems and create a plan to resolve them.

• Creation of a personal medication record (PMR) and medication-related action plan to address possible interventions and make appropriate referrals, including documenting these procedures.
  – The PMR is a comprehensive record of all of a patient’s medications, including herbal products, over-the-counter products, and dietary supplements, and is intended for patients to use in medication self-management.
  – Updated PMRs should be created with any medication change.
  – The medication-related action plan is a patient-centric document containing a list of actions that the patient can take to improve his or her own self-management and includes only information that is within the pharmacist’s scope of practice or has been agreed on by other relevant members of the healthcare team.

• Pharmacotherapy consults, which incorporate a pharmacist’s expertise for safe, appropriate, and cost-effective use of medications, for patients who have already developed medication-related problems or who are at high risk of developing them.

These strategies have several important benefits, including preventing or managing adverse medication reactions and hypersensitivities. They ensure an adequate diagnosis and indication for each therapy and help determine whether symptoms are caused by a medical condition or are simply effects of a medication the patient is already taking. It also aids in transitions of care, including transitions from primary to specialty care or from ambulatory care to inpatient facilities. Such documents also aid in future treatment decisions and allow for appropriate patient education about drug effects and adherence. They may also reduce polypharmacy and healthcare costs by assuring a patient is not given medication simply to treat adverse drug reactions or manage drug-drug interactions.

Pharmacist care services and comprehensive medication management are also considered integral components of the patient-centered medical home [Patient-Centered Primary Care Collaborative 2012].

<table>
<thead>
<tr>
<th>→ KEY POINT</th>
</tr>
</thead>
<tbody>
<tr>
<td>• An accurate medication history helps to prevent errors with prescription, over-the-counter, and supplement and/or herbal medications.</td>
</tr>
</tbody>
</table>

**Therapeutic drug monitoring (TDM):** TDM of drug concentrations from plasma, serum, or blood is used to individualize dosing of narrow therapeutic index drugs, allowing drug concentrations to be maintained within a specific target range. Although measurement of drug concentration at the site of action is not always possible, it is believed that with TDM, the concentration of a drug in intracellular fluids is more closely associated with therapeutic and adverse effects than the dose of a medication. TDM is most commonly performed for medications that have a narrow therapeutic window and significant pharmacokinetic variability. Medications that are dosed based on TDM include immunosuppressant drugs used to prevent organ rejection (e.g., cyclosporine and tacrolimus), anti-seizure medications (e.g., phenytoin and carbamazepine), and mood stabilizers (e.g., lithium and lamotrigine). Certain antibiotics, including vancomycin or aminoglycosides, are also dosed based on TDM.

The use of TDM with dosing of ARVs is not currently recommended in the routine management of most patients with HIV. However, limited prospective data suggest that certain clinical scenarios exist in which TDM may be beneficial, such as suspicion of clinically significant drug-drug interactions that result in reduced plasma concentrations of an ARV, which may reduce viral control, or when such interactions result in increased concentrations of an ARV, thereby increasing the risk of adverse drug effects [AIDShivf 2015]. The effects may be more pronounced when drug-drug interactions are accompanied by pathophysiologic changes that alter the pharmacokinetics of a drug, including its absorption, distribution, metabolism, or excretion. These changes include, but are not limited to, reduced renal or hepatic function, vomiting or other conditions that reduce absorption, and pregnancy.

**Resources**

Online and print materials are available to help healthcare professionals and patients with the management of interactions between ARVs and other commonly used medications. Use caution when consulting print resources and/or online resources that are not routinely updated, because drug-drug interaction data change consistently with new research, case reports, or approval of new medications by the U.S. Food and Drug Administration.
Classifications and Mechanisms of Drug-Drug Interactions

Antiretroviral (ARV) medications themselves, though increasingly safe and effective, may cause adverse events that affect organ systems [Dharan and Cooper 2017; Gallant, et al. 2018]. Tenofovir disoproxil fumarate (TDF) has been shown to reduce bone mineral density and may impair renal function. Tenofovir alafenamide (TAF) does not appear to have a similar effect on bone density or kidney function, and increased bone density and improved renal function has been observed in patients who are switched from TDF to TAF [Chan, et al. 2017; Raffi, et al. 2017]. Controversial and conflicting data suggest a possible association between abacavir and cardiovascular disease [Llibre and Hill 2016]. A convincing pathophysiologic mechanism for this association has not yet been described and is likely to be multifactorial [Alvarez, et al. 2017]. Association should not imply causation, but caution may be warranted when prescribing abacavir to patients with underlying risk factors for cardiovascular disease. Boosted protease inhibitors (PIs) and some non-nucleoside reverse transcriptase inhibitors may exacerbate metabolic disorders by reducing insulin sensitivity or causing lipid abnormalities [Carr, et al. 1998; Noor, et al. 2004; Aberg, et al. 2012]. These inherent adverse events may lead to poor control and the need for additional concurrent medications for management of these metabolic conditions. An unintended consequence of the additional medications is the increased likelihood of drug-drug interactions.

Table 1: Mechanisms of Antiretroviral (ARV) Drug-Drug Interactions, below, shows the influence of specific ARVs on liver enzymes and describes the effect of specific ARVs on these drug transport proteins.

Pharmacodynamic Interactions

Pharmacodynamic interactions are drug-drug interactions that involve the direct effects of the interacting drugs and a change in a patient’s response to the drugs [Trevor, et al. 2015]. Pharmacodynamic interactions may involve pharmacologic receptors, and drugs may be agonists or antagonists of other drugs.

- Pure agonists attach to the same binding site receptor as another drug, thus causing the same effect.
- Partial agonists bind to a different receptor site on the same receptor and may cause the same effect as another drug, but to a lower intensity.
- Antagonists attach to the same receptor site as another drug, but the effect of this binding opposes the effect seen with another drug.

An example of a pharmacodynamic interaction is the concomitant use of zidovudine with other drugs that cause bone marrow suppression, including ribavirin or ganciclovir.

To minimize pharmacodynamic interactions, identify and address potential additive or antagonistic physiologic effects when treating a patient with more than 1 medication. Adding or removing a pharmacokinetic booster from a patient’s medication regimen may alter the levels of coadministered drugs and affect the efficacy or safety of these drugs.
<table>
<thead>
<tr>
<th>ARV</th>
<th>CYP Substrate</th>
<th>CYP Inhibitor</th>
<th>CYP Inducer</th>
<th>UGT1A1</th>
<th>Drug Transport Protein</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Integrase Strand Inhibitors (INSTIs)</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>BIC [2]</td>
<td>3A4 (minor)</td>
<td>—</td>
<td>—</td>
<td>Substrate</td>
<td>Inhibitor of: MATE1; OCT2</td>
<td>Chelation</td>
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<tr>
<td>DTG [3]</td>
<td>3A4 (minor)</td>
<td>—</td>
<td>—</td>
<td>Substrate</td>
<td>P-gp substrate; inhibitor of MATE2, OCT2</td>
<td>Chelation</td>
</tr>
<tr>
<td><strong>Pharmacokinetic Boosters</strong></td>
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<tr>
<td>COBI [6]</td>
<td>3A4; 2D6 (minor)</td>
<td>3A4; 2D6 (minor)</td>
<td>—</td>
<td>—</td>
<td>Inhibitor of: P-gp; BCRP; OATP; OCT; MATE1</td>
<td>—</td>
</tr>
<tr>
<td>RTV [7]</td>
<td>3A4; 2D6 (minor)</td>
<td>3A4; 2C8; 2C9; 2C19; 2D6</td>
<td>1A2; 2B6; 2C9; 2C19</td>
<td>Inducer</td>
<td>Inhibitor of: P-gp; BCRP; OATP; OCT; MATE1</td>
<td>—</td>
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<tr>
<td><strong>Protease Inhibitors (PIs)</strong></td>
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<tr>
<td>ATV [8]</td>
<td>3A4</td>
<td>3A4; 2C8 (minor)</td>
<td>—</td>
<td>Inhibitor</td>
<td>P-gp substrate, inhibitor, inducer; OATP inhibitor</td>
<td>GI absorption (pH-dependent)</td>
</tr>
<tr>
<td>DRV [9]</td>
<td>3A4</td>
<td>3A4</td>
<td>2C9</td>
<td>—</td>
<td>P-gp substrate; OATP inhibitor</td>
<td>—</td>
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<tr>
<td><strong>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</strong></td>
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<td>DOR [10]</td>
<td>3A4; 3A5</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>EFV [11]</td>
<td>2B6 (primary); 2A6; 3A4</td>
<td>3A4</td>
<td>3A4; 2B6</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ETR [12]</td>
<td>3A4; 2C9; 2C19</td>
<td>2C9; 2C19</td>
<td>3A4</td>
<td>—</td>
<td>P-gp inducer</td>
<td>—</td>
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<td>RPV [13]</td>
<td>3A4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Gl absorption (pH-dependent)</td>
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<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
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<tr>
<td>ABC [14]</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Substrate of: MATE1 substrate</td>
<td>Alcohol dehydrogenase substrate</td>
</tr>
<tr>
<td>FTC [15]</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>MATE1 substrate</td>
<td>—</td>
</tr>
<tr>
<td>3TC [16]</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Substrate of: MATE1/2; OCT2</td>
<td>—</td>
</tr>
<tr>
<td>TAF [17]</td>
<td>3A4 (minor)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>Substrate of: P-gp; BCRP; OATP</td>
<td>—</td>
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<tr>
<td>TDF [18]</td>
<td>—</td>
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<td>—</td>
<td>Substrate of: P-gp; OATP; MRP</td>
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<tr>
<td><strong>Entry Inhibitor</strong></td>
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<tr>
<td>MVC [19]</td>
<td>3A4</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>P-gp substrate</td>
<td>—</td>
</tr>
</tbody>
</table>
Table 1: Mechanisms of Antiretroviral (ARV) Drug-Drug Interactions [1]*

<table>
<thead>
<tr>
<th>ARV</th>
<th>CYP Substrate</th>
<th>CYP Inhibitor</th>
<th>CYP Inducer</th>
<th>UGT1A1</th>
<th>Drug Transport Protein</th>
<th>Other</th>
</tr>
</thead>
</table>

Table 1A: Induction Potential of Ritonavir* and Cobicistat Used as Boosters [Foisy, et al. 2008; Marzolini, et al. 2016; Tseng, et al. 2017]

<table>
<thead>
<tr>
<th>Cytochrome</th>
<th>Ritonavir</th>
<th>Cobicistat</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>Moderate inducer</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>CYP2B6</td>
<td>Moderate inducer</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>Moderate inhibitor</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>Moderate inducer</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>Strong inducer</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>Moderate inhibitor</td>
<td>Mild inhibitor</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>Strong inhibitor</td>
<td>Strong inhibitor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Transporter</th>
<th>Ritonavir</th>
<th>Cobicistat</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gP</td>
<td>Moderate inhibitor</td>
<td>Moderate inhibitor</td>
</tr>
<tr>
<td>UGT</td>
<td>Moderate inducer</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>BCRP</td>
<td>Moderate inhibitor</td>
<td>Moderate inhibitor</td>
</tr>
<tr>
<td>OATP1B1</td>
<td>Moderate inhibitor</td>
<td>Moderate inhibitor</td>
</tr>
<tr>
<td>OATP1B3</td>
<td>Moderate inhibitor</td>
<td>Moderate inhibitor</td>
</tr>
<tr>
<td>MATE1</td>
<td>Moderate inhibitor</td>
<td>Moderate inhibitor</td>
</tr>
<tr>
<td>MATE2-K</td>
<td>Clinically negligible effect</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>OAT1</td>
<td>Clinically negligible effect</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>OAT3</td>
<td>Weak inducer</td>
<td>Clinically negligible effect</td>
</tr>
<tr>
<td>OCT2</td>
<td>Clinically negligible effect</td>
<td>Clinically negligible effect</td>
</tr>
</tbody>
</table>

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; IC, inhibitory concentration; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting protein; OCT, organic cation transporter; P-gP, P-glycoprotein; UGT, uridine 5′-diphospho-glucuronosyltransferase. *The information above is expected when ritonavir is given at doses used to boost other protease inhibitors. Effects may change at higher doses of ritonavir because this drug has a mixed effect (both induction and inhibition) on several CYP isoenzymes when studied at higher doses.
Pharmacokinetic Interactions

Pharmacokinetic interactions involve the modification of drug absorption, distribution, metabolism, and excretion [Trevor, et al. 2015].

Absorption: Modification of gastric pH will influence the absorption of drugs that require the acidity of the stomach (e.g., the absorption of both rilpivirine and atazanavir are reduced when these drugs are given concomitantly with proton pump inhibitors such as omeprazole [Klein, et al. 2008; Schafer and Short 2012]). Some substances will form insoluble complexes with other drugs in a process known as chelation (e.g., the use of integrase inhibitors such as raltegravir with divalent or trivalent cations such as aluminum and magnesium [Wallace, et al. 2003]). Medications that influence the motility of the gastrointestinal tract may also affect absorption of other drugs.

Distribution: When 2 medications that are heavily protein bound are given at the same time, competition for protein binding sites leads to an increase in free drug concentrations, which are available to exert therapeutic effects or increase toxicity of the medications. In most cases, a rapid equilibrium is reached between the free and bound drugs, and these drug-drug interactions are rarely clinically significant [Benet and Hoenier 2002]. An exception is when a drug has a narrow therapeutic index (e.g., warfarin, digoxin, lithium, and aminoglycoside antibiotics); displacement of such a drug may have a dramatic effect on the level of activity of the agent [Zaccara and Perucca 2014].

Metabolism: The liver is the major site of drug metabolism, which occurs in 2 phases. Medications that alter phase I metabolism affect the oxidation, reduction, or hydrolysis of another medication. This typically involves the cytochrome P450 (CYP) isoenzymes, and drugs are classified as substrates, inducers, or inhibitors of specific enzymes. One of the most commonly described CYP enzymes is 3A4, which is responsible for the metabolism of many commonly used medications. However, other enzymes exist, and many play important roles in interactions related to ARVs. Each enzyme has a specific action: some drugs may be substrates, inhibitors, or inducers of more than 1 enzyme, and may even be substrates of one while inhibiting or inducing others. This creates complex interaction possibilities, and the therapeutic effects of these interactions may be unknown.

A drug is defined as a substrate if a certain enzyme metabolizes it. Rilpivirine and maraviroc are substrates of CYP3A4 [Perry 2010; Deeks 2014d]. Enzyme inducers increase the numbers of specific enzyme subtypes inside the body, thus increasing the metabolism of substrates of that enzyme or reducing the drug’s bioavailability. Examples of strong CYP3A inducers include efavirenz and rifampin [Ogburn, et al. 2010]. Moderate inducers of CYP3A include etravirine [Deeks and Keating 2008]. Some drugs, including nevirapine, autoinduce their own metabolism, causing the lead-in period seen when dosing that drug [Cammett, et al. 2009]. Inhibitors block metabolism of substrate drugs by directly binding to enzymes, increasing the bioavailability of substrate drugs. The most common examples of CYP3A inhibitors are the pharmacokinetic enhancers ritonavir and cobicistat and other PIs [Deeks 2014a; Tseng, et al. 2017].

Drugs that alter phase II metabolism affect glucuronidation, methylation, sulfation, or other forms of conjugation. Careful monitoring for therapeutic efficacy and safety are required in these circumstances. Examples of this type of enzyme include uridine diphosphate glucuronosyltransferase (UGT), which also plays a role in the glucuronidation of some drugs, including integrase strand transfer inhibitors (INSTIs) [Adams, et al. 2012]. Other agents, such as atazanavir, can inhibit UGT enzymes [Gammal, et al. 2016]. The interaction between raltegravir and atazanavir is of limited clinical significance. However, rifampin also induces UGT enzymes, and concomitant administration of rifampin and INSTIs greatly reduces bioavailability of these drugs, often necessitating dose adjustments [Miller, et al. 2017].

Excretion: Renal elimination involves both passive and active processes. Tubular secretion is a drug transport protein-mediated process, and competitive inhibition of tubular secretion is a common mechanism of drug-drug interactions in the kidney. Other drugs are more rapidly eliminated in acidic or alkaline urine, and alterations in the urine pH will influence rate of elimination.

To minimize pharmacokinetic interactions, identify and address a drug’s effect on metabolizing enzymes or drug transport proteins when treating a patient with more than 1 medication [Trevor, et al. 2015]. Consider Table 1: Mechanisms of Antiretroviral (ARV) Drug-Drug Interactions, above, as a helpful starting point, but be aware that the chart is not meant to be a finite resource on the pharmacokinetic effects of the listed ARV agents.

Other Drug-Drug Interactions

Drug-drug interactions may also result from modification of drug transport proteins, which exist throughout the body (e.g., kidney, liver, small intestine, and blood-brain barrier). As their name suggests, these drugs are important in the transfer of a drug or other endogenous substance from one body compartment to another [Ivanyuk, et al. 2017; Yoshida, et al. 2017]. P-glycoprotein (P-gP) is a well-known example of a drug transport protein, and this efflux transporter
attempts to keep foreign substances, including some drugs, out of a cell [Lund, et al. 2017]. Inducing P-gP may decrease the amount of drug inside a cell, reducing its therapeutic efficacy. Inhibiting P-gP may increase the amount of drug inside a cell, increasing its efficacy, or leading to adverse events.

Several other drug transport proteins have been discovered, and families of these proteins include multidrug and toxin extrusion, organic cation transporter [Yin, et al. 2016], organic anion transporter, breast cancer resistance protein [Mao and Unadkat 2015], and organic anion transporting polypeptide (OATP) enzymes [Kovacsics, et al. 2017; Yu, et al. 2017]. The clinical significance of these proteins or the influence of drugs on the activity of these proteins is incompletely understood, but this area of pharmacotherapeutic research is rapidly evolving. An example of such an interaction is TDF with diclofenac [Morelle, et al. 2009], which are both substrates of OATP1B3 and compete for renal secretion. This increases the levels of these agents and may increase the risk of tubular toxicity due to prolonged tenofovir availability inside the tubular cells.

### Drug-Drug Interactions by Antiretroviral (ARV) Drug Class

<table>
<thead>
<tr>
<th>RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinicians should consult an experienced HIV care provider for assistance in managing drug-drug interactions between antiretroviral (ARV) agents and less common medications. (A3)</td>
</tr>
</tbody>
</table>

**Caveats:** Many of the formal interaction studies involving ARVs are carried out in small samples of patients who do not have HIV or other known comorbid conditions. Although the results of such studies may be extrapolated to larger populations of patients with HIV, several important considerations should be kept in mind. The U.S. Food and Drug Administration has issued draft guidance on the design, analysis, and clinical implications of drug-drug interaction studies to aid in the interpretation of future interactions [FDA 2017].

Given the limited financial and clinical resources available to researchers, it is impossible to design and run randomized controlled trials to determine the effects of every possible drug-drug interaction. Therefore, many drug-drug interactions are theoretical—based not on evidence or data, but instead on what is known about the pharmacokinetic properties of the various individual agents. As a result, there is often an incomplete correlation between predicted drug-drug interactions and in vivo pharmacokinetics. There is also significant person-to-person variability in drug-drug interactions, and small sample sizes may not be adequate to identify the effects such an interaction may have on a specific patient.

Patients with HIV may be at greater risk of pharmacokinetic variability due to the nature of the infection itself or the drugs taken for antiretroviral therapy (ART). At the same time, both the medications and HIV itself may alter the physiologic processes of the liver, kidney, brain, gastrointestinal system, or other organ systems, which may affect absorption, distribution, metabolism, or elimination of pharmacologically active agents. Additionally, patients with HIV are at a greater risk of the effects of polypharmacy, and the effects of multiple drugs on the pharmacokinetic pathways or pharmacodynamic effects of a single agent are not well documented. Therefore, when treating patients who are taking several medications for multiple comorbid conditions, expert advice may be necessary and is often recommended to ensure appropriate management of drug-drug interactions.

ARVs can have complex interactions with other medications commonly used by patients with HIV. When questions arise regarding the management of drug-drug interactions not described here, a clinician cannot assume that no interaction exists. Several theoretical drug-drug interactions may exist given the unique nature of the pharmacokinetic and pharmacodynamic effects seen with each medication, and the clinical significance of these interactions is not always known. The interactions described here reflect medications used to treat comorbid conditions commonly seen in primary care or family health clinics.

