Investigating vascular diseases in people living with HIV by nuclear imaging

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Received Mar 10, 2021; accepted Mar 11, 2021
doi:10.1007/s12350-021-02613-x

See related article, pp. 1566–1575

In addition to the progressive loss of adaptive immunity leading to the acquired immunodeficiency syndrome (AIDS), HIV-1 infection impacts almost all bodily systems including the cardiovascular system (CVS) and central nervous system (CNS). Compared to HIV-negative individuals, people living with HIV (PLWH) have about 2-fold increased relative risk (RR) of coronary arterial disease (CAD)[1] and 3-fold increased RR of stroke.[2] Despite initial concern that metabolic toxicity of antiretroviral therapy (ART) may underlie these risks, international randomized controlled trials have confirmed that immediate initiation of non-interrupted ART reduces vascular complications in addition to the restoration of immune function.[3] In the present era, the life expectancy of PLWH is approaching that of HIV-negative populations. Yet, in this context of long-term survival, the burden of non-communicable diseases in aging populations of PLWH on suppressive ART emerges as a major health care concern. Vascular diseases, especially CAD and stroke, are under the spotlight not only because of their historical appearance in the pre-ART era but also their universal role in morbidity and mortality in all populations. In this issue of JNC, Taglieri et al. compare the arterial inflammation in the ascending and descending aorta using ^{18}F-Fluorodeoxyglucose (^{18}FDG) PET in a group of PLWH on stable ART.

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J Nucl Cardiol 2022;29:1576–82.
1071-3581/$34.00

THE BURDEN OF VASCULAR DISEASES AMONG PLWH IN THE ART ERA

PLWH consistently show a higher risk of cardiovascular disease (CVD) than HIV-negative populations despite stable ART. In a systematic review of 80 longitudinal CVD studies with 793,635 PLWH, the global burden of HIV-associated CVD has tripled over the past 2 decades.[4] PLWH presenting with the acute coronary syndrome (ACS) are 10 years younger than HIV-negative patients.[5] In a nation-wide, retrospective Danish study, PLWH had an increased RR of 1.6 of developing a cerebrovascular event than HIV-negative individuals after controlling for intravenous drug use and other traditional vascular risk factors.[6] A modeling study of 8791 treated Dutch PLWH predicted that annual CVD incidence and costs will increase by 55% and 36%, respectively, between 2015 and 2030.[7] Understanding the interaction and between HIV and atherosclerosis, as well the management, is thus crucial to maintain long-term quality of life and resilient aging of PLWH.

ATHEROSCLEROSIS IN PLWH ON SUPPRESSIVE ART

HIV appears to alter the course and presentation of atherosclerosis and CAD. Compared to Type I ACS that are the predominant cardiac events in HIV-negative populations, up to 50% of myocardial infarctions in PLWH are Type II ACS[8] attributed to a mismatch of oxygen demand and supply in PLWH.[9] Structurally, non-calcified coronary plaque is more prevalent in PLWH than in HIV-negative individuals.[10] A number of persistent phenomena may promote atherosclerosis in PLWH despite suppressive ART. Systemic immune dysregulation, including monocyte/macrophage activation and T-cell dysregulation, persists in PLWH on suppressive ART.[11] Increased markers of monocyte/macrophage activation, such as plasma sCD14

and sCD163, associate with atherosclerosis in both HIV-positive and HIV-negative individuals.[12] These markers remain elevated among PLWH despite HIV suppression.[12] Low CD4/CD8 ratio, a marker of T-cell dysregulation and immunosenescence, remains prevalent in PLWH despite plasma HIV suppression[13,14] and is associated with CAD events in PLWH.[15]

HIV reservoir may play a role in atherosclerosis. HIV reservoir is still able to produce HIV-encoded proteins including transactivator of transcription (Tat), negative factor (Nef), and envelope protein gp120 through low-level transcription during plasma viral suppression.[16,17] These proteins are linked to inflammation, endothelial dysfunction, and endothelin 1 production.[18] Increased microbial translocation in the gut, currently considered as an important contributor of atherosclerosis,[19] persists among PLWH on suppressive ART.

