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Low free testosterone in HIV-infected men is not associated with subclinical cardiovascular disease

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Abstract

Objectives—Low testosterone (T) is associated with cardiovascular disease (CVD) and increased mortality in the general population; however, the impact of T on subclinical CVD in HIV disease is unknown. This study examined the relationships among free testosterone (FT), subclinical CVD, and HIV disease.

Methods—This was a cross-sectional analysis in 322 HIV-uninfected and 534 HIV-infected men in the Multicenter AIDS Cohort Study. Main outcomes were coronary artery calcification presence, defined as a coronary artery calcium (CAC) score > 10 (CAC score was the geometric mean of the Agatston scores of two computed tomography replicates), and far wall common carotid intima-media thickness (IMT)/carotid lesion presence by B-mode ultrasound.

Results—Compared with the HIV-uninfected men in our sample, HIV-infected men were younger, with lower body mass index (BMI) and more often Black. HIV-infected men had lower FT (age-adjusted FT 88.7 ng/dL vs. 101.7 ng/dL in HIV-uninfected men; $P = 0.0004$); however, FT was not associated with CAC, log carotid IMT, or the presence of carotid lesions. HIV status was not associated with CAC presence or log carotid IMT, but was associated with carotid lesion presence (adjusted odds ratio 1.69; 95% confidence interval 1.06, 2.71) in HIV-infected men compared with HIV-uninfected men.

Conclusions—Compared with HIV-uninfected men, HIV-infected men had lower FT, as well as more prevalent carotid lesions. In both groups, FT was not associated with CAC presence, log carotid IMT, or carotid lesion presence, suggesting that FT does not influence subclinical CVD in this population of men with and at risk for HIV infection.

Keywords

cardiovascular disease; HIV; testosterone

Introduction

Increased rates of myocardial infarction and accelerated cardiovascular disease (CVD) progression have been observed among HIV-infected individuals [1], particularly among those taking antiretroviral therapy [2,3]. Identifying modifiable CVD risk factors among individuals with HIV infection is important to decrease CVD risk. Several population-based studies have shown that low serum testosterone (T) is associated with increased all-cause mortality [4] and CVD-related death [5] in men. Low serum T may be a risk factor for CVD by several mechanisms, including increased visceral adiposity (leading to glucose intolerance and diabetes mellitus), inflammation, and a more direct effect on the vasculature [6–8]. There is an increased prevalence of hypogonadism in HIV-infected men [9] and hypogonadism may persist despite effective antiretroviral therapy [10]. Although CVD in HIV-infected men may be a consequence of underlying viral mechanisms or antiretroviral therapy, it is crucial to investigate other clinically reversible factors such as low T that might result in an increased susceptibility to atherosclerotic disease.

To our knowledge, this is the first investigation of the potential role of T in the pathogenesis of CVD in HIV-infected individuals. The aim of our study was to examine the relationship between free testosterone (FT) and early stages of CVD and to explore nontraditional risk factors for CVD in an HIV-infected population, using an HIV-uninfected comparison group.

Methods

We used data from a subpopulation of the Multicenter AIDS Cohort Study (MACS; see Appendix) to assess the relationship between FT and coronary artery calcium (CAC) presence, carotid intima-media thickness (IMT), and carotid lesion presence among men with and at risk from HIV infection.

Study population

The MACS was initiated in 1984 as a study of men who have sex with men conducted at four study sites in Baltimore/Washington, DC, Chicago, Los Angeles, and Pittsburgh. A total of 6973 men were enrolled over three time periods: 1813 HIV-infected and 3141 HIV-uninfected men in 1984–1985, 425 HIV-infected and 243 HIV-uninfected men in 1987–1990, and 705 HIV-infected and 646 HIV-uninfected men, primarily minorities, in 2001–2003. Six hundred and thirty-seven of the 4089 men who were seronegative at enrolment subsequently became HIV-infected. Details of the study design and methods have been published previously [11].

