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Multicenter AIDS Cohort Study (MACS) Quantitative Coronary Plaque Progression Study: Rationale and Design

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Abstract

Background and Aims—The association of human immunodeficiency virus (HIV) with coronary atherosclerosis has been established; however, the progression of coronary atherosclerosis over time among participants with HIV is not well known. The Multicenter AIDS Cohort Study (MACS) Quantitative Coronary Plaque Progression Study is a large prospective multicenter study quantifying progression of coronary plaque assessed by serial coronary computed tomography angiography (CTA).

Design—HIV-infected and uninfected men who were enrolled in the MACS Cardiovascular substudy were eligible to complete a follow-up contrast coronary CTA 3–6 years after baseline. We measured coronary plaque volume and characteristics (calcified and non-calcified plaque including fibrous, fibrous fatty and low attenuation) and vulnerable plaque among HIV infected and uninfected men using semi-automated plaque software to investigate the progression of coronary atherosclerosis over time.

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Conflict of Interest disclosure statement

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Summary—We describe a novel, large prospective multicenter study investigating incidence, transition of characteristics, and progression in coronary atherosclerosis quantitatively assessed by serial coronary CTAs among HIV infected and uninfected men.

Keywords

Coronary artery disease; plaque progression; vulnerable plaque; coronary computed tomographic angiography; human immunodeficiency virus

INTRODUCTION

Recent advances in human immunodeficiency virus (HIV) treatment, such as highly active antiretroviral therapy (HAART), have extended life expectancy in HIV infected individuals. HIV is no longer considered a fatal disease and instead has become a chronic disease condition. However, due to immune activation and inflammation from the HIV virus, metabolic abnormalities (i.e. dyslipidemia and insulin resistance) due to antiretroviral medications, and a high prevalence of traditional cardiovascular disease (CVD) risk factors, HIV infected individuals are more likely to have subclinical coronary artery disease (CAD) than those without HIV infection¹. This could potentially result in an increase in future CVD risk. There have been a few studies reporting plaque progression measured by carotid ultrasound assessed intima media thickness and focal plaque^{2, 3}, but we are unaware of any large-scale studies assessing progression of coronary atherosclerotic quantitative plaque volume and composition in HIV-infected and uninfected participants over time.

Coronary computed tomography angiography (CTA) can non-invasively identify the presence, extent and severity of coronary atherosclerosis with high accuracy^{4, 5}. Recent advances in coronary CTA technology allow extensive detail in regards to coronary atherosclerosis such as plaque characteristics and volumes, which can provide further insight into the pathophysiology of coronary atherosclerosis and its association with future CVD risk^{6, 7}. We are conducting the MACS Quantitative Coronary Plaque Progression Study to explore the association between HIV and the progression of coronary atherosclerosis in a large, well-characterized study population.

Materials and Methods

Study design

The Multicenter AIDS Cohort Study (MACS) is an ongoing prospective cohort study of the natural and treated histories of HIV infection, conducted at four sites in the U.S (Baltimore, Maryland/Washington D.C.; Chicago, Illinois; Pittsburgh, Pennsylvania; and Los Angeles, California). Begun in 1984, the MACS has enrolled gay and bisexual men with and without HIV infection who are followed through semi-annual study visits. Study visits include standardized interviews, physical examinations, and the collection of blood and other biologic samples. MACS participants underwent baseline coronary CT scans from 2010–2013 in the MACS cardiovascular CT study¹. The present study will determine differences in the presence, extent and severity of coronary artery disease (CAD) progression over time by HIV serostatus, among participants who undergo a follow-up CTA between 2015 and

2017 (Figure 1). Each institution obtained Institutional Review Board approval. All participants provided informed consent.

Study objectives

Primary objective—The MACS cardiovascular CT study previously demonstrated that HIV infected men have a greater prevalence and extent of coronary plaque, particularly non-calcified plaque, compared to HIV uninfected participants ¹. The primary objective of the MACS Quantitative Coronary Plaque Progression Study is to investigate whether HIV-infected men have a greater progression of total plaque volumes, both calcified and non-calcified coronary atherosclerosis including fibrous, fibrous-fatty and low attenuation plaque, than HIV uninfected men over a 3–6-year follow-up period. We will evaluate coronary atherosclerosis through the use of semi-automated plaque analysis software, which is a novel method to more accurately identify the characteristics of non-calcified plaque and overall volumes in coronary atherosclerosis ^{8–11}.

