Imaging atherosclerotic burden and inflammation: Insights into the spectrum of atherosclerotic disease in HIV

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HIV disease, left inadequately treated, leads to an inexorable decline in immune function resulting in AIDS and ultimately in death from opportunistic infections. However, advances in treatment of HIV have resulted in a dramatic reduction in AIDS-related mortality.[1] With the widespread use of highly active antiretroviral therapy (HAART), HIV infection has been transformed to a chronic disease associated with long-term viral suppression but at the cost of an increase in atherothrombotic diseases.[2,3] Hence currently there is substantial interest in developing a better understanding of the mechanisms underlying the increased risk of atherothrombosis in HIV disease.

While HIV infection is characterized by a decline of peripheral blood CD4+ T cells, a paradoxical chronic immune activation of T cells and monocytes is routinely seen in virally suppressed HIV disease.[4-6] Multiple studies in HIV-infected individuals show that this persistently heightened state of immune activation likely contributes to the increased incidence of atherosclerosis,[2,7,8] itself a chronic inflammatory condition. Numerous potential causes may contribute to this chronic immune activation, including increased microbial translocation from the gut due to CD4+ T lymphocytes depletion,[9] persistent low-level viral replication,[10] increased levels of lipopolysaccharide (LPS), sCD14,[11] HIV gene products, and CMV-specific T-cell activation [12] among other mechanisms. In this regard, an increasing number of studies have begun to assess the relationship between atherosclerosis and immune activation in HIV-infected individuals.

Recent studies by our group and others have shown substantial increases in subclinical coronary plaque.[13,14] Using CT angiography, we have observed increases in non-calcified plaque volume[15] and vulnerable plaque features in association with sCD163 an immune activation marker, indicative of monocyte activation.[16] In a large study of over 700 HIV-infected patients and control subjects in the MACS cohort patients, Post et al similarly demonstrated increased non-calcified plaque.[14] In a follow-up analysis, sCD163 was shown to increase in association with overall plaque indices, again using CTA.[17] These studies support the notion, across a broad range of patients with HIV infection, (including elite controllers who have well controlled viremia without ART),[18] that immune activation is increased in HIV, and is associated with increased coronary atherosclerotic indices.

Additionally, numerous studies have shown that HIV infection is associated with an increase in extra-coronary atherosclerosis, such as can be demonstrated by measurement of carotid intima-media thickness (cIMT). Hsue et al demonstrated that cIMT is greater in HIV patients than in age-matched control subjects and progresses much more rapidly than in individuals without HIV infection.[19] The severity of carotid atherosclerosis seen in treated HIV infection (as IMT) correlates with markers of immune activation.[20] Others have shown that the rate of progression of cIMT in HIV is predicted by markers of immune activation and

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microbial translocation, respectively.[8] Moreover, the abnormally advanced atherosclerotic disease is manifest even in children with HIV compared to age-matched controls.[21] A link between HIV disease, premature and progressive atherosclerosis, and immune activation is becoming increasingly well established.

There is, not surprisingly, substantial interest in studying atherosclerotic inflammation in the context of HIV. Imaging of arterial inflammation is now routinely performed using fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET imaging has been used successfully in clinical oncology and for detection of occult infection. Tissue accumulation of FDG is reflective of the rate of tissue glycolysis, which is higher in areas containing metabolically active tumor cells and in inflamed tissues. A large body of basic cellular physiology data demonstrates that activated macrophages have an unusually high metabolic rate[22,23] especially after classical/innate activation[24] hence avidly accumulate FDG.[25] While one pre-clinical study suggested that hypoxia is a more substantial stimulus of macrophage glycolysis than inflammatory stimuli,[26] that study stands in opposition to the much boarder literature; further, hypoxia itself is a potent stimulus of macrophage pro-inflammatory activation.[27] Moreover, FDG accumulation within the artery wall has repeatedly been found to correlate with atherosclerotic plaque macrophage density of.[28-30] Further, several studies have demonstrated that increased plaque inflammation (measured using FDG-PET) predicts an increased rate of atherosclerotic plaque progression.[31,32] In addition, higher arterial FDG uptake is associated with a substantially increased risk for *subsequent* stroke and MI.[33-35] Taken together, these studies provide justification for using arterial FDG-PET/CT imaging to provide a meaningful measure of arterial inflammation in human clinical studies.