Compared to HIV-negative populations, PLWH also have higher rate of cytomegalovirus (CMV) and Hepatitis C virus (HCV) co-infections that are linked with atherosclerosis and CVD.[20,21] Commonly used antiretroviral agents, such as protease Inhibitors, are associated with dyslipidemia that worsens atherosclerosis. Most importantly, PLWH on suppressive ART persistently show metabolic dysfunction in glucose and lipid metabolism.[22] As a result, HIV plays both direct and indirect roles in atherosclerosis.

ADVANTAGES OF NUCLEAR IMAGING IN ASSESSING ATHEROSCLEROSIS IN HIV

Given the fact that augmented inflammation is likely the central mechanism of HIV-related atherosclerosis, conventional vascular imaging may be limited by its focus on assessment of structural changes, underestimating inflammatory processes. Despite this, even conventional vascular imaging can reveal distinctions between PLWH and HIV-negative comparison patients. In a prospective study of 811 men and 1011 women from the Multicenter AIDS Cohort Study and the Women's Interagency HIV Study, participants with HIV on ART had increased plaque at common carotid artery detected by repeated B-mode ultrasound imaging than HIV-negative individuals.[23] In another study that examined the progression of subclinical atherosclerosis over 2 years by coronary artery calcium scan and coronary computed tomography angiography, Framingham risk score (FRS) but not HIV infection was associated with progression of subclinical atherosclerosis.[24] Yet, the HIV-positive group in the latter study had a similar FRS as the HIV-negative control group despite a younger age, highlighting again the complex relationship between HIV, traditional risk factors, and atherosclerosis.

In the last decade, vascular PET imaging has emerged as a promising tool for risk stratification for atherosclerotic vascular disease. Early studies confirmed the capability of FDG-PET to evaluate the risk of carotid atheroma that leads to recurrent ischemic stroke.[25] The close association between FDG uptake and CD68+ macrophage burden in plaques further supports its usefulness to evaluate vascular inflammation,[26] making FDG-PET a potentially superior tool for evaluating HIV-related atherosclerosis compared to conventional imaging such as CT angiogram and ultrasound. A number of nuclear imaging studies focused on HIV-related atherosclerosis have been reported in the last decade (Table 1). In an early FDG-PET study that examined the effect of ART in 12 treatment-naïve PLWH, aortic FDG uptake did not show significant change 6 months after ART initiation.[27] The result suggests that vascular inflammation is not readily reverted in the initial months post ART, while the long-term benefit of suppressive ART in atherosclerosis remains less clear. Titanji et al. recently reviewed the outcomes of intervention studies that aimed to alleviate cardiovascular inflammation in HIV.[28] Of note, atorvastatin, a lipid-lowering agent, only reduces non-calcified plaque volume and high-risk coronary plaque features in PLWH without reducing ^{18}FDG uptake within the aorta.[29] However, subcutaneous administration of canakinumab, a IL-1ß inhibitor, results in reduction in both aortic TBR and plasma inflammatory markers.[30]

EVALUATING ATHEROSCLEROSIS IN PLWH ON SUPPRESSIVE ART BY NUCLEAR IMAGING

The work from Taglieri et al. provides insight on atherosclerosis in PLWH on long-term suppression. The team compared the arterial inflammation (AI), denoted by the maximum target-to-background ratio (TBRmax) in ^{18}FDG PET at the ascending and descending aorta and carotid artery between PLWH and uninfected controls with no known cardiovascular diseases but at least 3 traditional cardiovascular risk factors. Of note, the HIV-positive group was well maintained with ART, indicated by the long duration of ART usage, high frequency of plasma viral suppression, and relatively normal median CD4+ T-cell count of 871 cells/mm^3. Despite similar American College of Cardiology/atherosclerotic cardiovascular disease (ASCVD) scores between the two groups, participants with HIV showed worse TBRmax at the ascending aorta. Further, the HIV status remained independently associated with worse TBRmax.

