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RETINAL VESSEL CALIBER AMONG PEOPLE WITH AIDS: RELATIONSHIPS WITH DISEASE-ASSOCIATED FACTORS AND MORTALITY

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Abstract

Purpose—To evaluate relationships between retinal vessel caliber, AIDS-related factors, and mortality.

Design—Longitudinal, observational, cohort study.

Methods—We evaluated data for participants without ocular opportunistic infections at initial examination (baseline) in the Longitudinal Studies of the Ocular Complications of AIDS (1998–2008). Semi-automated evaluation of fundus photographs (1 eye/participant) determined central retinal artery equivalent (CRAE), central retinal vein equivalent (CRVE), and arteriole:venule

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The SOCA Research Group:
LSOCA is registered at http://www.clinicaltrials.gov (NCT00000168). A list of key personnel at participating clinical centers can be found in a prior printed publication.[16]

ratio (AVR) at baseline. Multiple linear regression models, using forward selection, identified independent relationships between indices and various host- and disease-related variables.

Results—Included were 1250 participants. Mean follow-up for determination of mortality was 6.1 years. Smaller CRAE was related to increased age ($p<0.001$) and hypertension ($p<0.001$); larger CRAE was related to lower hematocrit ($p=0.002$). Larger CRAE and CRVE were associated with black race ($p<0.001$). Larger CRVE was related to smoking ($p=0.004$); smaller CRVE was related to age ($p<0.001$) and higher mean corpuscular volume ($p=0.001$). We observed the following relationships with AIDS-associated factors: smaller CRAE and larger CRVE with history of highly active antiretroviral therapy (HAART; $p<0.001$); and larger CRAE with lower CD4+ T-lymphocyte count ($p=0.04$). We did not identify independent relationships with HIV RNA blood levels. There was a 12% (95% CI, 2–21%) increase in mortality risk per quartile of decreasing AVR ($p=0.02$).

Conclusions—Variations in retinal vascular caliber are associated with AIDS-specific factors, and are markers for increased mortality risk. Relationships are consistent with the hypothesis that the vasculature is altered by known atherogenic effects of chronic HAART or the prolonged inflammatory state associated with AIDS.

Advances in digital image analysis software have enabled large, population-based studies to measure retinal vessel caliber reliably and reproducibly as a potent biomarker of vascular disease.[1–3] Morphologic variations of retinal arterioles and venules are likely to reflect variations in cerebral and coronary vessels,[4] with which they are anatomically and physiologically similar.[5] Abnormalities in vessel caliber have been described in many disease states, including hypertension, diabetes mellitus, coronary artery disease, stroke, and renal dysfunction.[6–12] Variations in the retinal vascular caliber have not been studied among people with AIDS, although this population is known to be at increased risk for cardiovascular morbidity.[13, 14]

In this study, we investigated relationships between vessel caliber indices and demographic, medical, and laboratory characteristics of participants in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA). Based on relationships seen in the setting of other diseases,[15] we hypothesize that narrower arterioles and more dilated venules will be related to systemic morbidity and mortality.

METHODS

Patient Population

LSOCA is an NIH-sponsored, prospective, epidemiological study of people with AIDS, which began in September 1998. A description of its design and methods, and a summary of data for study participants at study enrollment (baseline) have been published previously.[16] Data were collected from study participants every 6 months per protocol. The current study includes data collected through December 31, 2008 for participants without ocular opportunistic infections at baseline.

Data Collection

We collected the following baseline demographic, medical, and laboratory information: age, gender, race/ethnicity (self-reported), hemoglobin, hematocrit, mean corpuscular volume (MCV), platelet count, leukocyte count, and absolute neutrophil count. We also collected the following AIDS-related information at baseline: time since AIDS diagnosis, lymphopenia as AIDS-defining illness, CD4+ T-lymphocyte count (baseline and nadir), CD8+ T-lymphocyte count, HIV RNA blood level (baseline and peak), use of highly active antiretroviral therapy (HAART; on HAART at baseline; ever on HAART), and Karnofsky

score (a global measure of a one's ability to conduct normal activities[17]). We identified the following potential co-morbidities at baseline: history of smoking, hypertension, diabetes mellitus, renal disease, coronary heart disease, peripheral vascular disease, and stroke.

