How to identify HIV-infected individuals at risk for atherosclerotic events?

Franck Boccara and Ariel Cohen

There is concern about coronary heart disease (CHD) in the HIV-infected population using antiretrovirals. Across Europe and North America, this population is at a higher risk of myocardial infarction (MI) than the general population [1–3], although the difference seems to diminish in recent years [4]. Consequently, identifying HIV-infected individuals at risk for CHD, and more broadly for all atherosclerotic cardiovascular disease (ASCVD) events including CHD and stroke, is desirable albeit extremely challenging.

In this issue of AIDS, the article of Zanni et al. [5] aimed at evaluating the concordance between the presence of high-risk morphology coronary plaques detected by coronary CT and the new ACC/AHA guidelines [6] for treating high cholesterol to reduce atherosclerotic cardiovascular (ASCV) risk in HIV-infected individuals in primary prevention.

Currently, the evaluation of ASCV risk in asymptomatic individuals is based on identification of several traditional risk factors including sex, age, tobacco, hypertension, diabetes mellitus, lipids parameters levels [low-density lipoprotein cholesterol (LDLc) and high-density lipoprotein cholesterol (HDLc)] and family history of premature CHD [7]. On the basis of these risk factors, risk estimators have been developed to help clinicians estimate risk of fatal and nonfatal CHD [8]. The cardiovascular risk scores available are based on validated cohort from the general population with a median age of occurrence of the first MI in men around 65 years. In contrast, the median age of occurrence of the first MI in the HIV population is younger than in the general population (50 years) [1].

Patients under 50 years old at MI onset in both the general and HIV-infected populations have fewer traditional cardiovascular risk factors than older patients (higher rate of tobacco use) [9–11]. In the PACS-HIV study [12] comparing HIV-infected and uninfected patients with a first episode of acute coronary syndrome (mean age 49 ± 9.4 years; 94% were men), 40% of the entire cohort have zero or one traditional risk factor, with no difference between the two groups (data not published). The risk of CHD in the HIV-infected population is influenced not only by traditional cardiovascular risk factors, which are highly prevalent in this population (particularly tobacco), but also by other emergent risk factors such as illicit drugs use, the impact of long-term exposure to antiretroviral therapy (ART) and the effect of HIV itself [1]. However, these emergent risk factors are not included in the available cardiovascular risk calculators. Subsequently, the young age of occurrence of MI coupled with the lowest rate of traditional risk factors associated with emergent risk factors in the HIV-infected population leads to the underestimation of cardiovascular risk with the traditional cardiovascular risk scores.

The DAD study group found that the Framingham risk score underestimates the risk of MI in the HIV-infected
population [13] as well as in the young general population. The same group developed an HIV-specific cardiovascular risk calculator including antiretroviral drugs exposure [14]. For this group, the DAD score model estimated outcomes more accurately than the Framingham risk score. However, the DAD score has not been validated in other cohorts.

The new ACC/AHA guidelines have engendered much discussion and controversy [6]. Notably, the absence of an LDLc threshold for initiating and managing the intensity of statin therapy has been a source of debate. These thresholds are intended to guide physician about when and how to treat high-risk individuals and to help patients with observance and adherence to this therapy. Moreover, the new ASCV score seems to overestimate cardiovascular risk in both the North American and the European populations [15]. For instance, in a Dutch population (aged 55 years or older), the proportions of individuals eligible for statins differed substantially among the different guidelines. The new ACC/AHA guidelines recommend statins for nearly all men (96%) and two-thirds of women, a substantially larger percentage than with the ATP-III (52% in men and 36% in women) or the European Society of Cardiology (ESC) guidelines [16] (66% in men and 39% in women). Moreover, in this study, all three risk models provided poor calibration and moderate to good discrimination. The performance (or accuracy) of these three risk estimation models concerning HIV-infected population should be evaluated in national and international HIV cohorts. Although no risk assessment algorithm will ever be perfect, these approaches will continue to be updated and improved, as more data become available.

