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Progression of Carotid Intima-Media Thickness and Coronary Artery Calcium over Six Years in an HIV-infected Cohort

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Abstract

Objective—To evaluate changes in cardiovascular disease risk surrogate markers in a longitudinal cohort of HIV-infected adults over 6 years.

Design—Internal and common carotid artery intima-media thickness, coronary artery calcium, vascular and HIV risk factors were prospectively examined over 6 years in HIV-infected adults from 2002 to 2010.

Setting—Longitudinal cohort study with participants from urban center and surrounding communities.

Subjects, participants—345 HIV-infected participants were recruited from a longitudinal cohort study. 211 participants completed the study and were included in this analysis.

Main Outcome Measures—Total and yearly internal and common carotid artery intima-media thickness change; coronary artery calcium score progression.

Results—Participants were 27% female and 49% non-white; mean age at start was 45 ± 7 years. The median change in internal and common carotid arteries over six years was 0.15mm (0.08,0.28) and 0.12mm (0.09,0.15), respectively. Age, baseline triglycerides ≥ 150mg/dL, and pack-years smoking were associated with internal carotid artery intima-media thickness change; age, cholesterol, nadir CD4+ count, and protease inhibitor use were associated with common carotid artery intima-media thickness change. Diabetes, HIV viral load, and HAART duration were associated with coronary artery calcium progression.

Conclusions—Carotid intima-media thickness and coronary artery calcium progressed in this HIV-infected cohort. Some HIV-specific characteristics were associated with surrogate marker changes, but the majority of risk factors continue to be traditional. Aggressive identification and

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management of modifiable risk factors may reduce progression of cardiovascular disease risk in this population.

Introduction

As mortality from HIV infection declines and the HIV-infected population ages, concerns about elevated cardiovascular disease (CVD) risk have increased. Several studies have indicated an elevated risk for CVD in HIV-infected persons compared to uninfected persons [1-3]. Traditional risk factors are considered major determinants of cardiovascular risk in this group [4-6]. HIV infection itself also contributes to this increased risk [7], and recently investigators have cited chronic immune activation and inflammation as possible mechanisms for this elevated propensity for CVD [8].

Surrogate markers of CVD have been used in the general population to identify persons at risk before clinical signs of CVD develop, and carotid intima-media thickness (IMT) has been associated with CVD incidence [9]. In HIV-infected persons, surrogate markers have been used in conjunction with the Framingham Risk score (FRS) in an attempt to better quantify cardiovascular risk [10, 11].

We followed a cohort of 211 HIV-infected adults for 6 years, measuring two different surrogate markers, carotid IMT and coronary artery calcium (CAC), as well as lifestyle factors, C-reactive protein (CRP) and HIV disease parameters at baseline, three and six years, to better understand cardiovascular risk progression over time in this population. We previously published the results of our three-year analysis of surrogate marker progression in this cohort [12]. We herein report the findings from this cohort at 6 years.

Subjects & Methods

Subjects

From an original cohort of HIV-infected persons enrolled in the longitudinal study, Nutrition for Healthy Living (NFHL), 211 participants completed both a cardiovascular substudy (CARE) and its continuation study (CARE II). The NFHL study, begun in 1995, aimed to investigate nutrition and metabolism in HIV-infected adults; exclusion criteria included diabetes, uncontrolled hypertension, and myocardial infarction or stoke within the past 6 months, but participants who developed these conditions continued in the study. CARE, begun in 2000, included any consenting NFHL participant. Details of the original study are described elsewhere [13]. Subjects completing baseline ultrasonography and computed tomography (CT) were recruited for CARE II, with repeat examinations at 6 years. Informed consent and approval by the Tufts Medical Center/Tufts University Institutional Review Board were obtained for NFHL, CARE, and CARE II studies.

Clinical Data

Clinical information was collected at baseline and every 12 months (initially every 6 months) for 6 years. Clinical and laboratory data were obtained during the same visit, or closest study visit, to surrogate marker measurements. Demographic data were assessed via interviewer-administered questionnaires. Participants chose one designation that best defined their race from an investigator-defined list and investigators then categorized participants as white or non-white for the purposes of characterizing the cohort. Blood pressure (BP) measurements were obtained using a digital automatic BP monitor. Highly active antiretroviral therapy (HAART) was defined as the use of 3 or more drugs, including 1 or more protease inhibitors (PI) or nonnucleoside reverse transcriptase inhibitors (NNRTI). All baseline and 6-year study visits were within 6 months of baseline and 6-year

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imaging visits, respectively. Framingham risk was defined as low if FRS <10%, as moderate if 10-20%, and as high if >20%.

