Title

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Permalink

https://escholarship.org/uc/item/04g09775

Journal

HIV Medicine, 16(10)

ISSN

1464-2662

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Publication Date

2015-11-01

DOI

10.1111/hiv.12262

Peer reviewed

HIV infection is associated with increased coronary non-calcified plaque among participants with coronary artery calcium score of zero: Multicenter AIDS Cohort Study (MACS)

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Abstract

Objectives—HIV infected individuals bear increased cardiovascular risk even in the absence of traditional cardiovascular risk factors. In the general population, coronary artery calcium (CAC) scanning is of value for cardiovascular risk stratification, but whether a CAC score of zero implies a low non-calcified coronary plaque burden in HIV infected persons is unknown.

Methods—We assessed the prevalence of non-calcified coronary plaque and compared non-calcified coronary plaque burden between HIV infected and HIV uninfected participants who had CAC scores of zero in the Multicenter AIDS Cohort Study (MACS) using coronary CT angiography.

Results—HIV infection was associated with the presence of non-calcified coronary plaque among these men with CAC scores of zero. In a model adjusted only for age, race, center, and pre or post 2001 cohort, the prevalence ratio for the presence of non-calcified plaque was 1.27 (95% confidence interval 1.04–1.56, p = 0.02). After additionally adjusting for CVD risk factors, HIV infection remained associated with the presence of non-calcified coronary plaque (PR 1.31; 95% CI 1.07–1.6, p = 0.01).

Conclusions—In conclusion, among men with CAC scores of zero, HIV infection is associated with an increased prevalence of non-calcified coronary plaque independent of traditional cardiovascular risk factors. This finding suggests that CAC scanning may underestimate plaque burden in HIV infected men.

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Introduction

The availability of potent combination anti-retroviral therapy (cART) has transformed HIV infection into a chronic illness with marked reduction in HIV-related mortality [1, 2], and coronary artery disease has emerged as an important cause of death for HIV-infected patients treated with cART [3].

HIV-infected persons have a high burden of subclinical atherosclerosis including increased amount of non-calcified coronary plaque compared to HIV uninfected individuals [4, 5], even among subjects at low cardiovascular risk by traditional measures [6]. In the general population, coronary artery calcium (CAC) scoring using non-contrast computed tomography (CT) images may be considered for risk stratification in patients at intermediate clinical risk by traditional risk scoring systems [7], but whether a CAC score of zero implies a low amount of non-calcified plaque in HIV-infected patients is unknown. We assessed the prevalence of non-calcified coronary plaque and compared non-calcified coronary plaque burden between HIV infected and HIV uninfected participants who had CAC scores of zero in the Multicenter AIDS Cohort Study (MACS).

Methods

The MACS is a prospective cohort study of demographically similar HIV infected and HIV uninfected men who have sex with men. Subjects were enrolled in the study from 1984 to 1985, 1987 to 1991, and 2001 to 2003 [8]. The study is conducted at 4 sites: Chicago, Pittsburgh, Baltimore/Washington DC, and Los Angeles. Participants undergo standardized evaluations semi-annually with medical/behavioral histories, physical examinations and laboratory assessments. Men enrolled in the cardiovascular sub-study [5] were age 40 to 70 years, weighed less than 300 pounds, and were without prior coronary revascularization. Exclusion criteria were atrial fibrillation, intravenous contrast allergy, and chronic kidney disease as assessed by an estimated glomerular filtration rate less than 60 ml/min/1.73m^2 by the Modification of Diet in Renal Disease equation within 30 days of the CT scan.

The CT scanning methods and analytic approach were previously described [9]. Briefly, non-contrast CT and coronary CT angiography were performed using a 64 slice multi-detector scanner at 3 centers and a 320 slice scanner at the fourth center. Men were pre-treated with beta-blockers or calcium channel blockers as needed to slow the heart rate and with sublingual nitroglycerin unless contraindicated. Images were analyzed by a single core laboratory (Harbor UCLA Medical Center) and the readers were blinded to participant data. Coronary plaque was assessed and measured in each of the 15 coronary segments specified by the American Heart Association. Plaque size was subjectively graded on a scale from 1 (no plaque) to 3 (severe plaque) [5, 9]. Stenosis in each segment was graded on a scale from 0 to 4, 0 (0%), 1 (1–29%), 2 (30–49%), 3 (50–69%) and 4 (>70%). Each plaque was assessed as calcified, non-calcified, or mixed (corresponding to less than 50% area of plaque calcified). The non- calcified plaque score was calculated by summing the individual segment scores with non-calcified plaque over all 15 coronary segments. CAC scores were calculated using the method of Agatston [9].

