Novel insights on HIV/AIDS and cardiac disease: shedding light on the HAART of Darkness

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This editorial refers to ‘Contribution of the human immunodeficiency virus/acquired immunodeficiency syndrome epidemic to de novo presentations of heart disease in the Heart of Soweto Study cohort’, by K. Sliwa et al., on page 866 and ‘Acute coronary syndromes in human immunodeficiency virus patients: a meta-analysis investigating adverse event rates and the role of antiretroviral therapy’, by F. D’Ascenzo et al., on page 875

Never see him! I saw him clearly then. I shall see this eluent phantom as long as I live, and I shall see her too, a tragic and familiar shade, resembling in this gesture another, tragic also, and bedecked with powerless charms, stretching bare brown arms over the glitter of the infernal stream, the stream of darkness
Joseph Conrad, Heart of Darkness

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) pandemic in Africa and worldwide indeed represents the heart of darkness for any practising physician, given the overwhelming implications in terms of mortality, morbidity, and resource use. While innumerable studies have been conducted on HIV/AIDS and more will rightfully come, the impact of this condition on cardiovascular health is still far from clear. Indeed, HIV/AIDS is only (at least apparently) 31 years old, and the introduction of potent drug combinations (namely highly active antiretroviral therapy [HAART]) even more recent.

Given these ongoing improvements in our understanding and treatment of HIV/AIDS as a whole, leading to increased life expectancy in patients with HIV/AIDS, greater attention has been paid to the impact of this condition on other body organs and systems, in light of the pleomorphic manifestations of HIV infection, opportunistic diseases, and drug toxicities.

The heart is now key for the prognosis of HIV/AIDS patients in developed countries, as cardiovascular disease is the most common cause of death there, topping even AIDS itself. Several factors and mechanisms have been shown and suggested to be involved, including direct myocardial and coronary HIV infection, autoimmune responses, and an adverse risk factor profile (Figure 1). Moreover, the very same drugs which are used to treat HIV/AIDS, namely HAART, have been implicated in adverse effects on dyslipidaemia and insulin resistance, with the common occurrence of hypercholesterolaemia and hypertriglyceridaemia, with evidence supporting their direct impact on development of atherosclerosis. Another potential aetiological feature is represented by secondary prevention goals which are less commonly reached in these patients.

Despite the availability of many single centre and multicentre reports, a clear picture of how cardiovascular disease manifests in patients with HIV/AIDS is confounded in most available studies coming from developed countries by the presence of several co-morbidities and prolonged history of drug intake.

The booming incidence and prevalence of HIV/AIDS in sub-Saharan Africa is most unfortunate. Careful analysis of HIV/AIDS in this specific geographical area may offer important insights into this condition, with implications for all physicians worldwide.

The results of a study conducted in the Chris Hani Baragwanath Hospital, the second largest hospital in the world with 3200 beds, has now been reported by Sliwa et al. Exploiting the perspective offered by this unique tertiary care centre, the authors report on the impact of HIV/AIDS on admissions for cardiovascular disease, providing an outstanding opportunity to bridge, at least in part, our knowledge gaps and become acquainted with what HIV/AIDS implies for cardiovascular practitioners.

In particular, of 5328 patients admitted for a first diagnosis of cardiovascular disease between 2006 and 2008, 518 (10%) were found to be infected by HIV (with 54% of them already receiving HAART). This substantial sample of 518 cases showed that the most common cardiac condition was HIV-related cardiomyopathy (38%), usually biventricular dysfunction or left ventricular dysfunction. Pericardial effusion and pericarditis were present in 13%, valvular heart disease was diagnosed in 11%, hypertension in 8%, pulmonary hypertension or right heart failure in 8%, peripartum cardiomyopathy in 3%, and cerebrovascular disease in

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3%. Coronary artery disease in HIV patients, which has received a great deal of attention in developed countries, was also diagnosed in 3% of cases, only 1% more than congenital heart disease. Yet, the peculiarity of such coronary involvement persists even in the population receiving care in this South African institution, with intracoronary thrombus often representing the most important finding, in a background of no or only mild coronary atherosclerosis. Despite this plethora of cardiac manifestations, Sliwa and colleagues did not report any specific bradycardia or tachyarrhythmic manifestation of HIV/AIDS, with the notable exception of six patients with bradycardia/atrioventricular block, five cases of atrial fibrillation, and one with tachyarrhythmia, thus suggesting that these specific types of complication are relatively infrequent in such patients. Moreover, subjects with HIV/AIDS receiving a new cardiovascular diagnosis were younger than those without HIV/AIDS, at least at adjusted analyses.

