PIs, Abacavir and Cardiovascular Disease: What's the Risk?

February 11, 2009 By Tim Horn

Results from two ongoing studies reported on Monday, February 9, at the 16th Conference on Retroviruses and Opportunistic Infections (CROI) in Montreal confirm earlier reports that ongoing use of the protease inhibitor Kaletra (lopinavir/ritonavir), as well as Lexiva (fosamprenavir), Agenerase (amprenavir) or Crixivan (indinavir), is associated with an increased risk of heart attack independent of other factors associated with cardiovascular disease.

These studies also echoed other recent data finding an association between cardiovascular disease (CVD) and the use of abacavir (found in Ziagen, Epzicom and Trizivir), wih the French study only showing an increased risk only among those who have been on the drug for less than a year and both studies suggesting an elimination of the risk once the drug is stopped. Further evidence linking abacavir and CVD was considered possible in the Australian STEAL study, comparing the fixed-dose combination tablets Epzicom (abacavir/lamivudine) and Truvada (tenofovir/emtricitabine). Conversely, the results of a government-funded AIDS Clinical Trials Group study failed to find a link between abacavir use and a higher risk of a heart attack.

Protease Inhibitors and Heart Attack Risk

Results from the French ANRS CO4 study were reported by Dominique Castagliola, MD, of the University of Pierre and Marie Curie in Paris. The database contains the records of more than 11,000 people living with HIV, 289 of whom had a first heart attack between 2000 and 2006. For comparison purposes, each individual who had experienced a heart attack was matched up with five similar individuals in the database—of the same sex and age—without histories of heart attacks.

After factoring out variables such as traditional cardiovascular risk factors—including family history, smoking, high blood pressure and lipid levels—researches found that cumulative exposure to most of the protease inhibitors, with the exception of Invirase (saquinavir), was associated with an increased risk of a heart attack. Statistically speaking, the findings only proved significant for Kaletra (a 38 percent increased annual risk) and Lexiva or Agenerase (a 55 percent increased annual risk). In other words, for every year a patient remained on any of these three protease inhibitors, his or her risk of a heart attack increased.

In the international D:A:D study, reported by Jens Lundgren, MD, of the Copenhagen HIV Program,

cumulative exposure to Kaletra and Crixivan was the most likely to further increase the risk of a heart attack on an annual basis. D:A:D, a growing study, now contains more than 33,000 HIV-positive individuals enrolled in one of 11 cohorts around the world. While enrolled in the study, 580 patients have experienced a heart attack.

D:A:D has thus far evaluated associations between heart attack risk and four protease inhibitors: Crixivan, Invirase, Kaletra and Viracept (nelfinavir). The D:A:D analysis excludes Agenerase, Aptivus (tipranavir), Lexiva, Prezista and Reyataz until long-term use of the drugs, in a large number of patients, has been achieved.

As with the ANRS CO4 study, the D:A:D researchers adjusted the data to account for other risk factors associated with cardiovascular disease. After doing so, cumulative exposure to either Kaletra or Crixivan—but not Invirase or Viracept—was linked to a higher risk of a heart attack. For every year patients remained on Crixivan, the risk increased by 12 percent; for every year patients remained on Kaletra, the risk increased by 13 percent.

With respect to the most popular non-nucleoside reverse transcriptase inhibitors (NNRTIs) that have been in use for several years, neither Viramune (nevirapine) nor efavirenz (found in Sustiva and Atripla) were associated with an increased risk of heart attacks. Data for the newest NNRTI, Intelence (etravirine), and the least used NNRTI, Rescriptor (delavirdine), were not reported.

It is important to note, however, that these are relative, not absolute, risks. Thus, for a person without other factors for cardiovascular disease, a 12 or 13 percent annual increase in the relative risk of a heart attack generally translates into an actual annual risk of a heart attack of less than 0.4 percent. In fact, the actual number of people who had heart attacks in D:A:D—out of the massive number of people participating in the study—has been very low.

Abacavir and Heart Attack Risk

Both ANRS CO4 and D:A:D reported increased risks of heart attacks among people using abacavir, even if they were new to an ARV regimen containing abacavir. The STEAL study, with data discussed by Andrew Carr, MD, of the University of New South Wales in Sydney reported the possibility of a higher number of heart problems among patients using Epzicom compared with Truvada, whereas ACTG study A5001, reported by Constance Benson, MD, of the University of California in San Diego, found no such evidence.

Among recent users of abacavir—those who had been on the drug for less than one year—ANRS CO4 found that that the relative risk of a heart attack was doubled—a statistically significant finding. Among those who had used the drug in the past, but for less than a year, Castagliola noted a slight increased risk of a heart attack, but this finding was not statistically significant—a finding that jives with other studies suggesting that, when abacavir treatment is stopped, the risk of a heart attack drops immediately. And for those who had been on abacavir for more than a year, there was no additional risk of a heart attack.

No other nucleoside reverse transcriptase inhibitors (NRTIs) were associated with an increased risk of a heart attack, regardless of whether they were started recently or used for a long period of time.

D:A:D, following up on its initial abacavir findings reported at the 15th CROI last year in Boston, again found an increased relative risk of a heart attack associated with two NRTIs: abacavir and Videx (didanosine). Among recent users of abacavir, there was a 68 percent increase in the relative risk of a heart attack. And while ANRS CO4 did not find an increased risk among those using the drug for longer than a year, D:A:D indicates that the risk of a heart attack remains elevated for as long as someone remains on the drug.

Among users of Videx, there was a 41 percent increased risk of a heart attack—findings similar to those reported last year.

No other NRTIs were associated with an increased relative risk of a heart attack, including tenofovir (found in Viread, Truvada and Atripla), which wasn't included in the 15th CROI D:A:D presentation.

It is important to stress that while the relative risk of a heart attack associated with abacavir use was high, the absolute risk was quite low. Approximately 35 of every 1000 patients (3.5 percent) taking abacavir in D:A:D—and this includes people with other risk factors for CVD—were at risk for a heart attack over a ten-year period. Rates were even lower among those with few or no other risk factors, including younger individuals who don't smoke, have normal blood pressure and have healthy blood lipid levels.

The STEAL study, comparing Epzicom to Truvada in 360 patients switching off of their NRTIs in favor of GlaxoSmithKline's and Gilead's fixed-dose combination tablets, found no difference between the two drugs with respect to rates of undetectable viral loads after 96 weeks of follow-up. However, it did find a trend toward a higher number of CVD manifestations among those taking Epzicom. There were seven reports of ischemic CVD—three heart attacks, one leg arterial disease, one stroke and one coronary artery bypass—in Epzicom users, compared with one CVD manifestation among Truvada users. However, this difference was shy of statistical significance, meaning it could have been due to chance.

Of note, Truvada was associated with more bone mineral density loss.

ACTG A5001 is an evaluation of more than 3,200 patients starting there first ARV regimen in one of five ACTG studies, many of whom also enrolled in another study (ALLRT) for long-term monitoring. About 780 of the patients enrolled in the clinical trials were allotted to take abacavir.

While 63 severe cardiovascular disease events, including 27 heart attacks, were reported among patients in the studies, rates were no higher among abacavir users. 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 factors that were statistically significant—unlikely to be due to

chance—were older age (the risk doubled every 10 years) and history of smoking.

If there truly is a link between abacavir use and an increased risk of a heart attack, the reason is far from clear. Another AIDSmeds report from CROI will review the latest research presented at the conference exploring this important question.
