CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

HIV and Coronary Artery Disease: A Heart to HAART Discussion

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Health Canada estimates that there were approximately 56,000 people living with the human immunodeficiency virus (HIV) in Canada at the end of 2002, approximately one-third of whom were undiagnosed.[1] The increased use of highly active antiretroviral therapy (HAART) over the past decade has changed the face of this disease in the developed world, taking it from a rapidly-advancing terminal illness to a more chronically-managed medical condition. Because HIV patients are living longer, the chronic effects of the disease and its treatment on morbidity and mortality have become more salient topics in the medical literature. The heart is frequently affected in HIV patients and common manifestations include pericardial disease and dilated cardiomyopathy.[2] This issue of *Cardiology Rounds* focuses on the association between HIV and coronary artery disease (CAD), a burgeoning field that we are just beginning to understand.

Epidemiological links

Autopsy data first described an association between HIV and CAD. The first report was published in 1987 by Joshi et al, who reported an autopsy series of 6 HIV-infected children, aged 13 months to 7 years; 3 of these children had coronary pathology.[3,4] Gross examination of the arteries displayed evidence of endothelial inflammation with infiltration of lymphocytes and mononuclear giant cells, leading to intimal fibrosis and subsequent luminal narrowing. In 1993, an autopsy series of 8 HIV-positive adults (whose mean age was 27 years) revealed significant eccentric atherosclerotic narrowing in the proximal coronary arteries of 6 of the subjects. These patients lacked traditional risk factors for atherosclerosis, thus suggesting an association between HIV and CAD.[5]

In 1996, in addition to the nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) became widely available in North America as adjunctive therapy for HIV. This heralded the era of highly active antiretroviral therapy (HAART). PIs represented a major breakthrough in HIV treatment and resulted in important reductions in morbidity and mortality.[3] In spite of the autopsy data, clinically apparent CAD had been infrequently documented in HIV patients in the pre-HAART era. Soon after HAART treatment became widely available, however, clinicians began to notice that cardiovascular events were occurring in relatively young HIV patients taking these medications. There was uncertainty as to whether this increase in cardiac events was due to chronic HIV infection (because patients were now living long enough to manifest it) or an adverse effect of the new medications (which could cause many metabolic abnormalities).[6]

After 1998, worrisome case series began to be published that supported previous anecdotal reports. The French Hospital Database on HIV was a retrospective cohort study of almost 20,000 HIV-positive men. The authors found that treatment with a PI for

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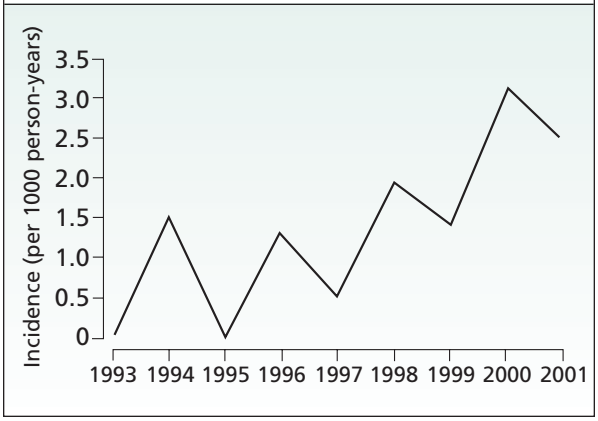
Figure 1: Incidence of myocardial infarction in the HIV Outpatient Study (HOPS) cohort



Adapted from Holmberg et al.[8]

