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HIV-ASSOCIATED CARDIOVASCULAR DISEASE: AN UPDATE

In this Issue...
With the increasing life expectancy of patients infected with HIV in the current era of antiretroviral therapy, there is more awareness of non-HIV-related causes of death, including cardiovascular disease. Newer studies refine the magnitude of risk of HIV-associated heart disease and suggest that identification of subclinical disease could lead to earlier and more effective treatment interventions.

In this issue, we review recent studies addressing:

- the prevalence of coronary plaque in people infected with HIV
- the pathogenesis of vulnerable coronary plaque
- the risk of recurrent coronary events after a first acute coronary syndrome
- nonatherosclerotic HIV-associated heart disease, including atrial fibrillation and structural abnormalities identified on cardiac MRI

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Identify the prevalence and pathogenesis of subclinical coronary plaque in HIV-infected persons.
- Describe risk factors and treatment strategies to mitigate HIV-associated coronary risk.
- Summarize the increasing prevalence of nonatherosclerotic HIV-associated coronary disease.

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Guest Faculty Disclosure

Thomas Metkus, MD, has indicated that he has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of his presentation.

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Wendy S. Post, MD has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of her presentation.

Unlabeled/Unapproved Uses

The authors have indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

Program Directors' Disclosures

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COMMENTARY

With the increasing life expectancy of patients infected with HIV in the current era of antiretroviral therapy, there is more awareness of non-HIV related causes of death, including cardiovascular disease. Epidemiology studies have demonstrated an increased propensity for both subclinical atherosclerosis and acute coronary events, including myocardial infarction, among people with HIV compared with the general population. The body of literature regarding the pathogenesis of atherosclerosis in patients infected with HIV and the optimal means of primary and secondary prevention continues to grow. In addition, there is growing interest in nonatherosclerotic HIV-related heart disease, including structural heart disease and arrhythmia. In this issue we review recent studies addressing the prevalence of coronary plaque in people infected with HIV, the pathogenesis of vulnerable plaque, and the risk of recurrent coronary events after a first acute coronary syndrome in people with HIV. We also review two studies addressing nonatherosclerotic HIV-associated heart disease, including atrial fibrillation and structural abnormalities identified on cardiac MRI. Future studies should focus on prospective assessment of clinical cardiovascular endpoints.

As lifespans in people with HIV approach those of those without the infection and antiretroviral therapy continues to become more available worldwide (including in developing nations), one can anticipate that the prevalence of HIV-related heart disease will continue to increase. Intervention trials of novel dyslipidemia therapy, antiplatelet therapy, and cardiac devices should be designed to include representative numbers of patients with HIV. These efforts will ensure that the identification and prognosis of HIV-related heart disease continues to improve. Unanswered future questions also include whether earlier treatment of HIV with antiretroviral therapy will prevent HIV-associated cardiac disease. The studies reviewed in this issue address important issues in the field of HIV-associated atherosclerotic and nonatherosclerotic heart disease.

Commentary References

HIV INFECTION AND SUBCLINICAL ATHEROSCLEROSIS


Studies with clinical cardiovascular endpoints such as myocardial infarction and stroke in people with HIV infection are challenging due to the large sample sizes needed to detect modest differences in event rates between groups. Advanced imaging of subclinical coronary disease, therefore, can serve as an important surrogate endpoint in defining the association of HIV serostatus with coronary disease. In this study, the authors performed coronary CT angiography on men in the Multicenter AIDS Cohort Study (MACS), a prospective cohort study of demographically similar men with and without HIV infection.
The men had no prior history of coronary revascularization. Plaque extent and morphology were assessed in each of 15 coronary segments, and clinical variables and laboratory data were collected at the MACS study visits. A total of 1001 men had noncontrast CT scans to assess for coronary calcium, an indicator of subclinical coronary atherosclerosis. In addition, 759 men underwent coronary CT angiography to assess coronary stenosis and plaque morphology and characteristics. The men with HIV had a higher prevalence of current tobacco use, lower HDL and LDL cholesterol, and higher triglyceride levels. HIV was well controlled, with over 80% of men having undetectable viral loads. The median CD4+ T cell count was 601 cells/µL. Approximately half of the men were maintained on protease inhibitor and half on NNRTI therapy.

