Adverse Effects of Antiretroviral Medications

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Adverse effects have been reported with all antiretroviral (ARV) medications. Commonly reported reasons for switching or discontinuing oral or injectable therapy were due to adverse effects, especially with the initiation of antiretroviral therapy (ART) regimens in the late 1990s and early 2000s.[1] Fortunately, newer ART regimens are associated with fewer serious and intolerable adverse effects. Generally, <10% of participants who are ART-naive and who enrolled in randomized trials of newer agents experience treatment-limiting adverse events.[2,3] However, the short-term and long-term complications of ART may be underestimated because most clinical trials use specific inclusion criteria that exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short (generally 2–4 years).

ART is recommended for all people with HIV regardless of CD4 T lymphocyte cell count, and with current treatments and approaches/strategies, therapy must be continued indefinitely. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART adverse effects must be anticipated and managed. From a safety and tolerability standpoint, the focus of management has evolved from identifying and managing toxicities related to early ARVs to individualizing therapy to avoid or mitigate long-term adverse effects, such as atherosclerotic cardiovascular disease, diabetes and other metabolic complications, kidney dysfunction, neuropsychiatric events, and accelerated declines in bone mineral density.

Antiretroviral Regimen Selection

When selecting an ARV regimen, clinicians must consider potential adverse effects and any prior history of drug intolerance. Additionally, several factors may predispose people with HIV to adverse effects of ARV medications. These factors include:

- Concomitant use of medications with overlapping and additive toxicities.
- Comorbid conditions that increase the risk of adverse effects. For example, underlying liver disease from alcohol use, coinfection with viral hepatitis, and/or liver steatosis[4,5] may increase the risk of hepatotoxicity when some protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).[6]
- Certain ARVs that may exacerbate pre-existing conditions. For example, psychiatric disorders may be exacerbated by efavirenz (EFV), rilpivirine, and, infrequently, by integrase strand transfer inhibitors.[7,8]
- Drug–drug interactions that may increase the toxicities of ARV medications or concomitant medications. For example, when pharmacokinetic boosters such as ritonavir or cobicistat are used.[9]
- Genetic factors that predispose people with HIV to some adverse effects of medications that are no longer commonly used in clinical practice, such as abacavir (ABC) hypersensitivity reaction,[10,11] EFV neuropsychiatric toxicity[9,12] or QTc (QT corrected for heart rate) prolongation,[13,14] and atazanavir (ATV)-associated hyperbilirubinemia.[15]
- Dosing errors, which can predispose people with HIV to adverse effects when medications are administered at incorrect doses—whether at doses that are too high or at inappropriate intervals—and can increase the likelihood of adverse effects.

Management of Adverse Effects

ART-associated adverse effects can range from acute and potentially life-threatening to chronic and insidious. When people with HIV experience treatment-limiting toxicities associated with ART, selecting new ART regimens that pose either no or a lower risk of exacerbating the condition or contributing to further complications is warranted. Serious life-threatening effects (e.g., hypersensitivity reaction due to ABC, symptomatic hepatotoxicity, severe cutaneous reactions) require the immediate discontinuation of all ARV medications and re-initiation of an alternative regimen without overlapping toxicity. Toxicities that are not life-threatening (e.g., urolithiasis with ATV, renal tubulopathy with TDF) can usually be managed by substituting another ARV medication for the presumed causative medication without interrupting ART. Chronic, non–life-threatening adverse effects (e.g., dyslipidemia) can be addressed either by switching the potentially causative medication for another medication or by managing the adverse effect with nonpharmacological interventions or pharmacologic interventions such as statins. Management strategies must be individualized for each person with HIV. When adverse effects occur during the use of long-acting injectable ARV drugs, management may be challenging due to the persistence of drug in the body over the course of many months to years. Oral lead-in regimens for cabotegravir plus rilpivirine are available to assess short-term tolerability.

Switching from an effective ARV agent or regimen to a new agent or regimen must be done carefully and only when the potential benefits of the change outweigh the potential risks of altering treatment. The fundamental principle of regimen switching is to maintain viral suppression. When selecting a new agent or regimen, providers should be aware that drug-resistant viruses previously acquired or selected, even those not detected by past genotypic resistance testing, are archived in HIV reservoirs. The resistant virus, even if absent from subsequent resistance test results, may reappear under selective drug pressure. See Optimizing Antiretroviral Therapy in the Setting of Viral Suppression for further discussion. It is critical that providers review the following information before implementing any treatment switch:

- Medical and complete ARV history, including prior virologic responses to ART
- All previous drug resistance test results
- Viral tropism (if maraviroc is being considered)
- HLA-B*5701 status (if ABC is being considered)
- Comorbidities
- Pregnancy status and the desire and/or ability to become pregnant or use contraceptives
- Hepatitis B virus (HBV) status. People with evidence of chronic HBV infection should not discontinue ARVs active against HBV (e.g., TDF, tenofovir alafenamide, lamivudine, emtricitabine). If discontinuation is necessary due to adverse effects, consult the HBV/HIV Coinfection section for guidance.
- Adherence history
- Prior intolerances to any ARVs
- Concomitant medications and supplements, considering any potential drug interactions with ARVs
- Cost to people with HIV and options for patient assistance programs if needed (see Cost Considerations and Antiretroviral Therapy)

For the first few months after an ART switch, the person should be closely monitored for any new adverse effects, and HIV viral load should be monitored to ensure continued viral suppression.

