Published in final edited form as:

AIDS. 2013 January 2; 27(1): 49–57. doi:10.1097/QAD.0b013e328358b29c.

Effects of Aging and Smoking on Carotid Intima Media Thickness in HIV-infection

Kathleen V. FITCH, MSN*, Sara E. LOOBY, PhD, MSN*, Alison ROPE, BA, Peace ENEH, BA, Linda HEMPHILL, MD, Hang LEE, PhD, and Steven K. GRINSPOON, MD

Massachusetts General Hospital (MGH) Program in Nutritional Metabolism (K.V.F., S.E.L., A.R., P.E., S.K.G.), MGH Cardiovascular Division (L.H.), MGH Biostatistics Center (H.L.)

Abstract

Objectives—To investigate the effects of aging and smoking on carotid intima-media thickness (cIMT) among patients with and without HIV.

Methods—Data from a community sample of HIV-infected and HIV-uninfected participants were analyzed. Carotid intima-media thickness was measured via carotid ultrasound and smoking history was obtained via patient interview.

Results—Data on 166 male and female participants with stable HIV-infection and 152 healthy HIV-uninfected participants were analyzed. Among the HIV-infected and HIV-uninfected participants, a significant association was observed between age and cIMT [$r=0.51$, $P<0.0001$ (HIV), $r=0.39$, $P<0.0001$, (non-HIV)], and between smoking burden and cIMT [$r=0.42$, $P<0.0001$ (HIV), $r=0.24$, $P=0.003$ (non-HIV)]. In multivariate regression modeling among all participants (HIV and non-HIV), a significant three-way interaction was observed between age, smoking burden, and HIV status with respect to cIMT ($P<0.010$), controlling for gender, race and traditional cardiovascular disease (CVD) risk factors, such that increased cIMT was associated with increased smoking burden and age to a greater degree among HIV-infected vs. HIV-uninfected participants. Among HIV-infected participants a significant interaction between smoking burden and age with respect to cIMT was seen ($P=0.027$), controlling for race, gender, CVD risk factors, immunological function and antiretroviral therapy use.

Conclusion—A significant interaction between HIV, age and smoking on cIMT was observed, suggesting that HIV-infection modifies the relationship of age and smoking on cIMT in this population. These findings emphasize the need to encourage smoking cessation in this population, due to its deleterious effect on subclinical atherosclerosis in older HIV-infected patients.

Keywords

HIV; Aging; Cardiovascular Diseases; Smoking

Please address correspondence and reprint requests to: Steven K. Grinspoon, MD, LON5-207; 55 Fruit St.; Boston, MA 02114, sgrinspoon@partners.org, Phone: 617-724-9109.

*These authors contributed equally to this work.

Disclosures

The authors have no relevant conflicts to disclose.

Clinical Trial Registration: Unique Identifier: NCT00465426

K. Fitch: Performed study, data analysis, wrote manuscript; S. Looby: Performed study, data analysis, wrote manuscript; A. Rope: Performed study, data analysis; P. Eneh: Performed study, data analysis; L. Hemphill: Performed study, edited manuscript; H. Lee: Data analysis; S. Grinspoon: Study conception and design, data analysis, wrote manuscript

Introduction

Improved antiretroviral therapy (ART) access and effectiveness has resulted in a remarkable decrease in AIDS-related mortality and a simultaneous increase in life expectancy among HIV-infected patients [1, 2]. In the United States, nearly 24% of those living with HIV are 50 years and older [3], and this number is anticipated to increase to 50% by 2015 [4]. As HIV-infected patients progress to advanced age, new challenges have emerged with regard to assessment and treatment strategies for HIV and its associated co-morbid illnesses, including cardiovascular disease (CVD).

HIV-infected patients are at increased risk for CVD [5], and this risk may increase with aging [6, 7]. The etiology of CVD in this population is multifactorial. Recent data suggest that HIV-infected patients experience advanced immune aging through HIV-induced alterations in monocyte phenotype and function [8]. In addition to virus-related effects, traditional CVD risk factors such as diabetes and hyperlipidemia, as well as vascular changes including atherosclerosis and increased carotid intima-media thickness (cIMT) are observed in those with HIV [9–14]. Moreover, smoking, a modifiable risk factor for CVD, is highly prevalent among HIV-infected patients and it is estimated that between 50 and 70% of those living with HIV in the U.S. are current smokers [15].

Although prior studies have investigated predictors of CVD in HIV-infected patients, little is known regarding the determinants of CVD in relation to aging comparing HIV-infected and HIV-uninfected patients. This study investigated the effects of age and smoking as well as the interaction of these variables on cIMT among a cohort of HIV-infected and HIV-uninfected participants.

