CLINICAL GUIDELINES PROGRAM
NEW YORK STATE DEPARTMENT OF HEALTH AIDS INSTITUTE | HIV · HCV · SUBSTANCE USE · LGBT HEALTH

Resource: ART Drug-Drug Interactions

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→ Summary of updates in the April 26, 2023 edition

- Added Table 18A: Lenacapavir (LEN) Interactions to Drug-Drug Interactions by Antiretroviral Drug Class section
- Added LEN interactions information throughout Drug-Drug Interactions by Common Medication Class section

Contents

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 reported drug-drug interactions to identify those that should or must be avoided and those that can be managed to alleviate adverse effects

The NYSDOH AI Medical Care Criteria Committee offers guidance on the interactions between ARVs and medications commonly used in the management of coexisting conditions seen in healthcare 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 HIV transmission. This resource 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
- WebMD Drug Interaction Checker
- Clinical Info HIV.gov Drug Database
- Toronto General Hospital Immunodeficiency Clinic Drug Interaction Tables

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.

Note on "experienced" and "expert" HIV care providers: Throughout this guideline, when reference is made to "experienced HIV care provider" or "expert HIV care provider," those terms are referring to the following 2017 NYSDOH AI definitions:

- Experienced HIV care provider: Practitioners who have been accorded HIV Experienced Provider status by the American Academy of HIV Medicine or have met the HIV Medicine Association's definition of an experienced provider are eligible for designation as an HIV Experienced Provider in New York State. Nurse practitioners and licensed midwives who provide clinical care to individuals with HIV in collaboration with a physician may be considered HIV Experienced Providers as long as all other practice agreements are met (8 NYCRR 79-5:1; 10 NYCRR 85.36; 8 NYCRR 139-6900). Physician assistants who provide clinical care to individuals with HIV under the supervision of an HIV Specialist physician may also be considered HIV Experienced Providers (10 NYCRR 94.2)
- Expert HIV care provider: A provider with extensive experience in the management of complex patients with HIV.

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 effects 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 polypharmacy-related risk factors 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 [Zingmond, et al. 2017; Walckiers, et al. 2015]
- Age older than 50 years:
  - As people age, more diseases develop, which increases the risk of polypharmacy. Comorbidities commonly seen in an aging population, such as hypertension, chronic obstructive pulmonary disease, and diabetes mellitus, are increasingly prevalent in individuals with HIV [Gleason, et al. 2013].
  - Age-related physiologic changes may alter drug responses in older individuals [Gujjarlamudi 2016].
- Treatment provided by more than 1 care provider (including specialists)
- Limited care provider communication
- Prescriptions filled 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]. In addition, formulary changes for inpatient institutions may result in medication errors upon discharge, leading to omissions, duplications, or combinations that can create significant drug-drug interactions.

→ 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. 2013].

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 ARVs with multiple mechanisms of action suppresses virus replication to a greater extent and for a longer period than using 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 using a potent CYP3A4 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 effects caused by higher or more frequent dosing of the active agent. In turn, adherence may be improved by reducing pill burden. Similarly, using a potent inhibitor of a drug transporter allows for reduced or less frequent dosing 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. Despite its ability to boost other medications, ritonavir is likely to cause more drug-to-drug interactions because it exerts a broader effect on CYP450 enzymes in addition to CYP3A4.

In the current era of HIV treatment, it is well established that when used as prescribed, antiretroviral therapy (ART) effectively suppresses 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, switching 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 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 effects 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 effects 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 or changing 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 effects. Although this is not seen when combining ARVs to suppress HIV viral load, it can be seen when combining antihypertensive medicines (which may cause hypotension) or antidiabetic medicines (which may lead to additive hypoglycemia). In addition, an additive effect may result from medications with overlapping adverse effect profiles. A historic example is the use of zidovudine with other drugs that cause bone marrow suppression, including ribavirin or ganciclovir [Sim, et al. 1998; Aulitzky, et al. 1988].

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, 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 effects, they are more likely to discontinue medications. Adverse effects 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 an ART regimen 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 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 Effects

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 or 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 effects 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 or adverse 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, ear drops, 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 effects, such as encouraging patients to avoid seeing multiple prescribers, avoid filling their prescriptions at multiple pharmacies, and keep each of their healthcare providers informed of treatment decisions made by other specialists [Lavan, et al. 2016; Lehnbom, et al. 2014]. 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 effects 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, reduce the risk of adverse drug effects and drug-drug interactions, and improve medication adherence. The CMS website provides more information on requirements and services. Core elements of the MTM model include [American Pharmacists Association 2021]:

- Medication therapy review: 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.
- Personal medication record (PMR) and medication-related action plan: Records created for an individual patient 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 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: Inclusion of a pharmacist's expertise for safe, appropriate, and cost-effective use of medications for patients who have already developed or are at high risk of developing medication-related problems.

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 ensuring 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].

→ KEY POINT

- An accurate and frequently updated medication history helps to prevent errors with prescription, over-the-counter, and supplement and/or herbal medications.

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, tacrolimus), antiseizure medications (e.g., phenytoin, carbamazepine), and mood stabilizers (e.g., lithium, lamotrigine). Certain antibiotics, including vancomycin or aminoglycosides, are also dosed based on TDM.

The use of TDM with ARV dosing 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 [DHHS(a) 2021]. 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.

◊ RESOURCES

For clinicians:	For patients:
• Drug-Drug Interaction Tables, Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (Clinical Info HIV.gov) • HIV Drug Interactions and HEP Drug Interactions (University of Liverpool) • Immunodeficiency Clinic Drug Interaction Tables (Toronto General Hospital) • Medscape Drugs & Diseases • Lexicomp Interactions Module • Micromedex 2.0 Drug Interactions • Clinical Pharmacology Drug Interaction Report • Wolters Kluwer Facts & Comparisons eAnswers	• HIV Treatment: Everything You Need to Know (The Body) • HIV Drug Guide (Positively Aware) • Drug Interaction Checker (WebMD)

Classifications and Mechanisms of Drug-Drug Interactions

Antiretroviral (ARV) medications themselves, though increasingly safe and effective, may cause adverse effects that affect organ systems [Gallant, et al. 2018; Dharan and Cooper 2017]. 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 have been observed in patients who are switched from TDF to TAF [Lampertico, et al. 2020; 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 [Aberg, et al. 2012; Noor, et al. 2004; Carr, et al. 1998]. These inherent adverse effects 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. 2013]. 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 1: Mechanisms of Antiretroviral (ARV) Drug-Drug Interactions
Cited references are listed at bottom of table; also see drug package inserts.

ARV	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	Drug Transport Protein	Other
Integrase Strand Inhibitors (INSTIs)						
BIC [1]	3A4 (minor)	—	—	Substrate	Inhibitor of MATE1; OCT2	Chelation
CAB [2]	—	—	—	Substrate	P-gP substrate OATP1 inhibitor	—
DTG [3]	3A4 (minor)	—	—	Substrate	P-gP substrate Inhibitor of MATE2; OCT2	Chelation
EVG [4]	3A4	—	2C9	Substrate	—	Chelation
RAL [5]	—	—	—	Substrate	—	Chelation
Pharmacokinetic Boosters						
COBI [6]	3A4; 2D6 (minor)	3A4; 2D6 (minor)	—	—	Inhibitor of P-gP; BCRP; OATP; OCT; MATE1	—
RTV [7]	3A4; 2D6 (minor)	3A4; 2C8; 2C9; 2C19; 2D6	1A2; 2B6; 2C9; 2C19	Inducer	Inhibitor of P-gP; BCRP; OATP; OCT; MATE1	—
Protease Inhibitors (PIs)						
ATV [8]	3A4	3A4; 2C8 (minor)	—	Inhibitor	P-gP substrate, inhibitor, inducer OATP inhibitor	GI absorption (pH-dependent)
DRV [9]	3A4	3A4	2C9	—	P-gP substrate OATP inhibitor	—
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)						
DOR [10]	3A4; 3A5	—	—	—	—	—
EFV [11]	2B6 (primary); 2A6; 3A4	3A4	3A4; 2B6	—	—	—
ETR [12]	3A4; 2C9; 2C19	2C9; 2C19	3A4	—	P-gP inducer	—
RPV [13]	3A4	—	—	—	—	GI absorption (pH-dependent)

Table 1: Mechanisms of Antiretroviral (ARV) Drug-Drug Interactions
Cited references are listed at bottom of table; also see drug package inserts.

ARV	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	Drug Transport Protein	Other
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)						
ABC [14]	—	—	—	Substrate	—	Alcohol dehydro-genase substrate
FTC [15]	—	—	—	—	MATE1 substrate	—
3TC [16]	—	—	—	—	Substrate of MATE1/2; OCT2	—
TAF [17]	3A4 (minor)	—	—	—	Substrate of P-gP; BCRP; OATP	—
TDF [18]	—	—	—	—	Substrate of P-gP; OATP; MRP	—
Entry Inhibitors (EIs)						
FTR [19]	3A4	—	—	—	Substrate of P-gP; BCRP Inhibitor of OATP; BCRP	—
IBA [a] [20]	—	—	—	—	—	—
MVC [21]	3A4	—	—	—	P-gP substrate	—
Capsid Inhibitor						
LEN [22]	3A4 (minor)	3A4 (moderate)	—	Substrate (minor)	P-gP substrate	—

Drug name abbreviations: 3TC, lamivudine; ABC, abacavir; ATV, atazanavir; BIC, bictegravir; CAB, cabotegravir; COBI, cobicistat; DRV, darunavir; DOR, doravirine; DTG, dolutegravir; EFV, efavirenz; ETR, etravirine; EVG, elvitegravir; FTC, emtricitabine; FTR, fostemsavir; IBA, ibalizumab; LEN, lenacapavir; MVC, maraviroc; RAL, raltegravir; RPV, rilpivirine; RTV, ritonavir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Other abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; GI, gastrointestinal; MATE, multidrug and toxin extrusion; MRP, multidrug resistance protein; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; P-gP, P-glycoprotein; UGT, uridine diphosphate glucuronosyltransferase.

Note:

a. Based on the IBA mechanism of action and target-mediated drug disposition, drug-drug interactions are not expected.

Sources: [DHHS(b) 2021; Tseng, et al. 2017; Marzolini, et al. 2016; Taneva, et al. 2015; Kiser, et al. 2008]; 1. [Markham 2018]; 2. [FDA(d) 2021]; 3. [McCormack 2014]; 4. [Deeks(c) 2014; Perry 2014]; 5. [Deeks 2017]; 6. [Deeks(a) 2014]; 7. [Tseng, et al. 2017; Deeks(b) 2014; Croom, et al. 2009]; 8. [Croom, et al. 2009]; 9. [Deeks(b) 2014]; 10. [Deeks 2018; Yee, et al. 2017]; 11. [Ogburn, et al. 2010]; 12. [Deeks and Keating 2008]; 13. [Deeks(d) 2014]; 14. [Barbarino, et al. 2014]; 15. [Reznicek, et al. 2017]; 16. [Muller, et al. 2013]; 17. [Scott and Chan 2017]; 18. [Kohler, et al. 2011; Kearney, et al. 2004]; 19. [FDA 2020]; 20. [FDA(c) 2021]; 21. [Perry 2010]; 22. [FDA(c) 2022].

Table 2: Induction Potential of Ritonavir [a] and Cobicistat Used as Boosters		
	Ritonavir	**Cobicistat**
Cytochrome		
CYP1A2	Moderate inducer	Clinically negligible effect
CYP2B6	Moderate inducer	Clinically negligible effect
CYP2C8	Moderate inhibitor	Clinically negligible effect
CYP2C9	Moderate inducer	Clinically negligible effect
CYP2C19	Strong inducer	Clinically negligible effect
CYP2D6	Moderate inhibitor	Mild inhibitor
CYP3A4	Strong inhibitor	Strong inhibitor
Transporter		
P-gP	Moderate inhibitor	Moderate inhibitor
UGT	Moderate inducer	Clinically negligible effect
BCRP	Moderate inhibitor	Moderate inhibitor
OATP1B1	Moderate inhibitor	Moderate inhibitor
OATP1B3	Moderate inhibitor	Moderate inhibitor
MATE1	Moderate inhibitor	Moderate inhibitor
MATE2-K	Clinically negligible effect	Clinically negligible effect
OAT1	Clinically negligible effect	Clinically negligible effect
OAT3	Weak inducer	Clinically negligible effect
OCT2	Clinically negligible effect	Clinically negligible effect

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OATP, organic anion transporting protein; OCT, organic cation transporter; P-gP, P-glycoprotein; UGT, uridine diphosphate glucuronosyltransferase.

Note:

a. 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.

Sources: [Tseng, et al. 2017; Marzolini, et al. 2016; Foisy, et al. 2008]

Pharmacokinetic Interactions

Pharmacokinetic interactions involve the modification of drug absorption, distribution, metabolism, and excretion [Trevor, et al. 2013].

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 [Schafer and Short 2012; Klein, et al. 2008]). Some substances will form insoluble complexes with other drugs in a process known as chelation (e.g., using 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 heavily protein-bound medications 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 Hoener 2002]. An exception is when a drug has a narrow therapeutic index (e.g., warfarin, digoxin, lithium, 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 [Deeks(d) 2014; Perry 2010]. 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, are autoinducers of their own metabolism, causing the lead-in period seen when dosing those drugs [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 [Tseng, et al. 2017; Deeks(a) 2014].

Drugs that alter phase II metabolism affect glucuronidation, methylation, sulfation, or other forms of conjugation. Careful monitoring for therapeutic efficacy and safety is 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. 2013]. 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 ARVs.

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 effects.

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 Drug Class

☑ RECOMMENDATION

- Clinicians should consult an experienced HIV care provider for assistance in managing drug-drug interactions between antiretroviral (ARV) agents and less common medications. (A3)

Caveats: Many of the formal interaction studies involving ARVs are carried out in small samples of participants who do not have HIV or other known comorbid conditions. Although the results of such studies may be extrapolated to larger populations of individuals 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, an incomplete correlation often exists between predicted drug-drug interactions and in vivo pharmacokinetics. Significant person-to-person variability also exists 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 coadministered drugs they prescribe. 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 prescribed in primary care, and drug-drug interactions may lead to symptoms attributed to ARVs rather than the physiologic effect of 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 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)

Class or Drug	Mechanism of Action	Clinical Comments
Proton pump inhibitors (PPIs) [Brooks, et al. 2017; Falcon and Kakuda 2008; Kiser, et al. 2008]	• ATV requires acidic gastric pH for absorption, and acid-reducing agents interfere with ATV absorption. • PPIs may markedly reduce ATV concentration and AUC.	• **Unboosted ATV:** Do not coadminister with PPIs if it is possible to use an alternative acid-reducing agent, alternative PI, or boosted ATV. • **Timing:** Administer ≥12 hours before RTV- or COBI-boosted ATV. • **ART-naive:** Do not exceed omeprazole 20 mg per day or equivalent (pantoprazole 40 mg; lansoprazole 30 mg; esomeprazole 20 mg). • **ART-experienced:** Not recommended; consultation with experienced HIV care provider or GI specialist is recommended before prescribing PPI. 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.
Histamine-2 receptor antagonist (H2RA) [Brooks, et al. 2017; Wang, et al. 2011; Falcon and Kakuda 2008]	• ATV requires acidic gastric pH for absorption, and acid-reducing agents interfere with ATV absorption. • H2RAs reduce ATV absorption.	• **ART-naive:** Administer ATV 300 mg + RTV 100 mg simultaneously with or ≥10 hours after H2RA. – **If patient *is not* taking TFV**: Do not exceed famotidine 20 mg twice per day (40 mg daily) or equivalent, e.g., ranitidine or nizatidine 150 mg twice per day (300 mg daily). – **If patient *is* taking TFV:** Do not exceed famotidine 40 mg twice per day (80 mg daily) or equivalent, e.g., ranitidine or nizatidine 300 mg twice per day (600 mg daily). • **ART-experienced:** Administer ATV 300 mg + COBI 150 mg or RTV 100 mg simultaneously with or ≥10 hours after H2RA.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
		• **Pregnancy:** In trimesters 2 and 3, increase dose of ATV to 400 mg per day with RTV 100 mg per day. (Volume of distribution increases as duration of pregnancy increases, which can reduce ATV levels, especially during second and third trimesters of pregnancy.) – H2RA use is contraindicated if pregnant patient takes TFV + boosted ATV during pregnancy. – If patient is pregnant and is taking TFV, ATV is dosed at 400 mg per day with RTV 100 mg per day; unboosted ATV is not recommended.
Antacids [Brooks, et al. 2017]	ATV requires acidic gastric pH for absorption; acid-reducing agents interfere with ATV absorption.	**Antacids and all buffered medications:** Administer ATV at least 2 hours before or 1 to 2 hours after.
Alpha-adrenergic antagonists for benign prostatic hyperplasia	Boosted or unboosted ATV (i.e., with or without COBI or RTV) inhibits CYP3A4 and other transporters.	• **Alfuzosin, silodosin** Concomitant use is contraindicated. • **Doxazosin, terazosin:** PIs may be used concurrently; potential increases in doxazosin and terazosin levels are possible. Dose reduction may be necessary. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Simvastatin, lovastatin [Feinstein, et al. 2015; Chauvin, et al. 2013]	• Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and drug transporter P-gP; boosted ATV greatly increases concentrations. • COBI inhibits CYP3A4, CYP2D6, OATP1B1, and P-gP.	Concomitant use is contraindicated due to potential for myopathy, including rhabdomyolysis. Consider using low doses of alternative statins less likely to be affected by boosted ATV use.
Pravastatin, pitavastatin [Kis, et al. 2013]	• Pravastatin is a substrate for OATP1B1. • ATV inhibits OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted PIs.	Use with lowest effective doses of pravastatin and pitavastatin, and monitor for adverse effects, including myopathy and rhabdomyolysis.
Atorvastatin [Vildhede, et al. 2014]	• Atorvastatin is a substrate for CYP3A4 and OATP1B1. • Boosted ATV inhibits both CYP3A4 and OATP1B1. • Boosted ATV may moderately increase concentrations.	• Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. • Do not coadminister with COBI-boosted ATV due to increased risk of rhabdomyolysis and myopathy.
Rosuvastatin [Busti, et al. 2008]	• Rosuvastatin is a substrate of OATP1B1/1B3. • ATV inhibits OATP1B1. • Boosted ATV may moderately increase concentrations.	• Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. • If use is necessary, do not exceed 10 mg per day.
Fluvastatin	Interaction has not been studied, but potential for moderate increase is possible.	Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Anticoagulants, factor Xa inhibitors [Egan, et al. 2014]	• Boosted PIs inhibit most factor Xa inhibitors (not dabigatran) via CYP3A or P-gP. • ATV is a minor inhibitor of CYP2C8. • RTV and COBI inhibit P-gP. • **Apixaban** is a substrate of 2C8. • **Dabigatran** is a substrate of P-gP. • **Warfarin:** Metabolism of warfarin could potentially decrease (or more rarely) increase. • **Rivaroxaban, dabigatran, apixaban:** Concentrations may increase, increasing bleeding risk.	• **Avoid concomitant use** or use lowest effective dose of factor Xa inhibitor to avoid increased bleeding risk. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; if patient is already taking 2.5 mg twice per day, avoid concomitant use. • **Dabigatran:** – Separate doses of dabigatran and boosted PIs by at least 2 hours. – RTV boosting of PIs may be safer than COBI boosting with concomitant dabigatran [Kakadiya, et al. 2018]. – Avoid dabigatran in patients with renal impairment (CrCl <50 mL/min) who are taking boosted PIs. • **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For patients with DVT and PE: Administer edoxaban 30 mg once daily. • **Rivaroxaban:** Do not coadminister. • **Warfarin:** Use cautiously with warfarin; if use is necessary, increase INR monitoring. – If INR increases, decrease warfarin dose. – If INR decreases, increase warfarin dose slowly.
PY2-antagonists [Teng 2015; Egan, et al. 2014]	• **Ticagrelor:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted ATV may decrease production of clopidogrel's active metabolite. • **Prasugrel:** Boosted ATV may decrease production of prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.
Aliskiren	Boosted PIs inhibit P-gP, which may decrease aliskiren elimination, increasing risk of adverse effects.	Do not coadminister.
Atenolol	• COBI-boosted PIs may increase atenolol concentrations via inhibition of MATE1 elimination. • Similar interaction is not seen with RTV-boosted PIs.	• Start at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. • If a patient is already using atenolol but starting a COBI-boosted PI, monitor for atenolol-related adverse effects and reduce atenolol dose as needed. • RTV is the preferred PK booster when a patient is also using atenolol.
Calcium channel blockers (CCBs)	Boosted PIs may increase CCB concentrations by as much as 50%.	When using with boosted PIs, decrease original CCB dose by as much as 50%, and titrate slowly to achieve clinical effect.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antiarrhythmic drugs [Roden, et al. 2007]	Boosted PIs inhibit antiarrhythmic drug metabolism via CYP3A and CYP2D6.	Avoid concomitant use to avoid increased risk of QT prolongation and other adverse effects of antiarrhythmic drugs.
Eplerenone [Keating and Plosker 2004]	ATV inhibits hepatic CYP3A4 isoenzyme and can increase serum concentrations of eplerenone.	Avoid concomitant use due to increased risk of hyperkalemia and hypotension.
Long-acting beta agonists (LABAs)	CYP3A inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • Boosted PIs may also increase QT prolongation.
Inhaled, intranasal, and injected corticosteroids [Saberi, et al. 2013; Daveluy, et al. 2009]	• Boosted PIs are strong inhibitors of CYP3A, and many corticosteroids are substrates of these enzymes. • Risk of Cushing's syndrome occurs when boosted ATV is coadministered with the following corticosteroids: – Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone – Systemic: Betamethasone, budesonide, dexamethasone – Injectable: Betamethasone, triamcinolone	• **Use beclomethasone if possible.** Because this agent is less likely to be affected by boosted PIs, it is less likely to cause symptoms of Cushing's syndrome and other systemic corticosteroid adverse effects. • **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Betamethasone, triamcinolone (injectable):** Concomitant use is contraindicated unless potential benefits outweigh risk. • **Dexamethasone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid.
Oral prednisone	• Prednisone is a CYP3A4 and P-gP substrate. • Boosted PIs are strong inhibitors of CYP3A4 and P-gP.	• Short-term use is not contraindicated. • For chronic use of prednisone, monitor carefully for potential Cushing's syndrome.
Benzodiazepines	• Benzodiazepines are substrates of CYP3A and may be increased in presence of strong inhibitors of this enzyme. • **Alprazolam:** Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition. • **Diazepam:** CYP3A4 inhibition may reduce metabolism of diazepam.	• Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). If used, administer lowest effective dose; monitor closely for adverse effects. • **Diazepam:** Monitor for excess sedation.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antipsychotics	• **Haloperidol:** Boosted PIs may moderately increase haloperidol concentrations. • **Aripiprazole, brexpiprazole:** RTV-boosted PIs may increase aripiprazole and brexpiprazole levels. • **Risperidone:** Boosted PIs may moderately increase risperidone levels. • **Clozapine:** Interaction has not been studied but boosted ATV may theoretically increase clozapine concentrations, increasing risk of adverse effects. • **Iloperidone, lumateperone, lurasidone, cariprazine:** Levels are likely to be increased by all PIs, whether boosted or not.	• **Quetiapine dosing:** – Patients on stabilized quetiapine: Reduce dose to 1/6 if initiating ART; monitor for QT prolongation. – Patients stabilized on boosted PI: Use lowest dose and titrate slowly to achieve clinical effect; monitor for QT prolongation. • **Lurasidone:** No data available. Avoid coadministration; consider alternative antipsychotic or ARV. • **Haloperidol:** Monitor for QT prolongation. • **Iloperidone:** Decrease iloperidone dose by 50%. • **Aripiprazole:** Initiate at 25% of standard starting dose and titrate slowly to achieve clinical effect; monitor carefully for efficacy and adjust dose as necessary. • **Brexpiprazole:** Administer at 50% of brexpiprazole dose and adjust dose as necessary. • **Lumateperone:** Do not coadminister. • **Pimozide:** Concomitant use is contraindicated. • **Risperidone:** Initiate at low dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Ziprasidone:** Monitor for adverse effects, including QTc prolongation. • **Cariprazine:** Consult DHHS guideline for full dosing recommendations and clinical comments [DHHS(c) 2021]. • **Clozapine:** Monitor carefully for clozapine-related adverse effects.
HCV PIs ("-previr" drugs) [Soriano, et al. 2017]	CYP3A4 and OATP1B1 inhibition by ATV may increase plasma concentrations of other PIs.	Avoid concomitant use to avoid adverse effects of NS3/4A PIs.
Daclatasvir [Soriano, et al. 2017]	Boosted PIs inhibit daclatasvir metabolism via CYP3A4.	Decrease daclatasvir dose to 30 mg per day.
Etravirine (ETR) [Orrell, et al. 2015]	• ETR is a substrate and inducer of CYP3A4. • COBI and ATV are substrates and inhibitors of CYP3A4.	• Administration with RTV-boosted ATV results in decreases in ATV exposure, but decrease is not considered relevant; no dose adjustments are necessary. • Due to potential for decreased ARV efficacy, avoid use of ETR with COBI. When these medications are given together, COBI concentrations are decreased. • When possible, avoid concomitant use of ETR and unboosted ATV. ETR with unboosted ATV results in significant decreases in ATV exposure.
Lenacapavir (LEN)	CYP3A4 and P-gP inhibition potentially increases LEN levels.	Do not coadminister.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Sleep medications [Kishi, et al. 2015]	• COBI inhibits CYP3A. • **Suvorexant** is a substrate of CYP3A. • **Zolpidem, suvorexant:** Boosted PIs may increase zolpidem and suvorexant concentrations. • **Ramelteon:** RTV-boosted PIs may reduce ramelteon efficacy.	• **Zolpidem:** Administer lowest effective dose; monitor for adverse effects, including excess sedation. • **Eszopiclone:** Start with 1 mg per day and titrate slowly to achieve clinical effect; monitor for adverse effects, including excess sedation. • **Suvorexant:** Coadministration is not recommended (may increase somnolence, dizziness, and risk of sleep hangover); use alternative sleep medication or ARV. • **Ramelteon:** Monitor for efficacy in cigarette smokers.
Nonopioid pain medications	• **Eletriptan:** Metabolism inhibited by boosted PIs. • **TCAs:** PIs and TCAs can both cause QT prolongation. • **Pregabalin:** No significant interactions are expected.	• **Eletriptan:** Do not coadminister; use alternative triptan medication. • **TCAs:** With concomitant use of high-dose TCAs and PIs, consider monitoring for QT prolongation and other cardiac adverse effects or consider alternative medications.
Other antiplatelet drugs	• **Cilostazol** is metabolized by CYP3A; thus, 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 alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use alternative ARV or boost with COBI if necessary.
Antidiabetic drugs	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; thus, concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** is a substrate of CYP3A, so levels may be increased. • **Canagliflozin:** Use with ATV may decrease canagliflozin concentrations. • **GLP-1 agonists:** Caution is needed when coadministering ATV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing ATV absorption. Furthermore, exenatide may slow gastric emptying. • **TZDs, exenatide:** No significant interactions are expected.	• **Metformin:** Monitor for metformin-related adverse effects; 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:** If patient already tolerates canagliflozin 100 mg daily, increase dose to 200 mg daily. If patient already tolerates canagliflozin 200 mg daily and requires additional glycemic control, the management strategy should be based on renal function. – In patients with eGFR ≥60 mL/min/1.73 m^2, canagliflozin dose may be increased to 300 mg daily. – In patients with eGFR <60 mL/min/1.73 m^2, consider adding another antihyperglycemic agent. • **GLP-1 agonists:** May recommend ATV dosing 4 hours before. • **TZDs:** No dose adjustments are necessary.
Trazodone	Boosted ATV may increase trazodone concentrations.	Monitor for antidepressant and/or sedative effects.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Anticonvulsants	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system. • **Zonisamide:** CYP3A4 inhibition may increase zonisamide concentrations.	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** – Coadministration is not recommended; use alternative anticonvulsant. – If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. – Perform TDM. • **Zonisamide:** Monitor for efficacy and adverse effects; adjust dose as needed.
Opioid analgesics	Complex mechanisms of metabolism and 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; dose these analgesics accordingly.
Tramadol	Tramadol exposure is increased with CYP3A inhibition, but this reduces conversion to more potent active metabolite seen when tramadol is metabolized by CYP2D6.	When tramadol is given with COBI or RTV, monitoring for tramadol-related adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.
Hormonal contraceptives	• Complex drug interaction potential has been described. • **Drospirenone:** Concomitant use may cause hyperkalemia.	• **Etonogestrel:** No data available. Consider alternative or additional contraceptive methods or alternative ARV. • **Ethinyl estradiol; norgestimate and metabolites:** Dose with at least 35 mcg (no data available on other progestins). • **Drospirenone:** Do not coadminister.
Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** Increased PDE5 inhibitor concentrations are expected. • **Flibanserin:** Increased flibanserin concentrations are expected.	• **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects. • **Avanafil, flibanserin:** Do not coadminister.
Methadone, buprenorphine (BUP), naloxone (NLX)	• **BUP:** 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. • **BUP/NLX:** COBI-boosted PIs 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 methadone concentration.	• **BUP:** When administering with RTV-boosted PIs, monitor for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress. • **BUP, BUP/NLX:** When administering with COBI-boosted PIs, titrate carefully to achieve clinical effect. • **Methadone:** Based on efficacy and safety, initiate at lowest possible dose and titrate to achieve clinical effect; monitor for signs and symptoms of opiate withdrawal.
Immunosuppressants	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted PIs.	• **Everolimus, sirolimus:** Do not use with boosted PIs. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.

