

## CATIE-News

CATIE's bite-sized HIV and hepatitis C news bulletins.

### **Drug interaction warning for hepatitis C: serious side effects when using telaprevir and bosentan**

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Higher-than-normal pressure in the arteries that supply the lungs with oxygen-rich blood—a condition called pulmonary arterial hypertension (PAH)—can occur in a small proportion of HIV-positive people. If left untreated, PAH can lead to serious consequences.

#### **Hepatitis C treatment**

The current standard of care for people infected with a hepatitis C virus strain called genotype 1 in Canada and other high-income countries is one of the following combinations:

- boceprevir (Victrelis) + ribavirin + a long-lasting form of interferon called peg-interferon
- telaprevir (Incivek) + ribavirin + peg-interferon

Both telaprevir and boceprevir are processed by enzymes in the liver, as are many other drugs, including some used for the treatment of HIV infection.

Multiple medicines that are processed by the same liver enzymes have the potential to interact, influencing the speed at which each medicine is broken down. Such interactions have the potential to do the following:

- Slow the breakdown of a drug. This can raise the concentration of drug(s) in the blood beyond safe levels, leading to new side effects or worsening pre-existing side effects.
- Speed up the breakdown of a drug. This can lower the concentration of drug(s) in the blood to a point where it is only partially effective or not effective at all. For people with viral infections, this may lead to serious problems. When drug concentrations are low for a prolonged period, virus-infected cells can survive and evolve to better resist therapy. This can cause treatment failure and can reduce future treatment options.

This is why consulting with a knowledgeable pharmacist is an important part of care for people with HIV, HCV, TB and other chronic infections.

#### **An unexpected result**

A medical team in Paris, France, has reported an unexpected and disturbing drug interaction between a drug used to treat PAH—bosentan (Tracleer)—and the HCV drug telaprevir. The interaction led to serious side effects.

#### **Case details**

A 58-year-old man infected with HIV, HCV and hepatitis B virus (HBV) sought emergency care. On examining him, the hospital found he had the following symptoms:

- severe confusion
- blurred vision
- dizziness
- lower-than-normal blood pressure
- difficulty maintaining his balance
- difficulty walking

Seventeen days earlier he had begun treatment for HCV, as he had severe liver damage from this viral infection. At the time of his hospitalization he was taking the following medicines:

- **HCV** treatment: telaprevir 750 mg three times daily + ribavirin 600 mg twice daily + peg-interferon 180 mcg once weekly
- **HIV** treatment: raltegravir (Isentress) 400 mg twice daily + Truvada (containing 200 mg FTC and 300 mg tenofovir) once daily
- **PAH**: bosentan 125 mg twice daily

The man had been HIV positive for several decades; his viral load was less than 400 copies/ml and his CD4+ count was 500 cells.

Blood tests done at the time of hospitalization revealed that levels of the liver enzymes ALT (alanine aminotransferase) and AST (aspartate aminotransferase) in his blood were elevated, suggestive of liver injury. As a result of these and other test results, as well as his symptoms, doctors stopped treatment of his HCV and PAH. Two days later, the man's neurological symptoms cleared. Five days after interrupting his HCV therapy, levels of his liver enzymes returned to normal.

## Drug levels

Further analyses of the man's initial blood samples found that the concentration of bosentan was four-fold greater than was expected. Levels of HIV drugs were within their normal ranges, as was the concentration of telaprevir. Interferon and ribavirin were not likely to have caused the interaction.

Once he recovered from bosentan toxicity, doctors resumed his HCV therapy and levels of this virus in his blood swiftly fell. Furthermore, no new interactions occurred.

To treat his PAH, doctors prescribed a new drug, ambrisentan (Volibris). They chose this drug because, based on available information from pharmacologists, it was unlikely to interact with telaprevir. Indeed, after he started taking this drug, no side effects emerged.

## Bosentan and other drugs

The problem of drug interactions associated with bosentan has been found in a clinical trial with HIV-negative volunteers who took the HIV medicine lopinavir-ritonavir (in Kaletra) and bosentan. In that study, levels of bosentan in the blood rose five-fold greater than usual. Side effects reported were headache; no increase in liver enzymes was detected. Bear in mind that in the study volunteers were **not** co-infected and only received bosentan for four days. The research team that did this study with Kaletra expects that a similar increase in bosentan levels in the blood could occur with other common combinations of protease inhibitors such as darunavir-ritonavir or atazanavir-ritonavir.

## For the future

The report from the Parisian medical team is a reminder to healthcare professionals and patients that drug-drug interactions do happen. Over the next five years, more therapies will be licensed for the treatment of HCV infection. While there is urgency to get potent, tolerable and interferon-free therapies for HCV, it is important to remember that with emerging and relatively new therapies, every possible drug interaction has not been studied and unexpected ones can occur. Vigilance is always necessary when taking multiple medications for different conditions, particularly understudied combinations of drugs.

## Reporting side effects

It is important to report side effects (also called adverse effects) to regulatory authorities.

## In Canada

Health Canada has instructions and links for reporting suspected adverse effects via mail, Internet and telephone here:

<http://www.hc-sc.gc.ca/dhp-mps/medeff/report-declaration/index-eng.php#a1>

### **In the U.S.**

The Food and Drug Administration (FDA) has links and instructions as to how to report suspected adverse events via the Internet or telephone here:

<http://www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm>

### **Resources**

[Understanding pulmonary hypertension](#)

[Pulmonary arterial hypertension and HIV](#)

[hepcinfo.ca](http://hepcinfo.ca) - CATIE's hepatitis C website

—Sean R. Hosein

### **REFERENCES:**

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2. Dingemans J, van Giersbergen PL, Patat A, et al. Mutual pharmacokinetic interactions between bosentan and lopinavir/ritonavir in healthy participants. *Antiviral Therapy* . 2010;15(2):157-63.

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