Focusing on specific subtypes of HIV/AIDS-related cardiac disease, patients presenting with cardiomyopathy had significantly higher viral loads (189 277 ± 372 035 vs. 102 611 ± 300 722, \( P < 0.001 \)) and significantly lower CD4 counts (212 ± 184 vs. 281 ± 273, \( P < 0.001 \)) than those presenting with other cardiac manifestations. This confirms previous reports suggesting that HIV/AIDS-related cardiomyopathy and pericardial disease are more typical of pre-HAART phases and the accompanying state of uncontrolled viral replication. Moreover, such differences support the hypothesis of a direct mechanistic role for HIV in cardiomyocyte injury and death, most probably by means of apoptosis. Despite such important findings, research is still needed to gain further insights into other issues, such as the impact of asymptomatic left ventricular dysfunction on prognosis. Indeed, beta-blockers and angiotensin-converting enzyme inhibitors, which represent the cornerstone of treatment of other types of left ventricular dysfunction, should be formally tested in this peculiar setting, to appraise correctly their impact on survival, symptoms, and ventricular remodelling.

Of utmost interest for European practitioners is the fact that coronary artery disease was relatively infrequent (3%), despite most patients already receiving HAART before admission. Indeed, patients with concomitant coronary artery disease and HIV/AIDS had significantly lower viral loads (4769 ± 3109, \( P < 0.001 \)) and numerically higher CD4 counts (298 ± 184, \( P = 0.11 \)) than patients with HIV/AIDS-related cardiomyopathy, thus suggesting that HIV infection plays a limited role, at least in a relatively young patient population, in coronary atherothrombosis.
This finding indirectly contradicts previous evidence suggesting that HIV infection and HAART exposure are strong independent risk factors for premature coronary artery disease, in agreement with a recent meta-analysis by Hulten et al. which has directly called into question the role of publication bias and residual confounding. Yet, it must be emphasized that Sliwa and colleagues reported that coronary angiography and intravascular ultrasound excluded severe coronary stenoses and conversely showed fresh thrombus in all cases. This piece of evidence appears to be in agreement with other reports suggesting that coronary artery disease in patients with HIV/AIDS has a different pathophysiology from coronary artery disease in those without HIV/AIDS, with a different natural history and, possibly, different optimal management.

Additional strengths of this study include the large sample size, the prospective design, the systematic application of explicit criteria for diagnosis and clinical assessment of both HIV/AIDS and cardiac conditions, and compliance with Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. This study, like any other research endeavour, also has weaknesses. First, as with all prospective studies focusing on life-threatening conditions such as HIV/AIDS in underprivileged settings, ethical standards should be carefully examined. In the present case, only verbal consent for study participation was required. Whereas we do not find this choice particularly problematic in this very specific setting, we should remain watchful for future threats to research ethical standards. Other potentially important limitations are the cross-sectional design with reliance on logistic multivariable adjustment, lack of insights on children with HIV/AIDS (as only adults were enrolled), and absence of data on in-hospital and long-term clinical outcomes. In addition, the fact that HIV testing was performed when only clinically indicated might lead to underestimation of the real HIV infection prevalence. Finally, it is unclear whether HIV/AIDS patients admitted for a given cardiac condition (e.g. cardiomyopathy) are more likely also to develop in the future other cardiac manifestations of HIV/AIDS (e.g. coronary artery disease) or have a risk similar to those with HIV/AIDS, but no cardiac involvement. We might suspect that HIV/AIDS-related cardiac involvement may represent a risk factor for ongoing and recurrent HIV/AIDS-related cardiac disease.

In conclusion, we remind the busy European cardiologist who may question the pertinence of this study for his or her everyday practice that it is paramount that we do not dismiss this work for its African scope or its focus on HIV/AIDS. This condition remains stigmatized, side-lined, and neglected in an altogether inappropriate fashion. Moreover, ongoing migration of people from developing to developed countries and increased life expectancy of patients with HIV/AIDS mean that a thorough knowledge and understanding of cardiac manifestation of HIV/AIDS is and will continue to be crucial for any European cardiovascular specialist.

Conflict of interest: none declared.

References