After adjustment for age and race, the men with HIV had a higher prevalence of coronary calcium, indicative of subclinical atherosclerosis (prevalence ratio 1.21, 95% CI 1.08-1.35). Men with HIV also had a higher prevalence of coronary plaque on coronary CT angiography, adjusted for age and race and also for cardiovascular risk factors including hypertension, smoking, diabetes, and serum lipids (PR 1.13, 95% CI 1.05-1.24). In addition, men with HIV were more likely to have noncalcified "soft" plaque, whereas there was no difference in calcified plaque between groups. In minimally adjusted models, men with HIV had more mixed plaque, with both calcified and noncalcified components, and this relationship attenuated when adjusting for cardiovascular risk factors. Lower nadir CD4+ T cell count and longer duration of HAART were associated with the presence of a coronary stenosis greater than 50% severity. Overall, HIV serostatus was associated with both presence and extent of subclinical coronary atherosclerosis. Age was associated with increasing prevalence of noncalcified coronary plaque among men with HIV but not among men without HIV. Noncalcified plaque may be potentially more unstable and prone to rupture, increasing the risk for acute coronary syndromes. It is not known whether HIV predisposes to delayed calcification of noncalcified plaque or to formation of new noncalcified plaques.

This study confirms findings in smaller cohorts that HIV serostatus is associated with more noncalcified coronary plaque, after adjusting for cardiovascular risk factors, and demonstrates that lower nadir CD4+ T cell count and longer duration of HAART are associated with coronary stenosis. Overall, these findings suggest that HIV infection is associated with subclinical coronary disease, even in the absence of traditional risk factors.

**ARTERIAL WALL INFLAMMATION AND HIGH RISK CORONARY PLAQUE IN HIV-INFECTED PERSONS**


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The mechanism of the increased propensity of patients with HIV toward cardiovascular events including myocardial infarction (MI) is proposed to include, in part, systemic inflammation, which predisposes to MI. Morphologic features of coronary plaque seen on imaging, including positive remodeling of the vessel wall, and low radiographic attenuation on CT imaging, have been shown to be associated with an increased risk of MI (plaque rupture) in the general population—these plaques have been called "vulnerable plaques." Given the hypothesized link between systemic inflammation and plaque rupture and MI in patients with HIV, Drs. Tawakol and colleagues assessed whether inflammation of the blood vessel wall was associated with more vulnerable coronary plaque in subjects with HIV, with the goal to provide a pathobiologic link between high-risk coronary disease and systemic inflammation.

Fifty-three patients with HIV infection and no history or symptoms suggestive of heart disease underwent coronary CT angiography to assess coronary plaque and FDG-PET imaging of the aorta (a radiologic imaging procedure that detects inflammation in the blood vessel wall). Twelve of the 53 subjects had no coronary disease and were
excluded from further analysis. Arterial inflammation was expressed as the ratio between radiologic tracer uptake in the aortic wall to the mean radiographic signal in the venous system. Each of 18 coronary artery segments was assessed for plaques, which were quantified and described morphologically. The subjects were divided into two groups based on the degree of aortic inflammation above or below the median value. Mean age was 51 years. There was a low prevalence of traditional cardiovascular risk factors, which was similar in both groups. HIV was well controlled in both groups; however, the group with less systemic inflammation had a lower mean CD4+ T cell count (485 versus 669, P = 0.04). Both groups had an average of three coronary plaques identified on CTA. Subjects in the high-inflammation group had more low-attenuation plaques and more low-attenuation plaques with positive remodeling (both signs of the potential for plaque vulnerability and instability). High aortic inflammation was associated with vulnerable plaque in multivariate regression models adjusting for age, duration of HIV infection, CD4 cell count, LDL level, and gender.

The authors conclude that arterial inflammation is associated with high-risk "vulnerable" coronary plaque, even in a group of patients with HIV infection with few traditional cardiovascular risk factors. The low-attenuation plaques of interest pathologically contain lipid-rich material with macrophages contained by a thin fibrous cap. This biology is consistent with the imaging and serologic findings of Dr. Tawakol and colleagues. None of the studied subjects were receiving statin therapy, which is known to be antiinflammatory. Future studies could be directed at whether statin therapy reduces arterial inflammation and transitions high-risk, low-attenuation plaques to more stable plaques. The absolute risk of progression of these vulnerable plaques and the effect of risk-factor modification in people with HIV infection are also areas in need of further study.

