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Combination Antiretroviral Therapy and the Risk of Myocardial Infarction

Reported by Jules Levin

This large international study in 20,000 individuals finds the annual rate for myocardial infarction was low 0.6% but that combination therapy increased the risk 26% per year. The study was conducted for about 5 years. So the authors said we're not sure what we would see if we continue to follow patients. Other factors besides combination therapy appear to contribute to the risk and can be addressed: cholesterol, tryglicerides, exercise, diet, smoking. Previous studies have reached conflicting conclusions on this issue, some supporting our findings and others not, but an Editorial by Peter Sklar & Henry Mazur says taken in aggregate, the weight of the evidence suggests that HIV-infected patients treated with combination antiretroviral regimens are at increased risk for the development of premature atherosclerotic complications. Atherosclerosis may. The authors add it can take decades to progress to a clinically detectable degree, and thus further follow-up of our cohort is necessary to determine whether a substantial absolute increase in morbidity and mortality from therapy-related cardiovascular disease will emerge. Regarding the use of HAART in treating HIV-infected patients, Sklar & Mazur say "given the complexity of the medical care of patients with HIV infection, we need to have unequivocal evidence that changes in our successful treatment paradigm are warranted. Antiretroviral therapies have been among the miracles of recent decades, yet we must work toward mitigating the toxic effects that have the potential to diminish the quality and duration of patients' survival over the long term".

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study Group

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Supported by the Oversight Committee for the Evaluation of Metabolic Complications of HAART, a collaborative committee with representation from academic institutions, the European Agency for the Evaluation of Medicinal Products, the Food and Drug Administration, the patient community, and all pharmaceutical companies with licensed anti-HIV drugs in the U.S. market: Abbott, Agouron, Boehringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Merck, Pfizer, and Hoffmann-LaRoche.

".....combination antiretroviral therapy was associated with a 26 percent relative increase in the rate of myocardial infarction per year of exposure during the first four to six years of use. This finding is plausible because combination antiretroviral therapy can cause adverse metabolic changes that are known risk factors for cardiovascular disease. However, only randomized trials might be able to prove whether the observed association

reflects a causal relation. In addition, the relative increase in the risk of myocardial infarction per year cannot be extrapolated beyond the duration of follow-up in the study.....

.....the annual rate of myocardial infarction, even among those exposed to therapy for four to six years, was less than 0.6 percent, and only a portion of the apparent excess risk could be attributed to combination antiretroviral therapy. Other known risk factors for myocardial infarction probably contributed to the occurrence of these events. Hence, the substantial benefits of combination antiretroviral therapy continue clearly to outweigh the increased risk of myocardial infarction associated with this therapy. However, atherosclerosis may take decades to progress to a clinically detectable degree, and thus further follow-up of our cohort is necessary to determine whether a substantial absolute increase in morbidity and mortality from therapy-related cardiovascular disease will emerge..... The results suggest that the total cholesterol and triglyceride levels have a possible role. Conversely, significant contributions from diabetes, hypertension, and lipodystrophy were not identified..... we found no evidence to suggest that the duration of HIV-1 infection, the level of prior immunodeficiency, or the degree of HIV-1 RNA replication affected the association between exposure to therapy and the risk of myocardial infarction. Moreover, none of these variables had any independent effect on the risk of myocardial infarction.....

..... Previous studies have reached conflicting conclusions on this issue, some supporting our findings and others not. Most studies have been retrospective in nature and, to varying degrees, have had other limitations, including short exposure times, a small number of end points, the use of composite end points, changes in hospital admission policies over time, and lack of source verification for the end points. Two of the largest three studies failed to detect a relation, whereas the third did. Both of the studies that did not detect a relation were based on retrospective extraction of hospital admission codes from administrative data bases. One reported a surprising decrease in admission rates over time, which may be explained by changes in admission policies as well as selection and ascertainment biases. The other reported comparable admission rates among patients who were receiving protease inhibitors and those who were not. However, a recent update suggested that the rate of admission increased over time and with longer periods of exposure to protease inhibitors, although the analysis was based on few events and was not tested statistically for significance...."

