Published in final edited form as:

AIDS. 2008 August 20; 22(13): 1589–1599. doi:10.1097/QAD.0b013e328306a6c5.

Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study

Lawrence A. Kingsley^{a,b}, Juliana Cuervo-Rojas^c, Alvaro Muñoz^c, Frank J. Palella^d, Wendy Post^e, Mallory D. Witt^f, Matthew Budoff^g, and Lewis Kuller^b

^a Department of Infectious Diseases and Microbiology, University of Pittsburgh, Pittsburgh, Pennsylvania ^b Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania ^c Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland ^d Northwestern University, Chicago, Illinois ^e School of Medicine, Baltimore, Maryland ^f University of California, David Geffen School of Medicine and the Los Angeles Biomedical Research Institute at Harbor-UCLA Los Angeles ^g Division of Cardiology, Harbor-UCLA Medical Center, Torrance, California, USA

Abstract

Objective—To evaluate the association of HIV infection and cumulative exposure to highly active antiretroviral therapy (HAART) with the presence and extent of coronary artery calcification (CAC).

Design—A cross-sectional study of 947 male participants (332 HIV-seronegative, 84 HAART-naive and 531 HAART-experienced HIV-infected) from the Multicenter AIDS Cohort Study.

Methods—The main outcome was CAC score calculated as the geometric mean of the Agatston scores of two computed tomography replicates. Presence of CAC was defined as calcification score above 10, and extent of CAC by the score for those with CAC present. Multivariable regression was used to evaluate the association between HIV infection and HAART and presence and extent of calcification.

Results—Increasing age was most strongly associated with both prevalence and extent of CAC for all study groups. After adjustment for age, race, family history, smoking, high-density lipoprotein-C, low-density lipoprotein-C and hypertension, HIV infection (odds ratio, 1.35; 95% confidence interval, 0.70, 2.61) and long-term HAART use (odds ratio, 1.33; 95% confidence interval, 0.87, 2.05) increased the odds for presence of CAC. In contrast, after adjustment for these covariates, the extent of CAC was lower among HAART users. Among those not taking lipid-lowering therapy, HAART usage of at least 8 years was associated with significantly reduced CAC scores (relative CAC score, 0.43; 95% confidence interval, 0.24, 0.79).

Conclusion—HAART use may have different effects on the presence and extent of coronary calcification. Although prevalence of calcification was marginally increased among long-term HAART users, the extent of calcification was significantly reduced among HAART users compared with HIV-seronegative controls.

Introduction

The relationship between highly active antiretroviral therapy (HAART) use and metabolic disturbances such as hyperlipidemia, hyperglycemia, insulin resistance, hypertension, and

alterations in body fat distribution [1–5] has raised concern regarding potential HAART-associated increases in atherosclerotic coronary heart disease (CHD) risk.

Several studies have assessed HAART-associated ischemic cardiovascular disease risks. Four studies [6–9] failed to reveal an adverse association; one study [10] found increased CHD risk at younger ages with a risk reduction at older ages, and five studies [11–15] found an increase in cardiovascular risk. Another study [16] showed a two fold increased risk of acute myocardial infarction (MI) among HIV-infected men and women compared with HIV-negative controls; however, it lacked data on HAART usage. Adding further to the controversy are data from the SMART study [17], which showed an increased risk of CHD events among those who stopped HAART, suggesting a role for HIV or other immunological factors in CHD risk.

Other studies have evaluated the relationship between subclinical coronary atherosclerosis and HIV infection and HAART with equivocal results. Three studies [18–20] showed no association with HIV or HAART and the others were in drug users [21,22] or not controlled for traditional CHD risk factors [23].

The contradictory findings in existing research are likely related not only to different study designs or populations, but also to the inherent limitations of observational methods to control confounding, limited follow-up periods, lack of antiretroviral therapy data and the absence of HIV seronegative controls. The Multicenter AIDS Cohort Study (MACS), a multiethnic cohort of HIV-infected and HIV-seronegative men, by virtue of its prospective nature, continuous ascertainment of relevant covariates and collection of detailed information about antiretroviral drug usage, constitutes an optimal cohort in which to evaluate these issues whilst avoiding many of these methodological limitations.

The present report focuses on subclinical coronary atherosclerosis. The primary aim of our study was to estimate the effects of chronic HIV infection and cumulative HAART exposure on the presence and extent of coronary artery calcification (CAC) assessed by computed tomography (CT). We selected CAC as the measure of subclinical atherosclerosis as calcification is not normally present in the arterial wall [24] and begins to appear consistently in Type IV intracoronary lesions or atheromas [25]. Likewise, CAC measurements correlate strongly with the total area of atherosclerotic plaque [26,27], have high reproducibility [28], and have established value in coronary event risk prediction [29,30].

Methods

Study population

Eligibility criteria included informed consent, age at least 40 years, absence of coronary disease (heart attack, heart surgery, other major heart illness) or cerebrovascular disease, and weight less than 136.4 kg. The baseline visit was completed between April 2004 and January 2006. Of 947 individuals enrolled, 332 were HIV-seronegative, 84 were HIV-infected but HAART-naïve, and 531 were HIV-infected and HAART-experienced.

Computed tomography imaging

Electron beam tomography (EBT) or multidetector computed tomography (MDCT) was used to measure CAC. Three of four MACS sites performed EBT and used an Imatron (C-150 or C300) (GE Imatron, San Francisco, USA) and one performed MDCT with a Siemens S4+ (Siemens, Erlangen, Germany). For purposes of increased reliability and quality control, cardiac scans were performed twice for each individual.

The main outcome was the calcification score, calculated as the geometric mean of the Agatston Scores [31] generated from two CT replicates. Agatston score agreement between replicates was excellent. For those with coronary calcium present (i.e., CAC >0), there was 94.5% agreement between the two measurements and the bias (in the log₁₀ scale) was -0.003 with a standard deviation ratio of 1.006, and a correlation of 0.971. Only in the CAC score range of above 0 and below 10 were there modest discordances in the CT replicates; therefore, for all analyses the presence of calcium was defined as a geometric mean of scores above 10, and the quantity of CAC measured was defined by the geometric mean for those with CAC present. Four individuals did not have two CT readings and so the first reading was used.

Exposure and covariates

Clinical data were taken from the two visits that took place at 1 year and at 6 months prior to baseline. To maximize available information from the two visits, we used the following rules: for continuous variables, we took the average of the values seen at both visits or, if one value was missing, the available value was used; and for binary variables, presence at either of the two visits constituted a positive outcome.

HAART initiation was defined as the midpoint between the last semiannual visit at which no therapy use was reported and the first visit reporting its use. The definition of HAART was guided by the DHHS/Kaiser Panel [32] guidelines and defined as: two or more nucleoside reverse transcriptase inhibitors (NRTI) in combination with at least one protease inhibitor or one non-nucleoside reverse transcriptase inhibitor (NNRTI) (89% of observations classified as HAART), one NRTI in combination with at least one protease inhibitor and at least one NNRTI (6%), a regimen containing ritonavir and saquinavir in combination with one NRTI and no NNRTI (1%), and an abacavir or tenofovir containing regimen of three or more NRTI in the absence of both protease inhibitors and NNRTI (4%).