Methods

Study population

Data were collected between 2000–2009 in 166 HIV-infected participants and 152 HIV-uninfected participants at the Massachusetts General Hospital (MGH) and the Massachusetts Institute of Technology (MIT). The purpose of the data collection was to compare cardiovascular risk data and cIMT as a measure of subclinical atherosclerosis among HIV-infected and HIV-uninfected participants matched for age and race. Consecutive HIV-infected and HIV-uninfected participants between 18 and 65 years of age were enrolled without regard to fat distribution. Participants were included from two non-interventional studies (one of women and one of men and women; with and without HIV) of similar endpoints. For participants receiving ART, a stable regimen for a minimum of 6 months prior to evaluation was required. Participants were excluded if they had a history of diabetes mellitus; were receiving concurrent therapy with insulin, antidiabetic agents, glucocorticoids, growth hormone, growth hormone releasing hormone, or anabolic steroids; had a major opportunistic infection within the 6 weeks prior to the study; or were pregnant or breast-feeding within the past year. The HIV-uninfected participants were recruited from the same sources as HIV-infected participants, were of similar socioeconomic backgrounds, had similar exclusion criteria and tested negative for HIV disease. Data from these cohorts have been previously published [16–20], but did not include an analysis on the effects of aging or smoking on cIMT. All participants provided informed consent. The studies were approved by the Institutional Review Boards at both MGH and MIT.

Measurements

Eligible participants were seen at the General Clinical Research Centers of MGH or MIT. All testing was performed following a 12-hour overnight fast.

Smoking status was assessed and smoking burden was calculated using the smoking pack year standard calculation: number of cigarettes smoked per day $\times$ number of years smoked)/20 (1 pack has 20 cigarettes) [21].

Anthropometric measurements were determined in the morning, prior to breakfast. All anthropometric measurements were obtained using a non-elastic tape; measurements were obtained in triplicate and then averaged. Body mass index was calculated by dividing weight in kilograms by the square of height in meters. All measurements were completed by trained research dietitians.

Fasting glucose, triglycerides, cholesterol, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol were measured using standard techniques.

HIV parameters included assessment of CD4 cell count by flow cytometry, HIV viral load (ultrasensitive assay), and undetectable viral load (yes/no) at the time of cIMT assessment, duration HIV as a continuous variable and as a stratified variable (duration < 5 years, 5–10 years, and > 10 years), current antiretroviral (ART) use, duration protease inhibitor (PI), nucleoside reverse transcriptase inhibitor (NRTI) and non-nucleoside reverse transcriptase inhibitor (NNRTI) use, and prior history of opportunistic infection. Information on nadir CD4 count was not available.

Measurement of Carotid Intima Media Thickness

Imaging was conducted using a high-resolution 7.5-MHz phased-array transducer (SONOS 2000/2500; Hewlett-Packard, Andover, MA). Digital images were captured directly to a Windows NT workstation using a high-quality, high-speed frame capture card made by Data Translation (Marlboro, MA). Participants were positioned with a wedge of approximately 35 degrees such that the subject's head and torso were at an incline to reduce respiratory variation and subsequent motion in the jugulars. Imaging of the left and right common carotid artery was performed. Imaging was performed in B-mode, and the transducer was swept in cross-section to note the position and orientation of the bifurcation of the carotid artery. The transducer was then applied to the longitudinal view, with images acquired at two angles, 90 and 45 degrees. The 90-degree imaging plane is a frontal plane of the head at the common carotid artery. The 45-degree imaging plane at the common carotid artery is 45 degrees from the 90-degree plane. In each plane, the transducer was manipulated until the best image of the far wall of the distal 1 cm of the common carotid was acquired. Fifty-frame digital video clips of this region were acquired onto the Windows NT imaging workstation. Differences in interadventitial diameter of the common carotid artery across the 50 frames were used to judge the cardiac cycle and select a frame of minimum diameter (diastole) as the analysis frame. Either the 90- or 45-degree image in diastole was selected as the best view for image quality. Edge detection and mean intima media thickness calculation were accomplished with an in-house computer program. The published reproducibility of the technique is excellent with a SD of 0.007 mm [22]. The intima media thickness over the length of the left segment is reported.

Statistical Analysis

All statistical analysis was performed using SAS JMP statistics software (version 9.0; SAS Institute Inc., Cary, NC). Continuous variables are summarized as means and standard deviations and all categorical variables as proportions. We compared between-group differences among HIV-infected and HIV-uninfected participants for demographic and clinical characteristics using the Student's t-test for continuous variables and the Chi-square test for categorical variables. We performed univariate regression analysis to assess the

relationship between age and cIMT, and smoking and cIMT stratified by HIV status among all participants.

We then performed multivariate regression modeling among all participants (HIV and non-HIV) in a combined analysis to examine how the effects of aging on cIMT differed by HIV status and smoking history. Simple models to assess the interaction between HIV status, smoking, and age with respect to cIMT were developed. In these models, predictor variables were age in years, HIV status, smoking pack years, and their two and three-way interaction terms. We next developed a comprehensive, fully adjusted model in which we included age, HIV status, smoking pack years and their two and three-way interactions terms, as well as gender, race and traditional CVD risk factors, including fasting glucose, LDL and blood pressure and use of lipid lowering and antihypertensive drugs. Sensitivity analyses were run including non-HDL, HDL, and triglyceride levels. All results are reported as mean (SD). Statistical significance was defined as *P* value of less than 0.05 in all models. For multivariate regression modeling, actual and scaled estimates are shown.