Selection criteria

This analysis used data from MACS participants who were 40 years old or older, weighed less than 300 pounds, and had no history of coronary heart disease (including angina, myocardial infarction and coronary revascularization). They were all enrolled in the MACS Cardiovascular Substudy, which has been previously described [12,13]. Of the 945 substudy participants, 89 were excluded for various reasons: 14 because there was no stored serum sample at the time of the substudy visit, 71 because they were on T therapy, and four because the quantity of stored serum was insufficient for hormone assays. Hormone assays were performed on stored serum from a total of 856 men. The protocol was approved by

Institutional Review Boards at each site and each study participant signed an informed consent form.

Outcomes

Coronary arterial calcification (CAC)—Electron beam tomography (EBT) or multidetector computed tomography (MDCT) was used to measure CAC in this population. Three of four sites performed EBT using an Imatron machine (C-150 or C300) (GE Imatron, San Francisco, CA) and the other site performed MDCT with a Siemens S4+ (Siemens, Erlangen, Germany). For purposes of increased reliability and quality control, cardiac scans were performed twice for each subject. The main outcome measure used in the analysis was the geometric mean of the Agatston scores [14] of the two computed tomography (CT) replicates. For all analyses we used the presence of calcium, defined as a geometric mean above 10, as previously described [12].

Carotid intima-media thickness (IMT)—High-resolution B-mode carotid artery ultrasound was used to image the far wall of the right common carotid artery (CCA), internal carotid artery, and carotid bulb according to the procedure of Hodis and colleagues [15]. Sonographers at each of the MACS sites were uniformly trained at the University of Southern California Atherosclerosis Research Unit Core Imaging and Reading Center. Subclinical atherosclerosis was measured by right distal common carotid IMT and by carotid lesion presence, defined as a focal IMT > 1.5 mm in any of the imaged segments. IMTs were centrally measured from standardized ultrasound images of the carotid artery by automated computerized edge detection [16]. The coefficient of variation of repeated measures of IMT, with repeat scans guided by the initial images, was 1.0% (intraclass correlation coefficient = 0.99) at MACS sites ($n = 38$ healthy volunteers).

Measures of interest

The hormone assays were performed on frozen samples in the laboratory of Dr Shalender Bhasin (Boston University, Boston, MA). T levels in archived serum were measured using liquid chromatography tandem mass spectrometry (LC-MS/MS). The LC-MS/MS system includes equipment for extraction of serum samples and automated sample loading, as well as a cohesive high-turbulence liquid chromatography system, and a Thermo-Finnigan Quattro Tandem Mass Spectrometer (Thermo Fisher Scientific Inc., Waltham, MA, USA). This assay has a sensitivity of 2 ng/dL, and the interassay coefficient of variation ranged from 3.3 to 7.7%. Sex-hormone binding globulin (SHBG) was measured using radioimmunoassay (RIA). The SHBG assay uses a two-site directed immunofluorometric assay with a sensitivity of 2.5 nmol/L and is highly specific, with less than 0.1% cross-reactivity with known circulating proteins. Finally, FT was calculated from total T and SHBG measurements using the Vermeulen equation [17].

Additional variables of interest included race, body mass index (BMI), the presence of hypertension, current smoking status and the use of lipid-lowering agents. These variables were collected from semi-annual interview data. Fasting specimens for high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, insulin and glucose to calculate homeostatic model assessment of insulin resistance (HOMA-IR) [18] were collected. In HIV-infected individuals, CD4 cell count and viral load were collected. Current and prior exposure to the major antiretroviral classes, i.e. protease inhibitors (PIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and nucleoside reverse transcriptase inhibitors (NRTIs), was collected from semi-annual data. Current and prior exposure to individual antiretroviral agents was also collected.

Statistical analysis

This was a cross-sectional analysis of data from a single visit. We compared demographic and clinical characteristics of participants with and without HIV infection, using χ^2 tests to compare counts and prevalence measurements. To compare continuous variables, we used the two-sample *t*-test or Wilcoxon rank sum test, depending on the distribution of the variables.