HIV infection status and antiretroviral exposure categories were considered those recorded 1 year prior to the CT. Thus, HIV seronegative individuals and those with less than 1 year of infection comprised the seronegative group. The HAART-naïve group were those who did not initiate therapy or had less than 1 year of HAART usage prior to CT. Time since HAART initiation was categorized as the 8-year median duration of therapy.

Family history of cardiovascular disease was discerned by asking participants whether they had 'relatives who have suffered from a heart attack.' When information was available from only one visit, this was used. When there was disagreement in the two prior visits, we used responses from the most recent visit, as information about family events can be updated. For tobacco use, participants were asked whether they had a history of 'ever smoking'. For use of lipid-lowering medication, antidiabetic medication, and antihypertensive medication, similar methods were used. For each of these variables, the observed agreement between information obtained at two prior visits was excellent (range 86–95%).

Plasma glucose levels were classified according to the American Diabetes Association Position Statement [33], taking into account whether the available results were based upon data from fasting versus non-fasting specimens. Overall, 77% of glucose measurements were performed on fasting samples and 23% on non-fasting samples. Three categories were generated: normal glucose, if fasting plasma glucose (FPG) was less than 100 mg/dl or nonfasting plasma glucose (NFBPG) was less than 200 mg/dl; impaired fasting glucose (IFG) if FPG was 100–125 mg/dl; and diabetes mellitus if FPG was at least 126 mg/dl or NFBPG at least 200 mg/dl. Use of antidiabetic medication influenced result categorization in the following way: a participant was considered to have normal glucose when neither of the two visits indicated hyperglycemia and the individual reported no use of antidiabetic agents;

classification of IFG occurred when either of the visits indicated IFG (but not diabetes mellitus) and no use of antidiabetic medication was reported; and classification in the diabetes mellitus category occurred when plasma glucose levels indicated diabetes mellitus or use of antidiabetic agents was reported.

Serum levels of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and triglycerides were averaged for two visits prior to CT. Categories for mean levels were defined according to the Third Report of the National Cholesterol Education Program [34]. Dyslipidemia was defined as TC at least 240 mg/dl (high in NCEP), or LDL at least 160 mg/dl (high and very high), or HDL less than 40 mg/dl (low), or triglycerides at least 200 mg/dl (high and very high), or use of lipid-lowering medications.

Hypertension was defined according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [35]. Systolic and diastolic blood pressure measurements were averaged over two visits prior to CT. Hypertension was defined as a systolic pressure at least 140 mmHg or a diastolic pressure at least 90 mmHg or use of antihypertensive agents at either two visits prior to CT.

Serum lipid measurements

The fasting serum lipid panel included TC, HDL-C, calculated LDL-C [$\text{LDL-C} = \text{TC} - (\text{HDL} + (\text{triglycerides}/5))$], and triglycerides. A measured LDL-C was performed if the triglyceride was above 400 mg/dl. The nonfasted panel included TC, HDL-C, and measured LDL-C. The lipid measurements were performed by the Heinz Nutrition Laboratory, University of Pittsburgh Graduate School of Public Health. TC, HDL-C, LDL-C and triglycerides were determined by standard methodology [36–39]. CD4+ T-lymphocyte-cell counts were determined using flow cytometry per standardized protocol [40].

Statistical analyses

Exploratory data analysis was performed to compare the distributions of potential confounders and mediators according to HIV-therapy categories using Pearson's χ^2 -test to assess statistical significance. Presence and extent of CAC were evaluated according to the main exposure and covariables of interest adjusting for age using logistic regression and lognormal regression subject to truncation, respectively. Likelihood ratio tests were used to assess statistical significance.

Multiple logistic regression was used to evaluate the association between HIV-HAART and presence of CAC. For continuous variables, the assumption of linearity in the log-odds scale was evaluated by plotting the log-odds of CAC presence versus quintiles of their distributions. Those with non-linearity were categorized according to relevant clinical definitions. Age was categorized in five groups: below 45, 45–49, 50–54, 55–59, 60–80 years; body mass index (BMI) in three categories: below 25, 25–29, at least 30; LDL in two categories: below 130 and at least 130 mg/dl; HDL in two categories: at least 40 and below 40 mg/dl; insulin in two categories: 15 or less and more than 15 $\mu\text{units/ml}$. Ever smoking, family history of MI and hypertension were included as dichotomous variables. Variance inflation factors were used for checking colinearity, and Hosmer–Lemeshow tests were used to assess the fit of the models. The models presented include potential confounders, and variables known to be affected by HIV-HAART, which have the potential to mediate their effect on atherosclerosis. This latter approach is used to explore the degree by which the effects of HIV-HAART are due to the metabolic alterations they induce. Adjusted odds ratios (OR) with 95% confidence intervals (CI) were obtained from logistic models.

Multiple log-normal regression was used to evaluate the association between HIV-HAART and the extent of CAC among those with CAC score above 10. The calcification score was modeled as a log-normal distribution subject to truncation. This model accounts for the restriction of the analysis to those with CAC score above 10. The models presented include potential confounders and mediators of the effect of HIV-HAART, categorized in the same form as for the logistic analyses. Adjusted OR of the extent of CAC with 95% CI are presented. All significance tests were at the 0.05 level and all analyses were conducted using STATA version 8 (Stata Corp., Texas, USA).

Results

Table 1 presents the distribution of relevant demographic and clinical characteristics according to HIV therapy status. The HIV-seronegative men ($n=332$) were older, had higher BMI, and were more likely to have hypertension and elevated LDL-C than the HIV-positive individuals. The HIV-infected groups ($n=615$) were more likely to have had a family history of CHD, higher serum insulin levels, and lower serum levels of TC, albumin, HDL-C and glycosylated hemoglobin. The HAART-experienced HIV-infected men ($n=531$) also exhibited substantial fasting hypertriglyceridemia. Important differences in use of lipid-lowering treatment were also observed. Lipid-lowering drug use was twice as likely among long-term HAART users (40%) versus the older HIV-seronegative controls (20%). Thus, the groups differed in several established cardiovascular risk factors with the potential to confound the estimation of HIV-HAART effects on CAC as in the case of age, race, family history of CHD and smoking, or to act as metabolic mediators of their effects as in the case of dyslipidemia or insulin resistance.

The overall prevalence of coronary calcification in the study population was 32% and the age-adjusted (to age 55) prevalence was 44%. Consistent with prior reports [41], the strongest association observed was between increasing age and CAC prevalence and extent. The prevalence of calcification was 12, 23, 34, 52 and 73% and the median calcification score was 43, 57, 83, 98 and 198 for those who were younger than 45, 45–49, 50–54, 55–59 and 60–80 years, respectively. Table 2 shows the age-adjusted associations between individuals' characteristics, cardiovascular risk factors, other important variables and the presence of calcification in both the total study population as well as among those not using lipid-lowering medications. The latter was done to avoid the potential confounding and modifier influence of use of lipid-lowering therapy. All HIV-infected groups had a modestly increased prevalence of CAC score above 10 compared with HIV seronegatives. The highest prevalence of CAC (51%) was observed among those who had received HAART for 8 or more years. CAC was most prevalent among Caucasians, smokers, those with a family history of CHD, hyperinsulinemia, dyslipidemia (lipid profile abnormality or treatment for it), low HDL-C and high LDL-C. In those not receiving lipid-lowering medication smoking, hyperinsulinemia and increased LDL-C were significantly associated with the presence of CAC.

