Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

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Drug-Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018)

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 the other drugs a patient is taking. 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 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 it is necessary to prescribe interacting drugs, 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 20.

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 [ATV] and rilpivirine [RPV]).
- 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 3A4 (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.

- The cytochrome P450 enzyme system is responsible for the metabolism of many drugs, including the non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), the CCR5 antagonist maraviroc (MVC), and the INSTI elvitegravir (EVG). 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 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 drugs are potent inhibitors of the CYP3A4 enzyme, resulting in higher systemic exposures of the coadministered ARV that is metabolized by this pathway. 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, 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 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.

Tables 21a through 22b 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.

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 PK drug-drug interaction, the first step is to assess whether there are other, equally effective treatment options that can be used in order to avoid the interaction. If that is not possible, TDM may be useful in assessing whether a dose adjustment is needed.

Assays for some ARV drug concentrations are commercially available; however, it may take 1 week or longer for the results to be reported. When interpreting the results, clinicians should take into account the patient's medication adherence, the timing of last 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, it is necessary to repeat TDM after the adjusted drug reaches steady state in order to assure appropriate dosing.

TDM information should not be used alone; it must be integrated with other clinical information, including virologic responses and signs and symptoms of drug toxicities, to assure safe and effective therapy.

Table 20. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018) (page 1 of 2)

PK 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 (e.g., transporters); however, the table lists the most common mechanisms of known interactions and focuses on absorption and CYP- and UGT1A1-mediated interactions.

Note: N/A indicates that there are no clinically relevant interactions by these mechanisms. Identified mechanisms are specific to individual ARV drugs and not combinations of ARV drugs.

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				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
INSTIs								
BIC	N/A	Concentration decreased by products that contain polyvalent cations (e.g., Ca, Mg, Al, Fe, Zn)	Substrate	3A4	N/A	N/A	Substrate	Inhibitor of renal transporters OCT2 and MATE1
DTG	N/A		Substrate	3A4 (minor)	N/A	N/A	Substrate	Inhibitor of renal transporters OCT2 and MATE1
EVG	N/A		N/A	3A4	N/A	2C9	Substrate	N/A
RAL	N/A		N/A	N/A	N/A	N/A	Substrate	N/A
PK Enhancers (Boosters)								
COBI	N/A	N/A	Inhibitor	3A4	3A4, 2D6	N/A	N/A	N/A
RTV	N/A	N/A	Substrate, inhibitor	3A4, 2D6	3A4, 2D6	1A2, 2B6, 2C8, 2C9, 2C19	Inducer	N/A
PIs **Note:** When PIs are coadministered with PK enhancers (boosters), the pharmacologic properties of both agents should be considered when assessing potential drug interactions.								
ATV	Concentration decreased	N/A	Substrate, inducer, inhibitor	3A4	3A4	N/A	Inhibitor	OATP inhibitor
DRV	N/A	N/A	Substrate, inducer	3A4	3A4	2C9	N/A	OATP inhibitor
FPV	Concentration decreased by H2 antagonist	N/A	Substrate, inhibitor	3A4	3A4	N/A	N/A	N/A
LPV	N/A	N/A	Substrate	3A4	3A4	N/A	N/A	OATP inhibitor
SQV	N/A	N/A	Substrate, inhibitor	3A4	3A4	N/A	N/A	OATP inhibitor
TPV	N/A	N/A	Substrate, inducer	3A4	2D6	3A4, 1A2, 2C19	N/A	OATP inhibitor
NNRTIs								
DOR	N/A	N/A	N/A	3A4, 3A5	N/A	N/A	N/A	N/A
EFV	N/A	N/A	N/A	2B6 (primary), 2A6, 3A4	3A4	3A4, 2B6, 2C19	N/A	N/A

Table 20. Mechanisms of Antiretroviral-Associated Drug Interactions (Last updated October 25, 2018; last reviewed October 25, 2018) (page 2 of 2)

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				Other Mechanisms of Known Drug Interactions
	Increasing Gastric pH	Cationic Chelation	P-glyco-protein	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1	
NNRTIs, continued								
ETR	N/A	N/A	N/A	3A4, 2C9, 2C19	2C9, 2C19	3A4	N/A	N/A
NVP	N/A	N/A	N/A	3A4, 2B6	N/A	3A4, 2B6	N/A	N/A
RPV	Concentration decreased	N/A	N/A	3A4	N/A	N/A	N/A	N/A
NRTIs								
ABC	N/A	N/A	N/A	N/A	N/A	N/A	Substrate	Alcohol dehydrogenase substrate
FTC	N/A	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	N/A
TAF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A	OATP substrate
TDF	N/A	N/A	Substrate	N/A	N/A	N/A	N/A	Competition of active renal tubular secretion
ZDV	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Glucuronidation
CCR5 Antagonist								
MVC	N/A	N/A	Substrate	3A4	N/A	N/A	N/A	N/A
Fusion Inhibitor								
T-20	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Key to Acronyms: 3TC = lamivudine; ABC = abacavir; Al = aluminum; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; Ca = calcium; COBI = cobicistat; CYP = cytochrome P; DOR = doravirine; DRV = darunavir; DTG = dolutegravir; EFV = efavirenz; ETR = etravirine; EVG = elvitegravir; Fe = iron; FPV = fosamprenavir; FTC = emtricitabine; INSTI = integrase strand transfer inhibitor; LPV = lopinavir; MATE = multidrug and toxin extrusion transporter; Mg = magnesium; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitors; NRTI = nucleoside reverse transcriptase inhibitors; NVP = nevirapine; OCT2 = organic cation transporter 2; OATP = organic anion-transporting polypeptide; PK = pharmacokinetic; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQV = saquinavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; TPV = tipranavir; UGT = uridine diphosphate glucuronosyltransferase; ZDV = zidovudine; Zn = zinc