



Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Drug-Drug Interactions (Last updated July 14, 2016; last reviewed July 14, 2016)

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 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 other drugs a patient is taking. A thorough review of concomitant medications in consultation with a clinician with expertise in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions. Recommendations for managing a particular 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 are prescribed concomitantly. When prescribing interacting drugs is necessary, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities.

Mechanisms of Pharmacokinetic Interactions

PK interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. The most common mechanisms of interactions are described below and listed for each ARV drug in [Table 17](#).

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 ARVs that require gastric acidity for optimal absorption (ie, atazanavir [ATV] and rilpivirine [RPV]).
- Products that contain polyvalent cations, such as aluminum, calcium, magnesium-containing antacids, supplements, or iron products, can bind to integrase inhibitors (INSTIs) and reduce absorption of these ARV agents.
- Drugs that induce or inhibit the enzyme CYP3A4 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.

1. The cytochrome P450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTI), protease inhibitors (PI), CCR5 antagonist maraviroc (MVC), and the INSTI elvitegravir (EVG). Cytochrome P450 3A4 (CYP3A4) is the most common enzyme responsible for drug metabolism, though multiple enzymes may be involved in the metabolism of a drug. ARVs and concomitant medications may be inducers, inhibitors, and/or substrates of these enzymes.
2. The uridine diphosphate (UDP)-glucuronosyltransferase (UGT) 1A1 enzyme is the primary enzyme responsible for the metabolism of the INSTIs dolutegravir (DTG) and raltegravir (RAL). Drugs that induce or inhibit the UGT enzyme can affect the PKs of these INSTIs.

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 of these agents are potent inhibitors of the CYP3A4 enzyme, resulting in

higher drug exposures of the coadministered ARV metabolized by this pathway. Importantly, RTV and COBI may 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, phenytoin, voriconazole, oral contraceptives, and certain HMG-CoA reductase inhibitors (or statins).

Other Mechanisms of Pharmacokinetic Interactions

Knowledge of drug transporters is evolving, elucidating additional drug interaction mechanisms. For example, DTG decreases the renal clearance of metformin by inhibiting organic anion 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.

[Tables 18-20b](#) 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 modifications or alternative therapy.

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 1 of 2)

Pharmacokinetic interactions may occur during absorption, metabolism, or elimination of the ARV and/or the interacting drugs. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs (eg, transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

Note: Ellipses (...) indicate that there are no clinically relevant interactions by these mechanisms.

ARV Drugs by Drug Class	Mechanisms That May Affect or Be Affected by Oral Absorption of ARV Drugs			Enzymes That Metabolize or Are Induced or Inhibited by ARV Drugs				Other Mechanisms of Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
Integrase Strand Transfer Inhibitors (INSTIs)								
Dolutegravir (DTG)	...	Concentration decreased by products containing polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	Substrate	3A4 (small contribution)	Substrate	Inhibitor of renal transporters OCT2 and MATE
Elvitegravir (EVG)	...	Concentration decreased by products containing polyvalent cations (eg, Ca, Mg, Al, Fe, Zn)	...	3A4	...	2C9	Substrate	...
Raltegravir (RAL)	Substrate
Pharmacokinetic (PK) Enhancers (Boosters)								
Cobicistat (COBI)	Inhibitor	3A4	3A4, 2D6
Ritonavir (RTV)	Substrate, inhibitor	3A4, 2D6	3A4, 2D6 (lesser extent)	1A2, 2C8, 2C9, 2C19	Inducer	...
Protease Inhibitors (PIs)								
Note: When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
Atazanavir (ATV)	Concentration decreased	...	Substrate, inducer, inhibitor	3A4	3A4, 2C8 (weak)	...	Inhibitor	OATP inhibitor
Darunavir (DRV)	Substrate	3A4	3A4	2C9	...	OATP inhibitor

Table 17. Mechanisms of Antiretroviral-Associated Drug Interactions (page 2 of 2)

ARV Drugs by Drug Class	Mechanisms That May Affect or be Affected by Oral Absorption of ARV Drugs			Enzymes That Metabolize or are Induced or Inhibited by ARV Drugs				Other Mechanisms of Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glycoprotein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
Protease Inhibitors (PIs), continued								
Note: When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
Fosamprenavir (FPV)	Concentration decreased by H2 antagonist	...	Substrate, inhibitor	3A4	3A4	3A4 (weak)
Lopinavir (LPV)	Substrate	3A4	3A4	OATP inhibitor
Saquinavir (SQV)	Substrate, inhibitor	3A4	3A4	OATP inhibitor
Tipranavir (TPV)	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	...	OATP inhibitor
Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)								
Efavirenz (EFV)	2B6 (primary), 2A6, 3A4	2C9, 2C19, 3A4	3A4, 2B6
Etravirine (ETR)	Inducer	3A4, 2C9, 2C19	2C9, 2C19	3A4
Nevirapine (NVP)	3A4, 2B6	...	3A4, 2B6
Rilpivirine (RPV)	Concentration decreased	3A4
Nucleoside Reverse Transcriptase Inhibitors (NRTIs)								
Abacavir (ABC)	Substrate	Alcohol dehydrogenase substrate
Emtricitabine (FTC)
Lamivudine (3TC)
Tenofovir alafenamide (TAF)	Substrate	OATP substrate
Tenofovir disoproxil fumarate (TDF)	Substrate	Competition of active renal tubular secretion
Zidovudine (ZDV)	Glucuronidation
CCR5 Antagonist								
Maraviroc (MVC)	Substrate	3A4
Fusion Inhibitor								
Enfuvirtide (T20)

Key to Abbreviations: Al = aluminium; ARV = antiretroviral; Ca = calcium; CYP = cytochrome P; Fe = iron; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; **OATP = organic anion-transporting polypeptide**; OCT2 = organic cation transporter 2; UGT1A1 = uridine diphosphate glucuronosyltransferase; Zn = zinc