Finally, we performed multivariate regression modeling to assess for an interaction between age and smoking within the HIV group, controlling for race, gender, and relevant CVD risks known to affect cIMT (LDL, glucose, blood pressure, lipid lowering drug use, antihypertensive drug use) as well as CD4, HIV viral load, and ART use. Sensitivity analyses including HIV duration as a continuous or stratified variable (< 5 years, 5–10 years, and > 10 years), current ART use, virologic suppression as a categorical variable (yes/no), and history of prior opportunistic infection (yes/no), were also performed.

Results

Demographic and Cardiovascular Risk Factors

Table 1 reports demographic characteristics and data on traditional CVD risk factors. Mean participant age was 44 (8) [mean (SD)] years in the HIV-infected group, similar to the control group 43 (8) years (*P*=0.44). The majority of the participants were women in each group. Race did not differ among the entire cohort.

HIV-infected participants differed from HIV-uninfected participants in specific cardiovascular risk parameters (Table 1). Notably, HIV-infected participants had a significantly higher smoking burden of 12.4 (13.7) pack years and a larger percentage were current smokers (62.1%) compared to HIV-uninfected participants [4.0 (10.4) pack years and 32.9% smokers, *P*< 0.0001 for each comparison]. HIV-infected participants demonstrated a relatively higher Framingham Risk Score 4.0 (4.9) vs. 1.9 (2.8)% (*P*<0.0001), though the Framingham Risk Score was relatively low in each group (<5% in both groups). Glucose, triglyceride and non-HDL levels were higher and HDL levels lower in the HIV group. Body mass index, waist circumference, total and LDL cholesterol, and systolic blood pressure were not different between the groups. Carotid intima media thickness was 0.68 (0.15) mm in the HIV-infected group and 0.66 (0.12) mm in the HIV-uninfected group (*P*=0.066).

Among HIV-infected participants, mean duration of HIV infection was 10 (6) years, CD4 cell count 647 (329) cells/mm³, 60% had an undetectable HIV viral load, 82% were currently receiving ART and 59% had a history of prior opportunistic infection. Duration of each class of ART is shown in Table 1.

Relationship between Age, Smoking and cIMT

A significant association was observed between age and cIMT among HIV (*r*=0.51, *P*<0.0001) and HIV-uninfected participants (*r*=0.39, *P*<0.0001). Similarly a significant

association was observed between smoking burden and cIMT among HIV ($r=0.42$, $P<0.0001$) and HIV-uninfected participants ($r=0.24$, $P=0.003$) (Figure 1).

Multivariate Modeling to Assess Interactions between HIV Status, Smoking and Age Effects on cIMT among All Participants

In modeling performed among all participants (HIV-infected and HIV-uninfected), assessing for interactions with HIV status, there was a significant interaction between age and HIV status with respect to cIMT ($P=0.045$) (Table 2a), such that cIMT increased more with age in HIV than HIV-uninfected participants (Figure 1a).

Further multivariate regression modeling was performed to explore the cumulative effect of HIV status, age, and smoking burden with respect to cIMT among all participants (HIV-infected and HIV-uninfected). A significant three-way interaction between HIV status, smoking and age with respect to cIMT was observed ($P=0.006$) (Table 2b and Figure 2). The three-way interaction was significantly larger than any other effect in the model (see scaled estimate, Table 2b). In this model there was also a significant two-way interaction between HIV and age on cIMT ($P=0.053$). In a fully adjusted final model, including all of the terms in the initial model, as well as gender, race, blood pressure, LDL, fasting glucose, as well as lipid lowering and antihypertensive drug use, the three-way interaction between smoking, age and HIV remained highly significant for cIMT ($P=0.010$) (Table 2c). Sensitivity analyses including non-HDL, HDL and triglyceride levels showed similar results with a significant interaction between smoking, age and HIV with respect to cIMT (data not shown).

Relationship of Age and Smoking to cIMT among HIV-infected Subjects

Among HIV-infected participants, smoking (pack years) ($P=0.007$), age ($P<0.0001$), and the interaction term between smoking and age ($P=0.036$) were all significant with respect to cIMT (Table 3a). The interaction between smoking and age with respect to cIMT was also significant in a fully adjusted model ($P=0.027$), controlling for gender, race, traditional CVD risk factors, lipid lowering and antihypertensive medications, ART use, CD4 and viral load (Table 3b). In this model, duration of PI, NRTI and NNRTI use were not significantly related to cIMT. Sensitivity analyses including non-HDL, HDL and triglyceride levels showed similar results with a significant interaction between smoking and age with respect to cIMT (data not shown).

