

Increased cardiovascular risk in HIV infection: drugs, virus and immunity

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Recent studies have linked the use of specific anti-retroviral drugs or classes of drugs with an increased risk in subclinical atherosclerosis or actual cardiovascular events. The protease inhibitors were the first such class of ‘culprits’ identified as increasing such a risk; however, results are conflicting [1–4]. Most recently, the nucleoside reverse transcriptase inhibitors abacavir and didanosine, originally not considered to have adverse consequences on the cardiovascular system, were reported to be associated with a respective 90 and 49% increase in myocardial infarctions (MIs) in a large cohort with over 150 000 person-years of follow-up [5]. Abacavir has a peculiar history. Although it is considered to be a ‘metabolically friendly’ drug, as early as 2005, the Uppsala Monitoring Centre, which analyses adverse reactions reported in the WHO database, noted that there was a suspiciously high number of MIs in patients taking abacavir with and without protease inhibitors; however, in the sponsor’s trials of more than 9600 patients, no increase in the risk of MI was observed [6]. Regardless of the contradictory data, it is difficult to ignore any factors associated with a 90% increase in a potentially morbid complication, but should we?

To complicate matters, HIV itself has been associated with nearly a two-fold increase in risk of acute MI in HIV-infected individuals compared with HIV-uninfected controls [7]. Furthermore, recent data from the Strategies for Management of Antiretroviral Therapy (SMART) study, where patients who strategically interrupted antiretroviral treatment in order to limit their supposed drug-related adverse effects, found themselves in the

awkward position of having significantly more cardiovascular events, so many in fact, this study was prematurely terminated [8]. So, do the drugs help or hurt?

The contradictory findings from the studies that have reported clinical cardiovascular endpoints have limitations: many are observational with inherent biases, follow-up is relatively short, specific antiretroviral usage history is unclear and most have no HIV-uninfected controls. In order to answer the very important question of what exactly is the cardiovascular risk for HIV-infected individuals taking antiretroviral therapy for the rest of their lives, an enormous study with well documented ‘hard’ clinical endpoints would be required. The Data Collection on Adverse events of Anti-HIV Drugs (DAD) Study, although enormous, is not a randomized study but an analysis of data from a collaboration of observational cohorts, each with its own potential biases. In that report, 517 patients had an MI [5]; treatment was not randomized and selection bias, particularly for a drug like abacavir with no previous well known link to cardiovascular disease, is a real possibility. A study with the power and complexity to answer the treatment-risk question rigorously is probably not feasible. So what are the alternatives?

The alternatives are to accept the data available from studies that have well documented clinical endpoints while continuing to investigate subclinical atherosclerosis with tests that have strong predictive values for cardiovascular disease, such as brachial artery flow-mediated dilation (FMD), carotid artery intima-media

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thickness (CIMT) and measurement of coronary artery calcium (CAC). Utilizing these evaluations for assessment of cardiovascular risk offers the potential of actually performing randomized controlled studies in a setting that is realistic and feasible, such as in a sub-study of one of the large planned antiretroviral treatment trials in previously untreated patients. The main criticism to this approach, of course, is that there will be few if any hard clinical endpoints; one must have faith that surrogate markers are actually predictive in the population studied.

The cardiovascular disease surrogate markers studies with and without combination highly active antiretroviral therapy (HAART) have shown equivocal results, and in general, exonerate specific antiretroviral drugs as major cardiovascular risks. The studies using CIMT as an endpoint have mostly identified the traditional risk factors as significant causative factors. For example, in the tightly controlled ACTG 5078 Study, triads consisting of HIV-infected patients on protease inhibitors, HIV-infected patients not on protease inhibitors, and HIV-uninfected controls were all matched for age, sex, race, smoking status, blood pressure and menopausal status: there was no association between protease inhibitor exposure or HIV infection and CIMT [9,10]. A surprising result was also seen in the ACTG 5152 Study, where endothelial function was assessed by brachial artery FMD. In this trial, treatment-naïve patients from a large parent study were randomized to receive three different treatment regimens, some of which contained protease inhibitors or non-nucleoside reverse transcriptase inhibitors and another group that received a nucleoside-sparing therapy. Virtually all patients had markedly abnormal FMD prior to treatment, and all had rapid and pronounced improvement once any of the therapies were started suggesting that HIV infection and not the specific drugs acutely impacted endothelial function [11]. The major concern of this study was its relatively short duration of 6 months; longer follow-up is definitely needed. One can still conclude, however, that not being on suppressive HAART, whether one is treatment-naïve or interrupting therapy, may be deleterious in terms of cardiovascular risk.

In this issue of *AIDS*, data on subclinical atherosclerosis from two large prospectively followed cohorts, the all male Multicenter AIDS Cohort Study (MACS) and the Women's Interagency HIV Study (WIHS), are presented. These are large cross-sectional analyses from well described cohorts which include both men and women, HIV-infected and uninfected and patients on HAART and HAART-naïve. In the MACS Study, 947 patients including 332 uninfected, 84 not on HAART and 531 on HAART were evaluated with CAC. Although CAC was marginally increased in HAART users, the extent of the lesions was significantly less in the HAART users than in the HIV-uninfected controls, particularly those not on antilipid therapy [12]. In the WIHS/MACs combined study, 1331 HIV-infected women and 600 HIV-infected

men plus 534 uninfected women and 325 uninfected men were studied with CIMT as an endpoint. The only significant HIV-related risk identified with subclinical atherosclerosis was low CD4+ T-cell count: patients with less than 200 CD4+ T cells/ μ l compared with HIV-uninfected individuals had a two-fold increase in prevalence of carotid lesions for women and a 1.74 increase for men. Among the HIV-infected patients, viral load, low CD4 cell count, a history of clinical AIDS and antiretroviral medications were not associated with an increase in CIMT compared with uninfected controls. There was, however, a marginal risk associated with protease inhibitor use in men but not in the women, although women had significantly less drug exposure [13].

Naturally, there are limitations to these studies: they are cross-sectional in nature, they are surrogate marker studies for subclinical atherosclerosis, and there are no actual events. Regardless, these data are generated from prospectively followed cohorts, which include men, women, patients on therapy and those that are not and most importantly, they include uninfected controls. Both studies point out that the so-called 'traditional risks' for cardiovascular disease are the most important factors. Any treatment that adversely affects such risk factors, such as a drug's effect on lipids, likely explains a significant portion of the increase in overall cardiovascular risk that has been reported. We will be better able to identify therapy-related cardiovascular risk factors if we focus on well designed substudies measuring atherosclerosis and endothelial function within the large trials being planned for treatment-naïve patients. One thing we can say with certainty is that treatment of HIV disease with restoration of immunity is good for the heart – this is the most important message today.

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