Imaging to End Points
Cardiovascular Disease Risk Assessment in HIV

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The remarkable evolution of the HIV epidemic from a near uniformly fatal condition to a chronic viral infection now managed for many patients with 1 pill once a day marks one of the great accomplishments of medicine in recent decades. Life expectancy estimates for people living with HIV with access to antiretroviral therapy are beginning to approach life expectancy estimates of the general population.[1] However, not long after the widespread use of combination antiretroviral therapy for the treatment of HIV, clinicians began to recognize undesirable effects of HIV therapy such as dyslipidemia and alterations in body fat distribution. These observations stimulated considerable attention from HIV providers and researchers to identify and understand cardiovascular disease (CVD) risk associated with HIV and its therapy.

See Article by Janjua et al

Early large cohort studies designed to evaluate CVD outcomes in the context of HIV demonstrated an increased risk of myocardial infarction in association with increasing years of antiretroviral therapy exposure, and observational patient registries showed that rates of myocardial infarction in people living with HIV are increased compared with uninfected contemporaries.[2,3] Subsequent cohort studies have consistently validated these observations, identifying ≈1.5-fold higher risk of acute myocardial infarction in people living with HIV compared with uninfected controls. In these studies, the enhanced risk of CVD associated with a diagnosis of HIV was found to be independent of traditional CVD risk factors, which are often enriched in HIV-infected populations.[4,5] Considerable efforts are underway to optimize CVD risk assessment and to characterize the unique contribution that HIV and immune activation play in the pathophysiology of CVD in people living with HIV. Recent estimates for the aging characteristics of the HIV-infected population suggest that by 2030 as many as 73% of people living with HIV will be over the age of 50 years[6]; therefore, the prevalence of CVD, an anticipated consequence of aging, can be expected to rise. Strategies for accurate identification of at-risk patients and development of effective approaches to CVD risk reduction will become increasingly important for the care of people living with HIV in the future.

In the current issue of *Circulation: Cardiovascular Imaging*, Janjua et al[7] present the results of a study that leverages a large multi-institutional patient data registry to expand our current knowledge of CVD risk in HIV and provides an important link between an observed biomarker of atherosclerosis, namely carotid plaque, and subsequent CVD events. This retrospective study used available data from diagnostic contrast-enhanced computed tomography (CT) scans from people living with HIV without history of atherosclerosis (n=209) and similar non-HIV–infected controls (n=168), to compare the presence and characteristics of carotid plaque and to determine the relationship between carotid plaque and subsequent CVD events.

The study shows that people living with HIV had significantly higher rates of any carotid plaque, noncalcified carotid plaque, and high-risk plaque compared with controls. However, there were important differences between the HIV group and controls. The majority (60%) of HIV subjects had ≥1 traditional CVD risk factors, whereas 64% of controls had no CVD risk factors identified ($P<0.001$). In addition, 25% of the HIV subjects had a history of cocaine exposure compared with only 4% of controls, and hepatitis C infection was present in 18% of the HIV subjects. Nontraditional risk factors for atherosclerotic disease such as cocaine and chronic hepatitis C infection are associated with carotid plaque in HIV.[8] Further, chronic cocaine use was associated with a 2-fold increased risk of coronary artery plaque in HIV, independent of traditional risk factors and antiretroviral therapy exposure.[9] Differences in routine practices for inquiring about and documenting traditional CVD risk factors and substance use by providers caring for people living with HIV and those without HIV infection may create reporting bias and underestimate the prevalence of these risk factors in the control group. Nonetheless, the mismatch in traditional CVD risk factors, as well as cocaine exposure, may account for the much of the observed difference between groups in the presence of carotid plaque.

The present report may not have had optimally matched controls or been sufficiently large to tease out the contribution of non-HIV risk factors toward the prevalence of carotid plaque; however, the novel and informative observation that carotid plaque predicted later CVD events advances the field of CVD investigation in HIV. In multivariable analysis adjusted for traditional CVD risk factors, the presence of any carotid plaque among HIV subjects was associated with an increased risk of a CVD events (hazard ratio, 2.84; confidence

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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(*Circ Cardiovasc Imaging*. 2017;10:e007120. DOI: 10.1161/CIRCIMAGING.117.007120.)