Vessel caliber indices were determined in a semi-automated manner by certified graders at the University of Wisconsin Fundus Photograph Reading Center (IVAN software, Department of Ophthalmology and Visual Science, University of Wisconsin, Madison, WI) using a standardized protocol, described previously.[1] Briefly, the six largest arterioles and venules in a ring-shaped area located between 0.5DD and 1.0 DD from the optic disc margin are identified. Computer software measures the caliber of these individual vessels, then combines them into two summary variables for the eye: the projected caliber size of the central retinal artery (central retinal artery equivalent [CRAE]), and the projected caliber size of the central retinal vein (central retinal vein equivalent [CRVE]), using formulas derived by Parr and Spears[18, 19] and by Hubbard,[1] with revision by Knudtson.[20] These indices are used to calculate the arteriole:venule ratio (AVR), as CRAE/CRVE.

We categorized study participants who died during follow-up on the basis of immediate and contributing causes of death, using available death certificates; specifically, we identified whether death was associated with diseases characterized by vasculopathy (renal disease, cardiovascular disease, stroke), liver disease, AIDS-related opportunistic infections or malignancies, other AIDS-related disorders, or trauma, as described in a previous LSOCA publication about this cohort.[21]

Definitions

For purposes of this study, HAART was defined as the concurrent use of three or more antiretroviral drugs. Study definitions for the following conditions can be found in a previous publication about this cohort:[21] diabetes mellitus; hypertension; cardiovascular disease; stroke; peripheral vascular disease; and renal disease.

Data Analysis and Statistical Techniques

Unless otherwise noted, the unit of analysis was the eye, and one eye per study participant was evaluated. Wong and associates have demonstrated a strong correlation between the eyes of an individual, for both CRAE and CRVE, and concluded that measurements from one eye accurately reflect a person's systemic microvascular status.[22] If vessel caliber indices could be determined for both eyes, the eye with better photographic quality was selected as the study eye. Values for each vessel caliber index were grouped by quartiles and modeled ordinally. With regard to CRAE and CRVE, the first quartile contained narrower arterioles and venules, respectively, while the fourth quartile contained wider arterioles and venules. With regard to AVR, the first quartile included relatively narrower arterioles vs. venules, while the fourth quartile included relatively wider arterioles vs. venules.

Ordered logistic regression was used to assess the cross-sectional relationship between baseline factors (demographic, medical, laboratory, visual function) and vessel caliber index quartiles as the response variable. A forward selection model with p-value entry criterion of 0.05 was used to create adjusted models, using the following covariates: age, black race, hematocrit, MCV, history of HAART (previous use, use at baseline, or both), time since diagnosis of AIDS, and history of smoking. Factors for which there were statistically significant associations on adjusted models were chosen as covariates in subsequent adjusted models.

Vessel caliber indices were used as predictors in (1) cross-sectional analyses using logistic regression of selected co-morbidities at baseline and linear regression of Karnofsky score at baseline; and (2) longitudinal analyses using Cox regression of incident death during follow-

up. The Fisher exact test was used to examine the relationship between baseline vessel caliber indices and causes of, or factors contributing to, death.

Because diabetes mellitus can cause vascular disease similar to that seen in people with AIDS,[23] we performed subgroup analyses, looking for significant ($p<0.01$) interactions between diabetes mellitus and relationships that involve vessel caliber. Similar subgroup analyses were performed to look for interactions with hypertension.

P-values were two-sided and were not adjusted for multiple comparisons. Statistical analyses were performed using SAS (SAS/STAT User's Guide, Version 9.2, 2010; SAS Institute, Cary, North Carolina, USA) and Stata (Stata Statistical Software: Release 11, 2009; StataCorp LP, College Station, Texas, USA) statistical packages.