Sensitivity analyses including duration HIV, suppressed viral load, prior history of opportunistic infection and current ART showed similar results with a significant interaction between smoking and age within the HIV group (Supplemental Table 1). Similar results were seen when HIV duration was included as a stratified categorical variable (duration < 5 years, 5–10 years, and > 10 years). Of note cIMT increased with increasing HIV duration ($r=0.25$, $P=0.001$), but HIV duration co-varied with and was also significantly associated with increasing age ($r=0.42$, $P<0.0001$). In multivariate modeling, age, but not HIV duration was associated with cIMT (Supplemental Table 1).

Discussion

In this third decade of HIV, clinicians are challenged to address the clinical needs of an aging HIV-infected population. Although recent articles have described anticipated concerns regarding HIV and aging, very few published data are available on the concurrent impact of HIV and aging on co-morbidities, including CVD, that are prevalent in this population. Specifically, while many publications have shown a relationship between specific CVD risk parameters/atherosclerotic indices and age [11, 23–25], few have compared these

relationships to age in simultaneously assessed HIV-infected and HIV-uninfected subjects [7, 12]. In addition, the cumulative impact of smoking, a commonly observed habit among HIV-infected patients, on CVD risk in this population is uncertain and no study, to our knowledge, has sought to simultaneously investigate the potential interaction between aging, smoking and HIV, with respect to atherosclerotic indices. Our data show for the first time that these factors interact and are associated with increased cIMT and that HIV-infection modifies the relationship of age and smoking on cIMT in this population. These data demonstrate that older, HIV smokers have a disproportionately higher cIMT than older HIV-uninfected smokers, and suggest the critical need for risk modification to reduce the accelerated effects of aging on atherosclerotic indices in HIV patients in general and among HIV smokers in particular.

It is well known that cIMT increases with age among both HIV-infected and HIV-uninfected patients [14, 26]. However, few studies have compared the effects of aging on CVD risk in HIV-infected and HIV-uninfected populations. Triant et al. demonstrated that the relative risk for acute myocardial infarction between HIV-infected and HIV-uninfected participants increased with increasing age in a large clinical care cohort [7]. More recently Guraldi et al. investigated the prevalence of specific CVD risk factors and CVD disease itself in a clinical cohort, also showing relatively greater increases with age in HIV-infected vs. HIV-uninfected participants [6]. In addition, Guaraldi et al., using coronary artery calcification score, demonstrated increased vascular aging among HIV-infected participants, with a relative difference of 15 years in predicted vs. actual coronary age, though direct comparison to an HIV-uninfected control group was not made in this study [27]. Kaplan et al. investigated cIMT at different ages by HIV status, but did not analyze whether this relationship differed between HIV-infected and HIV-uninfected participants [26].

Our data advance the investigation of aging effects on CVD in HIV by comparing the relative relationships between age and cIMT, a standard index of atherosclerotic disease, in HIV-infected vs. HIV-uninfected patients. We compared the relationships between age and cIMT among all participants controlling for HIV status. In this regard, we saw a stronger relationship between cIMT and age in HIV-infected vs. HIV-uninfected participants and this interaction, which has not previously been examined, was significant.

The mechanism by which cIMT increases more with age in HIV-infected vs. HIV-uninfected patients is not well understood. Important traditional risk factors other than smoking, including systolic blood pressure, LDL, waist circumference, and age, were similar between the groups, and Framingham risk scores were low on average among the HIV-infected participants. Differences in fasting blood glucose, triglyceride, HDL and non-HDL levels were seen between the groups, but the interaction between HIV, smoking and age remained significant adjusting for these variables in multivariate modeling. We did not permit diabetics, or those on insulin or steroids into the study because of the known association of increased cIMT in diabetes. Inclusion of such subjects would potentially confound assessment of the relationship between smoking and aging in HIV-infected vs. HIV-uninfected patients.

Persistent chronic immune activation, resulting in greater atherosclerosis, has been postulated to occur in HIV-infected patients. Indeed we have shown that sCD163, a marker of monocyte activation, is increased in association with noncalcified coronary plaque, even among virologically suppressed HIV-infected compared to HIV-uninfected patients [28]. Kaplan et al. have shown a relationship between T cell activation and cIMT in HIV-infected patients [29]. More recently, Hearps et al. published an interesting study in which she showed that the monocytes from young HIV-infected patients resembled those of elderly controls with an increased activation phenotype, implying a premature activation of

monocytes with aging in HIV-infected patients [8]. Further studies are needed to investigate the interaction of monocyte and T cell activation with aging and atherosclerotic disease in HIV-infected vs. HIV-uninfected patients.

Use of ART and other factors may contribute to advanced vascular aging in HIV-infected patients, although we did not see evidence of this in the current study, controlling for current ART use or duration of PI, NRTI or NNRTI use. Moreover, we tested whether virologic suppression per se and prior history of opportunistic infection, e.g. to define those with more significant prior immune dysfunction, were associated with cIMT in the modeling and they were not. Duration of HIV was associated with increased age and cIMT, but age, and not duration of HIV, remained significant in multivariate regression modeling for cIMT. Inclusion of these variables did not affect the relationship between aging and smoking seen in the HIV group.