Laboratory Methods

Plasma levels of total cholesterol, triglycerides, and high-density lipoprotein (HDL) cholesterol were measured via standard enzymatic methods; low-density lipoprotein (LDL) cholesterol was measured directly via Roche Diagnostics kit (Roche, Inc, Indianapolis, IN). High-sensitivity CRP, fasting glucose and insulin were measured simultaneously with lipids. The quantitative insulin sensitivity check index (QUICKI) was calculated according to the following formula: QUICKI = 1 / [log(insulin) + log(glucose)] [14]. CD4+ cell counts were determined by flow cytometry; HIV RNA was quantified by Roche Amplicor (Roche, Inc, Indianapolis, IN) (lower limit of detection, 400copies/mL).

Surrogate Marker Measurement

Baseline ultrasonography and CT images were obtained January 2002 through January 2004; 6-year images were obtained September 2009 through December 2010. Ultrasound protocols were adapted from the Cardiovascular Health Study [15], performed by centrally trained and certified ultrasonographers, recorded on super-VHS tape, and read at a central facility. Carotid IMT measurements were obtained via high-resolution B ultrasound images of the bilateral common and internal carotid arteries. One longitudinal, lateral view of the distal 10mm of the common carotids and 3 longitudinal views of the internal carotids were used. The mean of the maximum of the near- and far-wall carotid IMT was used for the final analysis, given its association with CVD risk [16]. Baseline and 6-year ultrasounds were read after study completion by a single reader (paired replicate scans) to control for temporal drift and inter-reader variability.

CAC scores were obtained by ultrafast CT scan of the heart with synchronized ECG to select images least affected by cardiac motion, as described elsewhere [17, 18]. After initial automatic image selection, pixel regions within these images were considered for calcium scoring. Scores were computed using standardized scoring techniques [19]. For this analysis, CAC was analyzed as a binary variable (detectable/undetectable) and as a multichotomous variable: CAC =0, CAC >0 but <100, or CAC ≥100. In multivariate models, we defined CAC progression as a binary variable (progression/no progression) as in our 3-year analysis, using the method of Berry et al., as follows [12, 20]. Progression was defined as CAC score >0 if CAC=0 at baseline. If CAC score was greater than zero but less than 100 at baseline, then progression was defined as >10 Agatston units annualized change at follow-up. If CAC ≥100 at baseline, then progression was defined as >10% annualized percent change (annualized change divided by baseline CAC score) at follow-up. At baseline and three years, all participants received their imaging reports; participants with >50% carotid stenosis or CAC scores >400 were informed of their results, along with their care providers.

Statistical Analysis

Nonnormally distributed variables, including internal carotid IMT, are reported as median (interquartile range). Comparisons between those with and without CAC progression were conducted using χ^2 or Fisher's exact test for categorical variables, Student's *t* test for continuous, normally distributed variables, and the Wilcoxon rank-sum test for all continuous non-normal variables. Separate multivariate regression models were generated to determine independent factors associated with change or progression of each surrogate marker. Changes in both carotid IMT measures from baseline to year six were entered as outcome variables in linear regression models (common carotid IMT change was normally distributed and internal carotid IMT change was non-normally distributed); CAC progression (yes/no) was used as the outcome variable in logistic regression models. CVD-

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related risk factors (age, gender, smoking, lipids, glucose, FRS, and metabolic syndrome), HIV-specific risk factors (HAART, CD4+, nadir CD4+, HIV RNA, and PI use), and nontraditional risk factors (CRP, Apo-E lipoprotein) were evaluated as exposures. Since many of the exposure variables were correlated, we ran preliminary analyses on groups of related variables to identify the exposures most strongly associated with each outcome. For example, we compared models using the FRS with models using the individual components of the FRS to determine whether the FRS or its individual components were more strongly associated with change or progression. For each model, exposure variables with $p<0.20$ in bivariate analyses were included in initial multivariate models. Final models of IMT change and CAC progression were then determined by stepwise regression techniques. We used baseline measures for all exposures, except pack-years of cigarette smoking and nadir CD4+, which was determined by self-report at enrollment or by laboratory measurement throughout the study, whichever was lowest. Statistical significance was defined as a p-value of <0.05. Statistical analyses were performed using SAS for Windows, Version 9.2; SAS Institute, Inc.