RESULTS

As of December 31, 2008, 2,221 individuals had enrolled in LSOCA, 1,712 of whom had no ocular opportunistic infections. The demographic, medical, laboratory, and ophthalmic examination data for this subpopulation are described in a previous publication.[21] Median age of the cohort was 43 years (range 38–48 years), and 34% of participants self-reported race/ethnicity as being black. Participants were significantly more likely to be excluded if they were older (mean age 44±10 years for those excluded vs. 43±8 years for those included, $p=0.03$) or black (34% of black participants were excluded vs. 25% of non-black participants, $p=0.0003$). These differences were attributed to the quality of the fundus photographs; participants who were older or black were more likely to have problems with dilation, resulting in photographs of lower quality that could not be used to determine vascular caliber indices.

Median time since AIDS diagnosis was 4.2 years (range 1.6–7.1 years), and median CD4+ T-lymphocyte count at baseline was 192 cells/uL (range 81–350 cells/uL). HAART had been used before or at baseline in 90% of participants; 85% of participants were using HAART at baseline. Among the 1,712 eligible participants, 1250 eyes had vessel caliber measurements at baseline. The Figure illustrates the normal distribution of the vessel caliber indices.

Table 1 shows relationships between vessel caliber indices and demographic, medical, and selected laboratory factors at baseline. Table 2 shows the relationships between vessel caliber indices and AIDS-specific factors. Crude (univariate) analyses demonstrated that at least one vessel caliber index was statistically associated with the following factors: age, gender, black race, weight, history of smoking, hemoglobin, hematocrit, MCV, time since AIDS diagnosis, lymphocytopenia, HIV RNA blood level, and history of HAART. On multivariate analyses, at least one vessel caliber index remained independently associated with the following factors: age, black race, hematocrit, MCV, history of smoking, time since AIDS diagnosis, and history of HAART. There was also an independent association between increased CRAE and decreased CD4+ T-lymphocyte count. There were no significant relationships between any vessel caliber index and cotton-wool spots (all p values ≥ 0.54, data not shown).

Table 3 shows the relationships between vessel caliber indices and the presence at baseline of selected systemic diseases that are characterized by vasculopathy. Only hypertension remained significantly associated with vessel caliber on multivariate analyses; for participants grouped by CRAE and AVR, those in the first quartiles (narrowest arterioles; smallest AVR) had the highest prevalence of hypertension. With regard to Karnofsky scores, we found that lower scores (worse health) were strongly related to larger CRVE ($p=0.001$) and smaller AVR ($p<0.001$; data not shown).

Table 4 shows the relationship of vessel caliber indices at baseline with death of 304 participants during follow-up. Larger CRVE (p=0.006) and smaller AVR (p<0.001) were strongly related to death on crude analyses; only the relationship with AVR remained significant after adjustment for comorbidities (p=0.02). HIV RNA blood level and HAART use at enrollment were the primary confounders that attenuated the effect of CRVE on mortality. The unadjusted relative risk (RR) for mortality per quartile of CRVE was 1.15 (p=0.006, as noted above); with adjustment, RR was 1.07 (p=0.21). During follow-up, 15 of 1250 participants developed cytomegalovirus (CMV) retinitis. Because AIDS-related CMV retinitis is associated with an increased risk of mortality,[24] we repeated our analyses after excluding these 15 individuals, and the relationship between AVR and death remained significant (data not shown).

Death certificates were available for 92 participants (30.3%). Table 5 shows the relationships between vessel caliber indices at baseline and causes of mortality during follow-up. There was a weak relationship between smaller CRAE and diseases characterized by microvasculopathy (cardiovascular disease, renal disease, and stroke) as causes of, or contributors to, death (p=0.08).

Of the 1250 participants, 249 (19.9%) had hypertension, and only 103 (8.2%) had diabetes mellitus. Neither hypertension nor diabetes mellitus had a significant effect on relationships between vessel caliber indices and any other factors demonstrated for the total population.

