International Journal of Cardiology 265 (2018) 195–203

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Cardiovascular disease burden among human immunodeficiency virus-infected individuals☆

Ozan M. Demir [a,b], Luciano Candilio [a,b], Daniel Fuster [c], Robert Muga [c], Giuseppe Barbaro [d], Antonio Colombo [a], Lorenzo Azzalini [a,*]

[a] Interventional Cardiology Division, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Milan, Italy
[b] Department of Cardiology, Hammersmith Hospital, Imperial College NHS Healthcare Trust, London, United Kingdom
[c] Department of Internal Medicine, Addiction Unit, Hospital Germans Trias i Pujol, Universitat Autònoma de Barcelona, Badalona, Spain
[d] Department of Internal Medicine and Infectious Diseases, Policlinico Umberto Primo, Rome, Italy

ARTICLE INFO

Article history:
Received 27 November 2017
Received in revised form 17 March 2018
Accepted 30 March 2018

Keywords:
Human immunodeficiency virus
Cardiovascular disease
Coronary artery disease

ABSTRACT

Human Immunodeficiency Virus (HIV) infection affects 36.7 million people worldwide, it accounted for 1.1 million deaths in 2015. The advent of combined antiretroviral therapy (cART) has been associated with a decrease in HIV-related morbidity and mortality. However, there are increasing concerns about long-lasting effects of chronic inflammation and immune activation, leading to premature aging and HIV-related mortality. Cardiovascular diseases, especially coronary artery disease, are among the leading causes of death in HIV-infected patients, accounting for up to 15% of total deaths in high income countries. Furthermore, as cART availability expands to low-income countries, the burden of cardiovascular related mortality is likely to rise. Hence, over the next decade HIV-associated cardiovascular disease burden is expected to increase globally. In this review, we summarize our understanding of the pathogenesis and risk factors associated with HIV infection and cardiovascular disease, in particular coronary artery disease.

1. Introduction

Human Immunodeficiency Virus (HIV) infection affects 2.1 million people in the Western hemisphere and 36.7 million people worldwide. HIV infection accounted for 1.1 million deaths in 2015. Combined antiretroviral therapy (cART) has been associated with a decrease in HIV-related morbidity and mortality, and HIV-infected patients without substance use or major comorbidities tend to have a similar survival to their HIV-negative counterparts. However, there are increasing concerns about long-lasting effects of chronic inflammation, immune activation and increased intestinal permeability, leading to premature aging, characterized by impairment of renal and liver function, neuropsychological decline, and osteoporosis related mortality. In the developed world, cardiovascular (CV) mortality is currently one of the leading causes of death in an aging HIV-infected population that benefit from cART therapy [1].

The association between HIV infection and CV disease is due to a combination of traditional risk factors for the development of atherosclerosis (e.g. smoking, diabetes, lipid abnormalities), non-traditional risk factors (e.g. chronic inflammatory response and lipoprotein-a levels), the effect of antiretroviral agents, the virus itself and consequences of the immune response. Cardiovascular diseases, and especially coronary artery disease (CAD), are among the leading causes of death in HIV-infected patients, accounting for up to 15% of total deaths in high income countries [2]. Furthermore, as cART availability expands to low-income countries, the burden of CV related mortality is likely to rise. Hence, over the next decade HIV-associated CV disease burden is expected to increase globally. In this review, we summarize our understanding of the pathogenesis and risk factors associated with HIV infection and CV disease, in particular CAD (Fig. 1).

2. Cardiovascular risk factors

In HIV-infected patients, higher rates of traditional and modifiable risk factors are found [3,4]. Furthermore, the impact of traditional CV

☆ This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

* Corresponding author at: Division, Cardio-Thoracic-Vascular Department, San Raffaele Scientific Institute, Via Olgettina, 60, 20132 Milan, Italy.
E-mail address: azzalini.lorenzo@hsr.it (L. Azzalini).

