Cardiac Risk: Not So Simple

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(See the article by Worm et al, on pages 318–30.)

Understanding the risk of cardiovascular disease in persons with human immunodeficiency virus (HIV) infection is complex. Controversy exists as to how much risk can be attributed to host genetics, traditional risk factors, adverse effects from antiretroviral therapy, and the inflammatory state associated with HIV itself [1]. Nevertheless, the INTERHEART study [2], conducted in the general population, clearly suggests there is synergy among cardiovascular risk factors, such that the co-occurrence of 2 or more risk factors (eg, hypertension and dyslipidemia), may have greater-than-additive effects on overall cardiovascular risk. Thus, all factors potentially contributing to coronary heart disease (CHD) need to be considered when managing persons infected with HIV. The difficulties in determining risks among those with HIV infection have largely been due to the lack of matched controls, small sample size, and lack of standardized definitions, plus the unknown contribution from HIV itself. Previously, the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) investigators reported an increased relative rate (RR) of myocardial infarction (MI) with cumulative use of protease inhibitors (RR per year of exposure, 1.16 [95% confidence interval [CI], 1.10–1.23]) but not nonnucleoside reverse-transcriptase inhibitors (RR per year of exposure, 1.05 [95% CI, 0.98–1.13]). In a subsequent analysis focusing on nucleoside reverse-transcriptase inhibitor use, an unexpected increased risk of MI was found with recent use of abacavir (RR, 1.90 [95% CI, 1.47–2.45]) and didanosine (RR, 1.49 [95% CI, 1.14–1.95]), but not with cumulative use [3]. Criticism of the study at that time was that abacavir had been preferentially prescribed to those with metabolic syndromes, lipoatrophy, dyslipidemia, renal disease, and CHD and that the study results reflected provider prescribing bias, especially given that there was an inadequate duration of time to evaluate the effects of tenofovir, a nucleotide similarly prescribed as abacavir except among those with renal disease. In a study by Worm et al [4] in this issue of the Journal, with 1 additional year of follow-up of the cohort, the D:A:D investigators were able to examine the association of tenofovir with CHD and found no such association. Of the drugs studied in their analysis, only indinavir, ritonavir-boosted lopinavir, didanosine, and abacavir were associated with an increased risk of having an MI. Although use of these agents was associated with increased cardiovascular risk, it is important to compare this risk with those resulting from other factors. For example, according to prior D:A:D results, protease inhibitor–associated risk was considerably lower than the annual increase in risk associated with advanced age (RR, 1.39; P < .001), male sex (RR, 1.91; P = .002), or current smoking (RR, 2.83; P < .001) [3].

The association between abacavir and MI created a storm of controversy. It was unexpected, even by the D:A:D investigators, and as several other groups tried to confirm their findings, the community was confronted with mixed results and clinical indecision. Although the association observed with respect to protease inhibitor use has been consistent in a number of cohorts, this is not the case with respect to abacavir. Three studies (1 prospective study [5] and 2 nested case-control studies [6, 7]) have reported statistically significant associations between exposure to abacavir and MI risk. One controlled trial that randomized abacavir assignment [8] also reported an association with all cardiovascular adverse events, but only 3 of these events were MIs, so...
this specific association could not be validated. At the same time, 4 other studies (a retrospective observational cohort study [9], a pooled descriptive analysis of 52 manufacturer trials [10], a clinical trial that randomized abacavir assignment [11], and a pooled analysis from 5 clinical trials with and without randomized assignment to abacavir [12]) found no association between abacavir use and risk of MI. Making sense of these varied results is complicated by the very low underlying MI event rates observed, which has left most of these cohorts underpowered to detect even modest effect sizes. Furthermore, differences in study designs, populations, and scope of data collection have all meant that none of the studies have been able to specifically address the same specific question with respect to recent abacavir exposure as that noted in the D:A:D cohort. Interestingly, with limited additional abacavir data, in the analysis presented by Worm et al [4] in this issue of the Journal, there is a small and marginally significant association with cumulative abacavir use that was not previously detected.

The one consistent finding across all studies that have investigated cardiovascular risk and associations with antiretroviral exposure is that the group of patients observed to have events have tended to be a population with higher risk than the group of patients without events (older; with higher rates of smoking, hypertension, and dyslipidemia; and with preexisting CHD). In the current D:A:D study, among the patients who were reported to have an MI, 48.4% had a calculated 10-year predicted cardiac risk in the moderate and high categories. These patients also were older, had a higher prevalence of tobacco use, and were more likely to have diabetes mellitus and/or hypertension, compared with those who did not have an MI.

Large, well-designed observational cohorts, such as the D:A:D study, are crucial to understanding adverse effects of long-term exposure to antiretroviral therapy. However, their subsequent data analysis is fraught with very challenging issues. In the presence of many related and temporal confounding effects, it could be easy to be misled by apparent, induced associations [13]. Even with adjustment for time-varying confounders, such analyses may induce or attenuate associations between treatment exposure and outcome [14]. The D:A:D investigators have always been careful to stress these limitations in discussion of their results, and they have been thorough in their scope of sensitivity analyses that might reveal such biases. Although the D:A:D investigators advise readers to interpret their studies with caution, it remains unclear how clinicians interpret statements of this sort. Certainly, the results of D:A:D studies have become a rich source for marketing by pharmaceutical companies, which has contributed, in our opinion, to overemphasis of the results. Relatively recent advances in statistical methodology [15, 16] have the potential to help in this area, and their routine use in observational studies, such as D:A:D, has the potential to be of much assistance in this very complex area. Still, even these newer methods have their limitations and rely on key assumptions that may be difficult to assess.

What does this potential risk of CHD from antiretrovirals really mean? How does one apply these findings when choosing antiretroviral regimens? Clearly, not everyone develops abnormal lipid levels or alterations in glucose metabolism. Certain combinations may be more associated with adverse lipid metabolism than others, and these associations may vary among individuals by sex and ethnicity [1]. Choosing an effective antiretroviral regimen has become an art. The underlying problem is HIV infection itself, and one must choose a regimen that the individual can tolerate and adhere to, taking into account other comorbidities, drug interactions, and occupational and social activities, with the goal to achieve complete virologic suppression. More attention should be given to the traditional factors that are associated with the most risk (eg, smoking, hypertension, and obesity). In addition, the relatively small contribution of CHD risk from HIV therapies must be weighed against the potential benefits of reducing viral replication. The D:A:D study is one of the largest observational cohorts, representing thousands of individuals living with HIV infection. As this population continues to age, the D:A:D observational findings will continue to provide valuable insight on prescriber practices, patient outcomes, risk, and development of comorbidities and complications associated with HIV infection and its therapy. This current study [4] not only sparked controversy, it sparked further scientific study to understand the pathogenesis of cardiac risk and interventions to decrease such risk.

References

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