DRUG–DRUG INTERACTIONS

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Pharmacokinetic (PK) drug–drug interactions (DDIs) between antiretroviral (ARV) drugs and concomitant medications are common and may lead to increased or decreased drug exposure. When prescribing or switching drugs in an ARV regimen, clinicians should consider the potential for DDIs—both those affecting ARVs and those affecting concomitant medications. In some instances, changes in drug exposure may increase the frequency and/or severity of toxicities or affect therapeutic responses, risking treatment failure and/or resistance. Pharmacodynamic interactions can also lead to increased toxicity when medications that have overlapping adverse effects are coadministered.

Recommendations for managing a specific drug interaction may differ depending on whether a new ARV is being initiated in a person on a stable concomitant medication or a new concomitant medication is being initiated in a person on a stable ARV regimen. Furthermore, the magnitude and significance of interactions are difficult to predict when several drugs with competing metabolic pathways and drug transporter systems are prescribed together. When it is necessary to prescribe interacting medications, clinicians should be vigilant in monitoring for therapeutic efficacy and/or concentration-related toxicities. A thorough review of concomitant medications in consultation with an expert in ARV pharmacology can help in designing a regimen that minimizes undesirable interactions.

Drug–Drug Interaction Resources

Previous iterations of these guidelines contained extensive ARV DDI tables (last updated in September 2024). These tables remain available in the Archived Guidelines.

To screen for DDIs and review recommendations for dose modifications and monitoring of ARVs or concomitant medications, clinicians may use interactive web-based resources, such as the Liverpool HIV Drug Interaction Checker.

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:

- **Changes in gastric pH:** Acid-reducing agents, such as proton pump inhibitors, histamine 2 (or H2) antagonists, or antacids can reduce the absorption of ARV drugs that require gastric acidity for optimal absorption (i.e., atazanavir, rilpivirine [RPV]).[1,2]
- **Binding of ARV drugs:** 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 medications.[3,4]

- **Effects on metabolic enzymes or transporters:** Drugs that induce or inhibit the enzyme cytochrome P450 (CYP), predominantly 3A4, or the efflux transporter P-glycoprotein in the intestines may reduce or promote the oral bioavailability or absorption of other drugs.

Pharmacokinetic Interactions Affecting Hepatic Metabolism

Two major enzyme systems are frequently responsible for clinically significant drug interactions[5,6]:

- The CYP enzyme system is responsible for the metabolism of many ARV medications, including several INSTIs, non-nucleoside reverse transcriptase inhibitors, protease inhibitors, maraviroc, fostemsavir, and lenacapavir (LEN). CYP3A4 is the most common enzyme responsible for drug metabolism, although 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 responsible for the metabolism of INSTIs, particularly cabotegravir (CAB) and raltegravir. Drugs that induce or inhibit the UGT enzyme can affect the PK of these INSTIs.

Some ARVs have mixed metabolic pathways involving both CYP3A4 and UGT1A1. Notably, the INSTIs bictegravir and dolutegravir (DTG), as well as the capsid inhibitor LEN, are metabolized through both enzyme systems. 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 (i.e., concentrations) 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. When coadministered with ARVs metabolized by the CYP3A4 pathway, the resultant systemic exposure of the ARVs is higher. Importantly, apart from CYP3A4, RTV and COBI have different effects on other CYP- or UGT-metabolizing enzymes and drug transporters. These 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 (statins).

Transporter-Mediated Pharmacokinetic Interactions

Drug transporters are expressed in various tissues, and they play an important role in drug disposition.[7] 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 DDIs is complex, and the clinical significance of some interactions is unclear but is under investigation.

Other Mechanisms of Pharmacokinetic Interactions

Enzymes Involved in Nucleoside Metabolism

Islatravir (ISL) requires intracellular phosphorylation to its active triphosphate form (ISL-TP) to exert its antiviral effect.[8] This activation step and its metabolic pathway create two key interaction considerations:

- **Deoxycytidine kinase (dCK) substrate competition:** Coadministration with other dCK substrates, such as certain nucleoside ARVs (e.g., lamivudine, emtricitabine), **is contraindicated.** Coadministration with nucleoside antimetabolites (e.g., cytarabine) **is not recommended,** as it may reduce ISL-TP formation, potentially compromising therapeutic efficacy.
- **Adenosine deaminase (ADA) inhibition:** Concurrent use of ADA inhibitors (e.g., pentostatin) **is not recommended,** because it may significantly increase ISL plasma concentrations and increase the risk of adverse reactions.

Drug–Drug Interactions With Long-Acting Antiretroviral Medications

As with all antiretroviral therapy, individuals receiving long-acting (LA) ARVs should be regularly monitored for DDIs, including those that may alter the concentrations of the ARVs or the concomitant medications. The extended half-lives of LA ARVs, such as injectable LEN and LA CAB/RPV, introduce unique DDI management challenges not encountered with daily oral regimens, which may complicate both the detection and resolution of DDIs. Electronic medical records may not detect or alert clinicians regarding these interactions because LA ARV medications can be listed outside of current medication lists or may be ordered as one-time injections as opposed to continuous therapy. Patients should be counseled to promptly report any new medication changes so that interactions can be identified and addressed in a timely manner.