***Circ Cardiovasc Imaging* is available at http://circimaging.ahajournals.org**

DOI: 10.1161/CIRCIMAGING.117.007120

interval, 1.05–7.63; *P*=0.03). Similar associations were observed between noncalcified carotid plaque and high-risk plaque and the risk of subsequent CVD events in HIV subjects. These data are consistent with research in the general population. For example, Cao et al[10] showed that the presence of intermediate- and high-risk carotid plaque on carotid ultrasound conferred approximately a 2-fold increased risk of CVD event after adjustment for traditional CVD risk factors in the Cardiovascular Health Study, a study of adults (≥65 years) without known CVD. In the younger MESA cohort (Multi-Ethnic Study of Atherosclerosis), carotid plaque score was also a significant predictor of CVD events after adjustment for traditional risk factors (hazard ratio, 1.27; 95% confidence interval, 1.16–1.40; *P*<0.001).[11] The observed link between asymptomatic carotid plaque and subsequent CVD events in a cohort of people living with HIV supports the potential use of carotid plaque measurements as a biomarker of CVD risk stratification and CVD risk reduction.

The overwhelming majority of HIV research evaluating carotid atherosclerosis and carotid intima-media thickness has used ultrasound technology and not CT imaging, as used in the current report. Although both are noninvasive imaging approaches, the additional burden of radiation exposure and contrast administration limits the broader appeal for the use of CT as a general screening tool in large populations. Radiation risk is further accentuated by the presence of the thyroid gland in the field of view and may explain the conspicuously low number of carotid CT studies related to atherosclerosis in asymptomatic populations, particularly those that may require follow-up. Therefore, it would be difficult to justify using this technology as a means of identifying or monitor asymptomatic HIV subjects at high risk for cardiovascular events.

Admittedly, Janjua et al[7] did not prospectively apply carotid CT as a general screening tool. The investigators evaluated carotid CT retrospectively among a population with clinically indicated neck CT data, but additional limitations to this approach exist. The use of <3 mm spotty calcifications and 1 mm diameter foci of low attenuation (<40 HU) as signs of high-risk plaque would require higher resolution acquisitions (more radiation) and perfectly timed contrast administration. The latter component is even more critical as some high-risk plaques may enhance or washout rapidly depending on the inflammatory status in addition to the wide range of variability in densities noted in atherosclerotic plaque.[12–14] Many of the challenges associated with CT are overcome by high-field magnetic resonance imaging which has improved signal to noise and spatial and temporal resolution.[15–17] The technical versatility of magnetic resonance imaging also allows for plaque characterization.[12,14] The relative technical simplicity, mobility, and lower cost of ultrasound places this modality at an advantage for claustrophobic patients and locations that might not have the magnetic resonance imaging capabilities.[12,14] Given these factors and available alternatives, translation of the findings of this study into clinical practice may be challenging.

The era of big data has arrived, and its application in health care to infectious diseases and HIV are underway.[18] Although carotid CT may not be the optimal approach to prospective CVD risk screening, as access to large patient data registries with high-quality, reliable medical information and imaging data becomes more readily available, additional studies using retrospective data of this nature will be feasible. Triant et al[3] completed one of the earlier studies to use this approach to effectively demonstrate an increased risk of myocardial infarction in HIV relative to a general contemporary population. The application of this strategy to evaluate the role of incidental carotid plaque identified by CT to predict CVD events in HIV provides valuable new data that may be used to inform future research and management of CVD risk stratification and risk reduction in HIV.

As the HIV population ages, CVD associated morbidity and mortality is expected to rise. Multiple large observational cohorts have established a 1.5- to 2-fold increased risk of CVD in people living with HIV compared with uninfected controls. Excess CVD observed in HIV is likely attributable to multiple factors including traditional CVD risk factors, HIV-related inflammation and immune activation, and possible off-target effects of HIV therapy. Carotid plaque in the general population is predictive of CVD events, and Janjua et al[7] demonstrate that this relationship also holds true in HIV subjects. Research efforts continue to focus on identification of biomarker and imaging correlates of CVD in HIV, and large prospective trials such as REPRIEVE (Randomized Trial to Prevent Vascular Events in HIV), a study of pitavastatin to reduce incident CVD, are underway to establish optimal strategies to address the excess CVD risk associated with HIV infection.

Sources of Funding

This work was funded in part with resources from the Intramural Research Program of the National Institute of Allergy and Infectious Diseases.

Disclosures

Dr Hadigan is a coprincipal investigator with Dr Grinspoon on a collaborative UO1 grant investigating the use of tesamorlin for nonalcoholic fatty liver disease in HIV (U01 AI 115711-01).

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KEY WORDS: Editorials ■ atherosclerosis ■ cocaine ■ myocardial infarction ■ prevalence ■ risk factors

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Circ Cardiovasc Imaging. 2017;10:
doi: 10.1161/CIRCIMAGING.117.007120
Circulation: Cardiovascular Imaging is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 1941-9651. Online ISSN: 1942-0080