Adverse Effects of Antiretroviral Agents

(Last updated June 3, 2021; last reviewed June 3, 2021)

Adverse effects have been reported with all antiretroviral (ARV) drugs and were among the most common reasons for switching or discontinuing therapy, and for medication nonadherence in the earlier era of combination antiretroviral therapy (ART).[1] Fortunately, newer ARV regimens are associated with fewer serious and intolerable adverse effects than regimens used in the past. Generally, <10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events. However, the long-term complications of ART can be underestimated because most clinical trials use highly specific inclusion criteria which exclude individuals with certain underlying medical conditions, and the duration of participant follow-up is relatively short. As ART is recommended for all patients regardless of CD4 T lymphocyte (CD4) cell count, and because therapy must be continued indefinitely, the focus of patient management has evolved from identifying and managing early ARV-related toxicities to individualizing therapy to avoid long-term adverse effects, including diabetes and other metabolic complications, atherosclerotic cardiovascular disease, kidney dysfunction, bone loss, and weight gain. To achieve and sustain viral suppression over a lifetime, both long-term and short-term ART toxicities must be anticipated and managed. When selecting an ARV regimen, clinicians must consider potential adverse effects, as well as the individual's comorbidities, concomitant medications, and prior history of drug intolerances.

Several factors may predispose individuals to adverse effects of ARV medications, such as:

- 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[2,3] may increase the risk of hepatotoxicity when efavirenz (EFV) or protease inhibitors are used; and borderline or mild renal dysfunction increases the risk of nephrotoxicity from tenofovir disoproxil fumarate (TDF).
- Certain ARVs may exacerbate pre-existing conditions, for example, psychiatric disorders may be exacerbated by EFV, rilpivirine, and, infrequently, by integrase strand transfer inhibitors.[4,5]
- Drug-drug interactions that may increase toxicities of ARV drugs or concomitant medications, for example, when pharmacokinetic boosters such as ritonavir or cobicistat are used, or when isoniazid is used with EFV.[6]
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction,[7,8] EFV neuropsychiatric toxicity[6,9] and QTc prolongation,[10, 11] and atazanavir (ATV)-associated hyperbilirubinemia.[12]

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 B, Tables 3, 4, 5, 6, 7, 8, 9, and 10.

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 1 of 5)

Adverse effects for ARV drugs that are no longer commonly used in clinical practice (ddI, d4T, FPV/r, IDV, NFV, SQV/r, and TPV/r) have been removed from this table, with the exception of lipodystrophy and peripheral neuropathy associated with ddI and d4T. Because these effects may persist long after discontinuation of ddI or d4T, and patients may still present with these long-lasting toxicities, the drugs remain listed among the ARVs associated with these two effects. Refer to the product labels for information regarding the adverse effects associated with these older ARVs.

This table focuses on ARV-associated adverse effects that a patient may experience as a result of taking an ARV regimen. 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.

In this table, N/A indicates either that there are no reported cases for that particular side effect or that data for that specific ARV drug class are not available. See Appendix B, Tables 3, 4, 5, 6, 7, 8, 9, and 10 for additional information listed by drug.

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
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 renal tubulopathy and urine phosphate wasting. **TAF:** Associated with smaller declines in BMD than those seen with TDF.	Decreases in BMD observed after the initiation of any ART regimen.			N/A
Bone Marrow Suppression	**ZDV:** Anemia, neutropenia	N/A	N/A	N/A	N/A
Cardiac Conduction Effects	N/A	**RPV, EFV:** QTc prolongation	**ATV/r and LPV/r:** PR prolongation. Risk factors include pre-existing heart disease and concomitant use of medications that may cause PR prolongation.	N/A	**FTR:** QTc prolongation was seen at 4 times the recommended dose. Use with caution in patients with pre-existing heart disease or QTc prolongation, or concomitant use of medications that may prolong QTc interval.
Cardiovascular Disease	**ABC:** Associated with an increased risk of MI in some cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.	N/A	**Boosted DRV and LPV/r:** Associated with cardiovascular events in some cohorts	N/A	N/A

