Adverse Effects of Antiretroviral Drugs

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Introduction

The following tables summarize the most common and most serious adverse events associated with antiretroviral medications used to treat HIV infection. For drug-drug interactions, see the Database of Antiretroviral Drug Interactions .

Tables

Nucleoside Reverse Transcriptase Inhibitors

- NRTIs are associated with lactic acidosis, hepatic steatosis, and body fat redistribution (lipodystrophy).

Drug	Adverse Events	Comments
Abacavir	• Hypersensitivity syndrome (fever, myalgia, malaise, nausea, vomiting, symptoms suggestive of upper respiratory tract infection, anorexia); symptoms progressively worsen with each subsequent dose; rash occurs in about half of cases • Rash • Headache, nausea, vomiting, diarrhea	• Hypersensitivity reaction usually occurs in the first 6 weeks of treatment. • Hypersensitivity reaction may be more severe with once-daily abacavir dosing. • Risk of hypersensitivity related to certain genetic factors, particularly HLA B * 5701; consider screening for this before prescribing abacavir. • Counsel patients on signs of hypersensitivity syndrome. • In case of hypersensitivity syndrome, abacavir must be discontinued permanently.
Didanosine	• Pancreatitis • Peripheral neuropathy • Nausea, diarrhea	• Concomitant alcohol use may increase risk of pancreatitis. • Lower frequency of diarrhea with enteric-coated capsules. • Increased risk of lactic acidosis and hepatic steatosis when combined with stavudine; this combination should be avoided when possible, especially during pregnancy. • Increased risk of peripheral neuropathy when combined with stavudine. • Adjust dosage for renal insufficiency or failure.
Emtricitabine	• Headache, nausea, insomnia • Hyperpigmentation of palms and soles (occurs most frequently in dark-skinned people)	• Active against hepatitis B virus (not approved by the U.S. Food and Drug Administration [FDA] for treatment of hepatitis B). In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of emtricitabine. • Adjust dosage for renal insufficiency or failure.
Lamivudine	• Headache, dry mouth	• Adverse effects occur infrequently. • Active against hepatitis B virus. In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of lamivudine. • Adjust dosage for renal insufficiency or failure.
Stavudine	• Peripheral neuropathy • Pancreatitis • Dyslipidemia • Diarrhea	• Of the NRTIs, stavudine appears to convey the greatest risk of lipodystrophy and other mitochondrial toxicity. • Increased risk of lactic acidosis and hepatic steatosis when combined with didanosine; this combination should be avoided when possible, especially during pregnancy.

		• Increased risk of peripheral neuropathy when combined with didanosine. • Consider dosage adjustment for peripheral neuropathy. • Adjust dosage for renal insufficiency or failure.
Tenofovir	• Flatulence, nausea, diarrhea, abdominal discomfort • Asthenia • Acute renal insufficiency, Fanconi syndrome • Chronic renal insufficiency	• Active against hepatitis B but not FDA approved for treatment of hepatitis B. In patients with HIV and hepatitis B coinfection, hepatitis may flare upon discontinuation of tenofovir. • Gastrointestinal symptoms may be worse in lactose-intolerant patients; tenofovir is formulated with lactose. • Case reports of renal insufficiency; association between tenofovir and renal insufficiency is not clear. • Adjust dosage for renal insufficiency or failure.
Zidovudine	• Anemia, neutropenia • Fatigue, malaise, headache • Nausea, vomiting • Myalgia, myopathy • Hyperpigmentation of skin and nails	• Twice-daily dosing preferred over thrice-daily dosing. • Fatigue, nausea, headache, and myalgia usually resolve 2-4 weeks after initiation. • Adjust dosage for renal insufficiency or failure.

Nonnucleoside Reverse Transcriptase Inhibitors

- NNRTIs are associated with rash, and may cause Stevens-Johnson syndrome and toxic epidermal necrolysis.
- All NNRTIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

Drug	Adverse Events	Comments
Delavirdine	• Fatigue • Elevations in liver function tests, hepatitis • Nausea, diarrhea	• 100 mg tablets can be dissolved in water. • Seldom used; less potent than other NNRTIs.
Efavirenz	• Elevations in liver function tests • Abnormal dreams, drowsiness, dizziness, confusion • Hyperlipidemia	• Central nervous system symptoms are common; severity usually decreases within 2-4 weeks. • Teratogenic in animal studies; contraindicated during pregnancy and for use by women who may become pregnant.
Etravirine	• Elevations in liver function tests	• Tablets may be dissolved in water. • Has significant interactions with many other drugs (may differ from those of first generation NNRTIs); screen carefully for drug interactions before prescribing. • Does not interact with methadone.
Nevirapine	• Elevations in liver function tests, hepatitis, liver failure	• Initial dose of 200 mg per day for first 14 days, then 200 mg twice daily, decreases frequency of rash. • Most rash develops within first 6 weeks of therapy; rash is most common in women. • Hepatotoxicity may be life threatening. It is more common at higher CD4 cell counts, in women, and in patients with hepatitis B or C. Nevirapine should not be initiated for women with CD4 counts of >250 cells/µL or men with CD4 counts of >400 cells/µL, unless the benefit clearly outweighs the risk. Monitor liver tests closely for the first 16 weeks of treatment.

