Published in final edited form as:

Atherosclerosis. 2011 February ; 214(2): 468–473. doi:10.1016/j.atherosclerosis.2010.11.013.

Markers of Atherosclerosis and Inflammation and Mortality in Patients with HIV Infection

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Abstract

Objective—HIV-infected patients are at increased risk for cardiovascular disease, which may be mediated in part by inflammation. Surrogate marker studies suggest an increased prevalence of vascular abnormalities in HIV infection. We examined the association of all-cause mortality in HIV-infected patients with carotid artery intima-media thickness (cIMT) and high-sensitivity C-reactive protein (hsCRP).

Design and Methods—Baseline risk factors, cIMT and hsCRP were prospectively measured in 327 HIV-infected participants. Follow-up time with median of 3.1 years was calculated from baseline to death or censored dated 7/31/07. Cox Proportional Hazards models were used to study risk factors associated with mortality.

Results—Thirty eight (11.6 %) of participants have died since study enrollment. CIMENT was significantly higher in those who died and decedents were significantly more likely to have cIMT above the 75th percentile. Those who died had higher hsCRP than those alive and more had hsCRP values above 3 mg/L. CD4 count was lower and log₁₀ viral load was higher in decedents, but antiretroviral regimens were similar in both groups. CIMENT and hsCRP levels were significantly associated with mortality (HR=2.74, 95% CI 1.26 to 5.97, p=0.01; HR=2.38, 95% CI 1.15 to 4.9, p=0.02).

Conclusions—Our study demonstrated a strong association of carotid IMT and hsCRP with all-cause death in this HIV-infected population despite being similar with respect to exposure to antiretroviral medications. Together these surrogate markers may be indices of chronic inflammation and unfavorable outcomes in HIV-positive patients.

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Disclosures: None of the authors have any potential conflicts of interest in relation to this work.

Presented in part at the 9th International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV, 2007, Sydney, Australia and at the 49th Cardiovascular Disease Epidemiology and Prevention -and- Nutrition, Physical Activity and Metabolism, 2009. Palm Harbor, FL.

INTRODUCTION

Increased cardiovascular events, atherogenic and diabetogenic abnormalities are commonly observed in HIV-positive individuals¹. To what extent antiretroviral treatment, the virus or cardiovascular risk factors contribute to the increased risk of cardiovascular events remains to be clarified^{2;3}. Some recent studies have shown significantly higher cardiovascular events and increased risk of myocardial infarction with exposure to selected antiretroviral regimens⁴⁻⁸. In general, cardiovascular events in HIV-infected patients have been difficult to study for reasons of cohort size and time of follow-up⁹.

Asymptomatic thickening of the carotid artery wall is a well-established predictor of cardiovascular mortality and morbidity in the general population¹⁰. HsCRP, an inflammatory biomarker for cardiovascular disease and an increasingly popular screening tool for cardiovascular risk, is associated with future risk of coronary heart disease, ischemic stroke and death from vascular and non-vascular disease in previously healthy individuals¹¹. While traditional cardiovascular risk factors play an important role in prevalent atherosclerotic cardiovascular disease in HIV-infected patients, there are few data available on whether subclinical cardiovascular disease, as measured by carotid IMT, might predict outcomes^{12;13}.

In the present study, we evaluated the association between carotid IMT, cardiovascular and HIV-specific risk factors and all-cause mortality in a well-described cohort of HIV-infected patients.

METHODS

Subjects

We enrolled 327 HIV-positive men and women from the Cardiovascular AIDS Risk Evaluation (CARE), a longitudinal study, which examined cardiovascular, nutritional and metabolic issues in HIV-infected patients at 6-month intervals. Carotid ultrasounds were performed from 1/23/02 through 3/31/04. All patients provided informed consent for the study. The study was approved by the Institutional Review Board at Tufts Medical Center.

Deaths occurring since study enrollment were actively sought from participants who did not return for clinic visits or did not return telephone calls. Quarterly searches for death certificates were performed at the Department of Public Health in MA and RI. The National Death Index (NDI) registry was queried yearly for additional deaths of study participants. The most recent query was in 2009. The causes of death were ascertained by review of inpatient and outpatient medical records, queries to participants' primary physicians, review of autopsy reports, and death certificates. Each record was individually reviewed and discussed by a group of three physicians experienced in HIV care and the cause of death was critically evaluated. When cause of death could not be definitely documented, the probable cause was critically inferred, where possible, from the above clinical data, using autopsy diagnoses preferred over physician interviews and medical records, which in turn were preferred over chart reviews. Lastly, the death certificate diagnoses were used when no other source of information was available.

