



Pharmacy

Update: Black box warnings for FDA-approved antiretrovirals

Tina Edmunds-Ogbuokiri, PharmD,
FASCP

Adverse drug reactions (ADRs) continue to be a leading cause of death all over the world and in the United States. A major factor that contributes to the increased risk of ADRs after drug approval by the Food and Drug Administration (FDA) is the fact that drugs are studied in selected populations for limited periods of time. In HIV infection, this period has been shortened because of the so-called “fast-track” approvals carried out in order to make these agents quickly available for the treatment of this deadly and incurable disease. While expediting the availability of new medications for treatment of HIV-infected patients (who often have limited options) through this fast-track process, it becomes necessary that post-marketing surveillance strategies remain in place to provide data on adverse drug events that may be reported when the drugs become available to a wider population of patients and providers. Such new data are often brought to the attention of providers and patients through the “black box warnings.”

The so-called “black box” is a prominently displayed boxed warning added to the labeling of drugs or drug products by the Food and Drug Administration (FDA) when serious adverse reactions or special problems occur, particularly those that may lead to death or serious injury. Derived from both clinical trials data and post-marketing surveillance data, black box warnings are an important part of how the FDA evaluates, communicates and manages drug benefits and risks and conveys these findings to healthcare providers for optimal medication management in all patients, including HIV-in-

ected patients. The intent of this article is to review and update the black box warnings of antiretroviral agents, as presented through the Department of Health and Human Services Guidelines of May 2006, for the use of antiretroviral agents in the treatment of adults and adolescents with HIV infection.

Warnings associated with the non-nucleoside reverse transcriptase inhibitors

Nevirapine (Viramune) is the only non-nucleoside reverse transcriptase inhibitor that carries a pertinent black box warning information in its product labeling. The indication and usage section now recommends against using this drug in women with CD4+ cell counts > 250 cells/mm³ (and men with CD4+ cell counts >400 cells/mm³) at the time of initiation of the drug, unless the benefit far outweighs the risks. This recommendation is based on higher observed risk of serious liver toxicity in patients with higher CD4+ cell counts prior to initiation of therapy. Females have a three-fold higher risk of symptomatic liver toxicity than males and females with CD4+ cell counts > 250 cell/mm³ have a 12-fold higher risk of symptomatic liver toxicity than females with CD4+ cell counts of < 250 cells/mm³. In addition, the revised package insert now includes literature given to patients to inform them about the risk associated with use of nevirapine in the treatment of HIV infection. The May 2006 guidelines specifically state as follows: “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/mm³, 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 and 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.”

Warnings associated with the nucleoside reverse transcriptase inhibitors

Tenofovir (Viread) or in combination with emtricitabine (Truvada)

Lactic acidosis and severe hepatomegaly with steatosis have been reported, including fatal cases, with the use of nucleoside analogs alone or in combination with other antiretroviral agents.

Tenofovir is not indicated for the treatment of chronic hepatitis B (HBV) infection; safety and efficacy in patients with HIV/HBV co-infection 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 co-infected patients.



If appropriate, initiation of anti-HBV therapy may be warranted after discontinuation of tenofovir.

Stavudine (Zerit, D4T)

Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside reverse transcriptase inhibitors alone or in combination with other antiretroviral agents.

Fatal lactic acidosis has been reported among pregnant women who received the combination of stavudine and didanosine with other antiretroviral combinations.

Stavudine and didanosine should only be used during pregnancy if the potential benefit clearly outweighs the potential risk.

Fatal and non-fatal pancreatitis have occurred when stavudine was part of a combination regimen with didanosine with or without hydroxyurea.

Zidovudine (AZT, Retrovir) or in combination products (Combivir and Trizivir)

This agent can be associated with hematologic toxicities, including granulocytopenia and severe anemia, including and especially 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 nucleoside antiretroviral agents alone or in combination.

Zalcitabine (Hivid, ddC)

Zalcitabine can cause severe peripheral neuropathy. Use with caution among patients with pre-existing neuropathy, for instance due to diabetes or other diseases, as well as other drugs that cause neuropathy.

In 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 nucleoside antiretroviral agents alone or in combination.

Warnings associated with the protease inhibitors

Tipranavir (Aptivus)

When co-administered with ritonavir, 200mg twice daily, tipranavir 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 co-infection, as these patients have an increased risk of hepatotoxicity.

Ritonavir (Norvir)

Co-administration of ritonavir with certain non-sedating antihistamines, sedative-hypnotics, antiarrhythmics, or ergot alkaloids may result in potentially serious and life-threatening adverse events because of possible effects of ritonavir on hepatic metabolism of certain drugs.

Saquinavir (Fortovase, Invirase)

The low bioavailability of both saquinavir hard gel (Invirase) and soft gel (Fortovase) make them less desirable as sole PIs. The manufacturer currently recommends that all saquinavir be used as boosted PIs with ritonavir (Norvir). Since the hard gel capsule (Invirase) appears to have a better gastrointestinal tolerance than the soft gel preparation (Fortovase), it is preferred by some clinicians and patients. In a recent announcement from the manufacturer

(Roche Laboratories), Fortovase has recently been discontinued and will no longer be available (at least in the US market).

Invirase as saquinavir hard-gel capsules and tablets, as well as Fortovase (saquinavir soft gel capsules), are not bioequivalent and cannot be interchangeable.

Invirase may be used only if it is combined with ritonavir, which significantly inhibits saquinavir's metabolism to provide plasma saquinavir levels at least equal to those achieved with Fortovase.

Diligent recognition and application of the recommendations of black box warnings and other adverse drug reactions will assist providers in optimizing regimens for HIV-infected patients and, by so doing, improve our achievement of the desired clinical and immunological outcomes for patients with this challenging infection. ♦

REFERENCES AVAILABLE UPON REQUEST

The second part of this article will appear in the next issue of HIV Clinician.

Dr. Edmunds-Ogbuokiri is Associate Professor of Clinical Pharmacy, Xavier University College of Pharmacy; Co-PI, National Minority AIDS Education and Training Center, Xavier LPS; Pharmacy Faculty, Delta Region AETC.

Need slides for your presentations?

Visit the AETC National Resource Center site:

www.
AIDS-ETC.org