# Editorial

# Cardiovascular Disease Imaging in HIV

## Novel Phenotypes and New Targets for Risk Reduction

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Because of the success of new, potent antiretroviral therapy, life expectancy has significantly improved among HIV-infected patients.[1] However, an opposite trend has been noted for cardiovascular disease (CVD) among patients with HIV. Cardiovascular morbidity and mortality have increased since 1999,[2] and CVD has become a significant public health issue among HIV-infected patients in whom rates of myocardial infarction and stroke may be up to twice as high as compared with similarly age-matched patients in the general population.[3,4] Although HIV-infected patients may exhibit increases in specific CVD risks, including excess smoking rates, higher rates of insulin resistance and diabetes mellitus, and dyslipidemia, carefully controlled studies demonstrate that the excess rates of CVD persist after controlling for traditional risks.[3,4] One important question for the HIV community is whether statins work to improve CVD rates and whether traditional algorithms designed for the non-HIV population can be used to identify those patients with HIV who might benefit from statin therapy.

### See Article by Phan et al

Among patients with HIV, an important concern is whether risk prediction algorithms that rely on traditional risk factors, such as the newly recommended American College of Cardiology/American Heart Association (ACC/AHA) guidelines, can accurately identify those patients with HIV who should be recommended for statin therapy. Retrospective cohort studies have been inconsistent in determining the use of these equations. Some studies suggest that the new 2013 ACC/AHA algorithm, that was not determined based on data from patients with HIV, may indeed underestimate CVD rates, especially in young patients at lower risk thresholds, but also potentially overestimate at higher risk thresholds.[5] In addition, key questions of sex and racial differences remain as to the use of these equations. Uniquely, relative CVD rates (HIV versus control) are higher in women,[3] and the ideal risk prediction equation must be able to accurately identify women and other subpopulations of HIV at highest risk. Notably, adding HIV-specific risk did not improve model performance in these studies.[5] Together, these prior studies beg the questions of the unique, nontraditional mechanisms that may explain the observed increased event rates among patients with HIV, and how we may identify those patients at risk for CVD in HIV, and ultimately how we may treat such patients.

Imaging of CVD phenotypes in HIV may play an especially critical role to identify patients with subclinical CVD, at risk for increased CVD events, in whom traditional risk scores may be inaccurate. Research suggests that CVD in HIV is characterized by arterial inflammation and related to immune activation.[6] Initiation of antiretroviral therapy restores immune function but does not normalize indices of immune activation, including activated T cell and inflammatory monocyte subsets, and may be insufficient to reduce arterial inflammation.[7] Recent data using novel macrophage-specific imaging agents extend our knowledge of the basis of this disease and suggest significant macrophage infiltration in the vascular system.[8]

In this issue of *Circulation: Cardiovascular Imaging*, Phan et al[9] report a study supporting the notion that imaging of CVD phenotype may be especially valuable in patients with HIV. The authors demonstrate a high prevalence, 50%, of carotid plaque among their young cohort of patients with HIV, age 43 years, which is similar to asymptomatic noninfected patients who are 2 decades older [(62.2 [10.2] years old); 46.7% with carotid plaque.[10]] These data expand a growing body of literature describing the unique nature of CVD and using advanced cardiovascular imaging to help us to extend our understanding of the disease. Similar to the study of Phan et al,[9] other studies using coronary computed tomography angiography have demonstrated an increased presence and extent of coronary artery disease, including noncalcified coronary plaque[11,12] and high-risk coronary plaque features, such as low attenuation and positive remodeling, accompanied by increased indices of immune activation.[13] Overall, these data suggest that an increase in systemic inflammation and immune activation manifests itself in a premature CVD phenotype, including disease in large and small vascular beds in patients with HIV.

In addition, Phan et al[9] demonstrate the value of imaging by showing that only 32% of those with plaque would have been recommended for statins under the new guidelines, reinforcing the data of Zanni et al[14] demonstrating that the new guidelines would only recommend statins for 26% of patient with HIV with high-risk coronary plaque morphology. Data from the current study concur with prior data in HIV-infected and noninfected populations that the new 2013 ACC/AHA guidelines identify more HIV patients with subclinical CVD

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for statins than the Adult Treatment Panel III guidelines.[15] Of note, Phan et al[9] demonstrate that the presence of plaque, not the risk prediction scores, predicted overall mortality. In contrast, the new guidelines fare far better in non-HIV populations.[9] For example, the proportion of subjects with significant coronary artery calcium who would have been recommended for statin therapy increased from 34% (using the Adult Treatment Panel III) to 85% under the new guidelines, thus identifying a much higher proportion of high-risk phenotype than in HIV-infected populations.[15] However, differences in the presentation of subclinical plaque between HIV and non-HIV patients, for example, the presence of more noncalcified plaque in HIV, demand that optimal imaging strategies be developed for the HIV group. In this regard, the current study emphasizes that high-value imaging may provide a mechanistic link between biomarkers and events so important for understanding increased CVD risk associated with nontraditional risk factors, such as inflammation.