Clinical characteristics and laboratory data

Demographic information, clinical data and laboratory measurements were obtained within 3 months of the surrogate marker assessment. Interview-administered questionnaires were used to obtain demographic characteristics, as well as medical, family, smoking and drug use histories. Metabolic syndrome was diagnosed by NCEP/ATPIII criteria¹⁴. Plasma total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured on

a Roche Diagnostics Hitachi 911 chemistry analyzer (Indianapolis, IN), using standard enzymatic methods¹⁵. Low-density lipoprotein (LDL) cholesterol was measured directly using kits from Roche Diagnostics. Homocysteine, fasting glucose and insulin were measured at the same time as the lipids. QUICKI, a measure of insulin sensitivity, was calculated from insulin and glucose, using $QUICKI = (1/[\log(\text{insulin}) + \log(\text{glucose})])^{16}$. HsCRP was measured with a high sensitivity latex-enhanced turbidimetric assay from Wako Diagnostics with coefficients of variation <5%. CD4 count was measured by flow cytometry, and HIVRNA was obtained by Roche diagnostics (limit of detection 400 copies/ml) at the same time point.

Carotid Intima Media Thickness Measurements

Details of the standardized methods used for the measurement and interpretation of carotid IMT have been described previously¹³. The carotid IMT protocol was adapted from the Cardiovascular Health Study (CHS), using the same ultrasound reading center at the Department of Radiology at Tufts Medical Center¹⁰. In brief, trained technicians performed B-mode ultrasounds of the right and left near and far wall of the common carotid arteries. The mean of the maximum IMT of the near and far walls of the right and left sides were summarized into a continuous variable quantifying the maximal degree of wall thickening for the common carotid artery.

Statistical Analysis

Analyses were performed with SAS System for Windows, Version 9.2 (SAS Institute, Cary, NC). First, the distributions of all variables were examined. The different characteristics of the study population was compared based on survival status using t-test for continuous variables with normal distribution and Wilcoxon Rank sum test for variables with which were not normally distributed. The chi-square test was used to compare categorical variables.

Follow-up time was calculated according to the time participants enrolled in the study until death, or loss to follow up, or censored dated 7/31/07. The median of follow up time was 3.1 years (IQR: 3, 3.4). Death cases were determined based on the date noted on the death certificate. Kaplan-Meier survival curves were used to compare survival for different levels (75th percentile distribution) of common carotid IMT and dichotomous hsCRP cut-points (greater or less than 3 mg/L) over the entire follow up period. These cut-offs were chosen as they have been established in the general population as being indicative of increased CV disease risk and may signify the need for more aggressive risk-reduction intervention^{17,18}. Cox Proportional Hazards for all-cause mortality were estimated for baseline of common carotid IMT and hsCRP and other covariates. Since cardiovascular events remain rare in this population and the contribution of cardiovascular disease to death in HIV-infected patients until recently has been underrecognized, the association between all cause mortality and individual variables was examined. CD4+ count, HDL, LDL, hsCRP were dichotomized in order to deal with the non-linear relationship with the outcome. The cut off points for those variables were based on clinical significance. As the distribution of viral load is skewed, it was log transformed. Backward selection was conducted with variables which were statistically associated with all cause mortality at p-values <0.05. Additionally, age, race, gender, cigarette smoking, and BMI were forced in to the models. The global test of the proportional hazard assumption for the final model was performed. None of variable included violated the assumption of proportional hazard assumption.

