HHS Public Access

Author manuscript

JAMA Cardiol. Author manuscript; available in PMC 2018 January 10.

Published in final edited form as:

JAMA Cardiol. 2016 July 01; 1(4): 481–482. doi:10.1001/jamacardio.2016.1169.

Inflammation and Arterial Injury in Individuals With Human Immunodeficiency Virus Infection

James H. Stein, MD and **Priscilla Y. Hsue, MD**

Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, Madison (Stein); University of California, San Francisco, School of Medicine, San Francisco (Hsue)

The complex role of inflammation in the initiation of arterial injury, atherogenesis, and acute coronary syndromes has guided cardiology research for nearly 3 decades. Although inflammation is a nonspecific term, it is useful to think of atherosclerosis as a response to injury that may be heightened in the setting of chronic inflammatory diseases such as human immunodeficiency virus (HIV) infection and rheumatoid arthritis. Nevertheless, the underlying mechanisms of inflammation and their effects on atherosclerosis may be distinct in different disease states. Diverse diseases may have “inflammation” in common, but their immunological signatures differ and the inflammatory biomarkers that cardiologists are familiar with may be too far downstream from the pathogenesis of arterial injury to provide insights into the mechanisms by which they cause atherosclerotic cardiovascular disease (ASCVD). Similarly, the imaging modalities that we use to predict the risk of ASCVD and to study atherogenesis may not be well suited for investigating the inflammatory mechanisms of ASCVD in HIV disease. Our ability to monitor and intervene with respect to inflammation, and to assess its clinical impact, remains unclear.

In this issue of *JAMA Cardiology*, Zanni et al[1] demonstrated large, expected improvements using markers of immune activation and HIV replication among 12 young anti-retroviral therapy (ART)–naive individuals initiating an integrase-inhibitor–based HIV treatment regimen. They also demonstrated large decreases in lymph node inflammation measured by fluorodeoxyglucose F 18 ([^{18}F]-FDG)–positron emission tomography (PET) uptake after approximately 6 months; however, aortic plaque inflammation did not decrease.[1] Lymphoid tissue is an HIV reservoir during acute and chronic HIV infection. Despite ART that reduces HIV RNA levels to undetectable blood levels, viral replication continues in the lymphoid tissues. Indeed, ART-naive HIV-infected individuals have higher levels of [^{18}F]-FDG–PET activity in their lymph nodes than do treated and virologically suppressed individuals and different patterns of activation compared with those with acute HIV disease.

Although the lack of effect of ART on arterial [^{18}F]-FDG up-take reported by Zanni et al[1] may seem surprising, it underscores how little we understand about the effects of HIV and

Corresponding Author: James H. Stein, MD, Division of Cardiovascular Medicine, University of Wisconsin School of Medicine and Public Health, 600 Highland Ave, H4/520 CSC, MC 3248, Madison, WI 53792 (jhs@medicine.wisc.edu).

Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest

ART on arterial injury and function.[1] For example, previous studies of ART-naive individuals initiating their first treatment regimen consistently demonstrated improvements in $CD4^+$ T-cell counts and HIV loads with other ART regimens, but inconsistent effects on dynamic markers of arterial function, including flow-mediated vasodilation, stiffness, and wall thickness.[2-6] Interestingly, studies with participants who had more advanced HIV disease markers, such as a lower $CD4^+$ T-cell count and a longer duration of known HIV disease, seemed to describe greater improvements in vascular function markers, although these studies also differed by ART regimen, sample size, imaging techniques, and study designs. Regarding clinical ASCVD, in the Strategic Timing of Antiretroviral Treatment study of young HIV-infected individuals at low ASCVD risk, early initiation of ART had no impact on ASCVD events or arterial stiffness, although serious AIDS-related and non–AIDS-related events were less frequent.[6,7]

Measuring aortic inflammation in ART-naive individuals is a novel use of [^{18}F]-FDG–PET imaging; however, it is unclear whether the absence of a reduction in aortic [^{18}F]-FDG uptake in their study indicates a true “discordance” between the multiple markers of immune activation and inflammation measured, or whether it is simply a type I error due to the small sample size or the relatively short follow-up period.[1] With the exception of CXCL10, a chemokine that increases with viral infections and decreases with their treatment, there were no significant differences in any of the inflammatory biomarkers that the authors measured after ART, including several associated with ASCVD risk, which is consistent with the absence of changes in aortic [^{18}F]-FDG PET that they observed.[1]

It is very likely that the community of researchers who investigate the effects of HIV and its treatment on ASCVD risk are not measuring markers that are most germane to the vascular biology of atherosclerosis in individuals with HIV infection. Inflammatory biomarkers associated with ASCVD risk, such as high-sensitivity C-reactive protein, tend not to be related to HIV disease activity or its treatment. Similarly, statin therapy, which reduces the level of C-reactive protein in the general population, has not consistently reduced its levels in individuals with HIV. Furthermore, the immune activation markers reported by Zanni et al[1] that parallel the effect of ART on HIV disease (including lymph node activity) may not be relevant to atherogenesis. Although immune activation is linked to HIV disease, it is not a strong predictor of ASCVD events. In fact, in the general population, lymph node activity is not a known predictor of ASCVD, so it is not expected that changes in its activity would parallel changes in arterial inflammation. We simply do not understand the immunology of ASCVD well enough to dissect the cellular subtypes and their expression characteristics with interventions as pleiotropic and powerful as ART in viremic, HIV-infected individuals. Similarly, the short-term changes in arterial inflammation detected using [^{18}F]-DG PET may be too small or too variable to be detected in otherwise healthy, young individuals at low ASCVD risk over a short time frame.

