

A PEER-REVIEWED ARTICLE

D:A:D study shows that HIV therapy affects incidence rate of cardiac disease

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While highly active antiretroviral therapy (HAART) has been making incredible improvements in mortality rates from HIV infection, more information about the effects of HIV therapy on other aspects of our patients' health is being found in multiple different studies. HIV therapy has been shown to have effects on the incidence rate of heart disease in patients on antiretroviral therapy. This effect has best been demonstrated in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study.

D:A:D is a huge study with a collaborative effort internationally involving 11 cohorts of investigators, including 212 clinics in 21 countries of Europe, the United States, and Australia. There were a total of 33,347 patients enrolled in the study between December 1999 and January 2005 who are being followed prospectively at their regularly scheduled visits to outpatient clinics. Data is collected in a standardized format on sociodemographic features, laboratory results, treatments (both antiretroviral and other), and clinical features. All data is then merged into a central data set annually.

All incident cases of myocardial infarction (MI) have been reported to the central office for validation and coding, with categorization as either definite, possible, or unclassifiable and as either fatal or non-fatal. Validation and coding were accomplished without knowledge of the antiretroviral treatment histories of the affected patients. Poisson regression analysis was done to quantify the relationship between antiretroviral exposure history and the incidence of myocardial infarction and reported in two major publications, the first in the *New England Journal of Medicine* in April 2007, and the second in *The Lancet* in April 2008. The first article reported the association between the use of protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and the incidence of a myocardial infarction. The primary Poisson regression model was adjusted for calendar year, conventional risk factors for cardiac disease, and demographic factors. Additional analyses of the effect of antiretroviral therapy on conventional cardiac risk factors were also performed, specifically for diabetes, hypertension, and lipid abnormalities. Demographics of the subjects of the first article were 24.1% women, 77.9% white, 16.9% black, 3.3% Hispanic, with a median CD4 count of 200 cells/mm³ and an AIDS diagnosis in 26.4%. Additional demographic data at enrollment included: 14.4% hypertension, 60.8% current or former smokers, 42.0% with dyslipidemia, and 3.1% with diabetes. Patients included in the analysis for the *NEJM* article totaled 23,437 and were enrolled between December 1999 and April 2001.

A total of 150,775 person-years of exposure to antiretroviral therapy were included in the analysis, based on 93.6% of patients who received any antiretroviral agents over the study period. 79.4% had exposure to protease inhibitors (median 4.0 years) and 63.7% had exposure to non-nucleoside reverse transcriptase inhibitors (median 2.6

years). A myocardial infarction occurred in 345 patients with a 29.3% fatality rate. At the time of the event, 90.4% had been exposed to PIs and 60.9% to NNRTIs. Increased exposure to antiretroviral therapy was consistently shown to be associated with an increased risk of myocardial infarction (adjusted relative rate of 1.16 per year of exposure) with no statistical differences seen between men and women and between older and younger patients. After adjustment for exposure to calendar year, the other drug class, and known cardiac risk factors, the PIs had a relative rate per year of 1.16 and the NNRTIs a relative rate of 1.05. Also of significance was the increased crude incidence of myocardial infarction in those who received a PI with an NNRTI as compared to those in the entire cohort (5.77 versus 3.65 per 1000 person-years); this finding is thought to be due to the longer exposure to PIs in this group. Although the PIs as a class are known to increase lipid levels, these changes were not sufficient to fully explain the increased risk. Murine models suggest a possible association between PIs and atherosclerosis by possible direct cellular mechanisms. No relationships between nadir CD4 count or peak HIV RNA level with myocardial infarction were found.