One important question for the HIV community is whether statins work to improve CVD rates and whether information from imaging studies may be useful to identify those patients with HIV who might benefit from statin therapy. Statins demonstrate pleiotropic effects to improve immune function in patients with HIV, including monocyte activation indices, as well as indices of arterial inflammation,[16,17] and have been shown to reduce noncalcified coronary plaque in this population.[17] The effects on low-density lipoprotein, inflammatory and immune indices make statins an appealing potential therapeutic in HIV. However, prospective data from a large randomized control study are lacking to determine whether statins will be useful for primary prevention of CVD in HIV, what the mechanisms of this effect might be, for example, if because of low-density lipoprotein lowering or other pleiotropic effects to improve immune activation and inflammation, and whether effects on subclinical atherosclerotic disease will mirror and predict improved CVD rates from statins.

The Randomized Trial to Prevent Vascular Events in HIV trial (REPRIEVE [NCT02344290]), begun in 2015, will answer critical questions about the use and mechanisms of statin effects to prevent major adverse cardiovascular events in HIV. In this regard, the trial will also provide the first prospective data on the use of the 2013 ACC/AHA guidelines to identify adjudicated major adverse cardiovascular events. REPRIEVE will enroll 6500 patients with HIV in ≈130 sites around the world. Patients with HIV without known CVD are eligible and randomized to pitavastatin or placebo and followed for major adverse cardiovascular events, as well as key safety variables, including liver and muscle function, as well as critical secondary end points, including AIDS events and sex effects. Pitavastatin was chosen because it does not interfere with current antiretroviral therapy regimens and is glucoronidated rather than metabolized via the cytochrome P450 system. Recent studies suggest that pitavastatin is highly potent with respect to immune indices, with larger effects to reduce sCD14, oxidized low-density lipoprotein, and lipoprotein-associated phospholipase A2 than pravastatin.[18] REPRIEVE uses the ACC/AHA guidelines for initial assessment of eligibility, permitting enrollment of those with low to moderate risk. REPRIEVE is anticipated to complete enrollment in 2018 and will inform the field as to whether statins are useful for primary CVD prevention, whether they reduce key immune activation indices, and whether they are safe in HIV.

Embedded within REPRIEVE is an important mechanistic substudy in which 800 subjects will undergo computed tomography angiography for coronary plaque assessment at baseline and after 2 years, with detailed immunologic phenotyping, including flow cytometry for inflammatory monocyte and T cell subsets. Data from REPRIEVE will provide information on whether the improvement in CVD rates from statins is due exclusively to low-density lipoprotein reduction or other mechanisms and whether statins reduce subclinical coronary artery disease commensurate with an effect on events. The substudy may also help us to learn whether the presence of plaque is linked to future events and whether these events can be modified by statins. Moreover, REPRIEVE will determine whether specific information, including the presence of subclinical plaque, can be used to improve existing risk prediction equations in HIV. There is a critical need to perform additional research in patients with HIV to understand the unique mechanisms, predictors, and treatments for CVD in HIV. Studies designed to obtain such data in HIV, with their concomitant focus on detailed imaging, may also serve as a model for investigating other inflammatory diseases characterized by increased CVD rates.

## Disclosures

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## References

1. Lohse N, Obel N. Update of survival for persons with HIV infection in Denmark. *Ann Intern Med*. 2016;165:749–750. doi: 10.7326/L16-0091.
2. Feinstein MJ, Bahiru E, Achenbach C, Longenecker CT, Hsue P, So-Armah K, Freiberg MS, Lloyd-Jones DM. Patterns of cardiovascular mortality for HIV-infected adults in the United States: 1999 to 2013. *Am J Cardiol*. 2016;117:214–220. doi: 10.1016/j.amjcard.2015.10.030.
3. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007;92:2506–2512. doi: 10.1210/jc.2006-2190.
4. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D, Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff M, Watson C, Armah KA, Doebler D, Bryant K, Justice AC. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173:614–622. doi: 10.1001/jamainternmed.2013.3728.
5. Feinstein MJ, Nance RM, Drozd DR, Ning H, Delaney JA, Heckbert SR, Budoff MJ, Mathews WC, Kitahata MM, Saag MS, Eron JJ, Moore RD, Achenbach CJ, Lloyd-Jones DM, Crane HM. Assessing and refining myocardial infarction risk estimation among patients with human immunodeficiency virus: a study by the Centers for AIDS Research Network of Integrated Clinical Systems. *JAMA Cardiol*. 2017;2:155–162. doi: 10.1001/jamacardio.2016.4494.
6. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J, Grinspoon SK. Arterial inflammation in patients with HIV. *JAMA*. 2012;308:379–386. doi: 10.1001/jama.2012.6698.
7. Zanni MV, Toribio M, Robbins GK, Burdo TH, Lu MT, Ishai AE, Feldpausch MN, Martin A, Melbourne K, Triant VA, Suchindran S, Lee