Prescribers should become familiar with the potential for adverse effects and drug-drug interactions with all co-administered drugs they prescribe for their patients. Clinicians who manage the care of only a few patients with HIV may find it difficult to remember the potential mechanisms or effects of interactions between ARVs and other medications commonly seen in primary care settings, and drug-drug interactions may lead to symptoms attributed to ARV medications rather than the physiologic effect of an interaction. Consultation with a pharmacist or healthcare provider experienced in prescribing ART may assist in determining the true cause of symptoms and/or adverse effects. Adverse drug-drug interactions can be prevented when patients receive anticipatory guidance regarding possible interactions between prescribed medications and commonly available over-the-counter medications or supplements.
## Boosted Protease Inhibitors (PIs)

### Table 2: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton pump inhibitors (PPIs) [Falcon and Kakuda 2008; Kiser, et al. 2008; Brooks, et al. 2017]</td>
<td>ATV requires an acidic gastric pH for absorption, and acid-reducing agents interfere with the absorption of ATV.</td>
<td>• Do not coadminister if alternatives are possible; use alternative acid-reducing agent, or alternative PI, or boost ATV with RTV or COBI. • <strong>Treatment-naive:</strong> If use cannot be avoided, do not exceed omeprazole 20 mg per day or equivalent; administer 12 hours prior to ATV. • <strong>Treatment-experienced:</strong> 1) Consult with an experienced HIV care provider or a GI specialist. 2) Administer at least 12 hours before RTV- or COBI-boosted ATV.</td>
</tr>
</tbody>
</table>

| Histamine 2 receptor antagonist (H2RA) [Falcon and Kakuda 2008; Wang, et al. 2011; Brooks, et al. 2017] | ATV requires an acidic gastric pH for absorption, and acid-reducing agents interfere with the absorption of ATV. | • **Treatment-naive:** 1) Administer ATV 300 mg + RTV 100 mg simultaneously with, or at least 10 hours after H2RA. 2) Do not exceed famotidine 20 mg twice per day or equivalent [a] if patient is not taking TFV. 3) Do not exceed famotidine 40 mg twice per day or equivalent [a] if patient is taking TFV. • **Treatment-experienced:** 1) In second and third trimesters of pregnancy [b], increase dose to 400 mg per day. 2) H2RA use is contraindicated if pregnant patient takes TFV + boosted ATV. 3) If patient is taking TFV, ATV is dosed at 400 mg when boosted; unboosted ATV is not recommended. 4) Give drugs at the same time, or give ATV more than 10 hours after H2RA. 5) Administer ATV 300 mg + COBI 150 mg or RTV 100 mg simultaneously with and/or ≥10 hours after dose of H2RA. a. H2RA dose equivalents twice per day: famotidine 20 mg (40 mg), ranitidine 150 mg (300 mg), nizatidine 150 mg (300 mg). b. The volume of distribution increases as duration of pregnancy increases, which damages the PK parameters of medications such as some PIs. PK boosting protects some of these PIs, but caution is required during the second and third trimesters of pregnancy to ensure adequate therapeutic concentrations. |

| Antacids [Brooks, et al. 2017] | ATV requires an acidic gastric pH for absorption, and acid-reducing agents interfere with the absorption of ATV. | Give ATV 2 hours before or 1 to 2 hours after antacids (and all buffered medications). |
### Table 2: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Simvastatin, lovastatin [Chauvin, et al. 2013; Feinstein, et al. 2015]</td>
<td>• Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and the drug transporter P-gP. Greatly increases concentrations. • COBI is an inhibitor of CYP3A4, CYP2D6, OATP1B1, and P-gP.</td>
<td>• Avoid concomitant use due to potential for myopathy, including rhabdomyolysis. • Consider use of low doses of alternative statins less likely to be affected by boosted ATV use.</td>
</tr>
<tr>
<td>Pravastatin [Kis, et al. 2013]</td>
<td>• Pravastatin is a substrate for OATP1B1. • ATV is an inhibitor of OATP1B1.</td>
<td>Use the lowest effective dose of pravastatin and monitor for adverse events, including myopathy and rhabdomyolysis.</td>
</tr>
<tr>
<td>Atorvastatin [Vildhede, et al. 2014]</td>
<td>• Atorvastatin is a substrate for CYP3A4 and OATP1B1. • Boosted ATV inhibits both CYP3A4 and OATP1B1. • May moderately increase concentrations. • Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. • Avoid atorvastatin use when combined with COBI-boosted ATV due to an increased risk of rhabdomyolysis and myopathy. • If atorvastatin use is necessary, do not exceed dose of 20 mg per day.</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin [Busti, et al. 2008]</td>
<td>• Rosuvastatin is a substrate of OATP1B1/1B3. • ATV is an inhibitor of OATP1B1. • May moderately increase concentrations.</td>
<td>Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. • If rosuvastatin use is necessary, start with 10 mg per day.</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>Interaction has not been studied, but potential for moderate increase is possible.</td>
<td>Do not use, but if clinical use is desired, use the lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.</td>
</tr>
<tr>
<td>Pitavastatin, pravastatin Anticoagulants, factor Xa inhibitors [Egan, et al. 2014]</td>
<td>Although moderate increases are possible, low doses are considered safe when used with boosted PIs.</td>
<td>Use with lowest effective doses; dose adjustments are not necessary when using these statins with boosted EVG. • Avoid concomitant use or use the lowest effective dose of the factor Xa inhibitor to avoid increased bleeding risk. • <strong>Apixaban:</strong> Reduce apixaban dose to 2.5 mg twice per day; if patient is already taking 2.5 mg twice per day, avoid concomitant use. • <strong>Dabigatran:</strong> 1) Separate doses of dabigatran and boosted PIs by at least 2 hours. 2) RTV-boosted PIs may be safer than COBI boosting when using concomitant dabigatran [Kakadiya, et al. 2018]. 3) Avoid dabigatran in patients taking boosted PIs if the patient also has renal impairment (CrCl &lt;50 ml/min). • <strong>Warfarin:</strong> Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. Decrease dose if INR increases. Increase dose slowly if INR decreases.</td>
</tr>
<tr>
<td>Class or Drug</td>
<td>Mechanism of Action</td>
<td>Clinical Comments</td>
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</tr>
<tr>
<td>PY2-antagonists</td>
<td>• Ticagrelor is rapidly metabolized by CYP3A.</td>
<td>• To avoid increased bleeding risk, do not use ticagrelor with strong inhibitors of CYP3A. Do not use with clopidogrel unless alternative antiplatelet drug cannot be used.</td>
</tr>
<tr>
<td>Egan, et al. 2014; Teng 2015</td>
<td>• May result in decreased concentrations of clopidogrel's active metabolite.</td>
<td></td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Boosted PIs inhibit P-gP, which may decrease aliskiren elimination, increasing risk of adverse events.</td>
<td>Do not coadminister.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>COBI-boosted PIs may increase atenolol concentrations via inhibition of MATE-1 elimination. Similar interaction is not seen with RTV-boosted PIs.</td>
<td>If atenolol must be used with boosted PIs, use RTV as the PK booster.</td>
</tr>
<tr>
<td>Calcium channel blockers (CCBs)</td>
<td>Boosted PIs may increase CCB concentrations by as much as 50%.</td>
<td>Decrease original dose of CCB by as much as 50% when using with boosted PIs and slowly titrate to effect.</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs [Roden, et al. 2007]</td>
<td>Boosted PIs inhibit anti-arrhythmic drug metabolism via CYP3A and CYP2D6.</td>
<td>Avoid concomitant use to avoid increased risk of QT prolongation and other adverse events of anti-arrhythmic drugs.</td>
</tr>
<tr>
<td>Anti-mineral corticoid (eplerenone) [Keating and Plosker 2004]</td>
<td>ATV inhibits the hepatic CYP3A4 isoenzyme and can increase the serum concentrations of eplerenone.</td>
<td>Avoid concomitant use due to increased risk of hyperkalemia and hypotension.</td>
</tr>
<tr>
<td>Glyburide</td>
<td>Drug is mainly metabolized via CYP3A, so concentrations are increased with boosted ARVs.</td>
<td>Use the lowest effective dose of glyburide and monitor for signs of hypoglycemia.</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Levels may be increased via inhibition of CYP3A.</td>
<td>Limit dose of saxagliptin to 2.5 mg once per day.</td>
</tr>
<tr>
<td>Canagliflozin</td>
<td>Could lead to reduced canagliflozin exposure as a result of ATV’s induction of UGT enzymes.</td>
<td>With RTV-boosted ATV and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg and has GFR &gt;60 ml/min/1.73 m².</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>Exenatide may inhibit gastric secretion, reducing absorption of ATV.</td>
<td>Consider taking ATV 4 hours before exenatide.</td>
</tr>
<tr>
<td>Long-acting beta agonists</td>
<td>Inhibition of CYP3A increases plasma concentrations of these agents.</td>
<td>• Concomitant use is contraindicated unless benefits outweigh the risks; consider use of alternative ARV agent. If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. Boosted PIs may also increase QT prolongation.</td>
</tr>
</tbody>
</table>
**Table 2: Boosted Atazanavir (ATV) Interactions** (also see drug package inserts)

<table>
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<tr>
<th>Class or Drug</th>
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<tbody>
<tr>
<td>Inhaled, intranasal, and injected</td>
<td>Boosted PIs are strong inhibitors of CYP3A, and many corticosteroids are substrates of these enzymes. Risk of</td>
<td>• Use beclomethasone if possible. This agent is less likely to be affected by boosted ATV use; thus is less likely to cause symptoms of Cushing’s syndrome and other systemic corticosteroid adverse events.</td>
</tr>
<tr>
<td>corticosteroids [Daveluy, et al. 2009; Saberi, et al. 2013]</td>
<td>Cushing’s syndrome when coadministered with the following corticosteroids:</td>
<td><strong>Intranasal or inhaled fluticasone, mometasone, ciclesonide, budesonide, and triamcinolone:</strong> Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone).</td>
</tr>
<tr>
<td></td>
<td>• Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone.</td>
<td>• Systemic betamethasone, budesonide: Do not coadminister unless potential benefits outweigh risk.</td>
</tr>
<tr>
<td></td>
<td>• Systemic: Betamethasone, budesonide, dexamethasone.</td>
<td>• Systemic prednisolone, prednisone: Contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.</td>
</tr>
<tr>
<td></td>
<td>• Injectable: Betamethasone, triamcinolone.</td>
<td>• Injectable betamethasone, triamcinolone: Contraindicated unless potential benefits outweigh risk.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Systemic dexamethasone: Contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid.</td>
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</tr>
<tr>
<td>Oral prednisone</td>
<td>• Prednisone is a CYP3A4 and P-gp substrate.</td>
<td>• Short-term use is not contraindicated.</td>
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<tr>
<td></td>
<td>• Boosted PIs are strong inhibitors of CYP3A4 and P-gp.</td>
<td>• For chronic use of prednisone, careful monitoring of immune function is warranted and dose adjustment may be considered with therapeutic efficacy and adverse events.</td>
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<tr>
<td>Benzodiazepines</td>
<td>• Benzodiazepines are substrates of CYP3A and may be increased in the presence of strong inhibitors of this enzyme.</td>
<td>• Alprazolam, clonazepam, diazepam: Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). If used, administer lowest effective dose; monitor closely for adverse events.</td>
</tr>
<tr>
<td></td>
<td>• Alprazolam: Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition.</td>
<td>• Diazepam: Monitor for excess sedation.</td>
</tr>
<tr>
<td></td>
<td>• Diazepam: Metabolism of diazepam may be reduced via inhibition of CYP3A4.</td>
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<tr>
<td>Antipsychotics</td>
<td>• Haloperidol: Potential for moderately increased haloperidol concentrations with boosted PIs.</td>
<td>• Quetiapine: Reduce dose to 1/6 if initiating ARVs in patients on stabilized quetiapine; monitor for QT prolongation. If initiating in patient stabilized on boosted PI, use lowest dose and titrate slowly to desired effect; monitor for QT prolongation.</td>
</tr>
<tr>
<td></td>
<td>• Aripiprazole, brexpiprazole: RTV-boosted PIs may increase levels of aripiprazole and brexpiprazole.</td>
<td>• Lurasidone: No data; avoid coadministration; consider alternative anti-psychotic or ARV agent.</td>
</tr>
<tr>
<td></td>
<td>• Risperidone: Potential for moderate increase in risperidone levels.</td>
<td>• Haloperidol: Monitor for QT prolongation.</td>
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</tbody>
</table>
### Table 2: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)

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<th>Class or Drug</th>
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</tr>
</thead>
<tbody>
<tr>
<td>HCV PIs (“-previr” drugs) [Soriano, et al. 2017]</td>
<td>Inhibition of CYP3A4 and OATP1B1 by ATV may increase the plasma concentrations of other PIs.</td>
<td>Avoid concomitant use to avoid adverse events of NS3/4A PIs.</td>
</tr>
</tbody>
</table>
| Etravirine (ETR) [Orrell, et al. 2015] | • ETR is a substrate and inducer of CYP3A4.  
• COBI is a substrate/inhibitor of CYP3A4.  
• ATV is a substrate and inhibitor of CYP3A4. | • Use with RTV-boosted ATV results in decreases in ATV exposure, but the decrease is not considered relevant; can be administered together without dose adjustments.  
• Due to the potential for decreased ARV efficacy, avoid use of ETR with COBI. When these drugs are given together, concentrations of COBI are decreased.  
• When possible, avoid concomitant use of ETR and unboosted ATV. ETR with unboosted ATV results in significant decreases in ATV exposure. |
• COBI: Inhibitor of CYP3A.  
• Zolpidem, suvorexant: Potential for increased concentrations of zolpidem and suvorexant.  
• Ramelteon: RTV-boosted PIs may reduce efficacy. | • Zolpidem: Administer lowest effective dose; monitor for adverse effects, including excess sedation.  
• Eszopiclone: Start with 1 mg per day; titrate slowly to effect; monitor for adverse effects, including excess sedation.  
• Suvorexant: Coadministration is not recommended; use alternative sleep medication or ARV agent.  
• Ramelteon: Monitor efficacy in cigarette smokers. |
| Non-opioid pain medications | • Eletriptan: Metabolism inhibited by boosted PIs.  
• TCAs: PIs and TCAs can both cause QT prolongation.  
• Pregabalin: No significant interactions expected. | • Eletriptan: Do not coadminister; use alternative triptan medication.  
• TCAs: When using high-dose TCAs and PIs, consider monitoring for QT prolongation or other cardiac adverse events or using alternative medications. |
<table>
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<th>Class or Drug</th>
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</tr>
</thead>
</table>
| Other antiplatelet drugs     | - **Cilostazol**: Metabolized by CYP3A, and boosted PIs will increase concentrations of this drug.  
- **Dipyridamole**: RTV-boosted PIs may induce UGT enzymes, which are responsible for metabolism of dipyridamole (not seen with COBI).                                                                 | - **Cilostazol**: Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent.  
- **Dipyridamole**: Monitor for antiplatelet effect. Use another ARV agent or boost with COBI if necessary.                                                                                                                                                    |
| Antidiabetic drugs            | - **Metformin**: COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations.  
- **Glyburide**: Mainly metabolized by CYP3A, and thus concentrations are increased by inhibitors of this enzyme.  
- **Saxagliptin**: Substrate of CYP3A, so levels may be increased.  
- **Canagliflozin**: Use with ATV may decrease concentrations of canagliflozin.  
- **GLP-1 agonists**: Caution needed when coadministering ATV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing the absorption of ATV. Furthermore, exenatide has the potential to slow gastric emptying.  
- **TZDs, exenatide**: No significant interactions expected                                                                 | - **Metformin**: Monitor for metformin-related adverse events, and reduce dose as needed.  
- **Glyburide or alternative sulfonylureas**: Use lowest effective doses with boosted PIs; monitor for signs of hypoglycemia.  
- **Saxagliptin**: Limit dose to 2.5 mg once per day.  
- **Canagliflozin**: With RTV-boosted ATV and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg per day and has GFR >60 mL/min/1.73 m².  
- **GLP-1 agonist**: Consider taking ATV 4 hours before.  
- **TZDs**: No dose adjustments necessary.                                                                                                                                                                                                                           |
| Trazodone                    | May increase trazodone concentrations.                                                                                                                                                                                                                                                                                                              | Monitor antidepressant and/or sedative effects.                                                                                                                                                                                                               |
| Anticonvulsants              | - **Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin**: Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system.  
- **Zonisamide**: Zonisamide concentrations may be increased through CYP3A4 inhibition.                                                                                                                                                                                   | - **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin**: 1) Coadministration is not recommended; use alternative anticonvulsant.  
2) If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. 3) Perform therapeutic drug monitoring.  
- **Zonisamide**: Monitor efficacy and adverse effects; adjust dose as needed.                                                                                                                                                                                                |
| Opioid analgesics            | Complex mechanisms of metabolism and the formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted PIs.                                                                                                                                                                                  | Monitor for signs of opiate toxicity and analgesic effect, and dose these analgesics accordingly.                                                                                                                                                               |
Table 2: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tramadol</td>
<td>Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6.</td>
<td>When tramadol is given with COBI or RTV, monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.</td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>• Complex drug interaction potential has been described.</td>
<td>• Etonogestrel: No data; consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td>• Drospirenone: Potential for hyperkalemia.</td>
<td>• Ethinyl estradiol; norgestimate and metabolites: Dose with at least 35 mcg (no data on other progestins).</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drospirenone: Do not coadminister.</td>
</tr>
<tr>
<td>Erectile and sexual dysfunction agents</td>
<td>• PDE5 inhibitor: Increased PDE5 inhibitor concentrations expected.</td>
<td>• Sildenafil: Start with 25 mg every 48 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td>• Flibanserin: Increased flibanserin concentrations expected.</td>
<td>• Tadalafil: Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Vardenafil: Administer 2.5 mg every 72 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Avanafil: Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Flibanserin: Do not coadminister.</td>
</tr>
<tr>
<td>Methadone, buprenorphine (BUP), naloxone (NLX)</td>
<td>• RTV-boosted PIs: May greatly increase BUP concentrations, but clinical significance of this is unknown because BUP dosing is based on clinical opiate withdrawal scale.</td>
<td>• RTV-boosted PIs: Monitor BUP for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress.</td>
</tr>
<tr>
<td></td>
<td>• COBI-boosted PIs: 1) May increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX. 2) Does not appear to have any significant effect on the concentration of methadone.</td>
<td>• COBI-boosted PIs: 1) Use careful dose titration of BUP/NLX when administering with COBI-boosted ARVs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Methadone: Based on efficacy and safety, initiate at lowest possible dose, and monitor for signs and symptoms of opiate withdrawal, and titrate dose to effect.</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>• Everolimus, sirolimus: Metabolism decreased by boosted PIs.</td>
<td>• Everolimus, sirolimus: Do not use with boosted PIs.</td>
</tr>
<tr>
<td></td>
<td>• Cyclosporine, tacrolimus: Metabolism decreased by boosted PIs.</td>
<td>• Cyclosporine, tacrolimus: Dose based upon therapeutic drug monitoring.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor closely for adverse events.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; ATV, atazanavir; BUP, buprenorphine; AUC, area under the curve; COBI, cobicistat; CrCl, creatinine clearance; CYP, cytochrome P450; EVG, elvitegravir; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; MATE, multidrug and toxin extrusion; NLX, naloxone; NS3/4A, nonstructural protein 3/4A; PK, pharmacokinetic; OATP, organic anion transporting polypeptide; PDE-5, phosphodiesterase type 5; P-gp, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TCA, tricyclic antidepressant; TFV, tenofovir; TZD, thiazolidinedione; UGT, uridine diphosphategluconosyltransferase.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); drugs used as antihypertensive medicines (Table 16); asthma and allergy medications (Table 23); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36).
### Table 3: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Simvastatin, lovastatin [Chauvin, et al. 2013; Feinstein, et al. 2015] | • Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and the drug transporter P-gP.  
• COBI is an inhibitor of CYP3A4, CYP2D6, OATP1B1, and P-gP.  
• Greatly increases concentrations. | • Avoid concomitant use due to potential for myopathy, including rhabdomyolysis.  
• Consider use of low doses of alternative statins less likely to be affected by boosted DRV use. |
• Pravastatin is an OATP1B1 substrate.  
• COBI and RTV may modestly inhibit OATP1B1.  
• Moderate increases are possible; low doses are considered safe when used with boosted PIs. | If pravastatin use is necessary, use the lowest effective dose and monitor for signs of toxicity. |
• Boosted DRV inhibits CYP3A4.  
• May moderately increase concentrations. | • Use the lowest effective dose of atorvastatin when combined with RTV-boosted DRV.  
• If concomitant use of atorvastatin and boosted DRV is necessary, monitor closely for signs of myopathy and rhabdomyolysis. |
• COBI inhibits OATP.  
• May moderately increase concentrations. | • When possible, avoid concomitant use of rosuvastatin and boosted DRV.  
• If rosuvastatin use is necessary, start with 10 mg per day. Dose should not exceed 20 mg per day. |
| Fluvatatin | Interaction has not been studied, but potential for moderate increase is possible.  
• Boosted PIs inhibit factor Xa inhibitors via CYP3A or P-gP.  
• DRV is a minor inhibitor of CYP2C8.  
• **Apixaban:** Substrate of CYP2C8.  
• **Warfarin:** Could potentially decrease (or more rarely) increase metabolism of warfarin. | Do not use, but if clinical use is desired, use the lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.  
• Avoid concomitant use, or use the lowest effective dose of the factor Xa inhibitor to avoid increased bleeding risk.  
• **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day, and if patient is already taking 2.5 mg twice per day, avoid concomitant use.  
• **Dabigatran:** 1) Separate doses of dabigatran and boosted PIs by at least 2 hours. 2) RTV-boosted PIs may be safer than COBI boosting when using concomitant dabigatran [Kakadiya, et al. 2018]. 3) Avoid dabigatran in patients taking boosted PIs if the patient also has severe renal impairment.  
• **Warfarin:** 1) Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. 2) Decrease dose if INR increases. 3) Increase dose slowly if INR decreases. |
| Factor Xa inhibitors [Egan, et al. 2014] |  |  |
Table 3: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