On the basis of the article by Zanni et al. [5] in this issue of AIDS, it is reasonable to estimate that around 25% of HIV-infected patients would be eligible for statins with the new ACC/AHA guidelines, whereas the majority of HIV-infected individuals would be classified as low and intermediate risk and would not receive statins. The new ACC/AHA guidelines recommend performing the ASCV risk score in individuals between 40 and 75 years old if they are not included in the three following groups: prior ASCVD, LDLc more than 190 mg/dl or diabetic individuals. This emphasizes the importance of a lifetime risk score rather than an ASCV risk predicting 10-year risk. In fact, the median age of HIV-infected individuals in developed countries is around 40 years old and half of this population would not be evaluated with the new ASCV risk score. Some young individuals may have extensive previous exposure to increased LDLc. This young population may present subclinical atherosclerotic disease that would benefit from high intensity statin therapy. However, for these young individuals, the new guidelines would recommend either moderate intensity or no statin therapy. Whether new tools, such as biomarkers of infraclinical atherosclerosis, coronary artery calcium scoring, imaging of the morphology of coronary plaque and/or an ankle–brachial index, would improve cardiovascular risk stratification and prediction of ASCVD remains questionable [6]. Measurement of cardiovascular biomarkers may potentially provide additional risk stratification beyond conventional risk factors. However, the challenge is translating biomarker measurements into treatment strategies that will reduce long-term ASCV risk. Among asymptomatic young HIV-infected individuals particularly those at low or intermediate cardiovascular risk, early detection of subclinical coronary atherosclerosis, which may potentially cause substantial cardiac events, is of immediate concern [17,18].

In this issue of AIDS, Zanni et al. [5] compared the impact of the new 2013 ACC/AHA and the 2004 ATP III guidelines on the initiation of statins in HIV-infected individuals. Researchers analysed the two guidelines’ statin therapy recommendations among participants with and without subclinical high-risk morphology (HRM) coronary plaques as determined by coronary computed tomography angiogram (CTA). In the cohort of 108 HIV-infected individuals without known CVD, the authors found that the newest guidelines recommend statin therapy in a higher number of HIV-infected individuals than in the old guidelines (21 vs. 8%). Moreover, individuals with HRM coronary plaques would have more indication to statin therapy with the new guidelines (26 vs. 10%). They also found that the new ASCV score, ethnicity, family history of premature CVD and ART duration were associated with HRM coronary plaques in multivariate analysis. However, the authors conclude that even with the new guidelines, the majority of individuals with HRM coronary plaques would not be recommended statin therapy. Therefore, the authors point out the potential utility of HRM coronary plaque detection in HIV-infected individuals in order to better stratify the cardiovascular risk in this specific population.

Although the present study suggests performing images of the coronary arteries in order to identify HRM coronary plaques, whether doing so would identify HIV-infected individuals at a higher risk of cardiovascular events who would benefit from statins remains hypothetical. In fact, increasingly studies tend to differentiate calcified (stabilized plaque) and noncalcified coronary plaques that are more prone to rupture. On the patient level, this enables differentiation of vulnerable patients with calcified plaque and vulnerable patients with noncalcified plaque [19,20]. However, coronary CTA does not yet have a validated role in the screening of asymptomatic individuals [21] and its availability is poor in many different countries. Moreover, the clinical benefit of statins on the regression of vulnerable plaque independently of LDLc level has not yet been proven. In particular, it would be of interest to better stratify the cardiovascular risk of the HIV-infected population who are both young and at an increased risk of
MI as compared with the general population [22]. A randomized clinical trial including a large cohort of such intermediate HIV-infected individuals, stratified by the absence or presence of HRM coronary plaques, evaluating the clinical benefit of a high-intensity statin therapy over a long period could provide benefit to this population. However, early prevention of cardiovascular risk in early identified high-risk HIV-infected individuals based on aggressive prevention (lifestyle modifications, antihyper- tension and statin therapies, modification of antiretroviral drugs) and screening strategies is currently warranted and represent till now the cornerstone of our practice.

Further studies are needed to investigate whether coronary CTA could help identify young, asymptomatic individuals with subclinical coronary atherosclerosis who might benefit from intensified risk factor modification to prevent or delay the onset of clinical disease. New stratification approach such as personalized medicine associating genomic, metabolomic and morphologic phenotypes is still a long way off.

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Conflicts of interest

There are no conflicts of interest.

References