Risk of cardiovascular disease in HIV-infected patients

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The life expectancy of people living with HIV infection has improved dramatically since the use of highly active antiretroviral therapy (HAART). Now that patients with HIV infection are living longer, the focus of its treatment should shift to long-term management spanning decades. Diseases of ageing, including cardiovascular disease (CVD), have now become more important. The evidence of cardiovascular risk associated with HIV infection and antiretroviral therapy is explored and discussed in this article.

Keywords: antiretrovirals, abacavir, lipids, viral replications, toxicities, adverse drug reactions

Introduction

The adverse metabolic profile that has been observed in HIV-positive cohorts including insulin resistance, dyslipidaemia and visceral adiposity has also been recognized in the general population as one associated with increased risk of cardiovascular disease (CVD). A significant body of evidence suggests that there is a measurable increase in the risk of CVD in those living with HIV with varying effects from different antiretrovirals.

HIV, highly active antiretroviral therapy and CVD

The rate of hospitalization for coronary heart disease (CHD) among HIV-positive patients was more than twice that of their HIV-negative counterparts, irrespective of whether or not they were taking highly active antiretroviral therapy (HAART).1 In a review of administrative claims for >28000 HIV-positive patients, those in a younger age group (18–33 years) who were exposed to antiretroviral agents had twice the risk of CVD seen in age-matched, treatment-naive patients.2 A cohort study involving >4000 HIV-infected individuals and 1.3 million HIV-uninfected individuals demonstrated that HIV infection itself is an independent risk factor for acute myocardial infarction (MI).3 The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study Group demonstrated an increased incidence of MI that was proportional to the cumulative duration of HAART, particularly protease inhibitor (PI) therapy, but not non-nucleoside reverse transcriptase inhibitor (NNRTI) therapy. The group has suggested recently an association of MI with the use of specific antiretroviral (ARV) agents including the nucleoside reverse transcriptase inhibitor (NRTI) agents abacavir and didanosine.4 Similar findings were observed in a nested case control study presented by the French National Agency for Research on AIDS and Viral Hepatitis (ANRS) group.5 However, other studies have not found an association between antiretroviral therapy (ART) and increased CVD events. The HIV Out Patient Study (HOPS) found no association of CVD with specific ARV agents or classes but detected a significantly increased association with the traditional CVD risk factors.6 Moreover, the recently presented SMART (Strategies for Management of Anti-Retroviral Therapy) study has shown that interruption of ART was associated with excess risk of CVD.7 Sub-analysis of the same study8 has shown that whilst treatment interruptions were associated with lowering of all lipid levels including both total and high-density lipoprotein (HDL) cholesterol, a rise in inflammatory and coagulation markers including interleukin (IL)-6 and D-dimer to high levels was observed, which correlated with an increase in HIV-RNA level.7

The role of HIV itself has also been explored by Grunfield et al.9 in a case–control study in USA. Intima-medial thickness (IMT) in HIV-infected patients was significantly higher in the internal carotid arteries, which experience higher turbulence of blood flow. The participants were HIV-infected patients and controls were HIV-negative individuals with common ages ranging from 37 to 78 years, without pre-existing CVD. The size of the additional increased risk due to HIV was shown to be of similar magnitude to known CVD risk factors, such as smoking and diabetes or a 5–9 year increase in age. The study also demonstrated that this association was more pronounced in women than in men. Similar changes were observed in a small juvenile group of HIV-infected patients, ages ranging from 17 to 23 years, and the changes were irrespective of the duration of ARV exposure.10 Further evidence of a pro-inflammatory role for HIV was found in the results of the ACTG (AIDS Clinical Trials Group) A5102 study, which showed that although interrupting ART resulted in rapid improvements in lipid profiles, the risk of CVD increased.11 The exact reasons for this elevated CVD risk remain uncertain, but inflammatory and atherogenic
Abacavir and CVD

In the last few years several studies have tried to explore the association of abacavir use with increased risk of CVD. While four of the seven cohort studies (Table 1)—the D:A:D study,\textsuperscript{4} SMART,\textsuperscript{7} the ANRS analysis\textsuperscript{5} and Quebec’s Public Health Insurance Database (QPHID)\textsuperscript{13}—demonstrate such an association, the other three studies—the ACTG,\textsuperscript{16} the GlaxoSmithKline (GSK) analysis\textsuperscript{15} and the USA Veterans Administration (VA) study\textsuperscript{16}—do not. One randomized trial, the STEAL study,\textsuperscript{17} in which patients had a higher Framingham score, indicating a higher cardiovascular risk at study entry, had a marginally significant risk for CVD in those treated with abacavir compared with those on tenofovir.