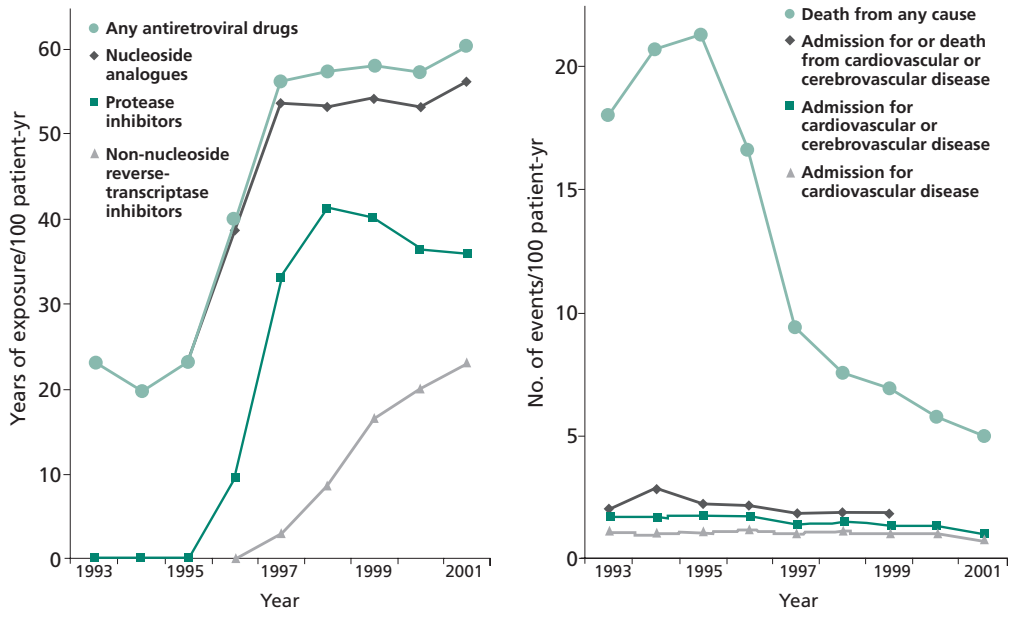
>18 months was associated with a twofold increase in the incidence of myocardial infarction (MI).[7]

The HIV Outpatient Study (HOPS) was a cohort study of 5700 HIV-positive patients in the United States (US). In this group, an increased frequency of MI was seen after 1996 (Figure 1) and PI use was associated with an odds ratio of 7.1 for having an event. This relationship was not affected by CD4 count, viral load, or history of opportunistic infections.[8]

In 2003, two large cohort studies were published in the *New England Journal of Medicine*, but with discordant results. The first was a US retrospective cohort study conducted by Bozzette et al in 36,766 HIV patients from 1993 to 2001, with a mean follow-up of 40 months.[9] The outcomes of interest were all-cause mortality, cardiovascular death, and cerebrovascular death. The authors demonstrated that as PI use increased from 1995 onwards, there was a commensurate decrease in overall mortality and no significant change in the rate of vascular hospital admissions or death (Figure 2). The limitations of this study were the relatively short mean duration of HAART therapy (15 months) and its paucity of women (2%).

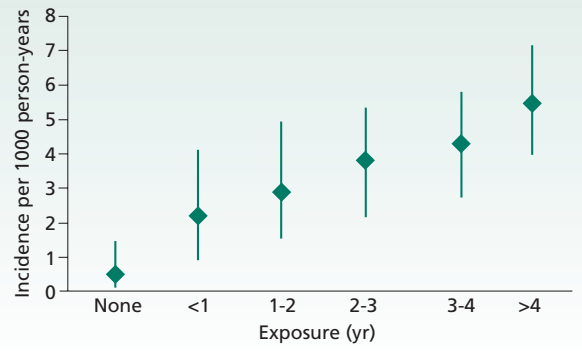
The results of the second study – The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) trial – were published in November, 2003.[10] This was a prospective observational study of 23,458 patients from 1999 to 2001; the outcome of interest was the relationship of MI to HAART therapy. The mean duration of HAART treatment was 24 months and the mean length of follow-up was 19 months. The authors found that the incidence of MI significantly increased with duration of HAART therapy, with each additional year of exposure conferring a 26% adjusted relative risk of this endpoint (Figure 3). The total mortality in the cohort was low at 2.4% and only 6.4% of these deaths were due to MI. Total cholesterol, triglycerides, and diabetes increased the risk of MI, while CD4 count, viral load, and history of opportunistic infection all had no effect. The authors of the DAD study concluded that HAART therapy was associated

