

DRUG–DRUG INTERACTIONS

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Overview

Pharmacokinetic (PK) drug–drug interactions between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. In some instances, changes in drug exposure may increase the frequency and/or severity of toxicities or affect therapeutic responses. When prescribing or switching one or more drugs in an ARV regimen, clinicians must consider the potential for drug–drug interactions—both those affecting ARVs and those affecting concomitant drugs. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a specific drug interaction may differ depending on whether a new ARV is being initiated in a patient on a stable concomitant medication or a new concomitant medication is being initiated in a patient on a stable ARV regimen. The magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways and drug transporter systems are prescribed concomitantly. When it is necessary to prescribe interacting drugs, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities. Tables [24a](#) through [25b](#) provide information on known or suspected drug interactions between ARV agents and commonly prescribed medications based on published PK data or information from product labels. The tables provide general guidance on drugs that should not be coadministered and recommendations for dose modification of ARVs or concomitant medicines or for alternative therapy.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common drug interaction mechanisms are described and listed for individual ARV drugs in [Table 23](#) below.

Pharmacokinetic Interactions Affecting Drug Absorption

The extent of oral absorption of drugs can be affected by the following mechanisms:

- Acid-reducing agents—such as proton pump inhibitors, H2 antagonists, or antacids—can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir and rilpivirine).
- Products that contain polyvalent cations—such as supplements, iron products, or antacids that contain aluminum, calcium, or magnesium—can bind to integrase strand transfer inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme cytochrome P450 (CYP) 3A4 or efflux transporter P-glycoprotein in the intestines may reduce or promote the absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are most frequently responsible for clinically significant drug interactions:

- The CYP enzyme system is responsible for the metabolism of many drugs, including non-nucleoside reverse transcriptase inhibitors, protease inhibitors, the CCR5 antagonist maraviroc, and the INSTI elvitegravir. CYP3A4 is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARV drugs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
- The uridine diphosphate glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTIs cabotegravir and raltegravir. Drugs that induce or inhibit the UGT enzyme can affect the PK of these INSTIs.
- The INSTIs bicitegravir and dolutegravir (DTG) and the capsid inhibitor lenacapavir have mixed metabolic pathways, including both CYP3A4 and UGT1A1. Drugs that induce or inhibit these enzymes may have variable impact on the PK of these ARVs.

Pharmacokinetic Enhancers (Boosters)

PK enhancing is a strategy used to increase exposure of an ARV by concomitantly administering a drug that inhibits the enzymes that metabolize the ARV. Currently, two agents are used as PK enhancers: ritonavir (RTV) and cobicistat (COBI). Both drugs are potent inhibitors of the CYP3A4 enzyme and, thus, when coadministered with ARVs metabolized by the CYP3A4 pathway, the resultant systemic exposure of the ARVs is higher. Importantly, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. Complex or unknown mechanisms of PK-based interactions preclude extrapolation of RTV drug interactions to certain COBI interactions, such as interactions with warfarin, direct oral anticoagulants, phenytoin, voriconazole, oral contraceptives, and certain hydroxy-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

Drug transporters are expressed in various tissues, and they play an important role in drug disposition. Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic cation transporters in renal tubular cells. Similar transporters aid hepatic, renal, and biliary clearance of drugs and may be susceptible to drug interactions. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these drug transporters. The influence of drug transporters on drug–drug interactions is complex, and the clinical significance of these interactions is unclear but is under investigation. Further research is needed to better understand these pathways and the clinical significance of this drug interaction mechanism.

Role of Therapeutic Drug Monitoring in Managing Drug–Drug Interactions

Therapeutic drug monitoring (TDM) can guide the dosing of certain medications by using measured drug concentrations to improve the likelihood of desired therapeutic and safety outcomes. Drugs suitable for TDM are characterized by a known exposure-response relationship and a therapeutic range of concentrations. The “therapeutic range” is a range of concentrations established through clinical investigations that are associated with a greater likelihood of achieving the desired therapeutic response and/or reducing the frequency of drug-associated adverse reactions.

When concomitant use of an ARV drug and another medication is likely to result in a clinically important drug–drug interaction, the first step is to assess whether other, equally effective treatment options can be used to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Drug concentration assays for some ARV drugs are commercially available; however, result reporting may take 1 week or longer. When interpreting assay results, clinicians should consider the patient’s medication adherence, the timing of the patient’s last ARV dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If needed, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take. If a dose adjustment is needed, TDM must be repeated after the dose-adjusted drug reaches steady state to ensure appropriate dosing.

TDM information should not be used alone; it must be considered in conjunction with other clinical information—including virologic response, medication adherence, and signs and symptoms of drug toxicities—to assure safe and effective therapy.

Table 23. Mechanisms of Antiretroviral-Associated Drug Interactions

Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the antiretroviral (ARV) drug and/or the interacting drug. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and cytochrome P450 (CYP)– and uridine diphosphate glucuronosyltransferase (UGT) 1A1–mediated interactions.

Note: N/A indicates that there are no clinically relevant interactions by the mechanism. Identified mechanisms are specific to the ARV drugs described in the row and may not be reflective of complete ARV regimens. Some older ARVs—**unboosted atazanavir**, fosamprenavir, nelfinavir, **nevirapine**, tipranavir, and zidovudine—are not commonly used in clinical practice and are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels for information regarding drug interactions for these ARVs.

ARV Drugs by Drug Class	Mechanisms That May Affect Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs			
	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
INSTIs							
BIC	N/A	Concentrations of PO INSTIs are decreased by-products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn).	Substrate	3A4	N/A	N/A	Substrate
CAB	N/A		Substrate	N/A	N/A	N/A	Substrate
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate
EVG/c	N/A		Inhibitor	3A4	3A4, 2D6	2C9	Substrate
RAL	N/A		N/A	N/A	N/A	N/A	Substrate
PIs							
ATV/c	Concentration decreased	N/A	Substrate, inhibitor	3A4	3A4, 2D6, 2C8	N/A	Inhibitor
ATV/r	Concentration decreased	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6, 2C8	1A2, 2B6, 2C8, 2C9, 2C19	ATV: Inhibitor RTV: Inducer
DRV/c	N/A	N/A	Substrate, inhibitor	3A4	3A4, 2D6	N/A	No data

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DRV/r	N/A	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
LPV/r	N/A	N/A	Substrate	3A4, 2D6	3A4	1A2, 2B6, 2C8, 2C9, 2C19	Inducer
NNRTIs							
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A
RPV	Only RPV PO: Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A
NRTIs							
ABC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
FTC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
3TC	N/A	N/A	N/A	N/A	N/A	N/A	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A

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	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
Capsid Inhibitor							
LEN (SQ and PO)	N/A	N/A	Substrate	3A4	3A4	N/A	Substrate
CCR5 Antagonist							
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
gp120-Directed Attachment Inhibitor							
FTR	N/A	N/A	Substrate	3A4	N/A	N/A	N/A
Fusion Inhibitor							
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Key: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; ATV/c = atazanavir/cobicistat; ATV/r = atazanavir/ritonavir; BIC = bictegravir; Ca = calcium; CAB = cabotegravir; CCR5 = C-C chemokine receptor type 5; CYP = cytochrome P; DOR = doravirine; DRV/c = darunavir/cobicistat; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG/c = elvitegravir/cobicistat; Fe = iron; FTC = emtricitabine; FTR = fostemsavir; gp120 = glycoprotein 120; IBA = ibalizumab; INSTI = integrase strand transfer inhibitor; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; P-gp = P-glycoprotein; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; **SQ = subcutaneous**; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase; Zn = zinc