Clinical data from the MACS semi-annual research visit most proximal to the CT scan were used. Laboratory assessment included serum creatinine within 30 days of CT angiography, serum glucose levels, total and high density lipoprotein cholesterol and triglyceride levels, calculated LDL levels by the Friedewald equation or measured directly if non-fasting or triglycerides > 400 mg/dL. HIV-related characteristics included plasma HIV RNA levels and CD4+ T cell counts/mL (current and nadir), years on cART and history of clinical AIDS. Ethnicity and smoking status were self-reported. Hypertension was defined as blood pressure greater than 140/90 mmHg or the use of antihypertensive agents with self-reported history of hypertension. Diabetes was defined as fasting plasma glucose 126 mg/dL or use of medications prescribed for diabetes with a self-reported history of diabetes.

Demographics and HIV clinical factors were compared using Wilcoxon rank sum tests or chi square tests as appropriate. Poisson regression with robust variance was performed in men with Agatston score of 0 to assess associations between HIV serostatus and the presence of non-calcified coronary plaque. Models were adjusted for age, race, CT scanning center and pre- or post- 2001 cohort, and then additionally for coronary artery disease (CAD) risk factors, including systolic blood pressure, use of antihypertensive, diabetic, or lipid lowering medications, total and HDL cholesterol, body-mass index, smoking (pack years), and fasting serum glucose. For subjects with missing data for cardiovascular risk factors, multiple imputation was used. Data was imputed for use of antihypertensive medications (N=1), body-mass index (N=11), use of diabetes medications (N=1), use of medications for dyslipidemia (N=3), total and HDL cholesterol (N=7), systolic blood pressure (N=17), and fasting glucose (N=11).

Results

Coronary CT angiography and non-contrast cardiac CT scans were completed in 450 HIV infected subjects and 309 HIV uninfected participants. A CAC score of 0 was seen in 225 HIV infected participants (50%) and 149 HIV uninfected participants (48%); the analysis focused on these participants exclusively.

Of the 225 HIV infected men with CAC score of zero, 125 (55.6%) had non-calcified coronary plaque present on coronary CT angiography. Of 149 HIV uninfected men, 72 (48.3%) had non-calcified coronary plaque present. The median total plaque score was 2 among the men with non-calcified plaque present in both groups (interquartile range 1–3). Nearly all plaques were non-obstructive in both groups; 97.4% of HIV uninfected subjects with plaque and 97.3% of HIV infected subjects with plaque had stenosis severity less than 50%.

The Table describes the socio-demographic and clinical characteristics of the sample by HIV serostatus. HIV uninfected men were slightly older than HIV infected men (means 52.7 v. 50.2 years, p=0.001). A higher percentage of HIV infected men were non-Caucasian. Traditional cardiovascular risk factors were similar between groups, with the exception of a higher prevalence of current tobacco use in the HIV infected men. The HIV infected men also had lower plasma HDL cholesterol (50.2 v. 54.7 mg/dL, p = 0.002) and higher triglycerides (153.9 v. 115.7 mg/dL, p < 0.001).

Nearly all the HIV infected men were cART-treated; the median time since cART initiation was 11.6 years. A majority of infected men had undetectable plasma HIV RNA levels (< 50 copies/mL) and CD4+T cell counts > 500/mm^3.

After multivariate adjustment, HIV infection was associated with an increased prevalence of non-calcified coronary plaque among men with CAC scores of 0: In a Poisson model adjusted for age, race, center, and pre- or post-2001 cohort, the prevalence ratio (HIV-infected vs HIV-uninfected) for the presence of non-calcified plaque was 1.27 (95% confidence interval 1.04–1.56, p = 0.02). After additional adjustment for CVD risk factors, HIV infection remained associated with an increased prevalence of non-calcified coronary plaque [PR 1.31(1.07–1.60), p = 0.01]. Among HIV infected men, there were no associations between the presence of non-calcified plaque and HIV clinical factors including nadir CD4+ T cell count [PR 0.95 (0.87–1.03)], years of cART [PR 1.01 (0.66–1.17)], history of AIDS [PR 0.99 (0.71–1.4)], current CD4+ T cell count [PR 1.0 (0.97–1.05)], and presence of detectable plasma HIV RNA [PR 0.88 (0.66–1.17)] (all p > 0.05).

Discussion

We found that among men with a CAC score of zero, a substantial proportion had non-calcified coronary plaque. HIV infection was associated with an increased prevalence of plaque even after adjustment for cardiovascular risk factors.

Within the MACS cardiovascular disease study, approximately half of the men had CAC scores of zero. Given the age distribution of the population studied, co-morbid cardiac risk factors, and racial distribution, this percentage is comparable to other population estimates including those seen in the Multi-Ethnic Study of Atherosclerosis (MESA) [10]. Of the men with zero CAC, 48% of HIV uninfected subjects and 55% of HIV infected subjects had non-calcified coronary plaque. This plaque did not correlate with obstructive coronary disease. Despite the non-obstructive nature of these plaques, they may be prone to subsequent rupture and potential acute coronary syndromes [11]. Future studies will be needed to further characterize risk factors for rupture and for progression of non-obstructive plaques [11]. Other studies conducted among HIV uninfected persons have demonstrated the presence of non-calcified plaque in persons with zero CAC at a rate of 6.5% [12] and 10% [13], in contrast to our demonstrated rates of 48–55%. This difference may be due to differential risk factor profiles, demographics, or improved scanning techniques.