DISCUSSION

We studied variations in vessel caliber indices and their relationships to host and disease factors, but did not identify the prevalence of abnormal vessel caliber indices in our cohort, as normative data are not available.[15] A number of large, population-based studies have identified various systemic, genetic, and environmental factors that influence vessel caliber indices;[3, 6, 9–12, 25, 26] our results are consistent with these other studies with respect to the effects of age, race/ethnicity, and gender. Specifically, we found that older participants had significantly narrower arterioles, as shown in the Blue Mountain Eye Study (BMES),[26] the Beaver Dam Eye Study (BDES),[12] and the Multi-Ethnic Study of Atherosclerosis (MESA).[11] We found a strong association between age and vessel caliber indices, despite the fact that the age range for individuals in our cohort was considerably narrower than ranges in previous studies. Both BMES and MESA found that women had larger CRAE; we observed this relationship in our population, as well, but it did not remain significant in our adjusted model. Black participants were more likely to have larger arterioles and venules, consistent with findings in MESA. Relationships between vessel caliber indices and age, race/ethnicity, and gender are poorly understood, but they may reflect unrecognized environmental or genetic influences.[15] The fact that these relationships are present across different populations implies that not all of the variations in retinal vascular caliber observed in our cohort can be attributed directly to AIDS; for that reason, we adjusted for these factors in our analyses. Although there were significant differences in age and race/ethnicity of study participants who were and were not included in our analyses, the differences were small and not likely to influence our results or conclusions.

Infection with human immunodeficiency virus (HIV), its treatment, or both is thought to accelerate the aging process;[27] thus, retinal vascular variations might occur earlier in life among people with AIDS than is seen in the general population. We did note that the distributions of vessel caliber indices for our cohort were similar to those for non-diabetics in the Wisconsin Epidemiological Study of Diabetic Retinopathy,[28] despite the fact that the median age of that group (at least 55 years) was older than the median age of participants in our study (43 years).

Study participants with a self-reported history of smoking had significantly wider venules and smaller AVR, consistent with data from ARIC,[29] MESA,[11] Cardiovascular Health Study,[10] and Rotterdam studies.[9] It is known that smoking increases systemic markers of inflammation,[30] which may be a contributor to retinal vessel damage.

Among the potential co-morbidities studied, only hypertension was statistically related to vessel caliber indices. Hypertensives were more likely to have narrower arterioles and smaller AVR, as reported in many other studies, including the BDES, which demonstrated a strong relationship between retinal arteriolar narrowing and nitricoxide-dependent endothelial dysfunction, thought to be the underlying mechanism of hypertension-related arteriolar changes.[31] Prospective studies have found that retinal vascular variations predict development of clinical hypertension.[32] It is likely that vessel caliber indices will predict similar changes in people with AIDS.

We also found that low hematocrit was associated with wider arterioles and larger AVR; we could not find previous reports of this association in other populations, based on a PubMed search. Anemia is an important clinical problem in people with AIDS; it is a prognostic marker for disease progression, and has been associated with increased mortality.[33, 34] People with AIDS have multiple risk factors for anemia, including use of myelosuppressive drugs, poor nutritional status, and blood loss from gastrointestinal lesions.[35] They commonly have other hematologic abnormalities, as well, including macrocytosis, which is associated with vitamin B12 or folate deficiency from intestinal malabsorption and with use of certain medications, such as zidovudine, stavudine, and ganciclovir.[35, 36] We found that high MCV is independently related to the narrowing of retinal venules. It is possible that the relationships between these hematologic abnormalities and vessel caliber indices are not specific to AIDS, but were identified in our cohort because the abnormalities are more prevalent among people with AIDS than in other studied populations. It is possible that retinal vascular variations are caused by hypoxia, leading to vascular dilation,[36] or to a complex interaction of hemorheologic factors (abnormal vessel wall shear,[37] abnormal erythrocyte aggregation or deformability,[38] leukocyte activation[39]), leading to altered blood flow and ischemia.

