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EDITORIAL COMMENT

"Through the Looking Glass"

Imaging Cardiovascular Risk in Patients With HIV*

Ronak Rajani, BM, DM,[a] Roberta Lima Brum, MD,[b] Vitaliy Androshchuk, MBBCh[c]

Infection with HIV affects approximately 45 million people worldwide, making it a major ongoing public health challenge.[1] Although antiretroviral therapy has improved the quality of life and survival of patients living with HIV (PWH), ongoing challenges remain with the management of a high level of associated comorbidities and increased prevalence of cardiovascular disease (CVD). Contemporary data indicate an almost 2-fold increased risk of CVD which is usually experienced at a younger age than people without HIV infection.[2] This increased risk is likely related to a complex interplay between immune- and inflammatory-mediated activity with HIV infection, increased cardiovascular risk factors in PWH, antiretroviral therapy–mediated metabolic effects and specific socioeconomic factors observed in this population.

Given the high rates of CVD in PWH, there has been considerable interest in the use of international risk prediction tools to better identify those at risk to facilitate the early use of primary preventative strategies. Perhaps not surprisingly, these almost invariably have a poor discriminatory ability in predicting which PWH are at increased risk or not. This relates to the historical nature of the cohorts used to derive these equations, where risk factor profiles and primary preventative strategies were not equivalent to the contemporary era. Furthermore, some did not account for ethnicity, or were derived from largely Caucasian populations, and few accounted for the unique milieu of CAD risk factors that PWH have. The use of additional biomarkers such as lipoprotein (a), highly sensitive C-reactive protein, D-dimer, and coronary calcium scoring offer potential, but data remain limited on their incorporation into specific risk prediction algorithms and prospective clinical end points in PWH.

In this issue of *JACC: Advances*, Karady et al[3] provide valuable insight into the prevalence and phenotype of coronary atheroma in asymptomatic PWH compared to 2 different cohorts of patients without HIV. The PWH comprised 755 of 7,769 patients without cardiovascular symptoms from REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV) at low-moderate risk of CVD.[4] The comparison cohorts of (people without HIV infection) were low-intermediate risk asymptomatic patients from the SCAPIS (Swedish Cardiopulmonary Bioimage Study) and patients with stable angina from the PROMISE (PROspective Multicenter Imaging Study for Evaluation of chest pain).

The principal observations from this study are first that PWH has a greater prevalence of plaque (48.5%) compared to an asymptomatic population (40.3%) and a similar burden to a higher-risk cohort of symptomatic patients across all age strata. This finding being consistent across women and men. The second main finding is that noncalcified plaque follows a similar pattern with there being a similar prevalence of noncalcified plaque in PWH across all age groups to patients presenting with chest pain. Finally, in patients who had a coronary calcium score of 0 AU, there was substantially more plaque presence across all age groups compared to the other

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From the [a]Faculty of Life Sciences & Medicine, School of Biomedical Engineering and Imaging Sciences, King's College London, London, United Kingdom; [b]Department of Genitourinary Medicine and HIV, Chelsea and Westminster Hospital NHS Foundation Trust, London, United Kingdom; and the [c]Faculty of Life Sciences & Medicine, School of Cardiovascular Medicine & Sciences, King's College London, London, United Kingdom.

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cohorts (11% in those aged 40-44 years up to 24% in those aged 55-59 years). These findings corroborate those of prior studies that evaluated the association between HIV infection and the presence of coronary atherosclerotic plaque. In a systematic review and meta-analysis of 9 studies and 1,229 patients with HIV, the noncalcific coronary artery plaque was >3-fold higher in patients with HIV compared with the controls (58% vs 17%; OR: 3.26; 95% CI: 1.30-8.18).[5] More recently, a meta-analysis of 27 studies with 6,699 HIV-positive and 4,168 HIV-negative participants showed that the prevalence of noncalcified coronary plaque was more than double in HIV-positive vs HIV-negative patients (49% vs 20%, respectively).[6]