Results

These results include data on 211 participants completing both baseline and 6-year imaging studies. Baseline and 6-year characteristics are shown in Table I. Of 345 original participants with IMT data, 134 were lost to follow-up: 55 participants died, 32 declined to further participate, 2 were missing 6-year imaging studies, and 45 could not be contacted. Participants lost to follow-up had more advanced HIV disease, were more likely to use IV drugs, had lower total cholesterol, and were less likely to have metabolic syndrome than participants who continued (Table 2). Baseline IMT values and CAC scores for the entire cohort were measured at the baseline visit and were not significantly different between those lost to follow-up and those who continued. The mean time between baseline and 6-year imaging studies was 6.5 ± 0.5 years. Inter-reader variability for internal carotid artery (ICA) IMT at 6 years was 0.81; intra-reader variability was 0.96. Inter-reader variability at 6 years for common carotid artery (CCA) IMT was 0.75; intra-reader variability was 0.92. Surrogate markers at baseline and six years are shown in Table 3.

Carotid Intima-Media Thickness

There were 198 participants with data on IMT at baseline and 6 years. Of the entire cohort, 13 participants were excluded from this analysis: 11 were missing either baseline or follow-up ultrasound, and 2 had uninterpretable or unavailable baseline or follow-up ultrasounds. ICA IMT progression occurred in 43% (n=85). The median change in ICA IMT per year of follow-up was 0.023mm (0.013,0.045). Yearly progression was greater if ICA IMT was abnormal at baseline (0.04mm vs. 0.02mm, $p<0.001$). In multivariate analysis, factors that were positively associated with ICA IMT change were age, baseline triglycerides ≥ 150mg/dL (1.69mmol/L), and pack-years of tobacco smoking (Table 4(A)). For example, if a male of median age (45 years) with median number of pack-years of tobacco use (11) had triglycerides ≥150mg/dL, his predicted ICA IMT change over 6 years would be 0.30μm, on average. The same man with triglycerides <150mg/dL (1.69mmol/L) would have a predicted ICA IMT change of only 0.16μm over 6 years.

CCA IMT progression occurred in 59% (n=116). The median change in CCA IMT per year of follow-up was 0.019mm (0.014,0.024). Yearly progression was not different if CCA IMT was abnormal at baseline (0.016mm vs. 0.018mm, $p=0.21$). Table 4(B) shows the predictors of 6-year change in CCA IMT from the final multivariate regression model. Cholesterol, age, nadir CD4+ count, and PI use were all independently and positively associated with change in CCA IMT. Every one unit increase in cholesterol and age was associated with a 0.002mm difference in 6-year change in CCA IMT. Each 100cells/mm3 increase in nadir

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CD4+ count was associated with a difference in 6-year change in CCA IMT of 0.005mm. Participants using PIs at baseline had a 0.02mm greater 6-year change in CCA IMT than those not using PIs at baseline.

Coronary Calcium Score

There were 205 participants with data on CAC change. Six participants from the entire cohort were excluded from this analysis: 4 had coronary stents placed prior to follow-up, 1 lacked a baseline CT, and one died before follow-up CT. CAC progression occurred in 33% of the cohort. Of those with undetectable CAC at baseline, 43 % (n=41) had detectable CAC at follow-up. Of those with CAC >0 at baseline, 24% had worse CAC at follow-up (n= 26). The percentage of those with CAC >100 rose from 5% to 16% over 6 years. CAC was undetectable in 46% of the cohort at baseline and in 41% at 6 years. In multivariate analysis, baseline diabetes, HIV viral load, and HAART duration were significantly associated with increased odds of CAC progression (Table 4(C)). Population attributable risk for CAC progression was 30% for diabetes, 25% for detectable viral load, and 40% for HAART duration > 2 years.