Cigarette smoking, a leading cause of morbidity and mortality [30], is increased in HIV [15] and has been related to CVD events among HIV-infected patients [31]. Tobacco smoke directly affects key pathways which promote the development of atherosclerosis including vascular inflammation, lipid oxidation, and vasomotor function [32, 33]. Similar to prior studies [34, 35], we found increased smoking burden in HIV-infected patients, and also demonstrate that smoking burden is positively correlated with increased cIMT in HIV-infected and HIV-uninfected patients. Prior studies have looked at effects of smoking in HIV-infected and HIV-uninfected participants [14, 36], but have not assessed the differential affects of smoking on cIMT in these groups. As recent studies suggest, exposure to cigarette smoke itself can result in monocyte activation [37, 38], and this may be a mechanism of the synergy we find with respect to HIV disease in our study.

We assessed the interaction between age and smoking among all participants, including a term for HIV status and the relevant two and three-way interaction terms. In this regard, we found a strong and novel relationship such that cIMT increased more among aging HIV-infected than HIV-uninfected smokers. The interaction was highly significant and the scaled estimate showed that it was larger than any other effect in the model. These data suggest a potential mechanism by which increased smoking burden may interact synergistically with increased vascular aging to markedly increase atherosclerosis in HIV-infected patients.

Taken together, these data suggest that the increased burden of smoking may be a particular concern among the HIV population as it ages. Recent data from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) demonstrated that smoking conferred a significantly increased relative in risk of MI of 2.83, controlling for ART use and conventional risk factors for CVD, but this study did not include HIV-uninfected participants as a control group [31]. In our study, the interaction between smoking, age and HIV that we demonstrate with respect to cIMT was not the result of any increase or differences in other traditional risk factors between the groups, as we controlled for traditional risk factors, race and gender in our final model. Indeed the three-way interaction remained highly robust in a fully saturated model, controlling for all possible two-way interactions. Additional research is critical to further explore the mechanisms by which smoking may particularly synergize with aging, to induce atherosclerosis in the HIV-infected population.

Our study has limitations. The cross-sectional design limits the determination of causality, but our data from a representative group of HIV-infected patients and age-matched controls is informative, and demonstrates a highly robust and novel interaction between smoking, age, HIV and cIMT. Women comprised a majority of study subjects, but the percentages of women in the HIV-infected and HIV-uninfected groups were similar and we controlled for

gender in all analyses. The study size of over 300 participants with well phenotyped HIV-infected and HIV-uninfected participants was large enough to detect a significant interaction between HIV status, age and smoking burden on cIMT in comprehensive modeling, fully adjusted for relevant covariates. We did not have data on nadir CD4, or duration of viral suppression, to control for prior history of immune dysfunction, which may impact the relationship between aging, smoking and cIMT, but we did include data on prior opportunistic infection as a surrogate in this regard, without an effect in the modeling. Future studies should investigate the effects of current and prior immune dysfunction and immune activation on the relationship between smoking, aging and cIMT in HIV patients.

In summary, our data highlight for the first time that there is a significant, synergistic effect of HIV, age, and smoking burden on cIMT. This finding is critical as we approach an era when over half of patients living with HIV will be older than 50 years, and a disproportionate number of these older, HIV-infected patients smoke. Our findings advocate for assessment of CVD risk and utilization of necessary interventions to reduce CVD risk prior to midlife among the growing number of HIV-infected patients approaching advanced age. Importantly, these data support the critical need for clinicians to encourage smoking cessation as a measure to improve CVD risk among HIV-infected patients, particularly as this population continues to age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

Funding was provided by NIH R01 DK049302 and K24 DK064545-08 to S.K.G., and by NIH M01-RR-01066 and 1 UL1 RR025758-01, Harvard Clinical and Translational Science Center, from the National Center for Research Resources. NIH funding also provided through K23 NR011833-01A1 to S.E.L. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

We wish to thank the subjects who participated in this study and the nursing and bionutrition staff of the MGH and MIT Clinical Research Centers for their excellent patient care.

References

1. Lewden C, Chene G, Morlat P, Raffi F, Dupon M, Dellamonica P, et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm³ on long-term combination antiretroviral therapy reach same mortality rates as the general population. *J Acquir Immune Defic Syndr*. 2007; 46:72–77. [PubMed: 17621240]
2. Palella FJ Jr, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med*. 1998; 338:853–860. [PubMed: 9516219]
3. Centers for Disease Control and Prevention C. CDC: HIV/AIDS Facts. 2008. HIV/AIDS and Persons Aged 50 and Older; p. 1-2.
4. Mills EJ, Barnighausen T, Negin J. HIV and aging--preparing for the challenges ahead. *N Engl J Med*. 2012; 366:1270–1273. [PubMed: 22475591]
5. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med*. 2006; 145:397–406. [PubMed: 16983127]
6. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis*. 2011; 53:1120–1126. [PubMed: 21998278]

