### Table 9. Adverse Drug Reactions and Related “Black Box Warnings” in ProductLabeling for Antiretroviral Agents
(Updated January 29, 2008)

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<th>Antiretroviral Drug</th>
<th>Pertinent Black Box Warning Information</th>
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| **Abacavir (ZIAGEN®, EPZICOM, TRIZIVIR)** | • Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir:  
– This is a multi-organ clinical syndrome, characterized by two or more groups of the following signs or symptoms including (1) fever, (2) rash, (3) gastrointestinal (e.g., nausea, vomiting, diarrhea, or abdominal pain), (4) constitutional (including generalized malaise, fatigue, or achiness), and (5) respiratory symptoms (including dyspnea, cough, or pharyngitis).  
– Abacavir should be discontinued as soon as hypersensitivity reaction is suspected.  
– Any product containing abacavir should be permanently discontinued if hypersensitivity cannot be ruled out, even when other diagnoses are possible – because more severe symptoms can occur within hours after restarting abacavir and may 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. |
| **Didanosine (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. |
| **Emtricitabine (EMTRIVA, TRUVADA, ATRIPLA)** | • 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.  
• Emtricitabine is not indicated for the treatment of hepatitis B infection (HBV); the safety and efficacy have not been established in patients with HIV/HBV coinfection.  
• Severe acute exacerbations of hepatitis B have been reported in patients who discontinued emtricitabine – hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV coinfected patients.  
• If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir. |
| **Lamivudine** *(EPIVIR, COMBIVIR, EPIZICOM, 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.**  
• Severe acute exacerbations of hepatitis B infection have been reported in HBV/HIV coinfected patients upon discontinuation of lamivudine-containing products. Hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of lamivudine in patients with HIV/HBV coinfection.  
• If appropriate, initiation of anti-hepatitis B therapy may be warranted. |
| **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 a combination of stavudine and didanosine with other antiretroviral combinations.  
• The stavudine and didanosine combination should only be used during pregnancy if the potential benefit clearly outweighs the potential risks.  
• Fatal and nonfatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea. |
| **Tenofovir** *(VIREAD, TRUVADA, ATRIPLA)* | • 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.  
• Tenofovir is not indicated for the treatment of chronic hepatitis B (HBV) infection; safety and efficacy in patients with HIV/HBV coinfecion have not been established.  
• Severe acute exacerbations of hepatitis B have been reported in patients who discontinued tenofovir – hepatic function should be monitored closely with both clinical and laboratory follow-up for at least several months after discontinuation of tenofovir in HIV/HBV-coinfected patients.  
• If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir. |
| **Zidovudine** *(RETROVIR), or in combination products 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. |
| 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 nonspecific 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 200mg daily must be followed strictly.  
  • Nevirapine should not be restarted after severe hepatic, skin, or hypersensitivity reactions. |
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<td>Ritonavir (NORVIR)</td>
<td>• Coadministration of ritonavir with certain nonsedating antihistamines, sedative hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious or life-threatening adverse events because of possible effects of ritonavir on hepatic metabolism of certain drugs.</td>
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<td>Saquinavir (INVIRASE)</td>
<td>• used only if combined with ritonavir</td>
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| Tipranavir (APTIVUS) | • Tipranavir coadministered with ritonavir 200mg twice daily has been associated with reports of both fatal and nonfatal intracranial hemorrhage.  
  • Tipranavir coadministered with ritonavir 200mg twice daily has been associated with reports of clinical hepatitis and hepatic decompensation including some fatalities. Extra vigilance is warranted in patients with chronic hepatitis B or hepatitis C coinfection, as these patients have an increased risk of hepatotoxicity. |
| Maraviroc (SELZENTRY) | • Hepatotoxicity has been reported with maraviroc and may be preceded by evidence of a systemic allergic reaction (e.g., pruritic rash, eosinophilia, or elevated IgE).  
  • Immediately evaluate patients with signs or symptoms of hepatitis or allergic reaction. |