Information on the adverse effects of ARVs is outlined in several tables in these Guidelines. Table 20 provides clinicians with a list of the most common and/or severe ARV-associated adverse events for each drug class. The most common adverse effects of individual ARV agents are summarized in Appendix A. Drug Characteristics Tables.

Table 20. Common and/or Severe Adverse Effects Associated With Antiretroviral Medications

This table focuses on antiretroviral (ARV)-associated adverse effects that a person may experience as a result of taking an ARV regimen. The attribution of adverse effects to individual ARVs is inherently limited by the absence of long-term monotherapy trials, making it difficult to delineate the specific contribution of each medication within the combination regimens. These limitations should be considered carefully when assessing causality, as adverse effects may be related to the ARV regimen as a whole rather than to any single component.

Adverse effects for ARV medications that are no longer on the market or are not commonly used in clinical practice (didanosine [ddI], fosamprenavir/ritonavir, indinavir, lopinavir/ritonavir, nelfinavir, nevirapine, saquinavir/ritonavir, stavudine [d4T], tipranavir/ritonavir, zidovudine [ZDV]), with few exceptions, have been removed from this table. Clinicians should refer to the product labels or to the archived July 10, 2019, version of the Guidelines for information regarding the adverse effects associated with select older ARVs. Because some adverse effects may persist long after discontinuation of the older ARVs—such as d4T, ddI, zalcitabine, and ZDV—and people with HIV may still present with these long-lasting toxicities, these medications remain listed among the ARVs associated with adverse effects such as lipodystrophy and peripheral neuropathy.

For information regarding potential adverse effects of ARVs on fetuses and newborns when certain ARVs are taken around the time of conception or during pregnancy, refer to the Perinatal Guidelines.

This table highlights the common and/or severe adverse effects by ARV class and for individual ARVs, when appropriate. For ARV class–specific adverse effects, the table provides relative comparisons among individual ARVs for each class effect. In some cases, the terms “no known effect,” “rarely observed” (for select severe effects), “not common or severe,” or “no or limited data” are used, especially for the entry inhibitor and capsid inhibitor classes, where the evaluation of safety is based mostly on uncontrolled and nonrandomized clinical trials. See Appendix A. Drug Characteristics Tables for additional information listed by ARV medication.

Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
Cardiovascular Effects	Cardiac Conduction Effects	No known effect	**RPV and EFV:** QTc prolongation **RPV:** QTc prolongation occurred at 3 and 12 times the recommended dose. Consider alternatives when coadministered with drugs with known risk of Torsade de Pointes.	**ATV:** PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	No known effect	**FTR:** QTc prolongation was seen at 4 times the recommended dose. Consider alternatives when coadministered with drugs with a known risk of Torsade de Pointes.	No known effect

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Adverse Effect Type	Adverse Effect	NRTIs	NNRTIs	PIs	INSTIs	EIs	CI
	Cardiovascular Disease	**ABC:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in people with traditional CVD risk factors.	No known effect	**DRV/r:** Associated with cardiovascular events in some cohorts.	Not common or severe	No or limited data	No or limited data
Dermatologic Effects, Not Including Systemic Hypersensitivity Reaction	Rash	**FTC:** Skin hyperpigmentation	All NNRTIs	ATV, DRV	All INSTIs	MVC, IBA, FTR	Not common or severe
	Stevens-Johnson Syndrome/Toxic Epidermal Necrosis	No known effect	EFV, ETR > DOR, RPV	Rarely observed with DRV and ATV	Rarely observed with BIC, CAB, and RAL	No or limited data	Not common or severe
Gastrointestinal Effects	Cholelithiasis	No known effect	No or limited data	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	No known effect	No known effect	No known effect
	Gastrointestinal Effects	**ZDV > other NRTIs:** Nausea and vomiting	Not common or severe	GI intolerance (e.g., diarrhea, nausea, vomiting)	**EVG/c:** Nausea and diarrhea	No known effect	Not common or severe

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Hepatic Effects	Hepatic Effects	**When TAF, TDF, 3TC, and FTC are withdrawn in people with HBV/HIV coinfection or when HBV resistance develops:** People with HBV/HIV coinfection may develop severe hepatic flares.	**EFV:** Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. **RPV:** Risk may be further increased in people with HBV or HCV coinfection.	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported. **ATV:** Jaundice due to indirect hyperbilirubinemia	**DTG:** Rarely observed, but risk may be further increased in people with HBV or HCV coinfection. **BIC, CAB, EVG/c, RAL:** Not common or severe	**MVC:** Hepatotoxicity with or without rash or HSRs has been reported. **FTR:** Transaminase elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin observed in clinical trials.	Not common or severe
Hypersensitivity Reactions, Not Including Rash Alone or Stevens-Johnson Syndrome	Hypersensitivity Reaction	**ABC: Contraindicated** if person is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks.	Rarely observed	No known effect	Rarely observed	**MVC:** HSR reported as part of a syndrome related to hepatotoxicity. **IBA:** HSR, including infusion-related reactions and anaphylactic reactions, were reported.	No known effect