Table 1. Nuclear imaging studies that examine atherosclerosis in HIV

	Imaging modality	Objectives	Key findings
Subramanian et al.[31]	^{18}FDG (PET-CT) & CT angiogram	Examine the relationship between aortic TBR, traditional, and non-traditional risk markers of atherosclerosis in 27 PLWH and 54 HIV-negative controls	Compared to HIV-negative control, the HIV-positive group had higher aortic TBR that increased with plasma circulating macrophage activation maker (sCD163)
Yarasheski et al.[32]	^{18}FDG (PET-CT)	Examine the usefulness of ^{18}FDG imaging to detect arterial inflammation in 9 PLWH with modest CVD risk and 5 HIV-negative controls	Bilateral carotid ^{18}FDG uptake was greater in the HIV-positive group than the HIV-negative group Aortic ^{18}FDG uptake was higher in the HIV-positive group but did not achieve statistical significance.
Lo et al.[29]	^{18}FDG (PET-CT) & CT angiogram	Examine if atorvastatin can reduce arterial inflammation and achieve regression of coronary atherosclerosis in 40 PLWH	Atorvastatin reduced non-calcified plaque volume and high-risk coronary plaque features in the HIV-positive group but did not reduce ^{18}FDG uptake at aorta
Knudsen et al.[33]	^{18}FDG (PET-CT)	Compare ^{18}FDG uptake at aorta and carotid artery between 26 HIV-positive and 27 HIV-negative individuals without CVD	Vascular ^{18}FDG uptake by TBR was statistically similar between both groups, despite higher age and FRS in the HIV-positive group
Zanni et al.[27]	^{18}FDG (PET-CT) & CT angiogram	Determine the effects of initiating ART in 12 treatment-naïve PLWH	Uptake of ^{18}FDG was reduced at axillary lymph nodes but not at aorta 6–12 months after ART initiation

Table 1 continued

	Imaging modality	Objectives	Key findings
Tawakol et al.[51]	^{18}FDG (PET-CT)	Examine if arterial inflammation is linked to HIV disease activity and to inflammation within lymph node in 45 PLWH	HIV-infected group had elevated TBR at both aorta and axillary LN Aortic TBR was associated with plasma immune activation markers but not clinical immune markers like CD8 T-cell level and CD4/CD8 ratio
Zanni et al.[36]	^{99m}Tc-tilmanocept (SPECT/CT) & CT angiogram	Examine the usefulness of ^{99m}Tc-tilmanocept to determine arterial inflammation in 6 PLWH and 7 HIV-negative control	HIV-positive group showed higher aortic ^{99m}Tc-tilmanocept uptake than age-matched control of similar FRS ^{99m}Tc-tilmanocept uptake at aorta increased with non-calicified aortic plaque volume after adjusting for HIV status
Hsue et al.[30]	^{18}FDG (PET-CT)	Examine the effect of subcutaneous canakinumab, a IL-1ß inhibitor, to reduce arterial inflammation in 10 PLWH	There were statistically significant reduction in aortic TBR and plasma inflammatory markers (hsCRP, IL-6 and sCD163) 8 weeks after administration of canakinumab
Lawal et al.[34]	^{18}FDG (PET-CT)	Compare arterial inflammation in 121 HIV-positive and 121 HIV-negative participants with low risk of CVD	Aortic TBR was marginally higher in the HIV-positive group with significant overlapping between both groups
Guaraldi et al.[35]	^{18}FDG & ^{18}F- NaF (PET-CT)	Compare the coronary uptake of the two tracers in 93 PLWH with high and low CVD risk	^{18}F-NaF showed higher coronary uptake than ^{18}FDG in both high and low CVD risk participants However, the level of ^{18}F- NaF uptake was similar between high- and low-risk groups