The findings from the D:A:D cohort\textsuperscript{4} suggested that use of abacavir was associated with an increased risk of MI in terms of both cumulative and recent exposure to the drug. The ANRS cohort\textsuperscript{5} demonstrated an increased risk only while on abacavir for the first year of therapy, but not when continued for >1 year. Both ANRS\textsuperscript{5} and the D:A:D\textsuperscript{4} cohort suggest that the risk is modifiable, and once abacavir is withdrawn the risk attenuates. It is interesting to note that the D:A:D study did not find any association with stroke yet the sub-analysis of SMART and also the STEAL study found associations when the range of CVD incidences was expanded to have a suitable or significant number. The outcome of cerebrovascular accident (CVA) was not looked for in the ANRS cohort. Very recently, the same group from the ANRS in France updated the results of their studies and these suggest that people with traditional CVD risk factors were significantly more likely to receive either abacavir or tenofovir.\textsuperscript{18} Interestingly, when they controlled for the traditional CVD risk factors, cocaine abuse and intravenous drug use, the effect of abacavir alone on increased CVD risk in their cohort disappeared.

The VA study\textsuperscript{16} used hospital admission codes (ICD-9) to demonstrate an association between the use of abacavir and an increased risk of MI, which was very consistent with other cohort data.\textsuperscript{5,7,13} But they also found a significant association between the presence of chronic kidney disease (CKD) which they define as an estimated glomerular filtration rate (e-GFR) of <60 mL/min by the modification of diet in renal disease (MDRD) method. They found that the patients with CKD had a significantly increased risk of acute MI yet when they controlled for the presence of CKD, the effect of abacavir was no longer significant. Similarly, when they controlled for traditional CVD risk factors, the effect of abacavir was also attenuated and when traditional factors and CKD were combined the risk of CVD essentially disappeared. A similar trend was observed for CVA. The VA study, not surprisingly, showed that patients with CKD were significantly more likely to have received abacavir than tenofovir because of the known association between tenofovir and renal disease. The four of the five studies (Table 1)\textsuperscript{6,7,13,17} that did observe a link between abacavir use and CVD involved HIV-infected patients with or without impaired kidney function. All three studies\textsuperscript{14–16} that found no link were trials that excluded people with CKD. Thus the STEAL study\textsuperscript{17} is the only abacavir analysis that ruled out people with CKD yet still found that abacavir associated with MI. However, the studies were different in several respects and hence it would not be appropriate to compare them to each other and to draw any conclusion. Overall the data neither refute nor confirm the association of abacavir use with CVD. Moreover, an underlying mechanism whereby abacavir might cause MI has yet to be established. Plaque rupture, platelet activation,\textsuperscript{19} flow-mediated dilatation\textsuperscript{20} and pro-inflammatory cytokines\textsuperscript{21,22} have yet to be proved as underlying mechanisms in patients who had MI whilst taking abacavir. This is not surprising given that the drug abacavir has not been shown to be associated with atherogenic dyslipidemia, increased insulin resistance or adverse changes in body fat distribution yet seems to have an association with MI but not with CVA or stroke.

PIs and CVD

There are also data suggesting that cumulative exposure to recently used PIs including lopinavir/ritonavir\textsuperscript{5,13} and fosamprenavir\textsuperscript{3} may be associated with an increased risk of coronary events independent of their other metabolic effects including dyslipidaemia. However, no such association was observed with boosted saquinavir, and data for other PIs including atazanavir and darunavir were not yet available as the number of patients on these drugs is still insufficient for analysis.\textsuperscript{4,5}