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		HSR symptoms (in order of descending frequency): Fever, rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms Symptoms worsen with continuation of ABC. People should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.					
Injection Site Reactions	Injection Site Reaction	Not applicable	**RPV IM injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma. **When given with CAB IM, injection site pain:** RPV > CAB.	Not applicable	**CAB IM injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma. **When given with RPV IM, injection site pain:** RPV > CAB.	Not applicable	**LEN SQ injection:** Reported in 47–65% of people; reactions may include swelling, erythema, pain, nodules, inflammation, and induration. Nodules and induration may persist for months in some people. Injection site necrosis has been reported.

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Metabolic Effects	Bone Density Effects	**TDF:** Associated with greater loss of BMD than other NRTIs, especially when given with a PK booster. Osteomalacia may be associated with proximal tubulopathy and urine phosphate wasting. **TAF:** Associated with smaller declines in BMD than those seen with TDF.	No known effect	No known effect	Not common or severe	No known effect	No known effect
	Diabetes Mellitus and Insulin Resistance	**ZDV**	No known effect	Rarely observed	No known effect	No or limited data	No or limited data
	Dyslipidemia	**ABC:** ↑ TG and ↑ LDL **TAF:** ↑ TG, ↑ LDL, and ↑ HDL (no change in TC:HDL ratio) **TDF:** Associated with lower lipid levels than ABC or TAF.	**EFV:** ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-boosted PIs:** ↑ TG, ↑ LDL, ↑ HDL	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	No known effect	No known effect
	Lactic Acidosis	Reported with older NRTIs (e.g., d4T, ZDV, ddI), but not with ABC, 3TC, FTC, TAF, or TDF.	No known effect	No known effect	No known effect	No known effect	No known effect

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	Lipodystrophy	**Lipoatrophy:** Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, or TAF or TDF.	**Lipohypertrophy:** Trunk fat increase is observed with EFV-containing regimens; however, a causal relationship has not been established.	**Lipohypertrophy:** Trunk fat increase is observed with PI-containing regimens; however, a causal relationship has not been established.	**Lipohypertrophy:** Trunk fat increase is observed with RAL-containing regimens; however, a causal relationship has not been established.	No known effect	No known effect
	Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs, especially BIC and DTG, than with other drug classes. Greater weight increase has also been reported with TAF than with TDF and with DOR than with EFV.				No known effect	No known effect
Musculoskeletal Effects	Myopathy/ Rhabdomyolysis	ddI, D4T Rarely observed with ABC, TAF, or TDF.	No known effect	No known effect	Rarely observed	No known effect	No known effect

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Neuropsychiatric Effects	Nervous System/ Psychiatric Effects	**Peripheral neuropathy (can be irreversible):** Associated with history of exposure to ddI, ddC, or d4T.	**Neuropsychiatric events:** EFV > DOR, RPV > ETR **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation, ataxia, encephalopathy. Some symptoms may subside or diminish after 2–4 weeks. Bedtime dosing and taking without food may reduce symptoms. **RPV:** Depression, suicidality, sleep disturbances **DOR:** Sleep disorders and disturbances, dizziness, altered sensorium; depression, suicidality, and self-harm	No known effect	Insomnia, depression, and suicidality have been reported with INSTI use, primarily in people with pre-existing psychiatric conditions.	Not common or severe	Not common or severe

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Renal Effects	Renal Effects/Nephrolithiasis/ Urolithiasis	**TDF:** ↑ SCr, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, and non-anion gap metabolic acidosis. Concurrent use of TDF with COBI- or RTV-containing regimens appears to increase risk. **TAF:** Less renal effect than TDF.	**RPV:** Inhibits Cr secretion without reducing renal glomerular function	**ATV:** Associated with increased risk of chronic kidney disease in a large cohort study. **ATV:** Stone or crystal formation; adequate hydration may reduce risk **COBI (as a pharmacokinetic booster for DRV or ATV):** Inhibits Cr secretion without reducing renal glomerular function	**DTG, COBI (as a pharmacokinetic booster for EVG), and BIC:** Inhibits Cr secretion without reducing renal glomerular function	No or limited data	No or limited data

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; BIC = bictegravir; BMD = bone mineral density; CAB = cabotegravir; CI = capsid inhibitor; COBI = cobicistat; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FTC = emtricitabine; FTR = fostemsavir; GI = gastrointestinal; HBV = hepatitis B virus; HCV = hepatitis C virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; IBA = ibalizumab; IDV = indinavir; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LDL = low-density lipoprotein; LEN = lenacapavir; MI = myocardial infarction; MVC = maraviroc; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; QTc = QT corrected for heart rate; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQ = subcutaneous; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; ZDV = zidovudine

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