H, Hoffmann U, Williams KC, Tawakol A, Grinspoon SK. Effects of antiretroviral therapy on immune function and arterial inflammation in treatment-naive patients with human immunodeficiency virus infection. *JAMA Cardiol*. 2016;1:474–480. doi: 10.1001/jamacardio.2016.0846.

8. Zanni MV, Toribio M, Wilks MQ, Lu MT, Burdo TH, Walker J, Autissier P, Foldyna B, Stone L, Martin A, Cope F, Abbruzzese B, Brady T, Hoffmann U, Williams KC, El-Fakhri G, Grinspoon SK. Application of a novel CD206+ macrophage-specific arterial imaging strategy in HIV-infected individuals. *J Infect Dis*. 2017;215:1264–1269. doi: 10.1093/infdis/jix095.
9. Phan BAP, Weigel B, Ma Y, Scherzer R, Li D, Hur S, Kalapus SC, Deeks S, Hsue P. Utility of 2013 American College of Cardiology/American Heart Association cholesterol guidelines in HIV-infected adults with carotid atherosclerosis. *Circ Cardiovasc Imaging*. 2017;10:e005995. doi: 10.1161/CIRCIMAGING.116.005995.
10. Gepner AD, Young R, Delaney JA, Tattersall MC, Blaha MJ, Post WS, Gottesman RF, Kronmal R, Budoff MJ, Burke GL, Folsom AR, Liu K, Kaufman J, Stein JH. Comparison of coronary artery calcium presence, carotid plaque presence, and carotid intima-media thickness for cardiovascular disease prediction in the multi-ethnic study of atherosclerosis. *Circ Cardiovasc Imaging*. 2015;8. doi: 10.1161/CIRCIMAGING.114.002262. http://jaha.ahajournals.org/content/6/2/e005179.
11. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, Nasir K, Grinspoon SK. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2010;24:243–253. doi: 10.1097/QAD.0b013e328333ea9e.
12. Post WS, Budoff M, Kingsley L, Palella FJ Jr, Witt MD, Li X, George RT, Brown TT, Jacobson LP. Associations between HIV infection and subclinical coronary atherosclerosis. *Ann Intern Med*. 2014;160:458–467. doi: 10.7326/M13-1754.
13. Zanni MV, Abbara S, Lo J, Wai B, Hark D, Marmarelis E, Grinspoon SK. Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. *AIDS*. 2013;27:1263–1272. doi: 10.1097/QAD.0b013e32835eca9b.
14. Zanni MV, Fitch KV, Feldpausch M, Han A, Lee H, Lu MT, Abbara S, Ribaudo H, Douglas PS, Hoffmann U, Lo J, Grinspoon SK. 2013 American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-infected patients with/without subclinical high-risk coronary plaque. *AIDS*. 2014;28:2061–2070. doi: 10.1097/QAD.0000000000000360.
15. Pursnani A, Massaro JM, D'Agostino RB Sr, O'Donnell CJ, Hoffmann U. Guideline-based statin eligibility, coronary artery calcification, and cardiovascular events. *JAMA*. 2015;314:134–141. doi: 10.1001/jama.2015.7515.
16. Funderburg NT, Jiang Y, Debanne SM, Storer N, Labbato D, Clagett B, Robinson J, Lederman MM, McComsey GA. Rosuvastatin treatment reduces markers of monocyte activation in HIV-infected subjects on antiretroviral therapy. *Clin Infect Dis*. 2014;58:588–595. doi: 10.1093/cid/cit748.
17. Lo J LM, Ihenachor E, Wie J, Looby S, Oh J, Fitch K, Zimmerman C, Hwang J, Abbara S, Plutzky J, Robbins G, Tawakol A, Hoffmann U, Grinspoon S. Statin therapy reduces coronary artery plaque volume and improves high risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomized double-blind placebo-controlled trial. *Lancet HIV*. 2015;2(2):e52–e63.
18. Toribio M, Fitch KV, Sanchez L, Burdo TH, Williams KC, Sponseller CA, McCurdy Pate M, Aberg JA, Zanni MV, Grinspoon SK. Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV. *AIDS*. 2017;31:797–806. doi: 10.1097/QAD.0000000000001427.

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