Protease Inhibitors

- All PIs are associated with metabolic abnormalities including dyslipidemia, hyperglycemia, insulin resistance, and lipodystrophy. (Atazanavir is less likely to cause dyslipidemia.)
- PIs may increase the risk of bleeding in hemophiliacs.
- PIs may have significant interactions with other drugs; dosage adjustment of interacting agents may be required.

Drug	Adverse Events	Comments

Amprenavir	• Diarrhea, nausea, vomiting • Elevations in liver function tests • Rash	• May cause rash in patients sensitive to or intolerant of sulfonamides. • Capsule formulation no longer available in adult dosage; consider fosamprenavir. • Fosamprenavir formulation has a lower pill burden and a lower frequency of gastrointestinal side effects. • The oral solution should not be combined with metronidazole or disulfiram; it contains propylene glycol and may cause disulfiram-like reaction.
Atazanavir	• Hyperbilirubinemia, jaundice • Elevations in liver function tests • PR interval prolongation	• Proton pump inhibitors interfere with atazanavir absorption and are contraindicated for use by patients receiving atazanavir. • Other antacid medications and H2 blockers also interfere with absorption of atazanavir and should be used with caution by patients receiving atazanavir. • Indirect hyperbilirubinemia; does not require discontinuation of atazanavir. • May have less effect than other PIs on lipid levels.
Darunavir	• Rash • Elevations in liver function tests	• Increases pravastatin (and other statin) levels; no significant interaction with atorvastatin.
Fosamprenavir	• Diarrhea, nausea, vomiting • Elevations in liver function tests • Rash	• Prodrug of amprenavir. • May cause rash in patients sensitive to or intolerant of sulfonamides.
Indinavir	• Nephrolithiasis, flank pain • Hyperbilirubinemia • Elevations in liver function tests • Alopecia, dry skin, ingrown nails • Insomnia • Taste perversion	• To reduce risk of nephrolithiasis, patients should drink at least 1.5 liters of fluid daily. • When used as sole PI, should be taken on an empty stomach, 1 hour before or 2 hours after a meal, and should be taken every 8 hours (not 3 times per day).
Lopinavir/ ritonavir	• Diarrhea, nausea, vomiting • Dyslipidemia • Elevations in liver function tests • Taste perversion	• Available in tablets or oral solution. Tablets do not require refrigeration. • Oral solution contains 42% alcohol. • Avoid combining oral solution with metronidazole or disulfiram. Alcohol in the oral solution may cause disulfiram-like reaction.
Nelfinavir	• Diarrhea • Nausea, vomiting • Elevations in liver function tests • Fatigue	• Diarrhea is very common. It usually can be managed with antidiarrheals such as loperamide and diphenoxylate/atropine.
Ritonavir	• Nausea, vomiting, diarrhea, abdominal pain • Elevations in liver function tests • Fatigue • Circumoral or peripheral numbness • Taste perversion • Hyperuricemia	• Capsules are stable at room temperature for up to 30 days. • Avoid combining oral solution with metronidazole or disulfiram. Alcohol in the oral solution may cause disulfiram-like reaction. • Has significant interactions with many other medications.
Saquinavir	• Nausea, vomiting, diarrhea • Elevations in liver function tests • Headache • Oral ulcerations	• Available in hard-gel capsules and tablets • Must be used in combination with low-dose ritonavir.
Tipranavir	• Nausea, vomiting, diarrhea • Elevations in liver function tests • Increased total cholesterol and triglycerides • Rash • Intracranial hemorrhage	• Must be coadministered with ritonavir; should never be used without ritonavir boosting. • Should be taken with food. • May cause rash in patients sensitive to or intolerant of sulfonamides. • Case reports of intracranial hemorrhage; association between tipranavir and intracranial hemorrhage is not clear. • Many drug-drug interactions. Certain drug combinations should be avoided. Consult current information before prescribing.

Fusion Inhibitors

Drug	Adverse Events	Comments
Enfuvirtide	• Injection site reactions; erythema, cysts, and nodules at injection sites • Neutropenia • Possible increased frequency of pneumonia	• Requires extensive patient counseling on injection technique, adherence, and management of possible side effects.

Chemokine Coreceptor Antagonists

Drug	Adverse Events	Comments
Maraviroc	• Diarrhea, nausea • Elevations in liver function tests, hepatitis • Upper respiratory tract infections, cough • Fatigue, dizziness, headache • Joint pain, muscle pain	• Many drug-drug interactions; dose adjustment needed with many other antiretrovirals and/or other medications. Consult current information before prescribing.

Integrase Inhibitors

Drug	Adverse Events	Comments
Raltegravir	• Nausea, diarrhea, flatulence • Elevations in amylase and liver function tests • Headache • Dizziness, abnormal dreams • Pruritus, rash • Fatigue, muscle pain	