We first constructed two multivariable logistic regression models using data for all participants, with CAC presence and carotid lesion presence as the two outcomes being modelled and log-transformed FT as the primary independent variable in each model. Other covariates included in the models were HIV status, age, BMI, race (Black *vs.* other), smoking, HDL cholesterol 40 mg/dL, LDL cholesterol 160 mg/dL, HOMA-IR, hypertension, lipid-lowering agent use and clinic site.

We then modelled the relationship between carotid IMT and FT using a multivariable linear regression model. The dependent variable for the model was log-transformed IMT, and the primary independent variable was log-transformed FT. We included HIV status, age, BMI, race (Black *vs.* other), smoking, HDL cholesterol 40 mg/dL, LDL cholesterol 160 mg/dL, HOMA-IR, hypertension and lipid-lowering agent use in the model.

Next, we examined the relationship between CAC and carotid lesion presence and FT among HIV-infected participants using similar logistic regression models. In addition to the covariates mentioned above for the models including all participants, we adjusted for HIV clinical status and treatment parameters, including CD4 count >200 cells/ μ L, viral load >400 HIV-1 RNA copies/mL, and antiretroviral therapy status. Finally, we examined the relationship between IMT and FT among HIV-infected participants using a linear regression model adjusted for all factors mentioned above.

Analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC), and a two-sided *P*-value of < 0.05 was considered statistically significant.

Results

Cohort characteristics

Table 1 presents the distribution of relevant demographic and clinical characteristics according to HIV status. The HIV-infected men (*n* = 534) were younger and had lower BMI than the HIV-uninfected men. The HIV-infected men were more likely to belong to a race other than White and more likely to have hepatitis C virus (HCV) infection than the HIV-uninfected men. The mean LDL and HDL cholesterol values were higher in the HIV-uninfected group. Log HOMA-IR was higher in the HIV-infected men (*P* < 0.0001).

In our sample, adjusted mean log FT was lower in HIV-infected men than in HIV-uninfected men, with values being 4.49 and 4.62, respectively (*P* = 0.0004), corresponding to FTs of 88.7 and 101.7 ng/dL, respectively. FT was higher in HIV-uninfected individuals and decreased with age. The FT in an HIV-infected man was equivalent to the FT in an HIV-uninfected man 13 years older [β for HIV-infected *vs.* uninfected status: -0.13 (*P* < 0.001); β for age: -0.01 (*P* < 0.0001)].

CAC presence, carotid IMT, and carotid lesion presence by HIV status

The overall prevalence of CAC in HIV-infected and HIV-uninfected participants was 32.5%. The adjusted odds ratio (OR) of CAC presence was 1.44 [95% confidence interval (CI) 0.92, 2.24] and the adjusted OR for carotid lesion presence was 1.69 (95% CI 1.06, 2.71) in HIV-infected men compared with HIV-uninfected men. There was no difference in

the adjusted mean log carotid IMT between HIV-infected and HIV-uninfected men (Table 2).

Relationship of FT with CAC presence, IMT, and carotid lesion presence

Table 2 shows the adjusted associations between log FT and CAC presence, carotid IMT, and carotid lesion presence in all study participants. In this analysis, FT was not associated with CAC presence, IMT, or carotid lesion presence. HIV-infected status was not associated with CAC presence or carotid IMT but was associated with carotid lesion presence (OR 1.69; 95% CI 1.06, 2.71). The ORs of CAC presence and carotid lesion presence for HIV-infected compared with HIV-uninfected men were similar, although only the OR of carotid lesion presence achieved statistical significance. Increasing age was positively associated with all three outcomes, and smoking was positively associated with CAC presence and carotid lesion presence. Elevated LDL cholesterol was positively associated with CAC presence in adjusted analysis. Lipid-lowering agent use was not associated with CAC presence or IMT but was positively associated with carotid lesion presence. Insulin resistance was not associated with any of the outcomes.