Table 3: Boosted Atazanavir (ATV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Rifabutin, rifampin, rifapentine	• **Rifabutin** does not affect boosted PI levels, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased. • **Rifampin, rifapentine:** CYP3A induction reduces bioavailability of *all* PIs.	• **Rifabutin:** – RTV-boosted PIs: When used concomitantly, reduce rifabutin to 150 mg 3 times per week. – COBI-boosted PIs: Do not coadminister. • **Rifampin, rifapentine:** Concomitant use of PIs and rifampin or rifapentine is contraindicated.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other PIs.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Patients on RTV- or COBI-containing regimens should continue treatment for COVID-19 and HIV as indicated without adjustment. Monitor for increased PI-related adverse effects.
Mpox treatments	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with PIs will likely increase brincidofovir levels. Consider avoiding concurrent PIs if possible. If unable to change PI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone PI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce PI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Cidofovir, VIGIV:** Interactions are unlikely.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; AUC, area under the curve; COBI, cobicistat; CrCl, creatinine clearance; CYP, cytochrome P450; DHHS, U.S. Department of Health and Human Services; DVT, deep vein thrombosis; EVG, elvitegravir; GFR, glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; LFT, liver function test; MATE, multidrug and toxin extrusion; NS3/4A, nonstructural protein 3/4A; OATP, organic anion transporting polypeptide; PE, pulmonary embolism; PDE-5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor; PK, pharmacokinetic; RTV, ritonavir; TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring; TFV, tenofovir; TZD, thiazolidinedione; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); asthma and allergy medications (Table 27); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); gender-affirming hormones (Table 47).

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Simvastatin, lovastatin [Feinstein, et al. 2015; Chauvin, et al. 2013]	• Simvastatin and lovastatin are substrates for CYP3A4, CYP2D6, OATP1B1, and drug transporter P-gP; boosted DRV greatly increases concentrations. • COBI inhibits CYP3A4, CYP2D6, OATP1B1, and P-gP.	• Concomitant use is contraindicated due to potential for myopathy, including rhabdomyolysis. • Consider using low doses of alternative statins less likely to be affected by boosted DRV.
Pravastatin [Kellick, et al. 2014; Aquilante, et al. 2012]	• When combined with DRV, pravastatin levels are significantly increased. • Pravastatin is an OATP1B1 substrate. • COBI and RTV may modestly inhibit OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted PIs.	If use is necessary, use lowest effective dose and monitor for signs of toxicity.
Atorvastatin [McKeage, et al. 2009]	• Atorvastatin is a substrate for CYP3A4. • Boosted DRV inhibits CYP3A4. • Boosted DRV may moderately increase concentrations.	• When administered with RTV-boosted DRV, use lowest effective dose; do not exceed 20 mg daily. • If concomitant use is necessary, monitor closely for signs of myopathy and rhabdomyolysis.
Pitavastatin	• Boosted DRV is less likely to interact compared to other statins. • When administered with RTV-boosted DRV, pitavastatin AUC is decreased by 26%.	No dose adjustments are necessary.
Rosuvastatin [Custodio, et al. 2014; Samineni, et al. 2012]	• Rosuvastatin is a substrate of OATP1B1 and OATP1B3. • COBI inhibits OATP. • Boosted DRV may moderately increase concentrations.	• When possible, avoid concomitant use. • If use is necessary, start with 10 mg per day; dose should not exceed 20 mg per day.
Fluvastatin	Interaction has not been studied, but potential for moderate increase is possible.	Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.
Anticoagulants, factor Xa inhibitors [Egan, et al. 2014]	• Boosted PIs inhibit most factor Xa inhibitors (except dabigatran) via CYP3A or P-gP. • ATV is a minor inhibitor of CYP2C8. • RTV and COBI inhibit P-gP. • **Apixaban** is a substrate of CYP2C8. • **Dabigatran** is a substrate of P-gP. • **Warfarin:** Metabolism of warfarin could potentially decrease (or more rarely) increase. • **Rivaroxaban, dabigatran, apixaban:** Concentrations may increase, increasing bleeding risk.	• **Avoid concomitant use** or use lowest effective dose of factor Xa inhibitor to avoid increased bleeding risk. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; if patient is already taking 2.5 mg twice per day, avoid concomitant use. • **Dabigatran:** – Separate doses of dabigatran and boosted PIs by at least 2 hours. – RTV boosting of PIs may be safer than COBI boosting with concomitant dabigatran [Kakadiya, et al. 2018]. – Avoid dabigatran in patients with renal impairment (CrCl <50 mL/min) who are taking boosted PIs.

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
		• **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For patients with DVT and PE: Administer edoxaban 30 mg once daily. • **Rivaroxaban:** Do not coadminister. • **Warfarin:** Use cautiously with warfarin; if use is necessary, increase INR monitoring. – If INR increases, decrease warfarin dose. – If INR decreases, increase warfarin dose slowly.
Antiplatelet drugs and PY2-antagonists [Teng 2015; Egan, et al. 2014]	• **Cilostazol** is metabolized by CYP3A; thus, 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:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted DRV may decrease production of clopidogrel's active metabolite. • **Prasugrel:** Boosted DRV may decrease prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Cilostazol:** Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use alternative ARV or boost with COBI if necessary. • **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.
Alpha-adrenergic antagonists for benign prostatic hyperplasia	DRV boosted with COBI or RTV inhibits CYP3A4 and other transporters.	• **Alfuzosin, silodosin:** Concomitant use is contraindicated. • **Doxazosin, terazosin:** PIs may be used concurrently; potential increases in doxazosin and terazosin levels are possible. Dose reduction may be necessary. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Aliskiren	Boosted PIs inhibit P-gP, which may decrease aliskiren elimination, increasing risk of adverse effects.	Do not coadminister.
Atenolol	• COBI-boosted PIs may increase atenolol via inhibition of MATE1 elimination. • Similar interaction is not seen with RTV-boosted PIs.	• Start at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. • If patient is already using atenolol but starting COBI-boosted PI, monitor for atenolol-related adverse effects and reduce atenolol dose as needed. • RTV is the preferred PK booster when patient is also using atenolol.

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Calcium channel blockers (CCBs)	Boosted PIs may increase CCB concentrations by as much as 50%.	When using with boosted PIs, decrease original CCB dose by as much as 50% and titrate slowly to achieve clinical effect.
Eplerenone [Keating and Plosker 2004]	DRV inhibits hepatic CYP3A4 isoenzyme and can increase 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 is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; thus, concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** is a substrate of CYP3A, so levels may be increased. • **Canagliflozin:** Use with DRV may decrease canagliflozin concentrations. • **GLP-1 agonists:** Caution is needed when coadministering DRV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing DRV absorption. Furthermore, exenatide may slow gastric emptying. • **TZDs, exenatide:** No significant interactions are expected.	• **Metformin:** Monitor for metformin-related adverse effects; 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:** If the patient already tolerates canagliflozin 100 mg daily, increase dose to 200 mg daily. If the patient already tolerates canagliflozin 200 mg daily and requires additional glycemic control, the management strategy should be based on renal function. – In patients with eGFR ≥60 mL/min/1.73 m^2, canagliflozin dose may be increased to 300 mg daily. – In patients with eGFR <60 mL/min/1.73 m^2, consider adding another antihyperglycemic agent. • **GLP-1 agonists:** May recommend DRV dosing 4 hours before. • **TZDs:** No dose adjustments are necessary.
Long-acting beta agonists	CYP3A inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • Boosted PIs may also increase QT prolongation.
Inhaled and injected corticosteroids [Saberi, et al. 2013; Daveluy, et al. 2009]	• Boosted PIs are strong inhibitors of CYP3A and many corticosteroids are substrates of these enzymes. • Risk of Cushing's syndrome occurs when boosted DRV is coadministered with following corticosteroids: – Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone – Systemic: Betamethasone, budesonide, dexamethasone – Injectable: Betamethasone, triamcinolone	• **Use beclomethasone if possible.** Because this agent is less likely to be affected by boosted PIs, it is less likely to cause symptoms of Cushing's syndrome and other systemic corticosteroid adverse effects. • **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Betamethasone, triamcinolone (injectable):** Concomitant use is contraindicated unless benefits outweigh risk. • **Dexamethasone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid.

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Oral prednisone	• Prednisone is a CYP3A4 and P-gP substrate. • Boosted PIs are strong inhibitors of CYP3A4 and P-gP.	Avoid concomitant use unless risk outweighs benefits because of increased risk of corticosteroid-related adverse effects.
Benzodiazepines	The following benzodiazepines are substrates of CYP3A and may be increased in presence of strong inhibitors of this enzyme: • **Alprazolam:** Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition. • **Diazepam:** CYP3A4 inhibition may reduce metabolism of diazepam.	• Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). If used, administer lowest effective dose; monitor closely for adverse effects. • **Diazepam:** Monitor for excess sedation.
Antipsychotics	• **Haloperidol:** Boosted PIs may moderately increase haloperidol concentrations. • **Aripiprazole, brexpiprazole:** RTV-boosted PIs may increase aripiprazole and brexpiprazole levels. • **Risperidone:** Boosted PIs may moderately increase risperidone levels. • **Clozapine:** Interaction has not been studied but boosted DRV may theoretically increase clozapine concentrations, increasing risk of adverse effects. • **Iloperidone, lumateperone, lurasidone, cariprazine:** Levels are likely to be increased by all PIs, whether boosted or not.	• **Quetiapine:** – Patients on stabilized quetiapine: Reduce dose to 1/6 if initiating ART; monitor for QT prolongation. – Patients stabilized on boosted PI: Use lowest dose and titrate slowly to achieve clinical effect; monitor for QT prolongation. • **Lurasidone:** No data available. Avoid coadministration; consider alternative antipsychotic or ARV. • **Haloperidol:** Monitor for QT prolongation. • **Iloperidone:** Decrease iloperidone dose by 50%. • **Aripiprazole:** Initiate at 25% of standard starting dose and titrate slowly to achieve clinical effect; monitor carefully for efficacy and adjust dose as necessary. • **Brexpiprazole:** Administer at 50% of brexpiprazole dose and adjust dose as necessary. • **Lumateperone:** Do not coadminister. • **Pimozide:** Concomitant use is contraindicated. • **Risperidone:** Initiate at low dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Ziprasidone:** Monitor for adverse effects, including QTc prolongation. • **Cariprazine:** Consult DHHS guideline for full dosing recommendations and clinical comments [DHHS(c) 2021]. • **Clozapine:** Monitor carefully for clozapine-related adverse effects.
HCV PIs ("-previr" drugs) [Soriano, et al. 2017]	Inhibition of CYP3A4, P-gP, and OATP1B1 by boosted PIs may increase plasma concentrations of other PIs.	Avoid concomitant use to avoid adverse effects of NS3/4A PIs.
Daclatasvir [Soriano, et al. 2017]	Boosted PIs inhibit daclatasvir metabolism via CYP3A4.	Decrease daclatasvir dose to 30 mg per day.

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Sleep medications [Kishi, et al. 2015]	• COBI inhibits CYP3A. • **Suvorexant** is a substrate of CYP3A. • **Zolpidem, suvorexant:** Boosted PIs may increase zolpidem and suvorexant concentrations. • **Ramelteon:** RTV-boosted PIs may reduce ramelteon efficacy.	• **Zolpidem:** Administer lowest effective dose; monitor for adverse effects, including excess sedation. • **Eszopiclone:** Start with 1 mg per day and titrate slowly to achieve clinical effect; monitor for adverse effects, including excess sedation. • **Suvorexant:** Coadministration is not recommended (may increase somnolence, dizziness, and risk of sleep hangover); use alternative sleep medication or ARV. • **Ramelteon:** Monitor for efficacy in cigarette smokers.
Nonopioid pain medications	• **Eletriptan:** Metabolism inhibited by boosted PIs. • **TCAs:** PIs and TCAs can both cause QT prolongation. • **Pregabalin:** No significant interactions are expected.	• **Eletriptan:** Do not coadminister; use alternative triptan medication. • **TCAs:** With concomitant use of high-dose TCAs and PIs, consider monitoring for QT prolongation and other cardiac adverse effects or consider alternative medications.
Omeprazole	No clinically significant interactions reported.	Do not exceed omeprazole 40 mg per day.
Trazodone	Boosted DRV may increase trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Anticonvulsants	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system. • **Zonisamide:** CYP3A4 inhibition may increase zonisamide concentrations.	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** – Coadministration is not recommended; use alternative anticonvulsant. – If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. – Perform TDM. • **Zonisamide:** Monitor for efficacy and adverse effects; adjust dose as needed.
Opioid analgesics	Complex mechanisms of metabolism and 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; dose these analgesics accordingly.
Tramadol	Tramadol exposure is increased with CYP3A inhibition, but this reduces conversion to more potent active metabolite seen when tramadol is metabolized by CYP2D6.	When tramadol is given with COBI or RTV, monitoring for tramadol-related adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dose if indicated.
Hormonal contraceptives	• **RTV-boosted DRV:** Combination appears to decrease oral norethindrone concentrations. • **COBI-boosted DRV:** Combination has not been studied, but since COBI does not induce glucuronidation, it is expected to increase norethindrone concentration.	• **Norethindrone:** Consider alternative or additional contraceptive methods or alternative ARV. • **Etonogestrel:** No data available. Consider alternative or additional contraceptive methods or alternative ARV.
Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** Increased PDE5 inhibitor concentrations are expected. • **Flibanserin:** Increased flibanserin concentrations are expected	• **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects. • **Avanafil, flibanserin:** Do not coadminister.

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Methadone, buprenorphine (BUP), naloxone (NLX), naltrexone	• **BUP:** RTV-boosted PIs may greatly increase BUP concentrations, but clinical significance of this effect is unknown because BUP dosing is based on Clinical Opiate Withdrawal Scale. • **BUP/NLX:** COBI-boosted DRV 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 methadone concentration. – RTV-boosted DRV taken twice per day may reduce methadone concentrations.	• **BUP:** When administering with RTV-boosted DRV, monitor for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress. • **BUP, BUP/NLX:** When administering with COBI-boosted DRV, titrate carefully to achieve clinical effect. • **Methadone:** – Based on efficacy and safety, initiate at lowest possible dose and titrate to achieve clinical effect; monitor for signs and symptoms of opiate withdrawal. – When administering with RTV-boosted DRV taken twice per day, monitor for signs of opiate withdrawal and increase methadone dose if necessary.
Immunosuppressants	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted PIs.	• **Everolimus, sirolimus:** Do not use with boosted DRV. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.
Rifabutin, rifampin, rifapentine	• **Rifabutin** does not affect boosted PI levels, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased. • **Rifampin, rifapentine:** CYP3A induction reduces bioavailability of *all* PIs.	• **Rifabutin:** – RTV-boosted PIs: When used concomitantly, reduce rifabutin to 150 mg 3 times per week. – COBI-boosted PIs: Do not coadminister. • **Rifampin, rifapentine:** Concomitant use of PIs and rifampin or rifapentine is contraindicated.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other PIs.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Patients on RTV- or COBI-containing regimens should continue treatment for COVID-19 and HIV as indicated without adjustment. Monitor for increased PI-related adverse effects.
Mpox treatments	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with PIs will likely increase brincidofovir levels. Consider avoiding concurrent PIs if possible. If unable to change PI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone PI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce PI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Cidofovir, VIGIV:** Drug interactions are unlikely.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; AUC, area under the curve; BIC, bictegravir; COBI, cobicistat; CrCl, creatinine clearance; CYP, cytochrome P450; DHHS, U.S. Department of Health and Human Services; DTG, dolutegravir; DVT, deep vein thrombosis; GFR, glomerular filtration rate; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; HCV, hepatitis C virus; INR, international normalized ratio; INSTI: integrase strand transfer inhibitor; LFT, liver function test; MATE, multidrug and toxin extrusion; NS3/4A, nonstructural protein

Table 4: Boosted Darunavir (DRV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
3/4A; OATP, organic anion transporting polypeptide; OCT, organic cation transporter; PDE5, phosphodiesterase type 5; PE, pulmonary embolism; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring; TZD, thiazolidinedione; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); gender-affirming hormones (Table 47).		

Integrase Strand Transfer Inhibitors (INSTIs)

Table 5: Bictegravir (BIC) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antacids	BIC chelates with cations, forming insoluble compounds that inactivate both drugs.	• **Aluminum/magnesium-containing antacids:** Administer antacids at least 6 hours before or 2 hours after BIC. • **Calcium-containing antacids:** – Administer BIC and antacids together with food. – Do not coadminister BIC simultaneously with antacids on empty stomach.
Other polyvalent cations	BIC can chelate with cations, reducing absorption of both drugs.	**Calcium- or iron-containing supplements:** • If taken with food, BIC can be taken at same time. • If not taken with food, these supplements should be administered as with antacids.
Dofetilide [Feng and Varma 2016]	BIC inhibits renal OCT2 and MATE1, and these transporters eliminate dofetilide.	Avoid concomitant use (may cause QT prolongation or torsades de pointes).
Metformin [Custodio, et al. 2017]	BIC inhibits renal OCT2 and MATE1, which are involved in metformin elimination.	• Drug interaction studies suggest that prospective dose adjustment of metformin is not required when using BIC. • Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects.
Atenolol	Atenolol is eliminated via OCT2 and MATE1, which are inhibited by BIC. Coadministration may increase atenolol levels.	• Start at lower atenolol dose and titrate slowly to achieve clinical effect. • If patient is already using atenolol but starting BIC, monitor for atenolol-related adverse effects. • Reduce atenolol dose if necessary or switch to another ARV.
Cyclosporine	Cyclosporine may increase BIC concentrations to modest degree via P-gP inhibition.	Monitor for BIC-related adverse effects.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** CYP3A and P-gP induction decrease BIC levels. • **Rifampin, rifapentine:** CYP3A induction reduces bioavailability.	• **Rifampin:** Concomitant use is contraindicated. • **Rifabutin, rifapentine:** Concomitant use is not recommended [FDA(a) 2021].

Table 5: Bictegravir (BIC) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Drug interactions are unlikely; BIC levels may increase.
Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; DTG, dolutegravir; INSTI, integrase strand transfer inhibitor; MATE, multidrug and toxin extrusion; OCT, organic cation transporter; P-gP, P-glycoprotein; RTV, ritonavir; TDM, therapeutic drug monitoring. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); acid-reducing agents (Table 25); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); mpox treatments (Table 46); gender-affirming hormones (Table 47).		

Table 6: Cabotegravir (CAB) Interactions (also see drug package inserts) The combination CAB/RPV antiretroviral therapy regimen can be used during an oral medication lead-in period and then as monthly long-acting injections; also see Table 11: Rilpivirine (RPV) Interactions.		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce CAB concentrations through induction of CYP450, UGT1A, and/or P-gP system.	Concomitant use is contraindicated.
Rifabutin, rifampin, rifapentine	Coadministration may significantly reduce CAB concentrations through induction of CYP450, UGT1A, and/or P-gP system.	• **Rifampin, rifapentine:** Concomitant use is contraindicated with *oral* CAB. • **Rifabutin:** May be used with *oral* CAB without dosage adjustment. • **Rifabutin, rifampin, rifapentine:** Concomitant use is contraindicated with *injectable* CAB [FDA(b) 2021].
Antacids containing polyvalent cations (e.g., aluminum or magnesium hydroxide, calcium carbonate)	Antacids increase gastric pH, and CAB requires acidic environment for optimal absorption. Concomitant use may decrease CAB absorption.	• Administer antacid products at least 2 hours before or 4 hours after *oral* CAB. • No effect of antacid use is expected on *injectable* CAB.
Abbreviations: RPV, rilpivirine; UGT, uridine diphosphate glucuronosyltransferase. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); antidiabetic drugs (Table 24); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); COVID-19 therapeutics (Table 45); mpox treatments (Table 46); gender-affirming hormones (Table 47).		

Table 7: Dolutegravir (DTG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Dofetilide [Feng and Varma 2016; Max and Vibhakar 2014]	DTG inhibits renal OCT2 and MATE1, and these transporters eliminate dofetilide.	Avoid concomitant use (may cause QT prolongation or torsades de pointes).
Metformin [Gervasoni, et al. 2017; Song, et al. 2016]	DTG inhibits renal OCT2, MATE1, and MATE2, which are involved in metformin elimination.	• Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects. • Titrate to achieve clinical effect but do not exceed 1,000 mg daily; monitor for adverse effects, including lactic acidosis.
Divalent and trivalent cations (aluminum, magnesium, calcium, zinc, etc.) [Song, et al. 2015; Cottrell, et al. 2013]	DTG chelates with cations forming insoluble compounds that inactivate both drugs.	• Administer DTG 2 hours before or 6 hours after. • **Calcium- and iron-containing supplements:** DTG and supplement may be used concomitantly if taken with food.
Iron salts [Song, et al. 2015]	DTG chelates with cations, forming insoluble compounds that inactivate both drugs.	• Administer DTG 2 hours before or 6 hours after. • DTG and iron salts may be used concomitantly if taken with food.
Atenolol	Atenolol is eliminated via OCT2 and MATE1, which are inhibited by DTG. Coadministration may increase atenolol levels.	• Start at lower atenolol dose and titrate slowly to achieve clinical effect. • If patient is already using atenolol but starting DTG, monitor for atenolol-related adverse effects. • Reduce atenolol dose if necessary or switch to another ARV.
Etravirine (ETR) [Green, et al. 2017]	• ETR induces UGT1A1 and CYP3A enzymes. • DTG is a substrate of UGT1A1 and CYP3A enzymes.	• ETR reduces DTG concentrations. Do not use concomitantly unless boosted PI is also part of treatment regimen.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** No clinically significant interactions are expected. • **Rifampin:** CYP3A induction reduces DTG bioavailability. • **Rifapentine:** Reduced rifapentine levels are expected.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin:** When used concomitantly, administer DTG at 50 mg twice per day instead of 50 mg once per day in patients without suspected or documented INSTI-associated resistance mutations. Consider rifabutin in patients with INSTI resistance. • **Rifapentine, once weekly:** – If using concomitant DTG 50 mg once daily, monitor for virologic efficacy. – Do not coadminister with DTG 50 mg twice daily. • **Rifapentine, once daily:** Do not coadminister DTG.

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 19); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); acid-reducing agents (Table 25); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); mpox treatments (Table 46); gender-affirming hormones (Table 47).

Table 8: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antacids	EVG chelates with polyvalent cations, which may reduce absorption of both agents.	**Aluminum-, magnesium-, and/or calcium-containing antacids:** When taken with EVG, separate doses by at least 2 hours.
Alpha-adrenergic antagonists for benign prostatic hyperplasia	COBI-boosted EVG inhibits CYP3A4 and other transporters and is likely to increase levels of select drugs in this class.	• **Alfuzosin, silodosin:** Concomitant use is contraindicated. • **Doxazosin, terazosin:** May be used; increased levels are possible. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Factor Xa inhibitors [Egan, et al. 2014]	• Factor Xa inhibitors are substrates of P-gP and CYP3A. • COBI inhibits P-gP and CYP3A. • Concentrations may increase, increasing bleeding risk.	• **Rivaroxaban:** Do not coadminister. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; if patient is already taking 2.5 mg twice per day, avoid concomitant use. • **Dabigatran:** – In patients with good renal function, no dose adjustments are necessary. – In patients with moderate to severe renal dysfunction, do not use this combination. – Consider switching to another ARV regimen without booster to avoid interaction. • **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For patients with DVT and PE: Administer edoxaban 30 mg once daily.
Warfarin	Metabolism of warfarin could potentially decrease (or more rarely) increase.	Use cautiously with warfarin. If use is necessary, increase INR monitoring. • If INR increases, decrease warfarin dose. • If INR decreases, increase warfarin dose slowly.
Cilostazol, ticagrelor, clopidogrel [Tseng, et al. 2017; Egan, et al. 2014]	• **Cilostazol** may be metabolized by CYP3A; COBI-boosted EVG can increase concentrations of this drug. • **Ticagrelor:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted EVG significantly decreases production of clopidogrel's active metabolite. • **Prasugrel:** Boosted EVG decreases prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Cilostazol:** Monitor for antiplatelet effect. May be necessary to use alternative antiplatelet or alternative ARV. • **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.

Table 8: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Aliskiren	P-gP inhibitors, including boosted EVG, decrease aliskiren elimination, increasing adverse effects of medication.	Do not coadminister.
Other polyvalent cations (calcium, zinc, iron, etc.)	EVG chelates with polyvalent cations, which may reduce absorption of both agents.	Administer at least 2 hours before or 6 hours after EVG.
Atenolol	COBI-boosted EVG may increase atenolol concentrations via inhibition of MATE-1 elimination.	• Start at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. • If patient is already using atenolol but starting COBI-boosted EVG, monitor for atenolol-related adverse effects. Reduce atenolol dose as needed.
Calcium channel blockers (CCBs)	COBI-boosted EVG may increase CCB concentrations by as much as 50%.	When using with boosted EVG, decrease original CCB dose by as much as 50% and titrate slowly to achieve clinical effect.
Eplerenone [Tseng, et al. 2017; Keating and Plosker 2004]	• 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 eplerenone dose.
Simvastatin, lovastatin [Perry 2014]	• COBI inhibits CYP3A. • Simvastatin and lovastatin are CYP3A substrates. Boosted EVG greatly increases concentrations.	Concomitant use is contraindicated; may increase muscle aches and risk of rhabdomyolysis; choose alternative statin.
Pitavastatin, pravastatin [Tseng, et al. 2017]	• Pitavastatin and pravastatin are OATP1B1 substrates. • COBI inhibits OATP1B1. • Although moderate increases are possible, low doses are considered safe when used with boosted EVG.	Use lowest effective doses of pitavastatin and pravastatin; monitor for signs of toxicity, including myopathy.
Atorvastatin [Tseng, et al. 2017]	• Atorvastatin is a substrate of CYP3A4 and OATP1B1. • Boosted EVG inhibits both CYP3A and OATP1B1. • Boosted EVG may moderately increase concentrations.	• Avoid concomitant use of COBI 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, OATP1B3, and CYP2C9. • COBI inhibits OATP. • EVG induces CYP2C9. • Boosted EVG may moderately increase concentrations.	Use lowest effective dose of rosuvastatin and titrate carefully to achieve clinical effect; monitor for adverse effects.
Fluvastatin	Interaction has not been studied, but potential for moderate increase is possible.	Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose.
Antidiabetic drugs	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** levels may be increased via CYP3A inhibition. • **Canagliflozin** exposure could be reduced through EVG induction of UGT enzymes.	• **Metformin:** Monitor for metformin-related adverse effects; 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 for glycemic control. – If glycemic control is inadequate in patient taking EVG/RTV, consider increasing canagliflozin dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 mL/min/1.73 m^2.