A different pattern of associations emerged when evaluating the extent of coronary calcification, which was significantly associated with the presence of hypertension, and high LDL-C levels (Table 3). Among those with calcification who did not receive lipid-lowering therapy, note the strong inverse relationship between duration of HAART usage and CAC scores, with median CAC scores of 66 and 45 among those who received HAART for 1–7 and at least 8 years, respectively. Age-adjusted CAC scores were approximately half that of HIV-seronegative controls. An association was also observed between CAC score and CD4 T-lymphocyte count, with the median CAC level among those with CD4 cell count below 200 cells/ μ l approximately half that seen among those with CD4 cell count above 350 cells/ μ l.

Table 4 presents adjusted associations between HIV-therapy status and presence of calcification. The slight increase in the odds of CAC presence observed among both HAART-naïve and long-term users of HAART in comparison with those not infected with HIV, was not statistically significant after adjustment for age, race, smoking and family history of CHD. Adjustment for metabolic factors (BMI, insulin, hypertension, HDL-C, and LDL-C) further attenuates the association. Thus, the small increase in the odds of CAC presence among those having received HAART for at least 8 years appears to be mediated by the metabolic abnormalities associated with therapy. The magnitude of this association was similar among those not using lipid-lowering medication, with the small non-significant effect of long-term HAART use attenuated with adjustment for metabolic factors.

In contrast, as shown in Table 5, long-term HAART use was consistently associated with reduced calcification. Among individuals with calcification of the same race and the same age group, the HIV-positive with more than 8 years of HAART use had CAC scores, which were on average 0.66 times those of the HIV negative. Subsequent adjustment for important covariates had minor impact. Thus, the overall directionality is that though HIV infection and long-term HAART were marginally associated with increased odds for the presence of CAC, long-term HAART usage was associated with a decreased extent of calcification. Regression analyses restricted to the non-users of lipid-lowering therapy show a stronger effect of long-term exposure to HAART than that observed in the total population. The age and race adjusted ratio of CAC scores for those with HAART duration less than 8 years was 0.60 (95% CI, 0.36, 0.99), and for those with HAART for 8 or more years was 0.47 (95% CI, 0.27, 0.80). Further adjustment for smoking and family history did not alter this finding. Although adjustment for metabolic factors decreased the magnitude of the effect, CAC ratios remained consistently below 1.0. These results suggest that the effect of HAART on CAC is strongest among those not receiving lipid-lowering therapy.

Discussion

HAART may have different effects on the presence and extent of calcification. Why does the evidence support a similar or slight increased prevalence of CAC in HIV-infected men, yet a significantly lower extent of CAC among the long-term HAART users? First, HIV infection has been independently associated with lower serum levels of TC, LDL-C and HDL-C in the era before effective HIV therapies were available [1]. Therefore, many men in this study, especially those with lengthy durations of HIV infection prior to receiving HAART, may have had prolonged HIV-associated reductions of serum LDL and TC and consequently may have been at lower risk of developing coronary atherosclerosis. However, the concomitant reduction of HDL-C levels – which do not fully recover with the initiation of antiretroviral therapy – may have acted in the opposite direction given its considerable proatherogenic effects. Although use of specific agents from each of the three major antiretroviral drug classes has differing likelihoods of being associated with any or all of the described lipid changes, virtually all of the antiretroviral drug-associated serum lipid changes are potentially proatherogenic. These lipid changes should have been associated with an increased risk for development and progression of coronary atherosclerosis. However, the time period over which coronary atherosclerosis develops may be very long, as much as 10–20 years from the onset of an exposure – for example to antiretroviral therapy – and thus has not yet been reached. A third consideration is that the substantial increases in serum very low-density lipoprotein (VLDL) triglycerides may not have resulted in an increase in LDL particles, especially small LDL particles that may be more atherogenic.

The high prevalence of lipid-lowering drug therapy use among long-term HAART recipients (approximately 40%) compared with only about 20% among HIV seronegative individuals,

modifies the interpretation of our study results, as suggested by the multivariable models in strata of lipid-lowering therapy use. Long-term HAART recipients who did not receive lipid-lowering therapy tended toward a non-significant increase in prevalence of CAC in comparison with HIV seronegatives, very similar to that observed in the total study population. In contrast, the association between HAART use and lower CAC scores becomes stronger when restricting the analysis to those not taking lipid-lowering therapy. It remains possible that those with a higher atherosclerosis risk and CAC scores, perhaps those who had higher lipoprotein levels following HAART initiation, were selectively initiated on lipid-lowering drug therapy.

Further evidence suggesting that high-risk men were selectively initiated on lipid-lowering drug therapy was the higher age-adjusted prevalence of CAC among those receiving lipid-lowering drug therapy, 51 versus 41% of those not receiving lipid-lowering drug therapy. Overall, 44% of the men on lipid-lowering drug therapy had CAC.

The strongest determinant of lipid-lowering drug therapy receipt was age, with about 42% of men above 60 years of age receiving lipid-lowering drug therapy compared with only 15% of men below 45 years of age. Age was also the major determinant of the amount of CAC, rising over four-fold from men below 45 to those men above 60 years of age. The duration of HAART use and the prevalence of CAC increased with age as well as LDL-C levels, further confounding the relationship between HAART use and CAC scores. On the contrary, there is little evidence from clinical trials that lipid-lowering drug therapy slows or prevents the development of CAC.

Our results are further strengthened by the observation that this is a cohort of men with lengthy duration of HIV infection. As such, most of the HIV-infected participants who initiated HAART during the early years after availability received protease inhibitor-based HAART regimens. These earlier regimens included drugs now recognized to be among the most potentially atherogenic, including the protease inhibitors zidovudine and didanosine. It is interesting to speculate what a similar cohort of HIV-infected men receiving more recently available regimens, (e.g. those based on NNRTI), more lipid-friendly protease inhibitors such as atazanavir, and non-thymidine analogue reverse transcriptase inhibitors such as tenofovir and abacavir might experience in terms of both prevalence and severity of coronary atherosclerosis. Our cohort's experience with the most atherogenic antiretroviral treatments likely represents a unique natural experiment that will not be replicated.

The data presented are at odds with several studies showing an association between both HAART usage and increased late-stage CHD events [11–16]. Further questions are raised by results of the SMART study, which demonstrated an increased risk of CHD events among those who underwent HAART treatment interruption [17]. Taken together, these studies suggest different mechanisms for development of subclinical coronary atherosclerosis and progression to late-stage CHD events. HIV-induced chronic systemic inflammation must also be considered as it may lead to increased coagulation and endothelial damage, which might promote atherothrombosis [42].

Our findings must be considered in light of certain limitations. This was a cross-sectional study with lipid levels determined as the average of two measurements taken in the year prior to CT examination. Although effects of lipid-lowering drug therapy have been carefully evaluated in this analysis, the complete long-term effect on lipids over the entire course of HIV infection and antiretroviral therapy cannot be evaluated. We also did not measure atherosclerosis prior to lipid-lowering drug therapy, nor did we include those with preexisting coronary disease. Perhaps those few with extensive coronary disease might have

shown an association with long-term HAART. Finally, the CT method used did not detect non-calcified coronary plaque, which might be important in HIV-associated atherosclerosis.

Interesting as-yet-unanswered questions include the extent to which prelipid-treatment TC, LDL and HDL predict subsequent coronary atherosclerosis as well as whether those who initiated lipid treatment were at higher risk for atherosclerosis. Our data also raise a question as to whether the high proportion of HIV-infected men without evidence of CAC currently receiving lipid-lowering drug therapy should continue to do so, given the potential drug side effects and cost.