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<thead>
<tr>
<th>Class or Drug</th>
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<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Antiplatelet drugs and PY2-antagonists [Egan, et al. 2014; Teng 2015] | - **Cilostazol**: Metabolized by CYP3A, and boosted PIs will increase concentrations of this drug.  
  - **Dipyridamole**: RTV-boosted PIs may induce UGT enzymes, which are responsible for metabolism of dipyridamole (not seen with COBI).  
  - **Ticagrelor**: Results in increased exposure to ticagrelor.  
  - **Clopidogrel**: Results in decreased concentration of clopidogrel’s active metabolite. | - **Cilostazol**: Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent.  
  - **Dipyridamole**: Monitor for antiplatelet effect. Use another ARV agent or boost with COBI if necessary.  
  - **Ticagrelor**: Do not used with boosted PIs.  
  - **Clopidogrel**: Do not use with boosted PIs unless an alternative antiplatelet drug (or ARV agent) cannot be used. |
| Atenolol | Eliminated via OCT2 and MATE1, which are inhibited by DTG and BIC; limited potential for atenolol levels to increase if given with these INSTIs. | - Start at lower dose and adjust until desired clinical effect is achieved.  
  - If patient is already on atenolol but starting DTG or BIC, monitor for atenolol-related adverse events.  
  - Reduce dose of atenolol if necessary or switch to another ARV agent. |
| Calcium channel blockers (CCBs) | Boosted PIs may increase CCB concentrations by as much as 50%. | Decrease the original dose of CCB by as much as 50% when using with boosted PIs and slowly titrate to effect. |
| Eplerenone [Keating and Plosker 2004] | DRV inhibits the hepatic CYP3A4 isoenzyme and can increase the serum concentrations of eplerenone. | Avoid concomitant use to avoid increased risk of hyperkalemia and hypotension. |
| Antidiabetic drugs | - **Metformin**: COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations.  
  - **Glyburide**: Mainly metabolized by CYP3A, and thus concentrations are increased by inhibitors of this enzyme.  
  - **Saxagliptin**: Substrate of CYP3A, so levels may be increased.  
  - **Canagliflozin**: Use with DRV may decrease concentrations of canagliflozin.  
  - **GLP-1 agonists**: Caution needed when coadministering DRV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing the absorption of DRV. Furthermore, exenatide has the potential to slow gastric emptying.  
  - **TZDs, exenatide**: No significant interactions expected. | - **Metformin**: Monitor for metformin-related adverse events and reduce dose as needed.  
  - **Glyburide or alternative sulfonylureas**: Use lowest effective doses with boosted PIs; monitor for signs of hypoglycemia.  
  - **Saxagliptin**: Limit dose to 2.5 mg once per day.  
  - **Canagliflozin**: With RTV-boosted DRV and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg per day and has GFR >60 mL/min/1.73 m².  
  - **GLP-1 agonist**: Consider taking DRV 4 hours before.  
  - **TZDs**: No dose adjustments necessary. |
### Table 3: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

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<tr>
<th>Class or Drug</th>
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</thead>
<tbody>
<tr>
<td>Long-acting beta agonists</td>
<td>Inhibition of CYP3A increases plasma concentrations of these agents.</td>
<td>• Concomitant use is contraindicated unless benefits outweigh the risks; consider use of alternative ARV agents.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Boosted PIs may also increase QT prolongation.</td>
</tr>
<tr>
<td>Inhaled and injected corticosteroids</td>
<td>Enhanced PIs are strong inhibitors of CYP3A and many corticosteroids are substrates of these enzymes. Risk of Cushing’s syndrome when coadministered with the following corticosteroids:</td>
<td>• Intranasal or inhaled fluticasone, mometasone, ciclesonide, budesonide, triamcinolone: 1) Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid, e.g., beclomethasone. 2) This agent is less likely to be affected by boosted DRV use and thus is less likely to cause symptoms of Cushing’s syndrome and other systemic corticosteroid adverse events.</td>
</tr>
<tr>
<td>Oral prednisone</td>
<td>Prednisone is a CYP3A4 and P-gp substrate.</td>
<td>• Systemic prednisolone, prednisone: Contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.</td>
</tr>
<tr>
<td></td>
<td>• Boosted PIs are strong inhibitors of CYP3A4 and P-gp.</td>
<td>• Injectable betamethasone, triamcinolone: Contraindicated unless benefits outweigh risk.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Systemic dexamethasone: Contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid.</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>These benzodiazepines are substrates of CYP3A and may be increased in the presence of strong inhibitors of this enzyme.</td>
<td>Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam).</td>
</tr>
<tr>
<td></td>
<td>• Alprazolam: Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition.</td>
<td>• If used, administer lowest effective dose; monitor closely for adverse events.</td>
</tr>
<tr>
<td></td>
<td>• Diazepam: Metabolism of diazepam may be reduced via inhibition of CYP3A4.</td>
<td>• Diazepam: Monitor for excess sedation.</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Haloperidol: Potential for moderately increased haloperidol concentrations with boosted PIs.</td>
<td>Quetiapine: Reduce dose to 1/6 if initiating ARVs in patients on stabilized quetiapine.</td>
</tr>
<tr>
<td></td>
<td>• Aripiprazole, brexpiprazole: RTV-boosted PIs may increase levels of aripiprazole and brexpiprazole.</td>
<td>Lurasidone: No data; avoid coadministration; consider alternative antipsychotic or ARV agent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Haloperidol: Monitor for QT prolongation.</td>
</tr>
</tbody>
</table>
### Table 3: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Potential for moderate increase in risperidone levels.</td>
<td>Aripiprazole: Initiate at 50% of standard starting dose and titrate slowly; monitor carefully and adjust dose as necessary.</td>
</tr>
<tr>
<td>Clozapine</td>
<td>Interaction has not been studied but may theoretically increase concentrations of clozapine, increasing risk of adverse events.</td>
<td>Brexpiprazole: Monitor carefully and adjust dose as necessary.</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Initiate at 50% of standard starting dose and titrate slowly; monitor for adverse events.</td>
<td>Clozapine: Monitor carefully for adverse Clozaril-related events.</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>Monitor carefully and adjust dose as necessary.</td>
<td>All other antipsychotics should be used at the lowest dose possible in patients taking boosted ARVs, and careful monitoring for adverse events is warranted.</td>
</tr>
</tbody>
</table>

| HCV PIs ("-previr" drugs) | Inhibition of CYP3A4, P-gP, and OATP1B1 by boosted PIs may increase the plasma concentrations of other PIs. | Avoid concomitant use to avoid adverse events of NS3/4A PIs. |

| Daclatasvir | Boosted PIs inhibit daclatasvir metabolism via CYP3A4. | Decrease daclatasvir dose to 30 mg per day. |

| Sleep medications | These drugs are CYP3A substrates and may be increased by strong inhibitors of this enzyme. | Zolpidem: Administer lowest effective dose; monitor for adverse effects, including excess sedation. |
| [Kishi, et al. 2015] | Zolpidem, suvorexant: Potential for increased concentrations of zolpidem and suvorexant. | Eszopiclone: Start with 1 mg per day; titrate slowly to effect; monitor for adverse effects, including excess sedation. |
| Ramelteon | RTV-boosted PIs may reduce efficacy. | Suvorexant: Coadministration is not recommended; use alternative sleep medication or ARV agent (may increase somnolence, dizziness, and risk of sleep hangover). |
| COBI is an inhibitor of CYP3A. | Ramelteon: Monitor efficacy in cigarette smokers. |

| Non-opioid pain medications | Eletriptan: Metabolism inhibited by boosted PIs. | Eletriptan: Do not coadminister; use alternative triptan medication. |
| [Soriano, et al. 2017] | TCAs: PIs and TCAs can both cause QT prolongation. | TCAs: When using high-dose TCAs and PIs, consider monitoring for QT prolongation or other cardiac adverse events or using alternative medications. |
| Pregabalin | No significant interactions expected. | Do not exceed omeprazole 40 mg per day. |

| Non-opioid pain medications | Omeprazole | No significant interactions noted. |

| Trazadone | May increase trazodone concentrations. | Monitor antidepressant and/or sedative effects. |

| Carbamazepine, oxcarbazepine, phenobarbital, phenytoin | Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system. | Coadministration is not recommended; use alternative anticonvulsant. |
| | | If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. |
| | | Perform therapeutic drug monitoring. |
## Table 3: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

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<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zonisamide</td>
<td>Zonisamide concentrations may be increased through CYP3A4 inhibition.</td>
<td>Monitor efficacy and adverse effects; adjust dose as needed.</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Complex mechanisms of metabolism and the formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted PIs.</td>
<td>Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6.</td>
<td>When tramadol is given with COBI or RTV monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.</td>
</tr>
<tr>
<td>Hormonal contraceptives</td>
<td>• <strong>RTV-boosted</strong>: Combination appears to decrease oral norethindrone concentrations.</td>
<td><strong>Norethindrone</strong>: Consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td>• <strong>COBI-boosted</strong>: Combination has not been studied, but since COBI does not induce glucuronidation, it is expected to increase concentrations of norethindrone.</td>
<td></td>
</tr>
<tr>
<td>Erectile and sexual dysfunction agents</td>
<td>• <strong>PDE5 inhibitor</strong>: Increased PDE5 inhibitor concentrations expected.</td>
<td>• <strong>Sildenafil</strong>: Start with 25 mg every 48 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Flibanserin</strong>: Increased fibanserin concentrations expected.</td>
<td>• <strong>Tadalafil</strong>: Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Vardenafil</strong>: Administer 2.5 mg every 72 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Avanafil</strong>: Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Flibanserin</strong>: Do not coadminister.</td>
</tr>
<tr>
<td>Methadone, buprenorphine (BUP), naloxone (NLX), and naltrexone</td>
<td>• <strong>RTV-boosted</strong>: May greatly increase BUP concentrations, but the clinical significance of this is unknown because dosing of BUP is based on clinical opiate withdrawal scale.</td>
<td>• <strong>RTV-boosted</strong>: Monitor BUP for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress.</td>
</tr>
<tr>
<td></td>
<td>• <strong>RTV-boosted, taken twice per day</strong>: May reduce methadone concentrations.</td>
<td>• <strong>RTV-boosted, taken twice per day</strong>: Monitor methadone for signs of opiate withdrawal and increase dose of methadone if necessary.</td>
</tr>
<tr>
<td></td>
<td>• <strong>COBI-boosted</strong>: 1) May increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX. 2) COBI does not appear to have any significant effect on the concentration of methadone.</td>
<td>• <strong>COBI-boosted</strong>: 1) Use careful dose titration when giving BUP/NLX with COBI-boosted ARV. 2) Based on efficacy and safety, initiate methadone at lowest possible dose and monitor for signs and symptoms of opiate withdrawal and titrate dose to effect.</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td>• <strong>Everolimus, sirolimus</strong>: Metabolism decreased by boosted PIs.</td>
<td>• <strong>Everolimus, sirolimus</strong>: Do not use with boosted PIs.</td>
</tr>
</tbody>
</table>
### Table 3: Boosted Darunavir (DRV) Interactions (also see drug package inserts)

<table>
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<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine, tacrolimus:</td>
<td>Metabolism decreased by boosted PIs.</td>
<td>Cyclosporine, tacrolimus: Dose based upon therapeutic drug monitoring. Monitor closely for adverse events.</td>
</tr>
<tr>
<td><strong>Abbreviations:</strong> ARV, antiretroviral; BIC, bictegravir; BUP, buprenorphine; COBI, cobicistat; CYP, cytochrome P450; DTG, dolutegravir; GFR, glomerular filtration rate; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; INSTI: integrase strand transfer inhibitor; MATE, multidrug and toxin extrusion; NLX, naloxone; NS3/4A, nonstructural protein 3/4A; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TCA, tricyclic antidepressant; UGT, uridine diphosphate glucuronosyltransferase. <strong>No significant interactions/no dose adjustments necessary:</strong> Common oral antibiotics (Table 15); acid-reducing agents (Table 21); polyvalent cations (Table 22); asthma and allergy medications (Table 23); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Integrase Strand Transfer Inhibitors (INSTIs)

#### Table 4: Bictegravir (BIC) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>BIC chelates with cations, forming insoluble compounds that inactivate both drugs.</td>
<td>Administer BIC 2 hours before or 6 hours after taking antacids containing polyvalent cations.</td>
</tr>
<tr>
<td>Other polyvalent cations</td>
<td>BIC chelates with cations, which can inactivate both drugs.</td>
<td><strong>Calcium- or iron-containing supplements:</strong> If taken with food, BIC can be taken at the same time. If not taken with food, these supplements should be administered as with antacids.</td>
</tr>
<tr>
<td>Dofetilide [Feng and Varma 2016]</td>
<td>BIC inhibits renal OCT2 and MATE1, and these transporters eliminate dofetilide.</td>
<td>Avoid concomitant use (may cause QT prolongation or torsade de pointes).</td>
</tr>
<tr>
<td>Metformin [Custodio, et al. 2017]</td>
<td>BIC inhibits renal OCT2 and MATE1, which are involved in elimination of metformin.</td>
<td>• Drug interaction studies suggest that a prospective dose adjustment of metformin is not required when using BIC. • Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects.</td>
</tr>
<tr>
<td>Atenolol</td>
<td>• Atenolol is eliminated via OCT2 and MATE1, which are inhibited by BIC. • Coadministration may increase levels of atenolol.</td>
<td>• Start at a lower dose of atenolol and adjust slowly until desired clinical effect is achieved. • If patient is already on atenolol but starting DTG or BIC, monitor for atenolol-related adverse events. • Reduce dose of atenolol if necessary or switch to another ARV agent.</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Coadministration may significantly decrease BIC concentrations</td>
<td>Coadministration is not recommended. If an alternative anticonvulsant cannot be used, therapeutic drug monitoring may be warranted. Coadministration with strong inducers of CYP3A are not recommended because they may reduce concentrations of INSTIs.</td>
</tr>
</tbody>
</table>
Table 4: Bictegravir (BIC) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporine</td>
<td>May increase BIC concentrations to a modest degree via P-gP inhibition.</td>
<td>Monitor for BIC-related adverse events.</td>
</tr>
</tbody>
</table>

**Abbreviations:** CYP, cytochrome P450; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; MATE, multidrug and toxin extrusion; OCT, organic cation transporter; P-gP, P-glycoprotein.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); anticoagulants (Table 17); antiplatelet drugs (Table 18); statins (Table 19); acid-reducing agents (Table 21); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); inhaled and injected corticosteroids (Table 25); antidepressants (Table 26); benzodiazepines (Table 27); sleep medications (Table 28); antipsychotics (Table 33); erectile and sexual dysfunction agents (Table 34); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); methadone, buprenorphine, naloxone, and naltrexone (Table 37).

Table 5: Dolutegravir (DTG) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dofetilide</td>
<td>DTG inhibits renal OCT2 and MATE1, and these transporters eliminate dofetilide.</td>
<td>Avoid concomitant use (may cause QT prolongation or torsade de pointes).</td>
</tr>
<tr>
<td></td>
<td>[Max and Vibhakar 2014; Feng and Varma 2016]</td>
<td></td>
</tr>
</tbody>
</table>
| Metformin     | DTG inhibits renal OCT2, MATE1, and MATE2, which are involved in elimination of metformin. | • Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects.  
• Titrate metformin and do not exceed 1,000 mg when coadministered with DTG; monitor for adverse effects, including lactic acidosis. |
| Pioglitazone  | Pioglitazone is a weak inducer of CYP3A, and DTG is partially metabolized by this enzyme. | Avoid concomitant use because this may decrease DTG concentrations. |
|               | [Fantauzzi, et al. 2013] |                   |
| Divalent and trivalent cations (aluminum, magnesium, calcium, zinc, etc.) | DTG chelates with cations forming insoluble compounds that inactivate both drugs. | • Administer DTG 2 hours before or 6 hours after taking cations.  
• Calcium-containing supplements may be used concomitantly if taken with food. |
| Iron salts    | DTG chelates with cations, forming insoluble compounds that inactivate both drugs. | • Administer DTG 2 hours before or 6 hours after taking iron salts.  
• These drugs may be used concomitantly if taken with food. |
|               | [Song, et al. 2015] |                   |
| Atenolol      | Atenolol is eliminated via OCT2 and MATE1, which are inhibited by DTG. Coadministration may increase levels of atenolol. | • Start at a lower dose of atenolol and adjust slowly until desired clinical effect is achieved.  
• If patient is already on atenolol but starting DTG, monitor for atenolol-related adverse events.  
• Reduce dose of atenolol if necessary or switch to another ARV agent. |
|               | | |
Table 5: Dolutegravir (DTG) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproic Acid</td>
<td>• Coadministration may significantly decrease DTG concentrations.</td>
<td>• Coadministration is not recommended. If an alternative anticonvulsant cannot be used, monitor for safety and efficacy, including therapeutic drug monitoring.</td>
</tr>
<tr>
<td></td>
<td>• Coadministration with strong inducers of CYP3A (phenytoin, phenobarbital, etc.) may decrease DTG concentrations.</td>
<td>• Coadministration with strong inducers of CYP3A are not recommended because they may reduce concentrations of INSTIs.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Coadministration is not recommended. If an alternative anticonvulsant cannot be used, monitor for safety and efficacy, including therapeutic drug monitoring.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; CYP, cytochrome P450; INSTI, integrase strand transfer inhibitor; MATE, multidrug and toxin extrusion; OCT, organic cation transporter.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); anticoagulants (Table 17); antiplatelet drugs (Table 18); statins (Table 19); acid-reducing agents (Table 21); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); inhaled and injected corticosteroids (Table 25); antidepressants (Table 26); benzodiazepines (Table 27); sleep medications (Table 28); antipsychotics (Table 28); non-opioid pain medications (Table 31); opioid analgesics and tramadol (Table 32); hormonal contraceptives (Table 33); erectile and sexual dysfunction agents (Table 34); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); methadone, buprenorphine, naloxone, and naltrexone (Table 37); immunosuppressants (Table 38).