The current work adds to our current understanding of cardiovascular risk in PWH, but there are several limitations that the authors have acknowledged. Perhaps most importantly is that all the 3 cohorts were heterogenous. All 3 studies had different inclusion and exclusion criteria, geographic regions of enrolment, and different levels of collected baseline demographic data. For instance, the REPRIEVE cohort had less women and was made up of 35.4% Black/African Americans and 24.1% Hispanics compared to 11.8% and 6.5% in PROMISE. No data were available for SCAPIS. Furthermore, the rate of current smokers was greater in REPRIEVE than either of the 2 other cohorts. Finally, HIV status was not recorded in SCAPIS or PROMISE, whereas in REPRIEVE, having HIV infection was uniform. Without multivariable models and propensity matching the findings of the current study may be considered observational. It is also noteworthy that although the prevalence of any plaque and noncalcified plaque was similar to PROMISE, and greater than SCAPIS, the rates of obstructive disease was the lowest in REPRIEVE at 3.3% vs 4.7% SCAPIS and 10.8% in PROMISE. It is also unknown whether all 3 cohorts had an equivalent clinical assessment of symptoms. Although there are clear challenges in extracting plaque specific data from the 3 groups, it would have been interesting to know number of plaques, their distribution, plaque volume stenosis severity and presence of absence of high-risk plaque features within the 3 populations. Finally, it remains unknown as to whether the difference in plaque prevalence translated to an actual increased risk since no follow-up data were available.

Notwithstanding these limitations, there are several important clinical messages from these data that the authors are to be congratulated on. Given the challenges with existing risk prediction models, the authors reaffirm the notion that existing methods should be used with caution in PWH. These patients in turn may exhibit premature coronary aging by almost 10 years and have a similar prevalence of noncalcified plaque to symptomatic patients presenting with chest pain. This finding is of relevance to PWH who have increased cardiovascular risk. Given that noncalcified plaque is more prone to acute erosion and rupture this may potentially explain the high rates of cardiovascular events observed in PWH. This observation also highlights the frailty of using coronary artery calcium scoring and the ASCVD risk score for evaluating risk in PWH. Karady et al show higher prevalence rates of plaque across low and intermediate ASCVD risk groups (<5% and 5-7.5%, respectively) compared to PROMISE and SCAPIS. In patients with a coronary calcium score of 0 Agatston units, PWH had higher prevalence rates of plaque across all age groups, and ASCVD risk categories, than the SCAPIS and PROMISE cohorts.

Collectively these findings urge caution to clinicians who rely on population risk estimators and coronary calcification scoring for risk prediction in PWH. The role of direct coronary CTA as an imaging biomarker for better establishing risk for these patients is appealing but needs to be accompanied by careful patient selection, randomized controlled trial data, and evidence that specific interventions can impact upon patient outcomes. The alternative to an imaging-based patient specific approach is a population-based strategy of primary prevention with statins in PWH as advocated in the REPRIEVE trial. This randomized controlled trial of 7,769 PWH was stopped early following an observed MACE reduction of 35% over a median of 5.1 years in patients who were randomised to receive Pitavastatin 10 mg once daily.[4] However, as the findings of the current study demonstrate, up to 75% of PWH have no coronary plaque. A policy of indiscriminate statin use may result in lifelong overtreatment for some patients who truly are at low risk. Equally important is the liability to reduce precision-based interventions who are at very high risk. In this instance functional testing, more aggressive lipid modification, antiplatelet therapy and/or anti-inflammatory treatment may inadvertently be withheld.

Overall, further research is needed to elucidate the complex and poorly understood pathophysiology of HIV-related atherosclerosis. Although traditional risk factors are important contributors to CVD, the increased risk in PWH persists even after adjustment for these variables. Other possible mechanisms contributing to accelerated atherosclerosis need to be explored. This includes HIV-induced endothelial

dysfunction, immunodeficiency, cytomegalovirus co-infection, immune cell activation and chronic inflammation. As a result, current guidelines advocate treating HIV as a CVD enhancer and favour risk factor modification in these patients with diet and lifestyle changes, exercise, and consideration of statin therapy. Additional trials are warranted to establish whether enhanced primary prevention strategies, such as aspirin and or colchicine along with statin therapy, have a role in attenuating the risk of CVD in the setting of HIV infection.

In conclusion, Karady et al[3] provide a timely reminder that PWH have an increased prevalence of coronary plaque and noncalcified plaque, than otherwise would be suggested by conventional risk scoring assessments and coronary calcium scoring. Coronary CTA provides a valuable tool for understanding increased cardiovascular risk in PWH. Although, it is alluring to contemplate a role for coronary CTA in patient-specific screening to enable targeted primary preventative measures, this strategy lacks current validation. We eagerly await data from other ongoing studies evaluating the role of coronary CTA in other asymptomatic cohorts of PwoH. Meanwhile, along with statin use, all asymptomatic PWH are likely to benefit from careful individualised risk assessment, aggressive risk factor modification and dietary and lifestyle advice.

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ADDRESS FOR CORRESPONDENCE: Prof Ronak Rajani, Cardiovascular Directorate, St Thomas' Hospital, Westminster Bridge Road, London SE1 7EH, United Kingdom. E-mail: Ronak.Rajani@gstt.nhs.uk.

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