Conclusions

In spite of several recent studies, the impact of HIV and different ARV agents on the risk of CVD in HIV-infected patients remains somewhat obscure. Differences in study design, endpoints, patient populations and limited follow-up in some studies prevent definitive comparisons. Several gaps in knowledge and controversies need to be addressed in future research. It is not clear what the clinical significance of an increase in relative CVD risk is among HIV-infected patients if the absolute risk of CVD events remains low in this population. The assessment of traditional and non-traditional risk factors including drug-induced or HIV-related lipid abnormalities compared with those that arise naturally in the pathogenesis of atherosclerosis may not have a similar impact. Unmeasured confounding factors such as intensity of smoking, intensity of cocaine use, concomitant infections and low socio-economic status may yet have an effect on the association between HIV infection and risk of CVD in those patient populations. The inflammatory markers that are important in the general population including hs-CRP may not have the same impact in an HIV-infected patient population.\textsuperscript{23} Nevertheless, risk of CVD in the HIV-infected population appears to be relatively higher than in the general population and the underlying cause appears to be multifactorial involving mechanisms that are specific to HIV infection and ARV therapy in addition to the traditional CVD risk factors. The risks associated with modifiable risk factors including smoking, hypertension, insulin resistance and elevated lipids far outweigh the potential risks of ARV use. However, in the absence of any definite evidence it would be safer to consider abacavir and other ARV agents including lopinavir and fosamprenavir to have a small but potential increased risk for CVD particularly in patients who already...
<table>
<thead>
<tr>
<th>Study</th>
<th>Number of participants</th>
<th>Events (MI)</th>
<th>Association with ABC use</th>
<th>Results (methodology and endpoints varied)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D:A:D</td>
<td>33,308</td>
<td>580</td>
<td>yes</td>
<td>observational cohort analysis; association between recent and cumulative use of ABC and an increased risk of MI (recent use RR 1.68 95% CI 1.33–2.13, cumulative use RR 1.07, 95% CI 1.01–1.14); no association with CVA</td>
</tr>
<tr>
<td>ANRS</td>
<td>1,173</td>
<td>289</td>
<td>yes</td>
<td>retrospective case–control study; association between exposure to ABC for &lt;1 year (and stopping within 6 months) and an increased risk of MI; no association between exposure to ABC for &gt;1 year or stopping after 6 months exposure. Final model of exposure &lt;1 year, stop &lt;6 months OR 1.97, 95% CI 1.09–3.56, P=0.02. Association attenuated with confounders using traditional risk factors, intravenous drug and cocaine use</td>
</tr>
<tr>
<td>SMART</td>
<td>2,752</td>
<td>19</td>
<td>yes</td>
<td>retrospective sub-analysis of ARV-experienced patients; association between current use of ABC and an increased risk of CVD, including MI (HR 4.3, 95% CI 1.4–13.0)</td>
</tr>
<tr>
<td>Quebec (QPHID)</td>
<td>7,497</td>
<td>125</td>
<td>yes</td>
<td>retrospective case–control review from hospital admission codes (ICD-9); any exposure to ABC within 6 months had significant association (6 months exposure HR 1.55, 95% CI 1.03–2.32, any exposure HR 1.69, 95% CI 1.17–2.44)</td>
</tr>
<tr>
<td>STEAL</td>
<td>357</td>
<td>4</td>
<td>yes</td>
<td>randomized 96 week trial; marginal association between ABC use and MI events extended with other CVD events (HR 0.13, 95% CI 0.02, 0.98, P=0.04)</td>
</tr>
<tr>
<td>GSK analysis</td>
<td>14,174</td>
<td>18</td>
<td>no</td>
<td>retrospective review of 52 clinical trials; no association between ABC use and increased risk of CVD events (RR 0.81, 95% CI 0.36–1.75)</td>
</tr>
<tr>
<td>ACTG A5001</td>
<td>3,207</td>
<td>36</td>
<td>no</td>
<td>retrospective review of five ACTG trials (mostly treatment-naive patients); no association between recent ABC use and increased risk of CVD events (adjusted HR 1.0, 95% CI 0.4–2.9, P=0.98)</td>
</tr>
<tr>
<td>VA</td>
<td>19,424</td>
<td>278</td>
<td>no</td>
<td>retrospective review from hospital admission codes (ICD-9); marginal association between cumulative ABC use and ABC use in last regimen with new MI that is attenuated by traditional CVD risk factors (HR 1.18, 95% CI 0.92–1.5, P=0.19) and renal dysfunction prior to regimen initiation (HR 1.23 95% CI 0.95–1.58, P=0.11); similar trends for ABC use and CVA</td>
</tr>
</tbody>
</table>

ABC, abacavir; 95% CI, 95% confidence interval; OR, odds ratio; HR, hazard ratio; RR, relative risk; CVA, cerebrovascular accident; CVD, cardiovascular disease; MI, myocardial infarction.

*Studies that excluded or adjusted patients with chronic kidney disease.
have a higher risk from traditional CVD risk factors. Assessment and modification of these underlying risk factors should play an important role in the management of HIV infection. Choice of ARV regimens should be individualized for the patient to achieve maximal and durable viral suppression as well as avoiding long-term toxicities.

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References