Relationship of FT with CAC presence, carotid IMT, and carotid lesion presence among HIV-infected men

Table 3 shows the associations between FT and CAC presence, carotid IMT, and carotid lesion presence in HIV-infected men. FT was not associated with any of the outcomes. There was no association between HIV clinical status (as indicated by viral load and CD4 cell count) and subclinical CVD.

Among the HIV-infected men, in bivariate analysis, ever having used indinavir or high-dose ritonavir was positively associated with CAC presence (data not shown; $P < 0.05$ for both). Current NNRTI or ever having used an NNRTI was positively associated with IMT ($P < 0.05$ for both). Current PI, current indinavir, and current low-dose ritonavir were positively associated with carotid lesion presence ($P < 0.05$ for all). No drug variables affected the magnitude or direction of the relationship between FT and the outcomes. In multivariable analysis, only the association between current PI use and carotid lesion presence maintained statistical significance, and it was included in the final multivariate model for that outcome.

Discussion

In this cross-sectional study of a well-characterized population of men with and at risk for HIV infection, we did not observe a relationship between FT and subclinical CVD, although FT concentrations were significantly lower in HIV-infected men. Our negative findings are an important addition to the HIV literature, and suggest that there is a driver for subclinical CVD other than FT in HIV-infected men. HIV status was not related to subclinical CVD assessed by CAC or carotid IMT; however, there was an increased adjusted OR of carotid lesion presence in HIV-infected compared with HIV-uninfected men.

Testosterone and HIV

As previously reported in an analysis of MACS data examining the relationship between FT and insulin resistance/diabetes [19], we observed lower adjusted mean log FT in the HIV-infected men compared with the HIV-uninfected men. HIV infection demonstrated an age effect of approximately 13 years. Previous studies showed that hypogonadism has persisted among HIV-infected men in the antiretroviral therapy era [10,20], and our study had the advantages of both an HIV-uninfected comparison group, which was not present in the earlier studies, and the use of the gold-standard methodology of LC-MS/MS for T measurement. It should be noted that, whereas FT differed by HIV status, total T did not.

Higher concentrations of sex-hormone binding globulin (SHBG) in HIV-infected men increase total testosterone, while the more biologically active free fraction remains low. This underscores the importance of measuring FT in HIV-infected men to ensure an accurate assessment of gonadal status. Further, FT should be measured by a reliable assay, as recommended by current guidelines [21].

Testosterone and CVD

Low testosterone has been associated with CVD risk factors such as diabetes and hyperlipidaemia [22], aging-related comorbid conditions including CVD [23], and all-cause and CVD-related mortality [4,24,25]. A recent meta-analysis of the relationship between T and CVD [26] revealed a protective effect of T only among men older than 70 years of age [summary relative risk (RR) 0.84; 95% CI 0.83–0.96]. The protective mechanism of T among elderly men is unclear, and the authors proposed that low T in elderly men may simply be a signal of poor overall health.

Our study examined multiple measures of subclinical CVD and did not reveal an association between FT and CAC, carotid IMT, or the presence of carotid lesions. There have been mixed results in previous studies examining atherosclerosis by CAC, IMT, or X-ray in the general population. Among elderly men (age > 70 years) in the general population, low baseline FT was associated with progression of carotid atherosclerosis measured by serial IMT in one study [27]; however, another study found no association between baseline total T or FT levels and progression of atherosclerosis measured on serial IMT among men older than 55 years of age [28]. A cross-sectional study by Hak and colleagues showed an association between low total T and FT and aortic atherosclerosis measured by X-ray among men older than 55 years of age [29]. However, data for men in the Multiethnic Study of Atherosclerosis showed no association between T and abdominal aortic atherosclerosis measured by CT scan [30]. Mäkinen and colleagues also reported an inverse correlation between serum T and common carotid IMT in their cross-sectional study of men aged 40 to 70 years [31]. T may inhibit atherosclerosis through multiple mechanisms including an improved CVD risk profile, a direct vasodilatory effect on the endothelium and decreased inflammation [32]. In our study, we did not find an association between T and subclinical CVD by any of the measures used, which may be a consequence of the relatively young age of our study population compared with the men studied in the general population.

HIV and CVD

HIV-infected individuals may have premature CVD attributable to traditional CVD risk factors, HIV-related inflammation, or the effects of antiretroviral therapy. Early studies of CVD in HIV infection revealed multiple CVD risk factors among people with HIV infection, including diabetes, visceral fat accumulation, and lipid abnormalities, particularly among people taking PI- and/or NNRTI-based antiretroviral therapy [33]. Previous analysis of the MACS Cardiovascular Substudy data revealed a similar or slightly higher CAC presence in HIV-infected compared with HIV-uninfected men, with a reduced extent of CAC among long-term highly active antiretroviral therapy (HAART) users, many of whom were also using lipid-lowering therapy [12]. A previous analysis of IMT data from the MACS did not show an association between HIV disease and increased mean IMT, similar to the current analysis. However, HIV-infected individuals with more advanced HIV disease, as indicated by a lower CD4 cell count, had a higher prevalence of carotid lesions [13]. We did find an increased prevalence of carotid lesions among HIV-infected men compared with HIV-uninfected men in our sample. Our findings are slightly different from those of the previous detailed analysis of carotid IMT data from the MACS [13], which included more men and adjusted for different confounders in the analysis.

Antiretroviral therapy and CVD

Antiretroviral therapy is associated with insulin resistance, diabetes, and hyperlipidaemia, all of which contribute to the development of CVD [33–35]. Results from previous studies of the association between antiretroviral therapy and CVD have been inconsistent, with some showing no association [36,37] and others showing an association [2,38]. A large retrospective study of Veterans Affairs patients [36] showed no increase in CVD mortality related to antiretroviral therapy. Interestingly, a large prospective study of treatment interruptions based on CD4 cell count revealed that individuals who were on antiretroviral therapy continuously had a lower incidence of major CVD than individuals who had structured interruptions in their therapy [39].

Antiretroviral therapy has not consistently been associated with subclinical CVD assessed by IMT or CAC. In a previous analysis from the MACS Cardiovascular Substudy focused on IMT, low CD4 T-cell count, but not antiretroviral therapy, was positively associated with an increased prevalence of carotid lesions [13]. There was, however, a trend towards an association between PI use and carotid lesions in men. A small AIDS Clinical Trials Group (ACTG) study assessed subclinical CVD using IMT and revealed no atherogenic effect of HIV status or prolonged PI therapy [40]. An analysis of the MACS Cardiovascular Substudy focused on CAC revealed that increasing age was most strongly associated with both the prevalence and the extent of CAC, and long-term HAART use was associated with a decreased extent of calcification among individuals who had calcification [13]. In our study, current PI use was associated with carotid lesion presence, but not the other measurements of subclinical CVD.

Detecting subclinical CVD

CAC and IMT provide valuable information about early atherosclerotic changes to identify subclinical CVD. These tests are not currently recommended as screening tools in asymptomatic individuals, but may be helpful in individuals with intermediate CVD risk in whom additional information may influence treatment decisions. Both CAC and IMT have been prospectively associated with the development of CVD. Data from the large, prospective Multiethnic Study of Atherosclerosis revealed that CAC is a better predictor of coronary heart disease while IMT is a better predictor of stroke [41]. Noncalcified plaques, which are not measured by CAC, are more likely to rupture and cause acute myocardial infarction. However, individuals with more calcified plaques (higher CAC) are also more likely to have more noncalcified plaques.

