Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

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Adverse Effects of Antiretroviral Agents (Last updated February 12, 2013; last reviewed February 12, 2013)

Adverse effects have been reported with use of all antiretroviral (ARV) drugs; they are among the most common reasons for switching or discontinuing therapy and for medication nonadherence.[1] However, with the use of newer ARV regimens, rates of treatment-limiting adverse events in antiretroviral therapy (ART)-naive patients enrolled in randomized trials appear to be declining and are generally now occurring in less than 10% of study participants. However, because most clinical trials have a relatively short follow-up duration, the longer term complications of ART can be underestimated. In the Swiss Cohort study, during 6 years of follow-up, the presence of laboratory adverse events was associated with higher rates of mortality, which highlights the importance of adverse events in overall patient management.[2]

Several factors may predispose individuals to adverse effects of ARV medications. For example, compared with men, women (especially ART-naive women with CD4 counts >250 cells/mm^3) seem to have a higher propensity to develop Stevens-Johnson syndrome, rashes, and hepatotoxicity from nevirapine (NVP)[3-5] and have higher rates of lactic acidosis due to nucleoside reverse transcriptase inhibitors (NRTIs).[6-8] Other factors may also contribute to the development of adverse events:

- Concomitant use of medications with overlapping and additive toxicities;
- Comorbid conditions that may increase the risk of or exacerbate adverse effects (e.g., alcoholism[9] or coinfection with viral hepatitis[10-12] may increase the risk of hepatotoxicity);
- Drug-drug interactions that may lead to an increase in drug toxicities (e.g., interactions that result from concomitant use of statins with protease inhibitors [PIs]); or
- Genetic factors that predispose patients to abacavir (ABC) hypersensitivity reaction (HSR).[13, 14]

The therapeutic goals of ART include achieving and maintaining viral suppression and improving immune function, but an overarching goal should be to select a regimen that is not only effective but also safe. This requires consideration of the toxicity potential of an ARV regimen, as well as the individual patient's underlying conditions, concomitant medications, and prior history of drug intolerances.

In addition, it should be appreciated that, in general, the overall benefits of ART outweigh its risks and that some conditions (e.g., anemia, cardiovascular disease [CVD], renal impairment), may be more likely in the absence of ART.[15, 16]

Information on adverse events of ARVs is outlined in several tables in the guidelines. Table 13 provides clinicians with a list of the most common and/or severe known ARV-associated adverse events by drug class. The most common adverse effects of individual ARV agents are summarized in Appendix B, Tables 1–6.

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 1 of 5)

(See Appendix B for additional information listed by drug. Empty spaces in the table may mean no reported cases for the particular side effect or no data are available for the specific ARV drug class)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Bleeding events			**All PIs:** Increased spontaneous bleeding, hematuria in patients with hemophilia **TPV:** Reports of intracranial hemorrhage. Risks include CNS lesions, trauma, surgery, hypertension, alcohol abuse, coagulopathy, and concomitant use of anti-coagulant or anti-platelet agents, including vitamin E		
Bone marrow suppression	**ZDV:** Anemia, neutropenia				
Cardiovascular disease (CVD)	**ABC and ddI:** Associated with an increased risk of MI in some, but not all, cohort studies. Absolute risk greatest in patients with traditional CVD risk factors.		**PIs:** Associated with MI and stroke in some cohort studies. Data on newer PIs (**ATV, DRV, and TPV**) are limited. **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. **SQV/r:** QT interval prolongation in patients in a healthy volunteer study. Risks include underlying heart conditions, pre-existing prolonged QT or arrhythmia, or use with other QT-prolonging drugs. ECG is recommended before SQV initiation 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, and suicidal ideation. Symptoms usually 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 increased plasma EFV concentrations due to genetic factors or increased absorption with food.		**RAL:** Depression (uncommon)	

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Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Cholelithiasis			**ATV:** • History of kidney stones increases risk and patients may present with cholelithiasis and kidney stones concurrently • Typically presents as abdominal pain • Reported complications include cholecystitis, pancreatitis, choledocholithiasis, and cholangitis • Median time to onset is 42 months (range 1–90 months)		
Diabetes mellitus (DM)/insulin resistance	**ZDV**, **d4T**, and **ddI**		• Reported for some **PIs** (**IDV**, **LPV/r**), but not all PIs		
Dyslipidemia	**d4T > ZDV > ABC:** • ↑LDL and TG	**EFV** • ↑TG • ↑LDL • ↑HDL	↑LDL, ↑TG, ↑HDL: **All RTV-boosted PIs** ↑TG: **LPV/r** = **FPV/r** and **LPV/r** > **DRV/r** and **ATV/r**		
Gastrointestinal (GI) effects	**Nausea and vomiting:** **ddI** and **ZDV** > other **NRTIs** **Pancreatitis: ddI**		GI intolerance (e.g., diarrhea, nausea, vomiting) **Diarrhea:** Common with **NFV**; **LPV/r** > **DRV/r** and **ATV/r**	**Nausea and diarrhea:** **EVG/COBI/TDF/FTC**	