EDITORIAL

Peter Sklar, MD, MPH, and Henry Mazur, MD

".....Taken in aggregate, the weight of the evidence suggests that HIV-infected patients treated with combination antiretroviral regimens are at increased risk for the development of premature atherosclerotic complications. To balance efficacy with toxicity in determining the optimal strategy for the use of antiretroviral therapy, it is imperative to elucidate the magnitude and causes of the risk of premature atherosclerosis, the value of noninvasive tests for predicting cardiovascular and cerebrovascular risk, and the effectiveness of interventional strategies. It is logical to recommend changes in lifestyle, such as cessation of tobacco use, and to treat persons with atherogenic lipid profiles with dietary and pharmacologic interventions. While knowledge about mechanisms advances, it is prudent to consider therapy with hydroxymethylglutaryl-coenzyme A reductase inhibitors, the "statin" class of agents, which not only improve lipid profiles but also appear to improve endothelial function. However, given the complexity of the medical care of patients with HIV infection, we need to have unequivocal evidence that changes in our successful treatment paradigm are warranted.

Antiretroviral therapies have been among the miracles of recent decades, yet we must work toward mitigating the toxic effects that have the potential to diminish the quality and duration of patients' survival over the long term....." see full text of editorial at end of this report.

ABSTRACT

Background: It remains controversial whether exposure to combination antiretroviral treatment increases the risk of myocardial infarction.

Methods: In this prospective observational study, we enrolled 23,468 patients from 11 previously established cohorts from December 1999 to April 2001 and collected follow-up data until February 2002. Data were collected on infection with the human immunodeficiency virus and on risk factors for and the incidence of myocardial infarction. Relative rates were calculated with Poisson regression models. Combination antiretroviral therapy was defined as any combination regimen of antiretroviral drugs that included a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor.

Results: Over a period of 36,199 person-years, 126 patients had a myocardial infarction. The incidence of myocardial infarction increased with longer exposure to combination antiretroviral therapy (adjusted relative rate per year of exposure, 1.26 [95 percent confidence interval, 1.12 to 1.41]; $P < 0.001$). Other factors significantly associated with myocardial infarction were older age, current or former smoking, previous cardiovascular disease, and male sex, but not a family history of coronary heart disease. A higher total serum cholesterol level, a higher triglyceride level, and the presence of diabetes were also associated with an increased incidence of myocardial infarction.

Conclusions: Combination antiretroviral therapy was independently associated with a 26 percent relative increase in the rate of myocardial infarction per year of exposure during the first four to six years of use. However, the absolute risk of myocardial infarction was low and must be balanced against the marked benefits from antiretroviral treatment.

Although the benefits of combination antiretroviral therapy have revolutionized the care of patients with human immunodeficiency virus type 1 (HIV-1) infection, increasingly severe treatment-associated metabolic side effects have been observed, among them dyslipidemia, insulin resistance, and overt diabetes mellitus, which are well-known risk factors for cardiovascular disease.^{1,2,3,4,5,6} These side effects may increase the risk of premature myocardial infarction, although direct evidence of such an association is inconsistently reported in the existing literature.

To address this concern, and as part of an initiative by the European Agency for the Evaluation of Medicinal Products, the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study was initiated in 1999. The primary objective of the study was to determine whether exposure to combination antiretroviral therapy is independently associated with the risk of myocardial infarction.

The study methods have been described previously.⁵ In brief, we conducted a collaborative, observational study of 11 previously established cohorts comprising 23,468 HIV-1-infected patients followed at 188 clinics in 21 countries in Europe, the United States, and Australia.

The primary study end point was myocardial infarction. The study was designed to permit the detection of a twofold difference in the incidence of myocardial infarction between two equal groups according to their exposure to combination antiretroviral therapy. A total of at least 100 new cases of myocardial infarction were required to give the study sufficient power to detect such an increase in risk (two-sided type I error, 5 percent; power, 90 percent). On the basis of preliminary data from the EuroSIDA study, the incidence of myocardial infarction in these HIV-1-infected persons was assumed to be 3.3 per 1000 person-years (Kirk O: personal communication), and hence the study had to collect at least 30,000 person-years of follow-up data before the primary objective could be examined.

The presence of lipodystrophy was defined subjectively and not verified objectively. The training of study and medical personnel for each cohort and at each site was performed before the initiation of the study. Site monitoring was conducted annually and included a review of source documents for all the reported end points and all cases of death and an audit of the case notes for a random sample of 10 percent of the remaining patients.

The study was supervised by a steering committee with scientific and organizational independence from the financial sponsor of the study, a consortium of pharmaceutical companies that market licensed antiretroviral agents in Europe and the United States. Until the study reached the predetermined number of person-years of follow-up, members of the steering committee remained blinded to the number of end points that had occurred. An external expert from the MONICA project evaluated the documentation of primary end points, and before the event data base and main study data base were merged, an end-point committee reviewed the classification of the primary events.

