# Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (January 10, 2011)



**(See Appendix B for additional information listed by drug.)**

| Adverse Effects | NRTIs | NNRTIs | PIs | INSTI | EI |
|---|---|---|---|---|---|
| **Bleeding events** | | | **All PIs:** ↑ spontaneous bleeding, hematuria in hemophilia<br><br>**TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions; trauma; surgery; hypertension; alcohol abuse; coagulopathy, anti-coagulant, or anti-platelet agents including vitamin E | | |
| **Bone marrow suppression** | **ZDV:** Anemia, neutropenia | | | | |
| **Cardiovascular disease (CVD)** | **ABC** and **ddI:** Associated with myocardial infarction (MI) in some but not all cohort studies. Risk greatest among those with traditional CVD risk factors. | | **PIs:** Associated with MI and stroke in some cohort studies. Risk greatest among those with traditional CVD risk factors. Limited data on newer PIs (ATV, DRV, TPV).<br><br>**SQV/r**, **ATV/r,** and **LPV/r:** PR interval prolongation. Risks include structural heart disease, conduction system abnormalities, cardiomyopathy, ischemic heart disease, and coadministration with drugs that prolong PR interval.<br><br>**SQV/r:** QT interval prolongation in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG prior to SQV initiation is recommended and should be considered during therapy. | | |
| **Central nervous system (CNS) effects** | **d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare) | **EFV:** Somnolence, insomnia, abnormal dreams, dizziness, impaired concentration, depression, psychosis, suicidal ideation. Most symptoms subside or diminish after 2–4 weeks. Bedtime dosing may reduce symptoms. Risks include history of psychiatric illness, concomitant use of agents with neuropsychiatric effects, and ↑ plasma EFV concentrations due to genetic factors or absorption (i.e., with food). | | | |
| **Diabetes mellitus (DM)/Insulin resistance/** | **ZDV, d4T,** and **ddI** | | • Reported for some **PIs (IDV, LPV/r**), but not all PIs studied<br>• **ATV** +/- **RTV** not found to alter insulin sensitivity | | |
| **Dyslipidemia** | **d4T > ZDV > ABC:**<br>•↑ LDL and TG | **EFV**<br>•↑TG<br>•↑LDL<br>•↑HDL | ↑LDL, ↑TG, ↑HDL: **all RTV-boosted PIs**<br><br>↑TG: **LPV/r** = **FPV/r** and **LPV/r** > **DRV/r** and **ATV/r** | | |
| **Gastrointestinal (GI)** | Nausea and vomiting: **ddI** and **ZDV** > other **NRTIs**<br><br>Pancreatitis: **ddI** | | GI intolerance (diarrhea, nausea, vomiting)<br><br>Diarrhea: common with **NFV**. **LPV/r** > **DRV/r** and **ATV/r** | | |

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|---|---|---|---|---|---|
| **Hepatic effects** | Reported for most **NRTIs**<br><br>**ddI:** prolonged exposure linked to noncirrhotic portal hypertension, some cases with esophageal varicees<br><br>Steatosis: most commonly seen with **ZDV**, **d4T**, or **ddI**<br><br>Flares: hepatitis B virus (HBV)-coinfected patients may develop severe hepatic flare when **TDF**, **3TC**, and **FTC** are withdrawn or when HBV resistance develops. | **NVP > other NNRTIs**<br>**NVP:**<br>• Severe hepatic toxicity with **NVP** is often associated with skin rash or symptoms of hypersensitivity.<br>• For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm$^3$ and men with pre-**NVP** CD4 count >400 cells/mm$^3$. Risk is higher for women.<br>• 2-week dose escalation of **NVP** reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity.<br>• Given high risk in those with competent immune systems, **NVP** should never be used for post-exposure prophylaxis in HIV-uninfected individuals.<br>• **NVP** is contraindicated in patients with Child-Pugh classification B or C. | **All PIs:** Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all PIs to varying degrees. **TPV/r** has a higher frequency of hepatic events than other PIs.<br><br>**IDV, ATV**: jaundice due to indirect hyperbilirubinemia<br><br>**TPV/r:** Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C) | | |
| **Hypersensitivity reaction (HSR) (excluding rash alone or Stevens Johnson syndrome[SJS])** | **ABC**:<br>• HLA-B*5701 screening prior to initiation of **ABC**. Should not be started if HLA-B*5701 is positive.<br>• Symptoms of HSR include (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, respiratory symptoms<br>• Worsen with continuation of **ABC**<br>• Median onset 9 days; ~ 90% of reactions within first 6 weeks<br>• Onset of rechallenge reactions is within hours of rechallenge dose | **NVP**:<br>• Hypersensitivity syndrome of hepatic toxicity and rash that may be accompanied by fever, general malaise, fatigue, myalgias, arthralgias, blisters, oral lesions, conjunctivitis, facial edema, eosinophilia, granulocytopenia, lymphadenopathy, or renal dysfunction.<br>• For ARV-naïve patients, risk is greater for women with pre-**NVP** CD4 count >250 cells/mm$^3$ and men with pre-**NVP** CD4 count >400 cells/mm$^3$. Risk is higher for women.<br>• 2-week dose escalation of **NVP** reduces risk. | | | |
| **Lactic acidosis** | **NRTIs,** especially **d4T, ZDV,** and **ddI**<br>• Insidious onset with GI prodrome, weight loss, and fatigue. May be rapidly progressive, with tachycardia, tachypnea, jaundice, muscular weakness, mental status changes, respiratory distress, pancreatitis, and organ failure.<br>• Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L<br>• Increased risk: female sex, obesity<br><br>Laboratory findings:<br>• ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin<br>• ↑ amylase and lipase in patients with pancreatitis<br>• ↓ arterial pH, serum bicarbonate, serum albumin | | | | |