7. 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]
8. Hearps AC, Maisa A, Cheng WJ, Angelovich TA, Lichtfuss GF, Palmer CS, et al. HIV infection induces age-related changes to monocytes and innate immune activation in young men that persist despite combination antiretroviral therapy. *AIDS.* 2012; 26:843–853. [PubMed: 22313961]
9. 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]
10. Hadigan C, Meigs JB, Corcoran C, Rietschel P, Piecuch S, Basgoz N, et al. Metabolic abnormalities and cardiovascular disease risk factors in adults with human immunodeficiency virus infection and lipodystrophy. *Clin Infect Dis.* 2001; 32:130–139. [PubMed: 11118392]
11. Lo J, Abbara S, Shturman L, Soni A, Wei J, Rocha-Filho JA, et al. Increased prevalence of subclinical coronary atherosclerosis detected by coronary computed tomography angiography in HIV-infected men. *AIDS.* 2010; 24:243–253. [PubMed: 19996940]
12. Guaraldi G, Zona S, Orlando G, Carli F, Ligabue G, Fiocchi F, et al. Human immunodeficiency virus infection is associated with accelerated atherosclerosis. *J Antimicrob Chemother.* 2011; 66:1857–1860. [PubMed: 21653601]
13. Hsue PY, Hunt PW, Sinclair E, Brecht B, Franklin A, Killian M, et al. Increased carotid intima-media thickness in HIV patients is associated with increased cytomegalovirus-specific T-cell responses. *AIDS.* 2006; 20:2275–2283. [PubMed: 17117013]
14. Hsue PY, Lo JC, Franklin A, Bolger AF, Martin JN, Deeks SG, et al. Progression of atherosclerosis as assessed by carotid intima-media thickness in patients with HIV infection. *Circulation.* 2004; 109:1603–1608. [PubMed: 15023877]
15. Nahvi S, Cooperman NA. Review: the need for smoking cessation among HIV-positive smokers. *AIDS Educ Prev.* 2009; 21:14–27. [PubMed: 19537951]
16. Dolan SE, Hadigan C, Killilea KM, Sullivan MP, Hemphill L, Lees RS, et al. Increased cardiovascular disease risk indices in HIV-infected women. *J Acquir Immune Defic Syndr.* 2005; 39:44–54. [PubMed: 15851913]
17. Johnsen S, Dolan SE, Fitch KV, Kanter JR, Hemphill LC, Connelly JM, et al. Carotid intimal medial thickness in human immunodeficiency virus-infected women: effects of protease inhibitor use, cardiac risk factors, and the metabolic syndrome. *J Clin Endocrinol Metab.* 2006; 91:4916–4924. [PubMed: 17003092]
18. Lo J, Dolan SE, Kanter JR, Hemphill LC, Connelly JM, Lees RS, et al. Effects of obesity, body composition, and adiponectin on carotid intima-media thickness in healthy women. *J Clin Endocrinol Metab.* 2006; 91:1677–1682. [PubMed: 16522690]
19. Fitch KV, Stanley TL, Looby SE, Rope AM, Grinspoon SK. Relationship between neck circumference and cardiometabolic parameters in HIV-infected and non-HIV-infected adults. *Diabetes Care.* 2011; 34:1026–1031. [PubMed: 21378212]
20. Fitch KV, Stavrou E, Looby SE, Hemphill L, Jaff MR, Grinspoon SK. Associations of cardiovascular risk factors with two surrogate markers of subclinical atherosclerosis: endothelial function and carotid intima media thickness. *Atherosclerosis.* 2011; 217:437–440. [PubMed: 21570076]
21. Health NCIatNIH. Dictionary of Cancer Terms. Bethesda, MD: National Cancer Institute; 2012. Pack Year Definition.
22. Chan R, Kaufhold J, Hemphill LC, Lees RS, Karl WC. Anisotropic Edge-Preserving Smoothing in Carotid B-mode Ultrasound for Improved Segmentation and Intima-Media Thickness (IMT) Measurement. *Computers in Cardiology.* 2000; 27:37–40.
23. Hsue PY, Ordovas K, Lee T, Reddy G, Gotway M, Schnell A, et al. Carotid intima-media thickness among human immunodeficiency virus-infected patients without coronary calcium. *Am J Cardiol.* 2012; 109:742–747. [PubMed: 22169125]
24. Kingsley LA, Cuervo-Rojas J, Munoz A, Palella FJ, Post W, Witt MD, et al. Subclinical coronary atherosclerosis, HIV infection and antiretroviral therapy: Multicenter AIDS Cohort Study. *AIDS.* 2008; 22:1589–1599. [PubMed: 18670218]