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 3 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hepatic effects	Reported for most **NRTIs** **ddI:** Prolonged exposure linked to non-cirrhotic portal hypertension, some cases with esophageal varicees **Steatosis:** Most commonly seen with **ZDV, d4T**, or **ddI** **Flares:** HIV/HBV-co-infected patients may develop severe hepatic flares when **TDF**, **3TC**, and **FTC** are withdrawn or when HBV resistance develops.	**NVP > other NNRTIs** **NVP:** • Severe hepatic toxicity with **NVP** is often associated with skin rash or symptoms of hypersensitivity. • In ARV-naive 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. Overall risk is higher for women than men. • Risk is greatest in the first few months of treatment. • 2-week dose escalation of **NVP** reduces risk of rash and possibly hepatotoxicity if related to hypersensitivity. • **NVP** is contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C). • Liver failure observed in HIV-uninfected individuals receiving **NVP** for post-exposure prophylaxis. **NVP** should never be used for this indication.	**All PIs:** Drug-induced hepatitis and hepatic decompensation (and rare cases of fatalities) have been reported with all **PIs** to varying degrees. The frequency of hepatic events is higher with **TPV/r** than with other PIs. **IDV, ATV:** Jaundice due to indirect hyperbilirubinemia **TPV/r:** Contraindicated in patients with moderate to severe hepatic insufficiency (Child-Pugh classification B or C)		**MVC:** Hepatotoxicity with or without rash or HSRs reported

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 4 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Hypersensitivity reaction (HSR) (excluding rash alone or Stevens-Johnson syndrome [SJS])	**ABC:** • HLA-B*5701 screening should be performed before initiation of **ABC**. **ABC** should not be started if the HLA-B*5701 test result is positive. • Symptoms of HSR include (in descending frequency): fever, skin rash, malaise, nausea, headache, myalgia, chills, diarrhea, vomiting, abdominal pain, dyspnea, arthralgia, and respiratory symptoms. • Symptoms worsen with continuation of **ABC**. • Median onset of reactions is 9 days; approximately 90% of reactions occur within the first 6 weeks of treatment. • The onset of re-challenge reactions is within hours of re-challenge dose • Patients, regardless of HLA-B*5701 status, should not be re-challenged with **ABC** if HSR is suspected.	**NVP:** • 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. • In ARV-naive 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. Overall, risk is higher for women than men. • 2-week dose escalation of **NVP** reduces risk.		**RAL**	**MVC:** Reported as part of a syndrome related to hepatotoxicity
Lactic acidosis	**NRTIs**, especially **d4T**, **ZDV**, and **ddI**: • 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. • Mortality up to 50% in some case series, especially in patients with serum lactate >10 mmol/L • Females and obese patients at increased risk <u>Laboratory findings</u>: • ↑ lactate (often >5 mmol/L), anion gap, AST, ALT, PT, bilirubin • ↑ amylase and lipase in patients with pancreatitis • ↓ arterial pH, serum bicarbonate, serum albumin				

Table 13. Antiretroviral Therapy-Associated Common and/or Severe Adverse Effects (page 5 of 5)

Adverse Effects	NRTIs	NNRTIs	PIs	INSTI	EI
Lipodystrophy	**Lipoatrophy: Thymidine analogs (d4T > ZDV).** May be more likely when NRTIs combined with **EFV** than with a **RTV-boosted PI**.	Lipohypertophy: Trunk fat increase observed with **EFV**-, **PI**-, and **RAL**-containing regimens; however, causal relationship has not been established.			
Myopathy/elevated creatine phosphokinase (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 Concurrent use with **PI** appears to increase risk.		**IDV:** ↑ serum creatinine, pyuria; hydronephrosis or renal atrophy **IDV, ATV**: Stone, crystal formation; adequate hydration may reduce risk.	**EVG/COBI/TDF/FTC:** • **COBI** can cause non-pathologic decrease in CrCl. • May increase risk of **TDF**-related nephrotoxicity	
Osteopenia/osteoporosis	**TDF:** Associated with greater loss of BMD than 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)				
Rash		**All NNRTIs**	**ATV, DRV, FPV**	**RAL, EVG/COBI/TDF/FTC:** Uncommon	**MVC**
Stevens-Johnson syndrome (SJS)/ toxic epidermal necrosis (TEN)	**ddI, ZDV:** Reported cases	**NVP > DLV, EFV, ETR, RPV**	**FPV, DRV, IDV, LPV/r, ATV:** Reported cases	**RAL**	