RESULTS

Thirty eight (11.6%) of 327 participants of this sub-study have died since enrollment in 2002. In decedents, the median time from date of surrogate marker measurement to death was 24 months (range 2-55 months). The cause of death in our cohort was variable and not known for 3 of the participants. One had cardiac listed as the primary cause of death and one died secondary to a stroke. Three had cardiac issues and 2 had diabetes mellitus noted as contributory causes of death. One additional death was sudden and unexplained. Six died secondary to substance abuse and overdose. Cancer and lymphoma were the most common primary causes of death in our cohort, occurring in 7 subjects, followed by sepsis and septic shock in 6 subjects. Four participants had AIDS noted as their primary cause of death. Other common contributory causes of death listed were wasting and liver disease. Only 5 of those who died were being treated for dyslipidemia, however this was not statistically different from those who are alive. For descriptive purposes only sociodemographic and clinical characteristics of subjects stratified by their last known survival status are presented in Table 1. The unadjusted relationships of patient characteristics with survival are presented as hazard ratios (with values >1 indicating increased chance of death) that are calculated from Cox proportional hazard models which account for varying follow-up times between patients (Table 2). Higher cIMT was found to be significantly associated with survival when analyzed as at least 0.655mm vs. less than 0.655 (the 75th percentile and above is considered high risk by cIMT) adjusting for age, gender, race, BMI, cigarette smoking, CD4+count, viral load, LDL, HDL, hsCRP (HR=2.03, 95% CI 1.06 to 3.90). Additionally, hsCRP, smoking, higher VL, lower CD4 count, lower total cholesterol and lower LDL cholesterol were also associated with increased mortality. There was a trend for lower HDL cholesterol to be associated with higher mortality. Cox proportional hazard multivariate analysis revealed common carotid IMT and hsCRP to be independent predictors of mortality As shown in Table 3, the significant association of higher cIMT with increased mortality persisted even after controlling first for CD4 count, viral load and hsCRP, and then for demographic and other clinical factors found to also have unadjusted significant associations with survival. Adjusting for these covariates increased the magnitude of the HR for cIMT and survival compared to the unadjusted model as also seen in this table. Similar results were found when examining the association of hsCRP cut-offs with mortality, where hsCRP was found to be an independent predictor of mortality even after adjusting for the same covariates as for cIMT (Table 3). Figures 1 and 2 show the Kaplan-Meier survival curves by common cIMT and hsCRP levels, respectively. The estimate of survival for participants who had common cIMT levels less than 0.655 mm was above that of the group of patients who had common cIMT levels equal or greater than 0.655 mm (75th percentile) over the entire follow-up period. The estimate of survival for participants who had hsCRP levels less than 3 mg/L was above that of the group of patients who had hsCRP levels equal or greater than 3 mg/L over the entire follow-up period. When stratified by both and one or neither marker being abnormal, those with both abnormalities had an estimate of survival significantly lower from those with either only one abnormal marker or both normal markers (data not shown).

DISCUSSION

Despite a lack of overt cardiovascular disease, increased cIMT and hsCRP were strongly related to all-cause mortality in this study. To our knowledge, this study provides the first report of an association between cIMT, a surrogate marker of atherosclerosis, and mortality in HIV-infected patients. The significant association of hsCRP with mortality in HIV corroborates previous findings, but expands it to a broader population of HIV-infected patients.

CIMT measured using B-mode carotid ultrasonography is a well-recognized surrogate marker of generalized atherosclerosis¹⁹. A large number of studies in non-HIV infected patients have reported positive correlations of cardiovascular events with common carotid wall thickness and thus support its use in cardiovascular risk assessment¹⁰. CIMT also has been associated with both cardiovascular death and all-cause mortality in the general population. Several investigations have shown that HIV-infected individuals have more abnormal surrogate markers of atherosclerosis and a faster rate of progression when compared to HIV-negative controls^{12;13;20-24}. Traditional risk factors remain most strongly associated with asymptomatic atherosclerosis in HIV-positive patients and the impact of HAART remains controversial. Since cardiovascular hard end-points remain overall rare, there have been no studies to date in HIV-positive individuals correlating cardiovascular events with cIMT. While we were not able to show that cIMT was associated with cardiovascular-specific mortality in this analysis, we believe that the association with all-cause mortality may be a valid proxy for the relationship of atherosclerotic CV disease and longterm HIV infection and hypothesize that the combined effects of vascular aging and HIV on chronic inflammation and immune activation may accelerate the progression of cardiac complications. We speculate that age is not significantly associated with all-cause mortality in our cohort as this is a relatively young patient population and inflammation from chronic HIV infection, as well as cardiac risk factors introduced by unfavorable lifestyles and possibly the treatment of HIV infection, may predominate the pathogenesis of atherosclerosis in this population. It has previously been shown that increased vascular age is common among HIV-infected patients^{25,26}. In our cohort, the mean increase in vascular age is estimated to be 12 years higher than the chronologic age. Overall, any observed difference in all-cause mortality may be a reasonable reflection of the risk of future adverse events, including cardiac mortality.