Table 8: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Long-acting beta agonists (formoterol, salmeterol, etc.)	CYP3A inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • **Salmeterol:** Monitor for increased risk of cardiovascular-related adverse events.
Inhaled and injected corticosteroids	Risk of Cushing's syndrome occurs when boosted EVG is coadministered with the following corticosteroids: • Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone • Systemic: Betamethasone, budesonide, prednisolone, prednisone, dexamethasone • Injectable: Betamethasone, triamcinolone	• **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Betamethasone, triamcinolone (injectable):** Do not coadminister unless benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Dexamethasone (systemic):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid. Beclomethasone and flunisolide are likely safe alternatives.
Trazodone	Boosted EVG may increase trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Alprazolam, clonazepam, diazepam	Boosting with cobicistat may increase benzodiazepine concentrations via CYP3A4 inhibition.	Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam); if used, administer lowest effective dose; monitor closely for adverse effects.
Midazolam, triazolam	Levels likely to be increased by COBI-boosted EVG.	• **Midazolam:** – Oral: Concomitant use is contraindicated. – Parenteral: Administer in closely monitored setting. Consider dose reduction, especially if >1 dose is administered. • **Triazolam:** Concomitant use is contraindicated.
Antipsychotics	Several antipsychotic agents are CYP3A substrates, and inhibitors of this enzyme may increase their concentrations.	• **Quetiapine:** Reduce dose to 1/6 if initiating ART in patient on stabilized quetiapine. • **All other antipsychotics:** Use at lowest dose possible in patients taking boosted ARVs; monitor carefully for adverse effects.

Table 8: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
PDE5 inhibitors [Perry 2014]	• PDE5 inhibitors are CYP3A substrates. Increased PDE5 inhibitor concentrations are expected. • COBI inhibits CYP3A.	• **PDE5 inhibitors:** Avoid concomitant use or use with lowest effective dose of PDE5 inhibitor (may increase risk of hypotension, syncope, priapism, and other adverse effects). • **Avanafil:** No data available; do not coadminister. • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.
Suvorexant [Kishi, et al. 2015]	• Suvorexant is a CYP3A substrate. • COBI inhibits CYP3A.	Avoid concomitant use or use lowest effective dose (may increase somnolence, dizziness, and risk of sleep hangover).
Zolpidem, eszopiclone	These drugs are CYP3A substrates and may be increased by strong inhibitors of this enzyme.	• **Zolpidem:** Administer lowest possible dose of zolpidem; monitor for adverse effects. • **Eszopiclone:** Start with 1 mg of eszopiclone at bedtime and titrate slowly to achieve clinical effect.
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce concentrations of ARVs 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 TDM.
Eletriptan	Eletriptan is a CYP3A substrate and concentrations may be increased if given with strong inhibitors of this enzyme.	Do not coadminister; use alternative triptan medication.
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.	Monitor for signs of opiate toxicity and analgesic effect and dose these analgesics accordingly.
Tramadol	Tramadol exposure is increased with CYP3A inhibition, but this reduces conversion to the more potent active metabolite seen when tramadol is metabolized by CYP2D6.	When tramadol is given with COBI or RTV, monitoring for tramadol-related adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.
Hormonal contraceptives	**Drospirenone:** Concomitant use may cause hyperkalemia.	• **Ethinyl estradiol, norgestimate and metabolites; norethindrone:** Weigh risks and benefits; consider alternative contraceptive methods. • **Drospirenone:** Monitor for hyperkalemia; consider alternative contraceptive methods or alternative ARV. • **Etonogestrel:** No data available; consider alternative or additional contraceptive methods or alternative ARV.

Table 8: Boosted Elvitegravir (EVG) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Immunosuppressants	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted EVG.	• **Everolimus, sirolimus:** Do not use with boosted EVG. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** CYP3A induction is expected to decrease EVG levels. • **Rifampin, rifapentine:** CYP3A induction reduces EVG bioavailability.	• **Rifabutin:** Concomitant use is not recommended. When concomitant use cannot be avoided, dose rifabutin at 150 mg 3 times per week, and monitor for response to EVG-containing regimen. • **Rifampin, rifapentine:** Concurrent use with boosted EVG is not recommended.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Patients on RTV- or COBI-containing regimens should continue treatment as indicated. Monitor for increased EVG-related adverse effects.
Mpox treatments	• **Brincidofovir** is a substrate for OATP1B1, OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with EVG/COBI will likely increase brincidofovir levels. Consider avoiding concurrent EVG/COBI if possible. If unable to change EVG/COBI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone EVG/COBI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce EVG/COBI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; DVT, deep vein thrombosis; GFR, glomerular filtration rate; GI, gastrointestinal; INR, international normalized ratio; LFT, liver function test; MATE, multidrug and toxin extrusion; OATP, organic anion transporting polypeptide; PDE5, phosphodiesterase type 5; PE, pulmonary embolism; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); acid-reducing agents (Table 25); asthma and allergy medications (Table 27); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); gender-affirming hormones (Table 47).

Table 9: Raltegravir (RAL) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antacids and other polyvalent cations [Krishna, et al. 2016; Calcagno, et al. 2015; Kiser, et al. 2010]	RAL chelates with cations, forming insoluble compounds that inactivate both drugs.	• **Aluminum-magnesium hydroxide antacids:** Concomitant use is contraindicated; use alternative acid-reducing agent. • **Calcium carbonate antacids:** – RAL HD once per day is *contraindicated.* – RAL 400 mg twice per day: No dose adjustment or separation is necessary. • **Other polyvalent cations:** Administer at least 2 hours before or 6 hours after.
Anticonvulsants	Coadministration with strong UGT1A1 inducers (phenytoin, phenobarbital, etc.) may decrease RAL concentrations.	Coadministration with strong UGT1A1 inducers is not recommended.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** No clinically significant interactions are expected. • **Rifampin:** CYP3A4 induction reduces RAL bioavailability. • **Rifapentine:** Induction of metabolism may reduce RAL metabolism.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin:** – When used concomitantly, dose RAL at 800 mg twice per day instead of 400 mg twice per day. – Do not use RAL HD. • **Rifapentine:** – For 900 mg once-weekly rifapentine and RAL 400 mg twice daily, no dose adjustments are necessary. – Do not coadminister RAL with once-daily rifapentine.
Abbreviations: CYP, cytochrome P450; UGT, uridine diphosphate glucuronosyltransferase. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); mpox treatments (Table 46); gender-affirming hormones (Table 47).		

Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

Table 10: Doravirine (DOR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Strong inducers or inhibitors of CYP3A [Deeks 2018]	DOR is a CYP3A substrate, 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.

Table 10: Doravirine (DOR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce ARV concentrations 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 TDM if use cannot be avoided.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** CYP3A induction is expected to decrease DOR levels. • **Rifampin, rifapentine:** CYP3A induction reduces DOR bioavailability.	• **Rifabutin:** When used concomitantly, increase DOR to 100 mg twice per day. • **Rifampin, rifapentine:** – Concomitant use is contraindicated. – After stopping rifampin or rifapentine, wait 4 weeks before starting DOR.
Mpox treatments [a]	**Tecovirimat** is weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19; use may potentially increase or decrease plasma concentrations of other medications.	• **Tecovirimat** may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Brincidofovir, cidofovir, VIGIV:** Drug interactions are unlikely.

Abbreviations: ARV, antiretroviral agents; AUC, area under the curve; CYP, cytochrome P450; NNRTI, non-nucleoside reverse transcriptase inhibitor; TDM, therapeutic drug monitoring; VIGIV, vaccinia immune globulin intravenous.

Note:

a. No data are currently available on effects related to concurrent use of tecovirimat and HIV medications. However, midazolam AUC was reduced by 32% with concomitant tecovirimat use, and some experts recommend caution due to the mild CYP3A4 induction associated with tecovirimat. Among them is University of Liverpool HIV Drug Interactions, which makes the following dosing change recommendations, although they are not based on any clinical data: Increase dose to 100 mg twice daily for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); antidiabetic drugs (Table 24); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); gender-affirming hormones (Table 47).

Table 11: Rilpivirine (RPV) Interactions (also see drug package inserts) The combination CAB/RPV antiretroviral therapy regimen can be used during an oral medication lead-in period and then as monthly long-acting injections; also see Table 6: Cabotegravir (CAB) Interactions.		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Macrolides	Coadministration may increase RPV levels.	Consider alternatives. Increased RPV levels when combined with macrolides may lead to increased risk of torsades de pointes.

Table 11: Rilpivirine (RPV) Interactions (also see drug package inserts)
The combination CAB/RPV antiretroviral therapy regimen can be used during an oral medication lead-in period and then as monthly long-acting injections; also see Table 6: Cabotegravir (CAB) Interactions.

Class or Drug	Mechanism of Action	Clinical Comments
Proton pump inhibitors (PPIs) [Schafer and Short 2012]	• PPIs inhibit gastric acid secretion by proton pumps, thereby increasing gastric pH. • Oral RPV requires acidic environment for optimal absorption.	• Concurrent use of PPIs with *oral* RPV is contraindicated. • Use of PPIs with *injectable* RPV is acceptable.
Histamine-2 receptor antagonists (H2RAs) [Schafer and Short 2012]	• H2RAs inhibit gastric acid secretion by proton pumps, thereby increasing gastric pH. • Oral RPV requires acidic environment for optimal absorption. • Concomitant use may decrease RPV absorption.	• Administer H2RA at least 12 hours before or 4 hours after. • Use lowest effective dose. • Administer with food. • Use of H2RAs with *injectable* RPV is acceptable.
Antacids [Schafer and Short 2012]	• Antacids increase gastric pH. • RPV requires acidic environment for optimal absorption. • Concomitant use may decrease RPV absorption.	Administer antacids 2 hours before or 4 hours after.
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 RPV absorption. Furthermore, exenatide may slow gastric emptying.	May recommend RPV dosing 4 hours before.
Dexamethasone [Welz, et al. 2017]	Dexamethasone is a CYP3A inducer, which is primarily responsible for metabolism of RPV.	**Dexamethasone (systemic):** • Concomitant use is contraindicated; consider alternative steroids. • If using more than a single oral or IM dose, consider an alternative NNRTI after consultation with experienced HIV care provider (see package inserts for Cabenuva and Edurant).
Antiarrhythmic drugs [Sanford 2012]	Supratherapeutic RPV doses have caused QT prolongation and additive effects may be seen.	Avoid concomitant use (may cause QT prolongation and torsades de pointes).
Long-acting beta agonists (LABAs)	RPV and drugs from LABA class may both theoretically increase QT interval, especially at high doses.	• No dose adjustments are necessary. • Do not use more LABA than recommended; this can increase risk of QT prolongation.
Antipsychotics	No significant interactions reported.	No dose adjustments are 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 RPV concentrations through induction of CYP450, UGT1A, and/or P-gP system.	Concomitant use is contraindicated with oral and injectable RPV (see package inserts for Cabenuva and Edurant).
Methadone, buprenorphine (BUP)	• **BUP:** No significant interactions are expected. • **Methadone:** RPV mildly reduces methadone concentrations.	• **Methadone:** Monitor for signs of methadone withdrawal; increase dose as necessary. • **Methadone, BUP:** Use cautiously with RPV; supratherapeutic RPV doses have been known to cause increase in QT prolongation.

Table 11: Rilpivirine (RPV) Interactions (also see drug package inserts) The combination CAB/RPV antiretroviral therapy regimen can be used during an oral medication lead-in period and then as monthly long-acting injections; also see Table 6: Cabotegravir (CAB) Interactions.		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Rifabutin, rifampin, rifapentine	Coadministration may significantly reduce RPV concentrations through induction of CYP450, UGT1A, and/or P-gP system.	• **Rifabutin:** – Oral RPV: Increase RPV dose to 50 mg once daily [DHHS(a) 2021]. – Injectable RPV: Concomitant use is contraindicated. • **Rifampin, rifapentine:** Concomitant use with oral and injectable RPV is contraindicated [FDA(b) 2021].
Strong inducers or inhibitors of CYP3A	RPV is a CYP3A substrate, 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.
Mpox treatments [a]	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19; use may increase or decrease plasma concentrations of other medications.	• **Tecovirimat** may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Brincidofovir, cidofovir, VIGIV:** Drug interactions are unlikely.

Abbreviations: ARV, antiretroviral; AUC, area under the curve; CAB, cabotegravir; CYP, cytochrome P450; GLP-1, glucagon-like peptide-1; IM, intramuscular; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; TDM, therapeutic drug monitoring; VIGIV, vaccinia immune globulin intravenous.

Note:

a. No data are currently available on effects related to concurrent use of tecovirimat and HIV medications. However, midazolam AUC was reduced by 32% with concomitant tecovirimat use, and some experts recommend caution due to the mild CYP3A4 induction associated with tecovirimat. Among them is University of Liverpool HIV Drug Interactions, which makes the following dosing change recommendations, although they are not based on any clinical data: Increase dose to 50 mg daily for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); asthma and allergy medications (Table 27); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); anticonvulsants not specifically stated above (Table 34); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); naloxone and naltrexone (Table 42); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); gender-affirming hormones (Table 47).

Table 12: Efavirenz (EFV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Warfarin	Metabolism of warfarin could potentially increase (or more rarely decrease).	Use cautiously with warfarin; if use is necessary, increase INR monitoring. • If INR increases, decrease warfarin dose. • If INR decreases, increase warfarin dose slowly.
Bupropion [Robertson, et al. 2008]	EFV induces bupropion metabolism.	Monitor for clinical effect and increase as needed, but do not exceed recommended maximum dose.

Table 12: Efavirenz (EFV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Levonorgestrel/ norgestimate, levonorgestrel [Scarsi, et al. 2016; Carten, et al. 2012]	EFV may induce CYP3A, the enzyme that is primarily responsible for metabolism of levonorgestrel.	Levonorgestrel or norgestimate effectiveness may be decreased.
Cilostazol	EFV may reduce cilostazol concentrations.	Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV.
Dipyridamole	EFV may induce UGT enzymes, which are responsible for metabolism.	Monitor for antiplatelet effect; use alternative ARV if necessary.
Ticagrelor, clopidogrel	EFV reduces ticagrelor concentrations and conversion of clopidogrel to its active metabolite.	Use with EFV may reduce antiplatelet effect; monitor closely for efficacy and use alternative ARV if necessary.
Statins	• **Simvastatin, lovastatin:** EFV may decrease concentrations. • **Atorvastatin, pravastatin, fluvastatin:** EFV may modestly reduce concentrations. • **Pitavastatin, rosuvastatin**: No significant interactions are 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 for cholesterol-lowering effect of statins. May require increased dose. • **Pitavastatin, rosuvastatin:** No dose adjustments are necessary.
Pioglitazone	EFV may increase concentrations through CYP2C8 inhibition. No significant interactions are expected.	Monitor for signs of adverse effects with EFV; decrease dose if necessary.
Saxagliptin, sitagliptin	EFV may decrease concentrations.	Monitor for efficacy; if necessary, increase dose of DPP-4 inhibitor.
Inhaled and injected corticosteroids	Coadministration may reduce corticosteroid concentrations.	**Dexamethasone (systemic):** Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor for virologic response.
Trazodone	EFV may decrease trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Benzodiazepines	**Alprazolam, diazepam:** EFV may reduce alprazolam and diazepam concentrations.	• **Alprazolam:** Monitor for benzodiazepine withdrawal with concomitant EFV use. • **Alprazolam, clonazepam, diazepam:** Titrate slowly to achieve clinical effect; monitor for benzodiazepine efficacy.
Sleep medications	**Zolpidem:** EFV may reduce zolpidem concentrations.	• **Zolpidem, eszopiclone:** Monitor for efficacy; no dose adjustments are recommended. • **Suvorexant:** Monitor for efficacy; do not exceed 20 mg per day.
Antipsychotics	• **Quetiapine:** EFV may reduce quetiapine concentrations. • **Aripiprazole, brexpiprazole:** EFV may decrease aripiprazole and brexpiprazole concentrations. • **Risperidone, olanzapine:** EFV may decrease risperidone and olanzapine efficacy.	**Quetiapine, aripiprazole, brexpiprazole, risperidone, olanzapine:** Titrate slowly to achieve clinical effect; monitor for efficacy and adverse effects.
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce concentrations of ARVs 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 TDM if use cannot be avoided.

Table 12: Efavirenz (EFV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Lamotrigine, zonisamide	EFV may reduce lamotrigine or zonisamide efficacy.	Titrate slowly to achieve clinical effect; monitor for efficacy.
Opioid analgesics and tramadol	• **Morphine, hydromorphone:** Metabolism could be reduced by EFV. • **Oxycodone** may be metabolized faster to inactive metabolite by EFV. • **Meperidine:** Coadministration can potentially increase amount of neurotoxic metabolite, thereby increasing seizure risk. • **Tramadol:** EFV may reduce tramadol concentration without affecting pathway that increases development of more potent active metabolites.	• **Morphine, hydromorphone:** Monitor for signs of opiate toxicity when using with EFV. • **Oxycodone:** Dose adjustment of oxycodone may be required when dosing with EFV. • **Meperidine:** If possible, avoid concomitant use; use alternative opiate pain medication or ARV. • **Tramadol:** When given with tramadol, a priori dose adjustments are necessary.
Hormonal contraceptives	EFV decreases concentrations of combined progestins.	• **Ethinyl estradiol; norgestimate and metabolites:** Use alternative or additional contraceptive methods; unintended pregnancies have been reported in individuals using levonorgestrel implants. • **Norethindrone, drospirenone, etonogestrel:** Consider alternative or additional contraceptive method or alternative ARV. • **Ulipristal:** Monitor closely for reduced efficacy.
Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** EFV may reduce effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). • **Flibanserin:** EFV may reduce flibanserin concentrations.	• **PDE5 inhibitors:** Monitor for clinical effect; if dose increase is needed to achieve desired clinical effect, titrate under medical supervision to lowest effective dose. • **Flibanserin:** Do not coadminister.
Methadone [Kharasch, et al. 2012; Gruber and McCance-Katz 2010; Clarke, et al. 2001]	EFV induces methadone metabolism via CYP3A4 and reduces methadone concentrations.	Titrate to achieve clinical effect; monitor for signs and symptoms of opioid withdrawal.
Buprenorphine (BUP) [Gruber and McCance-Katz 2010; McCance-Katz, et al. 2006]	• EFV induces BUP metabolism via CYP3A4. • When given with BUP (monotherapy), EFV significantly reduces BUP concentrations, but no patients developed opioid withdrawal.	When given with BUP, dose adjustments are unlikely to be required, but monitor for withdrawal symptoms. If withdrawal symptoms occur, increase BUP dose accordingly.
NS3/4A inhibitors (glecaprevir, simeprevir, grazoprevir, etc.) [Garrison, et al. 2018; Soriano, et al. 2017]	EFV induces NS3/4A PI metabolism via CYP3A4.	Concomitant use is not recommended (may result in failure of HCV treatment regimens containing PIs, reducing SVR rates and increasing resistance).
Daclatasvir [Garrison, et al. 2018; Soriano, et al. 2017]	EFV induces daclatasvir metabolism via CYP3A4.	Increase daclatasvir dose to 60 mg per day.

Table 12: Efavirenz (EFV) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Sofosbuvir/velpatasvir (available as coformulated product) [Greig 2016]	EFV may decrease velpatasvir levels through CYP3A induction.	Coadministration of sofosbuvir/velpatasvir is contraindicated.
Cyclosporine, tacrolimus	EFV may lower concentrations.	• Adjust dose of cyclosporine and tacrolimus based on efficacy and TDM. • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** EFV induction of CYP3A reduces rifabutin bioavailability, but coadministration does not affect EFV levels. • **Rifampin, rifapentine:** No clinically significant interactions are expected.	• **Rifabutin:** With concomitant EFV, dose rifabutin at 450 mg to 600 mg daily. • **Rifampin:** – Dose EFV at 600 mg daily when administered concomitantly. – Do not use EFV 400 mg daily. • **Rifapentine:** No dose adjustments are necessary.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Drug interactions are unlikely; EFV levels may increase.
Mpox treatments	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19; use may increase or decrease plasma concentrations of other medications.	• **Tecovirimat** may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Brincidofovir, cidofovir, VIGIV:** Drug interactions are unlikely.
Gender-affirming hormones	• **Estradiol:** EFV could induce CYP3A and could decrease estradiol levels. • **Finasteride, testosterone:** Levels may decrease when taken concomitantly with EFV.	• **Estradiol:** No dose adjustments are recommended; when taken concomitantly with EFV, monitor for signs of estrogen deficiency or excess. • **Finasteride, testosterone:** No dose adjustments are necessary.
Lenacapavir (LEN)	CYP3A4 and P-gP induction associated with concomitant HIV treatment potentially deceases LEN levels.	Do not coadminister.

Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; DPP-4, dipeptidyl peptidase-4; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; NS3/4A, nonstructural protein 3/4A; PDE5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; SVR, sustained viral response; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); nonopioid pain medications (Table 35); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); alcohol, disulfiram, and acamprosate (Table 41).

Table 13: Etravirine (ETR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Aliskiren	ETR is a minor inhibitor of P-gP and may minimally increase aliskiren concentrations, but this has not been studied.	When using with ETR, monitor for aliskiren-related adverse effects; switch to alternative antihypertensive medicine or ARV if necessary.
Warfarin	Metabolism of warfarin could potentially increase (or more rarely decrease).	Use cautiously with warfarin; if use is necessary, increase INR monitoring. • If INR increases, decrease warfarin dose. • If INR decreases, increase warfarin dose slowly.
Antiplatelet drugs [Kakuda, et al. 2011; Rathbun and Liedtke 2010]	• **Cilostazol:** ETR may reduce cilostazol concentrations. • **Dipyridamole:** ETR may induce UGT enzymes, which are responsible for metabolism. • **Ticagrelor, clopidogrel:** ETR reduces ticagrelor concentrations and conversion of clopidogrel to its active metabolite. • **Vorapaxar:** When coadministered with ETR, vorapaxar levels expected to be reduced.	• **Cilostazol:** Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use another ARV if necessary. • **Ticagrelor, clopidogrel:** Use with ETR may reduce antiplatelet effect; monitor closely for efficacy and use alternative ARV if possible. • **Prasugrel:** When coadministered with ETR, no dose adjustments are necessary. • **Vorapaxar:** No data available.
Statins	• **Simvastatin, lovastatin:** ETR may decrease concentrations. • **Atorvastatin, pravastatin, fluvastatin:** ETR may modestly reduce concentrations.	• **Simvastatin, lovastatin:** Monitor for efficacy. May warrant increases in statin dose. Do not increase dose above maximum recommended statin dose. • **Atorvastatin, pravastatin, fluvastatin:** Monitor for cholesterol-lowering effect of statins. May require increased dose if necessary.
Saxagliptin, sitagliptin	ETR may decrease concentrations.	Monitor for efficacy; if necessary, increase dose of DPP-4 inhibitor.
Inhaled and injected corticosteroids	Coadministration may reduce corticosteroid concentrations.	**Dexamethasone (systemic):** Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor for virologic response.
Trazodone	ETR may decrease trazodone concentrations.	Monitor for antidepressant and/or sedative effects.
Bupropion	No significant interactions are expected.	Monitor for clinical effect and increase as needed, but do not exceed recommended maximum dose.
Alprazolam	ETR may reduce alprazolam concentrations.	Monitor for benzodiazepine withdrawal.
Diazepam	ETR may reduce diazepam concentrations.	No dose adjustments are necessary.
Sleep medications	**Zolpidem:** ETR may reduce zolpidem concentrations.	• **Zolpidem, eszopiclone:** Monitor for efficacy; no dose adjustments are recommended. • **Suvorexant:** Monitor for efficacy; do not exceed 20 mg per day.

Table 13: Etravirine (ETR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Antipsychotics	• **Aripiprazole, brexpiprazole:** ETR may decrease aripiprazole and brexpiprazole concentrations. • **Risperidone:** ETR may decrease risperidone efficacy.	**Aripiprazole, brexpiprazole, risperidone:** Titrate slowly to achieve clinical effect; monitor for efficacy and adverse effects.
Carbamazepine, oxcarbazepine, phenobarbital, phenytoin	Coadministration may significantly reduce concentrations of ARVs 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 TDM if use cannot be avoided.
Lamotrigine, zonisamide	ETR may reduce lamotrigine or zonisamide efficacy.	Titrate slowly to achieve clinical effect; monitor for efficacy.
Hormonal contraceptives	Information is based on what is known with EFV drug interactions.	• **Etonogestrel:** No data available; consider alternative or additional contraceptive methods or alternative ARV. • **Ulipristal:** Monitor closely for reduced efficacy.
Erectile and sexual dysfunction agents	• **PDE5 inhibitors:** ETR may reduce effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). • **Flibanserin:** ETR may reduce flibanserin concentrations.	• **PDE5 inhibitors:** Monitor for clinical effect; if dose increase is needed to achieve desired clinical effect, titrate under medical supervision to lowest effective dose. • **Flibanserin:** Do not coadminister.
Buprenorphine	No significant interactions are expected.	Titrate opioid or antagonist as required to achieve clinical effect; monitor for signs of withdrawal or opioid toxicity.
Methadone	ETR may slightly increase methadone concentrations.	• Titrate opioid or antagonist as required to achieve clinical effect; monitor for signs of withdrawal or opioid toxicity. • Monitor for signs of methadone toxicity; reduce dose if necessary.
Cyclosporine, tacrolimus	ETR may lower concentrations.	• Adjust cyclosporine and tacrolimus dose based on efficacy and TDM. • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.
HCV PIs ("-previr" drugs) [Mak, et al. 2018; Kaur, et al. 2015; Yeh 2015]	ETR may decrease HCV PI levels through CYP3A induction.	Do not coadminister.
Sofosbuvir/velpatasvir (available as coformulated product) [Greig 2016]	ETR may decrease velpatasvir levels through CYP3A induction and (weak) P-gP inhibition.	Do not coadminister.
Daclatasvir [Garrison, et al. 2018]	ETR induces CYP3A, lowering daclatasvir levels.	Increase dose of daclatasvir to 90 mg per day.

Table 13: Etravirine (ETR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Atazanavir (ATV) [Marzolini, et al. 2016; Orrell, et al. 2015]	• ETR is a substrate and inducer of CYP3A4. • COBI and ATV are substrates and inhibitors of CYP3A4.	• Administration with RTV-boosted ATV results in decreased ATV exposure, but decrease is not considered relevant; no dose adjustments are necessary. • Due to potential for decreased ARV efficacy, avoid use of ETR with COBI. When these medications are given together, COBI concentrations 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) [Green, et al. 2017]	• ETR induces UGT1A1 and CYP3A enzymes. • DTG is a substrate of UGT1A1 and CYP3A enzymes.	ETR reduces DTG concentrations. Do not use concomitantly unless boosted PI is also part of treatment regimen.
Lenacapavir (LEN)	CYP3A4 and P-gP induction associated with concomitant HIV treatment potentially deceases LEN levels.	Do not coadminister.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** When used concomitantly, increased rifabutin levels are expected and decreased ETR levels may occur. • **Rifampin, rifapentine**: CYP3A induction reduces ETR bioavailability.	• **Rifabutin:** – If ETR and rifabutin are used concomitantly, dose rifabutin at 300 mg daily, with no changes to ETR dose. Continue rifabutin 300 mg daily dosing until at least 2 weeks after rifabutin is stopped. – Concomitant use of boosted PI with ETR and rifabutin is contraindicated. • **Rifampin, rifapentine:** Concomitant use is contraindicated.
Mpox treatments	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19; use may increase or decrease plasma concentrations of other medications.	• **Tecovirimat** may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Brincidofovir, cidofovir, VIGIV:** Drug interactions are unlikely.
Gender-affirming hormones	• **Estradiol:** ETR could induce CYP3A and could decrease estradiol levels. • **Finasteride, testosterone:** Levels may decrease when taken concomitantly with ETR.	• **Estradiol:** No dose adjustments are recommended; when taken concomitantly with ETR, monitor for signs of estrogen deficiency or excess. • **Finasteride, testosterone:** No dose adjustments are recommended.

Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; DPP-4, dipeptidyl peptidase-4; EFV, efavirenz; HCV, hepatitis C virus; INR, international normalized ratio; NNRTI, non-nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PDE5, phosphodiesterase type 5; PI, protease inhibitor; RTV, ritonavir; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase; VIGIV, vaccinia immune globulin intravenous.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); alcohol, disulfiram, and acamprosate (Table 41); COVID-19 therapeutics (Table 45).

Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Table 14: Abacavir (ABC) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Alcohol [Yuen, et al. 2008; McDowell, et al. 2000]	ABC is metabolized via alcohol dehydrogenase, and competitive metabolism may increase exposure to ABC.	• Use may increase ABC concentrations; monitor for ABC-related adverse effects. • ABC does not appear to increase blood alcohol concentrations.
Rifabutin, rifampin, rifapentine	• **Rifabutin, rifapentine:** No clinically significant interactions are expected. • **Rifampin** may reduce ABC concentration.	• **Rifabutin, rifapentine:** No dose adjustments are necessary. • **Rifampin:** No dose adjustments are recommended for concomitant use with ABC.
Mpox treatments	**Cidofovir** is eliminated via glomerular filtration and active renal secretion by OAT1 and OAT3.	• **Cidofovir:** Avoid coadministration with nephrotoxic agents. Consider use of TAF in place of TDF and monitor for renal-related adverse effects. • **Brincidofovir, tecovirimat, VIGIV:** Drug interactions are unlikely.
Abbreviations: OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VIGIV, vaccinia immune globulin intravenous. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); anticonvulsants (Table 34); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); methadone, buprenorphine, naloxone, and naltrexone (Table 42); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); gender-affirming hormones (Table 47).		

Table 15: Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Adefovir [Jafari, et al. 2014]	• Adefovir and tenofovir have similar mechanisms of action and elimination as well as overlapping adverse effect profiles. • Competitive inhibition of elimination results in additive adverse effects.	Avoid concomitant use to avoid increased risk of hepatic steatosis, lactic acidosis, and potential renal failure.
Other nephrotoxic agents [Jafari, et al. 2014]	Competitive inhibition of elimination results in additive adverse effects.	• **TDF:** Avoid concomitant use or use the lowest effective dose of another medication to avoid renal impairment and kidney dysfunction. • **TAF:** Using TAF in these instances may be preferable because TAF is less nephrotoxic.
Sofosbuvir/velpatasvir/ voxilaprevir [brand name Vosevi] [Garrison, et al. 2017]	• TDF and TAF are substrates for BCRP and P-gP. • Voxilaprevir is a BCRP inhibitor. • Velpatasvir inhibits BCRP and P-gP.	• **TDF:** Avoid concomitant use if possible to avoid TDF-associated adverse effects. • **TAF:** Using TAF in these instances may be preferable.

Table 15: Tenofovir Disoproxil Fumarate (TDF) and Tenofovir Alafenamide (TAF) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Potent CYP3A4 or P-gP inducers (phenytoin, carbamazepine, St. John's wort, etc.) [Gibson, et al. 2016]	• CYP3A4 is a minor metabolic pathway for TAF, and as such, potent inducers of this enzyme may modestly reduce concentrations. • TAF is also a P-gP substrate, and inducers may decrease TAF concentrations.	**TAF:** Avoid coadministration of TAF with potent inducers of CYP3A4 or P-gP.
Rifampin, rifabutin, rifapentine	• **Rifabutin:** CYP3A and P-gP induction is expected to decrease TAF levels. • **Rifampin, rifapentine:** CYP3A induction may reduce TAF concentrations. • **Rifampin, rifabutin, rifapentine**: No clinically significant interactions with TDF are expected.	• **TAF:** – **Rifampin:** Do not coadminister with TAF; consider TDF as alternative. – **Rifabutin, rifapentine:** Do not coadminister with TAF unless benefit outweighs risk; monitor closely for virologic response. • **TDF + rifampin, rifabutin, rifapentine**: No dose adjustments are necessary.
Zonisamide	TDF may increase concentration of zonisamide.	**TDF:** When using with TDF, monitor for adverse effects.
Topiramate	No significant interactions reported.	**TDF:** When using with TDF, monitor renal function (topiramate may cause kidney stones; TDF is associated with renal toxicity).
Mpox treatments	**Cidofovir** is eliminated via glomerular filtration and active renal secretion by OAT1 and OAT3.	• **Cidofovir:** Avoid coadministration with nephrotoxic agents. Consider us of TAF in place of TDF and monitor for renal-related adverse effects. • **Brincidofovir, tecovirimat, VIGIV:** Drug interactions are unlikely.

Abbreviations: BCRP, breast cancer resistance protein; CYP, cytochrome P450; OAT, organic anion transporter; P-gP, P-glycoprotein; VIGIV, vaccinia immune globulin intravenous.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction drugs (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); gender-affirming hormones (Table 47).

Table 16: Lamivudine (3TC) and Emtricitabine (FTC) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Mpox treatments	**Cidofovir** is eliminated via glomerular filtration and active renal secretion by OAT1 and OAT3.	• **Cidofovir:** Avoid coadministration with nephrotoxic agents. Consider use of TAF in place of TDF and monitor for renal-related adverse effects. • **Brincidofovir, tecovirimat, VIGIV:** Drug interactions are unlikely.
Abbreviations: OAT, organic anion transporter; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VIGIV, vaccinia immune globulin intravenous. **No significant interactions/no dose adjustments necessary:** common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); anticoagulants (Table 21); antiplatelet drugs (Table 22); statins (Table 23); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); inhaled and injected corticosteroids (Table 29); antidepressants (Table 30); benzodiazepines (Table 31); sleep medications (Table 32); antipsychotics (Table 33); anticonvulsants (Table 34); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); hormonal contraceptives (Table 37); erectile and sexual dysfunction agents (Table 38); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); immunosuppressants (Table 43); rifamycins and other antituberculosis medications (Table 44); COVID-19 therapeutics (Table 45); gender-affirming hormones (Table 47).		

Entry Inhibitors (EIs)

Table 17: Fostemsavir (FTR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Potent CYP3A4 or P-gP inducers (phenytoin, rifampin, carbamazepine, St. John's wort, etc.)	CYP3A4 induction reduces FTR levels.	Do not coadminister.
Antineoplastic agent (mitotane)	CYP3A4 induction reduces FTR levels.	Do not coadminister.
Androgen receptor inhibitor (enzalutamide)	CYP3A4 induction reduces FTR levels.	Do not coadminister.
HCV antiviral agents	FTR increases grazoprevir and voxilaprevir levels.	Coadministration may increase grazoprevir or voxilaprevir exposure. Use alternative HCV regimen if possible.
Hormonal contraceptives	**Ethinyl estradiol:** Increased levels of ethinyl estradiol are expected.	**Ethinyl estradiol:** Daily dose should not exceed 30 mcg. Caution is advised, particularly in patients with additional risk factors for thromboembolic events.
Statins	**Atorvastatin, fluvastatin, pitavastatin, rosuvastatin, simvastatin:** Levels may increase with concurrent use of FTR.	Use lowest possible statin starting dose; monitor for statin-associated adverse effects.
Rifabutin, rifampin, rifapentine	• **Rifabutin:** Interaction is not expected. • **Rifampin, rifapentine:** CYP3A4 induction reduces FTR bioavailability.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin, rifapentine:** Do not coadminister.

Table 17: Fostemsavir (FTR) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Drug interactions are unlikely; FTR levels may increase.
Mpox treatments	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** FTR inhibits OATP1B1 and may increase brincidofovir levels. Avoid concurrent use if possible. If unable to change therapy, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone FTR dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce FTR levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.
Abbreviations: CYP, cytochrome P450; GI, gastrointestinal; HCV, hepatitis C virus; LFT, liver function test; OATP, organic anion transporting polypeptide; P-gP, P-glycoprotein; RTV, ritonavir. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); polyvalent cations (Table 26); inhaled and injected corticosteroids (Table 29); benzodiazepines (Table 31); sleep medications (Table 32); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); gender-affirming hormones (Table 47).		

Table 18: Maraviroc (MVC) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Potent CYP3A4 or P-gP inducers (St. John's wort)	Reduced MVC levels are due to CYP3A4 induction.	Do not coadminister.
COVID-19 therapeutics	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Drug interactions are unlikely; MVC levels may increase.
Mpox treatments [a]	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19.	**Tecovirimat** may reduce MVC levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.
Abbreviations: AUC, area under the curve; CYP, cytochrome P450; P-gP, P-glycoprotein; RTV, ritonavir.		

Table 18: Maraviroc (MVC) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Note: a. No data are currently available on effects related to concurrent use of tecovirimat and HIV medications. However, midazolam AUC was reduced by 32% with concomitant tecovirimat use, and some experts recommend caution due to the mild CYP3A4 induction associated with tecovirimat. Among them is University of Liverpool HIV Drug Interactions, which makes the following dosing change recommendations, although they are not based on any clinical data: Increase dose to 600 mg twice daily (if the patient is not taking another potent CYP3A4 inhibitor concurrently) for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped. If the patient is receiving concomitant treatment with a potent CYP3A4 inhibitor, MVC should be dosed at 150 mg twice daily for the duration of concurrent tecovirimat. **No significant interactions/no dose adjustments necessary:** Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); polyvalent cations (Table 26); inhaled and injected corticosteroids (Table 29); benzodiazepines (Table 31); sleep medications (Table 32); nonopioid pain medications (Table 35); opioid analgesics and tramadol (Table 36); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); methadone, buprenorphine, naloxone, and naltrexone (Table 42); gender-affirming hormones (Table 47).		

Capsid Inhibitor

Table 18A: Lenacapavir (LEN) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Direct oral anticoagulants (DOACs; apixaban, rivaroxaban, dabigatran, edoxaban, etc.)	DOAC levels potentially increase due to effect on CYP3A4 and P-gP.	• No dose adjustment needed; monitor for increased risk of bleeding. • Refer to DOAC prescribing information for use with moderate CYP3A4 and P-gP inhibitors.
Digoxin	Moderate inhibition of P-gP potentially increases digoxin levels.	Monitor digoxin concentrations when using with LEN.
Anticonvulsants	**Carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin:** CYP3A4 and P-gP induction potentially decreases LEN levels.	• **Carbamazepine, eslicarbazepine, phenytoin:** Do not coadminister. • **Oxcarbazepine, phenobarbital:** Coadministration is not recommended. • Consider alternative anticonvulsants such as levetiracetam.
Antipsychotics	**Pimozide:** Moderate inhibition of P-gP potentially increases pimozide levels.	**Pimozide:** Do not coadminister.
Cardiac medications	**Amiodarone, disopyramide, quinidine, ivabradine:** Moderate inhibition of P-gP potentially increases cardiac medication levels.	**Amiodarone, disopyramide, quinidine, ivabradine:** Do not coadminister.
• Efavirenz (EFV) • Etravirine (ETR) • Nevirapine (NVP) • Tipranavir (TPV)	CYP3A4 and P-gP induction associated with concomitant HIV treatment potentially deceases LEN levels.	• Do not coadminister. • Drug interactions with rilpivirine and doravirine are unlikely.
COBI- or RTV-boosted atazanavir (ATV)	CYP3A4 and P-gP inhibition potentially increases LEN levels.	• Do not coadminister. • Drug interactions with darunavir boosted with COBI are unlikely. • Other boosted PIs should also be avoided due to late of data.

Table 18A: Lenacapavir (LEN) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Rifabutin, rifampin, rifapentine	CYP3A4 and P-gP induction associated with rifamycins potentially decreases LEN levels.	• **Rifampin:** Concomitant use is contraindicated. • **Rifabutin, rifapentine:** Coadministration is not recommended. • Consider alternatives.
Dexamethasone, hydrocortisone (systemic)	• Moderate inhibition of CYP3A4 and P-gP potentially increases corticosteroid concentrations and the related risk of Cushing's syndrome and adrenal suppression. • **Dexamethasone (systemic):** Decreased LEN levels expected with dexamethasone doses >16 mg/day.	• **Dexamethasone, hydrocortisone (systemic):** Initiate at lowest dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Dexamethasone (systemic):** Do not coadminister with dexamethasone doses >16 mg/day.
Ergotamine derivatives (dihydroergotamine, ergotamine, methylergonovine, etc.)	Moderate inhibition of CYP3A4 potentially increases ergotamine derivative levels.	Do not coadminister.
St. John's wort	CYP3A4 and P-gP induction potentially decreases LEN levels.	Do not coadminister.
Lovastatin, simvastatin, lomitapide	**Lovastatin, simvastatin, lomitapide:** Moderate inhibition of CYP3A4 and P-gP potentially increases levels.	• **Simvastatin, lovastatin:** Initiate at lowest dose and titrate to achieve clinical effect; monitor closely for statin toxicity. • **Lomitapide:** Concomitant use is contraindicated.
Opioids metabolized via CYP3A (i.e., fentanyl, oxycodone, tramadol)	Moderate inhibition of CYP3A4 potentially increases opioid levels.	• Monitor for therapeutic effects and adverse reactions associated with CYP3A-metabolized opioid analgesics, including potentially fatal respiratory depression. • **Tramadol:** Consider tramadol dose reduction with concomitant use.
Methadone, buprenorphine	Moderate inhibition of CYP3A4 and P-gP potentially increases methadone or buprenorphine levels.	• **Patients initiating MAT while already on LEN:** Initiate MAT at lowest initial or maintenance dose. • **Patients initiating LEN while already on MAT:** MAT dose adjustments may be needed. • Monitor for excess sedation and/or respiratory depression.
Naloxegol (opioid antagonist)	Moderate inhibition of CYP3A4 potentially increases naloxegol levels.	Avoid concomitant use. If use is required, decrease naloxegol dose and monitor for adverse effects.
PDE5 inhibitors	Moderate inhibition of CYP3A4 and P-gP potentially increases PDE5 inhibitor levels.	**For pulmonary hypertension:** • **Tadalafil:** Concomitant use is not recommended. • For other medications, refer to dosing guidelines. **For erectile dysfunction**, refer to package inserts and guidance listed below: • **Avanafil:** Do not coadminister. • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.

Table 18A: Lenacapavir (LEN) Interactions (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Midazolam (oral), triazolam	Moderate inhibition of CYP3A4 and P-gP potentially increases sedative levels.	Use with caution; monitor for excess sedation.

Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; MAT, medication-assisted therapy; PDE5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; TDM, therapeutic drug monitoring.

No significant interactions/no dose adjustments necessary: Common oral antibiotics (Table 19); drugs used as antihypertensive medicines (Table 20); antiplatelet drugs (Table 22); antidiabetic drugs (Table 24); acid-reducing agents (Table 25); polyvalent cations (Table 26); asthma and allergy medications (Table 27); long-acting beta agonists (Table 28); antidepressants (Table 30); sleep medications (Table 32); antipsychotics (Table 33); nonopioid pain medications (Table 35); hormonal contraceptives (Table 37); alpha-adrenergic antagonists for benign prostatic hyperplasia (Table 39); tobacco and smoking cessation products (Table 40); alcohol, disulfiram, and acamprosate (Table 41); immunosuppressants (Table 43); COVID-19 therapeutics (Table 45); mpox treatments (Table 46); gender-affirming hormones (Table 47).

Drug-Drug Interactions by Common Medication Class

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 medications. 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 states 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 U.S. Department of Health and Human Services give each class of medications in the initial management of HIV. Appropriate HIV management 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 ARVs.

The informational material found within these tables is based on previously referenced primary, secondary, and tertiary literature, as well as the various publicly 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 (drug package inserts), which are also available online for each of the listed pharmacologic agents. Healthcare providers are encouraged to utilize these resources if they 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.

Consultation with an experienced HIV care provider is also recommended when assistance is needed in choosing an antiretroviral therapy (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.

→ KEY POINT

- Medications used to treat epilepsy, various types of malignancies, and tuberculosis and to prevent graft-versus-host disease following solid organ transplants are known to interact with several ARVs. 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 19: Common Oral Antibiotics (also see drug package inserts)		
→ Penicillins, cephalosporins, tetracyclines, macrolides, fluoroquinolones, sulfamethoxazole-trimethoprim [a], linezolid, dapsone		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Raltegravir (RAL) • Cabotegravir (CAB) • Elvitegravir (EVG), boosted • Boosted PIs • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR) • Fostemsavir (FTR)	• No significant interactions are expected. • 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 limited duration of most penicillin regimens, significance of this interaction is expected to be minimal.	No dose adjustments are necessary.
Rilpivirine (RPV)	**Macrolides:** Coadministration may increase RPV levels.	**Macrolides:** Consider alternatives. Increased RPV levels when combined with macrolides may lead to increased risk of torsades de pointes.
Abbreviations: COBI, cobicistat; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate. **Note:** a. Trimethoprim blocks creatinine secretion and could accentuate the effects of COBI, BIC, and DTG.		

Table 20: Drugs Used as Antihypertensive Medicines (also see drug package inserts)		
→ Angiotensin-converting enzyme (ACE) inhibitors [a], angiotensin II receptor blockers (ARBs), calcium channel blockers (CCBs), beta blockers, direct renin inhibitors, diuretics		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR) • Efavirenz (EFV) • Fostemsavir (FTR)	No significant interactions are expected.	No dose adjustments are necessary.
• Dolutegravir (DTG) • Bictegravir (BIC)	• **Atenolol** is eliminated via OCT2 and MATE1, which are inhibited by DTG and BIC. Coadministration may increase atenolol levels. • **ACE inhibitors, ARBs, CCBs, aliskiren, diuretics:** No significant interactions are expected.	• **Atenolol:** – Start at lower atenolol dose and titrate slowly to achieve clinical effect. – If patient is already using atenolol but starting DTG or BIC, monitor for atenolol-related adverse effects. – Reduce atenolol dose if necessary or switch to another ARV. • **ACE inhibitors, ARBs, CCBs, aliskiren, diuretics:** No dose adjustments are necessary.

Table 20: Drugs Used as Antihypertensive Medicines (also see drug package inserts)

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

Class or Drug	Mechanism of Action	Clinical Comments
Elvitegravir (EVG), boosted	• **Aliskiren:** P-gP inhibitors, including boosted EVG, decrease aliskiren elimination, increasing adverse effects of medication. • **Atenolol:** COBI-boosted EVG may increase atenolol concentrations via inhibition of MATE1 elimination. • **CCBs:** COBI-boosted EVG may increase CCB concentrations by as much as 50%. • **ACE inhibitors, ARBs, beta blockers, carvedilol, diuretics:** No significant interactions are expected.	• **Aliskiren:** Do not coadminister. • **Atenolol:** – Start patient at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. – If patient is already using atenolol but starting COBI-boosted EVG, monitor for atenolol-related adverse effects. Reduce atenolol dose as needed. • **CCBs:** When using with boosted EVG, decrease original CCB dose by as much as 50% and titrate slowly to achieve clinical effect. • **Beta blockers other than atenolol, diuretics:** No dose adjustments are necessary.
Boosted PIs	• **Aliskiren:** Boosted PIs inhibit Pg-P, which may decrease aliskiren elimination, increasing risk of adverse effects. • **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 are expected.	• **Aliskiren:** Do not coadminister. • **Atenolol:** – Start at lowest possible dose and titrate slowly to achieve clinical effect while monitoring for adverse effects. – If patient is already using atenolol but starting COBI-boosted PI, monitor for atenolol-related adverse effects and reduce atenolol dose as needed. – RTV is the preferred PK booster when patient is also using atenolol. • **CCBs:** When using with boosted PIs, decrease original CCB dose by as much as 50% and titrate slowly to achieve clinical effect. • **ACE inhibitors, ARBs, beta blockers, diuretics:** No dose adjustments are necessary.
Etravirine (ETR)	• **Aliskiren:** ETR is minor P-gP inhibitor and may minimally increase aliskiren concentrations, but this has not been studied. • **ACE inhibitors, ARBs, CCBs, diuretics:** No significant interactions are expected.	• **Aliskiren:** When using with ETR, monitor for aliskiren-related adverse effects; switch to alternative antihypertensive medicine or ARV if necessary. • **ACE inhibitors, ARBs, beta blockers, CCBs, diuretics:** No dose adjustments are necessary.

Abbreviations: ARV, antiretroviral; COBI, cobicistat; INSTI, integrase strand transfer inhibitor; MATE, multidrug and toxin extrusion; NRTI, nucleoside reverse transcriptase inhibitor; NSAID, nonsteroidal anti-inflammatory drug; OCT, organic cation transporter; P-gP, P-glycoprotein; PI, protease inhibitor; PK, pharmacokinetic; RTV, ritonavir; TDF, tenofovir disoproxil fumarate.

Note:

a. 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 21: Anticoagulants (also see drug package inserts)		
→ Warfarin, non-VKA oral anticoagulants (NOACs), low molecular weight heparins (LMWHs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR)	No significant interactions are expected.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	• **Warfarin:** Metabolism of warfarin could potentially decrease (or more rarely) increase. • **Rivaroxaban, dabigatran, apixaban:** Concentrations may increase, increasing bleeding risk. • **LMWHs:** No significant interactions are expected.	• **Warfarin:** Use cautiously with warfarin; if use is necessary, increase INR monitoring. – If INR increases, decrease warfarin dose. – If INR decreases, increase warfarin dose slowly. • **Rivaroxaban:** Do not coadminister. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; if patient is already taking 2.5 mg twice per day, avoid concomitant use. • **Dabigatran:** – In patients with good renal function, no dose adjustments are necessary. – In patients with moderate to severe renal dysfunction, do not use this combination. – Consider switching to another ARV regimen without booster to avoid interaction. • **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For patients with DVT and PE: Administer edoxaban 30 mg once daily. • **LMWHs:** No dose adjustments are necessary.
Boosted PIs	• **Warfarin:** Metabolism of warfarin could potentially decrease (or more rarely) increase. • **Rivaroxaban, dabigatran, apixaban:** Concentrations may increase, increasing bleeding risk. • **LMWHs:** No significant interactions are expected.	• **Avoid concomitant use** or use lowest effective dose of factor Xa inhibitor to avoid increased bleeding risk. • **Warfarin:** Use cautiously with warfarin; if use is necessary, increase INR monitoring. – If INR increases, decrease warfarin dose. – If INR decreases, increase warfarin dose slowly. • **Rivaroxaban:** Do not coadminister. • **Apixaban:** Reduce apixaban dose to 2.5 mg twice per day; if patient is already taking 2.5 mg twice per day, avoid concomitant use.

Table 21: Anticoagulants (also see drug package inserts)		
→ Warfarin, non-VKA oral anticoagulants (NOACs), low molecular weight heparins (LMWHs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
		• **Dabigatran:** – Separate doses of dabigatran and boosted PIs by at least 2 hours. – RTV boosting of PIs may be safer than COBI boosting with concomitant dabigatran [Kakadiya, et al. 2018]. – Avoid dabigatran in patients with renal impairment (CrCl <50 mL/min) who are taking boosted PIs. • **Edoxaban:** – For stroke prevention in patients with nonvalvular atrial fibrillation: No dose adjustments are necessary. – For DVT and PE: Administer edoxaban 30 mg once daily. • **LMWHs:** No dose adjustments are necessary.
• Efavirenz (EFV) • Etravirine (ETR) • Nevirapine (NVP)	• **Warfarin:** Metabolism of warfarin could potentially increase (or more rarely) decrease). • **NOACs, LMWHs:** EFV may reduce levels of NOACs metabolized via CYP3A4.	• Use cautiously with warfarin; if use is necessary, increase INR monitoring. – If INR increases, decrease warfarin dose. – If INR decreases, increase warfarin dose slowly. • **NOACs, LMWHs:** Avoid NOACs with EFV and NVP; use alternative HIV regimen.
Lenacapavir (LEN)	DOAC levels potentially increase due to effect on CYP3A4 and P-gP.	• No dose adjustment needed; monitor for increased risk of bleeding. • Refer to DOAC prescribing information for use with moderate CYP3A4 and P-gP inhibitors.
Abbreviations: ARV, antiretroviral; COBI, cobicistat; CrCl, creatinine clearance; CYP, cytochrome P450; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; INR, international normalized ratio; NRTI, nucleoside reverse transcriptase inhibitor; PE, pulmonary embolism; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir.		

Table 22: Antiplatelet Drugs (also see drug package inserts)		
→ Adenosine phosphate receptor inhibitors, cilostazol, dipyridamole		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR)	No significant interactions are expected.	No dose adjustments are necessary.

Table 22: Antiplatelet Drugs (also see drug package inserts)		
→ Adenosine phosphate receptor inhibitors, cilostazol, dipyridamole		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Elvitegravir (EVG), boosted	• **Cilostazol** may be metabolized by CYP3A; COBI-boosted EVG can increase concentrations of this drug. • **Ticagrelor:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted EVG significantly decreases production of clopidogrel's active metabolite. • **Prasugrel:** Boosted EVG decreases prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Cilostazol:** Monitor for antiplatelet effect. May be necessary to use alternative antiplatelet drug or alternative ARV. • **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.
Boosted PIs	• **Cilostazol** is metabolized by CYP3A; 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:** Strong CYP3A4 inhibitors may increase ticagrelor exposure. • **Clopidogrel:** Boosted PIs may decrease production of clopidogrel's active metabolite. • **Prasugrel:** Boosted PIs may decrease prasugrel's active metabolite; however, adequate antiplatelet activity is maintained. • **Vorapaxar:** Increased vorapaxar levels are expected.	• **Cilostazol:** Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use alternative ARV or boost with COBI if necessary. • **Ticagrelor:** To avoid increased bleeding risk, do not use ticagrelor with strong CYP3A inhibitors, particularly COBI and RTV. • **Clopidogrel, vorapaxar:** Do not coadminister. • **Prasugrel:** No dose adjustments are necessary.
• Efavirenz (EFV) • Etravirine (ETR)	• **Cilostazol:** EFV and ETR may reduce cilostazol concentrations. • **Dipyridamole:** EFV and ETR may induce UGT enzymes, which are responsible for metabolism. • **Ticagrelor, clopidogrel:** EFV and ETR reduce ticagrelor concentrations and conversion of clopidogrel to its active metabolite. • **Vorapaxar:** When coadministered with ETR, vorapaxar levels expected to be reduced.	• **Cilostazol:** Monitor for antiplatelet effect; may be necessary to use alternative antiplatelet drug or alternative ARV. • **Dipyridamole:** Monitor for antiplatelet effect; use alternative ARV if necessary. • **Ticagrelor, clopidogrel:** Use with EFV or ETR may reduce antiplatelet effect; monitor closely for efficacy and use alternative ARV if necessary. • **Prasugrel:** When coadministered with ETR, no dose adjustments are necessary. • **Vorapaxar:** No data available.
Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir; UGT, uridine diphosphate glucuronosyltransferase.		