Figure 2: Use of antiretroviral drugs and clinical events



Adapted from Bozzette et al.[9]

Figure 3: The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) trial



Adapted from DAD.[10]

with a significant increase in the relative risk of MI, increasing with years of exposure; however, the substantial benefits of combination antiretroviral therapy outweighed the increased risk of MI. The stark contrast of this study's results with that of Bozzette et al was disconcerting. Critics leaned towards the DAD trial as the superior study, since it was prospective and enrolled patients who had a longer duration of HAART exposure.[6]

Nevertheless, the majority of epidemiological data from the PI-era suggest an increased risk of cardiovascular events in HIV patients taking combination antiretroviral therapy.

Vascular considerations

As discussed above, even before the advent of HAART treatment, autopsy reports found evidence of accelerated atherosclerosis in HIV patients lacking traditional cardiovascular risk factors. This observation raised the possibility that, notwithstanding antiretroviral therapy, the virus itself may have direct atherogenic effects on blood vessels. In addition, microbial causes of vascular damage had been previously described with herpes simplex virus and cytomegalovirus.[11]

Measurement of carotid artery intima-media thickness (CIMT) via ultrasonography is a well-validated technique for assessing atherosclerosis, and the measurements are robust predictors of MI and stroke.[12] A study published in 2004 assessed CIMT in 148 HIV-positive patients, as well as 63 healthy controls.[12] These investigators found that mean CIMT was significantly higher at baseline in the HIV-positive group and the rate of progression over 1 year was also greater. In a multivariate regression analysis, HIV was an independent predictor of CIMT, as were age, low-density lipoprotein (LDL), and cigarette pack-years smoked. Interestingly, PI use did not predict increased CIMT, thus suggesting it is a direct effect of the viral infection and not its therapy.

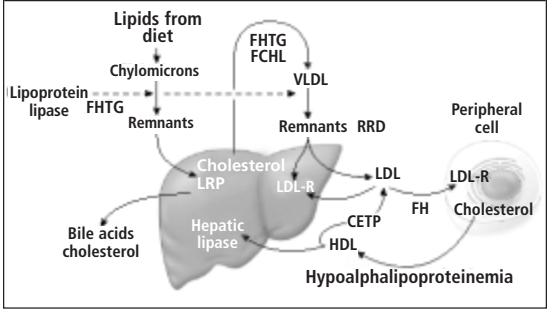
Even if the HIV virus is atherogenic, the effects of antiretroviral medications are likely additive and it is difficult to discern the effects of one from another. A rather provocative study was performed in 2002 where the PI, indinavir, was given to healthy HIV-negative men for 4 weeks. Doppler measurements of the brachial artery, conducted before and after treatment, revealed that the medication caused significant endothelial dysfunction that was independent of changes in lipid levels.[6] Thus, it appears that both the HIV virus and PIs have independent deleterious affects on blood vessels and, in combination, their impact is likely compounded.

Metabolic considerations

Untreated HIV infection is associated with characteristic lipid changes, specifically, elevated levels of triglycerides (TG) and decreased levels of high-density lipoprotein (HDL), LDL, and total cholesterol (TC).[13] An association between plasma TG levels and circulating interferon-gamma levels has also been observed in patients with the acquired immune deficiency syndrome (AIDS).[14] The mechanisms for these changes have not been elucidated. The use of PIs in persons with HIV has been linked to worrisome metabolic changes, including atherogenic lipid profiles, insulin resistance, and the development of the fat redistribution syndrome.