Discussion

In our cohort of HIV-infected participants, rates of ICA and CCA IMT progression have been remarkably consistent over time, from our three-year observation (0.020mm/year and 0.016mm/year, respectively [12] to our current six-year observation (0.023mm/year and 0.019mm/year, respectively). We also noted segment-specific differences in associations between risk factors and IMT measurements in the common and internal carotid arteries. In addition, we observed that changes in IMT and CAC over time are associated not only with traditional risk factors but also with HIV-related factors, and that these associations vary with type of surrogate marker evaluated. Differences in predictors between the 3-year and 6-year data are likely due to increased length of follow-up, the inclusion of pack-years smoking as an exposure variable, and changes in medication use over time. For example, the use of both antihypertensives and lipid-lowering agents was uncommon in our cohort at baseline (3% and 8%, respectively) but increased to 19% and 18%, respectively, at 6 years. Individual components of the FRS were more strongly associated with surrogate marker change than the composite score, however, this may be due to the overwhelming effect of age: when age at 6 years was imputed into baseline FRS, the imputed 6-year FRS was not statistically different from the FRS measured at year 6.

In a large group of 10,914 participants from the general population enrolled between age 45 and 64 in the Atherosclerosis Risk in Communities (ARIC) study, average change in CCA IMT was 0.035mm over three years, yielding an estimated change of 0.012mm/year [21]. A subsequent evaluation of 12,085 participants from the ARIC cohort demonstrated CCA IMT increases of 0.036 to 0.047mm over 5 years, depending on gender and race, yielding an estimated change of 0.007-0.009mm/year [22]. The 6-year progression of CCA IMT in an uninfected Finnish cohort (mean age 37.7 years) was 0.046mm (0.084), or an estimated change of 0.008mm/year [23]. In a similarly aged group, 30% non-white, yearly CCA IMT progression was 0.016±0.002mm/year over 5.8 years [24]. In an older population (mean age 60 years) evaluated for 3 years during a randomized trial of folate supplementation, yearly progression of CCA IMT in the control group was 0.0013mm/year [25]. As increases in CCA IMT of as little as 1 standard deviation have been associated with an increased hazard ratio for cardiovascular disease [26], the 0.019mm/year CCA IMT progression in our cohort may have clinical implications for HIV-infected populations.

Of those in our cohort with undetectable CAC at baseline, 33% had detectable CAC at 3 years [12] and 43% percent had detectable CAC at 6 years. In a study of uninfected adults

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aged 33-45, 9.6% had CAC [27]; in a subset of 2,415, 11% had detectable CAC at baseline, 18.4% had detectable CAC 5 years later, and 16.1% had CAC progression [28]. Thus, our data suggests that CVD risk surrogate marker progression occurs more rapidly and frequently in HIV infection, and is not completely accounted for in this cohort by increasing age. Strikingly, many participants developed CAC scores >100.

As in our prior analyses, factors associated with IMT and CAC progression at 6 years were predominately traditional risk factors, with a few notable exceptions. In our cohort, baseline duration of HAART increased the odds ratio for CAC progression over six years, albeit minimally. Since calcium deposition occurs later in the atherosclerotic process than increased IMT, the effect of HAART duration may be better assessed through this more distal measure. Alternatively, as very low CAC scores may be less accurate, minimal CAC deposition may be considered progression. As reported by the Multicenter AIDS cohort study, HAART may increase the likelihood of CAC deposition but limit its extent [29]. Lastly, duration of HAART at baseline may simply reflect cumulative exposure to HIV virus. HIV viral load was also associated with a higher odds ratio of CAC progression in our cohort; as expected, the odds ratio for viral load exceeds that obtained for HAART duration, as HAART is usually required for viral load suppression.

Very similar progression of CAC, 34%, was found in an HIV-infected cohort for whom CAC progression was associated with age, LDL, visceral adipose tissue and CD4 count [30]. The authors used the homeostasis model assessment rather than diabetes as a measure of insulin resistance and the follow-up (11 months) was markedly less than in our study [30]; this may account for differences in the associations reported. Others reported an association between epicardial adipose tissue and CAC progression, which occurred in 10.4% of their cohort over a median of 18.7 months [31]. Participants with metabolic syndrome had less CAC progression over 1 year if treated with metformin, particularly if CAC was >0 at baseline [32]. Interestingly, metformin had no effect on CCA, or on visceral, subcutaneous, or extremity adipose tissue [32]. We did not evaluate fat accumulation in this study; however, we did evaluate metabolic syndrome and/or its components, including waist circumference, and these were not significantly associated with CAC progression. Although 30% of our cohort had metabolic syndrome and 9% had diabetes, only 1% used glucose-lowering agents at baseline (9% at 6 years). We did note CAC regression in some subjects; therefore, the increase in medications we observed for lipids, glucose, and hypertension may have affected CAC progression in certain participants.