Secondary objective—The secondary objectives of this study are to determine whether HIV infected men have (1) a greater incidence of new non-calcified plaque and/or slower rates of transition from non-calcified to calcified plaque on a per-patient, per-vessel and per-segment basis, and (2) a greater prevalence and incidence of high-risk vulnerable plaques compared to HIV uninfected men. Vulnerable plaque will be defined as plaques with low attenuation, positive remodeling, and spotty calcification. Using the routine data collected during MACS semi-annual research examinations, we will also investigate whether clinical risk factors and medical treatments, such as specific HIV medications or statins, influence the characteristics, incidence and progression of coronary atherosclerosis over time.

Study eligibility

Participant eligibility—Details regarding inclusion and exclusion criteria for the MACS cardiovascular sub-study were described in a prior report ¹. In brief, all men were aged between 40 and 70 years, weighing <136kg (300 pounds), and did not have histories of cardiac surgery or coronary interventions at the time of their baseline cardiac CT scan. The CTA had additional exclusion criteria: atrial fibrillation, chronic kidney disease as defined by an estimated glomerular filtration rate <60 mL/min/1.73m² or allergy to contrast agents. A total of 1006 (n=621 HIV-infected/385 HIV-uninfected) men underwent a 64-slice non-contrast CT study for CAC scanning between January 2010–November 2013, 765 (453 HIV-infected/312 HIV-uninfected) of whom also completed contrast coronary CTA scanning ^{1,12}. Impaired kidney function was the primary reason for exclusion from CTA at baseline, and the differences in the participants with and without CTA scanning have been described¹. Participants with a baseline CTA scan were eligible to undergo a follow-up 64-slice coronary CTA scan from 2015–2017 if their estimated glomerular filtration rate was ≥60 mL/min/1.73m² and they had not experienced a contrast dye allergy. Considering study attrition, deaths, refusals, and incident renal insufficiency, we estimate that ~75% of participants will complete a follow-up coronary CTA, for an anticipated sample size of ~574 men (340 HIV-infected/234 HIV-uninfected).

Participant follow-up—Each site sent recruitment letters to eligible study participants ~3–5 years after their baseline CT scans. A trained MACS research assistant explained the CT progression study during a routine MACS study visit, determined eligibility, answered questions, and obtained informed consent, or recruitment took place by telephone with consent obtained at the CT study visit.

Details regarding collection of participant data on clinical variables has been described previously^{1,11}. Briefly, clinical demographics, HIV clinical variables (i.e. HIV RNA viral load levels, CD4+ T-cell counts, history of an AIDS-defining cancer or opportunistic infection, and duration of highly active antiretroviral therapy) and blood samples (i.e. fasting glucose, total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglyceride and creatinine) were collected every 6 months for general MACS research visits. Serum creatinine was also measured within 30 days of each coronary CTA study to determine scan contrast coronary CTA eligibility. All data is managed at the data center at Johns Hopkins University School of Medicine, Baltimore, Maryland.

Acquisition and interpretation of coronary CTA

All participants in the current serial coronary CTA study underwent 64 slice coronary CTA at baseline (Lightspeed VCT, GE Healthcare, Milwaukee, WI; Somatom Sensation and Definition CT, Siemens, Forchheim, Germany; Aquilion One, Toshiba, Otawara, Japan) and follow-up (Lightspeed VCT or REVOLUTION, GE Healthcare, Milwaukee, WI; Somatom Sensation and Definition CT, Siemens, Forchheim, Germany; Aquilion One, Toshiba, Otawara, Japan) and non-contrast CT for coronary artery calcium (CAC). If required, an oral and/or intravenous beta-blocker or a calcium channel blocker was administered in order to reach a target heart rate <65 beats/minute. Sublingual nitroglycerin was also administered prior to IV contrast injection, unless contraindicated.

Scan parameters for non-contrast CT are obtained as follows: prospective electrocardiogram-triggering, 512×512 matrix size, and peak tube voltage of 120 kVp. The contrast cardiac CTA scanning protocols have been previously reported^{1, 12}. Scanning parameters included: < 1mm slice thickness, 20mm field of view, 512×512 matrix size, and tube voltage of 120, 100 or 80 kVp (100 or 80 kVp used in participants with a body mass index <25kg/m²). Prospective or retrospective electrocardiogram-triggering is employed.