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Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Cholelithiasis	N/A	N/A	**ATV:** Cholelithiasis and kidney stones may present concurrently. Median onset is 42 months after ARV initiation.	N/A	N/A
Diabetes Mellitus and Insulin Resistance	ZDV	N/A	LPV/r, but not with boosted ATV or DRV	N/A	N/A
Dyslipidemia	**ZDV > ABC:** ↑ TG and ↑ LDL **TAF:** ↑ TG, ↑ LDL, and ↑ HDL (no change in TC: HDL ratio) TDF has been associated with lower lipid levels than ABC or TAF.	**EFV:** ↑ TG, ↑ LDL, ↑ HDL	**All RTV- or COBI-Boosted PIs:** ↑ TG, ↑ LDL, ↑ HDL **LPV/r > DRV/r and ATV/r:** ↑ TG	**EVG/c:** ↑ TG, ↑ LDL, ↑ HDL	N/A
Gastrointestinal Effects	**ZDV > Other NRTIs:** Nausea and vomiting	N/A	GI intolerance (e.g., diarrhea, nausea, vomiting) **LPV/r > DRV/r and ATV/r:** Diarrhea	**EVG/c:** Nausea and diarrhea	N/A
Hepatic Effects	**When TAF, TDF, 3TC, and FTC are withdrawn in Patients with HBV/HIV Coinfection or when HBV Resistance Develops:** Patients with HBV/HIV coinfection may develop severe hepatic flares. **ZDV:** Steatosis	**EFV:** Most cases relate to an increase in transaminases. Fulminant hepatitis leading to death or hepatic failure requiring transplantation have been reported. **NVP:** Severe hepatotoxicity associated with skin rash or hypersensitivity. A 2-week NVP dose escalation may reduce risk. Risk is greater for women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. NVP should **never** be used for post-exposure prophylaxis. EFV and NVP **are not recommended** in patients with hepatic insufficiency (Child-Pugh class B or C).	**All PIs:** Drug-induced hepatitis and hepatic decompensation have been reported. **ATV:** Jaundice due to indirect hyperbilirubinemia	**DTG:** Persons with HBV or HCV coinfection may be at higher risk of DTG-associated hepatotoxicity.	**MVC:** Hepatotoxicity with or without rash or HSRs reported. **FTR:** Transaminase elevation was seen more commonly in patients with HBV/HCV. Transient elevation of bilirubin observed in clinical trials.

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 3 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Hypersensitivity Reaction Excluding rash alone or Stevens-Johnson syndrome	**ABC: Contraindicated** if patient is HLA-B*5701 positive. Median onset for HSR is 9 days after treatment initiation; 90% of reactions occur within 6 weeks. **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. Patients should not be rechallenged with ABC if HSR is suspected, regardless of their HLA-B*5701 status.	**NVP:** Hypersensitivity syndrome of hepatotoxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, renal dysfunction, granulocytopenia, or lymphadenopathy. Risk is greater for ARV-naive women with pre-NVP CD4 counts >250 cells/mm^3 and men with pre-NVP CD4 counts >400 cells/mm^3. Overall, risk is higher for women than men. A 2-week dose escalation of NVP reduces risk.	N/A	**RAL:** HSR reported when RAL is given with other drugs also known to cause HSRs. All ARVs should be stopped if HSR occurs. **DTG:** Reported in <1% of patients in clinical development program	**MVC:** HSR reported as part of a syndrome related to hepatotoxicity.
Injection Site Reaction	N/A	**RPV IM Injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.	N/A	**CAB IM Injection:** Reported in >80% of patients; reactions may include localized pain/discomfort (most common), nodules, induration, swelling, erythema, hematoma.	**T-20 SQ Injection:** Reported in almost all patients; pain, tenderness, nodules, induration, ecchymosis, erythema.
Lactic Acidosis	**Reported with Older NRTIs, d4T, ZDV, and ddI**, but not with ABC, 3TC, FTC, TAF, or TDF.	N/A	N/A	N/A	N/A
Lipodystrophy	**Lipoatrophy:** Associated with history of exposure to d4T or ZDV (d4T > ZDV). Not reported with ABC, 3TC or FTC, TAF or TDF.	**Lipohypertrophy:** Trunk fat increase observed with EFV-, PI-, and RAL-containing regimens; however, causal relationship has not been established.			N/A
Myopathy/ Elevated Creatine Phosphokinase	**ZDV:** Myopathy	N/A	N/A	**RAL and DTG:** ↑ CPK, rhabdomyolysis, and myopathy or myositis have been reported.	N/A