Table 23: Statins (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR)	No significant interactions are expected.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	• **Simvastatin, lovastatin:** Boosted EVG greatly increases concentrations. • **Atorvastatin, rosuvastatin:** Boosted EVG may moderately increase concentrations. • **Fluvastatin:** Interaction has not been studied, but potential for moderate increase is possible. • **Pitavastatin, pravastatin:** Although moderate increases are possible, low doses are considered safe when used with boosted EVG.	• **Simvastatin, lovastatin:** Concomitant use is contraindicated; may increase muscle aches and risk of rhabdomyolysis; choose alternative statin • **Atorvastatin:** – Avoid concomitant use of COBI and atorvastatin. – If atorvastatin use is necessary, do not exceed 20 mg per day. • **Rosuvastatin:** Use lowest effective dose and titrate carefully to achieve clinical effect; monitor closely for adverse effects. • **Fluvastatin:** Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose. • **Pitavastatin, pravastatin:** Use lowest effective doses of pitavastatin and pravastatin; monitor for signs of toxicity, including myopathy.
Atazanavir (ATV), boosted	• **Simvastatin, lovastatin:** Boosted ATV greatly increases concentrations. • **Atorvastatin, rosuvastatin:** Boosted ATV may moderately increase concentrations. • **Fluvastatin:** Interaction has not been studied, but potential for moderate increase is possible. • **Pitavastatin, pravastatin:** Although moderate increases are possible, low doses are considered safe when used with boosted PIs.	• **Simvastatin, lovastatin:** Concomitant use is contraindicated due to potential for myopathy, including rhabdomyolysis. Consider using low doses of alternative statins less likely to be affected by boosted ATV use. • **Atorvastatin:** – Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. – Do not coadminister with COBI-boosted ATV due to increased risk of rhabdomyolysis and myopathy. • **Rosuvastatin:** – Use with lowest effective doses; monitor closely for safety and efficacy before increasing statin dose. – If use is necessary, do not exceed 10 mg per day. • **Fluvastatin:** Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose. • **Pitavastatin:** Use at lowest effective dose. • **Pravastatin:** If use is necessary, use lowest effective dose, and monitor for signs of toxicity.

Table 23: Statins (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Darunavir (DRV), boosted	• **Simvastatin, lovastatin:** Boosted DRV greatly increases concentrations. • **Atorvastatin, rosuvastatin:** Boosted DRV may moderately increase concentrations. • **Fluvastatin:** Interaction has not been studied, but potential for moderate increase is possible. • **Pravastatin:** Although moderate increases are possible, low doses are considered safe when used with boosted PIs. • **Pitavastatin:** – Boosted DRV is less likely to interact compared to other statins. – When administered with RTV-boosted DRV, pitavastatin AUC is decreased by 26%.	• **Simvastatin, lovastatin:** – Concomitant use is contraindicated due to potential for myopathy, including rhabdomyolysis. – Consider using low doses of alternative statins less likely to be affected by boosted DRV. • **Atorvastatin:** – When administered with RTV-boosted DRV, use lowest effective dose; do not exceed 20 mg daily. – If concomitant use is necessary, monitor closely for signs of myopathy and rhabdomyolysis. • **Rosuvastatin:** – When possible, avoid concomitant use. – If use is necessary, start with 10 mg per day; dose should not exceed 20 mg per day. • **Fluvastatin:** Do not coadminister. If use is required, use lowest effective dose; monitor closely for safety and efficacy before increasing statin dose. • **Pitavastatin:** No dose adjustments are necessary. • **Pravastatin:** If use is necessary, use lowest effective dose and monitor for signs of toxicity.
• Efavirenz (EFV) [a] • Etravirine (ETR)	• **Simvastatin, lovastatin:** EFV and ETR may decrease concentrations. • **Atorvastatin, pravastatin, fluvastatin:** EFV and ETR may modestly reduce concentrations. • **Pitavastatin, rosuvastatin:** No significant interactions are 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 for cholesterol-lowering effect of statins. May require increased dose. • **Pitavastatin, rosuvastatin:** No dose adjustments are necessary.
Fostemsavir (FTR)	**Atorvastatin, fluvastatin, pitavastatin, rosuvastatin, simvastatin:** Levels may increase with concurrent use of FTR.	**All statins:** Use lowest possible statin starting dose; monitor for statin-associated adverse effects.
Lenacapavir (LEN)	**Lovastatin, simvastatin, lomitapide:** Moderate inhibition of CYP3A4 and P-gP potentially increases levels.	• **Simvastatin, lovastatin:** Initiate at lowest dose and titrate to achieve clinical effect; monitor closely for statin toxicity. • **Lomitapide:** Concomitant use is contraindicated.

Abbreviations: AUC, area under the curve; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir.

Note:

a. RTV-boosted PIs and EFV are known to cause metabolic dysfunction, which may increase blood cholesterol levels.

Table 24: Antidiabetic Drugs (also see drug package inserts)		
→ Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase IV (DPP-4) inhibitors, glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs [a] • Cabotegravir (CAB) • Raltegravir (RAL) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions are expected.	No dose adjustments are necessary.
• Dolutegravir (DTG) • Bictegravir (BIC)	• **Metformin:** – DTG inhibits renal OCT2, MATE1, and MATE2, which are involved in metformin elimination. – BIC inhibits renal OCT2 and MATE1, which are involved in metformin elimination. • **Sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors:** No significant interactions are expected.	• **Metformin:** – Administer at lowest dose possible to achieve glycemic control; monitor for adverse effects. – When coadministered with DTG, titrate to achieve clinical effect but do not exceed 1,000 mg daily; monitor for adverse effects, including lactic acidosis. – When coadministered with BIC, drug interaction studies suggest that prospective dose adjustment of metformin is not required. • **Sulfonylureas, TZDs, DPP-4 inhibitors, GLP-1 agonists, SGLT-2 inhibitors:** No dose adjustments are necessary.
Elvitegravir (EVG), boosted	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** levels may be increased via CYP3A inhibition. • **Canagliflozin** exposure could be reduced through EVG induction of UGT enzymes. • **TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No significant interactions reported.	• **Metformin:** Monitor for metformin-related adverse effects; 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 for glycemic control. – If glycemic control is inadequate in patient taking EVG/RTV, consider increasing canagliflozin dose to 300 mg per day if patient is tolerating 100 mg and has GFR >60 mL/min/1.73 m^2. • **TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No dose adjustments are necessary.
Boosted PIs [b]	• **Metformin:** COBI is known to inhibit MATE1, which is involved in metformin elimination, thus increasing metformin concentrations. • **Glyburide** is mainly metabolized by CYP3A; thus, concentrations are increased by inhibitors of this enzyme. • **Saxagliptin** is a substrate of CYP3A, so levels may be increased. • **Canagliflozin:** Use with ATV or DRV may decrease canagliflozin concentrations. • **GLP-1 agonists:** Caution is needed when coadministering ATV or DRV and GLP-1 agonists, such as exenatide, due to their potential to inhibit gastric secretion, thereby reducing PI absorption. Furthermore, exenatide may slow gastric emptying. • **TZDs, exenatide:** No significant interactions are expected.	• **Metformin:** Monitor for metformin-related adverse effects; 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:** If patient already tolerates canagliflozin 100 mg daily, increase dose to 200 mg daily. If patient already tolerates canagliflozin 200 mg daily and requires additional glycemic control, the management strategy should be based on renal function. – In patients with eGFR ≥60 mL/min/1.73 m^2, canagliflozin dose may be increased to 300 mg daily. – In patients with eGFR <60 mL/min/1.73 m^2, consider adding another antihyperglycemic agent. • **GLP-1 agonists:** May recommend ATV or DRV dosing 4 hours before. **TZDs:** No dose adjustments are necessary.

Table 24: Antidiabetic Drugs (also see drug package inserts)		
→ Metformin, sulfonylureas, thiazolidinediones (TZDs), dipeptidyl peptidase IV (DPP-4) inhibitors, glucosidase inhibitors, glucagon-like peptide 1 (GLP-1) agonists, sodium-glucose cotransporter 2 (SGLT-2) inhibitors		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
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 RPV absorption. Furthermore, exenatide may slow gastric emptying. • **Metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors:** No significant interactions reported.	• **GLP-1 agonists:** May recommend RPV dosing 4 hours before. • **Metformin, sulfonylureas, TZDs, DPP-4 inhibitors, SGLT-2 inhibitors:** No dose adjustments are necessary.
• Efavirenz (EFV) • Etravirine (ETR)	• **Pioglitazone:** EFV may increase concentrations through CYP2C8 inhibition. No significant interactions are expected. • **Saxagliptin, sitagliptin:** EFV and ETR may decrease concentrations. • **Metformin, sulfonylureas, TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No significant interactions reported.	• **Pioglitazone:** Monitor for signs of adverse effects with EFV; decrease dose if necessary. • **Saxagliptin, sitagliptin:** Monitor for efficacy; if necessary, increase dose of DPP-4 inhibitor. • **Metformin, sulfonylureas, TZDs, GLP-1 agonists, SGLT-2 inhibitors:** No dose adjustments are necessary.
Abbreviations: ATV, atazanavir; COBI, cobicistat; CYP, cytochrome P450; GFR, glomerular filtration rate; MATE, multidrug and toxin extrusion; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir; TDF, tenofovir disoproxil fumarate. **Notes:** a. 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. b. RTV-boosted PIs are known to cause metabolic abnormalities, which may increase blood glucose and decrease insulin sensitivity.		

Table 25: Acid-Reducing Agents (also see drug package inserts)		
→ Proton pump inhibitors (PPIs), histamine-2 receptor agonists (H2RAs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Raltegravir (RAL) • Elvitegravir (EVG), boosted • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR) • Fostemsavir (FTR)	No clinically significant interactions reported.	No dose adjustments are necessary.

Table 25: Acid-Reducing Agents (also see drug package inserts)		
→ Proton pump inhibitors (PPIs), histamine-2 receptor agonists (H2RAs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Atazanavir (ATV), unboosted	• ATV requires acidic gastric pH for absorption, and acid-reducing agents interfere with ATV absorption. • **PPIs** markedly reduce ATV concentration and AUC. • **H2RAs** reduce ATV absorption.	**PPIs:** Do not coadminister with *unboosted* ATV if it is possible to use an alternative acid-reducing agent, alternative PI, or boosted ATV. • **Timing:** Administer ≥12 hours before RTV- or COBI-boosted ATV. • **ART-naive:** If use cannot be avoided, do not exceed omeprazole 20 mg per day or equivalent (e.g., pantoprazole 40 mg; lansoprazole 30 mg; esomeprazole 20 mg). • **ART-experienced:** Consult with experienced HIV care provider or GI specialist. **H2RAs:** • **ART-naive:** Administer ATV 400 mg (unboosted) with food at least 2 hours before or 10 hours after. • **ART-experienced:** Do not use unboosted ATV + famotidine in combination. • Do not exceed dose equivalent to famotidine 20 mg of any H2RA. Total daily dose should not exceed 40 mg famotidine or equivalent, e.g., ranitidine or nizatidine 150 mg (300 mg daily).
Atazanavir (ATV), boosted	• ATV requires acidic gastric pH for absorption, and acid-reducing agents interfere with ATV absorption. • **PPIs** markedly reduce ATV concentration and AUC. • **H2RAs** reduce ATV absorption.	**PPIs:** • **Timing:** Administer ≥12 hours before RTV- or COBI-boosted ATV. • **ART-naive:** Do not exceed omeprazole 20 mg per day or equivalent (pantoprazole 40 mg; lansoprazole 30 mg; esomeprazole 20 mg). • **ART-experienced:** Not recommended; consultation with experienced HIV care provider or GI specialist is recommended before prescribing PPI. **H2RAs:** • **ART-naive:** Administer ATV 300 mg + RTV 100 mg simultaneously with or ≥10 hours after H2RA. – If patient is *not* taking TFV: Do not exceed famotidine 20 mg twice per day (40 mg daily) or equivalent, e.g., ranitidine or nizatidine 150 mg twice per day (300 mg daily). – If patient *is* taking TFV: Do not exceed famotidine 40 mg twice per day (80 mg daily) or equivalent, e.g., ranitidine or nizatidine 300 mg twice per day (600 mg daily).

Table 25: Acid-Reducing Agents (also see drug package inserts)		
→ Proton pump inhibitors (PPIs), histamine-2 receptor agonists (H2RAs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
		• **ART-experienced:** Administer ATV 300 mg + COBI 150 mg or RTV 100 mg simultaneously with or ≥10 hours after H2RA. • **Pregnancy:** In trimesters 2 and 3, increase dose of ATV to 400 mg per day with RTV 100 mg per day. (Volume of distribution increases as duration of pregnancy increases, which can reduce ATV levels, especially during second and third trimesters of pregnancy.) – H2RA use is contraindicated if pregnant patient takes TFV + boosted ATV during pregnancy. – If patient is pregnant and is taking TFV, ATV is dosed at 400 mg per day with RTV 100 mg per day; unboosted ATV is not recommended.
Darunavir (DRV)/ritonavir (RTV)	No clinically significant interactions reported.	**Omeprazole:** Do not exceed omeprazole 40 mg per day.
Rilpivirine (RPV)	• PPIs and H2RAs inhibit gastric acid secretion by proton pumps, thereby increasing gastric pH. • Oral RPV requires acidic environment for optimal absorption. • **H2RAs:** Concomitant use may decrease RPV absorption.	**PPIs:** • Concurrent use of PPIs with *oral* RPV is contraindicated. • Use of PPIs with *injectable* RPV is acceptable. **H2RAs:** • Administer H2RA at least 12 hours before or 4 hours after. • Use lowest effective dose. • Administer with food. • Use of H2RAs with *injectable* RPV is acceptable.
Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; AUC, area under the curve; COBI, cobicistat; GI, gastrointestinal; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PK, pharmacokinetic; TFV, tenofovir.		

Table 26: Polyvalent Cations (also see drug package inserts)		
→ Supplements, antacids, and laxatives that contain aluminum, calcium, magnesium, zinc, and iron		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Darunavir (DRV), boosted or unboosted • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR) • Fostemsavir (FTR)	No clinically significant interactions reported.	No dose adjustments are necessary.

Table 26: Polyvalent Cations (also see drug package inserts)		
→ Supplements, antacids, and laxatives that contain aluminum, calcium, magnesium, zinc, and iron		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
All INSTIs	INSTIs form complexes with cations, resulting in reduced concentrations of both INSTIs and cations. For specific recommendations, see individual INSTIs below.	**Any polyvalent cation:** If coadministration is necessary, administer at least 2 hours before or at least 6 hours after; monitor for virologic efficacy.
Dolutegravir (DTG)	DTG chelates with cations, forming insoluble compounds that inactivate both drugs.	• **Divalent and trivalent cations (aluminum, magnesium, calcium, zinc, etc.):** Administer DTG 2 hours before or 6 hours after. • **Calcium- and iron-containing supplements:** DTG and supplement may be used concomitantly if taken with food. • **Iron salts:** – Administer DTG 2 hours before or 6 hours after. – DTG and iron salts may be used concomitantly if taken with food.
Bictegravir (BIC)	BIC can chelate with cations, reducing absorption of both drugs.	• **Aluminum/magnesium-containing antacids:** Administer at least 6 hours before or 2 hours after BIC. • **Calcium-containing antacids:** – Administer BIC and antacids together with food. – Do not coadminister BIC simultaneously with antacids on empty stomach. • **Calcium- or iron-containing supplements:** – If taken with food, BIC can be taken at same time. – If not taken with food, these supplements should be administered as with antacids.
Elvitegravir (EVG), boosted	EVG chelates with polyvalent cations, which may reduce absorption of both agents.	• **Aluminum-, magnesium-, and/or calcium-containing antacids:** When taken with EVG, separate doses by at least 2 hours. • **Other polyvalent cations:** Administer at least 2 hours before or 6 hours after EVG.
Raltegravir (RAL)	RAL chelates with cations, forming insoluble compounds that inactivate both drugs.	• **Aluminum-magnesium hydroxide antacids:** Concomitant use is contraindicated; use alternative acid-reducing agent. • **Calcium carbonate antacids:** – RAL HD once per day is *contraindicated.* – RAL 400 mg twice per day: No dose adjustment or separation is necessary. • **Other polyvalent cations:** Administer at least 2 hours before or 6 hours after.

Table 26: Polyvalent Cations (also see drug package inserts)		
→ Supplements, antacids, and laxatives that contain aluminum, calcium, magnesium, zinc, and iron		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Atazanavir (ATV), boosted or unboosted	**Antacids:** ATV requires acidic gastric pH for absorption; acid-reducing agents interfere with ATV absorption.	**Antacids or buffered medications:** Administer ATV at least 2 hours before or 1 to 2 hours after.
Cabotegravir (CAB)	**Antacids containing polyvalent cations (i.e., aluminum or magnesium hydroxide, calcium carbonate):** Antacids increase gastric pH, and CAB requires acidic environment for optimal absorption. Concomitant use may decrease CAB absorption.	**Antacids containing polyvalent cations (i.e., aluminum or magnesium hydroxide, calcium carbonate):** • Administer antacid products at least 2 hours before or 4 hours after *oral* CAB. • No effect of antacid use is expected on *injectable* CAB.
Rilpivirine (RPV)	**Antacids:** • Antacids increase gastric pH. • RPV requires acidic environment for optimal absorption. • Concomitant use may decrease RPV absorption.	**Antacids:** Administer antacids 2 hours before or 4 hours after.
Abbreviations: ARV, antiretroviral; INSTI, integrase strand transfer inhibitor; NRTI, nucleoside reverse transcriptase inhibitor.		

Table 27: Asthma and Allergy Medications (also see drug package inserts)		
→ Albuterol, tiotropium, aclidinium, montelukast, loratadine, cetirizine, diphenhydramine		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Elvitegravir (EVG), boosted • Boosted PIs • Rilpivirine (RPV) • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR)	No significant interactions reported.	No dose adjustments are necessary.
Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.		

Table 28: Long-Acting Beta Agonists (LABAs; also see drug package inserts)		
→ Salmeterol, formoterol, etc.		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR)	No significant interactions reported.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	CYP3A inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • **Salmeterol:** Monitor for increased risk of cardiovascular-related adverse events.
Boosted PIs	CYP3A4 inhibition increases plasma concentrations of these agents.	• Concomitant use is contraindicated unless benefits outweigh possible risks; consider alternative ARV. • If coadministration is necessary, monitor frequently for QT prolongation, palpitations, and sinus tachycardia. • Boosted PIs may also increase QT prolongation.
Rilpivirine (RPV)	RPV and drugs from LABA class may both theoretically increase QT interval, especially at high doses.	• No dose adjustments are necessary. • Do not use more LABA than recommended; this can increase risk of QT prolongation.
Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.		

Table 29: Inhaled and Injected Corticosteroids (also see drug package inserts)		
→ Fluticasone, triamcinolone, budesonide, and methyl prednisone [a]		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions reported.	No dose adjustments are necessary.

Table 29: Inhaled and Injected Corticosteroids (also see drug package inserts)		
→ Fluticasone, triamcinolone, budesonide, and methyl prednisone [a]		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Elvitegravir (EVG), boosted	Risk of Cushing's syndrome occurs when boosted EVG is coadministered with the following corticosteroids: • Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone • Systemic: Betamethasone, budesonide, prednisolone, prednisone, dexamethasone • Injectable: Betamethasone, triamcinolone	• **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Do not coadminister unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Betamethasone, triamcinolone (injectable):** Do not coadminister unless potential benefits outweigh risk. • **Dexamethasone (systemic):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid. Beclomethasone and flunisolide are likely safe alternatives.
Boosted PIs	• Boosted PIs are strong inhibitors of CYP3A, and many corticosteroids are substrates of these enzymes. • Risk of Cushing's syndrome occurs when boosted PIs are coadministered with the following corticosteroids: – Intranasal or inhaled: Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone – Systemic: Betamethasone, budesonide, dexamethasone – Injectable: Betamethasone, triamcinolone	• **Use beclomethasone if possible.** Because this agent is less likely to be affected by boosted PIs, it is less likely to cause symptoms of Cushing's syndrome and other systemic corticosteroid adverse effects. • **Fluticasone, mometasone, ciclesonide, budesonide, triamcinolone (intranasal or inhaled):** Do not coadminister unless potential benefits outweigh risk; consider alternative corticosteroid (e.g., beclomethasone). • **Betamethasone, budesonide (systemic):** Do not coadminister unless potential benefits outweigh risk. • **Prednisolone, prednisone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; if use cannot be avoided, use for shortest effective duration. • **Betamethasone, triamcinolone (injectable):** Concomitant use is contraindicated unless potential benefits outweigh risk. • **Dexamethasone (systemic):** Concomitant use is contraindicated unless potential benefits outweigh risk; consider alternative corticosteroid. Consider beclomethasone or flunisolide as safe alternatives.

Table 29: Inhaled and Injected Corticosteroids (also see drug package inserts)		
→ Fluticasone, triamcinolone, budesonide, and methyl prednisone [a]		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Rilpivirine (RPV)	**Dexamethasone** is a CYP3A inducer, which is primarily responsible for metabolism of RPV.	**Dexamethasone (systemic):** • Concomitant use is contraindicated; consider alternative steroids. • If using more than a single oral or IM dose, consider an alternative NNRTI after consultation with experienced HIV care provider (see package inserts for Cabenuva and Edurant).
• Efavirenz (EFV) • Etravirine (ETR)	Coadministration may reduce corticosteroid concentrations.	**Dexamethasone (systemic):** Consider alternative corticosteroid for long-term use; if benefits of use outweigh risks, monitor for virologic response.
Lenacapavir (LEN)	• Moderate inhibition of CYP3A4 and P-gP potentially increases corticosteroid concentrations and the related risk of Cushing's syndrome and adrenal suppression. • **Dexamethasone (systemic):** Decreased LEN levels expected with dexamethasone doses >16 mg/day.	• **Dexamethasone, hydrocortisone (systemic):** Initiate at lowest dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Dexamethasone (systemic):** Do not coadminister with dexamethasone doses >16 mg/day.

Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor.

Note:

a. Short-term therapy with oral prednisone or prednisolone is not expected to cause significant drug-drug interactions with ARVs in most cases; however, increased monitoring may be required if a patient is taking an ARV, 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 for 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 30: Antidepressants (also see drug package inserts)		
→ Including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), trazodone, bupropion, and monoamine oxidase inhibitors (MAOIs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR)	No significant interactions reported.	No dose adjustments are necessary.

Table 30: Antidepressants (also see drug package inserts)		
→ Including selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), trazodone, bupropion, and monoamine oxidase inhibitors (MAOIs)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• Elvitegravir (EVG), boosted • Boosted PIs	**Trazodone:** Concomitant use may increase trazodone concentrations.	**Trazodone:** Monitor for antidepressant and/or sedative effects.
• Efavirenz (EFV) • Etravirine (ETR)	• **Trazodone:** EFV and ETR may decrease trazodone concentrations. • **Bupropion:** – EFV may induce CYP2B6, the enzyme that is primarily responsible for bupropion metabolism. – No significant interactions are expected with ETR.	• **Trazodone:** Monitor for antidepressant and/or sedative effects. • **Bupropion:** Monitor for clinical effect and increase as needed, but do not exceed recommended maximum dose.
Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.		

Table 31: Benzodiazepines [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions reported.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	• **Boosting with cobicistat:** May increase benzodiazepine concentrations via CYP3A4 inhibition. • **Midazolam, triazolam:** Levels likely to be increased by COBI-boosted EVG	• **Alprazolam, clonazepam, diazepam:** Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam); if used, administer lowest effective dose; monitor closely for adverse effects. • **Midazolam:** – Oral: Concomitant use is contraindicated. – Parenteral: Administer in closely monitored setting. Consider dose reduction, especially if >1 dose is administered. • **Triazolam:** Concomitant use is contraindicated.
Boosted PIs	• **Alprazolam:** Boosted ARVs may increase alprazolam concentrations via CYP3A4 inhibition. • **Diazepam:** CYP3A4 inhibition may reduce metabolism of diazepam.	• Consider alternative benzodiazepine (e.g., lorazepam, oxazepam, temazepam). If used, administer lowest effective dose; monitor closely for adverse effects. • **Diazepam:** Monitor for excess sedation.

Table 31: Benzodiazepines [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Efavirenz (EFV)	**Alprazolam, diazepam:** EFV may reduce alprazolam and diazepam concentrations.	• **Alprazolam:** Monitor for benzodiazepine withdrawal if patient starts taking EFV. • **Alprazolam, clonazepam, diazepam:** Titrate slowly to achieve clinical effect; monitor for benzodiazepine efficacy.
Etravirine (ETR)	**Alprazolam, diazepam:** ETR may reduce alprazolam and diazepam concentrations.	**Alprazolam:** Monitor for benzodiazepine withdrawal.
Lenacapavir (LEN)	**Midazolam (oral), triazolam:** Moderate inhibition of CYP3A4 and P-gP potentially increases sedative levels.	**Midazolam (oral), triazolam:** Use with caution; monitor for excess sedation.
Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor. **Note:** a. Lorazepam, oxazepam, and temazepam do not interact clinically with and do not require dose adjustments when coadministered with ARVs.		

Table 32: Sleep Medications (also see drug package inserts)		
→ Non-benzodiazepine "Z-drugs," melatonin, ramelteon, suvorexant		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions reported.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	• Suvorexant is a CYP3A substrate. • COBI inhibits CYP3A. • **Zolpidem, eszopiclone:** These drugs are CYP3A substrates and may be increased by strong inhibitors of this enzyme.	• **Suvorexant:** Avoid concomitant use or use lowest effective dose (may increase somnolence, dizziness, and risk of sleep hangover). • **Zolpidem:** Administer lowest possible dose of zolpidem; monitor for adverse effects. • **Eszopiclone:** Start with 1 mg of eszopiclone at bedtime and titrate slowly to achieve clinical effect.
Boosted PIs	• **Zolpidem, suvorexant:** Boosted PIs may increase zolpidem and suvorexant concentrations. • **Ramelteon:** RTV-boosted PIs may reduce ramelteon efficacy.	• **Zolpidem:** Administer lowest effective dose; monitor for adverse effects, including excess sedation. • **Eszopiclone:** Start with 1 mg per day and titrate slowly to achieve clinical effect; monitor for adverse effects, including excess sedation. • **Suvorexant:** Coadministration is not recommended (may increase somnolence, dizziness, and risk of sleep hangover); use alternative sleep medication or ARV. • **Ramelteon:** Monitor for efficacy in cigarette smokers.

Table 32: Sleep Medications (also see drug package inserts)		
→ Non-benzodiazepine "Z-drugs," melatonin, ramelteon, suvorexant		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• Efavirenz (EFV) • Etravirine (ETR)	**Zolpidem:** EFV and ETR may reduce zolpidem concentrations.	• **Zolpidem, eszopiclone:** Monitor for efficacy; no dose adjustments are 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 33: Antipsychotics [a] (also see drug package inserts)		
→ First-generation, second-generation, atypical		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Doravirine (DOR)	No significant interactions are expected.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	Several antipsychotic agents are substrates of CYP3A, and inhibitors of this enzyme may increase their concentrations.	• **Quetiapine:** Reduce dose to 1/6 if initiating ART in patients on stabilized quetiapine. • **All other antipsychotics:** Use at lowest dose possible in patients taking boosted ARVs; monitor for adverse effects.
Boosted PIs	• **Haloperidol:** Boosted PIs may moderately increase haloperidol concentrations. • **Aripiprazole, brexpiprazole:** RTV-boosted PIs may increase aripiprazole and brexpiprazole levels. • **Risperidone:** Boosted PIs may moderately increase risperidone levels. • **Clozapine:** Interaction has not been studied but boosted PIs may theoretically increase clozapine concentrations, increasing risk of adverse effects. • **Iloperidone, lumateperone, lurasidone, cariprazine:** Levels are likely to be increased by all PIs, whether boosted or not.	• **Quetiapine:** – Patients on stabilized quetiapine: Reduce dose to 1/6 if initiating ART; monitor for QT prolongation. – Patients stabilized on boosted PI: Use lowest dose and titrate slowly to achieve clinical effect; monitor for QT prolongation. • **Lurasidone:** No data available. Avoid coadministration; consider alternative antipsychotic or ARV agent. • **Haloperidol:** Monitor for QT prolongation. • **Iloperidone:** Decrease iloperidone dose by 50%. • **Aripiprazole:** Initiate at 25% of standard starting dose and titrate slowly to achieve clinical effect; monitor carefully for efficacy and adjust dose as necessary.