Coronary CTA image analysis for coronary plaque type and volume—CT images are transferred to the core CT reading center (Harbor UCLA Medical Center, Torrance, California, USA) and analyzed by trained, experienced readers blinded to participant characteristics and HIV serostatus. Coronary CTA scans are assessed using a 17-segment American Heart Association coronary tree model in accordance with the Society of Cardiovascular Computed Tomography guidelines¹³. Experienced readers evaluate coronary CTAs for the presence, characteristics and volume in coronary plaques using a semi-automated quantitative plaque analysis software (QAngioCT Research Edition version 3.0.37, Medis medical imaging systems, Leiden, The Netherlands) (Figures 2–4). The software automatically extracts centerlines and performs automated detection of the inner

lumen and vessel wall contours from the ostium to the distal end of each artery and straightens the multiplanar reformatted images. The contours for the coronary lumen or vessel are manually modified when necessary. In order to visualize the lumen, vessel and plaque, 740 and 220 Hounsfield units (HU) are used for window and width levels¹⁴. Vessel and plaque volumes are measured in segments with sufficient image quality and with a lumen diameter ≥ 1.5 mm. Vessel length is defined as the length of coronary arteries in measured segments. If participants underwent coronary intervention during follow-up, segments with stents are excluded from the analyses. Since the attenuation of coronary plaque is influenced by lumen contrast intensity, coronary plaque including non-calcified plaque (fibrous, fibrous-fatty and low attenuation plaque [LAP]) and calcified plaque are defined based upon plaque densities, which are adjusted to lumen contrast intensity¹⁵.

To accurately assess serial coronary CTAs for the determination of plaque progression, we match the location and length of each segment between baseline and follow-up to compare the progression in coronary atherosclerosis at a per-patient, per-vessel and per-segment levels. Vulnerable plaque is defined as fulfilling two of these three criteria: a plaque with remodeling index >1.1 , spotty calcification and presence of low attenuation plaque (LAP)¹⁶. As previously reported¹⁶, spotty calcifications are defined as calcifications in non-calcified plaque, with length <3 mm and arc of ≥ 90 degrees. Coronary arterial remodeling is defined as a remodeling index (lesion diameter/reference diameter) greater than 1.1. Hounsfield Unit (HU) <30 within the non-calcified plaque is manually measured and is used to determine the presence of LAP^{16, 17}.

Statistical methods

Clinical and demographic characteristics will be compared between HIV- and HIV+ participants, using the Chi-square or Wilcoxon rank-sum tests. Incident plaque progression will be described by HIV serostatus at the individual, vessel, and coronary artery segment level. Per-patient, per-vessel, and per-segment analyses will be conducted to demonstrate the differences in plaque characteristics, volume and change over time. Univariable and multivariable regression analyses will be used to determine if HIV infection is associated with each plaque progression outcome, using Poisson models for incident dichotomous outcomes and linear or generalized Gamma models for continuous outcomes. Analyses will account for inter-scan duration. Per-segment and per-vessel analyses will adjust for correlation within individuals. We will also investigate whether clinical risk factors and medical treatments influence the characteristics, incidence and progression of coronary atherosclerosis over time, as covariates in the multivariable regression models. Sensitivity analyses will be conducted to assess the robustness of the associations between HIV and plaque progression under varying assumptions.

DISCUSSION

The MACS Quantitative Coronary Plaque Progression Study is a novel, prospective multicenter study investigating the progression of coronary atherosclerosis among HIV-infected compared to uninfected men. We have enrolled >540 participants who have returned 3–6 years after their baseline scan to undergo a second coronary CTA. This is the

largest study, to our knowledge, of coronary CTA in a cohort that includes both HIV+ and HIV- participants who undergo serial coronary CTA examinations.

Recent advances in coronary CTA software have applied time-saving, accurate methods to evaluate coronary plaque volume by semi-automated quantitative CT analysis. Studies demonstrate accurate evaluations of plaque volume between readers, and also when compared to intravenous ultrasound (IVUS) ⁸⁻¹¹. Coronary CTA is a non-invasive modality that can illustrate the entire heart with a 3-dimensional image, allowing visualization of all coronary arteries with immense detail in order to determine overall atherosclerosis burden, as well as its progression over time. IVUS is generally utilized for measuring limited coronary segments, and is generally utilized in high risk patients who clinically require invasive coronary angiography. Serial IVUS studies performed for research purposes are not usually performed in low CVD risk research participants.

Recent studies indicate that clinical risk factors are associated with overall plaque volume on coronary CTA quantitatively measured by semi-automated software ¹⁸ as well as progression in plaque characteristics and volume ¹⁹. Also, changes in plaque volume and characteristics on serial coronary CTA studies associated with pharmacologic therapies have been reported ²⁰⁻²³. These studies suggest that non-invasive assessment by coronary CTA scans may be an alternative and more practical method for the identification of plaque progression and characteristics than IVUS. In this regard, the assessment in plaque volume by coronary CTAs could potentially aid in monitoring risk factors and therapies to stabilize coronary atherosclerosis ¹⁴.

