Review Article

Acute coronary syndrome in HIV patients: from pathophysiology to clinical practice

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Abstract: A majority of human immunodeficiency virus (HIV) infected subjects in developed countries have access to highly active anti-retroviral therapy (HAART), which is associated with significantly improved long term survival. In this setting, clinical attention needs to be focused on the impact of premature atherosclerotic cardiovascular disease (CVD), which already represents a leading cause of morbidity and mortality in these patients. While the higher prevalence of traditional risk factors remains the main culprit of increased CVD risk, HIV infection itself and antiretroviral toxicity are confounding proatherogenic factors. It is therefore critical to treat modifiable risk factors, keeping close attention to drug interactions in these patients with high cardiovascular risk profile.

Key Words: Acute coronary syndrome; human immunodeficiency virus; highly active anti-retroviral therapy

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Introduction

Since 1998, when Keith Henry, in a letter to The Lancet (1), reported two cases of myocardial infarction in young men on protease inhibitors (PIs), multiple studies and databases (2,3), documented an increased risk of myocardial infarction and endothelial dysfunction in patients on highly active antiretroviral therapy (HAART) and PIs. Our understanding of the underlying histopathology and impact of this condition on cardiovascular health has advanced during the last decade.

Up-to-date treatment of HIV-infected patients is associated with improved long-term survival, but, at the same time, an increase in cardiovascular morbidity and mortality, including chronic stages of this disease. Moreover, the same drugs used in the HIV-treatment have been implicated in insulin resistance and in the atherosclerosis process due to adverse effects on dyslipidemia.

In a recent study (4) Guaraldi *et al*. show that specific and oftentimes multiple age-related non-infectious comorbidities were more common among HIV-infected patients than in the general population. In addition, HIV-specific cofactors (lower nadir CD4 cell count and more prolonged HAART exposure) were identified as risk factors.

These accumulating data demonstrate that cardiovascular morbidity and mortality play a crucial role in the prognosis of HIV patients on HAART therapy in developed countries.

Traditional cardiovascular risk factors in HIV patients

The risk of coronary heart disease in HIV patients is significantly influenced by traditional factors such as age, smoking, diabetes, and dyslipidemia. Triant *et al*. show that HIV patients admitted for acute myocardial infarction had significantly higher proportions of hypertension (21.2% *vs*. 15.9%), diabetes (11.5% *vs*. 6.6%), and dyslipidemia (23.3% *vs*. 17.6%) than a non-HIV cohort (P<0.0001 for each comparison) (5). HIV-infected men had also a higher prevalence of smoking (6). However, even after adjusting

for traditional risk factors, rates of atherosclerosis were still higher in HIV infected subjects than in those who were not (5). Other studies of HIV-infected patients with acute coronary syndrome (ACS) found that this population was younger, more often male, and smokers compared with HIV-uninfected patients (7-12). In a recent article, Baccarat *et al*. share these findings reporting a mean age of first occurrence of ACS in HIV-infected patients of 50 years, with predominantly male-gender, and tobacco-smoking as the most prevalent coronary risk factor. The authors also report a much higher proportion of HIV-infected patients with ACS using illicit drugs compared with HIV-uninfected patients (23% *vs*. 6%, P<0.001) (13). In a recent meta-analysis performed by our group (D'Ascenzo *et al*.) investigating rates mid term outcomes of patients with HIV presenting with ACS in northern countries, we report an overall average incidence of traditional cardiovascular risk factors, except for diabetes, as can be expected in a young population (14).

HIV and cardiovascular risk: A linear association?

Although the underlying mechanisms are not fully understood, HIV infection has been shown to increase the risk of coronary events.

In the Kaiser Permanente database, comparing HIV-positive and -negative members, the hospitalization rate for coronary heart disease was significantly higher (6.5 *vs*. 3.8, P=0.003), as was the incidence of myocardial infarction (4.3 *vs*. 2.9, P=0.07). This data are supported by larger cohort study of almost 4000 HIV-infected patients and more than 1 million controls, describing that the risk of acute myocardial infarction was higher for HIV-positive patients than for HIV-negative patients even after adjusting for age, gender, race, hypertension, diabetes and dyslipidemia (5).

Several causative mechanisms have been supposed, including HIV-associated dyslipidemia, endothelial damage or dysfunction, inflammation and hypercoagulability.