The MACS will perform a 3-year follow-up assessment of CAC. This will enable the study to address remaining primary questions, including whether there is slowed progression of coronary calcification among those on HAART and those receiving lipid-lowering therapy, identification of factors associated with incident coronary calcification, and associations between lipoprotein particle distribution, particle size and coronary atherosclerosis.

Acknowledgments

The MACS includes the following: Baltimore: The Johns Hopkins University Bloomberg School of Public Health; Joseph B. Margolick (Principal Investigator), Haroutune Armenian, Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Joel Gallant, John Hylton, Lisette Johnson, Shenghan Lai, Ned Sacktor, Ola Selnes, James Shepard, Chloe Thio. Chicago: Howard Brown Health Center, Feinberg School of Medicine, Northwestern University, and Cook County Bureau of Health Services; John P. Phair (Principal Investigator), Joan S. Chmiel (Co-Principal Investigator), Sheila Badri, Bruce Cohen, Craig Conover, Maurice O'Gorman, David Ostrow, Frank Palella, Daina Variakojis, Steven M. Wolinsky. Los Angeles; University of California, UCLA Schools of Public Health and Medicine: Roger Detels (Principal Investigator), Barbara R. Visscher (CoPrincipal Investigator), Aaron Aronow, Robert Bolan, Elizabeth Breen, Anthony Butch, Thomas Coates, Rita Effros, John Fahey, Beth Jamieson, Otoniel Martínez-Maza, Eric N. Miller, John Oishi, Paul Satz, Harry Vinters, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young, Zuo Feng Zhang. M01 RR00425 (National Center for Research Resources grant awarded to the GCRC at Harbor-UCLA Research and Education Institute). Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence Kingsley (CoPrincipal Investigator), James T. Becker, Robert L. Cook, Robert W. Evans, John Mellors, Sharon Riddler, Anthony Silvestre. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health; Lisa P. Jacobson (Principal Investigator), Alvaro Muñoz (CoPrincipal Investigator), Haitao Chu, Stephen R. Cole, Christopher Cox, Gypsyamber D'Souza, Stephen J. Gange, Janet Schollenberger, Eric C. Seaberg, Sol Su. NIH: National Institute of Allergy and Infectious Diseases; Robin E. Huebner. National Cancer Institute; Geraldina Dominguez. National Heart, Lung and Blood Institute; Cheryl McDonald. U01-AI-35042, 5-MO1-RR-00722 (GCRC), U01-AI-35043, U01-AI-37984, U01-AI-35039, U01-AI-35040, U01-AI-37613, U01-AI-35041. Website <http://www.statelpi.jhsph.edu/macs/mac.html>.

Study concept and design: Kingsley, Kuller, Cuervo-Rojas, Muñoz. Acquisition of data: Kingsley, Palella, Post, Witt, Budoff. Analysis and interpretation of data: Kingsley, Kuller, Cuervo-Rojas, Munoz, Palella, Post, Witt, Budoff. Drafting of the manuscript: Kingsley, Kuller, Cuervo-Rojas, Munoz, Palella, Post, Witt, Budoff. Critical revision of the manuscript for important intellectual content: Kingsley, Kuller, Cuervo-Rojas, Munoz, Palella, Post, Witt, Budoff. Statistical analysis: Cuervo-Rojas, Munoz. Obtained funding: Kingsley, Munoz, Palella. Administrative, technical, or material support: Kingsley, Munoz, Budoff (all CT readings).

References

1. Riddler SA, Smit E, Cole SR, Li R, Chmiel JS, Dobs A, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003; 289:2978–2982. [PubMed: 12799406]
2. Brown TT, Cole SR, Li X, Kingsley LA, Palella FJ, Riddler SA, et al. Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the multicenter AIDS cohort study. *Arch Intern Med*. 2005; 165:1179–1184. [PubMed: 15911733]
3. Brown T, Li X, Cole S, Kingsley L, Palella F, Riddler S, et al. Cumulative exposure to nucleoside analogue reverse transcriptase inhibitors is associated with insulin resistance markers in the multicenter AIDS cohort study. *AIDS*. 2005; 19:1375–1383. [PubMed: 16103768]

4. Seaberg E, Muñoz A, Lu M, Detels R, Margolick J, Riddler S, et al. Association between highly active antiretroviral therapy and hypertension in a large cohort of men followed from 1984 to 2003. *AIDS*. 2005; 19:953–960. [PubMed: 15905677]
5. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005; 352:48–62. [PubMed: 15635112]
6. Bozzette SA, Ake CF, Tam HK, Chang SW, Louis TA. Cardiovascular and cerebrovascular events in patients treated for human immunodeficiency virus infection. *N Engl J Med*. 2003; 348:702–710. [PubMed: 12594314]
7. Escaut L, Monsuez JJ, Chironi G, Merad M, Teicher E, Smadja D, et al. Coronary artery disease in HIV infected patients. *Intensive Care Med*. 2003; 29:969–973. [PubMed: 12739013]
8. Klein D, Hurley L, Quesenberry C Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? *J Acquir Immune Defic Syndr*. 2002; 30:471–477. [PubMed: 12154337]
9. Coplan PM, Nikas A, Japour A, Cormier K, Maradit-Kremers H, Lewis R, et al. Incidence of myocardial infarction in randomized clinical trials of protease inhibitor-based antiretroviral therapy: an analysis of four different protease inhibitors. *AIDS Res Hum Retroviruses*. 2003; 19:449–455. [PubMed: 12882653]
10. Currier JS, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, et al. Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr*. 2003; 33:506–512. [PubMed: 12869840]
11. The DAD Study Group. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007; 356:1723–1735. [PubMed: 17460226]
12. d'Arminio A, Sabin C, Phillips A, Reiss P, Weber R, Kirk O, et al. Cardio- and cerebrovascular events in HIV-infected persons. *AIDS*. 2004; 18:1811–1817. [PubMed: 15316342]
13. MaryKrause M, Cotte L, Simon A, Partisani M, Costagliola D, the Clinical Epidemiology Group from the French Hospital Database. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS*. 2003; 17:2479–2486. [PubMed: 14600519]
14. Rickerts V, Brodt H, Staszewski S, Stille W. Incidence of myocardial infarctions in HIV-infected patients between 1983 and 1998: the Frankfurt HIV-cohort study. *Eur J Med Res*. 2000; 5:329–333. [PubMed: 10958765]
15. Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet*. 2002; 360:1747–1748. [PubMed: 12480430]
16. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab*. 2007; 92:2506–2512. [PubMed: 17456578]
17. The Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med*. 2006; 355:2283–2296. [PubMed: 17135583]
18. Acevedo M, Sprecher DL, Calabrese L, Pearce GL, Coyner DL, Halliburton SS, et al. Pilot study of coronary atherosclerotic risk and plaque burden in HIV patients: 'a call for cardiovascular prevention'. *Atherosclerosis*. 2002; 163:349–354. [PubMed: 12052482]
19. Mangili A, Gerrior J, Tang A, O'Leary D, Polak J, Schaefer E, et al. Risk of cardiovascular disease in a cohort of HIV-infected adults: a study using carotid intima-media thickness and coronary artery calcium score. *Clin Infect Dis*. 2006; 43:1482–1489. [PubMed: 17083026]
20. Talwani R, Falusi OM, Mendes de Leon CF, Nerad JL, Rich S, Proia LA, et al. Electron beam computed tomography for assessment of coronary artery disease in HIV-infected men receiving antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2002; 30:191–195. [PubMed: 12045682]
21. Lai S, Lai H, Celentano DD, Vlahov D, Ren S, Margolick J, et al. Factors associated with accelerated atherosclerosis in HIV-1-infected persons treated with protease inhibitors. *AIDS Patient Care STDS*. 2003; 17:211–219. [PubMed: 12816615]
22. Lai S, Lima JAC, Lai H, Vlahov D, Celentano D, Tong W, et al. Human immunodeficiency virus 1 infection, cocaine, and coronary calcification. *Arch Intern Med*. 2005; 165:690–695. [PubMed: 15795348]