Results

Base-Line Characteristics

The study cohort included 23,468 HIV-1-infected patients; 24.1 percent were women, and the median age of the patients was 39 years. The median known duration of HIV-1 infection was 3.5 years, and 26.2 percent of the patients had previously been found to have AIDS. At base line, 80.8 percent of the study population had been exposed to at least one antiretroviral drug and 74.5 percent to combination antiretroviral therapy. Overall, the median cumulative exposure to combination antiretroviral therapy was 1.9 years. Because of differences in the dates when various drug classes were first marketed, the rate of exposure to protease inhibitors was substantially higher and the duration substantially longer than the rate and duration of exposure to nonnucleoside reverse transcriptase inhibitors.

In this relatively young population, the prevalence of previous cardiovascular disease was only 1.5 percent. However, many of the subjects had cardiovascular risk factors: 56.2 percent were current or previous smokers and 2.8 percent had diabetes, 7.2 percent hypertension, and 45.9 percent dyslipidemia. 22% of patients reported lipodystrophy. 3.7% used lipid lowering agents. Body Mass Index: 4.8% had BMI >30; median BMI was 23.0. 11% had family history of cardiovascular disease. 5% of patients had total cholesterol >6.2 mmol/l; median was 4.2-6.0 mmol/l. 26% of patients had HDL cholesterol <0.9 mmol/l; median was 1.1 mmol/l. Ratio of total to HDL: 18% had >6.4; median 4.5. Triglycerides: 32% had >2.1 mmol/l; median was 1.7 mmol/l.

The median time between clinic visits (according to assessments of CD4+ cells) during the prospective follow-up period was three months, without consistent differences according to the duration of exposure to combination antiretroviral therapy. The total number of person-years of prospective follow-up until the first new myocardial infarction or until the censoring date for those who remained free of myocardial infarction was 36,199 (median individual follow-up time, 1.6 years [interquartile range, 1.3 to 1.9]). A total of 1909 participants (8.1 percent) had no reported clinic visits during the 12 months before February 1, 2002. During the follow-up period, 566 patients (2.4 percent) were known to have died; 36 of the deaths (6.4 percent) were due to myocardial infarction, and 26 (4.6 percent) were due to other cardiovascular events, such as stroke.

Incidence of Myocardial Infarction

A total of 126 patients had a myocardial infarction during follow-up (incidence, 3.5 events per 1000 person-years). Fifty-five percent of the myocardial infarctions were categorized as definite and 29 percent as possible; 16 percent were considered unclassifiable. One hundred fourteen of the infarctions (90 percent) occurred in men. Thirty-six of the events (29 percent) were fatal; 16 of the deaths were considered to have been caused by an unclassifiable coronary event (such as sudden death).

The incidence of myocardial infarction increased with increasing exposure to combination antiretroviral therapy (P for trend, <0.001). The patients with no exposure to therapy had a lower incidence of myocardial infarction than for any of the treated groups. Because the incidence increased gradually with more extended exposure, exposure time was fitted as a continuous variable in subsequent models. Fitted this way, the relative rate was 1.22 (95 percent confidence interval, 1.09 to 1.38) per additional year of exposure to combination antiretroviral therapy; it was 1.26 (95 percent confidence interval, 1.12 to 1.41) after adjustment for demographic risk factors, including age, which increased with increasing duration of therapy.

The incidence of primary events was assessed beginning at base line according to the cumulative duration of combination antiretroviral therapy since the initiation of therapy, stratified in one-year intervals from the initiation of therapy to four years, more than four years of exposure, and no exposure. The rate of myocardial infarction was generally lower among the patients not exposed to combination antiretroviral therapy than in any of the treated groups. The untreated patients had, *a priori*, a lower risk of myocardial infarction than the treated patients.²⁶ As compared with the rate of myocardial infarction among the patients treated for less than one year, the univariable relative rate among the patients with no exposure to therapy was 0.24 (95 percent confidence interval, 0.07 to 0.89); among those with one to less than two years of exposure, 1.34 (95 percent confidence interval, 0.58 to 3.10); among those with two to less than three years of exposure, 1.73 (95 percent confidence interval, 0.80 to 3.76); among those with three to four years of exposure, 1.98 (95 percent confidence interval, 0.94 to 4.15); and among those with more than four years of exposure, 2.55 (95 percent confidence interval, 1.25 to 5.20) (P for trend <0.001).