To determine if PIs have an effect on lipids and lipoproteins, independent of any contribution from HIV infection, Purnell et al conducted a prospective double-blind study in 21 healthy volunteers who were randomized to 2 weeks of ritonavir versus placebo.[15] There were no significant differences in baseline lipid levels between the 2 groups. After 2 weeks of therapy, the ritonavir arm had significantly increased mean TC and mean TG levels compared to the baseline levels of both and to the post-treatment placebo arm. Density gradient ultracentrifugation determined that the elevated TC was due to increases in very low-density lipoprotein (VLDL) and VLDL-remnants, but not LDL. Therefore, the principal metabolic effect of PI treatment was demonstrated to be an increase in TG and TG-rich lipoproteins. Possible mechanisms for this effect include increased secretion of VLDL particles, decreased lipolysis of particles by lipoprotein lipase,

Figure 4: Possible mechanisms for the effect of protease inhibitors to increase lipids



Adapted from Purnell, et al.[15]

FH = familial hypercholesterolemia
FHTG = familial hypertriglyceridemia
FCHL = familial combined hyperlipidemia
LDL = low-density lipoprotein
VLDL = very-low-density lipoprotein
CETP = cholesterol-ester transport protein
LRP = LDL-receptor-related protein
RRD = remnant removal disease
LDL-R = LDL receptors

decreased hepatic clearance of VLDL remnants, or some combination of the above (Figure 4).[15]

The lipid profile changes induced by PIs are of concern because they are potentially atherogenic. It is well-established that plasma triglyceride levels are particularly important as an independent risk factor for CAD.[16,17] In light of this, Stein et al conducted a cross-sectional study of 37 HIV patients to compare endothelial function and lipid parameters in patients on PI therapy (n =22) versus those not on this treatment (n=15).[18] The groups were similar with respect to age, duration of HIV, and CD4 count. Brachial Doppler ultrasound with flow-mediated vasodilation and nitroglycerin-mediated vaso-dilation was used to assess endothelial function. The PI group (Group 1) had significantly higher levels of TC, TG, VLDL, and VLDL remnants compared to those not on PIs (Group 2). Brachial artery flow-mediated vasodilation in Group 1 was significantly decreased when compared to both the normal values and to values in Group 2, while nitroglycerin-mediated vasodilation was normal in both. This finding implies impaired endothelium-dependent arterial relaxation in patients taking PIs. Linear regression revealed that 63% of the variance in endothelial function between the 2 groups was explained by differences in VLDL, VLDL-remnants, and glucose. Importantly, in Group 2, there was no difference in lipid profiles or endothelial function in patients on NNRTIs versus those not on them. The authors concluded that HIV patients taking PIs have markedly abnormal endothelial function that is largely mediated through increases in levels of TG and TG-rich lipoproteins.

Insulin resistance is also frequent in HIV patients, its prevalence is 25%-60% in those on PIs. However, there have been no reports of an increased incidence of frank diabetes to date.[3] The fat redistribution syndrome, also known as lipodystrophy, is associated with peripheral fat wasting and central adiposity. It is seen in up to 80% of HIV patients taking PIs.[19] No studies have demonstrated an increased risk of cardiovascular disease in HIV patients with lipodystrophy compared to those without the condition.

Clinical presentation and treatment

While observational reports suggest that HIV patients with CAD are often young and lack traditional cardiovascular risk factors, the clinical phenotype of the acute coronary syndrome (ACS) in HIV is not well-defined. In an attempt to better clarify this issue, Hsue et al retrospectively compared the characteristics of 68 HIV patients with ACS to those of 68 randomly selected controls admitted during the years 1993 to 2003.[20] Characteristics unique to HIV patients were the following:

- they tended to be younger (mean age 50 years versus 60 years)
- they were typically male (92% versus 66%)
- smoking was the most common risk factor (as opposed to diabetes and hyperlipidemia in HIV-negative patients)
- they tended to have lower TIMI risk scores
- their HDL levels were lower
- they had less extensive angiographic CAD than the controls
- they had a much higher restenosis rate after percutaneous coronary intervention (50% versus 18%, p=0.078). Note: in their combined analysis, HIV infection was an independent predictor of restenosis.