23. Robinson FPACRN, Hoff JA, Kondos GT. Coronary artery calcium in HIV-infected men treated with highly active anti-retroviral therapy. *J Cardiovasc Nurs.* 2005; 20:149–154. [PubMed: 15870584]
24. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain: a report of the American College of Cardiology Foundation Clinical Expert Consensus Task Force (ACCF/AHA Writing Committee to Update the 2000 Expert Consensus Document on Electron Beam Computed Tomography) developed in collaboration with the Society of Atherosclerosis Imaging and Prevention and the Society of Cardiovascular Computed Tomography. *J Am Coll Cardiol.* 2007; 49:378–402. [PubMed: 17239724]
25. Stary HC. The development of calcium deposits in athero-sclerotic lesions and their persistence after lipid regression. *Am J Cardiol.* 2001; 88:16E–19E.
26. Rumberger JA, Schwartz RS, Simons DB, Sheedy PF, Edwards WD, Fitzpatrick LA. Relation of coronary calcium determined by electron beam computed tomography and lumen narrowing determined by autopsy. *Am J Cardiol.* 1994; 73:1169–1173. [PubMed: 8203333]
27. Sangiorgi G, Rumberger JA, Severson A, Edwards WD, Gregoire J, Fitzpatrick LA, et al. Arterial calcification and not lumen stenosis is highly correlated with atherosclerotic plaque burden in humans: a histologic study of 723 coronary artery segments using nondecalfying methodology. *J Am Coll Cardiol.* 1998; 31:126–133. [PubMed: 9426030]
28. Detrano RC, Anderson M, Nelson J, Wong ND, Carr JJ, McNitt-Gray M, et al. Coronary calcium measurements: effect of CT scanner type and calcium measure on rescan reproducibility: MESA study. *Radiology.* 2005; 236:477–484. [PubMed: 15972340]
29. Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA.* 2004; 291:210–215. [PubMed: 14722147]
30. Arad Y, Goodman KJ, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol.* 2005; 46:158–165. [PubMed: 15992651]
31. Agatston A, Janowitz W, Hildner F, Zusmer N, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol.* 1990; 15:827–832. [PubMed: 2407762]
32. DHHS. Henry J. Kaiser Family Foundation Panel on Clinical Practices for the Treatment of HIV infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents 2006 revision. 2006:1–112.<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL05042006050.pdf>
33. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care.* 2005; 28(Suppl 1):S37–S42. [PubMed: 15618111]
34. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001; 285:2486–2497. [PubMed: 11368702]
35. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA.* 2003; 289:2560–2571. [PubMed: 12748199]
36. Allain CC, Poon LS, Chan CSG, Richmond W, Fu PC. Enzymatic determination of total serum cholesterol. *Clin Chem.* 1974; 20:470–475. [PubMed: 4818200]
37. Warnick GR, Albers JJ. A comprehensive evaluation of the heparin: manganese precipitation procedure for estimating high density lipoprotein cholesterol. *J Lipid Res.* 1978; 19:65–76. [PubMed: 202660]
38. Rifai N, Iannotti E, DeAngelis K, Law T. Analytical and clinical performance of a homogeneous enzymatic LDL-cholesterol assay compared with the ultracentrifugation-dextran sulfate-Mg²⁺ method. *Clin Chem.* 1998; 44:1242–1250. [PubMed: 9625048]

39. Bucolo G, David H. Quantitative determination of serum triglycerides by the use of enzymes. Clin Chem. 1973; 19:476–482. [PubMed: 4703655]
40. Giorgi JV, Cheng H, Margolick JB, Bauer KD, Ferbas J, Waxdal M, et al. Quality control in the flow cytometric measurement of T-lymphocyte subsets: the multicenter AIDS cohort study experience. The Multicenter AIDS Cohort Study Group. Clin Immunol Immunopathol. 1990; 55:173–186. [PubMed: 1969782]
41. McClelland RL, Chung H, Detrano R, Post W, Kronmal RA. Distribution of coronary artery calcium by race, gender, and age: results from the Multi-Ethnic Study of Atherosclerosis (MESA). Circulation. 2006; 113:30–37. [PubMed: 16365194]
42. van Leuven SI, Franssen R, Kastelein JJ, Levi M, Stoes ESG, Tak PP. Systemic inflammation as a risk factor for atherothrombosis. Rheumatology. 2008; 47:3–7. [PubMed: 17702769]

Table 1

Characteristics of study population by HIV infection and therapy status.

Characteristic	HIV+				Overall ^a (N =615)
	HIV- (N =332) n (%) ^b	HAART naïve (N =84) n (%) ^b	HAART 1-7 years (N =297) n (%) ^b	HAART 8 years (N =234) n (%) ^b	
Race [*]					
Caucasian	228 (69)	44 (52)	153 (52)	182 (78)	379 (62)
African-American	79 (24)	34 (41)	108 (36)	36 (15)	178 (29)
Hispanic and other	25 (7)	6 (7)	36 (12)	16 (7)	58 (9)
Age (years) ^{*,**}					
<45	58 (17)	30 (36)	107 (36)	51 (22)	188 (31)
45-49	80 (24)	19 (23)	81 (27)	72 (31)	172 (28)
50-54	69 (21)	21 (25)	66 (22)	50 (21)	137 (22)
55-59	70 (21)	12 (14)	31 (11)	48 (21)	91 (15)
60-80	55 (17)	2 (2)	12 (4)	13 (5)	27 (4)
Ever smoking [*]					
No	127 (39)	18 (24)	87 (30)	109 (48)	214 (36)
Yes	196 (61)	57 (76)	200 (70)	118 (52)	375 (64)
Family history CHD-MI ^{*,**}					
No	282 (90)	60 (82)	229 (84)	182 (82)	471 (83)
Yes	33 (10)	13 (18)	45 (16)	40 (18)	98 (17)
BMI (kg/m ²) ^{*,**}					
<25	124 (40)	32 (44)	136 (49)	115 (54)	283 (50)
25-29	133 (42)	30 (42)	110 (40)	77 (36)	217 (39)
30	55 (18)	10 (14)	30 (11)	21 (10)	61 (11)
Insulin level ^{*,**} (µunits/ml)					
15	185 (68)	38 (63)	140 (59)	92 (48)	270 (55)
>15	87 (32)	22 (37)	98 (41)	99 (52)	219 (45)
Hypertension ^{*,**}					
No	231 (75)	57 (80)	232 (84)	184 (87)	473 (85)
Yes	79 (25)	14 (20)	45 (16)	27 (13)	86 (15)