Pathogenesis of coronary artery disease (CAD) in HIV infection. (Figure 1)

Dyslipidemia and atherosclerosis

In the early stage of HIV infection, levels of total cholesterol and HDL-C are lower. The progressive lowering of CD4 cells lymphocyte counts have been associated with a reduced clearance of LDL-C particles, lower level of apolipoprotein B (15,16) and a decrease in high-density lipoprotein cholesterol (HDL-c). Also, the triglyceride levels may correlate to the degree of viremia (17). As supposed by Mujawar *et al*., these changes are triggered by deregulations of the intracellular lipid metabolism in HIV-infected macrophages due to the impairment of the ATP-binding cassette transporter A1 (ABCA1)-dependent cholesterol efflux (18).

Atherosclerosis in HIV patients appears to have a different pathogenetic features from atherosclerosis in the general population, with intermediate histologically features of lesions found in common CAD and transplant vasculopathy (19). A necroscopic study described diffuse and circumferential vessel involvement with unusual proliferation of smooth muscle cells mixed with abundant elastic fibres (20).

Furthermore, some postmortem examination studies had shown the presence of premature atherosclerosis in a high percentage of HIV-positive patients, including involvement in very young subjects, even before the introduction of protease inhibitors therapy (21,22).

Inflammation

Inflammation is associated with endothelial dysfunction in both treated and untreated HIV patients. Increased atherosclerosis with HIV infection can occur in the absence of antiretroviral therapy, detectable viremia, or overt immunodeficiency. Hsue *et al*. (23) compared carotid intima media thickness and levels of C-reactive protein (CRP) in HIV-positive and HIV-negative patients reporting greater values in all HIV patients groups, irrespective of level of viremia or antiretroviral therapy. Furthermore, CRP levels remained elevated in HIV infected subjects. This data suggests that persistent inflammation may account for early atherosclerosis in these patients.

Hypercoagulability

In addition to endothelial damage, HIV replication and immune activation may drive coagulation and fibrinolysis, in part, via up-regulation of tissue factor pathways. A positive correlation has also been noted among patients with untreated HIV infection and thrombocytopenia that usually worsens with advancing HIV disease (24,25). Beyond their role in acute setting of atherosclerotic events, chronic platelet activation is present in HIV infected patients, may promote atherogenesis, and increase the risk for thrombosis (26).

Antiretroviral therapy: treatment or poison?

In the decade many reports have investigated a possible association between myocardial infarction and HAART: several studies found a statistically significant association (27-30), while others did not (31,32). This heterogeneity

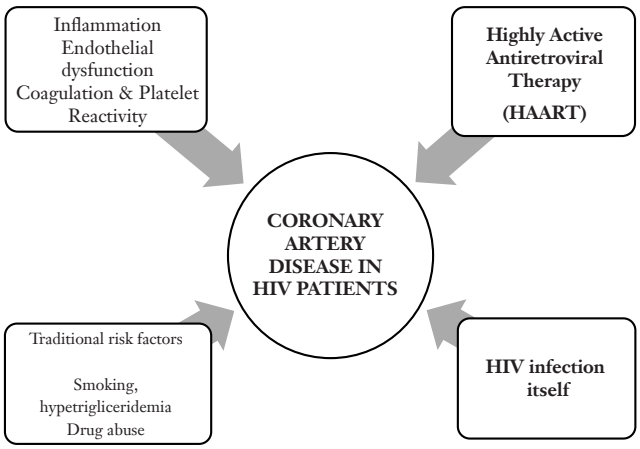

Figure 1 Pathogenesis of coronary artery disease (CAD) in HIV infection

arise from differences in study design (observational cohort studies *vs*. prospective randomized clinical trials), populations studied (differences in age, cardiovascular risk factor, previous exposition to ART treatment), and also from different outcome definition.

One of the most important was the Data Collection on Adverse Events of Anti-HIV Drugs (D.A.D) study (34) that prospectively followed more than 20,000 patients for a total of 94,469 person-years. The relative risk of myocardial infarction per year of protease inhibitor exposure was 1.16 (1.10-1-23; C.I. 95%) adjusting for hypertension, diabetes and Non-Nucleoside Reverse Transcriptase and remained significant even after adjusting for serum lipid level.

On the other hand, as recently reported, HIV patients with ACS had significantly lower viral loads (4769±3109, P<0.001) and numerically higher CD4 counts (298±184, P=0.11) (35,44) than patients with HIV/AIDS-related cardiomyopathy, thus suggesting that HIV infection probably plays a more limited role in the onset of coronaropathy.

The Strategies for Management of Antiretroviral Therapy (SMART) trial, one of the largest studies of antiretroviral treatment interruption, demonstrated that the rate of major cardiovascular events was higher if treatment was interrupted than with continuous treatment, with a hazard ratio of 1.57 (95% CI 1.0-2.46, P=0.05) (36). This association between treatment interruption and coronary events does not appear to be related to the level of viremia (37). These results suggest that suppression of HIV itself plays an important role in reducing pro-inflammatory cytokines. In fact elevated IL-6 level was significantly associated with the development of cardiovascular disease (OR 2.8, P=0.03). Moreover treatment-interruption may increase the risk of death as a consequence of further elevation of IL-6 and D-dimer levels (38).