Nadir CD4+ was associated with change in CCA IMT over 6 years. Although this association may appear counterintuitive, the effect size is quite small, and this may reflect the presence of more traditional risk factors associated with healthier HIV-infected persons. It has been reported that higher nadir CD4+ predicts less arterial stiffness in HIV-infected men [33], and that nadir CD4+ ≤200 predicts IMT progression at 1 year [34]; nevertheless, to our knowledge our study has the longest follow-up for this measure in HIV-infected persons. Baseline PI use was also associated with greater change in CCA IMT, which was also observed as a trend in the 3-year analysis. As we previously noted [12], this finding, not observed with CAC or ICA IMT progression, may reflect varying responses to HAART by arterial segment. The SUN study group also found reduced CCA IMT progression with an NNRTI- versus PI-based regimen at 2 years [35]. Nevertheless, there is limited difference in progression by any other HAART parameter to suggest that PI use is a primary determinant of CVD risk. Similarly, traditional risk factors eclipsed HIV-specific parameters in a prospective cohort of persons using PI therapy for ≥2 years [36]. In addition, the use of specific protease inhibitors changed over time: amprenavir, saquinavir, indinavir, and nelfinavir use declined during the study, while ritonavir use rose from 8% to 34% over six

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years. The overall percentage of participants using PIs did not differ significantly between baseline and year 6.

We did not find any associations between baseline CRP and surrogate marker progression at 6 years in our cohort. Inflammation contributes to the atherosclerotic plaque, representing the first lesion in CVD [37]. Prior studies have shown that CRP values are higher in HIV-infected persons [38]. Recently, Hsue *et al.* reported that high-sensitivity CRP was associated with IMT progression at the carotid bifurcation; this association was not found for internal or carotid IMT [39]. Our group previously reported an association between CRP and mortality in HIV-infected persons [40], and others reported that statin use reduced CRP in HIV-infected persons on PI regimens [41]. Therefore, interventions such as statins, aimed at reducing dyslipidemia, may have wider repercussions due to their effect on chronic inflammation.

This study has several limitations. Given the prospective cohort design, there is no HIV-uninfected control group. However, several other groups have reported similar increases in cardiovascular risk in HIV infection [11], and we have discussed data from HIV-uninfected cohorts for these same measures above. Some studies referenced above did not report method of IMT measurement or used a different measure, such as mean-mean IMT, which may limit direct comparisons to our cohort. CAC takes time to accumulate, so categorical definitions may limit detection of changes on a finer scale; however, although the percentage of persons with detectable CAC did not markedly differ over 6 years, the percentage of those with CAC>100 tripled. In addition, we used two distinct imaging modalities and report three surrogate markers to compensate for the limitations of each individual marker. New factors related to HIV infection, immunity, and inflammation have emerged that may impact cardiovascular risk, which we were unable to explore as these were not available at the design and funding of the original study. Differences between those participants lost to follow-up and those who continued may limit generalizability of the results to cohorts with these attributes; however, we collected demographic and clinical information for a large group over 6 years to thoroughly describe our study population and to limit confounding. Lastly, cause of death for all participants who died during the study is not available; nevertheless, the purpose of this study was to evaluate progression of surrogate markers of CVD risk, not clinical outcomes.

In conclusion, our data suggests that HIV-infected persons accumulate CVD risk over time beyond that experienced in the general population. Although traditional risk factors contribute to this risk, some HIV-specific factors may continue to emerge as important predictors over time. Interventions to reduce CVD risk may be effective even in those with the highest risk by FRS or surrogate markers. Continued attention to CVD risk modification in all individuals with HIV infection is essential for mitigating risk even at the earliest stages of HIV disease.