Characteristic	HIV+					Overall ^a (N =615)
	HIV- (N =332) n (%) ^b	HAART naïve (N =84) n (%) ^b	HAART 1-7 years (N =297) n (%) ^b	HAART 8 years (N =234) n (%) ^b		
Hypertension medication *						
No	243 (75)	64 (85)	226 (78)	160 (70)	450 (76)	
Yes	80 (25)	11 (15)	62 (22)	68 (30)	141 (24)	
Hypertension and hypertension medication , **						
No	182 (58)	49 (71)	188 (68)	131 (61)	368 (66)	
Yes	133 (42)	20 (29)	90 (32)	83 (39)	193 (34)	
Diabetes mellitus						
No	132 (48)	32 (53)	102 (42)	93 (48)	227 (46)	
Diabetes mellitus	22 (8)	3 (5)	19 (8)	20 (10)	42 (8)	
IFG	120 (44)	25 (42)	121 (50)	81 (42)	227 (46)	
Diabetes mellitus medication						
No	306 (95)	72 (96)	276 (96)	208 (91)	556 (94)	
Yes	17 (5)	3 (4)	12 (4)	20 (9)	35 (6)	
Diabetes mellitus and diabetes mellitus medication						
No	130 (47)	31 (52)	101 (41)	89 (45)	221 (44)	
Diabetes mellitus	31 (11)	4 (7)	24 (10)	31 (16)	59 (12)	
IFG	116 (42)	25 (41)	121 (49)	76 (39)	222 (44)	
Hb A1c (%) , **						
6	276 (86)	70 (91)	262 (94)	195 (89)	527 (92)	
>6	45 (14)	7 (9)	18 (6)	23 (11)	48 (8)	
Albumin (g/dl) **, **						
4	295 (92)	57 (74)	238 (85)	188 (86)	483 (84)	
<4	26 (8)	20 (26)	43 (15)	31 (14)	94 (16)	
TC , ** (mg/dl)						
<200	156 (49)	54 (71)	145 (52)	132 (60)	331 (58)	
200-239	120 (37)	14 (18)	89 (32)	53 (24)	156 (27)	
240	45 (14)	8 (11)	45 (16)	35 (16)	88 (15)	
HDL cholesterol , ** (mg/dl)						
40	253 (79)	44 (58)	178 (64)	123 (56)	345 (60)	

Characteristic	HIV+				
	HIV – (N = 332) n (%) ^b	HAART naïve (N = 84) n (%) ^b	HAART 1–7 years (N = 297) n (%) ^b	HAART 8 years (N = 234) n (%) ^b	Overall ^a (N = 615)
<40	68 (21)	32 (42)	101 (36)	97 (44)	230 (40)
LDL cholesterol ^{*,**} (mg/dl)					
<130	200 (62)	58 (76)	197 (71)	171 (78)	426 (74)
130–159	76 (24)	13 (17)	56 (20)	35 (16)	104 (18)
160	45 (14)	5 (7)	26 (9)	14 (6)	45 (8)
Triglycerides ^{*,**} (mg/dl)					
<150	179 (65)	44 (73)	118 (49)	73 (38)	235 (48)
150–199	54 (20)	6 (10)	32 (13)	33 (17)	71 (14)
200	41 (15)	10 (17)	92 (38)	88 (45)	190 (38)
Lipid-lowering medication ^{*,**}					
No	258 (80)	68 (91)	223 (77)	138 (60)	429 (73)
Yes	65 (20)	7 (9)	65 (23)	90 (40)	162 (27)
Dyslipidemia ^{*,**,*c}					
No	132 (46)	23 (34)	81 (31)	37 (17)	141 (26)
Yes	157 (54)	44 (66)	181 (69)	177 (83)	402 (74)
CD4+ T cells ^{*,**} (cells/ μ l)					
200	0 (0)	3 (4)	22 (8)	13 (6)	38 (7)
201–350	4 (1)	22 (29)	44 (16)	32 (15)	98 (17)
>350	317 (99)	52 (67)	214 (76)	173 (79)	439 (76)
History of AIDS [*]					
No		83 (99)	267 (90)	181 (77)	531 (86)
Yes		1 (1)	30 (10)	53 (23)	84 (14)

BMI, body mass index; CHD, coronary heart disease; HAART, highly active antiretroviral therapy; Hb A1c, hemoglobin A1c; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; MI, myocardial infarction; NA, Not applicable; TC, total cholesterol.

^aHIV+ (overall): all HIV-infected individuals regardless of experience with therapy.

^bPercentages are column based.

^cDyslipidemia was defined as TC at least 240 mg/dl, or LDL at least 160 mg/dl, or HDL below 40 mg/dl, or triglyceride at least 200 mg/dl, or use of lipid-lowering medications. Data were missing for lipid levels in 136 cases, and for use of lipid-lowering medication in 33 cases (three of them with abnormal, and 30 with unknown lipid levels). Among those with missing data on lipids, 21 reported taking lipid-

lowering medications and were classified as dyslipidemic. In the remaining 115 cases, data for evaluating dyslipidemia was missing: 30 cases with both lipid levels and use of medication unknown, and 85 cases reporting no use of lipid-lowering medication but with no data on lipid levels to rule out dyslipidemia.

* $P < 0.05$ (χ^2 -test for comparison across all HIV-therapy categories).

** $P < 0.05$ (χ^2 -test for comparison between HIV+ (overall) and HIV-).

Table 2Age-adjusted^a presence of coronary calcification according to characteristics of study population.

Characteristic	Presence of coronary calcification ^b	
	Study population	
	Total <i>n</i> (%) ^c	Not taking lipid-lowering medication <i>n</i> (%) ^c
Overall	947 (44)	687 (41)
HIV and therapy status		
HIV–	332 (40)	258 (38)
HIV+, HAART-naive	84 (48)	68 (43)
HIV+, HAART 1–7 years	297 (42)	223 (42)
HIV+, HAART 8 years	234 (51)	138 (47)
HIV+, overall ^d	615 (47)	429 (44)
Race		
Caucasian	607 (47) *	405 (42)
African–American	257 (35)	218 (38)
Hispanic and other	83 (36)	64 (31)
Ever smoking		
No	341 (37) *	235 (34) *
Yes	571 (48)	451 (45)
Family history CHD–MI		
No	753 (41) *	572 (38)
Yes	131 (54)	91 (50)
BMI (kg/m ²)		
<25	407 (44)	318 (40)
25–29	350 (42)	253 (41)
30	116 (47)	81 (42)
Insulin level (μunits/ml)		
15	455 (38) *	367 (35) *
>15	306 (51)	198 (49)
Hypertension		
No	704 (42)	529 (39)
Yes	165 (47)	122 (45)
Hypertension medication		
No	693 (44)	556 (41)
Yes	221 (43)	131 (41)
Hypertension and hypertension medication		
No	550 (42)	446 (39)
Yes	326 (46)	209 (44)
Diabetes mellitus		
No	359 (43)	290 (39)
Diabetes mellitus	64 (39)	34 (41)

