Acute coronary syndrome in human immunodeficiency virus patients: exploiting physiopathology to inform the clinical practice

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Abstract
Introduction
Nowadays in developed countries, human immunodeficiency virus-infected subjects could access a highly active anti-retroviral therapy. In this setting, greater attention has been paid to the impact of premature atherosclerotic cardiovascular disease that, actually, represents a leading cause of morbidity and mortality. Higher rates of traditional risk factors along with human immunodeficiency virus infection and adverse effects of anti-retroviral agents represent important proatherogenic factors. Physicians treating human immunodeficiency virus-positive patients should consequently aim at intensively modifying risk factors, controlling drug-to-drug interactions and selecting anti-retroviral drugs with a lower cardio-metabolic impact. The aim of this study was to discuss acute coronary syndrome in human immunodeficiency virus patients.

Conclusion
Short-term benefits of specific anti-retrovirals prevent cardiovascular disease in human immunodeficiency virus patients, but long-term benefits need more data and longer-term follow-ups to be correctly assessed.

Introduction
Since 1998, when Keith Henry, in a letter to The Lancet¹, reported about two cases of myocardial infarction in young men on protease inhibitors (PIs), multiple studies and databases²,³, started to prove an increased risk of myocardial infarction and endothelial dysfunction in patients on highly active anti-retroviral therapy (HAART) and PIs. Despite the recognition of this risk, only in the last decade did we get some answers about the underlying histopathology and impact of this condition on cardiovascular health.

Certainly nowadays HIV-infected patients receiving up-to-date treatment live longer but, at the same time, the cardiovascular risk of morbidity and death increases, and also the prevalence of chronic conditions related to this disease. Moreover, the same drugs used in HIV-treatment have shown a direct implication in insulin resistance and in the atherosclerosis process due to adverse effects on dyslipidaemia.

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

In such a scenario, a complex yet not completely understood interaction among traditional risk factors, comorbidities, anti-retroviral medications and the pro-inflammatory role of HIV emerge and it represents a novel interplay in the key model of the infectious agent-host-environment. The aim of this review was to exploit physiopathology to inform the clinical practice for acute coronary syndrome in HIV patients.

Discussion
The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964) and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All participants, in these referenced studies, gave informed consent to participate in these studies.

Traditional cardiovascular risk factors in HIV patients
The risk of coronary heart disease in HIV patients is influenced mostly by traditional factors such as age, smoking, diabetes and dyslipidaemia. Triant et al.⁵ conducted a large cohort study using a data registry with 3851 HIV vs. 1 044 589 non-HIV patients: acute myocardial infarction (AMI) was identified in 189 HIV and 26 142 non-HIV patients: the AMI rate per 1000 person-years increased in HIV vs. non-HIV patients [11.13 (95% confidence interval (CI) 9.58–12.68) vs. 6.98 (95% CI 6.89–7.06)]. The HIV cohort had significantly higher proportions of hypertension (21.2% vs. 15.9%), diabetes (11.5% vs. 6.6%) and smoking (18.7% vs. 12.8%)

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and dyslipidaemia (23.3% vs. 17.6%) than a non-HIV cohort ($P < 0.0001$ for each comparison). HIV-infected men had a higher prevalence of smoking$^6$. However, even after adjusting for traditional risk factors, rates of atherosclerosis are still higher in people who are infected with HIV than in those who are not$^5$. Other studies of HIV-infected patients with acute coronary syndrome (ACS) found these populations to be younger, more often male, and smokers compared with HIV-uninfected patients$^7$-$^12$. Boccara et al.$^{13}$ in a recent article shared their 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. They also reported a much higher proportion of HIV-infected patients using illicit drugs compared with HIV-uninfected patients (23% vs. 6%, $P = 0.001$). In a recent meta-analysis performed by our group, we reported an overall average incidence of traditional cardiovascular risk factors, except for diabetes, as can be expected in a young population$^{14}$.

### HIV and cardiovascular system: a complex interplay

Although the mechanism is not fully understood, HIV infection has been shown to increase the risk of coronary events.

In the Kaiser Permanente database, comparing HIV-positive and HIV-negative members, the hospitalisation rate for coronary heart disease was significantly higher (6.5 vs. 3.8, $P = 0.003$) as the difference in the myocardial infarction rate (4.3 vs. 2.9, $P = 0.07$). This data was supported by a larger cohort study of almost 4000 HIV-infected patients and more than 1 million controls where the risk of AMI was higher for HIV-positive patients than for HIV-negative patients even after adjusting for age, gender, race, hypertension, diabetes, and dyslipidaemia$^5$.

