New warning on hepatitis C drugs

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Health care providers should screen patients for hepatitis B infections (including past infections) before starting them on direct-acting antivirals for hepatitis C, warned Health Canada. The drugs have been found to reactivate hepatitis B, though the risk appears to be low. Still, both patients and heath care providers should be aware of the potential problem, noted Health Canada.

"As a result, Health Canada is working with manufacturers to strengthen the prescribing information for these drugs with a new warning about this risk," Health Canada said on its website. The brand names of the direct-acting antivirals available in Canada are: Daklinza, Epclusa, Galexos, Harvoni, Holkira Pak, Sovaldi, Sunvepra, Technivie and Zepatier.

In a safety review of the drugs, Health Canada found no Canadian cases of hepatitis B reactivation, but did find 13 cases internationally. Complications of hepatitis B infection include liver failure and death. If patients are already receiving direct-acting antivirals for hepatitis C, they should be monitored by their health care providers during and after treatment, recommended Health Canada.

"While Health Canada's notice may be prudent, I am not sure it is necessary given how infrequently hepatitis B reactivation occurs in these instances. It is important, however, for all patients who have hepatitis C to be tested for hepatitis B, particularly since the routes of transmission are similar," Dr. Morris Sherman, chairman of the Canadian Liver Foundation, said in a statement. "In terms of frequency, this is at best a rare event, but for the patient this can have potentially serious outcomes, such as acute hepatitis with liver failure, or progression to cirrhosis and liver cancer over the longer time frame."

The Health Canada warning and recommendations echo those of health regulators in other countries. The Pharmacovigilance Risk Assessment Committee of the European Medicines Agency (EMA) also released a warning last week, its second of the year.

"This is thought to be the consequence of the rapid treatment-induced reduction in hepatitis C virus, which is known to suppress the hepatitis B virus, and the lack of activity against hepatitis B virus of direct-acting antivirals," the EMA said in a press release.

The United States Food and Drug Administration (FDA) issued a safety announcement in October. The agency identified 24 cases of hepatitis B reactivation between Nov. 22, 2013 and July 18, 2016. In a few cases, noted the FDA, the reactivations resulted in serious liver problems or death.

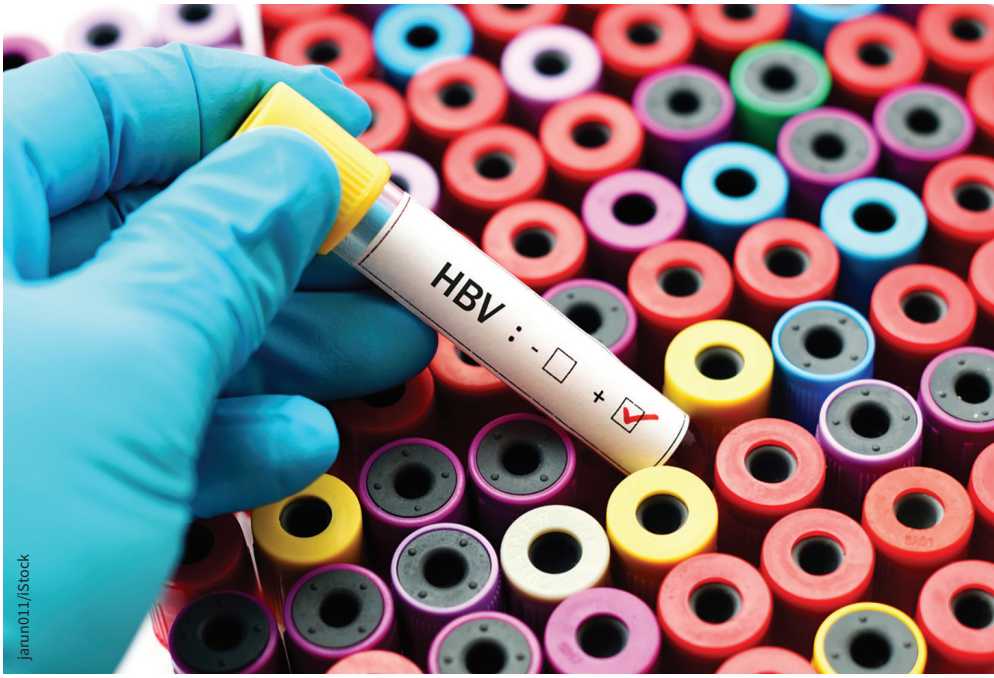
"As a result, we are requiring a *Boxed Warning*, our most prominent warning, about the risk of HBV [hepatitis B virus] reactivation to be added to the drug labels of these DAAs [direct-acting antivirals] directing health care professionals to screen and monitor for HBV in all patients receiving DAA treatment," stated the FDA.

"Serious life-threatening HBV reactivation is very rare, but the stakes are very high. Therefore this problem should be taken seriously," Dr. Charles Landis of the University of Washington's medical department, said in an email.

"I do think increased monitoring is enough to address the problem," added Landis, who cowrote a 2015 case report of hepatitis B reactivation for the *Journal of Medical Case Reports*.

The reactivation of hepatitis B by directing-acting antivirals, which are highly effective in treating hepatitis C, will pose a bigger problem in countries struggling to control both hepatitis C and B, such as China.

"With a CHC [chronic hepatitis C] population estimated to be 30 million, 3 to 12 million CHC Chinese will be at risk of HBV," Dr. George Lau, chairman of the



Direct-activing antivirals for hepatitis C can reactivate hepatitis B.

Humanity and Health Medical Group in Hong Kong, said in an email.

Lau was a coauthor on a recent observational study on hepatitis B reactivation among patients receiving direct-acting antivirals in *Clinical Gastroenterology and Hepatology*. The researchers followed 327 patients taking direct-acting antiviral agents for hepatitis C in areas of China where hepatitis B is endemic. Patients were tested for hepatitis B every two weeks during treatment and once a month for 12 weeks after treatment. Ten patients tested positive for hepatitis B, though only three cases were attributed to DAA-related reactivation.

"The US FDA warning based on our study and others is of paramount importance as DAAs will soon be made available in China," said Lau. "Left unnoticed, as reported in our study, a lot of our Chinese patients will suffer unnecessarily."

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