Characteristic	Presence of coronary calcification ^b	
	Study population	
	Total <i>n</i> (%) ^c	Not taking lipid-lowering medication <i>n</i> (%) ^c
IFG	347 (44)	247 (42)
Diabetes mellitus medication		
No	862 (44)	667 (41)
Yes	52 (44)	20 (37)
Diabetes mellitus and diabetes mellitus medication		
No	351 (42)	288 (38)
Diabetes mellitus	90 (42)	43 (38)
IFG	338 (44)	245 (42)
Hb A1 C (%)		
6	803 (44)	615 (41)
>6	93 (39)	56 (34)
Albumin (g/dl)		
4	778 (43)	571 (41)
<4	120 (43)	102 (35)
TC (mg/dl)		
<200	487 (39)	371 (36)
200–239	276 (48)	213 (45)
240	133 (47)	86 (46)
HDL cholesterol (mg/dl)		
40	598 (40) *	460 (38)
< 40	298 (50)	210 (45)
LDL cholesterol (mg/dl)		
<130	626 (40) *	463 (36) *
130–159	180 (53)	141 (53)
160	90 (44)	66 (39)
Triglycerides (mg/dl)		
<150	414 (40)	340 (38)
150–199	125 (48)	94 (45)
200	231 (47)	137 (42)
Lipid-lowering medication		
No	687 (41) *	687 (41)
Yes	227 (51)	NA
Dyslipidemia ^e		
No	273 (33) *	273 (33) *
Yes	559 (48)	329 (45)
CD4 T cells (cells/μl)		
200	38 (56)	36 (54)
201–350	102 (51)	79 (47)
>350	756 (42)	556 (39)

Characteristic	Presence of coronary calcification ^b	
	Study population	
	Total <i>n</i> (%) ^c	Not taking lipid-lowering medication <i>n</i> (%) ^c
History of AIDS		
No	531 (47)	373 (44)
Yes	84 (46)	56 (44)

BMI, body mass index; CHD, coronary heart disease; HAART, highly active antiretroviral therapy; Hb A1c, hemoglobin A1c; HDL, high-density lipoprotein; IFG, impaired fasting glucose; LDL, low-density lipoprotein; MI, myocardial infarction; NA, Non-applicable; TC, total cholesterol.

^a Age included as a continuous variable for adjustment in logistic models for presence of calcification.

^b Coronary calcification is present if calcification score above 10.

^c Percentages are row based; reported percentages are for individuals 55 years old in each category.

^d HIV+, overall: all HIV-infected individuals regardless of experience with therapy, presence of calcification compared with that for the group not infected with HIV.

^e Dyslipidemia was defined as TC at least 240 mg/dl, or LDL at least 160 mg/dl, or HDL below 40 mg/dl, or triglycerides at least 200 mg/dl, or use of lipid-lowering medications. Detailed explanation of missing data for total population in Table 1. Among those not taking lipid-lowering medication, data for dyslipidemia were considered missing in 85 cases with no lipid levels data.

* $P < 0.05$ (likelihood ratio test).

Table 3

Age-adjusted^a calcification scores among those with calcification^b according to characteristics of study population.

Characteristic	Calcification score ^c			
	Study population			
	Total		Not taking lipid-lowering medication	
	<i>n</i>	Median ^d (IQR)	<i>n</i>	Median ^d (IQR)
Overall	304	83 (35–98)	190	77 (33–181)
HIV and therapy status				
HIV–	117	105 (45–246)	78	108 (48–247) [*]
HIV+, HAART-naïve	26	102 (43–239)	17	101 (45–231)
HIV+, HAART 1–7 years	74	74 (32–175)	51	66 (29–150)
HIV+, HAART –8 years	87	64 (27–151)	44	45 (20–103)
HIV+, overall ^e	187	72 (31–170) ^{**}	112	60 (26–139) ^{**}
Race				
Caucasian	237	84 (35–198)	138	76 (32–177)
African-American	53	100 (42–236)	44	93 (40–218)
Hispanic and other	14	41 (17–97)	8	36 (15–85)
Ever smoking				
No	97	72 (31–171)	56	67 (29–157)
Yes	193	89 (38–211)	134	82 (35–192)
Family history CHD–MI				
No	224	89 (37–209)	148	80 (34–185)
Yes	53	63 (26–148)	32	56 (24–131)
BMI (kg/m ²)				
<25	127	80 (34–190)	84	76 (32–178)
25–29	113	73 (31–174)	72	66 (28–155)
30	38	122 (51–289)	23	124 (53–292)
Insulin level (μunits/ml)				
15	128	84 (35–203)	89	84 (35–202)
>15	113	78 (32–189)	64	69 (29–165)
Hypertension				
No	208	74 (32–173) [*]	136	69 (30–158)
Yes	64	111 (48–261)	41	107 (47–245)
Hypertension medication				
No	206	83 (35–198)	147	76 (32–180)
Yes	85	84 (36–200)	43	79 (33–185)
Hypertension and hypertension medication				
No	150	72 (31–172)	110	67 (29–155)
Yes	127	95 (40–226)	70	90 (38–209)
Diabetes mellitus				

Characteristic	Calcification score ^c			
	Study population			
	Total		Not taking lipid-lowering medication	
	<i>n</i>	Median ^d (IQR)	<i>n</i>	Median ^d (IQR)
No	111	86 (36–205)	77	85 (36–203)
Diabetes mellitus	20	63 (26–150)	9	61 (26–144)
IFG	115	83 (35–198)	71	74 (31–175)
Diabetes mellitus medication				
No	269	82 (35–195)	185	75 (32–177)
Yes	22	103 (44–245)	5	180 (77–419)
Diabetes mellitus and diabetes mellitus medication				
No	105	87 (36–211)	76	84 (35–202)
Diabetes mellitus	33	85 (35–206)	11	90 (37–218)
IFG	111	82 (34–200)	71	73 (30–175)
Hb A1 C (%)				
6	253	84 (35–201)	170	77 (33–183)
>6	31	78 (33–187)	13	89 (38–211)
Albumin (g/dl)				
4	252	87 (37–205)	163	80 (34–189)
<4	31	57 (24–136)	20	66 (28–157)
TC (mg/dl)				
<200	133	75 (31–179)	83	69 (29–165)
200–239	102	88 (37–210)	69	80 (34–190)
240	48	99 (42–237)	30	99 (42–236)
HDL cholesterol (mg/dl)				
40	178	87 (37–208)	116	86 (36–203)
<40	105	77 (32–184)	66	66 (28–156)
LDL cholesterol (mg/dl)				
<130	177	84 (36–200) [*]	107	80 (34–188)
130–159	75	66 (28–156)	55	60 (25–140)
160	31	139 (59–329)	20	138 (59–325)
Triglycerides (mg/dl)				
<150	124	70 (30–167)	91	72 (30–170)
150–199	44	101 (42–240)	28	105 (45–250)
200	78	95 (40–225)	38	78 (33–185)
Lipid-lowering medication				
No	190	77 (33–181)	190	77 (33–181)
Yes	101	99 (42–233)	NA	NA
Dyslipidemia ^f				
No	61	83 (35–198)	61	84 (35–198)
Yes	208	82 (34–197)	105	72 (30–170)
CD4 T cells (cells/μl)				

Characteristic	Calcification score ^c			
	Study population			
	Total		Not taking lipid-lowering medication	
	<i>n</i>	Median ^d (IQR)	<i>n</i>	Median ^d (IQR)
200	11	69 (29–163)	10	53 (23–124) *
201–350	36	54 (23–129)	24	37 (16–86)
>350	236	90 (38–213)	149	90 (39–209)
History of AIDS				
No	159	68 (28–169)	94	56 (24–134)
Yes	28	69 (28–170)	18	55 (23–130)

BMI, body mass index; CHD, coronary heart disease; HAART, highly active antiretroviral therapy; Hb A1c, hemoglobin A1c; HDL, high-density lipoprotein; IFG, impaired fasting glucose; IQR, inter quartile range; LDL, low-density lipoprotein; MI, myocardial infarction; NA, Non-applicable; TC, total cholesterol.