Table 33: Antipsychotics [a] (also see drug package inserts)		
→ First-generation, second-generation, atypical		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
		• **Brexpiprazole:** Administer at 50% of brexpiprazole dose and adjust dose as necessary. • **Lumateperone:** Do not coadminister. • **Pimozide:** Concomitant use is contraindicated. • **Risperidone:** Initiate at low dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Ziprasidone:** Monitor for adverse effects, including QTc prolongation. • **Cariprazine:** Consult DHHS guideline for full dosing recommendations and clinical comments [DHHS(c) 2021]. • **Clozapine:** Monitor carefully for clozapine-related adverse effects.
Ritonavir (RTV)	• **Haloperidol:** Boosted PIs may moderately increase haloperidol concentrations. • **Aripiprazole, brexpiprazole:** RTV-boosted PIs may increase aripiprazole and brexpiprazole levels. • **Risperidone:** Boosted PIs may moderately increase risperidone levels. • **Clozapine:** Interaction has not been studied but RTV may theoretically increase clozapine concentrations, increasing risk of adverse effects. • **Iloperidone, lumateperone, lurasidone, cariprazine:** Levels are likely to be increased by all PIs, whether boosted or not.	• **Quetiapine:** – Patients on stabilized quetiapine: If initiating ART, reduce dose to 1/6; monitor for QT prolongation. – Patients stabilized on boosted PI: Use lowest dose and titrate slowly to achieve clinical effect; monitor for QT prolongation. • **Lurasidone:** No data available. Avoid coadministration; consider alternative antipsychotic or ARV agent. • **Haloperidol:** Monitor for QT prolongation. • **Iloperidone:** Decrease iloperidone dose by 50%. • **Aripiprazole:** Initiate at 25% of standard starting dose and titrate slowly to achieve clinical effect; monitor carefully and adjust dose as necessary. • **Brexpiprazole:** Administer at 50% of brexpiprazole dose and adjust dose as necessary. • **Lumateperone:** Do not coadminister. • **Pimozide:** Concomitant use is contraindicated. • **Risperidone:** Initiate at low dose and titrate slowly to achieve clinical effect; monitor for adverse effects. • **Ziprasidone:** Monitor for adverse effects, including QTc prolongation. • **Cariprazine:** Consult DHHS guideline for full dosing recommendations and clinical comments [DHHS(c) 2021]. • **Clozapine:** Monitor carefully for clozapine-related adverse effects.

Table 33: Antipsychotics [a] (also see drug package inserts)		
→ First-generation, second-generation, atypical		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Atazanavir (ATV), unboosted	**Lurasidone:** ATV decreases lurasidone metabolism via CYP3A.	**Lurasidone:** Decrease lurasidone dose by 50%; monitor for adverse effects, including QT prolongation.
Rilpivirine (RPV)	No significant interactions reported.	No dose adjustments are necessary, but avoid excess doses of either antipsychotic or RPV because excess doses of both drugs may increase risk of QT prolongation.
Efavirenz (EFV)	• **Quetiapine:** EFV may reduce quetiapine concentrations. • **Aripiprazole, brexpiprazole:** EFV may decrease aripiprazole and brexpiprazole concentrations. • **Risperidone, olanzapine:** EFV may decrease risperidone and olanzapine efficacy.	**Quetiapine, aripiprazole, brexpiprazole, risperidone, olanzapine:** Titrate slowly to achieve clinical effect; monitor for efficacy and adverse effects.
Etravirine (ETR)	• **Aripiprazole, brexpiprazole:** ETR may decrease aripiprazole and brexpiprazole concentrations. • **Risperidone:** ETR may decrease risperidone efficacy.	**Aripiprazole, brexpiprazole, risperidone:** Titrate slowly to achieve clinical effect; monitor for efficacy and adverse effects.
Fostemsavir (FTR)	FTR may prolong QT.	Use caution when combining FTR with other medications known to prolong QT interval.
Lenacapavir (LEN)	**Pimozide:** Moderate inhibition of P-gP potentially increases pimozide levels.	**Pimozide:** Do not coadminister.

Abbreviations: ART, antiretroviral therapy; ARV, antiretroviral; CYP, cytochrome P450; DHHS, U.S. Department of Health and Human Services; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor.

Note:

a. Coadministration of antipsychotics and ARVs may result in QT prolongation; monitor closely.

Table 34: Anticonvulsants [a] (also see drug package inserts)		
→ Including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine, valproic acid, gabapentin, topiramate, zonisamide		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Tenofovir disoproxil fumarate (TDF)	• **Zonisamide:** TDF may increase concentration of zonisamide. • **Topiramate:** No significant interactions reported.	• **Zonisamide:** When using with TDF, monitor for adverse effects. • **Topiramate:** When using with TDF, monitor renal function (topiramate may cause kidney stones; TDF is associated with renal toxicity).
Tenofovir alafenamide (TAF)	Coadministration with strong CYP3A inducers (phenytoin, phenobarbital, etc.) may decrease TAF concentrations.	Coadministration with strong CYP3A inducers is not recommended because it may reduce TAF concentrations.
Other NRTIs	No interactions reported.	No dose adjustments are necessary.

Table 34: Anticonvulsants [a] (also see drug package inserts)		
→ Including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine, valproic acid, gabapentin, topiramate, zonisamide		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Cabotegravir (CAB)	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Coadministration may significantly reduce CAB concentrations through induction of CYP450, UGT1A, and/or P-gP system. • **Gabapentin, topiramate, zonisamide:** No significant interactions are expected.	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Concomitant use is contraindicated. • **Gabapentin, topiramate, zonisamide:** No dose adjustments are necessary.
• Dolutegravir (DTG) • Bictegravir (BIC)	Coadministration with strong CYP3A inducers (phenytoin, phenobarbital, etc.) may decrease DTG or BIC concentrations.	No dose adjustments necessary.
Raltegravir (RAL)	Coadministration with strong UGT1A1 inducers (phenytoin, phenobarbital, etc.) may decrease RAL concentrations.	Coadministration with strong UGT1A1 inducers is not recommended.
Elvitegravir (EVG), boosted	**Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin:** Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system.	**Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** • Coadministration is not recommended; use alternative anticonvulsant. • If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. • Perform TDM.
Ritonavir (RTV)	• **Phenytoin:** Concurrent use may reduce RTV and phenytoin concentrations, resulting in loss of viral suppression and seizure control. • **Lamotrigine:** RTV-boosted ARVs may reduce lamotrigine efficacy. • **Valproic acid:** RTV may reduce valproic acid concentrations.	• **Phenytoin:** – Coadministration is not recommended; use alternative anticonvulsant. – If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. – Perform TDM. • **Lamotrigine:** Titrate slowly to achieve clinical effect; monitor for efficacy. • **Valproic acid:** Consider using COBI when ARV boosting is required.
Boosted PIs	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Coadministration may significantly reduce concentrations of ARVs through induction of CYP450 system. • **Zonisamide:** CYP3A4 inhibition may increase zonisamide concentrations.	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** – Coadministration is not recommended; use alternative anticonvulsant. – If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. – Perform TDM. • **Zonisamide:** Monitor for efficacy and adverse effects; adjust dose as needed.
NNRTIs	**Carbamazepine, oxcarbazepine, phenobarbital, and phenytoin:** Coadministration may significantly reduce ARV concentrations through induction of CYP450 system.	**Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** • Coadministration is not recommended; use alternative anticonvulsant. • If benefit of use outweighs risk, monitor carefully for efficacy and toxicity. • Perform TDM if use cannot be avoided.

Table 34: Anticonvulsants [a] (also see drug package inserts)		
→ Including phenytoin, phenobarbital, carbamazepine, oxcarbazepine, lamotrigine, valproic acid, gabapentin, topiramate, zonisamide		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Rilpivirine (RPV)	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Coadministration may significantly reduce RPV concentrations through induction of CYP450, UGT1A, and/or P-gP system. • **Gabapentin, topiramate, zonisamide:** No significant interactions are expected.	• **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Concomitant use is contraindicated with oral and injectable RPV (see package inserts for Cabenuva and Edurant). • **Gabapentin, topiramate, zonisamide:** No dose adjustments are necessary.
• Efavirenz (EFV) • Etravirine (ETR)	• **Lamotrigine, zonisamide:** EFV and ETR may reduce lamotrigine and zonisamide efficacy. • **Gabapentin, topiramate:** No significant interactions reported.	• **Lamotrigine, zonisamide:** Titrate slowly to achieve clinical effect; monitor for efficacy. • **Gabapentin, topiramate:** No dose adjustments are necessary.
Fostemsavir (FTR)	**Carbamazepine, oxcarbazepine, phenobarbital, phenytoin:** Significantly reduced FTR levels are expected.	Avoid coadministration due to potential loss of FTR efficacy.
Lenacapavir (LEN)	**Carbamazepine, eslicarbazepine, oxcarbazepine, phenobarbital, phenytoin:** CYP3A4 and P-gP induction potentially decreases LEN levels.	• **Carbamazepine, eslicarbazepine, phenytoin:** Do not coadminister. • **Oxcarbazepine, phenobarbital:** Coadministration is not recommended. • Consider alternative anticonvulsants such as levetiracetam.
Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor; TDM, therapeutic drug monitoring; UGT, uridine diphosphate glucuronosyltransferase. **Note:** a. Levetiracetam is safe with all ARVs, with no significant interactions expected and no dose adjustments required.		

Table 35: Nonopioid Pain Medications (also see drug package inserts)		
→ Triptans, tricyclic antidepressants (TCAs), pregabalin, nonsteroidal anti-inflammatory drugs (NSAIDs) [a], acetaminophen		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions are expected.	No dose adjustments are necessary.

Table 35: Nonopioid Pain Medications (also see drug package inserts)		
→ Triptans, tricyclic antidepressants (TCAs), pregabalin, nonsteroidal anti-inflammatory drugs (NSAIDs) [a], acetaminophen		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Elvitegravir (EVG), boosted	• **Eletriptan:** Eletriptan is a CYP3A substrate and concentrations may be increased if given with strong inhibitors of this enzyme. • **Other nonopioid pain medications:** No significant interactions are expected.	**Eletriptan:** Do not coadminister; use alternative triptan medication.
Boosted PIs	• **Eletriptan:** Metabolism inhibited by boosted PIs. • **TCAs:** PIs and TCAs can both cause QT prolongation. • **Pregabalin:** No significant interactions are expected.	• **Eletriptan:** Do not coadminister; use alternative triptan medication. • **TCAs:** With concomitant use of high-dose TCAs and PIs, consider monitoring for QT prolongation and other cardiac adverse effects or consider alternative medications.

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; PrEP, pre-exposure prophylaxis; TDF, tenofovir disoproxil fumarate.

Note:

a. 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, 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 PrEP regimen about their use of NSAIDs.

Table 36: Opioid Analgesics and Tramadol (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Etravirine (ETR) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions reported.	No dose adjustments are 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 CYP3A inhibition, but this reduces conversion to 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 COBI or RTV, monitoring for tramadol-related adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.

Table 36: Opioid Analgesics and Tramadol (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Boosted PIs	• **Opioid analgesics:** Complex mechanisms of metabolism and formation of both active and inactive metabolites create interactions of unclear significance between these drugs and boosted PIs. • **Tramadol:** Tramadol exposure is increased with CYP3A inhibition, but this reduces conversion to more potent active metabolite seen when tramadol is metabolized by CYP2D6.	• **Opioid analgesics:** Monitor for signs of opiate toxicity and analgesic effect; dose these analgesics accordingly. • **Tramadol:** When tramadol is given with COBI or RTV, monitoring for tramadol-related adverse effects and analgesic effect may be required as clinically indicated; adjust tramadol dosage if needed.
Efavirenz (EFV)	• **Morphine, hydromorphone:** Metabolism could be reduced by EFV. • **Oxycodone** may be metabolized faster to inactive metabolite by EFV. • **Meperidine:** Coadministration can potentially increase amount of neurotoxic metabolite, thereby increasing seizure risk. • **Tramadol:** EFV may reduce tramadol concentration without affecting pathway that increases development of more potent active metabolites.	• **Morphine, hydromorphone:** Monitor for signs of opiate toxicity when using with EFV. • **Oxycodone:** Dose adjustment of oxycodone may be required when dosing with EFV. • **Meperidine:** If possible, avoid concomitant use; use alternative opiate pain medication or ARV. • **Tramadol:** When given with tramadol, a priori dose adjustments are necessary.
Lenacapavir (LEN)	Moderate inhibition of CYP3A4 potentially increases opioid levels.	• Monitor for therapeutic effects and adverse reactions associated with CYP3A-metabolized opioid analgesics, including potentially fatal respiratory depression. • **Tramadol:** Consider tramadol dose reduction with concomitant use.
Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; RTV, ritonavir.		

Table 37: Hormonal Contraceptives (also see drug package inserts)		
→ Combined oral contraceptives, including ethinyl estradiol, norethindrone, and levonorgestrel		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Doravirine (DOR)	No significant drug interactions reported.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	**Drospirenone:** Concomitant use may cause hyperkalemia.	• **Ethinyl estradiol, norgestimate and metabolites; norethindrone:** Weigh risks and benefits; consider alternative contraceptive methods. • **Drospirenone:** Monitor for hyperkalemia; consider alternative contraceptive methods or alternative ARV. • **Etonogestrel:** No data available; consider alternative or additional contraceptive method or alternative ARV.

Table 37: Hormonal Contraceptives (also see drug package inserts)		
→ Combined oral contraceptives, including ethinyl estradiol, norethindrone, and levonorgestrel		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
All PIs	Combination has not been studied.	**Etonogestrel:** No data available. Consider alternative or additional contraceptive methods or alternative ARV.
Atazanavir (ATV), unboosted	Complex drug interaction potential has been described.	• **Ethinyl estradiol:** Do not exceed 30 mcg (no data available on doses lower than 25 mcg). • **Norethindrone:** Do not exceed 30 mcg (no data available on oral contraceptives with <25 mcg of ethinyl estradiol or progestins other than norethindrone or norgestimate).
Atazanavir (ATV), boosted	• Complex drug interaction potential has been described. • **Drospirenone:** Concomitant use may cause hyperkalemia.	• **Ethinyl estradiol; norgestimate and metabolites:** Dose with at least 35 mcg (no data available on other progestins). • **Drospirenone:** Do not coadminister.
Darunavir (DRV)/ritonavir (RTV)	Combination appears to decrease oral norethindrone concentrations.	**Norethindrone:** Consider alternative or additional contraceptive methods or alternative ARV.
Darunavir (DRV)/cobicistat (COBI)	Combination has not been studied, but since COBI does not induce glucuronidation, it is expected to increase norethindrone concentrations.	**Norethindrone:** Consider alternative or additional contraceptive methods or alternative ARV.
Other boosted PIs	**Drospirenone:** Use with other boosted PIs may cause hyperkalemia.	• **Ethinyl estradiol:** Consider alternative or additional contraceptive methods or alternative ARV. • **Drospirenone:** Monitor for hyperkalemia; consider alternative contraceptive or alternative ARV.
Efavirenz (EFV)	• **Levonorgestrel/norgestimate, levonorgestrel:** EFV may induce CYP3A, the enzyme that is primarily responsible for metabolism of levonorgestrel. • EFV decreases concentrations of combined progestins.	• **Levonorgestrel/norgestimate, levonorgestrel:** Levonorgestrel or norgestimate effectiveness may be decreased. • **Ethinyl estradiol; norgestimate and metabolites:** Use alternative or additional contraceptive methods; unintended pregnancies have been reported in individuals using levonorgestrel implants. • **Norethindrone, drospirenone, etonogestrel:** Consider alternative or additional contraceptive methods or alternative ARV. • **Ulipristal:** Monitor closely for reduced efficacy.
Etravirine (ETR)	Information is based on what is known with EFV drug interactions.	• **Etonogestrel:** No data available; consider alternative or additional contraceptive methods or alternative ARV. • **Ulipristal:** Monitor closely for reduced efficacy.
Fostemsavir (FTR)	• **Ethinyl estradiol:** Increased ethinyl estradiol levels are expected. • **Norethindrone:** No interactions are expected.	**Ethinyl estradiol:** Daily dose should not exceed 30 mcg. Caution is advised, particularly in patients with additional risk factors for thromboembolic events.
Abbreviations: ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.		

Table 38: Erectile and Sexual Dysfunction Agents (also see drug package inserts)		
→ Sildenafil [a], vardenafil, tadalafil [b,c], and alprostadil for men; flibanserin [d] for women		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR)	No significant interactions reported.	No dose adjustments are necessary.
Elvitegravir (EVG), boosted	**PDE5 inhibitors:** PDE5 inhibitors are substrates of CYP3A. Increased PDE5 inhibitor concentrations are expected.	• **PDE5 inhibitors:** Avoid concomitant use or use with lowest effective dose of PDE5 inhibitor (may increase risk of hypotension, syncope, priapism, and other adverse effects). • **Avanafil:** No data available; do not coadminister. • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.
Atazanavir (ATV), unboosted	**Avanafil:** Increased avanafil concentration is expected (for other oral erectile dysfunction drugs, see above).	**Avanafil:** Do not exceed 50 mg every 24 hours.
Boosted PIs	• **PDE5 inhibitors:** Increased PDE5 inhibitor concentrations are expected. • **Flibanserin:** Increased flibanserin concentrations are expected.	• **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects. • **Avanafil, flibanserin:** Do not coadminister.
• Efavirenz (EFV) • Etravirine (ETR)	• **PDE5 inhibitors:** EFV and ETR may reduce effectiveness of PDE5 inhibitors (sildenafil, vardenafil, and tadalafil). • **Flibanserin:** EFV and ETR may reduce flibanserin concentrations.	• **PDE5 inhibitors:** Monitor for clinical effect; if dose increase is needed to achieve desired clinical effect, titrate under medical supervision to lowest effective dose. • **Flibanserin:** Do not coadminister.
Lenacapavir (LEN)	**PDE5 inhibitors:** Moderate inhibition of CYP3A4 and P-gP potentially increases PDE5 inhibitor levels.	**PDE5 inhibitors**, refer to package inserts and guidance listed below: • **Avanafil:** Do not coadminister. • **Sildenafil:** Start with 25 mg every 48 hours; monitor for adverse effects. • **Tadalafil:** Start with 5 mg and do not exceed 10 mg every 72 hours; monitor for adverse effects. • **Vardenafil:** Administer 2.5 mg every 72 hours; monitor for adverse effects.

Table 38: Erectile and Sexual Dysfunction Agents (also see drug package inserts)		
→ Sildenafil [a], vardenafil, tadalafil [b,c], and alprostadil for men; flibanserin [d] for women		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Abbreviations: COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; P-gP, P-glycoprotein; PI, protease inhibitor. **Notes:** a. Sildenafil for treatment of PAH: Concurrent administration of all PIs and EVG/COBI 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 39: Alpha-Adrenergic Antagonists for Benign Prostatic Hyperplasia (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Bictegravir (BIC) • Cabotegravir (CAB) • Dolutegravir (DTG) • Raltegravir (RAL) • Doravirine (DOR) • Rilpivirine (RPV) • Efavirenz (EFV) • Etravirine (ETR) • Fostemsavir (FTR) • Maraviroc (MVC)	No significant interactions reported.	No dose adjustments are necessary.
PIs	Boosted or unboosted atazanavir (i.e., with or without COBI or RTV) and darunavir boosted with COBI or RTV inhibit CYP3A4 and other transporters.	• **Alfuzosin, silodosin:** Concomitant use is contraindicated. • **Doxazosin, terazosin:** PIs may be used concurrently; potential increases in doxazosin and terazosin levels are possible. Dose reduction may be necessary. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Elvitegravir (EVG), boosted	COBI-boosted EVG inhibits CYP3A4 and other transporters and is likely to increase levels of select drugs in this class.	• **Alfuzosin, silodosin:** Concomitant use is contraindicated. • **Doxazosin, terazosin:** May be used; increased levels are possible. • **Tamsulosin:** Avoid unless benefits outweigh risk. If used together, monitor for tamsulosin-associated adverse effects, such as hypotension.
Abbreviations: COBI, cobicistat; CYP, cytochrome P450; PI, protease inhibitor; RTV, ritonavir.		

Table 40: Tobacco and Smoking Cessation Products (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Elvitegravir (EVG), boosted • Boosted PIs • Rilpivirine (RPV) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions reported.	No dose adjustments are necessary.
• Efavirenz (EFV) • Etravirine (ETR)	• No significant interactions are expected. • EFV (but not ETR) may increase bupropion metabolism.	• No dose adjustments are necessary. • **Bupropion:** Monitor for clinical effect and increase as needed, but do not exceed recommended maximum dose.
Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.		

Table 41: Alcohol, Disulfiram, and Acamprosate [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• Other NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Elvitegravir (EVG), boosted • Other boosted PIs • Rilpivirine (RPV) • Efavirenz (EFV) • Etravirine (ETR) • Doravirine (DOR) • Fostemsavir (FTR)	No significant interactions reported.	No dose adjustments are necessary.
Abacavir (ABC)	**Alcohol:** ABC is metabolized via alcohol dehydrogenase, and competitive metabolism may increase exposure to ABC.	**Alcohol:** • Use may increase ABC concentrations; monitor for ABC-related adverse effects. • ABC does not appear to increase blood alcohol concentrations.
• Ritonavir (RTV; oral solutions) • Lopinavir/ritonavir (LPV/RTV; oral suspension or capsules)	All contain alcohol and may potentiate symptoms of consumption of ethanol.	**Disulfiram:** ARVs formulated with alcohol induce same aversive effects as consumption of ethanol.

Table 41: Alcohol, Disulfiram, and Acamprosate [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Abbreviations: ARV, antiretroviral; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor. **Note:** a. 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 42: Methadone, Buprenorphine (BUP), Naloxone (NLX), and Naltrexone [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Bictegravir (BIC) • Cabotegravir (CAB) • Raltegravir (RAL) • Elvitegravir (EVG), boosted • Doravirine (DOR) • Fostemsavir (FTR)	**BUP, methadone:** No significant are interactions expected.	No dose adjustments are necessary.
Atazanavir (ATV), unboosted	• **BUP, norbuprenorphine:** ATV greatly increases BUP and norbuprenorphine concentrations; may decrease ATV concentrations. • **Methadone:** No significant interactions are expected.	• **BUP:** Coadministration is not recommended; RTV boosting may decrease effect. • **Methadone:** No dose adjustments are required; exercise caution because both drugs may increase QT prolongation.
Ritonavir (RTV)-boosted PIs	**BUP:** 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.	**BUP:** When administering with RTV-boosted PIs, monitor for signs of increased opioid toxicity, including sedation, impaired cognition, and respiratory distress.
Cobicistat (COBI)-boosted PIs	• **BUP/NLX:** COBI-boosted PIs 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 methadone concentration.	• **BUP, BUP/NLX:** When administering with COBI-boosted PIs, titrate carefully to achieve clinical effect. • **Methadone:** Based on efficacy and safety, initiate at lowest possible dose and titrate to achieve clinical effect; monitor for signs and symptoms of opiate withdrawal.
RTV-boosted darunavir (DRV), taken twice per day	• **BUP, BUP/NLX:** Combination has no effect on BUP/NLX concentrations. • **Methadone:** RTV-boosted DRV taken twice per day may reduce methadone concentrations.	**Methadone:** Monitor for signs of opiate withdrawal and increase methadone dose if necessary.
Rilpivirine (RPV)	• **BUP:** No significant interactions are expected. • **Methadone:** RPV mildly reduces methadone concentrations.	• **Methadone:** Monitor for signs of methadone withdrawal; increase dose as necessary. • **Methadone, BUP:** Use cautiously with RPV; supratherapeutic doses of RPV have been known to cause increase in QT prolongation.

Table 42: Methadone, Buprenorphine (BUP), Naloxone (NLX), and Naltrexone [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Efavirenz (EFV)	• **BUP:** When given with BUP (monotherapy), EFV significantly reduces BUP concentrations, but no patients developed opioid withdrawal. • **Methadone:** EFV induces methadone metabolism via CYP3A4 and 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:** Titrate to achieve clinical effect; monitor for signs and symptoms of opioid withdrawal.
Etravirine (ETR)	• **BUP:** No significant interactions are expected. • **Methadone:** ETR may slightly increase methadone concentrations.	• **BUP, methadone:** Titrate opioid or antagonist as required to achieve clinical effect; monitor for signs of withdrawal or opioid toxicity. • **Methadone:** Monitor for signs of methadone toxicity and reduce dose if necessary.
Lenacapavir (LEN)	**Methadone, BUP:** Moderate inhibition of CYP3A4 and P-gP potentially increases methadone or BUP levels.	• **Patients initiating MAT while already on LEN:** Initiate MAT at lowest initial or maintenance dose. • **Patients initiating LEN while already on MAT:** MAT dose adjustments may be needed. • Monitor for excess sedation and/or respiratory depression.
Abbreviations: ARV, antiretroviral; CYP, cytochrome P450; MAT, medication-assisted therapy; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor. **Note:** a. No significant interactions are expected between ARVs, naloxone, and naltrexone.		

Table 43: Immunosuppressants [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• NRTIs • Dolutegravir (DTG) • Raltegravir (RAL) • Rilpivirine (RPV) • Doravirine (DOR)	No significant interactions reported.	No dose adjustments are necessary.
Bictegravir (BIC)	**Cyclosporine** may increase BIC concentrations to modest degree via P-gP inhibition.	**Cyclosporine:** Monitor for BIC-related adverse effects.
Elvitegravir (EVG), boosted	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted EVG.	• **Everolimus, sirolimus:** Do not use with boosted EVG. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.
Boosted PIs	**Everolimus, sirolimus, cyclosporine, tacrolimus:** Metabolism decreased by boosted PIs.	• **Everolimus, sirolimus:** Do not use with boosted PIs. • **Cyclosporine, tacrolimus:** Dose based on TDM; monitor closely for adverse effects.

Table 43: Immunosuppressants [a] (also see drug package inserts)		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• Efavirenz (EFV) • Etravirine (ETR)	**Cyclosporine, tacrolimus:** EFV or ETR may lower concentrations.	**Cyclosporine, tacrolimus:** • Adjust dose of cyclosporine and tacrolimus based on efficacy and TDM. • Conduct TDM more frequently for 2 weeks when starting or stopping NNRTI therapy.
Abbreviations: NNRTI, non-nucleoside reverse transcriptase inhibitors; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein; PI, protease inhibitor; TDF, tenofovir disoproxil fumarate; TDM, therapeutic drug monitoring. **Note:** a. 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 2 medications at the same time.		

Table 44: Rifamycins and Other Antituberculosis Medications (also see drug package inserts)		
→ Rifampin, rifabutin, rifapentine [a]; isoniazid [b], pyrazinamide [b], ethambutol [b], rifaximin [b]		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• Emtricitabine (FTC) • Lamivudine (3TC) • Tenofovir disoproxil fumarate (TDF)	No clinically significant interactions are expected.	No dose adjustments are necessary.
Abacavir (ABC)	• **Rifabutin, rifapentine:** No clinically significant interactions are expected. • **Rifampin** may reduce ABC concentrations.	• **Rifabutin, rifapentine:** No dose adjustments are necessary. • **Rifampin:** No dose adjustments are recommended for concomitant use with ABC.
Tenofovir alafenamide (TAF)	• **Rifabutin:** CYP3A and P-gP induction is expected to decrease TAF levels. • **Rifampin, rifapentine:** CYP3A induction may reduce TAF concentrations.	• **Rifampin:** Do not coadminister with TAF; consider TDF as alternative. • **Rifabutin, rifapentine:** Do not coadminister with TAF unless benefit outweighs risk; monitor closely for virologic response.
Doravirine (DOR)	• **Rifabutin:** CYP3A induction is expected to decrease DOR levels. • **Rifampin, rifapentine:** CYP3A induction reduces DOR bioavailability.	• **Rifabutin:** When used concomitantly, increase DOR to 100 mg twice per day. • **Rifampin, rifapentine:** – Concomitant use is contraindicated. – After stopping rifampin or rifapentine, wait 4 weeks before starting DOR.
Efavirenz (EFV)	• **Rifabutin:** EFV induction of CYP3A reduces rifabutin bioavailability, but coadministration does not affect EFV levels. • **Rifampin, rifapentine**: No clinically significant interactions are expected.	• **Rifabutin:** With concomitant EFV, dose rifabutin at 450 mg to 600 mg daily. • **Rifampin:** – Dose EFV at 600 mg daily when administered concomitantly. – Do not use EFV 400 mg daily. • **Rifapentine:** No dose adjustments are necessary.