Although not yet routinely incorporated into cardiovascular risk assessment, CRP, a novel cardiovascular risk factor, may provide additional assistance in predicting cardiovascular disease in the general population²⁷. Higher CRP has been found to be associated with higher cIMT in HIV-negative patients and the association with stroke is strengthened in the presence of higher cIMT²⁸. The use of this inflammatory biomarker is currently being investigated in individuals with chronic inflammatory infections, such as HIV disease. CRP has previously been found to be a marker of HIV disease progression, independent of CD4 count and viral load²⁹. Additionally, CRP has been shown to be a predictor of mortality in HIV-infected women³⁰. In our study, hsCRP was found to be significantly higher in those who died compared to those who are alive, indicating that it could be useful a clinical marker to predict poorer outcomes in HIV-infected men and women. When applied in combination with cIMT, it may improve risk stratification for adverse outcomes in this population.

Atherogenic dyslipidemia (elevated triglycerides and low HDL cholesterol) is common in HIV-infected patients, which is seen prior to treatment as well as in those on long-term HAART. Similar to the general population, one of the essential steps in cardiovascular risk assessment in HIV infection is the determination of lipid levels, however very few are treated with lipid-lowering agents¹. Statins, which target mainly hypercholesterolemia and elevated LDL-cholesterol, are the most commonly used lipid-lowering medications used in HIV-infected patients³¹, but do not target the predominant lipid abnormalities seen in HIV. In our cohort, total cholesterol and LDL-cholesterol were significantly lower in those who died compared to those who are alive, reflecting more advanced HIV disease in those who died, supported further by lower CD4 counts and higher viral loads in decedents. Poorly controlled HIV infection has previously been shown to increase the risks for cardiovascular morbidity³². Conversely, low HDL cholesterol, an independent risk factor for cardiovascular disease and a component of the metabolic syndrome, is common among HIV-infected

patients, but treatments that specifically target this abnormality are difficult and rarely used in this population³³. Our data indicate a trend towards lower HDL-cholesterol in those who died compared to those who are alive. However, even after adjusting for these abnormalities, cIMT and hsCRP remained strongly associated with mortality in our cohort.

We recognize the limitations of the present study. First, this is not a large enough cohort to study cause-specific mortality. Although deaths were rigorously ascertained in this study, few of our participants had cardiac-related death listed as a primary or contributory cause of death. However, all-cause mortality is not subject to misclassification bias and may therefore be a “harder” end point than cause-specific mortality in this at-risk population with many concurrent comorbid illnesses³⁴. While cardiovascular events remain overall rare in this population and follow-up times are short, it is known that there is a high prevalence of asymptomatic cardiovascular disease in HIV-infected patients and vascular disease may be present and significant at the time of death, but was not recognized as the underlying cause. CRP, a marker of chronic inflammation, may further contribute to all-cause mortality in the HIV-infected population, as it may reflect both cumulative HIV and cardiovascular disease burden. Although our mortality analysis could not disentangle confounding of more advanced HIV disease in those who died, even after removing the four AIDS death, cIMT remained significantly associated with mortality in this study (HR=2.75, 95% CI 1.21 to 6.25). Further, substance abuse may have obscured some of the association of atherosclerosis with mortality as it could be hypothesized that drug users who died had significant underlying cardiac pathology which may have increased their susceptibility to overdose. Overall, all-cause death is an objective, unbiased end point and may therefore be more appropriate in the setting of a complex disease process. Second, we recognize the ongoing debate in both the general and HIV population as to which carotid segment is most associated with CV risk. However, our choice to use the common carotid measurement instead of the internal segment for this survival analysis was recently corroborated by a publication from the CARDIA cohort, which has a similar age and race distribution as our HIV-positive cohort and showed that a greater proportion of the variability in common carotid IMT can be explained by traditional cardiovascular risk factors than for the carotid artery bulb and internal carotid arteries (27% vs. 8%)³⁵. Further, the FRAM cohort recently published results indicating that the common, but not the internal, cIMT is a better predictor of HIV-related risk factors³⁶. In summary, we a priori chose to use only the common carotid measurement for this analysis due to the difficulty in visualization and lesser stability of measurements of the internal carotid segment. Third, this is a fixed covariate analysis at a single timepoint and conclusions are therefore limited to associations. We hope to provide more information about factors affecting mortality in HIV infection in longitudinal studies in the future. Fourth, there is a concern of overfitting the data by using too many independent variables in a model when the sample size is small and there are not many outcomes. However, adding age, an important predictor of cardiovascular disease and death, into the model did not significantly improve the model nor change any of the model coefficients by more than 5% compared to the model that did not include age as a covariate.