Several causative mechanisms have been supposed, including HIV-associated dyslipidaemia, endothelial damage or dysfunction, inflammation and hypercoagulability (Figure 1).

#### Pathogenesis of coronary artery disease in HIV infection

**Dyslipidaemia and atherosclerosis**

In the early stage of HIV infection, levels of total cholesterol and high-density lipoprotein cholesterol are lower. The progressive lowering of CD4 cells lymphocyte counts have been associated with a reduced clearance of low-density lipoprotein cholesterol (LDL-C) particles, lower level of apolipoprotein B$^{15,16}$ and a decrease in high-density lipoprotein cholesterol; the triglyceride levels may correlate to the degree of viraemia$^{17}$. As supposed by Mujawar et al.$^{18}$, this mechanism derived from dysregulation of intracellular lipid metabolism in HIV-infected macrophages due to the impairment of the ATP-binding cassette transporter A1-dependent cholesterol efflux.

Histologically, atherosclerosis in HIV patients appears to have a different pathogenesis from atherosclerosis in the general population with intermediate features between lesions in common coronary artery disease (CAD) and transplant vasculopathy$^{19}$. In a necroscopic study, the atherosclerotic process has 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 (also young and children) even before the introduction of PI therapy.\textsuperscript{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 anti-retroviral therapy (ART), detectable viremia or overt immunodeficiency. Hsue et al.\textsuperscript{23} compared carotid intima media thickness and levels of C-reactive protein in HIV-positive and HIV-negative patients reporting greater value in all HIV patient groups, irrespective of level of viremia or ART. Furthermore, C-reactive protein levels remained elevated in HIV controllers. 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, through 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.\textsuperscript{24,25} Beyond their role in an acute setting of atherosclerotic events, chronic platelet activation present in HIV infected patients may promote atherogenesis and increase the risk for thrombosis.\textsuperscript{26}

Anti-retroviral therapy: treatment or poison?

In the last ten years many reports investigated a possible association between myocardial infarction and HAART: several studies found a statistically significant association\textsuperscript{27–30} and others did not.\textsuperscript{31,32} This heterogeneity came from study design (observational cohort studies vs. prospective randomised clinical trials), populations studied (differing in age, cardiovascular risk factor, previous exposure 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 study\textsuperscript{33} that prospectively follows more than 20 000 patients for 94 469 person-years. The relative risk of myocardial infarction per year of PI exposure was 1.16 (1.10–1.23; CI 95%) adjusting for hypertension, diabetes and non-nucleoside reverse transcriptase (NNRT) and remained significant even after adjusting for serum lipid level.

A recently published meta-analysis\textsuperscript{34} including observational and randomized controlled trials reported the occurrence of cardiovascular disease (CVD) (defined as myocardial infarction (MI), ischaemic heart disease and cerebrovascular events) among HIV-positive adults. The relative risk of CVD compared with HIV-negative subjects was 1.61 (95% CI, 1.43–1.81) in HIV-infected patients not HAART-treated and 2.00 (95% CI, 1.70–2.37) in HAART-treated HIV-positive patients; this relative risk was reduced to 1.52 (95% CI, 1.35–1.70) when comparing HAART-treated patients to treatment-naive ones. This study also reported that the relative risk of MI was higher in PI-based versus non-PI-based therapies (RR, 1.41; 95% CI, 1.20–1.65) and it was higher for specific drugs (abacavir and lopinavir/ritonavir).

The Strategies for Management of Anti-retroviral Therapy trial, one of the largest studies of ART treatment interruption, showed 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, \(P = 0.05\)).\textsuperscript{35} This association between treatment interruption and coronary events does not appear to be related to the level of viremia.\textsuperscript{36}

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, \(P = 0.03\)). Furthermore in the treatment interruption, IL-6 and D-dimer results were significantly elevated one month after randomisation with a strong association with death (OR 12.6, \(P < 0.0001\) for IL-6; OR 13.1, \(P < 0.0001\) for D-dimer).\textsuperscript{37}

Coronary artery disease

As 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 PI therapy.