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 4 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Nervous System/ Psychiatric Effects	**History of Exposure to ddI, ddC, or d4T:** Peripheral neuropathy (can be irreversible).	**Neuropsychiatric Events:** EFV > RPV, DOR, 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. Risk factors include psychiatric illness, concomitant use of agents with neuropsychiatric effects, and genetic factors. **RPV:** Depression, suicidality, sleep disturbances. **DOR:** Sleep disorders and disturbances, dizziness, altered sensorium; depression and suicidality and self-harm.	N/A	**All INSTIs:** Insomnia, depression, and suicidality have been reported with INSTI use, primarily in patients with pre-existing psychiatric conditions.	N/A
Rash	**FTC:** Hyperpigmentation.	All NNRTIs.	ATV, DRV, and LPV/r.	All INSTIs.	MVC, IBA, FTR
Renal Effects/ 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 impact on renal biomarkers and lower rates of proteinuria than TDF.	**RPV:** Inhibits Cr secretion without reducing renal glomerular function.	**ATV and LPV/r:** 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 Boosting Agent for DRV or ATV):** Inhibits Cr secretion without reducing renal glomerular function.	**DTG, COBI (as a Boosting Agent for EVG), and BIC:** Inhibits Cr secretion without reducing renal glomerular function.	**IBA:** SCr abnormalities ≥Grade 3 reported in 10% of trial participants. FTR: SCr > 1.8 x ULN seen in 19% in a clinical trial, but primarily with underlying renal disease or other drugs known to affect creatinine.

Table 20. Common and/or Severe Adverse Effects Associated with Antiretroviral Therapy (Last updated June 3, 2021; last reviewed June 3, 2021) (page 5 of 5)

Adverse Effect	Drug Class				
	NRTIs	NNRTIs	PIs	INSTIs	EIs
Stevens-Johnson Syndrome/ Toxic Epidermal Necrosis	N/A	NVP > EFV, ETR, RPV.	Some reported cases for DRV, LPV/r, and ATV.	RAL.	N/A
Weight Gain	Weight gain has been associated with initiation of ART and subsequent viral suppression. The increase appears to be greater with INSTIs than with other drug classes. Greater weight increase has also been reported with TAF than with TDF, and greater with DOR than EFV.			INSTI > other ARV drug classes.	N/A

Key: 3TC = lamivudine; ABC = abacavir; ART= antiretroviral therapy; ARV = antiretroviral; ATV = atazanavir; ATV/r = atazanavir/ritonavir; BIC = bictegravir; BMD = bone mineral density; CAB = cabotegravir; CD4 = CD4 T lymphocyte; CNS = central nervous system; COBI = cobicistat; CPK = creatine phosphokinase; Cr = creatinine; CVD = cardiovascular disease; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delavirdine; DOR = doravirine; DRV = darunavir; DRV/r = darunavir/ritonavir; DTG = dolutegravir; ECG = electrocardiogram; EFV = efavirenz; EI = entry inhibitor; ETR = etravirine; EVG = elvitegravir; EVG/c = elvitegravir/cobicistat; FPV = fosamprenavir; FPV/r = fosamprenavir/ritonavir; 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; LPV/r = lopinavir/ritonavir; MI = myocardial infarction; MVC = maraviroc; NFV = nelfinavir; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NVP = nevirapine; PI = protease inhibitor; RAL = raltegravir; RPV = rilpivirine; RTV = ritonavir; SCr = serum creatinine; SQ = subcutaneous; SQV = saquinavir; SQV/r = saquinavir/ritonavir; T-20 = enfuvirtide; TAF = tenofovir alafenamide; TC = total cholesterol; TDF = tenofovir disoproxil fumarate; TG = triglycerides; TPV = tipranavir; TPV/r = tipranavir/ritonavir; ULN = upper limit of normal; ZDV = zidovudine