25. Mangili A, Gerrior J, Tang AM, O'Leary DH, Polak JK, Schaefer EJ, 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. *Clinical Infectious Diseases*. 2006; 43:1482–1489. [PubMed: 17083026]
26. Kaplan RC, Kingsley LA, Gange SJ, Benning L, Jacobson LP, Lazar J, et al. Low CD4+ T-cell count as a major atherosclerosis risk factor in HIV-infected women and men. *AIDS*. 2008; 22:1615–1624. [PubMed: 18670221]
27. Guaraldi G, Zona S, Alexopoulos N, Orlando G, Carli F, Ligabue G, et al. Coronary aging in HIV-infected patients. *Clin Infect Dis*. 2009; 49:1756–1762. [PubMed: 19886793]
28. Burdo TH, Lo J, Abbara S, Wei J, DeLelys ME, Preffer F, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. *J Infect Dis*. 2011; 204:1227–1236. [PubMed: 21917896]
29. Kaplan RC, Sinclair E, Landay AL, Lurain N, Sharrett AR, Gange SJ, et al. T cell activation and senescence predict subclinical carotid artery disease in HIV-infected women. *J Infect Dis*. 2011; 203:452–463. [PubMed: 21220772]
30. McGinnis JM, Foege WH. Actual causes of death in the United States. *JAMA*. 1993; 270:2207–2212. [PubMed: 8411605]
31. Friis-Moller N, Reiss P, Sabin CA, Weber R, Monforte A, El-Sadr W, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med*. 2007; 356:1723–1735. [PubMed: 17460226]
32. Nguyen AB, Rohatgi A, Garcia CK, Ayers CR, Das SR, Lakoski SG, et al. Interactions between smoking, pulmonary surfactant protein B, and atherosclerosis in the general population: the Dallas Heart Study. *Arterioscler Thromb Vasc Biol*. 2011; 31:2136–2143. [PubMed: 21817103]
33. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004; 43:1731–1737. [PubMed: 15145091]
34. Kaplan RC, Kingsley LA, Sharrett AR, Li X, Lazar J, Tien PC, et al. Ten-year predicted coronary heart disease risk in HIV-infected men and women. *Clin Infect Dis*. 2007; 45:1074–1081. [PubMed: 17879928]
35. Estrada V, Martinez-Larrad MT, Gonzalez-Sanchez JL, de Villar NG, Zabena C, Fernandez C, et al. Lipodystrophy and metabolic syndrome in HIV-infected patients treated with antiretroviral therapy. *Metabolism*. 2006; 55:940–945. [PubMed: 16784968]
36. Mercie P, Thiebaut R, Lavignolle V, Pellegrin JL, Yvorra-Vives MC, Morlat P, et al. Evaluation of cardiovascular risk factors in HIV-1 infected patients using carotid intima-media thickness measurement. *Ann Med*. 2002; 34:55–63. [PubMed: 12014436]
37. Alamanda V, Singh S, Lawrence NJ, Chellappan SP. Nicotine-mediated induction of E-selectin in aortic endothelial cells requires Src kinase and E2F1 transcriptional activity. *Biochem Biophys Res Commun*. 2012; 418:56–61. [PubMed: 22240023]
38. Monzon ME, Forteza RM, Casalino-Matsuda SM. MCP-1/CCR2B-dependent loop upregulates MUC5AC and MUC5B in human airway epithelium. *Am J Physiol Lung Cell Mol Physiol*. 2011; 300:L204–215. [PubMed: 21097527]

Figure 1.

Relationship between carotid intima media thickness and age, and smoking pack years. Figure 1a. For HIV participants (●, solid line) $r = 0.51$, $P < 0.0001$; non-HIV (○, dashed line) $r = 0.39$, $P < 0.0001$. Figure 1b. For HIV participants (●, solid line) $r = 0.42$, $P < 0.0001$; and non-HIV (○, dashed line) $r = 0.24$, $P = 0.003$.

Figure 2. Impact of HIV status, smoking pack years (PY) and age on carotid intima media thickness (cIMT). Three dimensional depiction of cIMT, stratified by smoking pack years, age and HIV status.

Table 1

Characteristics of the Study Population*

	Non-HIV Infected	HIV-Infected
Participants, n	152	166
Age, y	43 (8)	44 (8)
Women, n (%)	126 (82.9)	123 (74.1)
Caucasian, n (%)	94 (61.8)	108 (65.1)
Current smoker, n (%)	50 (32.9)	103 (62.1)
Smoking pack years [†]	4.0 (10.4)	12.4 (13.7)
HIV duration (yrs)		10 (6)
Current ART use, n (%)		136 (82)
PI duration (yrs)		3 (4)
NRTI duration (yrs)		5 (4)
NNRTI duration (yrs)		1 (3)
CD4 (#/mm ³)		647 (329)
Log HIV Viral load		2.3 (1.0)
Undetectable Viral Load, n (%)		93 (60)
History of Opportunistic Infection, n (%)		96 (59)
Lipid lowering therapy, n (%)	6 (4.0)	19 (11.5)
Antihypertensive therapy, n (%)	10 (6.6)	28 (16.9)
Blood pressure, mm Hg		
Systolic	114 (14)	116 (15)
Diastolic	72 (11)	75 (10)
Total cholesterol level		
mmol/L	4.6 (0.8)	4.7 (1.1)
mg/dL	176 (32)	182 (43)
LDL cholesterol level		
mmol/L	2.7 (0.8)	2.8 (1.0)
mg/dL	105 (31)	108 (38)
HDL cholesterol level		
mmol/L	1.4 (0.4)	1.2 (0.4)
mg/L	56 (15)	46 (15)