A major strength of our study is the use of an internal HIV-negative control group, which allowed us to examine the effect of HIV status on our outcomes. Another strength is our use of LC-MS/MS for the T assays. LC-MS/MS is considered the ‘gold standard’ against which all assays are compared. Previous studies of T in HIV-infected patients have used radioimmunoassay; however, LC-MS/MS ensures the accuracy and credibility of T measurements in this population. Most of the HIV-infected participants were on HAART, however, so results are not generalizable to antiretroviral-naïve individuals. Furthermore, it is difficult to determine the effect of antiretroviral therapy compared with the direct effects of HIV. Our ability to determine temporality is limited by the cross-sectional design of the study. Additionally, the timing of the collection of blood samples was not standardized, and therefore we cannot accurately assess the true gonadal state of each participant. In a supplementary analysis, we examined the preclinical CVD outcomes for samples drawn in the morning only and in the evening only separately, and found no association between T and CAC or IMT/carotid lesions when data were stratified by time of blood collection, similar to when all samples were analysed together. Finally, the HIV-infected and HIV-

uninfected patients had differences in their traditional CVD risk factors (hypertension, hyperlipidaemia, and smoking status), which we adjusted for in multivariate analysis.

To our knowledge, this is the first examination of the association between FT and CAC presence, carotid IMT, and carotid lesion presence in men with and at risk for HIV infection. We found that, despite lower FT levels and a higher prevalence of carotid lesions, FT was not associated with any of the measures of subclinical CVD. However, CVD is of increasing concern in an aging population with HIV infection. Additional research should be conducted to determine if all HIV-infected men should be screened for hypogonadism and whether treatment decreases CVD risk.

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Appendix

The Multicenter AIDS Cohort Study (MACS) includes the following. Baltimore: The Johns Hopkins University Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Michael Plankey (Co-Principal Investigator), Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Joel Gallant, Lisette Johnson-Hill, Ned Sacktor, Ola Selnes, James Shepard and 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), Steven M. Wolinsky (Principal Investigator), Sheila Badri, Craig Conover, Maurice O’Gorman, David Ostrow, Frank Palella and Ann Ragin. Los Angeles: University of California, UCLA Schools of Public Health and Medicine: Roger Detels (Principal Investigator), Otoniel Martínez-Maza (Co-Principal Investigator), Aaron Aronow, Robert Bolan, Elizabeth Breen, Anthony Butch, John Fahey, Beth Jamieson, Eric N. Miller, John Oishi, Harry Vinters, Barbara R. Visscher, Dorothy Wiley, Mallory Witt, Otto Yang, Stephen Young and Zuo Feng Zhang. Pittsburgh: University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence A. Kingsley (Co-Principal Investigator), James T. Becker, Ross D. Cranston, Jeremy J. Martinson, John W. Mellors, Anthony J. Silvestre and Ronald D. Stall. Data Coordinating Center: The Johns Hopkins University Bloomberg School of Public Health: Lisa P. Jacobson (Principal Investigator), Alvaro Munoz (Co-Principal Investigator), Alison Abraham, Keri Althoff, Christopher Cox, Gypsyamber D’Souza, Stephen J. Gange, Elizabeth Golub, Janet Schollenberger, Eric C. Seaberg and Sol Su. National Institutes of Health: National Institute of Allergy and Infectious Diseases: Robin E. Huebner. National Cancer Institute: Geraldina Dominguez. Website: www.statepi.jhsph.edu/mac/mac.html.