Table 6: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids</td>
<td>EVG chelates with polyvalent cations, which may reduce the efficacy of both agents.</td>
<td>Administer at least 2 hours before or 6 hours after EVG.</td>
</tr>
<tr>
<td>Factor Xa inhibitors [Egan, et al. 2014]</td>
<td>• Factor Xa inhibitors are substrates of P-gp and CYP3A.</td>
<td><strong>Rivaroxaban, edoxaban:</strong> Avoid concomitant use.</td>
</tr>
<tr>
<td></td>
<td>• COBI inhibits P-gp and CYP3A.</td>
<td><strong>Apixaban:</strong> Reduce apixaban dose to 2.5 mg twice per day, and if patient is already taking 2.5 mg twice per day, avoid concomitant use.</td>
</tr>
<tr>
<td></td>
<td>• May increase concentrations, increasing bleeding risk.</td>
<td><strong>Dabigatran:</strong> In patients with good renal function, no dose adjustments are necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Do not use this combination in patients with moderate to severe renal dysfunction.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Could potentially decrease (or more rarely) increase metabolism of warfarin.</td>
<td>**Use cautiously with warfarin, and if use is necessary, increase monitoring of INR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Decrease dose if INR increases. Increase dose slowly if INR decreases.</td>
</tr>
<tr>
<td>Cilostazol, ticagrelor, clopidogrel [Egan, et al. 2014; Tseng, et al. 2017]</td>
<td>• <strong>Cilostazol:</strong> Metabolized by CYP3A and boosted EVG will increase concentrations of this drug.</td>
<td><strong>Cilostazol:</strong> Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Ticagrelor:</strong> Results in increased exposure to ticagrelor.</td>
<td><strong>Ticagrelor:</strong> Do not use with boosted EVG.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Clopidogrel:</strong> Results in decreased concentration of clopidogrel’s active metabolite.</td>
<td><strong>Clopidogrel:</strong> Do not use with boosted EVG unless an alternative antiplatelet drug (or ARV agent) cannot be used.</td>
</tr>
<tr>
<td>Aliskiren</td>
<td>Cobicistat inhibits P-gp, which may decrease aliskiren elimination, increasing risk of adverse events.</td>
<td>Do not coadminister.</td>
</tr>
</tbody>
</table>
Table 6: Boosted Elvitegravir (EVT) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other polyvalent cations (calcium, zinc, iron, etc.)</td>
<td>EVT chelates with polyvalent cations.</td>
<td>Administer at least 2 hours before or 6 hours after EVT.</td>
</tr>
</tbody>
</table>
| Atenolol                               | COBI-boosted EVT may increase atenolol concentrations via inhibition of MATE-1 elimination. | • Start patient at lowest possible dose and monitor for adverse events before slowly increasing dose to effect.  
• If patient is already taking atenolol but starting a cobicistat-boosted EVT, monitor for atenolol-related adverse events. Reduce dose of atenolol as needed. |
| Calcium channel blockers (CCBs)        | COBI-boosted EVT may increase CCB concentrations by as much as 50%.                   | Decrease the original dose of CCB by up to 50% when using with boosted EVT and slowly titrate to effect. |
| Eplerenone [Keating and Plosker 2004; Tseng, et al. 2017] | • Eplerenone is metabolized by CYP3A.  
• COBI inhibits CYP3A. | • Avoid concomitant use (increased risk of hyperkalemia and hypertension).  
• If concomitant use is required, use lowest possible effective dose of eplerenone. |
| Simvastatin, lovastatin [Perry 2014]   | • COBI is an inhibitor of CYP3A.  
• Simvastatin and lovastatin are substrates of CYP3A.  
• Greatly increases concentrations. | Avoid concomitant use (may increase muscle aches and risk of rhabdomyolysis). |
• COBI inhibits OATP1B1.  
• Although moderate increases are possible, low doses are considered safe when used with boosted PIs. | • Use the lowest effective dose of pitavastatin and monitor for signs of toxicity, including myopathy.  
• Dose adjustments are not necessary when using these statins with boosted EVT. |
• COBI inhibits OATP1B1.  
• Although moderate increases are possible, low doses are considered safe when used with boosted PIs. | • Use the lowest effective dose of pravastatin and monitor for signs of toxicity, including myopathy.  
• Dose adjustments are not necessary when using these statins with boosted EVT. |
• Boosted EVT inhibits both CYP3A and OATP1B1.  
• May moderately increase concentrations. | • Avoid concomitant use of cobicistat and atorvastatin.  
• If atorvastatin use is necessary, do not exceed 20 mg per day. |
| Rosuvastatin [Custodio, et al. 2014]   | • Rosuvastatin is a substrate of OATP1B1 and OATP1B3.  
• COBI inhibits OATP.  
• Rosuvastatin is a substrate of CYP2C9.  
• EVT is an inducer of CYP2C9.  
• May moderately increase concentrations. | • When possible, avoid concomitant use of rosuvastatin and COBI-boosted EVT.  
• If rosuvastatin use is necessary, start with 10 mg per day. Dose should not exceed 20 mg per day. |
### Table 6: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluvastatin</td>
<td>Interaction has not been studied, but potential for moderate increase is possible.</td>
<td>Do not use, but if clinical use is desired, use the lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.</td>
</tr>
</tbody>
</table>
| Antidiabetic drugs                   | **Metformin**: COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations.  
**Gliburide**: Mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme.  
**Saxagliptin**: Levels may be increased via inhibition of CYP3A.  
**Canagliflozin**: Could lead to reduced canagliflozin exposure because of EVG’s induction of UGT enzymes.  
**Metformin**: Monitor for metformin-related adverse events and reduce dose as needed.  
**Gliburide or alternative sulfonlureas**: Use lowest effective doses with boosted EVG; monitor for signs of hypoglycemia.  
**Saxagliptin**: Limit dose to 2.5 mg once per day.  
**Canagliflozin**: Monitor glycemic control. With RTV-boosted EVG and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 ml/min/1.73m². |                                                                                                                                                                                                                                                                                                                                                                                  |
| Long-acting beta agonists (formoterol, salmeterol, etc.) | **Inhibition of CYP3A increases plasma concentrations of these agents.**  
**Increased risk of salmeterol-associated cardiovascular events.**  
Concomitant use is contraindicated unless benefits outweigh risks; consider use of alternative ARV agents.  
If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia.                                                                                                                                        |                                                                                                                                                                                                                                                                                                                                                                                  |
| Inhaled and injected corticosteroids | **Intranasal or inhaled**: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone.  
**Systemic**: Betamethasone, budesonide, prednisolone, prednisone, dexamethasone.  
**Injectable**: Betamethasone, triamcinolone.  
Intranasal or inhaled fluticasone, mometasone, ciclesonide, budesonide, and triamcinolone: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone).  
Systemic betamethasone, budesonide: Do not coadminister unless benefits outweigh risk.  
Systemic prednisolone, prednisone: Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.  
Injectable betamethasone, triamcinolone: Do not coadminister unless benefits outweigh risk.  
Systemic dexamethasone: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid.                                                                 |                                                                                                                                                                                                                                                                                                                                                                                  |
| Trazodone                            | May increase trazodone concentrations.                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Monitor antidepressant and/or sedative effects.                                                                                                                                                                                                                                                                                                                                                                                           |
| Alprazolam, clonazepam, diazepam     | These benzodiazepines are substrates of CYP3A and may be increased in the presence of strong inhibitors of this enzyme.  
Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam).  
If used, administer lowest effective dose; monitor closely for adverse events.                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                                  |
**Table 6: Boosted Elvitegravir (EVG) Interactions** (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Several of these agents are substrates of CYP3A, and inhibitors of this enzyme may increase their concentrations.</td>
<td>• <strong>Quetiapine</strong>: Reduce dose to 1/6 if initiating ARVs in patients on stabilized quetiapine.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Use all other antipsychotics at the lowest dose possible in patients taking boosted ARVs, and careful monitoring for adverse events is warranted.</td>
</tr>
<tr>
<td>PDE5 inhibitors</td>
<td>• COBI is an inhibitor of CYP3A.</td>
<td>• Avoid concomitant use or use with lowest effective dose of the PDE5 inhibitor (may increase risk of hypotension, syncope, priapism, and other adverse reactions).</td>
</tr>
<tr>
<td>[Perry 2014]</td>
<td>• PDE5 inhibitors are substrates of CYP3A.</td>
<td>• <strong>Sildenafil</strong>: Start with 25 mg every 48 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Flibanserin</strong>: Increased fibanserin concentrations expected.</td>
<td>• <strong>Tadalafil</strong>: Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Vardenafil</strong>: Administer 2.5 mg every 72 hours; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Flibanserin</strong>: Coadministration is contraindicated.</td>
</tr>
<tr>
<td>Suvorexant</td>
<td>• Suvorexant is a CYP3A substrate.</td>
<td>Avoid concomitant use or use the lowest effective dose (may increase somnolence, dizziness, and risk of sleep hangover).</td>
</tr>
<tr>
<td>[Kishi, et al. 2015]</td>
<td>• COBI is an inhibitor of CYP3A.</td>
<td></td>
</tr>
<tr>
<td>Zolpidem, eszopiclone</td>
<td>These drugs are CYP3A substrates and may be increased by strong inhibitors of this enzyme.</td>
<td>• <strong>Zolpidem</strong>: Administer lowest possible dose of zolpidem and monitor for adverse events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• <strong>Eszopiclone</strong>: Start with 1 mg of eszopiclone at bedtime and titrate slowly for maximum effect.</td>
</tr>
<tr>
<td>Carbamazepine,</td>
<td>Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system.</td>
<td>• Coadministration is not recommended; use alternative anticonvulstant.</td>
</tr>
<tr>
<td>oxcarbazepine,</td>
<td></td>
<td>• If benefit of use outweighs risk, monitor carefully for efficacy and toxicity.</td>
</tr>
<tr>
<td>phenobarbital,</td>
<td></td>
<td>• Perform therapeutic drug monitoring.</td>
</tr>
<tr>
<td>phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eletriptan</td>
<td>Eletriptan is a CYP3A substrate and concentrations may be increased if given with strong inhibitors of this enzyme.</td>
<td>Do not coadminister. Select an alternative triptan medication.</td>
</tr>
<tr>
<td>Opioid analgesics</td>
<td>Complex mechanisms of metabolism and formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted EVG.</td>
<td>Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly.</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6.</td>
<td>When tramadol is given with COBI or RTV, monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.</td>
</tr>
</tbody>
</table>
### Table 6: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal contraceptives</td>
<td><strong>Drospirenone</strong>: Potential for hyperkalemia.</td>
<td>• Ethinyl estradiol, norgestimate, metabolites; norethindrone: Weigh risks/benefits; consider alternative contraceptive method.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Drospirenone: Monitor for hyperkalemia; consider alternative contraceptive or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Etonogestrel: No data; consider alternative or additional contraceptive or alternative ARV agent.</td>
</tr>
<tr>
<td>Immunosuppressants</td>
<td><strong>Everolimus, sirolimus</strong>: Metabolism decreased by boosted EVG.</td>
<td>• Everolimus, sirolimus: Do not use with boosted EVG.</td>
</tr>
<tr>
<td></td>
<td><strong>Cyclosporine, tacrolimus</strong>: Metabolism decreased by boosted EVG.</td>
<td>• Cyclosporine, tacrolimus: Dose based upon therapeutic drug monitoring.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Monitor closely for adverse events.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; GFR, glomerular filtration rate; INR, international normalized ratio; MATE, multidrug and toxin extrusion; OATP, organic anion transporting polypeptide; P-gP, P-glycoprotein; Pi, protease inhibitor; RTV, ritonavir; UGT, uridine glucuronosyltransferase.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); acid-reducing agents (Table 21); asthma and allergy medications (Table 23); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); methadone, buprenorphine, naloxone, and naltrexone (Table 37).

---

### Table 7: Raltegravir (RAL) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antacids and other polyvalent cations</td>
<td>RAL chelates with cations, forming insoluble compounds that inactivate both drugs.</td>
<td>• Administer RAL 2 hours before or 6 hours after taking antacids.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CaCO₃ antacids can be taken with twice-daily RAL (400 mg) with no dose adjustments.</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Coadministration with strong inducers of UGT1A1 (phenytoin, phenobarbital, etc.) may decrease RAL concentrations.</td>
<td>Coadministration with strong inducers of UGT1A1 are not recommended.</td>
</tr>
</tbody>
</table>

**Abbreviation:** UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); drugs used as antihypertensive agents (Table 16); anticoagulants (Table 17); antiplatelet drugs (Table 18); statins (Table 19); antidiabetic drugs (Table 20); acid-reducing agents (Table 21); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); inhaled and injected corticosteroids (Table 25); antidepressants (Table 26); benzodiazepines (Table 27); sleep medications (Table 28); antipsychotics (Table 28); non-opioid pain medications (Table 31); opioid analgesics and tramadol (Table 32); hormonal contraceptives (Table 33); erectile and sexual dysfunction agents (Table 34); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); methadone, buprenorphine, naloxone, and naltrexone (Table 37); immunosuppressants (Table 38).
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Table 8: Doravirine (DOR) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Strong inducers or inhibitors of CYP3A [Deeks 2018] | DOR is a substrate of CYP3A, and as such, drugs that affect its metabolism affect its concentrations. | • Avoid concomitant use if possible.  
• Dose adjustments of DOR are not recommended.  
• Consider alternative concomitant agents. |
| Carbamazepine, oxcarbazepine, phenobarbital, phenytoin | Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system. | • Coadministration is not recommended; use alternative anticonvulsant.  
• If benefit of use outweighs risk, monitor carefully for efficacy and toxicity.  
• Perform therapeutic drug monitoring if use cannot be avoided. |

**Abbreviations:** ARV, antiretroviral agents; CYP, cytochrome P450.

**No significant interactions/no dose adjustments necessary:**
- Common oral antibiotics (Table 15)
- Drugs used as antihypertensive agents (Table 16)
- Anticoagulants (Table 17)
- Antiplatelet drugs (Table 18)
- Statins (Table 19)
- Antidiabetic drugs (Table 20)
- Polyvalent cations (Table 22)
- Asthma and allergy medications (Table 23)
- Long-acting beta agonists (Table 24)
- Inhaled and injected corticosteroids (Table 25)
- Antidepressants (Table 26)
- Benzodiazepines (Table 27)
- Sleep medications (Table 28)
- Antipsychotics (Table 28)
- Non-opioid pain medications (Table 31)
- Opioid analgesics and tramadol (Table 32)
- Hormonal contraceptives (Table 33)
- Erectile and sexual dysfunction agents (Table 34)
- Tobacco and smoking cessation products (Table 35)
- Alcohol, disulfiram, and acamprosate (Table 36)
- Methadone, buprenorphine, naloxone, and naltrexone (Table 37)
- Immunosuppressants (Table 38).

Table 9: Rilpivirine (RPV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Proton pump inhibitors (PPIs) [Schafer and Short 2012]   | • PPIs inhibit secretion of gastric acid by proton pumps thereby increasing the gastric pH.  
• RPV requires an acidic environment for optimal absorption. | Avoid concomitant use (may decrease RPV absorption).                                |
| Histamine 2 antagonists (H2As) [Schafer and Short 2012]  | • H2As inhibit secretion of gastric acid by proton pumps, thereby increasing the gastric pH.  
• RPV requires an acidic environment for optimal absorption. | • Give H2A at least 12 hours before or 4 hours after RPV.  
• Concomitant use may decrease RPV absorption.  
• Use lowest effective dose.  
• Administer with food. |
| Antacids [Schafer and Short 2012]                        | • Antacids increase gastric pH.  
• RPV requires an acidic environment for optimal absorption.  
• Concomitant use may decrease RPV absorption. | • Give antacids 2 hours before or 4 hours after RPV. |
### Table 9: Rilpivirine (RPV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 agonists</td>
<td>Caution needed when coadministering with RPV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing absorption of RPV. Furthermore, exenatide has the potential to slow gastric emptying.</td>
<td>Consider taking RPV 4 hours before exenatide.</td>
</tr>
<tr>
<td>Dexamethasone [Welz, et al. 2017]</td>
<td>Dexamethasone is an inducer of CYP3A, which is primarily responsible for the metabolism of RPV.</td>
<td>Systemic dexamethasone: 1) Contraindicated; consider use of alternative agents. 2) If using more than single dose, do not coadminister.</td>
</tr>
<tr>
<td>Anti-arrhythmic drugs [Sanford 2012]</td>
<td>Supratherapeutic doses of RPV have caused QT prolongation, and additive effects may be seen.</td>
<td>Avoid concomitant use (may cause QT prolongation and torsades de pointes).</td>
</tr>
</tbody>
</table>
| Long-acting beta agonists (LABAs) | RPV and drugs from the LABA class may both theoretically increase QT interval, especially at high doses. | • No dose adjustment necessary.  
• Do not use more LABA than recommended; this can increase risk of QT prolongation. |
| Antipsychotics | No significant interactions noted. | No dose adjustments necessary, but avoid excess doses of either antipsychotic or RPV because excess doses of both drugs may increase risk of QT prolongation. |
| Carbamazepine, oxcarbazepine, phenobarbital, phenytoin | Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system. | • Coadministration is not recommended; use alternative anticonvulsant.  
• If benefit of use outweighs risk, monitor carefully for efficacy and toxicity.  
• Perform therapeutic drug monitoring if use cannot be avoided. |
| Methadone, buprenorphine (BUP) | • BUP: No significant interactions are expected.  
• Methadone: Mildly reduces methadone concentrations. | • Methadone: Monitor for signs of methadone withdrawal and increase dose as necessary.  
• Use methadone or BUP cautiously with RPV because supratherapeutic doses of RPV have been known to cause increase in QT prolongation. |
| Strong inducers or inhibitors of CYP3A | RPV is a substrate of CYP3A, and as such, drugs that affect its metabolism affect its concentrations. | • Avoid concomitant use if possible.  
• Dose adjustments of RPV are not recommended.  
• Consider alternative concomitant agents. |