We have recently conducted a meta-analysis\textsuperscript{14} of 11 studies including 24 442 HIV-patients presented with ACS. The most common presentation was STEMI with a frequent occurrence of multivessel involvement. Both characteristics had an higher incidence than in contemporary ACS registries of non-HIV patients\textsuperscript{38,39} and combined together could, in part, explain the higher rates of in-hospital events registered in HIV patients.\textsuperscript{40}

Conversely, other studies have reported a more favourable in-hospital outcome in absence of significant haemodynamic compromise.\textsuperscript{41}

Certainly, PCI in HIV-infected patients was associated with a high incidence in the follow-up of non-fatal reinfarction, restenosis and in-stent thrombosis.\textsuperscript{42} This feature derived both from cardiovascular risk factors and enhanced from viral pathological processes and side effects of anti-retroviral drugs. Moreover it was reported that a high incidence of thrombo-embolic events and intraluminal demonstration of fresh thrombus probably related to the prothrombotic state.\textsuperscript{43}

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In a recent report of the Soweto Study Cohort\(^3\), about 518 HIV patients were admitted for a first diagnosis of cardiovascular disease between 2006 and 2008; Sliva and colleagues\(^\text{43}\) raised a question about real incidence of CAD reporting a relatively infrequent incidence of ACS (3%), despite most patients already receiving HAART before admission.

This finding is in agreement with a recent meta-analysis that casts doubt on the potential role of publication bias and confounding in overestimation of HIV and PI exposure risk\(^\text{44}\).

**Management of CVD in HIV**

- **Modification of risk factors**
  - The early detection and treatment of co-morbidities 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.
  - Even if HIV infection by itself and HAART treatment could increase the risk of plaque rupture and atherothrombosis\(^\text{13,45}\), routine secondary prevention does not take into account this challenge. Moreover as reported in some studies\(^\text{45}\), 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 and Adult AIDS Clinical Trials Group\(^\text{46}\). These recommendations are largely based on National Cholesterol Education Program Adult Treatment Panel III guidelines, and advocate adjusting individual cholesterol levels through estimation of Framingham predicted 10-year cardiovascular risk\(^\text{37}\).
  - Currently there is no difference in hyperlipidaemia goals treatment between HIV and non-HIV patients. The key points to consider in the choice of specific lipid-lowering therapy are the drug–drug interactions in the patient population. In general, all PIs inhibit CYP3A4, with the highest level of inhibition in 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. So the first agents for lowering LDL are pravastatin (not metabolised by CYP3A4) and fluvastatin (metabolised by CYP2C9) as the second choice. Rosuvastatin concentrations appear to increase when used in combination with some NNRTIs (atazanavir, ritonavir, lopinavir), thus, in that setting, we must consider 10 mg as the maximum safe dose\(^\text{46,49}\). Similarly, atorvastatin may be used at lower doses in HIV patients. Finally during PIs therapy, simvastatin and lovastatin are not recommended for the high risk of rhabdomyolysis as reported previously\(^\text{60}\). Lack of data makes it not possible to define further benefits related to anti-inflammatory properties of statins.

- **Critical appraisal of the validity of relevant articles**
  - Three unblinded independent reviewers (EC, FDA, GB-Z) abstracted the data about relevant studies reported in this article on pre-specified forms: authors, journal, year of publication, location of the study group, baseline features and type and timing of anti- retroviral therapy. To evaluate the overall quality of included studies, we separately abstracted and appraised study design, setting, data source, as well as risk of analytical, selection, adjudication, detection, and attrition bias (expressed as low, moderate or high risk of bias, as well as incomplete reporting).

**Conclusion**

- Short-term benefits of specific anti-retrovirals prevent cardiovascular disease in HIV patients, but long-term benefits need more data and longer-term follow-ups to be correctly assessed. The results of ongoing trials will provide important information on how to manage timing of HAART initiation optimising risk–benefit. The START trial includes anti-retroviral-naïve HIV-positive people with CD4 counts greater than 500 cells/mm\(^3\); it is taking place at about 90 sites in nearly 30 countries where participants are randomised to either receive ART treatment immediately or to defer treatment until their first CD4 count less than 350 cells/mm\(^3\) or they have clinical signs of advanced HIV disease. Such a randomised study will therefore address the question if the purported benefits of early therapy (as suggested by DHHS guidelines) may overcome the expected drug-associated side effects.

- Other challenges and open issues remain concerning the best time to start ART, the best regimen in patients with established CAD, the role of anti-inflammatory and antithrombotic drugs as well as the long-term clinical outcomes in HIV-positive patients, ‘doomed’ in the modern era, to live longer and to face age-related morbidities.

**Clinical applicability**

- HIV-infected patients live longer but are at an increased risk for CVD. Physicians could plan new strategies to reduce this risk optimizing HAART therapies and preventing the exposure to other traditional risk factors. The development of specific risk score will be necessary. Moreover, the management of patients that experienced a CV event should follow the same recommendations as those for general population, bearing in mind potential drug–drug interactions, for example with statins and PIs.

**References**


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