Key to Abbreviations: 3TC = lamivudine, ABC = abacavir, ALT = alanine aminotransferase, ARV = antiretroviral, AST = aspartate aminotransferase, ATV = atazanavir, ATV/r = atazanavir + ritonavir, BMD = bone mineral density, CrCl = creatinine clearance, CNS = central nervous system, COBI = cobicistat, CPK = creatine phosphokinase, CVD = cardiovascular disease, d4T = stavudine, ddC = zalcitabine, ddI = didanosine, DLV = delaviridine, DM = diabetes mellitus, DRV = darunavir, DRV/r = darunavir + ritonavir, ECG = electrocardiogram, EFV = efavirenz, EI = entry inhibitor, ETR = etravirine, EVG = elvitegravir, FPV = fosamprenavir, FPV/r = fosamprenavir + ritonavir, FTC = emtricitabine, GI = gastrointestinal, HBV = hepatitis B virus, HDL = high-density lipoprotein, HSR = hypersensitivity reaction, IDV = indinavir, 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, PT = prothrombin time, RAL = raltegravir, RPV = rilpivirine, RTV = ritonavir, SJS = Stevens-Johnson syndrome, SQV = saquinavir, SQV/r = saquinavir + ritonavir, TDF = tenofovir disoproxil fumarate, TEN = toxic epidermal necrosis, TG = triglyceride, TPV = tipranavir, TPV/r = tipranavir + ritonavir, ZDV = zidovudine

References

1. O'Brien ME, Clark RA, Besch CL, et al. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr*. 2003;34(4):407-414. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14615659.
2. Keiser O, Fellay J, Opravil M, et al. Adverse events to antiretrovirals in the Swiss HIV Cohort Study: Effect on mortality and treatment modification. *Antivir Ther*. 2007;12(8):1157-1164. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18240856.
3. Baylor MS, Johann-Liang R. Hepatotoxicity associated with nevirapine use. *J Acquir Immune Defic Syndr*. 2004;35(5):538-539. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15021321.
4. Bersoff-Matcha SJ, Miller WC, Aberg JA, al. e. Sex differences in nevirapine rash. *Clin Infect Dis*. 2001;32(1):124-129. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11118391&dopt=Abstract.
5. Fagot JP, Mockenhaupt M, Bouwes-Bavinck JN, et al; for EuroSCAR Study Group. Nevirapine and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *AIDS*. 2001;15(14):1843-1848. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11579247&dopt=Abstract.
6. Moyle GJ, Datta D, Mandalia S, et al. Hyperlactataemia and lactic acidosis during antiretroviral therapy: relevance, reproducibility and possible risk factors. *AIDS*. 2002;16(10):1341-1349. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=12131210&dopt=Abstract.
7. Bolhaar MG, Karstaedt AS. A high incidence of lactic acidosis and symptomatic hyperlactatemia in women receiving highly active antiretroviral therapy in Soweto, South Africa. *Clin Infect Dis*. 2007;45(2):254-260. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17578788.
8. Geddes R, Knight S, Moosa MY, Reddi A, Uebel K, H S. A high incidence of nucleoside reverse transcriptase inhibitor (NRTI)-induced lactic acidosis in HIV-infected patients in a South African context. *S Afr Med J*. 2006;96(8):722-724. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=17019496.
9. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clin Infect Dis*. 2004;38(Suppl 2):S80-89. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=14986279.
10. denBrinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of highly active antiretroviral therapy in HIV-1 infection. *AIDS*. 2000;14(18):2895-2902. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11153671&dopt=Abstract.
11. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA*. 2000;283(1):74-80. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10632283&dopt=Abstract.
12. Saves M, Raffi F, Clevenbergh P, et al; and APROCO Study Group. Hepatitis B or hepatitis C virus infection is a risk factor for severe hepatic cytolysis after initiation of a protease inhibitor-containing antiretroviral regimen in human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother*. 2000;44(12):3451-3455. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11083658&dopt=Abstract.
13. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med*. 2008;358(6):568-579. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18256392.

14. Saag M, Balu R, Phillips E, et al. High sensitivity of human leukocyte antigen-b*5701 as a marker for immunologically confirmed abacavir hypersensitivity in white and black patients. *Clin Infect Dis*. 2008;46(7):1111-1118. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=18444831.

15. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. Nov 30 2006;355(22):2283-2296. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17135583.

16. Lichtenstein KA, Armon C, Buchacz K, et al. Initiation of antiretroviral therapy at CD4 cell counts ≥350 cells/mm^3 does not increase incidence or risk of peripheral neuropathy, anemia, or renal insufficiency. *J Acquir Immune Defic Syndr*. Jan 1 2008;47(1):27-35. Available at http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17971714.