**Abbreviations:** ARV, antiretroviral; BUP, buprenorphine; CYP, cytochrome P450;  
**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); drugs used as antihypertensive agents (Table 16); anticoagulants (Table 17); antiplatelet drugs (Table 18); statins (Table 19); asthma and allergy medications (Table 23); antidepressants (Table 26); benzodiazepines (Table 27); sleep medications (Table 28); anticonvulsants not specifically stated above (Table 30); non-opioid pain medications (Table 31); opioid analgesics and tramadol (Table 32); erectile and sexual dysfunction agents (Table 34); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); naloxone and naltrexone (Table 37); immunosuppressants (Table 38).
<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Could potentially increase (or more rarely decrease) metabolism of warfarin.</td>
<td>• Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. • Increase dose slowly if INR decreases. Decrease dose if INR increases.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>EFV may induce CYP2B6, the enzyme that is primarily responsible for metabolism of bupropion.</td>
<td>Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose.</td>
</tr>
<tr>
<td>Levonorgestrel/norgestimate, levonorgestrel</td>
<td>EFV may induce CYP3A, the enzyme that is primarily responsible for metabolism of levonorgestrel.</td>
<td>Effectiveness of levonorgestrel or norgestimate may be decreased.</td>
</tr>
<tr>
<td>Cilostazol</td>
<td>May reduce concentrations of cilostazol.</td>
<td>Monitor for antiplatelet effect; may be necessary to use an alternative antiplatelet drug or alternative ARV agent.</td>
</tr>
<tr>
<td>Dipyridamole</td>
<td>EFV may induce UGT enzymes, which are responsible for metabolism.</td>
<td>Monitor for antiplatelet effect; use another ARV agent if necessary.</td>
</tr>
<tr>
<td>Ticagrelor, clopidogrel</td>
<td>EFV reduce ticagrelor concentrations and the conversion of clopidogrel to its active metabolite.</td>
<td>Use with EFV may reduce the antiplatelet effect; monitor closely and use an alternative ARV agent if necessary.</td>
</tr>
<tr>
<td>Statins</td>
<td>• Simvastatin, lovastatin: Could potentially decrease concentrations. • Atorvastatin, pravastatin, fluvastatin: May modestly reduce concentrations. • Pitavastatin, rosuvastatin: No interactions expected.</td>
<td>• Simvastatin, lovastatin: Monitor for efficacy. May warrant increases in statin dose. Do not increase dose above maximum recommended statin dose. • Atorvastatin, pravastatin, fluvastatin: Monitor cholesterol-lowering effect of statins. May require increased dose. • Pitavastatin, rosuvastatin: No dose adjustments necessary.</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>EFV may increase concentrations by inhibition of CYP2C8. No significant interactions expected.</td>
<td>Monitor for signs of adverse events with EFV; decrease dose if necessary.</td>
</tr>
<tr>
<td>Saxaglaptin, sitagliptin</td>
<td>EFV may decrease concentration.</td>
<td>Monitor for efficacy; if necessary, increase dose of the DPP-4 inhibitor.</td>
</tr>
<tr>
<td>Inhaled and injected corticosteroids</td>
<td>Coadministration may reduce concentrations of corticosteroids.</td>
<td>Systemic dexamethasone: Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor virologic response.</td>
</tr>
<tr>
<td>Trazodone</td>
<td>May decrease trazodone concentrations.</td>
<td>Monitor antidepressant and/or sedative effects.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>EFV induces bupropion metabolism.</td>
<td>Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose.</td>
</tr>
<tr>
<td>Class or Drug</td>
<td>Mechanism of Action</td>
<td>Clinical Comments</td>
</tr>
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<tr>
<td>Benzodiazepines</td>
<td>Alprazolam, diazepam: Potential for reduced alprazolam and diazepam concentrations.</td>
<td>• Alprazolam: Monitor for benzodiazepine withdrawal if EFV is added.</td>
</tr>
<tr>
<td></td>
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<td>• Alprazolam, clonazepam, diazepam: Monitor for benzodiazepine efficacy; titrate slowly as needed for effect.</td>
</tr>
<tr>
<td>Sleep medications</td>
<td>Zolpidem: Potential for reduced concentrations of zolpidem.</td>
<td>• Zolpidem, eszopiclone: Monitor for efficacy; no dose adjustments recommended.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Suvorexant: Monitor for efficacy; do not exceed 20 mg per day.</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>• Quetiapine: Concentrations of quetiapine may be reduced.</td>
<td>• Quetiapine: Monitor for efficacy; titrate slowly as needed; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td>• Aripiprazole, brexpiprazole: Concentrations of aripiprazole and brexpiprazole may be decreased.</td>
<td>• Aripiprazole, brexpiprazole: Monitor for efficacy; titrate dose slowly as needed; monitor for adverse effects.</td>
</tr>
<tr>
<td></td>
<td>• Risperidone, olanzapine: May decrease efficacy of risperidone and olanzapine.</td>
<td>• Risperidone, olanzapine: Monitor for efficacy; titrate slowly as needed; monitor for adverse effects.</td>
</tr>
<tr>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin</td>
<td>Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system.</td>
<td>• Coadministration is not recommended; use alternative anticonvulsant.</td>
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<td>• If benefit of use outweighs risk, monitor carefully for efficacy and toxicity.</td>
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<td>• Perform therapeutic drug monitoring if use cannot be avoided.</td>
</tr>
<tr>
<td>Lamotrigine, zonisamide</td>
<td>EFV may reduce efficacy of lamotrigine or zonisamide.</td>
<td>Monitor efficacy; titrate dose slowly as needed.</td>
</tr>
<tr>
<td>Opioid analgesics and tramadol</td>
<td>• Morphine, hydromorphone: Metabolism could potentially be reduced by EFV.</td>
<td>• Morphine, hydromorphone: Monitor for signs of opiate toxicity when using with EFV.</td>
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<td>• Oxycodone: May be metabolized faster to an inactive metabolite by EFV.</td>
<td>• Oxycodone: Dose adjustment of oxycodone may be required when dosing with EFV.</td>
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<td></td>
<td>• Meperidine: Coadministration can potentially increase amount of neurotoxic metabolite and thereby increase risk of seizures.</td>
<td>• Meperidine: If possible, avoid concomitant use; use alternative opiate pain medication or ARV agent.</td>
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<tr>
<td></td>
<td>• Tramadol: May reduce concentration of tramadol without affecting pathway that increases development of more potent active metabolites.</td>
<td>• Tramadol: When given with tramadol, a priori dose adjustments are necessary.</td>
</tr>
<tr>
<td>Class or Drug</td>
<td>Mechanism of Action</td>
<td>Clinical Comments</td>
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<tr>
<td>Hormonal contraceptives</td>
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<tr>
<td>Erectile and sexual dysfunction</td>
<td><strong>PDE5 inhibitor:</strong> Potential for reduced effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil).</td>
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<tr>
<td>dysfunction agents</td>
<td><strong>Flibanserin:</strong> Potential for reduced concentrations of flibanserin.</td>
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</table>
### Table 10: Efavirenz (EFV) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbreviations: ARV, antiretroviral; BUP, buprenorphine; CYP, cytochrome P450; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; NS3/4A, nonstructural protein 3/4A; PDE5, phosphodiesterase type 5; PI, protease inhibitor; SVR, sustained viral response; UGT, uridine diphosphate glucuronosyltransferase.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 15); drugs used as antihypertensive medicines (Table 16); acid-reducing agents (Table 21); polyvalent cations (Table 22); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); non-opioid pain medications (Table 31); alcohol, disulfiram, and acamprosate (Table 36).</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliskiren</td>
<td>ETR is a minor inhibitor of P-gP and may minimally increase concentrations of aliskiren, but this has not been studied.</td>
<td>• When using with ETR, monitor for aliskiren-related adverse events.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If present, switch to alternative antihypertensive agent or ARV agent.</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Could potentially increase (or more rarely decrease) metabolism of warfarin.</td>
<td>• Use cautiously with warfarin, and if use is necessary, increase monitoring of INR.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increase dose slowly if INR decreases. Decrease dose if INR increases.</td>
</tr>
<tr>
<td>Antiplatelet drugs [Rathbun and Liedtke 2010; Kakuda, et al. 2011]</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Cilostazol: May reduce concentrations of cilostazol.</td>
<td>• Cilostazol: Monitor for antiplatelet effect; may be necessary to use an alternative antiplatelet drug or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td>• Dipyridamole: ETR may induce UGT enzymes, which are responsible for metabolism.</td>
<td>• Dipyridamole: Monitor for antiplatelet effect; use another ARV agent if necessary.</td>
</tr>
<tr>
<td></td>
<td>• Ticagrelor, clopidogrel: ETR reduces ticagrelor concentrations and the conversion of clopidogrel to its active metabolite because ETR inhibits 2C19.</td>
<td>• Ticagrelor, clopidogrel: Use with ETR may reduce the antiplatelet effect; monitor closely and use an alternative ARV agent if possible.</td>
</tr>
<tr>
<td>Statins</td>
<td>• Simvastatin, lovastatin: Could potentially decrease concentrations.</td>
<td>• Simvastatin, lovastatin: Monitor for efficacy. May warrant increases in statin dose. Do not increase dose above maximum recommended statin dose.</td>
</tr>
<tr>
<td></td>
<td>• Atorvastatin, pravastatin, fluvastatin: May modestly reduce concentrations.</td>
<td>• Atorvastatin, pravastatin, fluvastatin: Monitor cholesterol-lowering effect of statins. May require increased dose.</td>
</tr>
<tr>
<td>Saxagliptin, sitagliptin</td>
<td>ETR may decrease concentration.</td>
<td>Monitor for efficacy; if necessary, increase dose of the DPP-4 inhibitor.</td>
</tr>
<tr>
<td>Inhaled and injected corticosteroids</td>
<td>Coadministration may reduce concentrations of corticosteroids.</td>
<td>Systemic dexamethasone: Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor virologic response.</td>
</tr>
<tr>
<td>Trazodone</td>
<td>May decrease trazodone concentrations.</td>
<td>Monitor antidepressant and/or sedative effects.</td>
</tr>
<tr>
<td>Bupropion</td>
<td>No significant interactions.</td>
<td>Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose.</td>
</tr>
<tr>
<td>Class or Drug</td>
<td>Mechanism of Action</td>
<td>Clinical Comments</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>Potential for reduced alprazolam concentrations.</td>
<td>Monitor for benzodiazepine withdrawal.</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Potential for reduced diazepam concentrations.</td>
<td>No dose adjustments necessary.</td>
</tr>
</tbody>
</table>
| Sleep medications | Zolpidem: Potential for reduced concentrations of zolpidem. | • Zolpidem, eszopiclone: Monitor for efficacy; no dose adjustments recommended.  
  • Suvorexant: Monitor for efficacy; do not exceed 20 mg per day. |
| Antipsychotics | • Aripiprazole, brexpiprazole: Concentrations of aripiprazole and brexpiprazole may be decreased.  
  • Risperidone: May decrease efficacy of risperidone. | • Aripiprazole, brexpiprazole: Monitor for efficacy; titrate dose slowly as needed; monitor for adverse effects.  
  • Risperidone: Monitor for efficacy; titrate slowly; monitor for adverse effects. |
| Carbamazepine, oxcarbazepine, phenobarbital, phenytoin | Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system. | • Coadministration is not recommended; use alternative anticonvulsant.  
  • If benefit of use outweighs risk, monitor carefully for efficacy and toxicity.  
  • Perform therapeutic drug monitoring if use cannot be avoided. |
| Lamotrigine, zonisamide | May reduce efficacy of lamotrigine or zonisamide. | Monitor efficacy; titrate dose slowly as needed. |
| Hormonal contraceptives | Information is based on what is known with EFV drug interactions. | • Etonogestrel: No data; consider alternative or additional contraceptive method or alternative ARV agent.  
  • Ulipristal: Efficacy may be reduced; monitor closely. |
| Erectile and sexual dysfunction agents | • PDE5 inhibitor: Potential for reduced effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil).  
  • Flibanserin: Potential for reduced concentrations of flibanserin. | • PDE5 inhibitors: Monitor clinical effect; if dose increase is needed to achieve desired clinical effect, titrate under medical supervision to lowest effective dose.  
  • Flibanserin: Do not coadminister. |
| Bupropion | No significant interactions noted. | Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose. |
| Buprenorphine | No significant interactions expected. | Monitor for signs of withdrawal or opioid toxicity and titrate dose of opioid or antagonist as required. |
| Methadone | May slightly increase concentrations of methadone. | • Monitor for signs of withdrawal or opioid toxicity and titrate dose of opioid or antagonist as required.  
  • Monitor for signs of methadone toxicity and reduce dose if necessary. |
### Table 11: Etravirine (ETR) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Cyclosporine, tacrolimus                                                      | Concentrations may be lower when used with ETR.                                     | • Dose adjust cyclosporine and tacrolimus based on efficacy and therapeutic drug monitoring (TDM).  
  • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy. |
| HCV PIs (“-previr” drugs)                                                     | ETR may decrease levels of HCV PIs through induction of CYP3A.                      | Do not coadminister HCV PIs with ETR.                                             |
| Sofosbuvir/velpatasvir (available as coformulated product)                    | ETR may decrease levels of velpatasvir through induction of CYP3A and (weak) inhibition of P-gP. | Do not coadminister sofosbuvir/velpatasvir with ETR.                             |
| Daclatasvir                                                                  | ETR induces CYP3A, lowering daclatasvir levels.                                     | Increase dose of daclatasvir to 90 mg per day.                                    |
| Atazanavir (ATV)                                                              | • ETR is a substrate and inducer of CYP3A4.                                         | • Use with RTV-boosted ATV results in decreases in ATV exposure, but the decrease is not considered relevant and ETR and RTV-boosted ATV can be administered together without dose adjustments.  
  • Due to the potential for decreased ARV efficacy, avoid use of ETR with COBI. When these medications are given together, the concentrations of COBI are decreased.  
  • When possible, avoid concomitant use of ETR and unboosted ATV. ETR with unboosted ATV results in significant decreases in ATV exposure. |
| Dolutegravir (DTG)                                                            | • ETR induces UGT1A1 and CYP3A enzymes.                                             | ETR reduces concentrations of DTG. Do not use concomitantly unless a boosted PI is also a part of the treatment regimen. |

**Abbreviations:** ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; EFV, efavirenz; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; UGT, uridine diphosphate glucuronosyltransferase.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); acid-reducing agents (Table 21); polyvalent cations (Table 22); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); non-opioid pain medications (Table 31); opioid analgesics and tramadol (Table 32); alcohol, disulfiram, and acamprosate (Table 36).
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Table 12: Abacavir (ABC) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol</td>
<td>ABC is metabolized via alcohol dehydrogenase, and competitive metabolism may increase exposure to ABC.</td>
<td>Use cautiously and monitor for adverse events of ABC.</td>
</tr>
</tbody>
</table>

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 15); drugs used as antihypertensive medicines (Table 16); anticoagulants (Table 17); antiplatelet drugs (Table 18); statins (Table 19); antidiabetic drugs (Table 20); acid-reducing agents (Table 21); polyvalent cations (Table 22); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); inhaled and injected corticosteroids (Table 25); antidepressants (Table 26); benzodiazepines (Table 27); sleep medications (Table 28); antipsychotics (Table 29); anticonvulsants (Table 30); non-opioid pain medications (Table 31); opioid analgesics and tramadol (Table 32); hormonal contraceptives (Table 33); erectile and sexual dysfunction agents (Table 34); tobacco and smoking cessation products (Table 35); methadone, buprenorphine, naloxone, and naltrexone (Table 37); immunosuppressants (Table 38).

Table 13: Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) Interactions (also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Adefovir                          | • Similar mechanisms of action and elimination, and thus, similar adverse event profiles.  
                                | • Competitive inhibition of elimination results in additive adverse events.           | Avoid concomitant use to avoid increased risk of hepatic steatosis and lactic acidosis. |
| Other nephrotoxic agents          | Competitive inhibition of elimination results in additive adverse events.            | • Avoid concomitant use or use the lowest effective dose of other drug to avoid renal impairment and kidney dysfunction.  
                                |                                                                                     | • May be preferable to use TAF in these instances because TAF is less nephrotoxic. |
| Sofosbuvir/velpatasvir/voxilaprevir | • TDF and TAF are substrates for BCRP and P-gP.                                      | Avoid concomitant use if possible to avoid TDF-associated adverse events.         |
|                                   | • Voxilaprevir is a BCRP inhibitor.                                                 | • May be preferable to use TAF in these instances.                                |
|                                   | • Velpatasvir inhibits BCRP and P-gP.                                               |                                                                                   |
| Potent CYP3A4 or P-gP inducers     | • CYP3A4 is a minor metabolic pathway for TAF, and as such, potent inducers of this enzyme may modestly reduce concentrations.  
                                | • TAF is also a substrate of P-gP, and inducers may decrease TAF concentrations.    | Avoid coadministration of TAF with potent inducers of CYP3A4 or P-gP              |
| Zonisamide                        | TDF may increase concentration of zonisamide.                                        | Monitor for adverse events of zonisamide with TDF.                                |
### Table 13: Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) Interactions
(also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>No significant interactions noted.</td>
<td>Monitor renal function when coadministered (topiramate may cause kidney stones; TDF is associated with renal toxicity).</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCRP, breast cancer resistance protein; CYP, cytochrome P450; P-gP, P-glycoprotein.

**No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 15); drugs used as antihypertensive medicines (Table 16); anticoagulants (Table 17); antiplatelet drugs (Table 18); statins (Table 19); antidiabetic drugs (Table 20); acid-reducing agents (Table 21); polyvalent cations (Table 22); asthma and allergy medications (Table 23); long-acting beta agonists (Table 24); inhaled and injected corticosteroids (Table 25); antidepressants (Table 26); benzodiazepines (Table 27); sleep medications (Table 28); antipsychotics (Table 29); non-opioid pain medications (Table 31); opioid analgesics and tramadol (Table 32); hormonal contraceptives (Table 33); erectile and sexual dysfunction drugs (Table 34); tobacco and smoking cessation products (Table 35); alcohol, disulfiram, and acamprosate (Table 36); methadone, buprenorphine, naloxone, and naltrexone (Table 37); immunosuppressants (Table 38).

### Table 14: Lamivudine (3TC) and Emtricitabine (FTC) Interactions
(also see drug package inserts)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

**Note:** There are no known clinically significant drug-drug interactions between 3TC or FTC and concomitant agents.
ARV Drug-Drug Interactions by Common Medication Class

- Table 15: Common Oral Antibiotics
- Table 16: Drugs Used as Antihypertensive Agents
- Table 17: Anticoagulants
- Table 18: Antiplatelet Drugs
- Table 19: Statins
- Table 20: Antidiabetic Drugs
- Table 21: Acid-Reducing Agents
- Table 22: Polyvalent Cations
- Table 23: Asthma and Allergy Medications
- Table 24: Long-Acting Beta Agonists
- Table 25: Corticosteroids
- Table 26: Antidepressants
- Table 27: Benzodiazepines
- Table 28: Sleep Medications
- Table 29: Antipsychotics
- Table 30: Anticonvulsants
- Table 31: Non-Opioid Pain Medications
- Table 32: Opioid Analgesics and Tramadol
- Table 33: Hormonal Contraceptives
- Table 34: Erectile and Sexual Dysfunction Agents
- Table 35: Tobacco and Smoking Cessation Products
- Table 36: Alcohol, Disulfiram, and Acamprosate
- Table 37: Methadone, Buprenorphine, Naloxone, and Naltrexone
- Table 38: Immunosuppressants
- Table 39: Rifamycins and Other Anti-Tuberculosis Medications
- Table 40: Gender Affirming Hormones

The following tables are not meant to serve as a definitive resource on all possible drug-drug interactions between common antiretroviral (ARV) and non-ARV drugs. Instead, they offer a brief introduction to the management of interactions between medications used to treat HIV and comorbidities commonly seen in primary care settings. The tables are organized by common disease state and prioritized by those most commonly seen in primary care. Within each table, the medications are prioritized according to the preference the NYSDOH AI and the U.S. Department of Health and Human Services gives each class of medications in the initial management of HIV. The appropriate management of HIV should be individualized according to patient-specific factors, and not all ARVs may be suitable for all patients.

In the event that an ARV does not have a clinically significant interaction with the class of medications described, it is still listed in the table. If an interaction is theoretical but its significance is unknown, the recommendation to monitor for safety and efficacy is provided. Drugs within a class that may have a significant interaction are described within the table. Other drugs that do not have clinically significant drug-drug interactions with ARVs but were reviewed are described in the footnotes of the individual tables. If a drug does not appear in the table or the footnotes, exercise extra caution when prescribing this medication to patients with HIV or AIDS. The resources provided here might be valuable for clinicians who seek more guidance on drug-drug interactions related to ARV medications.

The informational material found within these tables is based on previously referenced primary, secondary, and tertiary literature, as well as the various publically available databases described in the Resources section. Further information may be found in the literature, including the U.S. Food and Drug Administration’s reports or manufacturer’s prescribing information (package inserts), which are also available online for each of the listed pharmacologic agents. If healthcare providers are interested in learning more about specific drug-drug interactions or seek further information about the methodology of the research or the mechanisms and management of these interactions, they are encouraged to utilize these resources.

Consultation with an experienced HIV care provider is also recommended when assistance is needed in choosing an antiretroviral therapy regimen for a patient who has multiple comorbidities and may have multiple drug-drug interactions. For help locating an experienced HIV care provider, contact the Clinical Education Initiative at 866-637-2342.

→ KEY POINT

- Medications used to treat epilepsy, various types of malignancies, and tuberculosis, and those used to prevent graft-versus-host disease in solid organ transplants are known to interact with several ARV agents. Because of the serious nature of these conditions and the complexity of their treatment, many details of the specific interactions of these drugs have not been reviewed here. Clinicians should consult with the appropriate specialty service when questions arise pertaining to the management of these conditions.
**Table 15: Common Oral Antibiotics**

- Penicillins, cephalosporins, tetracyclines, macrolides, fluoroquinolones, sulfamethoxazole-trimethoprim*, linezolid, dapsone

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosted PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etravirine (ETR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate

**Note:** Penicillins and cefalexin are eliminated mainly by organic anion transporters, so may compete with TDF for active tubular excretion, thus increasing concentrations of both drugs. Because of the limited duration of most penicillin regimens, the significance of this interaction is expected to be quite small.

*Trimethoprim blocks creatinine secretion and could accentuate the effects of cobicistat, BIC, and DTG.

**Table 16: Drugs Used as Antihypertensive Medicines**

- Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers, direct renin inhibitors, diuretics

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions expected.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dolutegravir (DTG) or bictegravir (BIC)

- **Atenolol:** Eliminated via OCT2 and MATE1, which are inhibited by DTG and BIC, limited potential for atenolol levels to increase if given with these INSTIs.
- ACE inhibitors, ARBs, CCBs, aliskiren, diuretics: No significant interactions expected.

Elvitegravir (EVG), boosted

- **Aliskiren:** Inhibitors of P-gP, including boosted EVG, decrease aliskiren elimination, increasing adverse events of medication.
- **Atenolol:** COBI-boosted EVG may increase atenolol via inhibition of MATE1 elimination.
- **CCBs:** Boosted EVG may increase CCB concentrations by as much as 50%.

- **Atenolol:** Start at lower dose and adjust until desired clinical effect is achieved. If a patient is already on atenolol but starting DTG or BIC, monitor for atenolol-related adverse events. Reduce dose of atenolol if necessary or switch to another ARV agent.
- ACE inhibitors, ARBs, CCBs, aliskiren, diuretics: No dose adjustments necessary.

- **Aliskiren:** Do not coadminister.
- **Atenolol:** Start patient at lowest possible dose and monitor for adverse events before slowly increasing dose to effect. If a patient is already on atenolol but starting COBI-boosted EVG, monitor for atenolol-related adverse events. Reduce dose of atenolol as needed.
### Table 16: Drugs Used as Antihypertensive Medicines

Angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers, direct renin inhibitors, diuretics

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Boosted PIs       | • **Aliskiren**: Inhibitors of P-gp, including boosted PIs, decrease aliskiren elimination, increasing adverse events of medication.  
• **Atenolol**: COBI-boosted PIs may increase atenolol via inhibition of MATE1 elimination. Similar interaction is not seen with RTV-boosted PIs.  
• **CCBs**: Boosted PIs may increase CCB concentrations by as much as 50%.  
• **ACE inhibitors, ARBs, beta blockers, carvedilol, diuretics**: No significant interactions expected. | • **Aliskiren**: Do not coadminister.  
• **Atenolol**: Start patient at lowest possible dose and monitor for adverse events before slowly increasing dose to effect. If patient is already on atenolol, but starting a COBI-boosted PI, monitor for atenolol-related adverse events. Reduce dose of atenolol as needed. RTV is the preferred PK booster when patient is also using atenolol.  
• **CCBs**: Decrease original dose by as much as 50% when using with boosted PIs and slowly titrate to effect.  
• **ACE inhibitors, ARBs, beta blockers, diuretics**: No dose adjustments necessary. |
| Efavirenz (EFV) or etravirine (ETR) | • **Aliskiren**: ETR is a minor inhibitor of P-gp and may minimally increase concentrations of aliskiren, but this has not been studied. EFV is not expected to interact.  
• **ACE inhibitors, ARBs, CCBs, diuretics**: No significant interactions expected. | • **Aliskiren**: When using with ETR, monitor for aliskiren-related adverse events. If present, switch to alternative antihypertensive agent or ARV agent.  
• **ACE inhibitors, ARBs, beta blockers, CCBs, diuretics**: No dose adjustments necessary. |

**Abbreviations**: INSTIs, integrase strand transfer inhibitors; MATE, multidrug and toxin extrusion; NRTI, nucleoside reverse transcriptase inhibitor; NSAID, non-steroidal anti-inflammatory drug; OCT, organic cation transporter; P-gp, P-glycoprotein; PI, protease inhibitor; PK, pharmacokinetic; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

**Note**: Although not typically nephrotoxic, ACE inhibitors can, rarely, contribute to renal dysfunction, particularly when combined with high-dose NSAIDs. Clinicians are advised to ask patients who are taking TDF about their use of ACE inhibitors, such as lisinopril, with NSAIDs, such as ibuprofen or naproxen, and to monitor the patient’s renal function.

