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HIV Infection and Primary Prevention of Cardiovascular Disease: Lights and Shadows in the HAART Era

Flavia Ballocca[a,1], *Sebastiano Gili*[a,1], *Fabrizio D'Ascenzo*[a,*], *Walter Grosso Marra*[a], *Margherita Cannillo*[a], *Andrea Calcagno*[b], *Stefano Bonora*[b], *Andreas Flammer*[c], *John Coppola*[d], *Claudio Moretti*[a], *Fiorenzo Gaita*[a]

[a]*Division of Cardiology, Department of Medical Sciences, Città della Salute e della Scienza, Turin, Italy*
[b]*Division of Infectious Disease, Amedeo di Savoia Hospital, Turin, Italy*
[c]*University Heart Center, University Hospital Zurich, Switzerland*
[d]*Division of Cardiology, Department of Medicine, New York University School of Medicine, New York, New York*

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ABSTRACT

With the progressive increase in life-expectancy of human immunodeficiency virus (HIV)-positive patients in the "highly active antiretroviral therapy" (HAART) era, co-morbidities, particularly cardiovascular (CV) diseases (CVD) are emerging as an important concern. The pathophysiology of CVD in this population is complex, due to the interaction of classical CV risk factors, viral infection and the effects of antiretroviral therapy (ARV). The role of ARV drugs in HIV is double edged. While these drugs reduce systemic inflammation, an important factor in CV development, they may at the same time be proatherogenic by inducing dyslipidemia, body fat redistribution and insulin resistance. In these patients primary prevention is challenging, considering the lower median age at which acute coronary syndromes occur. Furthermore prevention is still limited by the lack of robust evidence-based, HIV-specific recommendations. Therefore we performed a comprehensive evaluation of the literature to analyze current knowledge on CVD prevalence in HIV-infected patients, traditional and HIV-specific risk factors and risk stratification, and to summarize the recommendations for primary prevention of CVD in this HIV population.

The introduction of highly active antiretroviral therapy (ARV; HAART) has dramatically altered the natural history of human immunodeficiency virus (HIV) infection. Infection with the HIV virus was once a devastating condition resulting in the development of acquired immunodeficiency syndrome. With the introduction of HAART, infection with HIV has morphed into a chronic condition with a life expectancy comparable to the general population.[1]

Statement of Conflict of Interest: see page 572.

* Address reprint requests to Fabrizio D'Ascenzo, Division of Cardiology, Department of Medical Sciences, Città Della Salute e Della Scienza, Corso Bramante 88, 10126, Turin, Italy.
E-mail address: fabrizio.dascenzo@gmail.com (F. D'Ascenzo). *URL:* http://www.cardiogroup.org (F. D'Ascenzo).

[1] Both authors contributed equally to the manuscript and have to be considered first co-authors.

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Abbreviations and Acronyms

ARV = Antiretroviral

ASCVD = Atherosclerotic cardiovascular disease

CHD = Coronary heart disease

CRP = C-reactive protein

CV = Cardiovascular

CVD = Cardiovascular disease

CYP = Cytochrome

D:A:D = Data Collection on Adverse Effects of Anti-HIV Drugs

FRS = Framingham Risk Score

GLUT = Glucose transporter

HAART = Highly active antiretroviral therapy

HDL-C = High-density lipoprotein cholesterol

hs-CRP = Highly-sensitive C-reactive protein

HTN = Hypertension

IL = Interleukin

LDL-C = Low-density lipoprotein cholesterol

MI = Myocardial infarction

NRTI = Nucleoside reverse transcriptase inhibitor

NNRTI = non- Nucleoside reverse transcriptase inhibitor

PAH = Pulmonary arterial hypertension

PIs = Protease inhibitors

sCD = Soluble CD

T2D = Type 2 diabetes

TGs = Triglycerides

TMA = Trimethylamine

As a result of HAART treatment, patients are living longer and morbidities not historically related to HIV infection but associated with aging have gained more and more relevance in the HIV population. Cardiovascular (CV) disease (CVD) nowadays is recognized as a significant health issue encountered in HIV patients: Sackoff, in a review of New York City death certificates, found in HIV patients aged 55 years or older that CVD was the greatest cause of mortality.[2] HIV-positive patients are exposed to a higher risk of CVD[3] and are usually affected at a younger age when compared to the general population. With the progressive increase in life expectancy of the HIV population,[4] CVD risk assessment and prevention are becoming a critical element in the management of HIV infected patients. Currently 30 million people worldwide and about 2.2 million people in North America and Western and Central Europe are estimated to live with HIV infection. This presents a real challenge from a public health perspective.[5]

From a clinical standpoint, almost every form of CVD has been reported in the HIV population, with coronary heart disease (CHD) representing the main clinical manifestation of CVD.[6–8] An increased prevalence of high-risk atherosclerotic plaques with features consistent with a destabilization has been described. The higher rates of acute coronary syndromes, particularly of ST-segment elevation myocardial infarction (MI), lead to high intra-hospital and one-year mortality.[9,10]

Despite the growing incidence of CVD in the HIV population, only limited data, mainly derived from non-HIV populations or small sample sized studies, allow an evidence-based approach to CVD prevention in the HIV infected patient. This would be an area calling for the development of focused research and prevention guidelines.[11,12]

The present review attempts to summarize our understanding and current knowledge pertaining to primary prevention of CVD in HIV-positive patients and to highlight the substantial gaps in evidence-based recommendations in treatment.

Why are HIV patients exposed to an increased risk of CVD?

A comprehensive understanding of CVD prevention in HIV patients needs to be viewed through the mechanisms involved in the development of CVD in this population. Pathogenesis of CVD in HIV-positive patients, even if not fully understood, is the result of the complex interplay of infection-related factors, HAART-related factors and traditional risk factors[13] (Fig 1).

Role of HIV infection

The existence of a relationship between HIV infection and development of CVD is suggested by the inverse correlation reported between the risk of MI and the nadir count of CD4+, as well as the increased risk of MI reported for RNA viral counts >50 copies/ml.[14–16]

HIV infection leads to an activation of the innate immune system and, despite medical therapy, this will lead to an activation of macrophages and monocytes.[17] This may suggest one mechanism since monocytes and macrophages play a significant role in atherogenesis. Soluble CD14 (sCD14), and, to a minor extent, soluble CD163 (sCD163), both known markers of monocyte/macrophage activation, have been identified as reliable predictors of increased atherosclerotic disease[18]; sCD14, has been associated with an increased risk of death in HIV-positive patients[19] with a history of CVD in a cross-sectional study including 540 patients.[20]

Deregulation of CD8+ T-cells has also been shown to relate to adverse CVD events in HIV-positive patients. It has been shown in patients with higher expression of CD8(+)CD38(+)HLA-DR(+) phenotypes, higher values of carotid intimal media thickness and arterial stiffness.[21,22]

HIV-positive patients on HAART therapy have high levels of systemic inflammatory response, which has been related to CVD mortality in the general population. HIV-positive patients typically have higher levels of several inflammatory cytokines (i.e., highly sensitive C-reactive protein (CRP;hs-CRP), and interleukin 6 (IL6)) as compared to the general population: HAART, while able to reduce these markers to lower levels as compared to HAART-naïve HIV-positive patients, is still inadequate to reach values comparable to HIV-negative patients.[23] The clinical