Little data exists on the prognosis and the optimal treatments for secondary prevention for patients with HIV who have had a myocardial infarction. Dr. D'Ascenzo and colleagues designed the Percutaneous Coronary Intervention and Surgical Revascularization in HIV Database to help fill this knowledge gap. The authors constructed a registry encompassing 12 US and European centers; 10,050 patients who presented with acute coronary syndromes were screened, and all those known to be infected with HIV were included retrospectively. Data including HIV and cardiovascular disease clinical variables were collected, and recurrent cardiac ischemic events and cardiac death were assessed over a mean follow-up of 24 months.

Two-hundred-one subjects with HIV infection (2.0% of the total number of patients with acute coronary syndrome) were included. Mean patient age was 54 years, and 88% of patients were male. Half of patients had hypertension, half had dyslipidemia, 20% had diabetes, and 23% were current smokers. Mean current CD4+ T cell count was 651 cells/mm3, and 17% of patients had detectable viral loads. Antiretroviral therapy was started a mean of 1.4 years before the acute coronary syndrome developed. Approximately one-third of patients presented with ST elevation myocardial infarction, one-third with non-ST segment elevation myocardial infarction, and one-third with unstable angina. Nearly half of patients had evidence of left main stem or multivessel coronary disease at angiography. Fifteen percent of patients died during follow-up period. Ten percent of patients had recurrent MI, 14% had subsequent coronary revascularization,
and 3% had stent thrombosis. Patients who died or had MI were more likely to have chronic kidney disease, CD4+ T cell count less than 200, and decreased LV ejection fraction. Being treated with an NRTI-sparing regimen was associated with greater likelihood of cardiac death.

The authors report that this is the largest study of acute coronary syndromes in patients with HIV, and their main conclusions are that lower CD4+ T cell count and use of an NRTI-sparing regimen are associated with increased cardiac risk. The population studied did have a high prevalence of typical cardiac risk factors, similar to those in other studies of HIV and CAD. These risk factors may have been synergistic with the chronic inflammatory response, particularly in those patients with lower CD4+ T cell counts. The high rate of stent thrombosis is also noteworthy; how the use of newer drug-eluting stents and novel antiplatelet agents such as prasugrel and ticagrelor would mitigate this risk in patients with HIV, as they do in the general population, is not known. Limitations of the study include its retrospective nature and relatively short duration of follow-up. It could be assumed that even more patients would be subject to recurrent events as the time horizon lengthens. The adjudication of endpoints relied on chart review rather than prospective data collection. Finally, there was no comparison to a control group without HIV who had acute coronary syndrome.

In summary, this large observational study demonstrated that treatment with an NRTI sparing regimen and a low CD4 count are associated with increased risk of cardiac death in subjects with HIV. While study limitations suggest that confirmation in future studies will be important, nonetheless, this study represents an important assessment of the presenting features and prognosis of acute coronary syndromes in patients with HIV infection.

ATRIAL FIBRILLATION/ATRIAL FLUTTER IN HIV-INFECTED PERSONS


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In addition to atherosclerosis, HIV infection has been associated with an increased risk of stroke. Although cerebral and coronary atherosclerosis share pathophysiologic mechanisms, atrial fibrillation (AF) with attendant cardioembolism may be an additional mechanism of stroke. Many of the conventional risk factors for atherosclerosis also place patients at risk for atrial fibrillation. Whether atrial fibrillation is associated with HIV infection has not been established. In this 2013 publication, Dr. Hsu and colleagues present a retrospective cohort study using the VA HIV Clinical Case registry, a database capturing demographics and clinical data of all patients with HIV who receive care in the VA system. Over 30,500 patients were included for this analysis, enrolled between 1996 and 2011. The endpoint of interest was new diagnosis of atrial fibrillation, assessed by ICD-9 code. HIV clinical factors including CD4+ T cell count and HIV viral load, comorbid cardiovascular risk factors, thyroid disease, and alcohol use, as well as lab and demographic data were assessed. Over a median follow-up length of 6.8 years, 780 patients (2.6%) developed atrial fibrillation or atrial flutter, yielding an incidence of 3.6 arrhythmic events per 1,000 person-years. AF was over 15 times more likely to be present in patients older than 65 compared to those younger than 35, and Caucasian patients had higher rates of AF at older ages compared to African American patients. Patients with CD4+ T cell counts less than 200 were 40% more likely to have AF compared to those with counts greater than 350, and patients with viral load greater than 100,000 copies/mL were 70% more likely to have AF compared to those with viral load less than 500 copies/mL. Common AF risk factors of hypertension, diabetes, smoking, obesity, coronary disease, and chronic kidney disease were more prevalent in patients with AF compared to those without.
The authors conclude that their report represents the first representative sample of the incidence of AF among patients with HIV and establishes that the severity of HIV disease represents a possible risk factor for AF development. For comparison, they present the incidence rates of AF in unselected major epidemiologic cohorts, including the ARIC, Framingham, and Rotterdam studies. The authors present an AF incidence rate of 8.7 per 100,000 person years for patients with HIV aged 55-64, while in the general population, incidence rates vary from 1.4-5.8 per 100,000 person years. Similarly, for subjects with HIV aged 65-74, the published incidence rate of 15.5 per 100,000 person years is compared to 5.3-12.9 per 100,000 person-years in subjects without HIV infection.