The second article, published in *The Lancet*, included an evaluation of the effects of the nucleoside- and nucleotide-reverse transcriptase inhibitor classes of medications with the risk of myocardial infarction. This portion of the study involved analysis of 33,347 enrolled patients and used the Poisson regression model to determine the relationships between cumulative, recent (current or within the preceding six months) and previous use of abacavir, didanosine, lamivudine, stavudine, and zidovudine; tenofovir, adefovir, emtricitabine, and zalcitabine were not included in the analysis. These five agents were included when a sufficient follow-up among individuals receiving the drugs was accrued for a reliable analysis. It was theorized that stavudine and zidovudine, previously shown to be associated with rises in lipid levels and increases in intima-media thickness as well as insulin resistance, would be associated with an increased relative rate of myocardial infarction. Follow-up time and events that occurred within the first two months after commencing therapy with abacavir were excluded to eliminate the effect of abacavir hypersensitivity. Patients were categorized as being of high, moderate, low, or unknown risk for cardiovascular disease using the patient's latest predicted 10-year risk as determined by the Framingham equation.

A total of 157,912 person-years were included in this analysis with 517 patients having had a myocardial infarction, giving an event rate of 3.3 per 1000 person-years. Of those who had an MI, 509 of the patients had exposure to antiretroviral therapy with 59 off therapy at the time of the myocardial infarction. The median latest CD4 count before the MI was 420 cells/mm³ and 51% of the patients had an HIV viral load < 50 copies/ml. As would be expected, the conventional risk factors for cardiac disease were found to have an association with an increased incidence of MI, such as male sex, current smokers, family history of coronary disease, diabetes, and hypertension. There were no significant data associating exposure to lamivudine, stavudine, or zidovudine with the occurrence of a myocardial infarction. Abacavir and didanosine were both shown to have an increased association that began very soon after starting the medication and remained elevated the entire time the patient was on the medication. The rate of MI was increased by 49% in those with recent use of didanosine and 90% in those with recent abacavir use as compared to those who had not used the medication ever or in the preceding six months; unlike that seen with protease inhibitors, this risk

did not continue to increase with ongoing use of either agent. The severity or classification of the myocardial infarction was not different in these groups as compared to the others.

In an editorial in the same issue of *The Lancet*, Drs. Stein and Currier bring up some relevant points for consideration. Patients with elevated lipids or at high risk for cardiac disease may have been selected for abacavir therapy in place of a protease inhibitor as a response to the *NEJM* article. The risk of inadequate viral suppression has been shown in the SMART study to be associated with an increased risk of cardiovascular complications, so changing from a suppressive regimen to a less-effective choice may lead to loss of virologic control. They stress the need for patients to modify cardiac risk factors while awaiting confirmatory research. A letter from Amy Cutrell et al from GlaxoSmithKline (GSK) in the same issue discussed a summarization of data from the GSK HIV data repository of 54 clinical trials involving 14,683 HIV-infected patients who were exposed to abacavir. The incidence of coronary/myocardial events was similar between those who received abacavir and those who had not. Stein and Currier point out though that this evaluation includes only 18 patients who had a myocardial infarction and the studies were not powered sufficiently to evaluate the risk for this complication.

What do these two studies mean clinically? They show that those who are on a protease inhibitor, either boosted with ritonavir or not, have a two-fold increased incidence of MI after 5 years (1.16 RR per year cumulative). Patients who are currently taking abacavir have nearly a doubling of risk while on the medication and those taking didanosine have nearly a 50% increased risk; increases with these two medications occur while the patient is taking the medication but the risk regresses within a few months after discontinuation of the medication. Patients should be assessed for risk of cardiovascular disease on the conventional risk factors; those at high risk should be encouraged to control those risk factors they can influence such as tobacco use or hypertension. The patient who is to begin a new HIV medication regimen should be counseled about the increased risk of MI when using these medications and the risk-benefit ratio has to be discussed with the individual patient; patients at high risk for coronary disease possibly may wish to avoid a regimen containing a PI or abacavir or didanosine unless the risk-benefit ratio favors their use due to limited effective ART choices and the patient understands the increased risk. For many patients who are already treatment experienced, the benefit of these medications to prolong life will likely far outweigh the risks, but the patient needs to be made aware of the risk in order to make a reasoned, informed decision. Patients who are currently on these medications should also be notified of the risk, with assessment done as to whether to continue the same medications or to make changes even though the risk of changing the medication with possible viral rebound may actually increase the cardiac risk further. ❖

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