New Studies Question Abacavir Role in Heart Attack Risk

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Use of the nucleoside reverse transcriptase inhibitor (NRTI) abacavir (found in Ziagen, Epzicom and Trizivir) is not associated with an increased risk of a heart attack or stroke, according to two studies reported on Monday, July 20, at the Fifth International AIDS Society (IAS) Conference on HIV Pathogenesis, Treatment and Prevention in Cape Town. The latest data add to the ongoing debate as to whether there is a link between abacavir and cardiovascular disease (CVD), with one study offering up a potential reason for the perceived increased risk: a higher number of people with underlying kidney disease being treated with abacavir.

Abacavir was initially associated with an increased risk of a heart attack in the 33,000-patient Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study. According to a report at the Conference on Retroviruses and Opportunistic Infections in February 2008 in Boston, abacavir increased the relative risk of a heart attack by 90 percent, despite the fact that the drug had never been known to contribute in any way to CVD.

The D:A:D findings were echoed later that year in the form of data from the Strategies for the Management of Antiretroviral Therapy (SMART) study, reported at the XVII International AIDS Conference (IAC) in Mexico City. According to SMART, patients using abacavir were 4.3 times more likely to have a heart attack than those not using the drug. As a possible explanation, the study investigators noted elevated blood "biomarkers"—high sensitivity C-relative protein (hsCRP) and interleukin-6 (IL-6)—among study participants taking abacavir, compared with those not on abacavir.

Other data evaluations have questioned these findings. In an analysis of 54 clinical trials conducted by abacavir's manufacturer, GlaxoSmithKline, heart attack and stroke rates were no higher among those using the NRTI. One GSK clinical in particular, the HEAT study, did not find any significant differences between those taking Epzicom, compared with those taking Truvada (tenofovir and emtricitabine), with respect to any inflammatory or CVD biomarker levels at any time point.

Data indicating a neutral effect of abacavir on CVD risk have also been reported by the federally funded AIDS Clinical Trials Group. In ACTG study A5001, an evaluation of more than 3,200 patients starting their first ARV regimen in one of five ACTG studies, a 2 percent increase in the risk of a heart attack among recent abacavir users was documented—but this finding was not statistically

significant. The CVD risk factors that were statistically significant—unlikely to be due to chance—were older age (the risk doubled every 10 years) and history of smoking.

The first of two related studies reviewed at IAS was headed by Roger Bedimo, MD, of the Veterans Administration North Texas Healthcare System. His group divided the medical records of 19,424 HIV-positive individuals into four categories, according to the type of HIV treatment they were receiving between 1996 and 2004: regimens that included abacavir, regimens that included NRTIs but not abacavir, substandard treatment (e.g., two-drug combinations), or no antiretroviral therapy at all. Patients were followed for an average of four years.

Without adjusting the data for other CVD risk factors, Bedimo's group found those using abacavir had a "modest" 27 percent increase in the relative risk of a heart attack and a 17 percent increase in the risk of a stroke. These increases, however, were not statistically significant.

When the researchers removed patients with traditional CVD risk factors—such as high cholesterol levels, high blood pressure, diabetes and smoking—from the analysis, the differences between the four study groups diminished further.

Interestingly, when the researchers removed patients with signs of chronic kidney disease—a known and significant risk factor for heart attacks and other forms of CVD—from the analysis, the risk of a heart attack or stroke associated with abacavir use was even weaker. This is a potentially important finding, because many HIV-positive individuals with chronic kidney disease are often prescribed regimens containing abacavir instead of tenofovir, given tenofovir's tendency to exacerbate underlying kidney problems.

According to Bedimo, a significantly higher number of HIV-positive people with chronic kidney disease were receiving an abacavir-inclusive regimen, compared with a tenofovir-inclusive regimen, in the VA analysis. In other words, the perceived increased risk of a heart attack or stroke among those taking abacavir may be explained, at least in part, by the higher number of HIV-positive individuals with chronic kidney disease using the drug.

Also of interest was an 80-patient analysis from the Spanish BICOMBO study, reported at IAS by Esteban Martinez, MD, of the University of Barcelona. BICOMBO was a 335-patient clinical trial comparing patients switching to either an Epzicom- or Truvada-based regimen from another drug combination.

At no point during the 48-week study did patients being treated with Epzicom have increased biomarkers associated with a greater heart attack or other CVD risk. No differences between the two groups were documented with respect to hsCRP or IL-6 levels. Similarly, no differences in biomarkers related to inflammation, blood vessel problems, blood sugar metabolism or blood clotting were reported