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CAW designed the research study; CAW, AMT, and AM provided significant advice and consultation; JFP conducted and supervised imaging studies as well as supervised the IMT measurements; SCS and AMT analyzed the data; GEV wrote the paper with input from all authors. CAW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Table I

Characteristics at Baseline and 6-year Follow-up.

	Median (IQR[a]) or n(%), n=211	
	Baseline	**6-year Follow-up**
Demographics		
Age, years	45 (40, 50)	52 (46, 56)
Female Gender	56 (27%)	56 (27%)
Non-White	103 (49%)	103 (49%)
Current Smoker	94 (45%)	101 (48%)
Current IDU[b]	1 (0%)	7 (3%)
Clinical Data		
Systolic BP[c], mmHg	120 (110, 130)	124 (112, 135)
Diastolic BP[c], mmHg	75 (69, 84)	78 (72, 84)
BMI, kg/m^2	25.9 (23.1, 28.9)	26.5 (22.7, 29.8)
Cholesterol, mg/dL		
Total	189 (155, 219)	176 (152, 209)
HDL[d]	37 (29, 46)	39 (31, 51)
LDL[e]	110 (85, 139)	98 (78, 129)
Triglycerides, mg/dL	141 (87, 225)	123 (86, 197)
Glucose, mg/dL	83 (74, 91)	89 (82, 100)
Insulin, mU/L	10.0 (6.2, 16.5)	14.0 (8.0, 22.0)
QUICKI[f]	0.34 (0.32, 0.37)	0.32 (0.30, 0.35)
Diabetes	19 (9%)	39 (18%)
CRP[g], mg/L	1.40 (0.50, 3.10)	1.63 (0.68,3.60)
Metabolic Syndrome	64 (30%)	85 (40%)
Framingham 10-year risk, %	6.1 (3.6, 10.8)	8.6 (5.3, 12.8)
Fiber Consumed (grams/d)	18 (11, 26)	17 (12, 24)
HIV Infection		
Duration of HIV, years	11.0 (6.6, 14.0)	17.8 (13.0, 20.6)
Duration of HAART[h], months	37 (3, 59)	99 (63, 133)
CD4+ count, cells/mm^3	433 (282, 616)	474 (287, 733)
Nadir CD4+ count, cells/mm^3	178 (75,295)	161 (70,276)
Log10 Viral Load Copies/mL[i]	2.30 (2.30, 3.64)	2.30 (2.30, 2.30)
Undetectable Viral load[j]	125 (59%)	162 (79%)
On HAART[h]	140 (66%)	181 (86%)
Current NRTI[k] use	150 (71%)	181 (86%)
Current NNRTI[l] use	75 (36%)	81 (38%)
Current PI[m] use	95 (45%)	120 (57%)

[a] IQR, interquartile range

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[b] IDU, intravenous drug use

[c] BP, blood pressure

[d] HDL, high density lipoprotein

[e] LDL, low density lipoprotein

[f] QUICKI, quantitative insulin sensitivity check index

[g] CRP, c-reactive protein

[h] HAART, highly active antiretroviral therapy

[i] all participants included: if viral load undetectable then log10 viral load set at 200 copies/mL

[j] Limit of detection, 400 copies/mL

[k] NRTI – nucleoside reverse transcriptase inhibitor

[l] NNRTI, non-nucleoside reverse transcriptase inhibitor

[m] PI, protease inhibitor.

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Table 2

Baseline Characteristics for Those Lost to Follow-Up and Those Included in Analysis