Association of Combination Antiretroviral Therapy and Other Cardiovascular Risk Factors with the Rate of Myocardial Infarction (multivariate model)

Exposure to combination therapy (per additional year): Relative Risk (RR) 1.26 ($p<0.001$).

Age (per additional year): 1.38 ($p<0.001$)

Male sex: 1.99 ($p=0.04$)

BMI was not associated

Smoking was associated with increased risk: current or former smoker RR 2.17 compared to 1 for never smoked ($p=0.07$)

Previous CVD: RR 5.84 compared to 1 for without previous CVD ($p<0.001$).

At base line and during follow-up, increased total cholesterol levels, increased triglyceride levels, and the presence of diabetes were all associated with an increased risk of myocardial infarction. The presence of hypertension at base line was not significantly associated with the risk of myocardial infarction, whereas the analysis of time-updated values did reveal an increased risk. The presence of lipodystrophy at any time was not significantly associated with the risk of myocardial infarction.

The association between combination antiretroviral therapy and the risk of myocardial infarction tended to decrease in the models that included total cholesterol or triglyceride levels, but not in those that included diabetes, hypertension, or lipodystrophy. In addition, when total cholesterol and triglyceride levels were included in the same model, the association with therapy was not further affected (relative rate, 1.16 [95 percent confidence interval, 1.02 to 1.33]).

None of the markers of HIV-1 disease were associated with myocardial infarction in the adjusted model. Including these variables in the model did not modify the association between duration of exposure to combination antiretroviral therapy and myocardial infarction.

EDITORIAL (cont)

Soon after the introduction of protease inhibitors and nonnucleoside reverse-transcriptase inhibitors for the management of human immunodeficiency virus (HIV) infection, clinicians observed unexpected cardiovascular events among patients receiving these new, combination, "highly active" antiretroviral regimens. Angina, myocardial infarction, and stroke were seen in patients who were relatively young. Providers became suspicious that these events were related either to chronic HIV infection, since patients were surviving for longer periods than they had in the past, or to the new anti-HIV regimens, which are associated with substantial metabolic abnormalities.

Between 1998 and 2003, several reports appeared to validate clinicians' concerns. The French Hospital Database on HIV, which included data from nearly 20,000 men who had been exposed to a protease inhibitor (54 of whom had had a myocardial infarction), found that patients who had been treated with a protease inhibitor for more than 18 months had twice the risk of myocardial infarction that was seen among patients with less drug exposure. The HIV Outpatient Study, which used a data base with more than 5700 outpatients, identified 21 myocardial infarctions and concluded that there was a trend toward an increased frequency of myocardial infarction since the widespread use of protease inhibitors beginning in 1996.² A review of claims for more than 28,000 HIV-infected Medicaid patients in California showed that younger patients (18 to 33 years of age) who were exposed to antiretroviral agents had

twice the risk of coronary heart disease seen among age-matched, untreated persons. The Kaiser Permanente Medical Care Program of Northern California compared rates of hospitalization for coronary artery disease and reported that the rate of such hospitalizations among HIV-infected patients, regardless of whether they used antiretroviral agents, was 1.5 times that among their uninfected counterparts. Thus, an emerging body of evidence suggested that as HIV-infected patients were living longer as a result of antiretroviral therapy, cardiovascular disease was developing at unexpected rates.

Earlier this year, an article in the Journal appeared to refute these observations. Bozzette and colleagues conducted a retrospective analysis of hospitalizations and deaths due to cardiovascular and cerebrovascular disease among approximately 36,000 patients with HIV infection in the Veterans Affairs (VA) Medical System.

The main outcomes were determined from hospital administrative data bases; data on mortality were obtained from the National Death Index. Between 1995 and 2001, the rate of admission for cardiovascular and cerebrovascular disease actually decreased, from 1.7 to 0.9 per 100 patient-years; the rate of death decreased from 21.3 to 5.0 deaths per 100 patient-years, a decrease of roughly 75 percent. Use of any class of antiretroviral therapy, alone or in combination, was associated with a decreased hazard of death from any cause. Thus, this large and carefully constructed study was reassuring in that cardiovascular disease, while present, was not becoming a substantial complication of HIV disease and its therapy.