More recently, Yarasheski et al and our group separately employed FDG-PET to assess arterial inflammation in HIV.[7,36] These two studies demonstrated increased arterial FDG-PET uptake in HIV-infected individuals, both in the carotid and descending aorta. Furthermore, we observed that the degree of arterial inflammation in HIV correlates with markers of monocyte activation,[7] and in a separate study, we observed that extra-coronary arterial inflammation correlates with the presence of high-risk coronary plaques.[37] Hsue et al recently extended those findings, and observed that the tissue measures on FDG accumulation relate to markers of viral persistence in HIV.[38] Hence a substantial literature has emerged in HIV-positive individuals, which links immune activation to arterial inflammation.

It is in the context of these prior studies that new data from Knudsen et al, in this issue of *Journal of Nuclear Cardiology*, should be considered. Knudsen et al performed FDG-PET in HIV-infected patients and controls and found no significant differences in arterial inflammation between the HIV-positive individuals and the HIV-negative control subjects (who were matched for some, but not all major CVD risk factors). At first blush, these data seem to contrast with those of Yarasheski et al and Subramanian et al However, a closer look at the data reveals some important differences in study design and potentially of the patient population that may have contributed to the results and which may provide important insights.

First, the Knudsen et al study showed no evidence of increased subclinical atherosclerosis (by cIMT), in the HIV-positive cohort compared to the HIV-negative controls. This finding runs counter to the findings from a sizeable number of studies, some of which suggest that HIV is associated with a premature aging phenotype, with advanced subclinical atherosclerosis by on average 15 years.[39] Of further note, the HIV-positive group in the Knudsen study did not manifest an increase in sCD163 or other immune activation markers, which also runs counter to a large body of data.[15,17]

It follows from these observations, that the HIV-positive population that was studied by Knudsen et al was somewhat atypical in that the group lacked evidence of either increased immune activation or pre-clinical atherosclerosis. Accordingly, it comes with less surprise that this particular population had no significant increase in arterial inflammation either. Indeed, in the study by Subramanian et al, higher levels of arterial inflammation were seen primarily in individuals with higher levels of immune activation (i.e., sSD138 levels). Thus perhaps the findings of the current study are appropriate for the specific population studied. Perhaps the lesson of the Knudsen study, viewed in the context of existing studies, is that among HIV-positive individuals without pre-clinical atherosclerotic disease or heightened immune activation, there is no increase in arterial inflammation. However, among HIV patients with subclinical atherosclerotic disease and increased immune activation (a group which represents a large proportion of the HIV population), arterial inflammation is increased.

The findings of Knudsen et al highlight the need for further study. Their study, taken together with the previous studies of arterial inflammation in HIV, suggests that a spectrum of arterial inflammation exists in HIV: from higher-to-lower arterial inflammation in individuals with or without immune activation/ pre-clinical atherosclerosis, respectively. Accordingly, a question of proximal importance is whether the spectrum of immune activation and atherosclerotic inflammation in HIV-positive individuals provides any disease insights. For example, can imaging measures of arterial inflammation predict the risk of atherothrombosis in an HIV-positive

population, (much as it can be used in non-infected populations). Furthermore, it remains to be seen whether measures of arterial inflammation could be used to study novel therapies in HIV-positive populations. Thus far, several multicenter randomized controlled trials have utilized serial FDG-PET imaging to evaluate the effect of drugs on atherosclerotic inflammation (in non-infected populations). Data from those studies suggest that treatment-related changes in arterial inflammation seem to be predictive of clinical efficacy. Accordingly, imaging treatment effects using arterial FDG-PET/CT imaging might provide needed insights regarding potential therapeutic efficacy of new therapies. With that stated, studies are now underway to evaluate whether anti-inflammatory strategies (such as low-dose methotrexate) can reduce peripheral markers of inflammation and arterial inflammation in HIV. Concurrently, other atherosclerosis imaging tools such as coronary CT angiography are also being used to study the impact of statin therapy on atherosclerosis progression in HIV. Directionally positive findings in those imaging surrogate studies could justify larger clinical outcome trials to define the therapeutic efficacy of those treatments.

The study of Knudsen et al provides an additional patch to a quilt of data emerging on atherosclerosis in HIV, and suggests that at least some individuals with HIV might have low levels of immune activation, have little evidence of pre-clinical atherosclerosis, or atherosclerotic inflammation, and might thus be spared of the advanced atherosclerotic disease that is otherwise reported in the majority of HIV-infected populations studied. More studies are needed to better understand the mechanisms underlying the increased risk of atherothrombosis in HIV. Ultimately, studies evaluating atherosclerosis in HIV might pave the way toward a new era, where infected individuals can be spared of both AIDS as well as the atherothrombotic complications associated with HIV infection.

Disclosures

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