Our group has previously demonstrated that HIV infection is associated with a greater prevalence and extent of non-calcified coronary plaque [5]. The current results suggest that even among men with a CAC score of zero, HIV infection remains associated with an increased prevalence of non-calcified coronary plaque. The pathophysiology may involve increased inflammation and immune activation both systemically [14] and in the blood vessel walls [15]. Whether this increased propensity toward non-calcified coronary plaque will translate into greater numbers of acute coronary syndrome events among HIV-infected patients with CAC scores of zero is unknown; while a CAC score of zero has been shown to be a powerful predictor of lifespan longevity in the general population [16], this remains to

be demonstrated among HIV-infected persons. Longitudinal studies to clarify this question are needed.

In multivariate models, no specific HIV-related clinical factor was associated with the presence of non-calcified coronary plaque. Although some studies have suggested that protease inhibitor exposure is associated with myocardial infarction [17], a large observational study of over 36,000 patients demonstrated no association between specific cART agents and myocardial infarction [18]. Nadir CD4+ T cell count has been associated with progression of carotid intima-media thickness [19], however our results may suggest that in the lower risk zero CAC subgroup, there is less prognostic import of HIV-related clinical factors, at least in relation to non-calcified coronary plaque. We may have had limited power to detect a difference in this patient subgroup.

There are some limitations to our analysis. Our population included men who have sex with men only and hence findings may not be generalizable to women or to other HIV-infected risk groups. The most recent enrollment period of this sample of the MACS cohort was over a decade ago and as such, cART prescribed was different than the current standard of care. We measured subclinical atherosclerosis as a surrogate for coronary events; future studies should incorporate clinical follow-up to identify subclinical plaque associations with coronary and cerebrovascular events.

In conclusion, we demonstrate that among men with CAC scores of zero, HIV infection is associated with an increased prevalence of non-calcified coronary plaque independent of traditional cardiovascular risk factors. This finding suggests that CAC scanning may underestimate the presence of non-calcified plaque in HIV infected men, and hence of overall CVD risk; further studies to evaluate optimal modes of both atherosclerosis imaging and CVD risk in this patient group are warranted.

Acknowledgments

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Table

Characteristics of study population (men with CAC of zero)

	HIV+ (N=225)	HIV− (N=149)	p-value[*]
Age (years)	50.2 (5.6)	52.7 (6.9)	0.001
Race (%)			<0.001
Caucasian	36.0	57.7	
African-American	44.9	30.9	
Hispanic/Other	19.1	11.4	
Hypertension (%)	38.6	34.5	0.43
Systolic blood pressure (mm Hg)	125.1 (14.3)	127.1 (15.3)	0.31
Hypertension medications (%)	24.0	20.9	0.49
Diabetes (%)	10.5	5.6	0.11
Diabetes medications (%)	7.6	3.4	0.09
Glucose (mg/dL)	99.1 (21.2)	98.0 (31)	0.21
Tobacco use (%)			0.02
Never smoker	31.1	24.8	
Current smoker	31.1	22.8	
Former smoker	37.8	52.3	
Smoking pack-years	2.5 (0–13.4)	2.1 (0–10.6)	0.80
Body Mass Index (kg/m^2)	26.3 (4.5)	26.9 (4.4)	0.16
Total Cholesterol (mg/dL)	185.9 (40.2)	188.3 (35.8)	0.42
LDL Cholesterol (mg/dL)	105.8 (34.6)	110 (32.8)	0.10
HDL Cholesterol (mg/dL)	50.2 (16.9)	54.7 (16.7)	0.002
Triglycerides (mg/dL)	153.9 (103.3)	115.7 (64.7)	<0.001
Lipid lowering medications (%)	22.9	16.9	0.16
Serum Creatinine (mg/dL)	1.0 (0.2)	1.0 (0.1)	0.67
<u>HIV clinical factors</u>			
Current HIV RNA undetectable, < 50 copies/mL, N (%)	175 (78.1)		
Current HIV RNA (copies/mL)[&]	611 (107–43300)		
Current CD4+ T-cell count (cells/mm^3)	589 (390–777)		
CD4+ T-cell count nadir (cells/mm^3)	251 (141–331)		
Initiated cART, N (%)	217 (96.4)		
Protease inhibitor use, N (%)	109 (48.4)		
NNRTI use, N (%)	103 (45.8)		
Duration of cART (years)	11.6 (8.1–13.5)		
Duration of Protease inhibitor use (years)	4.3 (0.3–8.7)		
Duration of NNRTI (years)	3.4 (0.2–6.9)		
History of AIDS, N (%)	22 (9.8)		

Data are reported as mean (standard deviation), percentage, or median (interquartile range: 25%–75%) for non-normally distributed variables. P values are unadjusted and are comparing infected and uninfected values.

[&]Among men with detectable viral load

NNRTI = non-nucleoside reverse transcriptase inhibitor