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|---|---|---|---|---|---|
| **Lipodystrophy** | Lipoatrophy: **Thymidine analogs (d4T > ZDV).** May be more likely when combined with **EFV** vs. **boosted PI**. | Lipohypertophy: Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established. | | | |
| **Myopathy/elevated CPK** | **ZDV:** myopathy | | | **RAL:** ↑ CPK. muscle weakness and rhabdomyolysis | |
| **Nephrotoxicity/ urolithiasis** | **TDF:** ↑ serum creatinine, proteinuria, hypophosphatemia, urinary phosphate wasting, glycosuria, hypokalemia, non-anion gap metabolic acidosis<br><br>Concurrent use of **PI** may increase risk. | | **IDV**: ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy<br>**IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk. | | |
| **Osteopenia/ osteoporosis** | **TDF:** Associated with greater loss of bone mineral density (BMD) compared with **ZDV, d4T,** and **ABC.** | Decreases in BMD observed in studies of regimens containing different **NRTIs** combined with either **NNRTIs** or **PIs**. | | | |
| **Peripheral neuropathy** | Peripheral neuropathy (pain and/or paresthesias, lower extremities > upper extremities): **d4T > ddI** and **ddC** (can be irreversible)<br><br>**d4T:** Associated with rapidly progressive ascending neuromuscular weakness resembling Guillain-Barré syndrome (rare) | | | | |
| **Rash** | | **All NNRTIs** | **ATV, DRV, FPV** | | **MVC** |
| **Stevens-Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN)** | **ddI, ZDV:** Reported cases | **NVP > DLV, EFV, ETR**<br>For **NVP** risks include:<br>•Female sex<br>•Black, Asian, Hispanic race/ethnicity | **FPV, DRV, IDV, LPV/r, ATV:** Reported cases | | |

**Acronyms:**
*Drug Classes*: EI = entry inhibitor; INSTI = integrase strand transfer inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PIs = protease inhibitor
*Antiretroviral Drugs*: 3TC = lamivudine; ABC = abacavir; ATV = atazanavir; ATV/r = atazanavir + ritonavir; d4T = stavudine; ddC = zalcitabine; ddI = didanosine; DLV = delaviridine; DRV = darunavir; DRV/r = darunavir + ritonavir; EFV = efavirenz; ETR = etravirine; FPV = fosamprenavir; FPV/r = fosamprenavir + ritonavir; FTC = emtricitabine; IDV = indinavir; LPV/r = lopinavir + ritonavir; MVC = maraviroc; NFV = nelfinavir; NVP = nevirapine; RAL = raltegravir; RTV = ritonavir; SQV/r = saquinavir + ritonavir; TDF = tenofovir; TPV = tipranavir; ZDV = zidovudine
*Other*: ALT = alanine aminotransferase; ARV = antiretroviral; AST = aspartate aminotransferase; BMD = bone mineral density; CNS = central nervous system; CPK = creatine phosphokinase; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram; GI = gastrointestinal; HBV = hepatitis B virus; HDL = high-density lipoprotein; HSR = hypersensitivity reaction; LDL = low-density lipoprotein; MI = myocardial infarction; PT = prothrombin time; SJS = Stevens-Johnson syndrome; TEN = toxic epidermal necrosis; TG = triglyceride