Table 1

Demographic and clinical characteristics of HIV-uninfected and HIV-infected participants

	HIV-uninfected (n = 322; 37.62%)	HIV-infected (n = 534; 62.38%)	P-value
Age (years) [mean (SD)]	52.6 ± 7.8	48.9 ± 6.4	<0.0001
Race: White [n (%)]	237 (73.6)	324 (60.7)	0.0001
BMI (kg/m ²) [median (IQR)]	26.0 (23.7, 29.1)	25.1 (22.8, 27.7)	0.0001
HCV positive [n (%)]	28 (8.7)	93 (17.4)	0.0006
Nadir CD4 cell count (cells/μL) [median (IQR)]	–	273 (163, 383)	–
CD4 cell count (cells/μL) [median (IQR)]	–	510 (349, 693)	–
HIV RNA < 400 copies/mL [n (%)]	–	358 (67.3)	–
CAC presence (%)	29.0	34.6	0.09
IMT (mm) [mean (SD)]	0.77 (0.13)	0.75 (0.15)	0.0006
Carotid lesion presence (%)	22.8	23.5	0.82
Diabetes prevalence (%)	8.0	11.4	0.16
Adjusted log HOMA-IR	1.1	1.3	<0.0001
Current smoker [n (%)]	87 (27.4)	185 (35.2)	0.02
On lipid-lowering agent [n (%)]	67 (20.8)	125 (23.4)	0.38
LDL cholesterol [mean (SD)] (mg/dL)	122.9 (35.6)	112.4 (36.8)	0.0003
HDL cholesterol [mean (SD)] (mg/dL)	49.7 (13.3)	45.1 (14.1)	<0.0001
LDL cholesterol 160 mg/dL [n (%)]	36 (13.4)	44 (10.5)	0.26
HDL cholesterol 40 mg/dL [n (%)]	76 (23.8)	209 (39.4)	<0.0001
Age-adjusted mean T (ng/dL)	596.9	606.2	0.68
Age-adjusted mean FT (ng/dL)	101.7	88.7	0.0004
Age-adjusted mean SHBG (nmol/L)	45.1	55.4	<0.0001
HbA1c (%) [mean (SD)]	5.7 (1.0)	5.4 (0.8)	<0.0001
Hypertension [n (%)]	141 (48.4)	186 (37.7)	0.015
Duration of HIV disease (days) [mean (SD)]	–	3794 (2981)	–
Antiretroviral therapy			
On antiretroviral therapy [n (%)]	–	498 (93.3)	–
NRTI			
Current NRTI* [n (%)]	–	365 (69.1)	–
Ever NRTI [n (%)]	–	469 (87.8)	–
Current ZDV [n (%)]	–	113 (21.4)	–
Ever ZDV [n (%)]	–	340 (63.7)	–
Current d4T [n (%)]	–	59 (11.2)	–
Ever d4T [n (%)]	–	282 (52.8)	–
PI			
Current PI* [n (%)]	–	214 (40.5)	–
Ever PI [n (%)]	–	367 (68.7)	–
Current indinavir [n (%)]	–	34 (6.4)	–
Ever indinavir [n (%)]	–	172 (32.2)	–
Current ritonavir, high dose [n (%)]	–	3 (0.6)	–

	HIV-uninfected (n = 322; 37.62%)	HIV-infected (n = 534; 62.38%)	P-value
Ever ritonavir, high dose [n (%)]	–	38 (7.1)	–
Current ritonavir, low dose [n (%)]	–	159 (30.1)	–
Ever ritonavir, low dose [n (%)]	–	228 (42.7)	–
Current lopinavir/ritonavir [n (%)]	–	87 (16.5)	–
Ever lopinavir/ritonavir [n (%)]	–	123 (23.0)	–
NNRTI			
Current NNRTI [‡] [n (%)]	–	223 (42.2)	–
Ever NNRTI [n (%)]	–	345 (64.6)	–

BMI, body mass index; CAC, coronary artery calcium; FT, free testosterone; HbA1c, haemoglobin A1c; HCV, hepatitis C virus; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; IMT, intima-media thickness; IQR, interquartile range; LDL, low-density lipoprotein; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; SHBG, sex-hormone binding globulin; SD, standard deviation; T, testosterone.

* Zidovudine (ZDV), lamivudine, didanosine, stavudine (d4T), abacavir, emtricitabine or tenofovir;

[‡] Saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, lopinavir, atazanavir, darunavir or tipranavir;

[‡] Nevirapine, delavirdine or efavirenz.