Given that immune activation and dysregulation persist among treated and virologically suppressed HIV-infected individuals and that HIV infection appears to carry an approximately 50% relative increased risk of clinical ASCVD despite effective treatment, it is imperative that the mechanisms underlying these phenomena be characterized more precisely so that treatments targeting them can be investigated in large randomized clinical

trials. The landmark AIDS Clinical Trials Group Study A5332, “Evaluating the Use of Pitavastatin to Reduce the Risk of Cardiovascular Disease in HIV-Infected Adults (REPRIEVE)” (NCT02344290), currently is investigating the effects of a statin vs placebo on major adverse cardiovascular disease events, inflammatory bio-markers, and computed tomography angiographic markers of stenosis and plaque stability in more than 6000 individuals with stable HIV infection. The AIDS Clinical Trials Group Study A5314, “Evaluating Safety and Effectiveness of Low-Dose Methotrexate at Reducing Inflammation in HIV-Infected Adults Taking Antiretroviral Medications” (NCT01949116), also is a randomized, placebo-controlled study that will provide mechanistic insights into the effects of low-dose methotrexate on arterial flow–mediated vasodilation, inflammatory biomarkers, and immunopheno types associated with increased ASCVD risk in HIV disease. Its substudy (NCT02312219) is investigating the effects of immune modulation with low-dose methotrexate on arterial inflammation using aortic [^{18}F]-FDG PET.

These studies, in conjunction with large randomized clinical trials of the effects of anti-inflammatory agents on recurrent ASCVD events in non–HIV-infected individuals, will help elucidate the effects of inflammation and immune activation on arterial injury and ASCVD risk, as well as their interplay in individuals with HIV infection. However, despite being describable using similar markers of inflammation, ASCVD is not an infection, so the ASCVD observed in individuals living with HIV likely has distinct mechanisms from those observed in un-infected individuals and likely will require distinct treatments as well. Because of the complexity of the effects of ART on inflammation and immune regulation and because of the inconsistent results of the ART initiation studies, we need to continue to harness the power of large, randomized clinical trials to better characterize the effects of ART and inflammation on arterial injury. By doing so, we eventually will be able to provide effective ASCVD risk-reducing treatments to the growing population of individuals who are living with HIV infection but now face dying of ASCVD.

Acknowledgments

Funding/Support: Drs Stein and Hsue were supported by grant HL1177131 from the National Heart, Lung, and Blood Institute.

Role of the Funder/Sponsor: The National Heart, Lung, and Blood Institute had no role in the preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Dr Stein reports being the principal investigator of a core ultrasonography research laboratory grant to the University of Wisconsin for a clinical trial of the effects of ART on arterial function (sponsored by Gilead). He is the principal investigator of grants and subcontracts to the University of Wisconsin from the National Institutes of Health regarding HIV, ART, and cardiovascular disease risk. Dr Hsue reports having been on the advisory board of and receiving honoraria from Gilead and having been on the advisory board of Merck, Bristol-Myers Squibb, and Amgen, outside the submitted work.

References

1. Zanni MV, Toribio M, Robbins GK, et al. Effects of antiretroviral therapy on immune function and arterial inflammation in treatment-naive patients with human immunodeficiency virus infection. JAMA Cardiol. published online May 25, 2016.
2. Torriani FJ, Komarow L, Parker RA, et al. ACTG 5152s Study Team. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent

antiretroviral therapy: the ACTG (AIDS Clinical Trials Group) Study 5152s. J Am Coll Cardiol. 2008; 52(7):569–576. [PubMed: 18687253]

3. Gupta SK, Shen C, Moe SM, Kamendulis LM, Goldman M, Dubé MP. Worsening endothelial function with efavirenz compared to protease inhibitors: a 12-month prospective study. PLoS One. 2012; 7(9):e45716. [PubMed: 23029197]
4. van Vonderen MG, Hassink EA, van Agtmael MA, et al. Increase in carotid artery intima-media thickness and arterial stiffness but improvement in several markers of endothelial function after initiation of antiretroviral therapy. J Infect Dis. 2009; 199(8):1186–1194. [PubMed: 19275490]
5. Stein JH, Ribaudo HJ, Hodis HN, et al. A prospective, randomized clinical trial of antiretroviral therapies on carotid wall thickness. AIDS. 2015; 29(14):1775–1783. [PubMed: 26372383]
6. Baker, JV., Huppler Hullsiek, K., Wyman, N. Early antiretroviral therapy does not improve vascular function: a START substudy. Paper presented at: Conference on Retroviruses and Opportunistic Infections (CROI); February 22-25, 2016; Boston, MA. Abstract 41
7. Lundgren JD, Babiker AG, Gordin F, et al. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. N Engl J Med. 2015; 373(9):795–807. [PubMed: 26192873]