Coronary artery disease

As we discussed above, several studies suggest that HIV patients are exposed to an increased risk of premature CAD linked predominantly to the hyperlipidaemia and insulin resistance that are associated with protease-inhibitor therapy.

Our group has recently conducted a meta-analysis (14) of 11 studies including 2442 HIV-patients presenting with ACS. The most common presentation was STEMI with a high prevalence of multivessel involvement. Both characteristic had an higher incidence than in contemporary ACS registries of non-HIV patients (39,40) and combined together could in part explain the higher rates of in-hospital events registered in HIV patients (41).

In contrast, other studies have reported a more favorable in-hospital outcome in absence of significant hemodynamic compromise (42).

PCI in HIV-infected patients has been associated with a high incidence of non-fatal reinfarction, restenosis and in-stent thrombosis (43). This worse outcome during follow-up appears related to both high prevalence of cardiovascular risk factors, impact of viral pathological process, and side effects of antiretroviral drugs. Moreover a high incidence of thrombo-embolic events and intraluminal demonstration of fresh thrombus has been reported, probably related to a prothrombotic state (44).

In a recent report of the Soweto Study Cohort (44) including 518 HIV patients admitted with a new diagnosis of cardiovascular disease between 2006 and 2008, Sliwa and colleagues report a relatively infrequent incidence of ACS (3%) in this population, despite a high number of patients already receiving HAART prior to admission. This finding is in agreement with a recent meta-analysis casting doubt on the potential role of publication bias and confounding in overestimation of HIV and PIs exposure risk (45).

Management of CVD in HIV

Modification of risk factors

The early detection and treatment of co-morbilities and modifiable risk factors through lifestyle changes such as smoking cessation, dietary changes, and exercise is likely to have a significant impact on cardiovascular risk in this population.

Because HIV infection by itself and HAART treatment

likely increase the risk of plaque rupture and atherothrombosis (46,47), routine primary and secondary prevention should be considered in HIV infected subjects. However, as reported in some study (48), LDL goals are less frequently achieved in HIV-infected patients during follow-up.

Management of hyperlipidaemia

Specific guidelines for the evaluation and management of HAART related hyperlipidaemia have been developed by the Infectious Disease Society of America (IDSA) and Adult AIDS Clinical Trials Group (AACTG) (49). These recommendations are largely based on National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, and advocate adjusting individual cholesterol level through estimation of Framingham predicted 10 years cardiovascular risk (50).

Currently there is no difference in hyperlipidemia goals treatment between HIV and not-HIV infected subjects. In the choice of specific lipid-lowering therapy it is critical to consider drug-drug interactions. In general, all PIs inhibiting CYP3A4, with the highest level of inhibition with ritonavir, followed by indinavir, nelfinavir, amprenavir, and saquinavir. Delavirdine, an NNRTI, is also an inhibitor of CYP3A4, whereas nevirapine and efavirenz result in induction of the enzyme. Therefore, the first choice agents for lowering LDL are pravastatin (not metabolized by CYP3A4), with fluvastatin (metabolized CYP2C9) as second choice. Rosuvastatin concentrations appear to be increased when used in combination with some NNRTIs (atazanavir, ritonavir, lopinavir), thus, in that setting, 10 mg should be considered the maximum safe dose (51,52). Similarly, atorvastatin should be used at lower doses in HIV patients. Finally during PIs therapy, simvastatin and lovastatin are not recommended because of the high-risk of rhabdomyolysis (53). Lack of data limits the precise estimation of benefits related to anti-inflammatory properties of statins.

Conclusions

Short-term benefits of HAART prevent cardiovascular disease in HIV patients, but the long-term benefit is incompletely understood and will require further data. The results of ongoing trials will provide important information on how to manage timing of HAART therapy, optimizing the risk-benefit ratio. The START trial (54) includes antiretroviral-naive HIV-positive people with CD4 counts greater than 500 cells/mm^3. It is an international multi-center trial including about 90 sites in nearly 30 countries (including Australia). Participants are randomized to receive either early antiretroviral treatment or defered treatment awaiting the first CD4 count <350 cells/mm^3 or onset of clinical signs of advanced HIV disease. In each group, 2,000 patients will be recruited.

Others challenges and open issues include the best regimen in CAD patients, the role of anti-inflammatory drugs, and the long-term clinical outcomes of HIV patients in the modern era of HAART treatment.

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