Table 44: Rifamycins and Other Antituberculosis Medications (also see drug package inserts)		
→ Rifampin, rifabutin, rifapentine [a]; isoniazid [b], pyrazinamide [b], ethambutol [b], rifaximin [b]		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Etravirine (ETR)	• **Rifabutin:** When used concomitantly, increased rifabutin levels are expected and decreased ETR levels may occur. • **Rifampin, rifapentine:** CYP3A induction reduces ETR bioavailability.	• **Rifabutin:** – If ETR and rifabutin are used concomitantly, dose rifabutin 300 mg daily, with no changes to ETR dose. Continue rifabutin 300 mg daily dosing until at least 2 weeks after rifabutin is stopped. – Concomitant use of boosted PI with ETR and rifabutin is contraindicated. • **Rifampin, rifapentine:** Concomitant use is contraindicated.
Nevirapine (NVP)	• **Rifabutin:** No clinically significant interactions are expected. • **Rifampin, rifapentine:** Coadministration reduces NVP concentrations.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin, rifapentine:** Do not coadminister.
Rilpivirine (RPV)	**Rifabutin, rifampin, rifapentine:** Coadministration may significantly reduce RPV concentrations through induction of CYP450, UGT1A, and/or P-gP systems.	• **Rifabutin:** – Oral RPV: Increase RPV dose to 50 mg once daily [DHHS(a) 2021]. – Injectable RPV: Concomitant use is contraindicated. • **Rifampin, rifapentine:** Concomitant use with oral and injectable RPV is contraindicated [FDA(b) 2021].
All PIs and boosted PIs	• **Rifabutin** does not affect boosted PI levels, but when used concomitantly, bioavailability of rifabutin and its active metabolite is increased. • **Rifampin, rifapentine:** CYP3A induction reduces bioavailability of *all* PIs.	• **Rifabutin:** – RTV-boosted PIs: When used concomitantly, reduce rifabutin to 150 mg 3 times per week. – COBI-boosted PIs: Do not coadminister. • **Rifampin, rifapentine:** Concomitant use of PIs and rifampin or rifapentine is contraindicated.
Bictegravir (BIC)	• **Rifabutin:** CYP3A and P-gP induction decreases BIC levels. • **Rifampin, rifapentine:** CYP3A induction reduces bioavailability.	• **Rifampin:** Concomitant use is contraindicated. • **Rifabutin, rifapentine:** Concomitant use is not recommended [FDA(a) 2021].
Cabotegravir (CAB)	• **Rifabutin, rifampin, rifapentine:** Coadministration may significantly reduce CAB concentrations through induction of CYP450, UGT1A, and/or P-gP system.	• **Rifampin, rifapentine:** Concomitant use is contraindicated with *oral* CAB. • **Rifabutin:** May be used with *oral* CAB without dosage adjustment. • **Rifabutin, rifampin, rifapentine:** Concomitant use is contraindicated with *injectable* CAB [FDA(b) 2021].
Dolutegravir (DTG)	• **Rifabutin:** No clinically significant interactions expected. • **Rifampin:** CYP3A induction reduces DTG bioavailability. • **Rifapentine:** Reduced rifapentine levels are expected.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin:** When used concomitantly, dose DTG at 50 mg twice per day instead of 50 mg once per day in patients without

Table 44: Rifamycins and Other Antituberculosis Medications (also see drug package inserts)		
→ Rifampin, rifabutin, rifapentine [a]; isoniazid [b], pyrazinamide [b], ethambutol [b], rifaximin [b]		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
		suspected or documented INSTI-associated resistance mutations. Consider rifabutin in patients with INSTI resistance. • **Rifapentine, once weekly:** – If using concomitant DTG 50 mg once daily, monitor for virologic efficacy. – Do not coadminister with DTG 50 mg twice daily. • **Rifapentine, once daily:** Do not coadminister.
Elvitegravir (EVG), boosted	• **Rifabutin:** CYP3A induction is expected to decrease EVG levels. • **Rifampin, rifapentine:** CYP3A induction reduces EVG bioavailability.	• **Rifabutin:** Concomitant use is not recommended. When concomitant use cannot be avoided, dose rifabutin at 150 mg 3 times per week and monitor for response to EVG-containing regimen. • **Rifampin, rifapentine:** Concurrent use with boosted EVG is not recommended.
Raltegravir (RAL)	• **Rifabutin:** No clinically significant interactions are expected. • **Rifampin:** CYP3A induction reduces RAL bioavailability. • **Rifapentine:** Induction of metabolism may reduce RAL metabolism.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin:** – When used concomitantly, dose RAL at 800 mg twice per day instead of 400 mg twice per day. – Do not use RAL HD. • **Rifapentine:** – For 900 mg once-weekly rifapentine and RAL 400 mg twice daily, no dose adjustments are necessary. – Do not coadminister RAL with once-daily rifapentine.
Fostemsavir (FTR)	• **Rifabutin:** Interaction is not expected. • **Rifampin, rifapentine:** CYP3A4 induction reduces FTR bioavailability.	• **Rifabutin:** No dose adjustments are necessary. • **Rifampin, rifapentine:** Do not coadminister.
Lenacapavir (LEN)	**Rifabutin, rifampin, rifapentine:** CYP3A4 and P-gP induction associated with rifamycins potentially decreases LEN levels.	• **Rifampin:** Concomitant use is contraindicated. • **Rifabutin, rifapentine:** Coadministration is not recommended. • Consider alternatives.

Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; P-gP, P-glycoprotein; PI, protease inhibitor; RTV, ritonavir; UGT, uridine diphosphate glucuronosyltransferase.

Notes:

a. **Rifapentine:** Has not been studied with many ARVs, 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 EFV (dose adjusted), RAL, or DTG, but additional studies are required before recommendations can be made about the use of this medicine with other ARVs.

b. **Isoniazid, pyrazinamide, ethambutol, rifaximin:** No clinically significant interactions with ARVs are expected; no dose adjustments are 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 45: COVID-19 Therapeutics (also see drug package inserts and emergency use authorizations [FDA(a) 2022; FDA(b) 2022])		
→ Molnupiravir, nirmatrelvir/ritonavir (RTV), monoclonal antibodies		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• All NRTIs • Doravirine (DOR) • Etravirine (ETR) • Rilpivirine (RPV) • Cabotegravir (CAB) • Dolutegravir (DTG) • Raltegravir (RAL)	No clinically significant interactions expected.	No dose adjustments are necessary.
• Efavirenz (EFV) • Nevirapine (NVP) • Bictegravir (BIC) • Fostemsavir (FTR) • Maraviroc (MRV)	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Drug interactions are unlikely; ARV levels may increase.
All PIs and boosted PIs	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other PIs.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Patients on RTV- or COBI-containing regimens should continue treatment for COVID-19 and HIV as indicated without adjustment. Monitor for increased PI-related adverse effects.
Elvitegravir (EVG), boosted	• **Molnupiravir and monoclonal antibodies** do not affect CYP450, P-gP, or other drug metabolism transporters. • **Nirmatrelvir/RTV:** Inhibition of CYP3A4, P-gP, and other transporters may increase plasma concentrations of other medications.	• **Molnupiravir, monoclonal antibodies:** Drug interactions are unlikely. • **Nirmatrelvir/RTV:** Patients on RTV- or COBI-containing regimens should continue treatment as indicated. Monitor for increased EVG-related adverse effects.
Abbreviations: ARV, antiretroviral; COBI, cobicistat; CYP, cytochrome P450; NRTI, nucleoside reverse transcriptase inhibitor; P-gP, P-glycoprotein.		

Table 46: Mpox Treatments (also see drug package inserts and CDC Treatment Information for Healthcare Professionals)		
→ Tecovirimat [a], vaccinia immune globulin intravenous (VIGIV), cidofovir, brincidofovir		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
• Bictegravir (BIC) • Cabotegravir (CAB), IM or oral • Dolutegravir (DTG) • Raltegravir (RAL)	No clinically significant interactions expected.	No dose adjustments are necessary.

Table 46: Mpox Treatments (also see drug package inserts and CDC Treatment Information for Healthcare Professionals)		
→ Tecovirimat [a], vaccinia immune globulin intravenous (VIGIV), cidofovir, brincidofovir		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
All NRTIs	**Cidofovir** is eliminated via glomerular filtration and active renal secretion by OAT1 and OAT3.	• **Cidofovir:** Avoid coadministration with nephrotoxic agents. Consider use of TAF in place of TDF and monitor for renal-related adverse effects. • **Brincidofovir, tecovirimat, VIGIV:** Drug interactions are unlikely.
All NNRTIs	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19; use may potentially increase or decrease plasma concentrations of other medications.	• **Tecovirimat** may reduce NNRTI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Brincidofovir, cidofovir, VIGIV:** Drug interactions are unlikely.
All PIs	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with PIs will likely increase brincidofovir levels. Consider avoiding concurrent PIs if possible. If unable to change PI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone PI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce PI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary. • **Cidofovir, VIGIV:** Drug interactions are unlikely.
Elvitegravir (EVG), boosted	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is weak inducer of CYP3A and weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** Coadministration with EVG/COBI will likely increase brincidofovir levels. Consider avoiding concurrent EVG/COBI if possible. If unable to change EVG/COBI, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone EVG/COBI dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce EVG/COBI levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.
Fostemsavir (FTR)	• **Brincidofovir** is a substrate for OATP1B1 and OATP1B3. • **Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19.	• **Brincidofovir:** FTR inhibits OATP1B1 and may increase brincidofovir levels. Avoid concurrent use if possible. If unable to change therapy, monitor for brincidofovir-related adverse effects, e.g., LFT elevations, hyperbilirubinemia, diarrhea, or other GI adverse effects. Postpone FTR dosing for at least 3 hours *after* brincidofovir administration. • **Tecovirimat** may reduce FTR levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.

Table 46: Mpox Treatments (also see drug package inserts and CDC Treatment Information for Healthcare Professionals)		
→ Tecovirimat [a], vaccinia immune globulin intravenous (VIGIV), cidofovir, brincidofovir		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Maraviroc (MVC)	**Tecovirimat** is a weak inducer of CYP3A and a weak inhibitor of CYP2C8 and CYP2C19.	**Tecovirimat** may reduce MVC levels, though effects are not likely to be clinically relevant. No dose adjustment in either drug is necessary.

Abbreviations: ARV, antiretroviral; AUC, area under the curve; CDC, Centers for Disease Control and Prevention; COBI, cobicistat; CYP, cytochrome P450; GI, gastrointestinal; IM, intramuscular; LFT, liver function test; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; PI, protease inhibitor.

Note:

a. No data are currently available on effects related to concurrent use of tecovirimat and HIV medications. However, midazolam AUC was reduced by 32% with concomitant tecovirimat use, and some experts recommend caution due to the mild CYP3A4 induction associated with tecovirimat. Among them is University of Liverpool HIV Drug Interactions, which makes the following dosing change recommendations, although they are not based on any clinical data:
   - **RPV:** Increase dose to 50 mg daily for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped.
   - **MVC:** Increase dose to 600 mg twice daily (if the patient is not taking another potent CYP3A4 inhibitor concurrently) for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped. If the patient is receiving concomitant treatment with a potent CYP3A4 inhibitor, MVC should be dosed at 150 mg twice daily for the duration of concurrent tecovirimat.
   - **DOR:** Increase dose to 100 mg twice daily for the duration of tecovirimat treatment and for 2 weeks after tecovirimat is stopped.

Table 47: Gender-Affirming Hormones [Hembree, et al. 2017; Irving and Lehault 2017] (also see drug package inserts)		
→ Cyproterone acetate, estradiol, finasteride, goserelin, leuprolide acetate, spironolactone, testosterone		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
ARV medications, *all*	• **Cyproterone acetate:** Interaction with ARVs has not been studied. • **Estradiol:** Interaction between ARVs and estradiol in transgender women has not been studied. • **Finasteride:** 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. • **Goserelin:** Interaction with ARVs has not been studied. Based on what is known about metabolism of goserelin, no clinically significant interactions are expected. • **Leuprolide acetate:** Interaction with ARVs has not been studied. Based on what is known about metabolism of leuprolide acetate, no clinically significant interactions are expected. • **Testosterone:** 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. • **Spironolactone:** No interactions expected.	• **Estradiol:** When prescribing ARVs, consider use of medications not expected to interact with estradiol. • **Finasteride:** No dose adjustments recommended.

Table 47: Gender-Affirming Hormones [Hembree, et al. 2017; Irving and Lehault 2017] (also see drug package inserts)		
→ Cyproterone acetate, estradiol, finasteride, goserelin, leuprolide acetate, spironolactone, testosterone		
Class or Drug	**Mechanism of Action**	**Clinical Comments**
Cobicistat (COBI)	• **Estradiol:** Based on 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. • **Finasteride:** When taken concomitantly, finasteride levels may be increased, but with minimal clinical significance. • **Testosterone:** Based on known mechanisms of metabolism, there is limited potential that COBI-boosted PIs or other ARVs may increase testosterone levels. Relevance of this interaction is expected to be low in transgender men.	• **Estradiol:** When taken concomitantly with COBI-boosted ARVs, monitor for signs of estrogen deficiency or excess. • **Finasteride, testosterone:** No dose adjustments are recommended.
Doravirine (DOR)	**Estradiol, testosterone:** No interactions expected.	N/A
Efavirenz (EFV)	• **Estradiol:** EFV could induce CYP3A and could decrease estradiol levels. • **Finasteride, testosterone:** Levels may decrease when taken concomitantly with EFV.	• **Estradiol:** No dose adjustments are recommended, but when taken concomitantly with EFV, monitor for signs of estrogen deficiency or excess. • **Finasteride, testosterone:** No dose adjustments recommended.
Etravirine (ETR)	• **Estradiol:** ETR could induce CYP3A and could decrease estradiol levels. • **Finasteride, 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, testosterone:** No dose adjustments are recommended.
Etravirine (ETR)	• **Estradiol:** ETR could induce CYP3A and could decrease estradiol levels. • **Finasteride, 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, testosterone:** No dose adjustments are recommended.
• Rilpivirine (RPV) • INSTIs, *non-boosted* • NRTIs, *non-boosted*	**Estradiol, finasteride, testosterone:** No interactions are expected.	N/A
Ritonavir (RTV)	• **Estradiol:** RTV may induce CYP1A2, which could decrease estradiol levels. This outweighs RTV inhibition of CYP3A. • **Testosterone:** No interactions are 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

Aberg JA, Tebas P, Overton ET, et al. Metabolic effects of darunavir/ritonavir versus atazanavir/ritonavir in treatment-naive, HIV type 1-infected subjects over 48 weeks. *AIDS Res Hum Retroviruses* 2012;28(10):1184-95. [PMID: 22352336] https://pubmed.ncbi.nlm.nih.gov/22352336

Adams JL, Greener BN, Kashuba AD. Pharmacology of HIV integrase inhibitors. *Curr Opin HIV AIDS* 2012;7(5):390-400. [PMID: 22789987] https://pubmed.ncbi.nlm.nih.gov/22789987

Alvarez A, Orden S, Andujar I, et al. Cardiovascular toxicity of abacavir: a clinical controversy in need of a pharmacological explanation. *AIDS* 2017;31(13):1781-95. [PMID: 28537935] https://pubmed.ncbi.nlm.nih.gov/28537935

American Pharmacists Association. Medication therapy management services. 2021 https://www.pharmacist.com/Practice/Patient-Care-Services/Medication-Management [accessed 2021 Jul 19]

Aquilante CL, Kiser JJ, Anderson PL, et al. Influence of SLCO1B1 polymorphisms on the drug-drug interaction between darunavir/ritonavir and pravastatin. *J Clin Pharmacol* 2012;52(11):1725-38. [PMID: 22174437] https://pubmed.ncbi.nlm.nih.gov/22174437

Aulitzky WE, Tilg H, Niederwieser D, et al. Ganciclovir and hyperimmunoglobulin for treating cytomegalovirus infection in bone marrow transplant recipients. *J Infect Dis* 1988;158(2):488-89. [PMID: 2841384] https://pubmed.ncbi.nlm.nih.gov/2841384

Barbarino JM, Kroetz DL, Altman RB, et al. PharmGKB summary: abacavir pathway. *Pharmacogenet Genomics* 2014;24(5):276-82. [PMID: 24625462] https://pubmed.ncbi.nlm.nih.gov/24625462

Benet LZ, Hoener BA. Changes in plasma protein binding have little clinical relevance. *Clin Pharmacol Ther* 2002;71(3):115-21. [PMID: 11907485] https://pubmed.ncbi.nlm.nih.gov/11907485

Boswell R, Foisy MM, Hughes CA. Dolutegravir dual therapy as maintenance treatment in HIV-infected patients: a review. *Ann Pharmacother* 2018;52(7):681-89. [PMID: 29442543] https://pubmed.ncbi.nlm.nih.gov/29442543

Brooks KM, George JM, Kumar P. Drug interactions in HIV treatment: complementary & alternative medicines and over-the-counter products. *Expert Rev Clin Pharmacol* 2017;10(1):59-79. [PMID: 27715369] https://pubmed.ncbi.nlm.nih.gov/27715369

Busti AJ, Bain AM, Hall RG, 2nd, et al. Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosuvastatin. *J Cardiovasc Pharmacol* 2008;51(6):605-10. [PMID: 18520949] https://pubmed.ncbi.nlm.nih.gov/18520949

Calcagno A, D'Avolio A, Bonora S. Pharmacokinetic and pharmacodynamic evaluation of raltegravir and experience from clinical trials in HIV-positive patients. *Expert Opin Drug Metab Toxicol* 2015;11(7):1167-76. [PMID: 26073580] https://pubmed.ncbi.nlm.nih.gov/26073580

Cammett AM, MacGregor TR, Wruck JM, et al. Pharmacokinetic assessment of nevirapine and metabolites in human immunodeficiency virus type 1-infected patients with hepatic fibrosis. *Antimicrob Agents Chemother* 2009;53(10):4147-52. [PMID: 19620337] https://pubmed.ncbi.nlm.nih.gov/19620337

Carr A, Samaras K, Chisholm DJ, et al. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998;351(9119):1881-83. [PMID: 9652687] https://pubmed.ncbi.nlm.nih.gov/9652687

Carten ML, Kiser JJ, Kwara A, et al. Pharmacokinetic interactions between the hormonal emergency contraception, levonorgestrel (Plan B), and efavirenz. *Infect Dis Obstet Gynecol* 2012;2012:137192. [PMID: 22536010] https://pubmed.ncbi.nlm.nih.gov/22536010

Chauvin B, Drouot S, Barrail-Tran A, et al. Drug-drug interactions between HMG-CoA reductase inhibitors (statins) and antiviral protease inhibitors. *Clin Pharmacokinet* 2013;52(10):815-31. [PMID: 23703578] https://pubmed.ncbi.nlm.nih.gov/23703578

Clarke SM, Mulcahy FM, Tjia J, et al. The pharmacokinetics of methadone in HIV-positive patients receiving the non-nucleoside reverse transcriptase inhibitor efavirenz. *Br J Clin Pharmacol* 2001;51(3):213-17. [PMID: 11298066] https://pubmed.ncbi.nlm.nih.gov/11298066

Cottrell ML, Hadzic T, Kashuba AD. Clinical pharmacokinetic, pharmacodynamic and drug-interaction profile of the integrase inhibitor dolutegravir. *Clin Pharmacokinet* 2013;52(11):981-94. [PMID: 23824675] https://pubmed.ncbi.nlm.nih.gov/23824675

Croom KF, Dhillon S, Keam SJ. Atazanavir: a review of its use in the management of HIV-1 infection. *Drugs* 2009;69(8):1107-40. [PMID: 19496633] https://pubmed.ncbi.nlm.nih.gov/19496633

Custodio J, Wang H, Hao J, et al. Pharmacokinetics of cobicistat boosted-elvitegravir administered in combination with rosuvastatin. *J Clin Pharmacol* 2014;54(6):649-56. [PMID: 24375014] https://pubmed.ncbi.nlm.nih.gov/24375014

Custodio J, West S, Yu A, et al. Lack of clinically relevant effect of bictegravir (BIC, B) on metformin (MET) pharmacokinetics (PK) and pharmacodynamics (PD). *Open Forum Infect Dis* 2017;4(Suppl 1):S429. [PMID: PMC5631370] https://pubmed.ncbi.nlm.nih.gov/PMC5631370

Daveluy A, Raignoux C, Miremont-Salame G, et al. Drug interactions between inhaled corticosteroids and enzymatic inhibitors. *Eur J Clin Pharmacol* 2009;65(7):743-45. [PMID: 19399485] https://pubmed.ncbi.nlm.nih.gov/19399485

Davies EA, O'Mahony MS. Adverse drug reactions in special populations - the elderly. *Br J Clin Pharmacol* 2015;80(4):796-807. [PMID: 25619317] https://pubmed.ncbi.nlm.nih.gov/25619317

Deeks ED. Raltegravir once-daily tablet: a review in HIV-1 infection. *Drugs* 2017;77(16):1789-95. [PMID: 29071467] https://pubmed.ncbi.nlm.nih.gov/29071467

Deeks ED. Doravirine: first global approval. *Drugs* 2018;78(15):1643-50. [PMID: 30341683] https://pubmed.ncbi.nlm.nih.gov/30341683

Deeks ED, Keating GM. Etravirine. *Drugs* 2008;68(16):2357-72. [PMID: 18973398] https://pubmed.ncbi.nlm.nih.gov/18973398

Deeks(a) ED. Cobicistat: a review of its use as a pharmacokinetic enhancer of atazanavir and darunavir in patients with HIV-1 infection. *Drugs* 2014;74(2):195-206. [PMID: 24343782] https://pubmed.ncbi.nlm.nih.gov/24343782

Deeks(b) ED. Darunavir: a review of its use in the management of HIV-1 infection. *Drugs* 2014;74(1):99-125. [PMID: 24338166] https://pubmed.ncbi.nlm.nih.gov/24338166

Deeks(c) ED. Elvitegravir: a review of its use in adults with HIV-1 infection. *Drugs* 2014;74(6):687-97. [PMID: 24671908] https://pubmed.ncbi.nlm.nih.gov/24671908

Deeks(d) ED. Emtricitabine/rilpivirine/tenofovir disoproxil fumarate single-tablet regimen: a review of its use in HIV infection. *Drugs* 2014;74(17):2079-95. [PMID: 25352394] https://pubmed.ncbi.nlm.nih.gov/25352394

Dharan NJ, Cooper DA. Reducing medical comorbidities associated with long-term HIV infection: beyond optimizing antiretroviral therapy regimens. *AIDS* 2017;31(18):2547-49. [PMID: 29120900] https://pubmed.ncbi.nlm.nih.gov/29120900

DHHS(a). Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV: Drug-drug interactions: Role of therapeutic drug monitoring in managing drug-drug interactions. 2021 Jun 3. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/overview [accessed 2018 Jul 6]

DHHS(b). Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV: Table 23. Mechanisms of antiretroviral-associated drug interactions. 2021 Jun 3. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/overview?view=full [accessed 2022 Jun 30]

DHHS(c). Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV: Table 24a. Drug interactions between protease inhibitors and other drugs. 2021 Jun 3. https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-interactions-between-protease?view=full [accessed 2022 Jun 30]

Edelman EJ, Gordon KS, Glover J, et al. The next therapeutic challenge in HIV: polypharmacy. *Drugs Aging* 2013;30(8):613-28. [PMID: 23740523] https://pubmed.ncbi.nlm.nih.gov/23740523

Egan G, Hughes CA, Ackman ML. Drug interactions between antiplatelet or novel oral anticoagulant medications and antiretroviral medications. *Ann Pharmacother* 2014;48(6):734-40. [PMID: 24615627] https://pubmed.ncbi.nlm.nih.gov/24615627

Falcon RW, Kakuda TN. Drug interactions between HIV protease inhibitors and acid-reducing agents. *Clin Pharmacokinet* 2008;47(2):75-89. [PMID: 18193914] https://pubmed.ncbi.nlm.nih.gov/18193914

FDA. Clinical drug interaction studies—study design, data analysis, and clinical implications. Guidance for industry. 2017 Oct. https://www.fda.gov/drugs/drug-interactions-labeling/drug-interactions-relevant-regulatory-guidance-and-policy-documents [accessed 2021 Jul 19]

FDA. Rukobia (fostemsavir) extended-release tablets, for oral use. 2020 Jul. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/212950s000lbl.pdf [accessed 2020 Nov 25]

FDA(a). Biktarvy (bictegravir, emtricitabine, and tenofovir alafenamide) tablets, for oral use. 2021 Mar. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/210251s010lbl.pdf [accessed 2021 May 28]

FDA(a). Fact sheet for healthcare providers: emergency use authorization for Lagevrio (molnupiravir) capsules. 2022 Mar. https://www.fda.gov/media/155054/download [accessed 2022 Jun 30]

FDA(b). Cabenuva (cabotegravir extended-release injectable suspension; rilpivirine extended-release injectable suspension), co-packaged for intramuscular use. 2021 Jan. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212888s000lbl.pdf [accessed 2021 May 28]

FDA(b). Fact sheet for healthcare providers: emergency use authorization for Paxlovid. 2022 Jun 28. https://www.fda.gov/media/155050/download [accessed 2022 Jun 30]

FDA(c). Trogarzo (ibalizumab-uiyk) injection, for intravenous use. 2021 Apr. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761065s011lbl.pdf [accessed 2021 May 28]

FDA(c). Sunlenca (lenacapavir) tablets, for oral use; Sunlenca (lenacapavir) injection, for subcutaneous use. 2022 Dec. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/215973s000lbl.pdf [accessed 2023 Mar 29]

FDA(d). Vocabria (cabotegravir) tablets, for oral use. 2021 Jan. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212887s000lbl.pdf [accessed 2021 Apr 12]

Feinstein MJ, Achenbach CJ, Stone NJ, et al. A systematic review of the usefulness of statin therapy in HIV-infected patients. *Am J Cardiol* 2015;115(12):1760-66. [PMID: 25907504] https://pubmed.ncbi.nlm.nih.gov/25907504

Feng B, Varma MV. Evaluation and quantitative prediction of renal transporter-mediated drug-drug interactions. *J Clin Pharmacol* 2016;56 Suppl 7:S110-21. [PMID: 27385169] https://pubmed.ncbi.nlm.nih.gov/27385169

Foisy MM, Yakiwchuk EM, Hughes CA. Induction effects of ritonavir: implications for drug interactions. *Ann Pharmacother* 2008;42(7):1048-59. [PMID: 18577765] https://pubmed.ncbi.nlm.nih.gov/18577765

Gallant J, Hsue P, Budd D, et al. Healthcare utilization and direct costs of non-infectious comorbidities in HIV-infected patients in the USA. *Curr Med Res Opin* 2018;34(1):13-23. [PMID: 28933204] https://pubmed.ncbi.nlm.nih.gov/28933204

Gammal RS, Court MH, Haidar CE, et al. Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for UGT1A1 and atazanavir prescribing. *Clin Pharmacol Ther* 2016;99(4):363-69. [PMID: 26417955] https://pubmed.ncbi.nlm.nih.gov/26417955

Garrison KL, German P, Mogalian E, et al. The drug-drug interaction potential of antiviral agents for the treatment of chronic hepatitis C infection. *Drug Metab Dispos* 2018;46(8):1212-25. [PMID: 29695614] https://pubmed.ncbi.nlm.nih.gov/29695614

Garrison KL, Mogalian E, Zhang H, et al. Evaluation of drug-drug interactions between sofosbuvir/velpatasvir/voxilapevir and boosted or unboosted HIV antiretroviral regimens. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy; 2017 Jun 14-17; Chicago, IL. http://www.natap.org/2017/Pharm/Pharm_19.htm