In conclusion, abnormal carotid IMT and elevated hsCRP identify HIV-infected individuals at high risk of death. These findings support a complex relationship among inflammation, subclinical atherosclerosis and immune activation in HIV-infected patients and suggest the need for further study. However, identification of carotid artery atherosclerosis and elevated hsCRP levels among asymptomatic HIV-infected persons helps identify a high-risk group for death and may allow for the introduction of early interventions aimed at asymptomatic atherosclerosis and inflammation to prevent future adverse cardiovascular events and death in this population.

Acknowledgments

Dr. Mangili is a recipient of grants from the NIH (K23AI071872 and the Center for AIDS Research) and the Campbell Foundation. This work was supported in part by R01HL065947, HL069003, HL081352, P30 DA 13868, P30 A142853, M01 RR00054, and UL RR025 752.

We would like to thank Sunil Abraham for his contributions to the study, and a special thanks to the men and women who volunteered to be participants.

Sources of support: Supported by NIH Grants K23 AI071872, R01HL065947, HL069003, HL081352, P30 DA 13868, P30 A142853, M01 RR00054, and UL RR025 752.

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Figure 1.
Kaplan-Meier survival curve for common cIMT

Figure 2.
Kaplan-Meier survival curve for hsCRP

Table 1

Comparison of the major characteristics of HIV patients who died and are alive

	N (%) or Mean $\pm$ SD or Median (IQR)			
	Overall (N=327)	Dead (N=38)	Alive (N=289)	p-value
<u>Sociodemographics</u>				
Mean Age, yrs	44 $\pm$ 7	46 $\pm$ 7	44 $\pm$ 7	0.05
Male	242(74)	23 (76)	219 (74)	0.73
White	172(52)	21 (55)	151 (52)	0.73
Current smoker	161(49)	27 (71)	134 (46)	<0.001
Current IDU	15(5)	6 (15)	9 (3)	<0.001
Lipid lowering medications	48 (15)	6 (16)	42 (15)	0.657
<u>Clinical Data</u>				
Systolic BP, mm Hg	118 $\pm$ 7	120 $\pm$ 17	118 $\pm$ 17	0.73
Diastolic BP, mm Hg	76 $\pm$ 10	75 $\pm$ 9	76 $\pm$ 11	0.50
BMI, kg/m	26.7 $\pm$ 5	27 $\pm$ 5	27 $\pm$ 5	0.35
Triceps skinfold, mm	12.9 $\pm$ 10.5	12 $\pm$ 9	13 $\pm$ 11	0.35
Cholesterol, mg/dl				
Total	187 $\pm$ 50	168 $\pm$ 50	190 $\pm$ 50	0.01
HDL	41.7 $\pm$ 17.6	37 $\pm$ 19	42 $\pm$ 17	0.12
LDL	109.4 $\pm$ 38.8	95 $\pm$ 39	112 $\pm$ 38	0.01
Triglycerides, mg/dl	183.9 $\pm$ 171.4	180 $\pm$ 124	184 $\pm$ 177	0.89
ApoA1 , mg/dl	128 $\pm$ 29	118 $\pm$ 35	129 $\pm$ 28	0.02
ApoB , mg/dl	85(21)	81 $\pm$ 22	85 $\pm$ 21	0.32
ApoE, mg/dl	4.8 $\pm$ 2.4	4.6 $\pm$ 1.6	4.8 $\pm$ 2.5	0.83
Lp(a) , mg/dl	27 $\pm$ 29	20 $\pm$ 23	28 $\pm$ 30	0.15
Glucose, mg/dl	84 $\pm$ 21	80 $\pm$ 22	85 $\pm$ 21	0.19
Insulin, mU/l	15 $\pm$ 17	14 $\pm$ 7	15 $\pm$ 18	0.71
QUICKI	0.34 $\pm$ 0.04	0.34 $\pm$ 0.03	0.34 $\pm$ 0.04	0.56
Homocysteine	9.1 $\pm$ 4.1	10 $\pm$ 5	9 $\pm$ 4	0.06
Metabolic syndrome	72(22)	10 (26)	62 (21)	0.462
<u>HIV infection</u>				
Duration of HIV, yrs	10 $\pm$ 5	11 $\pm$ 4	10 $\pm$ 5	0.08
Duration of HAART, mo	32 $\pm$ 26	30 $\pm$ 25	32 $\pm$ 26	0.84
CD4 count, cells/mm ³	458 $\pm$ 299	279 $\pm$ 367	471 $\pm$ 288	0.06
Log HIV-RNA, copies/mm ³	3.1 $\pm$ 1.1	3.64 $\pm$ 1.36	3.03 $\pm$ 0.99	<0.001
On HAART	239(73)	29 (76)	210 (73)	0.63
Current NRTI use	239(73)	28(73)	211(73)	0.93
Current NNRTI use	106(32)	10 (26)	96(33)	0.39
Current PI use	146(45)	20 (53)	126(44)	0.29
<u>Markers of Atherosclerosis</u>				
Mean cIMT, mm	0.61 $\pm$ 0.16	0.68 $\pm$ 0.27	0.59 $\pm$ 0.14	<0.001

