JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2017 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 69, NO. 1, 2017
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.09.979

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

HIV and Ischemic Heart Disease

Ahmed Vachiat, MBBCH, Keir McCutcheon, MBBCH, Nqoba Tsabedze, MBBCH, Don Zachariah, MBBCH, Pravin Manga, MBBCH, PHD

ABSTRACT

The association of coronary heart disease (CHD) and human immunodeficiency virus (HIV) infection has been well recognized for many years. The etiology of the increased prevalence of CHD in HIV-infected populations is the result of complex interactions among the viral infection, host factors, traditional risk factors, and therapies for HIV. As the HIV population is living longer, largely attributable to combination antiretroviral therapy, there is concern about the effect of the rising prevalence of CHD on morbidity and mortality, as well its effect on health systems around the world. This review will highlight the epidemiological evidence linking HIV infection and CHD. It will also focus on our current understanding of the pathogenesis and factors associated with HIV infection and CHD. In addition, the review will highlight modes of presentation and management strategies for mitigating risk and treatment of HIV-positive patients presenting with CHD. (J Am Coll Cardiol 2017;69:73–82) © 2017 by the American College of Cardiology Foundation.

Of the approximately 37 million people in the world living with human immunodeficiency virus (HIV), 70% live in sub-Saharan Africa (1,2). The increased prevalence of coronary heart disease (CHD) in this population is due to increased life expectancy globally, resulting from better access to combination antiretroviral therapy (cART) and high levels of traditional cardiovascular disease (CVD) risk factors (3). Although North America and Europe have substantial data on CHD in the HIV-infected population, there is a paucity of data regarding HIV-associated CHD from developing regions.

Despite the evidence that HIV infection carries a higher risk of developing coronary artery disease (CAD), the mechanisms responsible for the heightened risk are not well understood. The etiopathogenesis of HIV and atherosclerosis is secondary to the highly complex interplay between numerous factors (**Central Illustration**). It has been well recognized for many years that there is increased prevalence of traditional risk factors in HIV-infected individuals (4,5). In addition, the effects of certain cART treatment regimens lead to dyslipidemia, insulin resistance, and endothelial dysfunction (6,7). However, the role of HIV-related inflammation and immune activation is central to the increased risk of CAD (8). Furthermore, the outcome of the interaction between the different factors in an individual or population is also dependent on other variables, particularly environmental and genetic factors.

This review focuses on epidemiological evidence linking HIV infection and CHD, and on our current understanding of the pathogenesis and associated factors. We will also highlight modes of presentation and management strategies for mitigating risk and treatment of HIV-positive patients presenting with CHD. HIV and nonischemic heart disease are discussed in the accompanying review in this issue of the *Journal* (9).

EPIDEMIOLOGY

HIV infection has become a medically controllable chronic disease with non-acquired immunodeficiency syndrome (AIDS) defining illnesses as the main cause of morbidity and mortality (10). This is observed in regions with wide cART coverage, and is associated

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the Division of Cardiology, Department of Medicine, Faculty of Health Sciences, University of Witwatersrand, Johannesburg, South Africa. The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received April 21, 2016; revised manuscript received August 25, 2016, accepted September 20, 2016.

ABBREVIATIONS AND ACRONYMS

cART = combination antiretroviral therapy

CCTA = coronary computed tomography angiography

CHD = coronary heart disease

CIMT = carotid intima-media thickness

CVD = cardiovascular disease

MI = myocardial infarction

PI = protease inhibitor

with a concurrent rise in the incidence of noncommunicable diseases, particularly CHD (10).

Large observational studies in the United States and Europe have investigated the epidemiology of CHD in HIV-infected populations (**Table 1**) (5,11–20). These and other studies suggest that HIV infection increases the overall risk for developing CHD by 1.5- to 2.0-fold. Interestingly, an analysis of cohorts over different timeframes suggests that the prevalence rates are falling, presumably due to early recognition of risk factors and use of newer antiretroviral agents (21). Unfortunately, there are scant data on the effect of HIV infection on CHD prevalence in resource-poor countries. Some data suggest that CHD risk factors are prevalent in resource-limited countries, but CVD outcomes data are lacking (22).