^a Age included as a continuous variable for adjustment in lognormal regression models for the calcification score. The models account for truncation.

^b Coronary calcification is present if calcification score above 10.

^c Calcification score is the geometric mean of the Agatston Scores from two CT replicates.

^d Median (IQR) calcification scores are those for individuals 55 years old in each category.

^e HIV+, overall: all HIV-infected individuals regardless of experience with therapy, calcification scores compared with those for the group not infected with HIV.

^f Dyslipidemia was defined as TC at least 240 mg/dl, or LDL at least 160 mg/dl, or HDL less than 40 mg/dl, or triglycerides at least 200 mg/dl, or use of lipid-lowering medications. Among 304 participants with calcification, data were missing for lipid levels in 46 cases, and for use of lipid-lowering medication in 13 cases (two of them with abnormal and 11 with unknown lipid levels), with 33 with data missing to adjudicate dyslipidemia. Among those not taking lipid-lowering medication, data for dyslipidemia were considered missing in 24 cases with no lipid levels data.

* $P < 0.05$ (likelihood ratio test).

** $P < 0.05$ (likelihood ratio test), comparison between HIV+ overall and HIV–.

Table 4

Association of HIV infection and therapy status with presence of coronary calcification. Shown are the results of multivariable logistic regression for the presence of calcification defined as a CAC score of more than 10.

	HIV +HAART naive	HIV +HAART 1–7 years	HIV +HAART 8 years	HIV +(overall) ^d
Adjusted for Study population (<i>n</i>)	OR ^b (95% CI)	OR ^b (95% CI)	OR ^b (95% CI)	OR ^b (95% CI)
Age				
Total (<i>N</i> =947)	1.42 (0.81, 2.50)	1.05 (0.71, 1.54)	1.53 (1.04, 2.25)	1.28 (0.93, 1.77)
Not lipid-lowering medication ^c (<i>n</i> =687)	1.29 (0.67, 2.50)	1.18 (0.75, 1.87)	1.48 (0.91, 2.43)	1.30 (0.88, 1.92)
Age and race				
Total (<i>N</i> =947)	1.51 (0.86, 2.67)	1.10 (0.74, 1.62)	1.46 (0.99, 2.15)	1.30 (0.94, 1.80)
Not lipid-lowering medication ^c (<i>n</i> =687)	1.31 (0.67, 2.55)	1.22 (0.76, 1.93)	1.44 (0.88, 2.36)	1.31 (0.89, 1.94)
+ Family-CHD, smoking				
Total (<i>N</i> =882)	1.21 (0.65, 2.25)	0.96 (0.63, 1.46)	1.39 (0.92, 2.08)	1.17 (0.83, 1.64)
Not lipid-lowering medication ^c (<i>n</i> =662)	1.29 (0.65, 2.54)	1.19 (0.74, 1.93)	1.36 (0.81, 2.28)	1.27 (0.85, 1.90)
+ HDL, LDL, hypertension				
Total (<i>N</i> =841)	1.35 (0.70, 2.61)	0.89 (0.58, 1.38)	1.33 (0.87, 2.05)	1.12 (0.78, 1.61)
Not lipid-lowering medication ^c (<i>n</i> =628)	1.49 (0.72, 3.10)	1.19 (0.71, 1.97)	1.29 (0.74, 2.25)	1.26 (0.82, 1.95)
+ BMI (kg/m ²), insulin level				
Total (<i>N</i> =704)	1.44 (0.69, 3.02)	0.88 (0.54, 1.43)	1.19 (0.73, 1.93)	1.07 (0.71, 1.61)
Not lipid-lowering medication ^c (<i>n</i> =520)	1.69 (0.73, 3.90)	1.31 (0.73, 2.33)	1.18 (0.63, 2.20)	1.30 (0.79, 2.13)

BMI, body mass index; CAC, coronary artery calcium; CHD, coronary heart disease; Family-CHD, family history of CHD; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; OR, odds ratio.

^aHIV+ (overall): all HIV-infected individuals regardless of experience with therapy.

^bOR, Odds ratio: odds of calcification in HIV-therapy group relative to odds in group not infected with HIV.

^cAnalysis restricted to those not taking lipid-lowering medication.

Table 5

Association of HIV infection and therapy status with calcification score among those with coronary calcification. Shown are the results of multivariable logistic regression for the presence of calcification defined as a CAC score of more than 10.

Adjusted for Study population (n)	HIV +HAART naive	HIV +HAART 1–7 years	HIV +HAART –8 years	HIV +(overall) ^a
	CAC ratio ^b (95% CI)	CAC ratio ^b (95% CI)	CAC ratio ^b (95% CI)	CAC Ratio ^b (95% CI)
Age				
Total (N=304)	0.99 (0.54, 1.83)	0.69 (0.45, 1.07)	0.62 (0.42, 0.94)	0.69 (0.49, 0.97)
Not lipid-lowering medication ^c (n=190)	0.95 (0.47, 1.93)	0.61 (0.37, 1.00)	0.44 (0.26, 0.76)	0.57 (0.38, 0.86)
Age and race				
Total (N=304)	0.98 (0.53, 1.81)	0.69 (0.45, 1.07)	0.66 (0.44, 0.99)	0.71 (0.50, 0.99)
Not lipid-lowering medication ^c (n=190)	0.93 (0.45, 1.92)	0.60 (0.36, 0.99)	0.47 (0.27, 0.80)	0.57 (0.38, 0.86)
+ Family-CHD, smoking				
Total (N=276)	1.23 (0.63, 2.38)	0.80 (0.51, 1.24)	0.66 (0.43, 1.00)	0.76 (0.54, 1.07)
Not lipid-lowering medication ^c (n=180)	0.99 (0.48, 2.02)	0.64 (0.39, 1.07)	0.47 (0.27, 0.81)	0.60 (0.40, 0.91)
+ HDL, LDL, hypertension				
Total (N=259)	1.24 (0.63, 2.41)	0.80 (0.50, 1.29)	0.67 (0.43, 1.04)	0.77 (0.53, 1.12)
Not lipid-lowering medication ^c (n=168)	0.99 (0.48, 2.07)	0.68 (0.40, 1.15)	0.43 (0.24, 0.79)	0.60 (0.39, 0.94)
+ BMI (kg/m ²), insulin level				
Total (N=218)	1.12 (0.54, 2.35)	0.74 (0.43, 1.27)	0.76 (0.45, 1.30)	0.81 (0.53, 1.23)
Not lipid-lowering medication ^c (n=138)	1.00 (0.45, 2.24)	0.73 (0.40, 1.33)	0.59 (0.30, 1.16)	0.72 (0.44, 1.19)

BMI, body mass index; CAC, coronary artery calcium; CHD, coronary heart disease; CI, confidence interval; Family-CHD, family history of CHD; HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

^aHIV+ (overall): all HIV-infected individuals regardless of experience with therapy.

^bCAC ratio: coronary artery calcification scores in HIV-therapy group relative to scores in group not infected with HIV.

^cAnalysis restricted to those not taking lipid-lowering medication.