In this issue of the Journal, Friis-Møller and collaborators present data from the prospective, multinational Data Collection on Adverse Events of Anti-HIV Drugs (DAD) Study. This study collected data on more than 23,000 patients enrolled in 11 previously established cohorts in Europe, the United States, and Australia. Atherosclerotic events were prospectively identified and independently validated. Over a median follow-up time of 1.6 years through February 2002, 126 patients had a myocardial infarction. Including in their analysis the cumulative duration of drug exposure, the authors determined that during the first four to six years of combination therapy, there was a 26 percent relative increase in the rate of myocardial infarction per year of exposure to antiretroviral drugs. The study did not have sufficient power to permit comparisons among patients receiving different types of antiretroviral regimens.

Why did these studies reach contradictory conclusions? They both assessed large patient cohorts, yet in neither investigation was the HIV-infected study group compared with an uninfected control group. In addition, the follow-up periods (3.3 years in the VA study and 1.6 years in the DAD Study) were limited in comparison with the 16-year follow-up driving many of the risk estimates derived from the Framingham Study. In the DAD Study, outcomes were prospectively and independently verified, although not all events were classified as "definite." In the VA study, which relied on retrospective code abstraction, the accuracy of coded information could not be verified, and it was not certain that criteria for hospitalization were constant over this period of time. The absolute magnitude of the increase in risk observed in the DAD Study was small and could easily have been missed in the VA study. Subsequent, longer-term analyses of these cohorts will provide much-needed data.

If there is an increase in risk, is it due to HIV infection or to its treatment? It must be recognized that as HIV-infected patients live longer, their risk of cardiovascular disease, compounded by their preexisting burden of traditional risk factors, inevitably increases. More

than half the patients in the DAD cohorts were current or former smokers; approximately 3 percent had diabetes, 7 percent hypertension, 21 percent an elevated total cholesterol level, 26 percent a low high-density lipoprotein (HDL) cholesterol level, and 32 percent an elevated level of triglycerides. Thus, some degree of the cardiovascular risk discussed above may have been the result of predisposing factors, independently of HIV infection. Alternatively, some cardiovascular events may have been a consequence of HIV infection, of antiretroviral therapy, or of a synergistic relation among all these risk factors.

Is it plausible that HIV infection itself could promote atherosclerosis through a proinflammatory effect on endothelial cells, much like the mechanism that has been hypothesized for other infectious agents such as cytomegalovirus, herpes simplex virus, or chlamydia? Or could HIV infection promote cardiovascular disease indirectly, by way of the lipid abnormalities it induces? The acquisition of HIV infection is associated with reductions in the HDL cholesterol level (by 12 mg per deciliter [0.3 mmol per liter]), as well as reductions in the total cholesterol and low-density lipoprotein cholesterol levels (by 30 mg per deciliter [0.8 mmol per liter] and 22 mg per deciliter [0.6 mmol per liter], respectively). Hypertriglyceridemia is associated with disease progression and HIV viremia.

Is it plausible that the antiretroviral drugs themselves promote atherosclerosis directly or indirectly? When administered to healthy volunteers for four weeks, indinavir caused significant endothelial dysfunction (as measured by invasive monitoring of arterial blood flow in response to vasoactive compounds), independently of drug-induced alterations in blood pressure or lipid profiles. Endothelial dysfunction detected by this investigative technique is highly correlated with coronary artery disease and the development of subsequent clinical events, suggesting a direct mechanism by which the drugs may promote cardiovascular disease, perhaps by affecting the ability of endothelial cells to produce nitric oxide.

Much attention has been paid to the metabolic disturbances attributed to these drugs, which could indirectly promote atherosclerosis. Certain antiretroviral drugs, most notably the protease inhibitors, produce marked elevations in cholesterol and triglyceride levels. It is not uncommon for clinicians to see patients receiving protease-based antiretroviral regimens who have cholesterol levels above 250 mg per deciliter (6.5 mmol per liter) and triglyceride levels above 500 mg per deciliter (5.6 mmol per liter). In addition, certain antiretroviral agents are associated with insulin resistance. HIV-infected patients receiving antiretroviral therapy have also experienced changes in body habitus (lipodystrophy) that have themselves been associated with cardiovascular disease. Thus, treated patients may have lipodystrophy, diabetes, and atherogenic lipid profiles, which could be the routes by which these drugs cause premature atherosclerosis, perhaps in concert with direct toxic effects on the endothelium.

Are there studies of variables other than clinical end points that give further credibility to the possibility that we are observing a true phenomenon? When assessed by electron-beam computed tomography, coronary-artery calcifications have been shown to be more common in patients with HIV infection than in uninfected patients. Similarly, ultrasonographic evidence of carotid intimal thickening has been documented. Both of these findings are predictive of the occurrence of clinical events among patients without HIV infection and are thus causes for concern.