### Table 17: Anticoagulants

Warfarin, non-VKA oral anticoagulants (NOACs), low molecular weight heparins (LMWHs)

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| • NRTIs  
• Dolutegravir (DTG) or bictegravir (BIC)  
• Raltegravir (RAL)  
• Rilpivirine (RPV) | No significant interactions expected. | No dose adjustments necessary. |
### Table 17: Anticoagulants

*Warfarin, non-VKA oral anticoagulants (NOACs), low molecular weight heparins (LMWHs)*

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Elvitegravir (EVG), boosted&lt;br&gt;• Boosted PIs</td>
<td>• <strong>Warfarin</strong>: Could potentially decrease (or more rarely) increase metabolism of warfarin.&lt;br&gt;• <strong>Rivaroxaban, dabigatran, apixaban</strong>: May increase concentrations, increasing bleeding risk.&lt;br&gt;• <strong>LMWHs</strong>: No significant interaction expected.</td>
<td>• <strong>Warfarin</strong>: Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. Decrease dose if INR increases. Increase dose slowly if INR decreases.&lt;br&gt;• <strong>Rivaroxaban, dabigatran, apixaban</strong>: Avoid use of boosted PIs if possible.&lt;br&gt;• <strong>Apixaban</strong>: Reduce dose to 2.5 mg twice per day, and if patient is already taking 2.5 mg twice per day, avoid concomitant use.&lt;br&gt;• <strong>Dabigatran</strong>: 1) Separate doses of dabigatran and boosted PIs by at least 2 hours. 2) RTV-boosted PIs may be safer than COBI boosting [Kakadiya, et al. 2018]. 3) Avoid in patients taking boosted PIs if patient also has severe renal impairment.&lt;br&gt;• <strong>LMWHs</strong>: No dose adjustments necessary.</td>
</tr>
<tr>
<td>Efavirenz (EFV; Sustiva) or etravirine (ETR; Intelence)</td>
<td>• <strong>Warfarin</strong>: Could potentially increase (or more rarely decrease) metabolism of warfarin.&lt;br&gt;• <strong>NOACs, LMWHs</strong>: No significant interactions expected.</td>
<td>• <strong>Warfarin</strong>: Use cautiously with warfarin, and if use is necessary, increase monitoring of INR. Increase dose slowly if INR decreases. Decrease dose if INR increases.&lt;br&gt;• <strong>NOACs, LMWHs</strong>: No dose adjustments necessary.</td>
</tr>
</tbody>
</table>

**Abbreviations**: COBI, cobicistat; INR, international normalized ratio; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir.

### Table 18: Antiplatelet Drugs

*Adenosine phosphate receptor inhibitors, cilostazol, dipyridamole*

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NRTIs&lt;br&gt;• Dolutegravir (DTG) or bictegravir (BIC)&lt;br&gt;• Raltegravir (RAL)&lt;br&gt;• Rilpivirine (RPV)</td>
<td>No significant interactions expected.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>• <strong>Cilostazol</strong>: Metabolized by CYP3A and boosted EVG will increase concentrations of this drug.&lt;br&gt;• <strong>Ticagrelor</strong>: Results in increased exposure to ticagrelor.&lt;br&gt;• <strong>Clopidogrel</strong>: Results in decreased concentration of clopidogrel's active metabolite.</td>
<td>• <strong>Cilostazol</strong>: Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent.&lt;br&gt;• <strong>Ticagrelor</strong>: Do not use with boosted EVG.&lt;br&gt;• <strong>Clopidogrel</strong>: Do not use with boosted EVG unless an alternative antiplatelet drug (or ARV agent) cannot be used.</td>
</tr>
</tbody>
</table>
### Table 18: Antiplatelet Drugs

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PIs</td>
<td>• <strong>Cilostazol</strong>: Metabolized by CYP3A, and boosted PIs will increase concentrations of this drug.</td>
<td>• <strong>Cilostazol</strong>: Monitor for antiplatelet effect. May be necessary to use an alternative antiplatelet drug or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Dipyridamole</strong>: RTV-boosted PIs may induce UGT enzymes, which are responsible for metabolism of dipyridamole (not seen with cobicistat).</td>
<td>• <strong>Dipyridamole</strong>: Monitor for antiplatelet effect. Use another ARV agent or boost with COBI if necessary.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Ticagrelor</strong>: Results in increased exposure to ticagrelor.</td>
<td>• <strong>Ticagrelor</strong>: Do not used with boosted PIs.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Clopidogrel</strong>: Results in decreased concentration of clopidogrel’s active metabolite.</td>
<td>• <strong>Clopidogrel</strong>: Do not use with boosted PIs unless an alternative antiplatelet drug (or ARV agent) cannot be used.</td>
</tr>
</tbody>
</table>

| Efavirenz (EFV) or etravirine (ETR) | • **Cilostazol**: May reduce concentrations of cilostazol.                                                                                                                                                          | • **Cilostazol**: Monitor for antiplatelet effect; may be necessary to use an alternative antiplatelet drug or alternative ARV agent. |
|                                   | • **Dipyridamole**: EFV and ETR may induce UGT enzymes, which are responsible for metabolism.                                                                                                                        | • **Dipyridamole**: Monitor for antiplatelet effect; use another ARV agent if necessary.                      |
|                                   | • **Ticagrelor, clopidogrel**: EFV and ETR reduce ticagrelor concentrations and the conversion of clopidogrel to its active metabolite.                                                                             | • **Ticagrelor, clopidogrel**: Use with EFV or ETR may reduce the antiplatelet effect; monitor closely and use an alternative ARV agent if necessary.    |

**Abbreviations**: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir; UGT, uridine diphosphate glucuronosyltransferase.

### Table 19: Statins

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions expected.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegavir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>• <strong>Simvastatin, lovastatin</strong>: Greatly increases concentrations.</td>
<td>• <strong>Simvastatin, lovastatin</strong>: Do not use; choose another statin drug.</td>
</tr>
<tr>
<td>Boosted PIs</td>
<td>• <strong>Atorvastatin, rosvastatin</strong>: May moderately increase concentrations.</td>
<td>• <strong>Atorvastatin, rosvastatin</strong>: Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Fluvastatin</strong>: Interaction has not been studied, but potential for moderate increase is possible.</td>
<td>• <strong>Fluvastatin</strong>: Do not use, but if clinical use is desired, use the lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Pitavastatin, pravastatin</strong>: Although moderate increases are possible, low</td>
<td></td>
</tr>
</tbody>
</table>
Table 19: Statins

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>doses are considered safe when used with boosted PIs.</td>
<td></td>
</tr>
</tbody>
</table>
| Efavirenz (EFV) or etravirine (ETR) | • **Simvastatin, lovastatin**: Could potentially decrease concentrations.  
• Atorvastatin, pravastatin, fluvastatin: May modestly reduce concentrations.  
• **Pitavastatin, rosuvastatin**: No significant interactions expected. | • **Simvastatin, lovastatin**: Monitor for efficacy. May warrant increases in statin dose. Do not increase dose above maximum recommended statin dose.  
• **Atorvastatin, pravastatin, fluvastatin**: Monitor cholesterol-lowering effect of statins. May require increased dose.  
• **Pitavastatin, rosuvastatin**: No dose adjustments necessary. |

**Abbreviations:** NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

**Note:** Ritonavir-boosted PIs and EFV are known to cause metabolic dysfunction, which may increase blood cholesterol levels.

Table 20: Antidiabetic Drugs

→ Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase IV (DPP-4) inhibitors, a glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) agonists, sodium glucose cotransporter 2 (SGLT-2) inhibitors

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| • NRTIs  
• Raltegravir (RAL) | No significant interactions expected. | No dose adjustment necessary. |
| Dolutegravir (DTG) or bictegravir (BIC) | • **Metformin**: DTG increases metformin levels, but clinical significance is not yet known.  
• Sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors: No significant interactions expected. | • **Metformin**: 1) Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects. 2) Titrate metformin and do not exceed 1,000 mg when coadministered with DTG; monitor for adverse effects, including lactic acidosis.  
• Sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors: No dose adjustments necessary. |
| Elvitegravir (EVG), boosted | • **Metformin**: COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations.  
• **Glyburide**: Mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme.  
• TZDs, GLP-1 agonists, SGLT-2 inhibitors: No significant interactions noted. | • **Metformin**: Monitor for metformin-related adverse events and reduce dose as needed.  
• **Glyburide or alternative sulfonylureas**: Use lowest effective doses with boosted EVG; monitor for signs of hypoglycemia.  
• **Saxagliptin**: Limit dose to 2.5 mg once per day.  
• **Canagliflozin**: Monitor glycemic control.  
• TZDs, GLP-1 agonists, SGLT-2 inhibitors: No dose adjustments necessary. |
Table 20: Antidiabetic Drugs

Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase IV (DPP-4) inhibitors, a glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) agonists, sodium glucose cotransporter 2 (SGLT-2) inhibitors

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>• Boosted PIs</strong>&lt;br&gt;• Atazanavir (ATV), boosted</td>
<td><strong>Metformin</strong>: COBI is known to inhibit MATE1, which plays a role in the elimination of metformin, thus increasing metformin concentrations.&lt;br&gt;<strong>Glyburide</strong>: Mainly metabolized by CYP3A, and thus concentrations are increased by inhibitors of this enzyme.&lt;br&gt;<strong>Saxagliptin</strong>: Substrate of CYP3A, so levels may be increased.&lt;br&gt;<strong>Canagliflozin</strong>: Use with ATV may decrease concentrations of canagliflozin.&lt;br&gt;<strong>GLP-1 agonists</strong>: Caution needed when coadministering ATV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing the absorption of ATV. Exenatide also has the potential to slow gastric emptying.&lt;br&gt;<strong>TZDs, exenatide</strong>: No significant interactions expected.</td>
<td><strong>Metformin</strong>: Monitor for metformin-related adverse events and reduce dose as needed.&lt;br&gt;<strong>Glyburide or alternative sulfonylureas</strong>: Use lowest effective doses with boosted PIs; monitor for signs of hypoglycemia.&lt;br&gt;<strong>Saxagliptin</strong>: Limit dose to 2.5 mg once per day.&lt;br&gt;<strong>Canagliflozin</strong>: With RTV-boosted ATV and inadequate glycemic control, consider increasing dose to 300 mg per day if patient is tolerating 100 mg per day and has GFR &gt;60 mL/min/1.73 m².&lt;br&gt;<strong>GLP-1 agonist</strong>: Consider taking ATV 4 hours before.&lt;br&gt;<strong>TZDs</strong>: No dose adjustments necessary.</td>
</tr>
</tbody>
</table>

Rilpivirine (RPV) | GLP-1 agonists: Caution needed when coadministering with RPV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing the absorption of RPV. Exenatide also has the potential to slow gastric emptying.<br>**Metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors**: No significant interactions noted. | GLP-1 agonist: Consider taking RPV 4 hours before.<br>**Metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors**: No dose adjustments necessary. |

Efavirenz (EFV) or etravirine (ETR) | Pioglitazone: EFV may increase concentrations by inhibition of CYP2C8. No significant interactions expected.<br>**Saxagliptin, sitagliptin**: EFV and ETR may decrease concentration.<br>**Metformin, sulfonylureas, TZDs, GLP-1 agonists, SGLT-2 inhibitors**: No significant interactions noted. | Pioglitazone: Monitor for signs of adverse events with EFV; decrease dose if necessary.<br>**Saxagliptin, sitagliptin**: Monitor for efficacy; if necessary, increase dose of the DPP-4 inhibitor.<br>**Metformin, sulfonylureas, TZDs, GLP-1 agonists, SGLT-2 inhibitors**: No dose adjustment necessary. |

**Abbreviations**: COBI, cobicistat; CYP, cytochrome P450; GFR, glomerular filtration rate; MATE, multidrug and toxin extrusion; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.<br>**Note**: Ritonavir-boosted PIs are known to cause metabolic abnormalities, which may cause increased blood glucose and decreased insulin sensitivity. An increased risk for bone fractures has been reported with canagliflozin, particularly in patients with a history of or who are at high risk of cardiovascular disease; therefore, caution is recommended when coadministering SGLT-2 inhibitors in the long term with TDF due to potential additive bone toxicities.
Table 21: Acid-Reducing Agents

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td>No clinically significant interactions noted.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td>No dose adjustments needed.</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV) or etravirine (ETR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Atazanavir (ATV), unboosted</strong></td>
<td><strong>PPIs</strong>: Markedly reduce ATV concentration and AUC.</td>
<td><strong>PPIs</strong>: 1) Do not coadminister if alternatives are possible; use alternative acid-reducing agent, alternative PI, or boost ATV with RTV or COBI. 2) For ART-naive patients, if use cannot be avoided, do not exceed omeprazole 20 mg per day or equivalent [a] and administer 12 hours prior to ATV. 3) For ART-experienced patients [b], consult with an experienced HIV care provider or a GI specialist.</td>
</tr>
<tr>
<td><strong>Atazanavir (ATV), boosted</strong></td>
<td><strong>H2RAs</strong>: Reduce ATV absorption.</td>
<td><strong>H2RAs</strong>: 1) For ART-naive patients, administer ATV 400 mg (unboosted) with food at least 2 hours before or 10 hours after. 2) Do not exceed dose equivalent to famotidine 20 mg of any H2RA; total daily dose should not exceed 40 mg famotidine or equivalent. 3) Do not use unboosted ATV + famotidine in combination in PI-experienced patients.</td>
</tr>
</tbody>
</table>
### Table 21: Acid-Reducing Agents

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Darunavir (DRV)/ritonavir (RTV)</td>
<td>No clinically significant interaction noted.</td>
<td>• Omeprazole: Do not exceed omeprazole 40 mg per day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• No dose adjustment needed.</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>Significant reduction in plasma concentration of RPV.</td>
<td>• PPIs: Do not coadminister.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• H2RAs: Use lowest effective dose, administered no more than once per day and at least 12 hours before or 4 hours after RPV; administer with food.</td>
</tr>
</tbody>
</table>

**Abbreviations**: ARV, antiretroviral; AUC, area under the curve; COBI, cobicistat; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic; RTV, ritonavir; TFV, tenofovir; TDF, tenofovir disoproxil fumarate.

**Notes:**

a. PPI dose equivalents per day: Omeprazole 20 mg; pantoprazole 40 mg; lansoprazole 30 mg; esomeprazole 20 mg.
b. Treatment-experienced patients have taken ART and, in most cases, have experienced treatment failure. Heavily ART-experienced patients are more likely to experience resistance mutations, which increase the risk of virologic failure, and achlorhydria in the stomach, which reduces gastric acid and thus gastric pH.
c. H2RA dose equivalents twice per day: Famotidine 20 mg (40 mg); ranitidine 150 mg (300 mg); nizatidine 150 mg (300 mg).
d. Tenofovir significance: TFV has been shown to decrease ATV concentrations via an unknown mechanism. PK boosting typically overcomes this decrease in concentration, but when given along with an H2RA, adequate loss of concentration is seen to reduce ARV effect.
e. The volume of distribution increases as duration of pregnancy increases, which changes the PK parameters of medications, such as some PIs. PK boosting protects some of these PIs, but caution is required during the second and third trimesters of pregnancy to ensure adequate therapeutic concentrations.

### Table 22: Polyvalent Cations

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No clinically significant interactions noted.</td>
<td>No dose adjustments needed.</td>
</tr>
<tr>
<td>Darunavir (DRV), boosted or unboosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV) or Etravirine (ETR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All INSTIs</td>
<td>These form complexes with cations, resulting in reduced concentrations of both INSTIs and cations. For specific recommendations, see individual INSTIs below.</td>
<td>Any polyvalent cation: If coadministration is necessary, administer at least 2 hours before or at least 6 hours after, and monitor for virologic efficacy.</td>
</tr>
<tr>
<td>Dolutegravir (DTG)</td>
<td>Binds to cations, reducing effect of ARV agent and cations.</td>
<td>• Antacids: Administer at least 2 hours before or at least 6 hours after antacids containing polyvalent cations.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Supplements containing calcium or iron: DTG and supplement can be taken simultaneously with food.</td>
</tr>
</tbody>
</table>
### Table 22: Polyvalent Cations

> Supplements, antacids, and laxatives that contain aluminum, calcium, magnesium, zinc, and iron

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Bictegravir (BIC)      | Binds to cations, reducing effect of ARV agent and cations.                        | • **Antacids containing polyvalent cations:** Administer at least 2 hours before or at least 6 hours after.  
  • **Supplements containing calcium or iron:** BIC and supplement can be taken simultaneously with food. |
| Elvitegravir (EVG), boosted | Binds to cations, reducing effect of ARV agent and cations.                        | • **Polyvalent cations:** Administer at least 2 hours before or 6 hours after.  
  • **Al, Mg (+/- Ca) containing antacids:** When taken with EVG, separate doses by at least 2 hours. |
| Raltegravir (RAL)      | Binds to cations, reducing effect of ARV agent and cations.                        | • **Aluminum-magnesium hydroxide antacids:** Contraindicated; use alternative acid-reducing agent.  
  • **CaCO₃ antacids:** 1) RAL HD once per day is contraindicated. 2) RAL 400 mg twice per day: No dose adjustment or separation necessary.  
  • **Other polyvalent cations:** Administer at least 2 hours before or 6 hours after. |
| Atazanavir (ATV), boosted or unboosted | **Antacids containing calcium, magnesium, or aluminum:** May reduce absorption. | **Antacids or buffered medications:** Administer at least 2 hours before or 1 to 2 hours after. |
| Rilpivirine (RPV)      | **Antacids:** May reduce absorption.                                                | **Antacids:** Administer at least 2 hours before or at least 4 hours after.        |

**Abbreviations:** ARV, antiretroviral; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.

### Table 23: Asthma and Allergy Medications

> Albuterol, tiotropium, aclidinium, montelukast, loratadine, cetirizine, diphenhydramine

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>• Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elvitegravir (EVG), boosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Boosted PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Efavirenz (EFV) or etravirine (ETR)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 23: Asthma and Allergy Medications

- Albuterol, tiotropium, aclidinium, montelukast, loratadine, cetirizine, diphenhydramine

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>

**Abbreviations:** NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

### Table 24: Long-Acting Beta Agonists (LABAs)

- Salmeterol, formoterol, etc.

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV) or etravirine (ETR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>Increased risk of salmeterol-associated cardiovascular events.</td>
<td>Do not coadminister; consider use of alternative ARV agent.</td>
</tr>
<tr>
<td>Boosted PIs</td>
<td>Inhibition of CYP3A4 enzyme increases plasma concentrations of salmeterol.</td>
<td>• Contraindicated unless benefits outweigh possible risks; consider use of alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Boosted PIs may also increase QT prolongation.</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>Both drugs may theoretically increase QT interval, especially at high doses.</td>
<td>• No dose adjustment necessary.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Do not use more LABA than recommended; this can increase risk of QT prolongation.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

### Table 25: Inhaled and Injected Corticosteroids

- Fluticasone, triamcinolone, budesonide, and methyl prednisone

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Table 25: Inhaled and Injected Corticosteroids

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>Risk of Cushing’s syndrome when coadministered with the following:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Intranasal or inhaled</strong>: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Systemic</strong>: Betamethasone, budesonide, prednisolone, prednisone, dexamethasone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Injectable</strong>: Betamethasone, triamcinolone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhala or inhaled fluticasone, mometasone, ciclesonide, budesonide, and triamcinolone: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone).</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic betamethasone, budesonide</strong>: Do not coadminister unless potential benefits outweigh risk.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic prednisolone, prednisone</strong>: Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Injectable betamethasone, triamcinolone</strong>: Do not coadminister unless potential benefits outweigh risk.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic dexamethasone</strong>: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid.</td>
<td></td>
</tr>
<tr>
<td>Boosted PIs</td>
<td>Risk of Cushing’s syndrome when coadministered with the following corticosteroids:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Intranasal or inhaled</strong>: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Systemic</strong>: Betamethasone, budesonide, dexamethasone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- <strong>Injectable</strong>: Betamethasone, triamcinolone.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inhala or inhaled fluticasone, mometasone, ciclesonide, budesonide, and triamcinolone: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone).</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic betamethasone, budesonide</strong>: Do not coadminister unless potential benefits outweigh risk.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic prednisolone, prednisone</strong>: Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Injectable betamethasone, triamcinolone</strong>: Do not coadminister unless potential benefits outweigh risk.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic dexamethasone</strong>: Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid.</td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>Potential decrease in RPV concentration.</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Systemic dexamethasone</strong>: 1) Contraindicated; consider use of alternative agents. 2) If using more than single dose, do not coadminister.</td>
<td></td>
</tr>
</tbody>
</table>
### Table 25: Inhaled and Injected Corticosteroids

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efavirenz (EFV) or etravirine (ETR)</td>
<td>Coadministration may reduce concentrations of corticosteroids.</td>
<td>Systemic dexamethasone: Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor virologic response.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

**Note:** Short-term therapy with oral prednisone or prednisolone is not expected to cause significant drug-drug interactions with ARV agents in most cases; however, increased monitoring may be required if a patient is taking an ARV agent, including a boosted PI, that has adverse effects that are the same as those of prednisone, such as insulin resistance. Particular caution may be necessary in patients predisposed to insulin hypersensitivity. Long-term therapy with oral steroids (>2 weeks) is not recommended unless undertaken with guidance from an experienced HIV care provider.

### Table 26: Antidepressants

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>• Dolutegravir (DTG) or bictegravir (BIC)</td>
<td>Trazodone: May increase trazodone concentrations.</td>
<td>Trazodone: Monitor antidepressant and/or sedative effects.</td>
</tr>
<tr>
<td>• Raltegravir (RAL)</td>
<td>Trazodone: May decrease trazodone concentrations.</td>
<td>Trazodone: Monitor antidepressant and/or sedative effects.</td>
</tr>
<tr>
<td>• Rilpivirine (RPV)</td>
<td>Bupropion: EFV induces bupropion metabolism.</td>
<td>Bupropion: Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose.</td>
</tr>
</tbody>
</table>

**Abbreviations:** NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

### Table 27: Benzodiazepines

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>• Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Table 27: Benzodiazepines

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>Boosted ARV agents may increase benzodiazepine concentrations via CYP3A4 inhibition.</td>
<td>Alprazolam, clonazepam, diazepam: 1) Consider alternative benzodiazepine. 2) If used, administer lowest effective dose; monitor closely for adverse effects.</td>
</tr>
</tbody>
</table>
| Boosted PIs                   | • Alprazolam: Boosted ARV agents may increase alprazolam concentrations via CYP3A4 inhibition. | • Alprazolam, clonazepam, diazepam: Consider alternative benzodiazepine; if used, administer lowest effective dose; monitor closely for adverse effects.  
• Diazepam: Metabolism of diazepam may be reduced via inhibition of CYP3A4.  
• Diazepam: Monitor for excess sedation. |
| Efavirenz (EFV)               | Alprazolam, diazepam: Potential for reduced alprazolam and diazepam concentrations. | • Alprazolam: Monitor for benzodiazepine withdrawal if EFV is added.  
• Alprazolam, clonazepam, diazepam: Monitor for benzodiazepine efficacy; titrate slowly as needed for effect. |

Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.  
Note: Lorazepam, oxazepam, and temazepam do not interact clinically with and do not require dose adjustments when coadministered with ARV agents.

Table 28: Sleep Medications

→ Non-benzodiazepine “Z-drugs,” melatonin, ramelteon, suvorexant

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Raltegravir (RAL)              | • Zolpidem, suvorexant: Potential for increased concentrations of zolpidem and suvorexant. | • Zolpidem: Administer lowest effective dose; monitor for adverse effects, including excess sedation.  
• Eszopiclone: Start with 1 mg per day; titrate slowly to effect; monitor for adverse effects, including excess sedation.  
• Suvorexant: Coadministration is not recommended; use alternative sleep medication or ARV agent.  
• Ramelteon: Monitor efficacy in cigarette smokers. |
| Rilpivirine (RPV)              | • Ramelteon: RTV-boosted PIs may reduce efficacy.                                    |                                                                                   |
| Elvitegravir (EVG), boosted    | • Ramelteon: RTV-boosted PIs may reduce efficacy.                                    |                                                                                   |
| Boosted PIs                   | • Ramelteon: RTV-boosted PIs may reduce efficacy.                                    |                                                                                   |
### Table 28: Sleep Medications

- Non-benzodiazepine “Z-drugs,” melatonin, ramelteon, suvorexant

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Efavirenz (EFV) or etravirine (ETR) | Zolpidem: Potential for reduced concentrations of zolpidem. | **Zolpidem, eszopiclone:** Monitor for efficacy; no dose adjustments recommended.  
**Suvorexant:** Monitor for efficacy; do not exceed 20 mg per day. |

**Abbreviations:** ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir.

### Table 29: Antipsychotics*

- First-generation, second-generation, and atypical

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| NRTIs  
Dolutegravir (DTG) or bictegravir (BIC)  
Raltegravir (RAL) | No significant interactions expected. | No dose adjustments necessary. |
| Elvitegravir (EVG), boosted  
Ritonavir (RTV)  
Boosted PIs | **Risperidone:** Potential for moderate increase in risperidone levels.  
**Clozapine:** Interaction has not been studied but may theoretically increase concentrations of clozapine, increasing risk of adverse events. | **Quetiapine:** Reduce dose to 1/6 if initiating ARV in patient stabilized on quetiapine; monitor for adverse effects.  
**Lurasidone:** No data; avoid coadministration; consider alternative antipsychotic or ARV agent. If initiating in patient stabilized on boosted EVG, use lowest dose and titrate slowly to desired effect.  
**Risperidone:** Initiate at low dose; titrate slowly; monitor for adverse events.  
**Clozapine:** Interaction has not been studied but may theoretically increase concentrations of clozapine, increasing risk of adverse events. | **Olanzapine:** May induce CYP1A2, especially in cigarette smokers, which may decrease olanzapine concentrations.  
**Haloperidol:** Potential for moderately increased haloperidol concentrations with boosted PIs.  
**Aripiprazole, brexpiprazole:** RTV-boosted PIs may increase levels of aripiprazole and brexpiprazole.  
**Risperidone:** Potential for moderate increase in risperidone levels.  
**Clozapine:** Interaction has not been studied but may theoretically increase concentrations. | **Olanzapine:** Monitor for efficacy; titrate slowly as needed.  
**Quetiapine:** Reduce dose to 1/6 original dose if initiating boosted PI in patient stabilized on quetiapine; monitor for QT prolongation. If initiating in patient stabilized on boosted PI, use lowest dose and titrate slowly to desired effect; monitor for QT prolongation.  
**Lurasidone:** No data; avoid coadministration; consider alternative antipsychotic or ARV agent.  
**Haloperidol:** Monitor for QT prolongation. |
<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atazanavir (ATV), unboosted</td>
<td><strong>Lurasidone</strong>: Decreases lurasidone metabolism via CYP3A.</td>
<td><strong>Lurasidone</strong>: Reduce dose by 50%; monitor for adverse effects, including QT prolongation.</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>No significant interactions noted.</td>
<td>No dose adjustments necessary, but avoid excess doses of either antipsychotic or RPV because excess doses of both drugs may increase risk of QT prolongation.</td>
</tr>
</tbody>
</table>
| Efavirenz (EFV) | **Quetiapine**: Concentrations of quetiapine may be reduced.  
**Aripiprazole, brexpiprazole**: Concentrations of aripiprazole and brexpiprazole may be decreased.  
**Risperidone, olanzapine**: May decrease efficacy of risperidone and olanzapine. | **Quetiapine**: Monitor for efficacy; titrate slowly as needed; monitor for adverse effects.  
**Aripiprazole, brexpiprazole**: Monitor for efficacy; titrate dose slowly as needed; monitor for adverse effects.  
**Risperidone, olanzapine**: Monitor for efficacy; titrate slowly as needed; monitor for adverse effects. |
| Etravirine (ETR) | **Aripiprazole, brexpiprazole**: Concentrations of aripiprazole and brexpiprazole may be decreased.  
**Risperidone**: May decrease efficacy of risperidone. | **Aripiprazole, brexpiprazole**: Monitor for efficacy; titrate dose slowly as needed; monitor for adverse effects.  
**Risperidone**: Monitor for efficacy; titrate slowly; monitor for adverse effects. |

**Abbreviations**: ARV, antiretroviral; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

*Coadministration of antipsychotic and ARV agents may result in QT prolongation; monitor closely.*
Table 30: Anticonvulsants

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Tenofovir disoproxil fumarate (TDF)               | Zonisamide: May increase concentration of zonisamide.                                | • Topiramate: Monitor renal function when coadministered (topiramate may cause kidney stones; TDF is associated with renal toxicity).  
  • Zonisamide: Monitor for adverse events of zonisamide. |
| Tenofovir alafenamide (TAF)                        | Coadministration with strong inducers of CYP3A (phenytoin, phenobarbital, etc.) may decrease TAF concentrations. | Coadministration with strong inducers of CYP3A are not recommended because they may reduce concentrations of TAF. |
| Other NRTIs                                        | No interactions noted.                                                              | No dose adjustments necessary.                                                   |
| Dolutegravir (DTG) or bictegravir (BIC)            | • Valproic acid: Coadministration may significantly decrease DTG or BIC concentrations.  
  • Coadministration with strong inducers of CYP3A (phenytoin, phenobarbital, etc.) may decrease DTG or BIC concentrations. | Valproic acid: 1) Coadministration is not recommended; if alternative anticonvulsant cannot be used, monitor for safety and efficacy, including therapeutic drug monitoring. 2) Coadministration with strong inducers of CYP3A are not recommended because they may reduce concentrations of INSTIs. |
| Raltegravir (RAL)                                  | Coadministration with strong inducers of UGT1A1 (phenytoin, phenobarbital, etc.) may decrease RAL concentrations. | Coadministration with strong inducers of UGT1A1 are not recommended.            |
| Elvitegravir (EVG), boosted                        | Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin:  
  Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system. | Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: 1) Coadministration is not recommended; use alternative anticonvulsant. 2) If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. 3) Perform therapeutic drug monitoring. |
| Ritonavir (RTV)                                    | • Phenytoin: Concurrent use may reduce concentrations of RTV and phenytoin, resulting in loss of viral suppression and seizure control.  
  • Lamotrigine: RTV-boosted ARV agents may reduce efficacy of lamotrigine.  
  • Valproic acid: RTV may reduce concentrations of valproic acid. | • Phenytoin: 1) Coadministration is not recommended; use alternative anticonvulsant. 2) If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. 3) Perform therapeutic drug monitoring. Lamotrigine: Monitor efficacy; titrate dose slowly as needed.  
  • Valproic acid: Consider use of COBI when boosting of ARV agent is required. |
Table 30: Anticonvulsants

Including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine, valproic acid, gabapentin, topiramate, zonisamide

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin: Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system.</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: 1) Coadministration is not recommended; use alternative anticonvulsant. 2) If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. 3) Perform therapeutic drug monitoring. Zonisamide: Monitor efficacy and adverse effects; adjust dose as needed.</td>
</tr>
<tr>
<td></td>
<td>Zonisamide: Zonisamide concentrations may be increased through CYP3A4 inhibition.</td>
<td></td>
</tr>
<tr>
<td>NNRTIs</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin: Coadministration may significantly reduce concentrations of ARV agents through induction of CYP450 system.</td>
<td>Carbamazepine, oxcarbazepine, phenobarbital, phenytoin: 1) Coadministration is not recommended; use alternative anticonvulsant. 2) If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. 3) Perform therapeutic drug monitoring if use cannot be avoided.</td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td>Gabapentin, topiramate, zonisamide: No significant interactions expected.</td>
<td>Gabapentin, topiramate, zonisamide: No dose adjustments necessary.</td>
</tr>
<tr>
<td>Efavirenz (EFV) or etravirine (ETR)</td>
<td>Lamotrigine, zonisamide: May reduce efficacy of lamotrigine or zonisamide. Gabapentin, topiramate: No significant interactions noted.</td>
<td>Lamotrigine, zonisamide: Monitor efficacy; titrate dose slowly as needed. Gabapentin, topiramate: No dose adjustments necessary.</td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; INSTI, integrase strand transfer inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; UGT1A1, uridine diphosphate glucuronosyltransferase 1A1.

Table 31: Non-Opioid Pain Medications

Triptans, tricyclic antidepressants (TCAs), pregabalin, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td>No significant interactions expected.</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz (EFV) or etravirine (ETR)</td>
<td>Lamotrigine, zonisamide: May reduce efficacy of lamotrigine or zonisamide. Gabapentin, topiramate: No significant interactions noted.</td>
<td>Lamotrigine, zonisamide: Monitor efficacy; titrate dose slowly as needed. Gabapentin, topiramate: No dose adjustments necessary.</td>
</tr>
</tbody>
</table>
### Table 31: Non-Opioid Pain Medications

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Elvitegravir (EVG), boosted | **Eletriptan**: Metabolism inhibited by boosted EVG.  
**Other non-opioid pain medications**: No significant interactions expected. | **Eletriptan**: Do not coadminister; use alternative triptan medication. |
| Boosted PIs | **Eletriptan**: Metabolism inhibited by boosted PIs.  
**TCAs**: PI and TCAs can both cause QT prolongation.  
**Pregabalin**: No significant interactions expected. | **Eletriptan**: Do not coadminister; use alternative triptan medication.  
**TCAs**: When using high-dose TCAs and PIs, consider monitoring for QT prolongation or other cardiac adverse events or using alternative medications. |

**Abbreviations**: NRTI, nucleoside reverse transcriptase inhibitor; NSAID, non-steroidal anti-inflammatory drug; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

**Note**: Although TDF and NSAIDs (such as ibuprofen, meloxicam, or naproxen) are not absolutely contraindicated, NSAIDs may increase the risk of impaired renal function in patients taking high doses of these drugs, and particularly in patients who are predisposed to renal dysfunction. Clinicians are advised to ask patients about their use of over-the-counter or prescribed NSAIDs and to counsel patients to limit NSAID use to the lowest effective dose. Clinicians should also ask patients who are taking TDF as part of a pre-exposure prophylaxis regimen (PrEP) about their use of NSAIDs.

### Table 32: Opioid Analgesics and Tramadol

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| NRTIs  
Dolutegravir (DTG) or bictegravir (BIC)  
Raltegravir (RAL)  
Rilpivirine (RPV)  
Etravirine (ETR) | No significant interactions noted. | No dose adjustments required. |
| Elvitegravir (EVG), boosted | **Opioid analgesics**: Complex mechanisms of metabolism and formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted EVG.  
**Tramadol**: Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6. | **Opioid analgesics**: Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly.  
**Tramadol**: When tramadol is given with CQI, monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed. |
### Table 32: Opioid Analgesics and Tramadol

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boosted PIs</td>
<td>- Opioid analgesics: Complex mechanisms of metabolism and the formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted PIs.</td>
<td>- Opioid analgesics: Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly.</td>
</tr>
<tr>
<td></td>
<td>- Tramadol: Tramadol exposure is increased with inhibition of CYP3A, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6.</td>
<td>- Tramadol: When tramadol is given with COBI or RTV, monitoring for tramadol-related side effects and for the analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>- Morphine, hydromorphone: Metabolism could potentially be reduced by EFV.</td>
<td>- Morphine, hydromorphone: Monitor for signs of opiate toxicity when using with EFV.</td>
</tr>
<tr>
<td></td>
<td>- Oxycodone: May be metabolized faster to an inactive metabolite by EFV.</td>
<td>- Oxycodone: Dose adjustment of oxycodone may be required when dosing with EFV.</td>
</tr>
<tr>
<td></td>
<td>- Meperidine: Coadministration can potentially increase amount of neurotoxic metabolite and thereby increase risk of seizures.</td>
<td>- Meperidine: If possible, avoid concomitant use; use alternative opiate pain medication or ARV agent.</td>
</tr>
<tr>
<td></td>
<td>- Tramadol: May reduce concentration of tramadol without affecting pathway that increases development of more potent active metabolites.</td>
<td>- Tramadol: When given with tramadol, a priori dose adjustments are necessary.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir.

### Table 33: Hormonal Contraceptives

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant drug interactions noted.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td>Drosiprenone: Potential for hyperkalemia.</td>
<td>- Ethinyl estradiol, norgestimate, metabolites; norethindrone: Weigh risks/benefits; consider alternative contraceptive method.</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td>- Drosiprenone: Monitor for hyperkalemia; consider alternative contraceptive or alternative ARV agent.</td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td></td>
<td>- Etonogestrel: No data; consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
</tbody>
</table>
### Table 33: Hormonal Contraceptives

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>All PIs</td>
<td>Combination has not been studied.</td>
<td><strong>Etonogestrel:</strong> No data; consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td>Atazanavir (ATV), unboosted</td>
<td>Complex drug interaction potential has been described.</td>
<td><strong>Ethynyl estradiol:</strong> Do not exceed 30 mcg (no data on doses lower than 25 mcg).</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Norethindrone:</strong> Do not exceed 30 mcg (no data on oral contraceptives with &lt;25 mcg of ethynyl estradiol or progestins other than norethindrone or norgestimate).</td>
</tr>
<tr>
<td>Atazanavir (ATV), boosted</td>
<td>• Complex drug interaction potential has been described.</td>
<td><strong>Ethynyl estradiol; norgestimate and metabolites:</strong> Dose with at least 35 mcg (no data on other progestins).</td>
</tr>
<tr>
<td></td>
<td>• <strong>Drospirenone:</strong> Potential for hyperkalemia.</td>
<td><strong>Drospirenone:</strong> Do not coadminister.</td>
</tr>
<tr>
<td>Darunavir (DRV)/ritonavir (RTV)</td>
<td>Combination appears to decrease oral norethindrone concentrations.</td>
<td><strong>Norethindrone:</strong> Consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td>Darunavir (DRV)/cobicistat (COBI)</td>
<td>Combination has not been studied, but since COBI does not induce glucuronidation, it is expected to increase concentrations of norethindrone.</td>
<td><strong>Norethindrone:</strong> Consider alternative contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td>Other Boosted PIs</td>
<td><strong>Drospirenone:</strong> Potential for hyperkalemia.</td>
<td><strong>Ethynyl estradiol:</strong> Consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Drospirenone:</strong> Monitor for hyperkalemia; consider alternative contraceptive or alternative ARV agent.</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>Decreased concentrations of combined progestins.</td>
<td><strong>Ethynyl estradiol; norgestimate, metabolites:</strong> Use alternative or additional contraceptive methods; unintended pregnancies have been reported in individuals using levonorgestrel implant.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Norethindrone, drospirenone, etonogestrel:</strong> Consider alternative or additional contraceptive method or alternative ARV agent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Ulipristal:</strong> Efficacy may be reduced; monitor closely.</td>
</tr>
</tbody>
</table>
### Table 33: Hormonal Contraceptives

- Combined oral contraceptives, including ethinyl estradiol, norethindrone, and levonorgestrel

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine (ETR)</td>
<td>Information is based on what is known with EFV drug interactions.</td>
<td><strong>Etonogestrel:</strong> No data; consider alternative or additional contraceptive method or alternative ARV agent. <strong>Ulipristal:</strong> Efficacy may be reduced; monitor closely.</td>
</tr>
</tbody>
</table>

*Abbreviations:* ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

### Table 34: Erectile and Sexual Dysfunction Agents

- Sildenafil [a], vardenafil, tadalafil [b,c], and alprostadil for men; flibanserin [d] for women

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustment necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td><strong>PDES inhibitor:</strong> Increased PDES inhibitor concentrations expected. <strong>Flibanserin:</strong> Increased flibanserin concentrations expected.</td>
<td><strong>Sildenafil:</strong> Start with 25 mg every 48 hours; monitor for adverse effects. <strong>Tadalafil:</strong> Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects. <strong>Vardenafil:</strong> Administer 2.5 mg every 72 hours; monitor for adverse effects. <strong>Flibanserin:</strong> Caution to avoid adverse effects.</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td><strong>PDES inhibitor:</strong> Increased PDES inhibitor concentrations expected. <strong>Flibanserin:</strong> Increased flibanserin concentrations expected.</td>
<td><strong>Sildenafil:</strong> Start with 25 mg every 48 hours; monitor for adverse effects. <strong>Tadalafil:</strong> Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects. <strong>Vardenafil:</strong> Administer 2.5 mg every 72 hours; monitor for adverse effects. <strong>Flibanserin:</strong> Caution to avoid adverse effects.</td>
</tr>
<tr>
<td>Atazanavir (ATV), unboosted</td>
<td><strong>Avanafil:</strong> Increased concentration of avanafil expected (for other oral erectile dysfunction drugs, see above).</td>
<td><strong>Avanafil:</strong> Do not exceed 50 mg every 24 hours.</td>
</tr>
<tr>
<td>Boosted PIs</td>
<td><strong>PDES inhibitor:</strong> Increased PDES inhibitor concentrations expected. <strong>Flibanserin:</strong> Increased flibanserin concentrations expected.</td>
<td><strong>Sildenafil:</strong> Start with 25 mg every 48 hours; monitor for adverse effects. <strong>Tadalafil:</strong> Start with 5 mg; do not exceed 10 mg every 72 hours; monitor for adverse effects. <strong>Vardenafil:</strong> Administer 2.5 mg every 72 hours; monitor for adverse effects. <strong>Avanafil:</strong> Do not coadminister. <strong>Flibanserin:</strong> Do not coadminister.</td>
</tr>
</tbody>
</table>
### Table 34: Erectile and Sexual Dysfunction Agents

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Sildenafil [a], vardenafil, tadalafil [b,c], and alprostadil for men; flibanserin [d] for women | PDE5 inhibitor: Potential for reduced effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil).  
Flibanserin: Potential for reduced concentrations of flibanserin. | PDE5 inhibitors: Monitor clinical effect; if dose increase is needed to achieve desired clinical effect, titrate under medical supervision to lowest effective dose.  
Flibanserin: Do not coadminister. |

**Abbreviations:** COBI, cobicistat; NRTI, nucleoside reverse transcriptase inhibitor; PDE5, phosphodiesterase type 5; PI, protease inhibitor.