Gervasoni C, Minisci D, Clementi E, et al. How relevant is the interaction between dolutegravir and metformin in real life? *J Acquir Immune Defic Syndr* 2017;75(1):e24-26. [PMID: 28114188] https://pubmed.ncbi.nlm.nih.gov/28114188

Gibson AK, Shah BM, Nambiar PH, et al. Tenofovir alafenamide: a review of its use in the treatment of HIV-1 infection. *Ann Pharmacother* 2016;50(11):942-52. [PMID: 27465879] https://pubmed.ncbi.nlm.nih.gov/27465879

Gleason LJ, Luque AE, Shah K. Polypharmacy in the HIV-infected older adult population. *Clin Interv Aging* 2013;8:749-63. [PMID: 23818773] https://pubmed.ncbi.nlm.nih.gov/23818773

Green B, Crauwels H, Kakuda TN, et al. Evaluation of concomitant antiretrovirals and CYP2C9/CYP2C19 polymorphisms on the pharmacokinetics of etravirine. *Clin Pharmacokinet* 2017;56(5):525-36. [PMID: 27665573] https://pubmed.ncbi.nlm.nih.gov/27665573

Greig SL. Sofosbuvir/velpatasvir: a review in chronic hepatitis C. *Drugs* 2016;76(16):1567-78. [PMID: 27730529] https://pubmed.ncbi.nlm.nih.gov/27730529

Gruber VA, McCance-Katz EF. Methadone, buprenorphine, and street drug interactions with antiretroviral medications. *Curr HIV/AIDS Rep* 2010;7(3):152-60. [PMID: 20532839] https://pubmed.ncbi.nlm.nih.gov/20532839

Gujjarlamudi HB. Polytherapy and drug interactions in elderly. *J Midlife Health* 2016;7(3):105-7. [PMID: 27721636] https://pubmed.ncbi.nlm.nih.gov/27721636

Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society clinical practice guideline. *Endocr Pract* 2017;23(12):1437. [PMID: 29320642] https://pubmed.ncbi.nlm.nih.gov/29320642

Irving A, Lehault WB. Clinical pearls of gender-affirming hormone therapy in transgender patients. *Ment Health Clin* 2017;7(4):164-67. [PMID: 29955517] https://pubmed.ncbi.nlm.nih.gov/29955517

Ivanyuk A, Livio F, Biollaz J, et al. Renal drug transporters and drug interactions. *Clin Pharmacokinet* 2017;56(8):825-92. [PMID: 28210973] https://pubmed.ncbi.nlm.nih.gov/28210973

Jafari A, Khalili H, Dashti-Khavidaki S. Tenofovir-induced nephrotoxicity: incidence, mechanism, risk factors, prognosis and proposed agents for prevention. *Eur J Clin Pharmacol* 2014;70(9):1029-40. [PMID: 24958564] https://pubmed.ncbi.nlm.nih.gov/24958564

Kakadiya PP, Higginson RT, Fulco PP. Ritonavir-boosted protease inhibitors but not cobicistat appear safe in HIV-positive patients ingesting dabigatran. *Antimicrob Agents Chemother* 2018;62(2). [PMID: 29133562] https://pubmed.ncbi.nlm.nih.gov/29133562

Kakuda TN, Scholler-Gyure M, Hoetelmans RM. Pharmacokinetic interactions between etravirine and non-antiretroviral drugs. *Clin Pharmacokinet* 2011;50(1):25-39. [PMID: 21142266] https://pubmed.ncbi.nlm.nih.gov/21142266

Kaur K, Gandhi MA, Slish J. Drug-drug interactions among hepatitis C virus (HCV) and human immunodeficiency virus (HIV) medications. *Infect Dis Ther* 2015;4(2):159-72. [PMID: 25896480] https://pubmed.ncbi.nlm.nih.gov/25896480

Kearney BP, Flaherty JF, Shah J. Tenofovir disoproxil fumarate: clinical pharmacology and pharmacokinetics. *Clin Pharmacokinet* 2004;43(9):595-612. [PMID: 15217303] https://pubmed.ncbi.nlm.nih.gov/15217303

Keating GM, Plosker GL. Eplerenone: a review of its use in left ventricular systolic dysfunction and heart failure after acute myocardial infarction. *Drugs* 2004;64(23):2689-2707. [PMID: 15537370] https://pubmed.ncbi.nlm.nih.gov/15537370

Kellick KA, Bottorff M, Toth PP, et al. A clinician's guide to statin drug-drug interactions. *J Clin Lipidol* 2014;8(3 Suppl):S30-46. [PMID: 24793440] https://pubmed.ncbi.nlm.nih.gov/24793440

Kharasch ED, Whittington D, Ensign D, et al. Mechanism of efavirenz influence on methadone pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2012;91(4):673-84. [PMID: 22398970] https://pubmed.ncbi.nlm.nih.gov/22398970

Kis O, Zastre JA, Hoque MT, et al. Role of drug efflux and uptake transporters in atazanavir intestinal permeability and drug-drug interactions. *Pharm Res* 2013;30(4):1050-64. [PMID: 23224979] https://pubmed.ncbi.nlm.nih.gov/23224979

Kiser JJ, Bumpass JB, Meditz AL, et al. Effect of antacids on the pharmacokinetics of raltegravir in human immunodeficiency virus-seronegative volunteers. *Antimicrob Agents Chemother* 2010;54(12):4999-5003. [PMID: 20921313] https://pubmed.ncbi.nlm.nih.gov/20921313

Kiser JJ, Carten ML, Aquilante CL, et al. The effect of lopinavir/ritonavir on the renal clearance of tenofovir in HIV-infected patients. *Clin Pharmacol Ther* 2008;83(2):265-72. [PMID: 17597712] https://pubmed.ncbi.nlm.nih.gov/17597712

Kishi T, Matsunaga S, Iwata N. Suvorexant for primary insomnia: a systematic review and meta-analysis of randomized placebo-controlled trials. *PLoS One* 2015;10(8):e0136910. [PMID: 26317363] https://pubmed.ncbi.nlm.nih.gov/26317363

Klein CE, Chiu YL, Cai Y, et al. Effects of acid-reducing agents on the pharmacokinetics of lopinavir/ritonavir and ritonavir-boosted atazanavir. *J Clin Pharmacol* 2008;48(5):553-62. [PMID: 18440920] https://pubmed.ncbi.nlm.nih.gov/18440920

Kohler JJ, Hosseini SH, Green E, et al. Tenofovir renal proximal tubular toxicity is regulated by OAT1 and MRP4 transporters. *Lab Invest* 2011;91(6):852-58. [PMID: 21403643] https://pubmed.ncbi.nlm.nih.gov/21403643

Kovacsics D, Patik I, Ozvegy-Laczka C. The role of organic anion transporting polypeptides in drug absorption, distribution, excretion and drug-drug interactions. *Expert Opin Drug Metab Toxicol* 2017;13(4):409-24. [PMID: 27783531] https://pubmed.ncbi.nlm.nih.gov/27783531

Krishna R, East L, Larson P, et al. Effect of metal-cation antacids on the pharmacokinetics of 1200 mg raltegravir. *J Pharm Pharmacol* 2016;68(11):1359-65. [PMID: 27671833] https://pubmed.ncbi.nlm.nih.gov/27671833

Lampertico P, Buti M, Fung S, et al. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in virologically suppressed patients with chronic hepatitis B: a randomised, double-blind, phase 3, multicentre non-inferiority study. *Lancet Gastroenterol Hepatol* 2020;5(5):441-53. [PMID: 32087795] https://pubmed.ncbi.nlm.nih.gov/32087795

Lavan AH, Gallagher PF, O'Mahony D. Methods to reduce prescribing errors in elderly patients with multimorbidity. *Clin Interv Aging* 2016;11:857-66. [PMID: 27382268] https://pubmed.ncbi.nlm.nih.gov/27382268

Lehnbom EC, Stewart MJ, Manias E, et al. Impact of medication reconciliation and review on clinical outcomes. *Ann Pharmacother* 2014;48(10):1298-1312. [PMID: 25048794] https://pubmed.ncbi.nlm.nih.gov/25048794

Llibre JM, Hill A. Abacavir and cardiovascular disease: a critical look at the data. *Antiviral Res* 2016;132:116-21. [PMID: 27260856] https://pubmed.ncbi.nlm.nih.gov/27260856

Lund M, Petersen TS, Dalhoff KP. Clinical implications of P-glycoprotein modulation in drug-drug interactions. *Drugs* 2017;77(8):859-83. [PMID: 28382570] https://pubmed.ncbi.nlm.nih.gov/28382570

Mak LY, Seto WK, Lai CL, et al. An update on the toxicological considerations for protease inhibitors used for hepatitis C infection. *Expert Opin Drug Metab Toxicol* 2018;14(5):483-91. [PMID: 29718748] https://pubmed.ncbi.nlm.nih.gov/29718748

Mao Q, Unadkat JD. Role of the breast cancer resistance protein (BCRP/ABCG2) in drug transport--an update. *AAPS J* 2015;17(1):65-82. [PMID: 25236865] https://pubmed.ncbi.nlm.nih.gov/25236865

Markham A. Bictegravir: first global approval. *Drugs* 2018;78(5):601-6. [PMID: 29564777] https://pubmed.ncbi.nlm.nih.gov/29564777

Marzolini C, Gibbons S, Khoo S, et al. Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. *J Antimicrob Chemother* 2016;71(7):1755-58. [PMID: 26945713] https://pubmed.ncbi.nlm.nih.gov/26945713

Max B, Vibhakar S. Dolutegravir: a new HIV integrase inhibitor for the treatment of HIV infection. *Future Virol* 2014;9(11):967-78. [PMID:

McBane SE, Dopp AL, Abe A, et al. Collaborative drug therapy management and comprehensive medication management-2015. *Pharmacotherapy* 2015;35(4):e39-50. [PMID: 25884536] https://pubmed.ncbi.nlm.nih.gov/25884536

McCance-Katz EF, Moody DE, Morse GD, et al. Interactions between buprenorphine and antiretrovirals. I. The nonnucleoside reverse-transcriptase inhibitors efavirenz and delavirdine. *Clin Infect Dis* 2006;43 Suppl 4:S224-34. [PMID: 17109309] https://pubmed.ncbi.nlm.nih.gov/17109309

McCormack PL. Dolutegravir: a review of its use in the management of HIV-1 infection in adolescents and adults. *Drugs* 2014;74(11):1241-52. [PMID: 25005775] https://pubmed.ncbi.nlm.nih.gov/25005775

McDowell JA, Chittick GE, Stevens CP, et al. Pharmacokinetic interaction of abacavir (1592U89) and ethanol in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother* 2000;44(6):1686-90. [PMID: 10817729] https://pubmed.ncbi.nlm.nih.gov/10817729

McKeage K, Perry CM, Keam SJ. Darunavir: a review of its use in the management of HIV infection in adults. *Drugs* 2009;69(4):477-503. [PMID: 19323590] https://pubmed.ncbi.nlm.nih.gov/19323590

Miller MM, Kinney KK, Liedtke MD. Virologic failure of high-dose raltegravir with concomitant rifampin. *Infect Dis Clin Pract* 2017;25(3):168-70. [PMID:

Mixon AS, Neal E, Bell S, et al. Care transitions: a leverage point for safe and effective medication use in older adults--a mini-review. *Gerontology* 2015;61(1):32-40. [PMID: 25277280] https://pubmed.ncbi.nlm.nih.gov/25277280

Morelle J, Labriola L, Lambert M, et al. Tenofovir-related acute kidney injury and proximal tubule dysfunction precipitated by diclofenac: a case of drug-drug interaction. *Clin Nephrol* 2009;71(5):567-70. [PMID: 19473619] https://pubmed.ncbi.nlm.nih.gov/19473619

Muller F, Konig J, Hoier E, et al. Role of organic cation transporter OCT2 and multidrug and toxin extrusion proteins MATE1 and MATE2-K for transport and drug interactions of the antiviral lamivudine. *Biochem Pharmacol* 2013;86(6):808-15. [PMID: 23876341] https://pubmed.ncbi.nlm.nih.gov/23876341

Noor MA, Parker RA, O'Mara E, et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. *AIDS* 2004;18(16):2137-44. [PMID: 15577646] https://pubmed.ncbi.nlm.nih.gov/15577646

Ogburn ET, Jones DR, Masters AR, et al. Efavirenz primary and secondary metabolism in vitro and in vivo: identification of novel metabolic pathways and cytochrome P450 2A6 as the principal catalyst of efavirenz 7-hydroxylation. *Drug Metab Dispos* 2010;38(7):1218-29. [PMID: 20335270] https://pubmed.ncbi.nlm.nih.gov/20335270

Orkin C, Llibre JM, Gallien S, et al. Nucleoside reverse transcriptase inhibitor-reducing strategies in HIV treatment: assessing the evidence. *HIV Med* 2018;19(1):18-32. [PMID: 28737291] https://pubmed.ncbi.nlm.nih.gov/28737291

Orrell C, Felizarta F, Nell A, et al. Pharmacokinetics of etravirine combined with atazanavir/ritonavir and a nucleoside reverse transcriptase inhibitor in antiretroviral treatment-experienced, HIV-1-infected patients. *AIDS Res Treat* 2015;2015:938628. [PMID: 25664185] https://pubmed.ncbi.nlm.nih.gov/25664185

Patient-Centered Primary Care Collaborative. The patient-centered medical home: integrating comprehensive medication management to optimize patient outcomes: resource guide. 2012 Jun. https://www.pcpcc.org/sites/default/files/media/medmanagement.pdf [accessed 2018 Oct 16]

Perry CM. Maraviroc: a review of its use in the management of CCR5-tropic HIV-1 infection. *Drugs* 2010;70(9):1189-1213. [PMID: 20518583] https://pubmed.ncbi.nlm.nih.gov/20518583

Perry CM. Elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single-tablet regimen (Stribild(R)): a review of its use in the management of HIV-1 infection in adults. *Drugs* 2014;74(1):75-97. [PMID: 24338165] https://pubmed.ncbi.nlm.nih.gov/24338165

Raffi F, Orkin C, Clarke A, et al. Brief report: long-term (96-week) efficacy and safety after switching from tenofovir disoproxil fumarate to tenofovir alafenamide in HIV-infected, virologically suppressed adults. *J Acquir Immune Defic Syndr* 2017;75(2):226-31. [PMID: 28272164] https://pubmed.ncbi.nlm.nih.gov/28272164

Rathbun C, Liedtke MD. The next generation: etravirine in the treatment of HIV-1 infection in adults refractory to other antiretrovirals. *Virus Adapt Treat* 2010;2:91-102. [PMID:

Reznicek J, Ceckova M, Cerveny L, et al. Emtricitabine is a substrate of MATE1 but not of OCT1, OCT2, P-gp, BCRP or MRP2 transporters. *Xenobiotica* 2017;47(1):77-85. [PMID: 27052107] https://pubmed.ncbi.nlm.nih.gov/27052107

Robertson SM, Maldarelli F, Natarajan V, et al. Efavirenz induces CYP2B6-mediated hydroxylation of bupropion in healthy subjects. *J Acquir Immune Defic Syndr* 2008;49(5):513-19. [PMID: 18989234] https://pubmed.ncbi.nlm.nih.gov/18989234

Roden DM, Darbar D, Kannankeril PJ. 2007. Antiarrhythmic drugs. In: Willerson JT, Wellens HJ, Cohn JN et al., editors. Cardiovascular medicine. London: Springer London. https://doi.org/10.1007/978-1-84628-715-2_102

Rose AJ, Fischer SH, Paasche-Orlow MK. Beyond medication reconciliation: the correct medication list. *JAMA* 2017;317(20):2057-58. [PMID: 28426844] https://pubmed.ncbi.nlm.nih.gov/28426844

Saberi P, Phengrasamy T, Nguyen DP. Inhaled corticosteroid use in HIV-positive individuals taking protease inhibitors: a review of pharmacokinetics, case reports and clinical management. *HIV Med* 2013;14(9):519-29. [PMID: 23590676] https://pubmed.ncbi.nlm.nih.gov/23590676

Samineni D, Desai PB, Sallans L, et al. Steady-state pharmacokinetic interactions of darunavir/ritonavir with lipid-lowering agent rosuvastatin. *J Clin Pharmacol* 2012;52(6):922-31. [PMID: 21712498] https://pubmed.ncbi.nlm.nih.gov/21712498

Sanford M. Rilpivirine. *Drugs* 2012;72(4):525-41. [PMID: 22356290] https://pubmed.ncbi.nlm.nih.gov/22356290

Scarsi KK, Darin KM, Nakalema S, et al. Unintended pregnancies observed with combined use of the levonorgestrel contraceptive implant and efavirenz-based antiretroviral therapy: A three-arm pharmacokinetic evaluation over 48 weeks. *Clin Infect Dis* 2016;62(6):675-82. [PMID: 26646680] https://pubmed.ncbi.nlm.nih.gov/26646680

Schafer JJ, Short WR. Rilpivirine, a novel non-nucleoside reverse transcriptase inhibitor for the management of HIV-1 infection: a systematic review. *Antivir Ther* 2012;17(8):1495-1502. [PMID: 22878339] https://pubmed.ncbi.nlm.nih.gov/22878339

Scott LJ, Chan HL. Tenofovir alafenamide: a review in chronic hepatitis B. *Drugs* 2017;77(9):1017-28. [PMID: 28493172] https://pubmed.ncbi.nlm.nih.gov/28493172

Sim SM, Hoggard PG, Sales SD, et al. Effect of ribavirin on zidovudine efficacy and toxicity in vitro: a concentration-dependent interaction. *AIDS Res Hum Retroviruses* 1998;14(18):1661-67. [PMID: 9870320] https://pubmed.ncbi.nlm.nih.gov/9870320

Song I, Borland J, Arya N, et al. Pharmacokinetics of dolutegravir when administered with mineral supplements in healthy adult subjects. *J Clin Pharmacol* 2015;55(5):490-96. [PMID: 25449994] https://pubmed.ncbi.nlm.nih.gov/25449994

Song I, Zong J, Borland J, et al. The effect of dolutegravir on the pharmacokinetics of metformin in healthy subjects. *J Acquir Immune Defic Syndr* 2016;72(4):400-407. [PMID: 26974526] https://pubmed.ncbi.nlm.nih.gov/26974526

Soriano V, Labarga P, Fernandez-Montero JV, et al. Drug interactions in HIV-infected patients treated for hepatitis C. *Expert Opin Drug Metab Toxicol* 2017;13(8):807-16. [PMID: 28689442] https://pubmed.ncbi.nlm.nih.gov/28689442

Taneva E, Crooker K, Park SH, et al. Differential mechanisms of tenofovir and tenofovir disoproxil fumarate cellular transport and implications for topical preexposure prophylaxis. *Antimicrob Agents Chemother* 2015;60(3):1667-75. [PMID: 26711762] https://pubmed.ncbi.nlm.nih.gov/26711762

Teng R. Ticagrelor: pharmacokinetic, pharmacodynamic and pharmacogenetic profile: an update. *Clin Pharmacokinet* 2015;54(11):1125-38. [PMID: 26063049] https://pubmed.ncbi.nlm.nih.gov/26063049

Trevor AJ, Katzung BG, Kruidering-Hall M. Katzung & Trevor's pharmacology. Chapter 61: Drug interactions. 2013 https://accesspharmacy.mhmedical.com/content.aspx?bookid=514&sectionid=41817582 [accessed 2018 Oct 16]

Tseng A, Hughes CA, Wu J, et al. Cobicistat versus ritonavir: similar pharmacokinetic enhancers but some important differences. *Ann Pharmacother* 2017;51(11):1008-22. [PMID: 28627229] https://pubmed.ncbi.nlm.nih.gov/28627229

Vildhede A, Karlgren M, Svedberg EK, et al. Hepatic uptake of atorvastatin: influence of variability in transporter expression on uptake clearance and drug-drug interactions. *Drug Metab Dispos* 2014;42(7):1210-18. [PMID: 24799396] https://pubmed.ncbi.nlm.nih.gov/24799396

Walckiers D, Van der Heyden J, Tafforeau J. Factors associated with excessive polypharmacy in older people. *Arch Public Health* 2015;73:50. [PMID: 26557365] https://pubmed.ncbi.nlm.nih.gov/26557365

Wallace AW, Victory JM, Amsden GW. Lack of bioequivalence when levofloxacin and calcium-fortified orange juice are coadministered to healthy volunteers. *J Clin Pharmacol* 2003;43(5):539-44. [PMID: 12751275] https://pubmed.ncbi.nlm.nih.gov/12751275

Wandeler G, Buzzi M, Anderegg N, et al. Virologic failure and HIV drug resistance on simplified, dolutegravir-based maintenance therapy: systematic review and meta-analysis. *F1000Res* 2018;7:1359. [PMID: 30271590] https://pubmed.ncbi.nlm.nih.gov/30271590

Wang X, Boffito M, Zhang J, et al. Effects of the H2-receptor antagonist famotidine on the pharmacokinetics of atazanavir-ritonavir with or without tenofovir in HIV-infected patients. *AIDS Patient Care STDS* 2011;25(9):509-15. [PMID: 21770762] https://pubmed.ncbi.nlm.nih.gov/21770762

Welz T, Wyen C, Hensel M. Drug interactions in the treatment of malignancy in HIV-infected patients. *Oncol Res Treat* 2017;40(3):120-27. [PMID: 28253501] https://pubmed.ncbi.nlm.nih.gov/28253501

Wright A, Aaron S, Seger DL, et al. Reduced effectiveness of interruptive drug-drug interaction alerts after conversion to a commercial electronic health record. *J Gen Intern Med* 2018;33(11):1868-76. [PMID: 29766382] https://pubmed.ncbi.nlm.nih.gov/29766382

Yee KL, Sanchez RI, Auger P, et al. Evaluation of doravirine pharmacokinetics when switching from efavirenz to doravirine in healthy subjects. *Antimicrob Agents Chemother* 2017;61(2). [PMID: 27872069] https://pubmed.ncbi.nlm.nih.gov/27872069

Yeh WW. Drug-drug interactions with grazoprevir/elbasvir: practical considerations for the care of HIV/HCV co-infected patients. 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; 2015 May 26-28; Washington, DC. http://www.natap.org/2015/Pharm/Pharm_31.htm

Yin J, Duan H, Wang J. Impact of substrate-dependent inhibition on renal organic cation transporters hOCT2 and hMATE1/2-K-mediated drug transport and intracellular accumulation. *J Pharmacol Exp Ther* 2016;359(3):401-10. [PMID: 27758931] https://pubmed.ncbi.nlm.nih.gov/27758931

Yoshida K, Zhao P, Zhang L, et al. In vitro-in vivo extrapolation of metabolism- and transporter-mediated drug-drug interactions--overview of basic prediction methods. *J Pharm Sci* 2017;106(9):2209-13. [PMID: 28456729] https://pubmed.ncbi.nlm.nih.gov/28456729

Yu J, Zhou Z, Tay-Sontheimer J, et al. Intestinal drug interactions mediated by OATPs: a systematic review of preclinical and clinical findings. *J Pharm Sci* 2017;106(9):2312-25. [PMID: 28414144] https://pubmed.ncbi.nlm.nih.gov/28414144

Yuen GJ, Weller S, Pakes GE. A review of the pharmacokinetics of abacavir. *Clin Pharmacokinet* 2008;47(6):351-71. [PMID: 18479171] https://pubmed.ncbi.nlm.nih.gov/18479171

Zaccara G, Perucca E. Interactions between antiepileptic drugs, and between antiepileptic drugs and other drugs. *Epileptic Disord* 2014;16(4):409-31. [PMID: 25515681] https://pubmed.ncbi.nlm.nih.gov/25515681

Zahabi M, Kaber DB, Swangnetr M. Usability and safety in electronic medical records interface design: a review of recent literature and guideline formulation. *Hum Factors* 2015;57(5):805-34. [PMID: 25850118] https://pubmed.ncbi.nlm.nih.gov/25850118

Zingmond DS, Arfer KB, Gildner JL, et al. The cost of comorbidities in treatment for HIV/AIDS in California. *PLoS One* 2017;12(12):e0189392. [PMID: 29240798] https://pubmed.ncbi.nlm.nih.gov/29240798

Supplement: Guideline Development

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Developer	New York State Department of Health AIDS Institute (NYSDOH AI) Clinical Guidelines Program
Funding source	NYSDOH AI
Program manager	Clinical Guidelines Program, Johns Hopkins University School of Medicine, Division of Infectious Diseases. See Program Leadership and Staff.
Mission	To produce and disseminate evidence-based, state-of-the-art clinical practice guidelines that establish uniform standards of care for practitioners who provide prevention or treatment of HIV, viral hepatitis, other sexually transmitted infections, and substance use disorders for adults throughout New York State in the wide array of settings in which those services are delivered.
Expert committees	The NYSDOH AI Medical Director invites and appoints committees of clinical and public health experts from throughout New York State to ensure that the guidelines are practical, immediately applicable, and meet the needs of care providers and stakeholders in all major regions of New York State, all relevant clinical practice settings, key New York State agencies, and community service organizations.
Committee structure	• Leadership: AI-appointed chair, vice chair(s), chair emeritus, clinical specialist(s), JHU Guidelines Program Director, AI Medical Director, AI Clinical Consultant, AVAC community advisor • Contributing members • Guideline writing groups: Lead author, coauthors if applicable, and all committee leaders
Disclosure and management of conflicts of interest	• Annual disclosure of financial relationships with commercial entities for the 12 months prior and upcoming is required of all individuals who work with the guidelines program, and includes disclosure for partners or spouses and primary professional affiliation. • The NYSDOH AI assesses all reported financial relationships to determine the potential for undue influence on guideline recommendations and, when indicated, denies participation in the program or formulates a plan to manage potential conflicts. Disclosures are listed for each committee member.
Evidence collection and review	• Literature search and review strategy is defined by the guideline lead author based on the defined scope of a new guideline or update. • A comprehensive literature search and review is conducted for a new guideline or an extensive update using PubMed, other pertinent databases of peer-reviewed literature, and relevant conference abstracts to establish the evidence base for guideline recommendations. • A targeted search and review to identify recently published evidence is conducted for guidelines published within the previous 3 years. • Title, abstract, and article reviews are performed by the lead author. The JHU editorial team collates evidence and creates and maintains an evidence table for each guideline.

Table S1: Guideline Development: New York State Department of Health AIDS Institute Clinical Guidelines Program	
Recommendation development	• The lead author drafts recommendations to address the defined scope of the guideline based on available published data. • Writing group members review the draft recommendations and evidence and deliberate to revise, refine, and reach consensus on all recommendations. • When published data are not available, support for a recommendation may be based on the committee's expert opinion. • The writing group assigns a 2-part rating to each recommendation to indicate the strength of the recommendation and quality of the supporting evidence. The group reviews the evidence, deliberates, and may revise recommendations when required to reach consensus.
Review and approval process	• Following writing group approval, draft guidelines are reviewed by all contributors, program liaisons, and a volunteer reviewer from the AI Community Advisory Committee. • Recommendations must be approved by two-thirds of the full committee. If necessary to achieve consensus, the full committee is invited to deliberate, review the evidence, and revise recommendations. • Final approval by the committee chair and the NYSDOH AI Medical Director is required for publication.
External reviews	• External review of each guideline is invited at the developer's discretion. • External reviewers recognized for their experience and expertise review guidelines for accuracy, balance, clarity, and practicality and provide feedback.
Update process	• JHU editorial staff ensure that each guideline is reviewed and determined to be current upon the 3-year anniversary of publication; guidelines that provide clinical recommendations in rapidly changing areas of practice may be reviewed annually. Published literature is surveilled to identify new evidence that may prompt changes to existing recommendations or development of new recommendations. • If changes in the standard of care, newly published studies, new drug approval, new drug-related warning, or a public health emergency indicate the need for immediate change to published guidelines, committee leadership will make recommendations and immediate updates and will invite full committee review as indicated.