Table 2

Log hormone levels and coronary artery calcium (CAC) presence, log intima-media thickness (IMT), and lesion presence in HIV-infected and HIV-uninfected participants

	CAC presence OR (95% CI)	Log IMT β (P-value)	Lesion presence OR (95% CI)
Log FT	1.28 (0.80, 2.05)	−0.0003 (0.98)	0.87 (0.55, 1.38)
HIV-infected/HIV-uninfected	1.44 (0.92, 2.24)	−0.004 (0.75)	1.69 (1.06, 2.71)
Age	1.16 (1.12, 1.20)	0.01 (<0.0001)	1.10 (1.06, 1.13)
BMI	1.04 (0.99, 1.09)	0.01 (<0.0001)	1.01 (0.96, 1.06)
Race (Black)	0.46 (0.27, 0.79)	0.06 (<0.0001)	0.775 (0.45, 1.33)
Log HOMA-IR	1.03 (0.72, 1.47)	−0.01 (0.29)	0.974 (0.68, 1.40)
Current smoker (yes/no)	2.44 (1.50, 4.00)	−0.01 (0.69)	1.942 (1.19, 3.17)
LDL cholesterol 160 mg/dL	1.84 (1.03, 3.29)	0.01 (0.44)	1.05 (0.56, 1.97)
HDL cholesterol 40 mg/dL	1.36 (0.87, 2.10)	−0.01 (0.68)	1.08 (0.68, 1.70)
Hypertension (yes/no)	1.28 (0.84, 1.95)	0.04 (0.002)	1.49 (0.97, 2.29)
Lipid-lowering agent use	1.27 (0.79, 2.06)	0.02 (0.24)	1.67 (1.02, 2.72)

BMI, body mass index; CI, confidence interval; FT, free testosterone; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; OR, odds ratio.

Table 3

Log hormone levels and coronary artery calcium (CAC) presence/log intima-media thickness (IMT) in HIV-infected participants

	Outcome: CAC presence OR (95% CI)	Outcome: log IMT β (P-value)	Outcome: lesion presence OR (95% CI)
Log FT	1.45 (0.82, 2.55)	0.01 (0.51)	0.81 (0.47, 1.38)
Age	1.16 (1.10, 1.22)	0.01 (<0.001)	1.11 (1.06, 1.16)
BMI	1.02 (0.96, 1.10)	0.01 (0.001)	1.00 (0.94, 1.07)
Race (Black)	0.72 (0.37, 1.37)	0.04 (0.03)	0.79 (0.41, 1.52)
Log HOMA-IR	0.78 (0.48, 1.29)	-0.01 (0.48)	0.99 (0.62, 1.59)
Current smoker (yes/no)	2.13 (1.16, 3.90)	0.01 (0.59)	1.81 (0.98, 3.34)
LDL cholesterol 160 mg/dL	1.57 (0.71, 3.49)	0.01 (0.60)	0.73 (0.29, 1.84)
HDL cholesterol 40 mg/dL	1.66 (0.92, 2.97)	0.01 (0.79)	1.05 (0.57, 1.93)
Hypertension (yes/no)	0.87 (0.50, 1.52)	0.04 (0.01)	1.44 (0.83, 2.49)
Lipid-lowering agent use	1.55 (0.82, 2.91)	0.03 (0.11)	1.65 (0.86, 3.14)
CD4 count > 200 cells/ μ L	0.57 (0.22, 1.49)	-0.04 (0.20)	0.73 (0.27, 1.94)
HIV RNA > 400 copies/mL	0.84 (0.45, 1.56)	0.02 (0.21)	1.52 (0.79, 2.93)
Current PI	—	—	1.79 (1.01, 3.15)

BMI, body mass index; CI, confidence interval; FT, free testosterone; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; LDL, low-density lipoprotein; OR, odds ratio; PI, protease inhibitor.