Several years ago researchers with an observational study called DAD (the Data Collection on Adverse Events of Anti-HIV Drugs) announced that they had found that a small proportion of HIV-positive participants appeared to be at increased risk for heart attack when they had used the commonly prescribed anti-HIV drug abacavir (Ziagen, and in Kivexa and Trizivir). Another observational study called the French Hospital Database also found an increased risk for heart attacks among a small proportion of abacavir users. However, on further investigation, the French researchers found that heart attacks were most likely to occur among abacavir users who injected illicit substances such as cocaine and heroin. Unfortunately, the DAD study did not collect comprehensive data about injection drug use among its participants.

By their nature, observational studies are good at finding associations but they cannot prove that a drug caused a particular side effect. A clear link between cause (taking a certain drug) and effect (heart attack) is more likely to be found in the results of robust study designs, such as randomized clinical trials. The American Food and Drug Administration (FDA) recently concluded an analysis of more than 20 randomized clinical trials—a meta-analysis—with abacavir. These trials recruited nearly 10,000 HIV-positive people. The FDA’s meta-analysis found very low rates of heart attacks and concluded that the use of abacavir was not linked to an increased risk for heart attack.

The Veterans Affairs study

A large observational, or cohort, study from the Veterans Affairs (VA) department in the U.S. was recently released. In this study, VA researchers found that recent use (in the past six months) of abacavir was linked to an increased relative risk for cardiovascular disease. The VA researchers also unexpectedly found that the use of tenofovir (Viread, and in Truvada and Atripla) was statistically linked to an increased relative risk for heart failure.

In this CATIE News bulletin, we examine the latest VA analysis and place its findings in context.

Study details

Researchers with the VA compared characteristics of 10,931 HIV-positive people whose health information had been entered into their database between 1997 and 2005. In total, 3,235 participants received abacavir and 4,314 received tenofovir as part of their HIV treatment.

The average profile of study volunteers just before they began therapy with regimens containing either of these two drugs was as follows:

- age – 48 years
- 98% men, 2% women
• CD4+ count – 302 cells
• viral load – 70,000 copies/ml

In general, people who received abacavir had a similar profile to people who received tenofovir, with similar rates of the following:
  • diabetes
  • abnormal levels of cholesterol and triglycerides in the blood
  • smoking tobacco

However, more participants who received abacavir (10%) had chronic kidney disease than participants who received tenofovir (6%).

**Results—Overall outcomes**

In total, the following outcomes or events occurred over an average of 4.5 years of observation:
  • heart failure – 194 cases
  • hospitalization for coronary artery disease, stroke or peripheral artery disease – 501 cases

**Results—Focus on abacavir**

Among abacavir users, the following events occurred:
  • heart failure – 56 cases
  • hospitalization for coronary artery disease, stroke or peripheral artery disease – 123 cases

The VA’s analysis suggested that in people who had used abacavir for six months or less, there was a 50% increased relative risk in cardiovascular complications compared to people who did not use abacavir.

Long-term use of abacavir was not statistically significantly associated with cardiovascular disease or heart failure.

**Results—Focus on tenofovir**

Among tenofovir users, the following events occurred:
  • heart failure – 53 cases
  • hospitalization for coronary artery disease, stroke or peripheral artery disease – 90 cases

During the first six months of exposure to tenofovir, there was an 82% increased relative risk of heart failure compared to people who did not use this drug.

**Caution needed**

Perhaps the most important point to bear in mind when considering the recent VA results is that the results were obtained from an observational study. Such studies are good at finding associations, in this case between anti-HIV drugs and cardiovascular events. However, observational studies cannot conclusively prove that a specific drug caused a specific side effect. This problem arises because of potential confounding by factors that may have influenced the outcome of the study. Moreover, sometimes researchers may not be aware of or able to take into account every possible factor that could have inadvertently introduced bias when interpreting the results of an observational or cohort study.

Observational studies are useful for exploring ideas. However, their conclusions must be treated with caution and need to be confirmed in studies of a more robust design. Indeed, the VA team made this cautionary statement about its study results:

“...it is possible that our findings of antiretroviral use with cardiovascular events were due to chance.”

**A different study with different findings**
A recent analysis from an American observational study called Allrt (pronounced alert) makes for an interesting contrast to the VA analysis. In Allrt, researchers with the American AIDS Clinical Trials Group (ACTG) assessed health-related data from 5,056 HIV-positive participants who had been enrolled in different randomized clinical trials. In total, 1,704 participants were given abacavir. Unlike the VA study, Allrt enrolled women—about 18% of Allrt participants were women.

After six years of monitoring, Allrt found that abacavir was not linked to any short- or long-term risk for heart attacks. Furthermore, the ACTG team made this statement: “An increased risk of [heart attack] was detected for persons of older age and with classic [cardiovascular disease] risk factors such as smoking and prior cardiovascular disease history.”

**What is new?**

The recent VA analysis has not resolved the controversy about abacavir and its potential to affect cardiovascular health.

Furthermore, the VA researchers found a small but statistically significant increased risk for heart failure among tenofovir users. This is the first time that such an association has been reported. But because this novel finding came from an observational study, it does not prove that tenofovir causes heart failure. At most, the findings from the VA analysis suggest the possibility that there is a signal from tenofovir exposure that requires confirmation in other studies. Also, if the signal of toxicity from tenofovir is eventually confirmed, and this may take several years, researchers need to understand why heart failure occurred. One possible explanation is as follows: The VA team suggested that because tenofovir can cause kidney dysfunction, perhaps kidney dysfunction might have been the underlying issue that led to heart failure. Other studies have found that kidney injury may place HIV-negative and HIV-positive people at an increased risk for cardiovascular problems.

**A small proportion of affected people**

The good news is that heart attacks, stroke and heart failure were relatively uncommon in the VA analysis, with about 6% of abacavir users and about 3% of tenofovir users experiencing these incidents. In the Allrt analysis, heart attacks were also relatively uncommon.

Moreover, many participants in both the VA and Allrt studies had risk factors for cardiovascular disease that could be controlled. For instance, about 50% of the VA participants smoked tobacco. Getting support to help quit smoking increases the chances of successfully quitting. What’s more, smoking cessation greatly reduces the risk of many complications. For more information about improving cardiovascular health, see CATIE’s in-depth Fact Sheet.

Because studies suggest that heart failure may be an emerging complication among some HIV-positive people, a future CATIE News bulletin will focus on this issue.

—Sean R. Hosein

REFERENCES:


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