With regard to CVD outcomes, HIV-positive patients also have a greater risk of developing cardiovascular complications (4). Data from the Nationwide Inpatient Sample in the United States demonstrated that HIV-positive patients with myocardial infarction (MI) have lower MI-related intervention rates and higher death rates compared with their seronegative counterparts (23). They also have a 4.5-fold increased rate of sudden cardiac death, which has been associated with a history of previous MI, cardiomyopathy, heart failure, arrhythmia, hypertension, and dyslipidemia (24).

RISK FACTORS

TRADITIONAL RISK FACTORS. A number of studies indicate a high prevalence of traditional CHD risk factors in the HIV-positive populations (4,5). However, prevalence estimates vary widely, due to differences in risk cutoffs, genetic background, geographic location, and access to cART. In resource-rich countries, smoking rates are reported to be almost 2-fold higher in HIV-positive individuals (14,25). The D:A:D (Data Collection on Adverse Events of Anti-HIV Drugs) study group reported that in HIV-infected persons, there was almost a 3-fold increased risk of MI in current smokers as compared with HIV-infected nonsmokers (26). The same study group also found that diabetes and dyslipidemia were associated with an increased risk of MI (26). Patients with HIV also have a stepwise increase in their risk of MI, with a hazard ratio of 2.0 for those with 1 major CVD risk factor, increasing to 3.6 for those with 3 or more risk factors (20). Even low pre-hypertension (120 to 129/80 to 84 mm Hg) and high pre-hypertension (130 to 139/85 to 89 mm Hg) were associated with an increased risk of MI of 1.6 and 1.8, respectively (27). Many of the traditional risk factors, such as smoking, dyslipidemia, hypertension and central obesity, are likely related to the socioeconomic factors associated with HIV infection.

INFLAMMATION AND IMMUNE ACTIVATION. HIV infection, through attendant inflammation and immune dysfunction, is an independent predictor of CVD. Two recent large cohort studies found a strong and consistent association of HIV with a 44% to 48% increased risk of MI, independent of traditional risk factors, such as age, race, socioeconomic status, and substance abuse (5,19). The findings of the SMART (Strategies for Management of Antiretroviral Therapy) trial also suggest that HIV and attendant inflammation are important in conferring CHD risk (8). This is further supported by a recent study, which found that new cycles of HIV replication may also play a role in ongoing inflammation in patients with modest cART nonadherence (28). In HIV-infected patients, studies suggest that immunodeficiency (CD4+ cell counts <200 cells/mm^3) is significantly associated with a higher risk of MI (5,19).

EFFECT OF SEX. HIV has a distinct effect on women with respect to CHD risk. Although the majority of observational data included predominantly male patients, there is a significant difference in the relative risk of CHD for HIV-infected women, who have double the risk compared with HIV-infected men (4,17). This higher risk in women may relate to higher levels of immune activation (17).

ANTIRETROVIRAL THERAPY. Dyslipidemia (elevated total cholesterol and triglyceride levels), as well as endothelial dysfunction, may be caused by cART, particularly protease inhibitors (PIs) (6,7). These agents may also predispose to hypertension through hyperactivation of the renin-angiotensin-aldosterone system (29). In contrast, non-nucleoside reverse transcriptase inhibitors, integrase inhibitors, and CCR5 antagonists have thus far been shown to have neutral lipid effects, with no increased risk of CHD (30) (**Table 2**). Endothelial dysfunction secondary to cART has been attributed to reduced nitric oxide production, increased reactive oxygen species production, impaired cholesterol efflux, and accelerated foam cell formation (6).

PATHOGENESIS OF HIV-ASSOCIATED CAD. CAD in HIV-infected patients is the result of a number of interactions causing inflammation, endothelial