The current study will also analyze longitudinal effects of HIV medications, statins and clinical factors on coronary atherosclerosis and plaque composition. These data may help to determine effective CVD prevention approaches in HIV patients. In a recent small study of 40 HIV patients, statin therapy reduced non-calcified plaque volume and high risk plaque features measured by coronary CTA scans over time ²⁴. The current primary prevention guidelines for the general population suggest that statin therapy is appropriate for consideration in asymptomatic patients with 10 year atherosclerotic cardiovascular disease risk >7.5% ²⁵. Although adverse side effects of statins are infrequent, it still remains unclear whether statins should be routinely prescribed to the HIV population, as the prevalence of statin hepatotoxicity is not well documented, especially in those with liver dysfunction, and statin medications have the potential to interact with some anti-retroviral therapies. The Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE) is ongoing to examine whether statin use reduces the risk of CVD events in HIV-infected patients and will also include a longitudinal coronary CT substudy (*ClinicalTrials.gov*. NCT02344290). The goal of the MACS Quantitative Coronary Plaque Progression Study is to provide insight regarding the association between HIV, its clinical risk factors and progression in coronary atherosclerosis. These results may help to understand the underlying pathophysiology, as well as identify potentially effective treatments for future study in HIV patients to help prevent future CVD events.

Limitation

The clinical indications for coronary CTA in asymptomatic individuals is still unclear. Although a few studies have indicated the clinical utility of coronary CTA for assessing risk in asymptomatic patients^{26, 27}, its routine use is uncertain. However, there have been no studies conducted to investigate if coronary plaque characteristics, burden and its change are associated with future adverse cardiac events, which as a result may potentially provide further insight into the identification of risk among the asymptomatic high risk population. In addition, this study includes radiation exposure, generally <6 milliseiverts (mSv) for total of contrast and noncontrast cardiac CT scans; however, current advances in technology have allowed coronary CTA scans to reach low radiation doses within 1–2 mSv, and even <1mSv²⁸, which is equal or even lower than that for non-contrast CT in evaluating CAC among asymptomatic individuals. Lastly, we use a manual method for identifying LAP to determine vulnerable plaque as reported previously¹⁷. The quantitative identification of LAP by automated software may more accurately determine vulnerable plaque; however, this technology is not currently available.

Conclusion

The MACS Quantitative Coronary Plaque Progression Study is designed to explore the association between HIV, clinical characteristics and the progression in coronary atherosclerosis. This large cohort study including HIV-infected and uninfected men who undergo serial coronary CTA scans can provide pathophysiological insights about coronary atherosclerosis in HIV participants.

New Knowledge Gained

The current study examining the association between coronary plaque characteristics, burden and its change could potentially provide further insight into the mechanisms of cardiovascular risk among the asymptomatic HIV population.

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Abbreviations

Coronary CTA	Coronary computed tomographic angiography
CAD	Coronary artery disease
CVD	Cardiovascular disease
HIV	Human immunodeficiency virus

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1- CCTA: Coronary Computed Tomography Angiography 2- Includes 2 participants who seroconverted between baseline and follow-up 3- Study enrollment is ongoing

Figure 1.

Schema of the study

Abbreviations: CT-Computed tomography

Figure 2. Sample of the new plaque formation in the right coronary artery. No plaque was detected at baseline on straightened multi-planar reformat (A) and cross-sectional images (B). Five years later, new plaque was formed in the proximal segment on straightened multi-planar reformat (C) and cross-sectional images (D).

Figure 3. Sample of the change in plaque characteristics in the left circumflex. Non-calcified plaque including fibrous, fibrous fatty and low attenuation was detected in the proximal segment at baseline on straightened multi-planar reformat (A) and cross-sectional images (B). Four years later, the non-calcified plaque converted to more calcified plaque [straightened multi-planar reformat (C) and cross-sectional images (D)].

Figure 4. Sample of the vulnerable plaque overtime in the right coronary artery. Positive remodeling and large area of plaque were detected at baseline on straightened multi-planar reformat (A) and cross-sectional images (B). In 5 years, the characteristics and volumes in plaques at the proximal segment were slightly changed overtime [straightened multi-planar reformat (C) and cross-sectional images (D)].