This study suggests that HIV is associated with increased propensity toward atrial fibrillation, but given that the published study did not include a control group without HIV infection, this conjecture is hypothesis-generating only.

That more severe HIV disease was associated with increased risk of AF is compelling. Future studies should be directed at both mechanism of this association, be it increased systemic inflammation, drug effect, or other pathways, as well as the consequences, including documenting the stroke and heart failure risk associated with the increased propensity to AF.

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**MYOCARDIAL DISEASE IN HIV-INFECTED PATIENTS WITHOUT KNOWN STRUCTURAL HEART DISEASE**


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In contrast to the emerging body of literature investigating HIV-associated atherosclerosis, there is correspondingly little data as to nonatherosclerotic manifestations of HIV-related heart disease. In the pre-ART era, it was thought that HIV-associated structural heart disease and ventricular dysfunction were common. Current studies of patients with well-controlled HIV infection and access to ART suggest a low prevalence of structural heart disease, including myocardial systolic and diastolic dysfunction and valvular disease, as assessed by conventional echocardiography. Cardiac MRI can provide more detailed information about cardiac mechanics and metabolism and represents a helpful tool to screen for subclinical myocardial dysfunction and structural heart disease.

Dr. Holloway and colleagues present an observational study in which 90 HIV-infected subjects and 39 uninfected control subjects underwent cardiac MRI, MR spectroscopy, and measurement of biometrics including body composition. Subjects had no known history of cardiovascular disease. The majority of subjects with HIV (84%) had viral suppression to less than 50 copies/mL. One-third of patients were taking protease inhibitors, and 68% were taking an NNRTI. Subjects had been treated for mean of 7.4 years. Mean CD4+ T cell count was 546, and 55% of subjects had pretreatment CD4 nadir < 200 cells/µL. Prevalence of cardiac risk factors including hypertension, dyslipidemia, and diabetes were low in both groups. Subjects with HIV infection had lower HDL cholesterol and higher triglyceride levels than control subjects. Intramyocardial lipid levels on cardiac MRI were 47% higher in patients with HIV compared to control. Markers of left ventricular systolic strain and peak diastolic strain rate were significantly worse in subjects with HIV compared to control, suggesting abnormal cardiac function. Subjects with HIV had more evidence of myocardial fibrosis, in a pattern suggesting previous myocarditis, compared to control.

Prior to this study, little data had been published data documenting cardiac MRI findings in patients with HIV, and this is the first report of increased cardiac steatosis associated with HIV infection. Given the altered serum lipids observed in the cohort with HIV infection, the authors hypothesize that myocardial steatosis is a consequence of HIV-associated dyslipidemia and HIV-associated dysglycemia. The functional significance of increased myocardial lipid is unclear, but one could hypothesize a deleterious effect on myocardial
In summary, this study demonstrates that subjects with HIV infection have significant subclinical myocardial abnormalities, including cardiac steatosis and increased myocardial fibrosis. Whether these findings are the result the HIV infection itself or other factors such as dyslipidemia or associated infections is not known. Future studies should be aimed at defining the pathogenesis and clinical significance of these changes.

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**STATEMENT OF NEED:**

- As the demographics of HIV have shifted to include many older adults, clinicians require education regarding the treatment of common comorbidities.
- Clinicians may be unclear about issues specific to the diagnosis and treatment of women with HIV.
- Many clinicians require education regarding current treatment and new emerging hepatitis C medications in patients coinfected with HIV/HCV who require antiretroviral therapy.
- Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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