The detection of increased vascular ^{18}FDG uptake in this latest work from Taglieri et al. is in line with two early PET studies that compared vascular inflammation between HIV-positive participants on suppressive ART and HIV-negative controls.[31,32] While both studies detected higher inflammatory signals in participants with HIV, one further study showed an elevated aortic TBR in the group of PLWH in comparison with a FRS-matched HIV-negative control.[31] However, the difference in vascular FDG uptake by HIV status is less distinctive in young individuals with low CVD risk.[33,34] Taken together, the findings highlight that elevated atherosclerotic inflammation persists years after ART initiation and viral control. Additionally, applying traditional CVD risk stratification methods in PLWH, especially in those of moderate-to-high CVD risk, may underestimate the actual risk by overlooking the impact of HIV-related inflammation in atherosclerosis. More recently, radiomarkers including ^{18}F-NaF and ^{99m}Tc-tilmanocept have been tested for their validity in assessing HIV-related atherosclerosis. Compared to ^{18}FDG, ^{18}F-NaF appears to have better uptake at the vascular wall but lacks sensitivity to differentiate between high- and low-risk CVD.[35] ^{99m}Tc-tilmanocept is a radiomarker with CD206+ macrophage binding capacity. In a single-photon emission computed tomography/computed tomography (SPECT/CT) study, ^{99m}Tc-tilmanocept uptake is correlated with non-calicified aortic plaque volume and immunological markers including sCD14 level, absolute number of CD14+CD16− monocytes, and absolute CD8+ T-cell count.[36]

APPLICATION OF NUCLEAR IMAGING TO UNDERSTAND NEUROHIV

Nuclear imaging is similarly useful in neuroHIV research. Apart from CNS opportunistic infections secondary to overt immunodeficiency, HIV directly invades the CNS and eventually leads to different degrees of cognitive impairment in untreated PLWH. Epidemiology studies reveal that HIV-associated dementia, the most severe type of HIV-associated neurocognitive disorder (HAND), has become uncommon in the ART era.[37] However, milder forms of HAND persist at a prevalence ranging from 30-50% of PLWH. While residual neurological deficits resulting from pre-ART neurologic injury could account for part of the persistence of HAND in the ART era, CSF markers and MR spectroscopy studies confirm persistent cerebral inflammation in PLWH on suppressive ART.[38] Brain PET studies based on macrophage/microglia-specific ligands further reveal that PLWH on suppressive ART with worse cognitive performance have increased marker uptake in the brain,[39–41] highlighting the association between cognitive impairment and persistent cerebral inflammation.

Several hypotheses have been proposed for the persistence of HAND despite ART, including whether persistent cerebral inflammation might accelerate or augment the manifestation of underlying neurodegenerative diseases such as Alzheimer's disease (AD). This hypothesis is supported by the alterations of CSF AD biomarkers including beta-amyloid and Tau levels in PLWH with cognitive impairment.[42,43] However, recent PET studies do not show major differences in amyloid deposition stratified by HIV serostatus or HAND severity.[44,45] Others propose that cognitive impairment in PLWH in the ART era might be related to cerebrovascular diseases.[46] Asymptomatic intracranial atherosclerosis has been increasingly recognized as a risk factor of cognitive impairment in the general population.[47] A recent post-mortem study demonstrates preclinical atherosclerotic changes of small-to-medium-sized intracranial arteries in PLWH within the first 6 years of HIV infection,[48] suggesting that ART reduces inflammation but does not resolve arterial remodeling.[48] To date, longitudinal studies that investigate the impact of atherosclerosis on cognitive function in PLWH are not available.

In summary, persistent systemic immune activation in PLWH on suppressive ART likely continuously fuels the atherosclerosis process. PET imaging has emerged as an ideal tool to examine HIV-related atherosclerosis as it provides both structural information of plaque and quantitative information of inflammation when it is co-administrated with computed tomography (CT) or magnetic resonance imaging (MRI). With the availability of new PET ligands that target specific biological process or cell types, PET has the potential to serve not only as a tool for research but also as a means for disease and treatment effect monitoring. Longitudinal studies that correlate systemic immune activation, vascular inflammation, and plaque progression would help to clarify the CVD risks of PLWH on long-term suppressive treatment. Future studies should also specifically examine changes in vascular inflammation shortly after ART initiation and concomitant with immune reconstitution, as stroke events appears to be more common during the first year of ART.[49] Additionally, the role of the HIV reservoir in vascular inflammation should be explored as cell-associated HIV DNA and RNA in CD4+ T-cells are independently associated with progression of carotid intima-media thickness and incident plaque development in PLWH.[50] Lastly, standardizing the methodology of PET imaging acquisition and evaluation would facilitate multicenter study across populations.

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