	Non-HIV Infected	HIV-Infected
Triglyceride level		
mmol/L	0.9 (0.4)	1.7 (1.6)
mg/dL	79 (40)	151 (144)
Non-HDL Cholesterol		
mmol/L	3.1 (0.9)	3.5 (1.1)
mg/dL	120 (34)	136 (42)
Fasting glucose level		
mmol/L	4.7 (0.6)	4.8 (0.7)
mg/dL	84 (11)	87 (12)
BMI, kg/m ²	27.6 (4.7)	26.6 (5.4)
Waist circumference, cm	91.5 (13.2)	94.1 (13.7)
cIMT, mm [‡]	0.66 (0.12)	0.68 (0.15)
Framingham Risk Score, %	1.9 (2.8)	4.0 (4.9)

PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor; LDL = low density lipoprotein; HDL = high density lipoprotein

* Data are reported as mean (SD)

[‡] Missing values are not included in calculations (n=3)

[‡] Missing values are not included in calculations (n=4)

Table 2(a)

Model to Assess Interaction between HIV Status and Age on Carotid Intima Media Thickness among the Entire Cohort

$(R^2 = 0.22, P < 0.0001)$			
	β -estimate	Scaled Estimate	P-value
HIV	0.010744	0.01	0.117
Age	0.0078489	0.15	<0.0001
HIV*Age	0.001763	0.03	0.045

Table 2(b)

Model to Assess Interaction between HIV Status, Smoking and Age on Carotid Intima Media Thickness among the Entire Cohort

(R ² = 0.29, P<0.0001)			
	β-estimate	Scaled Estimate	P-value
HIV	−0.0145424	−0.01	0.136
Age	0.0047265	0.09	<0.0001
Smoking pack years	0.0040104	0.21	0.0007
HIV*Smoking pack years	−0.0018763	−0.10	0.111
HIV*Age	0.002244	0.04	0.053
Smoking pack years*Age	−0.000104	−0.10	0.31
HIV*Smoking pack years*Age	0.000282	0.28	0.006

Table 2(c)

Model to Assess Interaction between HIV Status, Smoking and Age on Carotid Intima Media Thickness among the Entire Cohort

(R² = 0.38, P<0.0001)			
	β-estimate	Scaled Estimate	P-value
HIV	−0.0147915	−0.01	0.125
Age	0.0040071	0.08	0.001
Smoking pack years	0.003811	0.20	0.001
Gender (male)	0.0114333	0.01	0.189
Race (non-Caucasian)	−0.020194	−0.02	0.004
Systolic blood pressure (mmHg)	0.0014115	0.08	0.006
Fasting glucose (mg/dL)	0.0004762	0.02	0.43
LDL cholesterol (mg/dL)	0.0001993	0.02	0.30
Antihypertensive therapy (no)	−0.006817	−0.01	0.57
Lipid lowering therapy (no)	0.0254359	0.03	0.053
HIV*Smoking pack years	−0.0015502	−0.08	0.176
HIV*Age	0.001429	0.03	0.211
Smoking pack years*Age	−0.000079	−0.08	0.43
HIV*Smoking pack years*Age	0.000261	0.26	0.010

LDL = low density lipoprotein

Table 3a

Relationship between Age, Smoking and cIMT within HIV

HIV-Infected ($R^2 = 0.34$, $P < 0.0001$)			
	β -estimate	Scaled Estimate	P-value
Smoking pack years	0.0021978	0.07	0.007
Age	0.0077079	0.14	<0.0001
Smoking pack years*Age	0.0001783	0.10	0.036

Table 3b

Relationship between Age, Smoking, Cardiovascular Risk Parameters and cIMT within HIV

HIV-Infected ($R^2 = 0.52$, $P < 0.0001$)			
	β-estimate	Scaled Estimate	P-value
Smoking pack years	0.0018595	0.06	0.036
Age	0.007022	0.13	0.0001
Smoking pack years* Age	0.0002109	0.12	0.027
Gender (male)	0.0067769	0.01	0.60
Race (non-Caucasian)	-0.036716	-0.04	0.001
Systolic blood pressure (mmHg)	0.0020505	0.10	0.017
LDL cholesterol (mg/dL)	0.0000867	0.01	0.76
Fasting glucose (mg/dL)	0.0007207	0.04	0.45
Lipid lowering therapy (no)	0.035188	0.04	0.060
Antihypertensive therapy (no)	0.0054578	0.01	0.76
Duration of PI	-0.000518	-0.07	0.110
Duration of NRTI	0.0001258	0.02	0.65
Duration of NNRTI	0.0002267	0.01	0.58
CD4 (#/mm ³)	0.0000780	0.05	0.082
HIV viral load (log)	0.0118981	0.02	0.34

LDL = low density lipoprotein; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor