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Table 19. Adverse Drug Reactions and Related "Black Box Warnings" in Product Labeling for Antiretroviral Agents

The Food and Drug Administration can require that warnings regarding special problems associated with a prescription drug, including those that might lead to death or serious injury, be placed in a prominently displayed box, commonly known as a "black box." Please note that other serious toxicities associated with antiretroviral agents are not listed in this table (see **Tables 15-23** for more extensive lists of adverse effects associated with antiretroviral drugs or for drug interactions).

Antiretroviral Drug	Pertinent Black Box Warning Information
Abacavir (Ziagen® or as combination product with zidovudine and lamivudine as Trizivir®)	• Fatal hypersensitivity reactions reported: – Signs or symptoms include fever, skin rash, fatigue, gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea, or abdominal pain), and respiratory symptoms (e.g., pharyngitis, dyspnea, or cough) – Abacavir should be discontinued as soon as hypersensitivity reaction is suspected – Abacavir **SHOULD NOT** be restarted – If restarted, more severe symptoms will recur within hours and might include life-threatening hypotension and death • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Amprenavir (Agenerase®) Oral Solution	• Because of the potential risk of toxicity from substantial amounts of the excipient propylene glycol in Agenerase Oral Solution, it is contraindicated for the following patient populations: – children age <4 years – pregnant women – patients with renal or hepatic failure – patients treated with disulfiram or metronidazole • Oral solution should be used only when Agenerase capsules or other protease inhibitors cannot be used.
Atazanavir (Reyataz™)	No box warning.
Delavirdine (Rescriptor®)	No box warning.
Didanosine (Videx® or Videx-EC®)	• Fatal and nonfatal pancreatitis have occurred with didanosine alone or in combination with other antiretroviral agents. – Didanosine should be withheld if pancreatitis is suspected – Didanosine should be discontinued if pancreatitis is confirmed • Fatal lactic acidosis has been reported among pregnant women who received a combination of didanosine and stavudine with other antiretroviral combinations. – Didanosine and stavudine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Efavirenz (Sustiva®)	No box warning.
Emtricitabine (Emtriva™)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues alone or in combination with other antiretrovirals.
Enfuvirtide (Fuzeon™)	No box warning.
Fosamprenavir (Lexiva™)	No box warning
Indinavir (Crixivan®)	No box warning.
Lamivudine (Epivir®), or as combination product in Combivir® and Trizivir®)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. • Epivir tablets and oral solution (used to treat HIV infection) contain a higher dose of lamivudine than Epivir-HBV tablets and oral solution (used to treat chronic hepatitis B). **Patients with HIV infection should receive only dosage and formulations appropriate for treatment of HIV.**
Lopinavir/ritonavir (Kaletra®)	No box warning.

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Antiretroviral Drug	Pertinent Black Box Warning Information
Nelfinavir (Viracept®)	No box warning.
Nevirapine (Viramune®)	• Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant and cholestatic hepatitis, hepatic necrosis, and hepatic failure, has been reported. Patients may present with non-specific prodromes of hepatitis and progress to hepatic failure. • Women with CD4 counts > 250 cells/mm^3, including pregnant women receiving chronic treatment for HIV infection are at considerably higher risk of hepatotoxicities. • Severe, life-threatening, and even fatal skin reactions, including Stevens-Johnson syndrome, toxic epidermal necrolysis, and hypersensitivity reactions characterized by rash, constitutional findings, and organ dysfunction have occurred with nevirapine treatment. • Patients should be monitored intensively during the first 18 weeks of nevirapine therapy to detect potentially life-threatening hepatotoxicity or skin reactions. • A 14-day lead-in period with nevirapine 200 mg daily must be followed strictly. • Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions.
Ritonavir (Norvir®)	• Co-administration of ritonavir with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events due to possible effects of ritonavir on hepatic metabolism of certain drugs.
Saquinavir (Fortovase®, Invirase®)	No box warning.
Stavudine (Zerit®)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination. • Fatal lactic acidosis has been reported among pregnant women who received combination of stavudine and didanosine with other antiretroviral combinations. • Stavudine and didanosine combination should only be used during pregnancy if • The potential benefit clearly outweighs the potential risks. • Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea.
Tenofovir (Viread®)	• Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals.
Zalcitabine (Hivid®)	• Zalcitabine can cause severe peripheral neuropathy, use with caution among patients with pre-existing neuropathy. • It rare cases, zalcitabine can cause pancreatitis, therapy should be withheld until pancreatitis is excluded. • Rare cases of hepatic failure and death have been reported among patients with underlying hepatitis B infection. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.
Zidovudine (Retrovir®), or as combination products in Combivir® and Trizivir®	• Zidovudine can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including among advanced HIV patients. • Prolonged zidovudine use has been associated with symptomatic myopathy. • Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of antiretroviral nucleoside analogues alone or in combination.