

# Immune Activation and Coronary Atherosclerosis in HIV-Infected Women: Where Are We Now, and Where Will We Go Next?

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(See the major article by Fitch et al on pages 1737–46.)

**Keywords.** HIV; atherosclerosis; coronary artery disease.

Understanding the pathophysiology of coronary heart disease (CHD) in the human immunodeficiency virus (HIV)-infected population with access to antiretroviral therapy (ART) has become an important focus of recent research. CHD is, in fact, an emerging complication for individuals infected with HIV and presents a challenge for physicians involved in the care of HIV-infected patients. Cardiovascular disease is currently the third leading cause of death in HIV-infected individuals, after AIDS-related complications and malignancies. CHD is now the leading cardiovascular cause of death and morbidities, far more than heart failure, in HIV-infected patients on ART [1], whereas congestive heart failure related to immunocompromise is the leading cause of death in countries with poor access to ART [2]. Many factors have been associated with myocardial infarction in the HIV

population, ranging from traditional risk factors (eg, hypertension, tobacco use, dyslipidemia, diabetes, family history of premature CHD, microalbuminuria, and chronic renal failure) [3] to infection with hepatitis C virus [3], genetic factors [4], HIV itself [5], chronic inflammation [6], and immune activation [7].

Little is known about CHD in HIV-infected women. In several studies on acute coronary syndrome in HIV-infected patients, the proportion of women varied from 3% to 19% (mean, 10%) [1]. These figures are similar to those reported for HIV-uninfected women from the general population in a North American registry, where women aged <50 years accounted for <10% of cases of myocardial infarction [8]. The age distributions of HIV-infected and HIV-uninfected populations are, however, very different; those in the HIV-infected population are 10 to 15 years younger. Data from a North American epidemiological study have shown that the relative risk (RR) of myocardial infarction is higher in HIV-infected women than in uninfected female controls, with an RR of 2.98 [9]. Similarly, a French epidemiological study reported that the standardized morbidity ratio (SMR) was 2.7 for HIV-infected women vs uninfected female controls [10]. Of note, both the RR and the SMR

were higher in HIV-infected women than in HIV-infected men (RR 1.4, SMR 1.4 [9, 10]). In the Women's Interagency HIV Study (primary prevention study), 12% of HIV-infected women had a highly predicted 10-year risk of CHD, similar to that in the HIV-uninfected women; the mean age of the women was 40 years [11]. These data indicate that there are unmet needs in HIV-infected women at risk for CHD. How do we identify these women, how do we prevent an acute event, and what mechanisms are involved in their elevated risk of myocardial infarction?

Fitch et al, in their article published in this issue of the *Journal*, focus on subclinical coronary atherosclerosis in HIV-infected women without symptoms or history of cardiovascular disease [12]. Using computed tomographic angiography (CTA), the authors report, for the first time, an increased prevalence of specific noncalcified coronary plaques and increased immune activation (monocyte activation) in asymptomatic HIV-infected women, when compared with female controls. These noncalcified plaques are potentially more prone to rupture than calcified plaques and, therefore, more likely to cause an acute coronary event. Fitch et al also found that age, HIV infection, and immune activation (particularly

Received and accepted 1 August 2013; electronically published 16 September 2013.

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**The Journal of Infectious Diseases** 2013;208:1729–31

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DOI: 10.1093/infdis/jit511

monocyte activation marker sCD163) were increased in HIV-infected women vs controls. These findings are in agreement with previous results from the same group that showed that HIV-infected men have a higher prevalence of atherosclerotic plaque and, in particular, noncalcified plaque associated with an increase of sCD163, compared with male controls [13, 14].

Whether monocyte activation is a causal pathway leading to increased coronary atherosclerosis, particularly vulnerable plaques, in the HIV population remains to be demonstrated, as their study, by design, did not address this question. HIV infection could, however, affect all steps of atherogenesis via monocyte disturbances [15], through the following 4 processes: enhanced monocyte activation, which is partially ameliorated during virological suppression; viremia-induced interferon- $\alpha$  production and adaptive T-cell responses; altered reverse transendothelial migration of monocyte-derived macrophages; and defective cholesterol efflux by HIV-infected macrophages, which is likely to promote foam cell accumulation in plaques, promoting plaque expansion and instability. Therefore, macrophages probably play a key role in HIV-related atherosclerosis. As previously mentioned, innate immune aging is increased in HIV-infected women compared with female uninfected controls (equivalent to women approximately 10 years older) [16]. An increasing number of studies have linked peripheral atherosclerosis with inflammation and immune activation in HIV-infected patients. Hsue et al [17], for example, reported that HIV-elite controllers (untreated patients with undetectable viral load and preserved CD4 T-cell count) had higher carotid intima media thickness than HIV-uninfected persons and thicknesses that were similar to those of all other HIV-infected groups, irrespective of the viral load or ART. In Hsue et al's study [17], C-reactive protein concentration was significantly higher in all HIV-infected groups than in the HIV-uninfected group. Chronic inflammation

may indeed be associated with early atherosclerosis in HIV-infected patients, most likely via endothelial dysfunction related to increased cytokine production (microbial translocation), cytomegalovirus immune response, and immune senescence. The results reported by Grinspoon et al [18] were in agreement with those from Hsue et al at the level of coronary atherosclerosis. In that study, sCD163 was higher in elite controllers than in HIV-negative controls.

Nevertheless, we must emphasize that the HIV-infected women included in the study by Fitch et al are at particularly high risk of CHD and appear representative of this specific population in Northern America, predominantly African Americans [11]. The high prevalence of active smokers (50%), diabetes mellitus (15%), obesity (mean  $\pm$  standard deviation body mass index,  $28 \pm 6$  kg/m<sup>2</sup>), intravenous drug users (5%), and cocaine users (10%) in the present cohort exposed those women to a high risk of acute coronary events and cardiac sudden death. The last 3 factors, along with immune activation, are not taken into account in calculated risk scores, and, therefore, new prevention tools for CHD are warranted in this population. Whether CTA could represent a useful and cost-effective routine test to prevent acute coronary events in this population needs further investigation. Moreover, the impact of cocaine use on coronary plaques is controversial. Lai et al observed the effects of cocaine on coronary plaques using CTA in HIV-infected African Americans [19–21]. They showed that cocaine use is associated with subclinical coronary atherosclerosis and the presence of calcified plaques [19, 20]. In contrast, ART and HIV replication were associated with noncalcified plaques in the same cohort [20, 21]. The acute and long-term effects of cocaine on coronary arteries can range from acute vasospasm, to arterial thrombus, to chronic arterial atherosclerotic aneurysms and plaques [22]. However, these effects are often intricate, with the potential to lead to difficulties in preventing coronary events in this setting.

The study by Fitch et al highlights the need for an important prevention strategy in this population since these subjects accumulate both traditional and emergent risk factors for CHD. The association of the growing epidemic of diabetes mellitus, due to steady increases in the rate of obesity, particularly among Black and Hispanic American women, along with increasing use of tobacco and cocaine, combined with HIV infection and ART, could, over the next decade, generate an explosive cocktail for cardiovascular diseases. The data reported by Fitch et al open many doors for physicians to discuss CHD prevention in HIV-infected women.

## Note

**Potential conflicts of interest.** F.B. has received honoraria or research support of Boehringer Ingelheim, Gilead Sciences, ViiV Healthcare, Merck, and Sanofi. A.C. has received honoraria or research support of Bayer, Bristol-Myers-Squibb (BMS), Boehringer Ingelheim, the RESeau Insuffisance CARDiaque (RESICARD) network, and Sanofi.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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