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Hepatitis B Drug Can Compromise HIV Treatment

Treating hepatitis B patients with the drug entecavir can cause those who are also infected with HIV to become resistant to two of the most important drugs in the anti-HIV arsenal, according to a new report in the *New England Journal of Medicine*.

In findings published June 21, 2007, online in the journal, the researchers reported that a patient infected with both hepatitis B and HIV who was treated with entecavir developed a mutant strain of HIV that is resistant to the antiviral drugs lamivudine and emtricitabine. Entecavir is manufactured by Bristol-Myers Squibb and is marketed under the trade name Baraclude.

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— **Robert F. Siliciano**

The research team was led by Chloe Thio and Howard Hughes Medical Institute investigator Robert Siliciano, both at The Johns Hopkins University School of Medicine. The analyses reported in the paper were performed by lead authors Moira McMahon, Benjamin Jilek, and Timothy Brennan in the Siliciano laboratory.

The group's initial report of the findings in February, 2007, at the Conference on Retroviruses and Opportunistic Infections led the drug's manufacturer, Bristol-Myers Squibb, to change its product labeling to warn of the potential for HIV drug resistance, notify prescribing physicians, and inform the Food and Drug Administration. The United States Department of Health and Human Services now recommends against using entecavir as the first option in treating hepatitis B in co-infected patients who are not already using drugs to suppress HIV. More than 4 million people worldwide are believed to be infected with both viruses.

The scientists emphasized that finding drug resistance in this setting underscores the need to test all antiviral drugs for anti-HIV activity before they are approved for use.

Entecavir is a chemically altered version of a chemical called a nucleoside. The drug blocks viral replication by plugging itself into a polymerase enzyme in the hepatitis B virus that helps produce new viral DNA. However, the hepatitis B polymerase closely resembles the reverse transcriptase enzyme that HIV uses to copy its genome inside an infected cell. Thus, there was a possibility that treating co-infected patients for hepatitis B with entecavir might also have an effect on HIV. But earlier tests by Bristol-Myers Squibb using techniques available at the time did not detect such an effect on HIV, said Siliciano. However, Thio, study co-author Robert Hegarty, and Braden Hale of the Naval Medical Center in San Diego recently identified three co-infected patients in whom entecavir treatment did inhibit HIV replication.

Siliciano and his colleagues analyzed entecavir's effects on HIV using a more sensitive test they had developed to measure inhibition of HIV replication. That test uses a strain of HIV engineered to be capable of only a single round of replication, making the assay more precise. The engineered virus carries the gene for a green fluorescent protein, so that its replication can be readily detected and quantified. The researchers test viral replication inside the same type of immune system T cell that the virus naturally infects.

This system is an extremely sensitive and reliable way to measure inhibition of HIV replication, said Siliciano. And when we applied it to test the effects of entecavir, we found the drug did have an effect on HIV. It was quite subtle and relatively easy to miss, but with the right assay it turned out to be a highly reproducible effect.

The researchers' studies revealed that entecavir does inhibit HIV's reverse transcriptase. They also found that one of the patients treated with entecavir developed a specific mutant form of HIV that rendered the virus resistant to lamivudine and emtricitabine.

This well-known mutation, called M184V, greatly reduces the effectiveness of two of the best anti-HIV drugs, said Siliciano. So HIV patients not yet on any HIV medications will lose the advantage of treatment with drugs that are part of the most recommended drug regimen for HIV.

The finding offers a broader lesson for drug development, said Siliciano. I think we need very careful screening of new antiviral agents that have activity against other viruses to make sure that they are not doing the same thing; that is, selecting for HIV resistance. This is particularly a problem for drugs like nucleoside analogs, which might easily affect polymerases from a variety of viruses since all viruses use the nucleoside triphosphates as substrates for synthesizing their genomes, he said.

An especially intriguing finding from the study, added Siliciano, was that entecavir showed a peculiar dosage effect on HIV replication. Probably the most interesting part of this study was that, while entecavir inhibits HIV

infection at a very low concentration—meaning that it has a very high affinity for reverse transcriptase, much better than the drugs that we currently use—it is actually not a very good HIV drug. The inhibition doesn't increase with dosage; it just plateaus. So the overall effect is that entecavir is actually a very potent, but not particularly effective, inhibitor of HIV replication, he said.

Altering the entecavir molecule to eliminate that plateau of effectiveness might well yield a new and effective anti-HIV drug, said Siliciano. Thus, he and his colleagues are further exploring the mechanism of the plateau and how it might be overcome.