**Notes:**
- a. Sildenafil for treatment of pulmonary arterial hypertension (PAH): Concurrent administration of all PIs and EVG/cobicistat is contraindicated.
- b. Tadalafil for treatment of PAH: When coadministered with any PIs or with EVG/COBI, start with 20 mg per day and increase to 40 mg per day based on tolerability.
- c. Tadalafil for treatment of benign prostatic hyperplasia: When coadministered with any PIs, the maximum recommended dose is 2.5 mg per day.
- d. Flibanserin should not be administered with alcohol in any circumstances.

### Table 35: Tobacco and Smoking Cessation Products

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boosted PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Efavirenz (EFV) or etravirine (ETR) | No significant interactions noted.  
EFV (but not ETR) may increase bupropion metabolism. | No dose adjustments necessary.  
**Bupropion:** Monitor clinical effect and increase as needed, but do not exceed recommended maximum dose. |

**Abbreviations:** NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
Table 36: Alcohol, Disulfiram, and Acamprosate

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Other NRTIs</td>
<td>No significant interactions noted.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>• Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elvitegravir (EVG), boosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Other boosted PIs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Efavirenz (EFV) or etravirine (ETR)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>Alcohol: Metabolized via same pathway as alcohol.</td>
<td>May increase ABC concentrations; monitor for adverse ABC effects. Does not appear to increase concentrations of alcohol in blood.</td>
</tr>
<tr>
<td>• Ritonavir (RTV) oral solutions</td>
<td>All contain alcohol and may potentiate symptoms of consumption of ethanol.</td>
<td>Disulfiram: ARV agents formulated with alcohol will induce same aversive effects as consumption of ethanol.</td>
</tr>
<tr>
<td>• Lopinavir/ritonavir (LPV/r; oral suspension or capsules)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Note: Clinicians are advised to inform patients that alcohol should be consumed with caution while taking a prescription medication and should educate patients about how medications may affect their response to alcohol. Clinicians are advised to caution patients against driving or operating heavy machinery after consuming alcohol.

Table 37: Methadone, Buprenorphine (BUP), Naloxone (NLX), and Naltrexone*

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>• NRTIs</td>
<td>BUP, methadone: No significant interactions expected.</td>
<td>No dose adjustments necessary.</td>
</tr>
<tr>
<td>• Dolutegravir (DTG) or bictegravir (BIC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Raltegravir (RAL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Elvitegravir (EVG), boosted</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir (ATV), unboosted</td>
<td>• BUP, norbuprenorphine: Greatly increases concentrations of BUP and norbuprenorphine; may decrease ATV concentrations.</td>
<td>• BUP: Coadministration is not recommended; RTV boosting may decrease effect.</td>
</tr>
<tr>
<td></td>
<td>• Methadone: No significant interactions expected.</td>
<td>• Methadone: No dose adjustments required; exercise caution because both drugs have potential to increase QT prolongation.</td>
</tr>
<tr>
<td>Ritonavir (RTV)-boosted PIs</td>
<td>BUP: May greatly increase BUP concentrations, but clinical significance of this is unknown because dosing of BUP is based on clinical opiate withdrawal scale.</td>
<td>BUP: Monitor for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress.</td>
</tr>
</tbody>
</table>
### Table 37: Methadone, Buprenorphine (BUP), Naloxone (NLX), and Naltrexone*

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| Cobicistat (COBI)-boosted PIs | • BUP: May increase BUP concentrations while decreasing NLX concentrations when given with sublingual BUP/NLX.  
• Methadone: COBI does not appear to have any significant effect on the concentration of methadone. | • BUP, NLX: Use careful dose titration when giving with COBI-boosted ARVs.  
• Methadone: Based on efficacy and safety: Initiate at lowest possible dose and monitor for signs and symptoms of opiate withdrawal and titrate dose to effect. |
| RTV-boosted darunavir (DRV), taken twice per day | • BUP, NLX: Combination had no effect on BUP/NLX concentrations.  
• Methadone: May reduce methadone concentrations. | Methadone: Monitor for signs of opiate withdrawal and increase dose of methadone if necessary. |
| Rilpivirine (RPV) | • BUP: No significant interactions expected.  
• Methadone: Mildly reduces methadone concentrations. | • Methadone: Monitor for signs of methadone withdrawal and increase dose as necessary.  
• Methadone, BUP: Use cautiously with RPV because supratherapeutic doses of RPV have been known to cause increase in QT prolongation. |
| Efavirenz (EFV) | • BUP: When given with BUP alone (monotherapy), significantly reduces BUP concentrations, but no patients developed opioid withdrawal.  
• Methadone: Reduces methadone concentrations. | • BUP: When given with BUP, dose adjustments are unlikely to be required, but monitor for withdrawal symptoms. If withdrawal symptoms occur, increase BUP dose accordingly.  
• Methadone: Monitor for signs and symptoms of opioid withdrawal and titrate methadone dose to effect. |
| Etravirine (ETR) | • BUP: No significant interactions expected.  
• Methadone: May slightly increase concentrations of methadone. | • Monitor for signs of withdrawal or opioid toxicity and titrate dose of opioid or antagonist as required.  
• Methadone: Monitor for signs of methadone toxicity and reduce dose if necessary. |

*No significant interactions expected between ARVs, naloxone, and naltrexone.

**Abbreviations:** ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

### Table 38: Immunosuppressants*

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
</table>
| NRTIs  
Dolutegravir (DTG)  
Raltegravir (RAL)  
Rilpivirine (RPV) | No significant interactions noted. | No dose adjustments necessary. |
### Table 38: Immunosuppressants*

<table>
<thead>
<tr>
<th>Class or Drug</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bictegravir (BIC)</td>
<td><strong>Cyclosporine:</strong> May increase BIC concentrations to a modest degree via P-gp inhibition.</td>
<td>Monitor for BIC-related adverse events.</td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>• <strong>Everolimus, sirolimus:</strong> Metabolism decreased by boosted EVG.</td>
<td>• <strong>Everolimus, sirolimus:</strong> Do not use with boosted EVG.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Cyclosporine, tacrolimus:</strong> Metabolism decreased by boosted EVG.</td>
<td>• <strong>Cyclosporine, tacrolimus:</strong> Dose based upon therapeutic drug monitoring; monitor closely for adverse events.</td>
</tr>
<tr>
<td>Boosted PIs</td>
<td>• <strong>Everolimus, sirolimus:</strong> Metabolism decreased by boosted PIs.</td>
<td>• <strong>Everolimus, sirolimus:</strong> Do not use with boosted PIs.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Cyclosporine, tacrolimus:</strong> Metabolism decreased by boosted PIs.</td>
<td>• <strong>Cyclosporine, tacrolimus:</strong> Dose based upon therapeutic drug monitoring; monitor closely for adverse events.</td>
</tr>
<tr>
<td>Efavirenz (EFV) or etravirine (ETR)</td>
<td><strong>Cyclosporine, tacrolimus:</strong> Concentrations may be lower when used with EFV or ETR.</td>
<td><strong>Cyclosporine, tacrolimus:</strong> 1) Dose adjust cyclosporine and tacrolimus based on efficacy and therapeutic drug monitoring (TDM). 2) Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.</td>
</tr>
</tbody>
</table>

**Abbreviations:** NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; P-gp, P-glycoprotein; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate.

*Note: Cyclosporine can cause renal toxicity, which may be increased with coadministration of TDF. Clinicians are advised to monitor for signs of renal dysfunction in patients who are taking these two medications at the same time.*

### Table 39: Rifamycins and Other Anti-Tuberculosis Medications

<table>
<thead>
<tr>
<th>ARV Class and Drugs</th>
<th>Rifabutin Interactions and Recommendations</th>
<th>Rifampin Interactions and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside Reverse Transcriptase Inhibitors (NRTIs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>• <strong>Rifabutin:</strong> No clinically significant interactions.</td>
<td><strong>Rifampin:</strong> No dose adjustments recommended for concomitant use with ABC.</td>
</tr>
<tr>
<td></td>
<td>• <strong>Rifampin:</strong> May reduce concentration of ABC.</td>
<td></td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td><strong>Rifabutin, rifampin:</strong> No clinically significant interactions.</td>
<td><strong>N/A</strong></td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>• <strong>Rifabutin, rifampin:</strong> No clinically significant interactions.</td>
<td><strong>N/A</strong></td>
</tr>
</tbody>
</table>
### Table 39: Rifamycins and Other Anti-Tuberculosis Medications

<table>
<thead>
<tr>
<th>ARV Class and Drugs</th>
<th>Rifabutin Interactions and Recommendations</th>
<th>Rifampin Interactions and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tenofovir alafenamide (TAF)</strong></td>
<td>Rifabutin induction of CYP3A and P-gP is expected to decrease TAF levels. Rifampin induction of CYP3A may reduce concentration of TAF.</td>
<td>Rifabutin: Concomitant use with TAF is contraindicated. Rifampin: Concomitant use with TAF is contraindicated.</td>
</tr>
<tr>
<td><strong>Tenofovir disoproxil fumarate (TDF)</strong></td>
<td>Rifabutin, rifampin: No clinically significant interactions.</td>
<td>N/A</td>
</tr>
</tbody>
</table>

### Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

<table>
<thead>
<tr>
<th>ARV Class and Drugs</th>
<th>Rifabutin Interactions and Recommendations</th>
<th>Rifampin Interactions and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doravirine (DOR)</strong></td>
<td>Rifabutin induction of CYP3A is expected to decrease DOR levels. Rifampin induction of CYP3A reduces bioavailability of DOR.</td>
<td>Rifabutin: When used concomitantly, increase DOR dosage to 100 mg twice per day. Rifampin: Concomitant use with DOR is contraindicated.</td>
</tr>
<tr>
<td><strong>Efavirenz (EFV)</strong></td>
<td>Rifabutin: EFV induction of CYP3A reduces bioavailability of rifabutin, but coadministration has no effect on EFV levels. Rifampin: No clinically significant interactions.</td>
<td>Rifabutin: If EFV and rifabutin are used concomitantly, increase dose of rifabutin by 50%, especially if rifabutin is dosed 3 times weekly.</td>
</tr>
<tr>
<td><strong>Etravirine (ETR)</strong></td>
<td>Rifabutin: When used concomitantly with ETR, increased rifabutin levels are expected and decreased ETR levels may be seen. Rifampin induction of CYP3A reduces bioavailability of ETR.</td>
<td>Rifabutin: If ETR and rifabutin are used concomitantly, rifabutin should be dosed at 300 mg daily, with no changes to the dose of ETR. Continue this dosing until at least 2 weeks after rifabutin is stopped. Concomitant use of a boosted PI with ETR and rifabutin is contraindicated. Rifampin: Concomitant use is contraindicated.</td>
</tr>
<tr>
<td><strong>Nevirapine (NVP)</strong></td>
<td>Rifampin induction of CYP3A reduces bioavailability of NVP.</td>
<td>Rifampin: Concomitant use is contraindicated.</td>
</tr>
<tr>
<td><strong>Rilpivirine (RPV)</strong></td>
<td>Rifabutin induction of CYP3A and P-gP decreases RPV levels. Rifampin induction of CYP3A reduces bioavailability of RPV.</td>
<td>Rifabutin: Concomitant use is contraindicated. Rifampin: Concomitant use is contraindicated.</td>
</tr>
</tbody>
</table>

### Protease Inhibitor (Pis) and Boosted PIs

<table>
<thead>
<tr>
<th>ARV Class and Drugs</th>
<th>Rifabutin Interactions and Recommendations</th>
<th>Rifampin Interactions and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Pis</strong></td>
<td>Rifabutin: Does not affect levels of boosted Pis, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased.</td>
<td>Rifabutin: When used concomitantly, reduce rifabutin dose to 150 mg 3 times per week.</td>
</tr>
</tbody>
</table>
### Table 39: Rifamycins and Other Anti-Tuberculosis Medications

<table>
<thead>
<tr>
<th>ARV Class and Drugs</th>
<th>Rifabutin Interactions and Recommendations</th>
<th>Rifampin Interactions and Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin, rifabutin, rifapentine [a], isoniazid [b], pyrazinamide [b], ethambutol [b], rifaximin [b]</td>
<td>• Rifampin induction of CYP3A reduces bioavailability of ALL protease inhibitors.</td>
<td>• Rifampin: Concomitant use of PIs and rifampin is contraindicated.</td>
</tr>
</tbody>
</table>

#### Integrase Strand Transfer Inhibitors (INSTIs)

<table>
<thead>
<tr>
<th>Bictegravir (BIC)</th>
<th>Rifabutin induction of CYP3A and P-gP decreases BIC levels.</th>
<th>Rifabutin induction of CYP3A reduces bioavailability.</th>
<th>Rifabutin: Concomitant use is contraindicated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dolutegravir (DTG)</td>
<td>Rifabutin: No clinically significant interactions.</td>
<td>Rifampin induction of CYP3A reduces bioavailability of DTG.</td>
<td>Rifampin: When used concomitantly, dose DTG at 50 mg twice per day instead of 50 mg once per day.</td>
</tr>
<tr>
<td>Elvitegravir (EVG), boosted</td>
<td>Rifabutin induction of CYP3A expected to decrease levels of EVG.</td>
<td>Rifampin induction of CYP3A reduces bioavailability of EVG.</td>
<td>Rifabutin: Concomitant use is not recommended.</td>
</tr>
<tr>
<td>Raltegravir (RAL)</td>
<td>Rifabutin: No clinically significant interactions.</td>
<td>Rifampin induction of CYP3A reduces bioavailability of RAL.</td>
<td>Rifampin: When used concomitantly, dose RAL at 800 mg twice per day instead of 400 mg twice per day.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- Do not use RAL HD.</td>
</tr>
</tbody>
</table>

**Abbreviations:** ARV, antiretroviral; CYP, cytochrome P450; P-gP, P-glycoprotein.

**Notes:**

a. Rifapentine has not been studied with many antiretrovirals, but its CYP3A inducing effects are expected to be lower than those seen with rifampin but higher than those seen with rifabutin. Global research has suggested that rifapentine combined with isoniazid may be safe and effective for patients using efavirenz or (dose adjusted) raltegravir or dolutegravir, but further studies are required before recommendations can be made about the use of this medicine with other antiretroviral agents.

b. Isoniazid, pyrazinamide, ethambutol, rifaximin: No clinically significant interactions with ARVs expected; no dose adjustments necessary. Rifaximin is a rifamycin drug that is not used to treat tuberculosis, but may be seen in patients with hepatic encephalopathy or some forms of infectious diarrhea.
### Table 40: Gender Affirming Hormones
[Hembree, et al. 2017; Irving and Lehault 2017]

<table>
<thead>
<tr>
<th>ARV Drug Class or Medication</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARV medications, all</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Cyproterone acetate: The interaction with ARVs has not been studied.</td>
<td>• Estradiol: When prescribing ARVs, consider the use of medications not expected to interact with estradiol.</td>
<td></td>
</tr>
<tr>
<td>• Estradiol: The interaction between ARVs and estradiol in transgender women has not been studied.</td>
<td>• Finasteride: No dose adjustments recommended.</td>
<td></td>
</tr>
<tr>
<td>• Finasteride: The interaction with ARVs has not been studied. Finasteride is metabolized by CYP3A4; levels may increase when taken concomitantly with COBI-boosted ARVs, but clinical significance is expected to be minimal.</td>
<td>• Goserelin: The interaction with ARVs has not been studied. Based upon what is known about metabolism of goserelin, no clinically significant interactions are expected.</td>
<td></td>
</tr>
<tr>
<td>• Goserelin: The interaction with ARVs has not been studied. Based upon what is known about metabolism of goserelin, no clinically significant interactions are expected.</td>
<td>• Leuprolide acetate: The interaction with ARVs has not been studied. Based upon what is known about metabolism of leuprolide acetate, no clinically significant interactions are expected.</td>
<td></td>
</tr>
<tr>
<td>• Leuprolide acetate: The interaction with ARVs has not been studied. Based upon what is known about metabolism of leuprolide acetate, no clinically significant interactions are expected.</td>
<td>• Testosterone: The interaction between ARVs and testosterone in transgender men has not been studied. Testosterone has been used in androgen-deficient cisgender men with HIV without clinical drug interactions.</td>
<td></td>
</tr>
<tr>
<td>• Testosterone: The interaction between ARVs and testosterone in transgender men has not been studied. Testosterone has been used in androgen-deficient cisgender men with HIV without clinical drug interactions.</td>
<td>• Spironolactone: No interactions expected.</td>
<td></td>
</tr>
<tr>
<td>• Spironolactone: No interactions expected.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cobicistat (COBI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estradiol: Based upon known mechanisms of metabolism, COBI-boosted PIs or other ARVs may have mixed effects on estradiol levels. COBI does not induce CYP1A2, and as such may increase estradiol levels by inhibition of CYP3A.</td>
<td>• Estradiol: When taken concomitantly with COBI-boosted ARVs, monitor for signs of estrogen deficiency or excess.</td>
<td></td>
</tr>
<tr>
<td>• Finasteride: When taken concomitantly, finasteride levels may be increased, but with minimal clinical significance.</td>
<td>• Finasteride: No dose adjustments are recommended.</td>
<td></td>
</tr>
<tr>
<td>• Testosterone: Based upon known mechanisms of metabolism, there is limited potential that COBI-boosted PIs or other ARVs may increase testosterone levels. The relevance of this interaction is expected to be low in transgender men.</td>
<td>• Testosterone: No dose adjustments are recommended.</td>
<td></td>
</tr>
<tr>
<td>Doravirine (DOR)</td>
<td>• Estradiol: No interactions expected.</td>
<td>N/A</td>
</tr>
<tr>
<td>• Testosterone: No interactions expected.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 40: Gender Affirming Hormones
[Hembree, et al. 2017; Irving and Lehault 2017]

→ Cyproterone acetate, estradiol, finasteride, goserelin, leuprolide acetate, spironolactone, testosterone

<table>
<thead>
<tr>
<th>ARV Drug Class or Medication</th>
<th>Mechanism of Action</th>
<th>Clinical Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz (EFV)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estradiol: EFV could induce CYP3A and could decrease estradiol levels.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Finasteride: Levels may decrease when taken concomitantly with EFV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Testosterone: Levels may decrease when taken concomitantly with EFV.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Estradiol: No dose adjustments are recommended, but when taken concomitantly with EFV, monitor for signs of estrogen deficiency or excess.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Finasteride: No dose adjustments recommended.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Testosterone: No dose adjustments recommended.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| **Etravirine (ETR)**         |                     |                   |
| • Estradiol: ETR could induce CYP3A and could decrease estradiol levels. |
| • Finasteride: Levels may decrease when taken concomitantly with ETR. |
| • Testosterone: Levels may decrease when taken concomitantly with ETR. |
| • Estradiol: No dose adjustments are recommended, but when taken concomitantly with ETR, monitor for signs of estrogen deficiency or excess. |
| • Finasteride: No dose adjustments recommended. |
| • Testosterone: No dose adjustments recommended. |

| **INSTIs, non-boosted**     |                     |                   |
| INSTIs, non-boosted          |                     |                   |
| (dolutegravir, DTG;          | Estradiol: No       |                   |
| raltegravir, RAL)            | interactions expected. |
| • Estradiol: No interactions expected. |
| • Finasteride: No interactions expected. |
| • Testosterone: No interactions expected. |
| N/A                          |                     |                   |

| **NRTIs, non-boosted**      |                     |                   |
| NRTIs, non-boosted          | Estradiol: No       |                   |
| (abacavir, ABC; emtricitabine, FTC; lamivudine, 3TC; tenofovir alafenamide, TAF; tenofovir disoproxil fumarate, TDF) | interactions expected. |
| • Estradiol: No interactions expected. |
| • Finasteride: No interactions expected. |
| • Testosterone: No interactions expected. |
| N/A                          |                     |                   |

| **Rilpivirine (RPV)**       | Estradiol: No       |                   |
| • interactions expected. |
| • Finasteride: No interactions expected. |
| • Testosterone: No interactions expected. |
| N/A                          |                     |                   |

| **Ritonavir (RTV)**         | Estradiol: RTV may induce CYP1A2, which could decrease estradiol levels. This outweighs the RTV inhibition of CYP3A. |
| • Testosterone: No interactions expected. |
| N/A                          |                     |                   |

**Abbreviations:** ARV, antiretroviral; CYP, cytochrome P450; INSTI, integrase strand transfer inhibitor; N/A, not applicable; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.
References


hepatitis C infection. *Drug Metab Dispos* 2018;46(8):1212-1225. [PMID: 29695614]