The approach for managing a particular DDI may differ depending on the scenario: whether the LA ARV medication is being initiated in a person already receiving stable concomitant medications, whether new medications are being introduced to a person already on LA ARV medications, or if the LA ARV medication is discontinued. Each scenario requires a tailored approach, including potential dose adjustment, alternative drug selection, and development of a monitoring strategy.

For example, LEN can increase concentrations of certain concomitant medications initiated within 9 months of the last LEN dose.[9] Thus, the DDI risk of LA ARVs may persist well into the post-discontinuation period and may not be immediately apparent to clinicians. Clinicians should screen for potential DDIs throughout the period of residual drug exposure as described in the relevant prescribing information for LA ARV medications.

Finally, if oral ARV bridging is required due to a missed LA ARV injection, the DDI profile of the bridging regimen should be reviewed and managed accordingly.

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 medication and another medication is likely to result in a clinically important DDI, 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 medications are commercially available; however, results may take 1 week or longer to be reported. When interpreting assay results, clinicians should consider the person's medication adherence, the timing of the person's last ARV dose and blood draw, and the time elapsed since coadministration of the interacting drug combination. If available, a specialist in ARV clinical pharmacology should be consulted when interpreting the results and deciding what actions to take, which may include further monitoring and/or dosage adjustments.

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) medication and/or the interacting drug. This table does not include a comprehensive list of all possible mechanisms of interactions for individual ARV drugs; 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: Information regarding P-glycoprotein, CYP substrate, inhibitor, and inducer status and UGT1A1 is referenced from product labels. N/A indicates that there are no clinically relevant interactions by the mechanism. Identified mechanisms are specific to the ARV medications described in the row and may not be reflective of complete ARV regimens. Some older ARVs—unboosted atazanavir, fosamprenavir, nelfinavir, nevirapine, tipranavir, and oral zidovudine—are not commonly used in clinical practice and/or are no longer recommended by the Panel for the Use of Antiretroviral Agents in Adults and Adolescents With HIV for use in adults and adolescents; therefore, they are **not** included in this table. Please refer to the U.S. Food and Drug Administration product labels or the Liverpool HIV Drug Interaction Checker 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 (IM and PO)	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

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	Increasing Gastric pH	Cationic Chelation	P-gp	CYP Substrate	CYP Inhibitor	CYP Inducer	UGT1A1
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
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 (IM and PO)	**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
ISL[a]	N/A	N/A	N/A	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
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
Capsid Inhibitor							
LEN (PO and SQ)	N/A	N/A	Substrate, inhibitor	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
Post-Attachment Inhibitor							
IBA	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a] See subsection regarding ISL interactions.

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 P450; 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; IM = intramuscular; INSTI = integrase strand transfer inhibitor; ISL = islatravir; LEN = lenacapavir; LPV/r = lopinavir/ritonavir; Mg = magnesium; MVC = maraviroc; N/A = not applicable; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; P-gp = P-glycoprotein; PI = protease inhibitor; PO = oral; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SQ = subcutaneous; TAF = tenofovir alafenamide; TDF = tenofovir disoproxil fumarate; UGT = uridine diphosphate glucuronosyltransferase; Zn = zinc

Knowledge Gaps

- Research is needed to understand optimal clinical management strategies for DDIs between LA injectable ARV medications and key medication categories (e.g., commonly prescribed medications, CYP3A4 inducers).
- More research is needed to evaluate DDIs between ARV medications and newer anti-tuberculosis medications.
- Research is needed to determine the clinical utility of TDM for management of ARV drug interactions (including LA ARV medications) in specific clinical scenarios, such as renal or hepatic impairment, obesity, and pregnancy.
- Research is needed to develop, test, and implement novel modalities for TDM of ARVs (e.g., alternate biological matrices, including dried blood spot and urine) that can inform DDI management.
- Research is needed to characterize the PK and clinical impact of multidrug interactions occurring when more than two medications are used concomitantly with ART.
- More research is needed to understand transporter-mediated ARV DDIs and their clinical significance.
- More research is needed to understand real-world prescribing practices (e.g., via observational studies), whether they follow established dosing and monitoring recommendations for ARV DDIs with high-risk medications (e.g., narrow therapeutic index drugs or high potential for adverse events), and the outcomes of those practices in order to implement strategies for safely prescribing ARV medications.
- More research is needed to understand if sex may influence the adverse clinical outcomes of ARV DDIs and to inform any dosing strategies that can minimize these effects.
- Research is needed to facilitate the translation and application of DDI study findings (particularly PK modeling studies) to clinical practice for optimal interaction management.

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