	Median (IQR[a]) or n(%)		
	Lost to Follow-Up (n=134)	**In Analysis (n=211)**	**p-value**
Demographics			
Age, years	47 (41,51)	45 (40,50)	0.15
Female Gender	35 (26%)	56 (27%)	0.93
Non-White	59 (44%)	89 (42%)	0.74
Current Smoker	72 (54%)	94 (45%)	0.10
Current IDU[b]	12 (9%)	1 (0%)	<0.001
Clinical Data			
Systolic BP[c], mmHg	120 (108,132)	120 (110,130)	0.9
Diastolic BP[c], mmHg	75 (66,82)	75 (69,84)	0.4
BMI, kg/m^2	26.4 (23,30)	25.9 (23,29)	0.4
Cholesterol, mg/dL			
Total	167 (144,197)	189 (155,219)	0.01
HDL[d]	35 (29,50)	37 (29,46)	0.97
LDL[e]	105 (82,130)	110 (85,139)	0.1
Triglycerides, mg/dL	151 (92,193)	141 (87,225)	0.78
Glucose, mg/dL	84 (76,96)	83 (74,91)	0.3
CRP[f], mg/L	1.8 (0.7,3.9)	1.4 (0.5,3.1)	0.1
Metabolic Syndrome	15 (11%)	64 (30%)	<0.001
Food insecure	45 (39%)	56 (27%)	0.02
ICA[g]	0.60 (0.51,0.75)	0.71 (0.66,0.78)	<0.001
CCA[h]	0.57 (0.50,0.66)	0.55 (0.51,0.62)	0.20
CAC[i]	0.4 (0,23)	0.4 (0,5.2)	0.37
HIV Infection			
Duration of HIV, years	12.4 (9,15)	11.0 (7,14)	0.005
Duration of HAART[j], months	56 (25,80)	37 (3,59)	<0.001
CD4+ count, cells/mm^3	365 (208,549)	433 (282,616)	0.005
Nadir CD4+ count, cells/mm^3	140 (47,273)	178 (75,295)	0.06
Log10 Viral Load (copies/mL)	2.7 (2.3,4.4)	2.3 (2.3,3.6)	0.01
Undetectable Viral load[k]	64 (49%)	125 (59%)	0.07
On HAART[j]	97 (72%)	142 (67%)	0.3

[a] IQR, interquartile range

[b] IDU, intravenous drug use

[c] BP, blood pressure

[d] HDL, high density lipoprotein

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[e] LDL, low density lipoprotein

[f] CRP, c-reactive protein

[g] ICA, internal carotid artery

[h] CCA, common carotid artery

[i] CAC, coronary artery calcium

[j] HAART, highly active antiretroviral therapy

[k] Limit of detection at 400 copies/mL.

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Table 3

Surrogate Markers of Atherosclerosis at Baseline and 6-year Follow-up.

	Median (IQR[a]) or N (%), n=211	
	Baseline	**6-Year Follow-up**
Carotid Artery Median IMT[b], mm		
Internal	0.71 (0.66, 0.78)	0.88 (0.76, 1.08)
Common	0.55 (0.51, 0.62)	0.68 (0.63, 0.72)
Plaque Presence (>1.5mm)		
Internal	6 (3%)	24 (11%)
Common	0 (0%)	1 (0%)
Calcium Scores		
CAC[c]	0.4 (0.0, 5.2)	1.9 (0.0, 46.4)
Zero	95(46%)	84(41%)
0< CAC[c] <100	99(49%)	89(43%)
≥ 100	11(5%)	33(16%)

[a] IQR, interquartile range

[b] IMT, intima-media thickness

[c] CAC, coronary artery calcium.

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Table 4

Multivariate Regression Analysis of IMT Change and CAC Progression.

A. IMT[a] Progression, Internal carotid		
Risk Factor	**Beta-coefficient (μm) (SE)**	**p-value**
Intercept	-0.24 ± 0.1	0.05
Age	0.008 ± 0.003	0.002
Baseline high triglycerides (≥150mg/dL)	0.14 ± 0.04	<0.001
Pack-years tobacco	0.003 ± 0.001	0.03
B. IMT[a] Progression, Common carotid		
Risk Factor	**Beta-coefficient (μm) ± SE**	**p-value**
Intercept	-0.03 ± 0.03	0.35
Cholesterol (mg/dL)	0.0002 ± 0.0001	0.005
Age	0.002 ± 0.0006	<0.001
Nadir CD4+ (100 cells/mm^3)	0.005 ± 0.002	0.03
PI[b] use at baseline	0.02 ± 0.008	0.05
C. CAC[c] progression		
Risk Factor	**Odds Ratio (Confidence Interval)**	**p-value**
Baseline diabetes	7.4 (2.5,21.5)	<0.001
HIV viral load (log 10 copies/mL)	1.7 (1.2,2.4)	0.001
HAART[d] duration (months)	1.02 (1.01,1.03)	0.004

[a] IMT, carotid intima-media thickness

[b] PI, protease inhibitor

[c] CAC, coronary artery calcium

[d] HAART, highly active antiretroviral therapy.