	N (%) or Mean $\pm$ SD or Median (IQR)			
	Overall (N=327)	Dead (N=38)	Alive (N=289)	p-value
cIMT $\geq$ 0.655 mm	83 (25)	15 (41)	68 (23)	0.03
hs-CRP, mg/L	1.45 (0.7, 3.3)	3.2 (1.5, 4.8)	1.3 (0.6, 2.9)	<.0001
hs-CRP $\geq$ 3mg/L	90 (28)	19 (51)	71 (25)	<0.001

Footnote: IDU, injection drug user; BP, blood pressure; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Apo, apolipoprotein; Lp(a), lipoprotein (a); hs-CRP, high-sensitivity C-reactive protein; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Table 2

Hazard Ratios of CV and HIV-specific risk factors and All-Cause Mortality

	HR	95% CI		p-value
Age, by 10 year increase	1.44	0.93	2.23	0.11
White	1.12	0.59	2.12	0.74
Male vs Female	1.30	0.61	2.78	0.49
Current Smoker	2.73	1.35	5.52	0.01
Current IDU	5.38	2.24	12.94	<0.001
BMI	1.02	0.96	1.08	0.49
Systolic BP by 10 mmHg increase	1.08	0.90	1.30	0.42
Diastolic BP by 10 mmHg increase	0.92	0.68	1.25	0.60
Cholesterol, by 10 mg/dl increase				
Total	0.91	0.84	0.98	0.01
HDL	0.81	0.64	1.02	0.08
LDL	0.88	0.80	0.97	0.01
Triglycerides, by 10 mg/dl increase	1.00	0.98	1.02	0.92
CD4, <200 vs > 200	3.96	2.03	7.71	<.0001
Viral Load, >100K vs. < 100K	7.26	3.64	14.48	<.0001
cIMT, mm	7.27	2.30	23.03	<0.001
cIMT $\geq$ 0.655 vs. cIMT<0.655	2.03	1.06	3.90	0.03
hsCRP, mg/L	1.09	1.05	1.12	<.0001
hsCRP $\geq$ 3mg/L vs. <3 mg/L	2.72	1.42	5.18	<0.001

Cox Proportional Hazard Models looking at relationship of common cIMT and hsCRP with all cause mortality adjusted for other covariates

Table 3

Hazard Ratio for cIMT modeled as a binary variable: ≥0.655 vs. <0.655				Hazard Ratio for hsCRP modeled as a binary variable: >=3 vs. <3			
	HR	95% CI	p-value		HR	95% CI	p-value
Model 1	2.05	1.06	3.96	0.03	2.72	1.42	5.18
Model 2	2.72	1.37	5.41	0.01	2.56	1.32	4.96
Model 3	2.53	1.17	5.45	0.02	2.33	1.15	4.72
Model 4	2.63	1.18	5.87	0.02	2.33	1.13	4.79
Model 5	2.74	1.26	5.97	0.01	2.38	1.15	4.90

Footnote: Model 1: cIMT, unadjusted; Model 2: cIMT adjusted for CD4 (< 200 vs. ≥ 200) and hsCRP (≥ 3 vs. < 3); Model 3: cIMT adjusted for CD4 (< 200 vs. ≥ 200), hsCRP (≥ 3 vs. < 3), age, gender, race, BMI, and cigarette smoking; Model 4: cIMT adjusting for hsCRP (≥ 3 vs. < 3), CD4 (< 200 vs. ≥ 200), age, gender, white, bmi, cigarette smoking, HDL (≥ 40 vs. < 40) and LDL (≥ 130 vs. < 130). Model 5: cIMT adjusting for hsCRP (≥ 3 vs. < 3), CD4 (< 200 vs. ≥ 200), viral load, age, gender, white, bmi, cigarette smoking, HDL (≥ 40 vs. < 40), LDL (≥ 130 vs. < 130).