https://doi.org/10.1016/j.ijcard.2018.03.137
0167-5273/

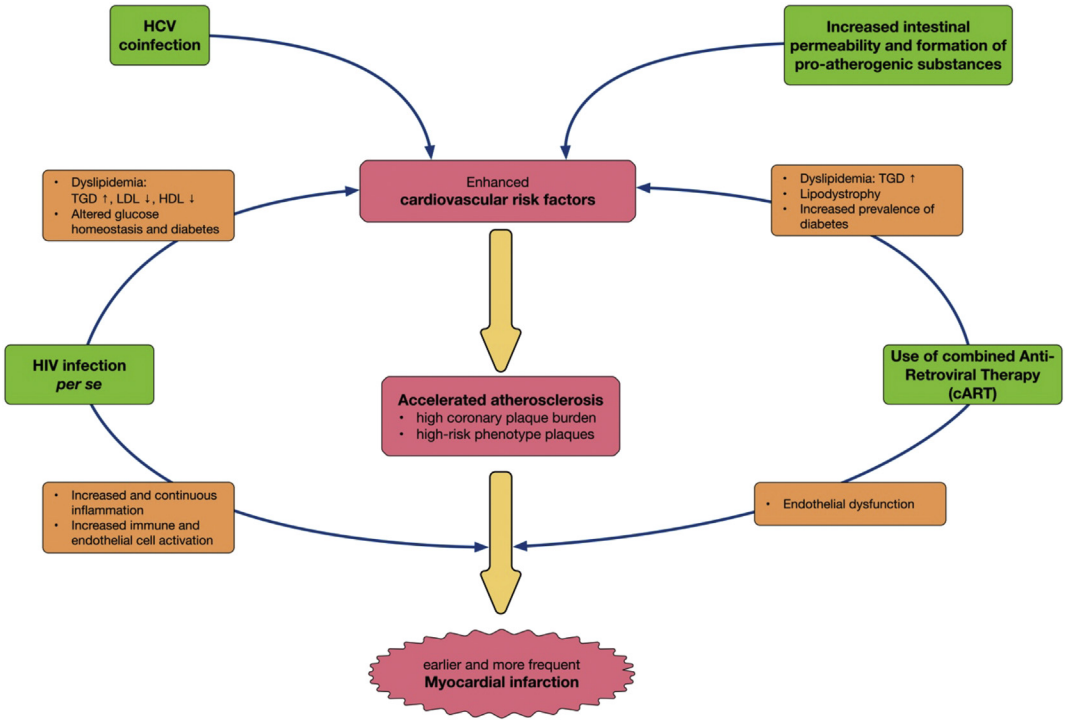

Fig. 1. Pathogenesis of coronary artery disease in human immunodeficiency virus individuals.

risk factors is enhanced by intrinsic features of the infection, by the effects of cART, and by several novel risk factors, resulting in higher overall CV risk, when compared with age-matched controls.

2.1. Traditional and behavioural risk factors

In HIV-infected patients several traditional risk factors contribute disproportionally to overall CV burden. They exhibit a typical pattern of dyslipidaemia: low levels of both high density lipoprotein (HDL) and low density lipoprotein (LDL) cholesterol and high levels of triglycerides, driven by direct effect of HIV on the structure and function of HDL and LDL particles [5]. An increase in basal lipolysis and hepatic de novo lipogenesis, as well as a decrease in insulin-induced lipolysis suppression and an impairment of peripheral fatty acid trapping, are also observed [6]. There is a higher prevalence of diabetes mellitus which is associated with lower CD4+ cell count and lipodystrophy, which is a change in body fat distribution including both lipoatrophy (especially on the face and limbs) and lipohypertrophy (especially of central visceral fat, liver and muscles) [7]. In this setting of globally enhanced CV risk burden, myocardial infarction (MI) has an earlier onset in HIV-infected patients, even after adjusting for traditional risk factors, co-morbidities and illicit drug use [8].

2.2. Effects of cART regimens on CV risk

Antiretroviral agents have been associated with higher risk of cardiovascular events due to a plethora of multifactorial issues and interactions. There are numerous mechanistic theories on the causative relationship between cART regimens and CV risk. The main culprits include lipid abnormalities, diabetes mellitus, endothelial dysfunction, atherosclerosis, and platelet dysfunction [9]. Initiation of cART regimens triggers complex modulation of the aforementioned pattern of dyslipidaemia seen in treatment-naïve patients, there is also an effect that is independent of lipid levels. Increase in triglycerides is usually the most prominent alteration, although it carries limited additional CV risk [10]. Furthermore, both incidence and prevalence of diabetes mellitus were found to be strongly associated with cART therapy [7]. Other effects of first generation protease inhibitors (PI) included endothelial dysfunction as well as enhanced atherosclerosis via elevated intima-media thickness, increased pulse wave velocity and reduced flow-mediated vasodilatation [11]. The interaction of drugs used in newer regimens of cART with lipid metabolism and CV disease pathophysiology is poorly defined. Newer combinations of antiretroviral agents, or those including PI atazanavir, among others, appear to have a better profile in terms of cardiovascular risks [12], although this finding could result from more aggressive CV risk factors treatment or insufficient observational time. Abacavir, a nucleoside analogue reverse-transcriptase inhibitor, has been associated with development of CV disease in HIV-infected patients. A recent study demonstrated that abacavir conferred over 2-fold increased risk of CV disease, which was independent of other factors (renal dysfunction or other CVD risk factors) [13]. Moreover, studies have demonstrated an association between abacavir and myocardial infarction in HIV-positive patients [14]. Despite all the controversies and early concerns about increase in CV risk in patients treated with cART, the importance of its early initiation and continuous use remains unquestioned, as a higher incidence of opportunistic infections, all-cause death and cardiovascular conditions is present in patients undergoing intermittent or no cART [15]. It has been suggested that sustained viral suppression leads to a reduction of inflammatory cytokines which outweighs the deleterious proatherogenic and dysmetabolic side effects of cART. Moreover, higher CD4+ cell count, higher CD4+ cell nadir count and reduced viremia, were associated with a reduction of MI incidence; hence this suggests that early initiation of cART could potentially have a role in reducing the incidence of MI [16–18].

2.3. Novel risk factors

2.3.1. HIV infection "elite controllers"

HIV infection "*elite* controllers" are a rare group of HIV-infected patients who maintain control over the infection without administration