Treatment of CAD and/or dyslipidemias in HIV patients is complicated by the fact that statins should be used with caution since most are metabolized by the cytochrome (CY)P-450 3A4 system. Since PIs inhibit this enzymatic pathway, they could impede the metabolism of statins and greatly increase the risk of hepatotoxicity or myotoxic-

ity.[3] A 2000 consensus statement recommended non-drug therapy as first-line treatment for HIV patients. However, if statin therapy *is* indicated for a patient taking HAART, pravachol is the agent of choice since it is not metabolized via the CYP 3A4 pathway.[21] Atorvastatin is a reasonable second choice, while simvastatin should be avoided. Gemfibrozil (600 mg BID) or fenofibrate (200 mg OD) are suggested for isolated hypertriglyceridemia. The consensus guidelines mandate that all HIV patients have a lipid profile done before starting HAART and then, every 3 months. Regular monitoring of creatinine kinase levels and liver enzymes is suggested for patients on statins.[21]

Conclusion

The development of HAART therapy and its consequent reductions in HIV mortality represent landmark achievements in modern medicine. However, with HIV patients living longer, the cardiac sequelae of this disease and its therapy are gaining increased prominence. The epidemiologic data of the post-HAART era suggest an association between PI use and the development of CAD. The only published prospective HIV cohort study to date demonstrates that there is a 26% relative risk of having an MI for each year of PI use. Mechanistic studies suggest that this risk is largely due to an increase in TG and TG-rich lipoproteins, which results in endothelial dysfunction.

Retrospective data have found that HIV patients with ACS tend to be younger and have an increased risk of restenosis after percutaneous intervention. The management of dyslipidemias in this population is complicated by drug interactions between the statins and PIs and, currently, pravastatin is the recommended agent. Since HIV patients are living longer, their duration of PI exposure is increasing and it is conceivable that the extent of CAD in this population may increase. There is currently a paucity of outcome data with respect to ACS in this patient population and the mechanisms of dyslipidemias in HIV patients also need to be better elucidated. Over the next decade, it is likely that this population will present unique challenges to cardiologists and further research is necessary to aid us in optimally-treating these patients.

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Abstract of Interest

An open-label, prospective, observational study of the incidence of coronary artery disease in patients with HIV infection receiving highly active antiretroviral therapy.

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BACKGROUND: The association of highly active antiretroviral therapy (HAART) regimens that include protease inhibitors (PIs) with metabolic and somatic disorders has raised concerns about the possibility of an increased risk of coronary artery disease (CAD) in patients with HIV infection.

OBJECTIVE: The aim of this study was to assess the incidence of CAD in previously untreated HIV infected outpatients who received reverse transcriptase inhibitors with or without PIs.

METHODS: In this open-label, multicenter, prospective, observational trial, previously untreated and asymptomatic HIV-infected Italian patients were followed to assess the incidence of CAD (primary end point) according to the HAART regimen they received: 2 nucleoside analogue reverse transcriptase inhibitors (NRTIs) in combination with PIs (group PI+) or 1 non-nucleoside reverse transcriptase inhibitor in combination with 2 NRTIs (group PI-). Patients underwent clinical examination and laboratory testing every 4 months.

RESULTS: A total of 1551 HIV-infected patients (994 [64%] men; median age, 35 years; range, 22-50 years) were followed for a median 36 months (range, 34-42 months). The cumulative annual incidence of CAD-related events was 9.8/1000 in group PI+ and 0.8/1000 in group PI- ($P < 0.001$). The annual incidence of myocardial infarction was 5.1/1000 in group PI+ and 0.4/1000 in group PI- ($P < 0.001$). Independent of patient age, the incidence of CAD was greater among men ($P < 0.001$) and patients who smoked >20 cigarettes per day ($P < 0.001$). Lipodystrophy and metabolic alterations were observed in 62% of patients in group PI+ and in 4% of patients in group PI- ($P < 0.001$). Of 23 patients receiving PIs who developed CAD, 17 (73.9%) had lipodystrophy and all 23 had hypertriglyceridemia and hypercholesterolemia.

CONCLUSIONS: According to our findings, HAART that includes PIs may accelerate the onset of CAD-related events in young, male, heavy smokers who develop metabolic disorders and lipodystrophy during therapy. Patients with increased coronary risk should receive careful cardiac monitoring if treated with PIs.
Clin Ther 2003;25(9):2405-18.

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