We also identified AIDS-specific risk factors for variations in vessel caliber indices. Participants who had ever been on HAART were more likely to have narrower arterioles and venules. The Rotterdam study has linked decreased CRAE to increased intima-media thickness, a marker for subclinical atherosclerosis, measured in carotid arteries.[9] Intima-media thickening increases the risk of myocardial infarction and cardiovascular morbidity in HIV-infected individuals.[40] Our findings are consistent with the notion that HAART has a pro-atherogenic effect on the vasculature.[14] Vessel caliber indices were also weakly associated with duration of AIDS and low CD4+ T-lymphocyte count. Chronic HIV infection and HAART are associated with a heightened state of inflammation,[41] which could be another mechanism for changes in the retinal vasculature.

A previous study of this cohort showed that abnormal contrast sensitivity is associated with increased mortality; evidence suggested that the association was based on an increased prevalence of life-threatening systemic diseases characterized by vasculopathies among those with abnormal contrast sensitivity.[21] We also investigated whether variations in vessel caliber indices were markers for increased risk of death. Mortality increased by 12% per quartile of decreasing AVR ($p=0.02$). This relationship was significant, despite adjustment from known confounders, including hypertension, suggesting that AVR is an independent risk factor. We found that mortality risk also increased by 15% per quartile of retinal venular widening on crude analysis, but this relationship was not independent of other covariates. HIV RNA blood level and HAART use at enrollment were the primary confounders that

attenuated the effect of CRVE on mortality; thus, variations in CRVE may be a specific marker for AIDS-related influences on mortality. These observations are similar to findings from the BDES and BMES; both studies found that smaller AVR and larger retinal venules were associated with an increased risk of death from cardiovascular disease.[42, 43] We also identified a weak relationship between vessel caliber indices and death caused by diseases associated with vasculopathy.

There are several limitations to this study. Causation cannot be shown with cross-sectional analyses. Our ability to study the relationship between vessel caliber indices and causes of death was limited by the relatively small number of participants for whom death certificates were available. Lipids might influence the retinal vasculature, but we did not have serum lipid values at baseline for all participants. With regard to vessel caliber indices, values used in this study are not true measures of vessel caliber; they are based on the observable blood column, but do not take into account the immeasurable plasma cuff at the periphery of the vessel lumen. The normal systolic and diastolic cardiac cycle will alter retinal vessel caliber, but fluctuations are small and random, and not felt to be capable of causing major miscalculations.[15] AVR has been used as a measure in previous cross-sectional studies of the retinal vasculature, and was therefore reported herein, to allow comparison to previous studies in other populations; however, there is a potential problem with use of AVR; CRAE and CRVE variations in the same direction could result in an unchanged ratio, masking retinal vascular abnormalities. Liew and associates have suggested that a statistical alternative is to report an interaction term between CRAE and CRAE, in addition to reporting each as a separate variable.[44] Because AVR is based only on CRAE and CRVE, if AVR is significantly associated with a factor, either CRAE or CRVE will almost certainly be associated with the factor, after each index is adjusted for the other; thus, we are confident that the significant associations identified with AVR in the current study are relevant. Nevertheless, use of an interaction term in future studies may reveal additional associations, and may help to elucidate the specific type of vascular changes most closely associated with HIV-related disease.

In conclusion, our study has shown that people with AIDS have variations in the retinal vasculature that are related to duration of AIDS, treatment with antiretroviral drugs, hematologic abnormalities, and some measures of the severity of immunodeficiency. These vascular variations predict an increased risk of death. The fact that we saw many of the same relationships between vessel caliber indices and demographic factors seen in other populations supports the validity of our analysis techniques. The ability to visualize retinal vessels directly provides investigators with a potential tool to study early structural changes associated with life-threatening systemic vascular diseases. Such knowledge might lead to early risk factor intervention. Additional longitudinal studies are warranted to determine which of the vessel caliber indices will be most useful clinically for the study of people with AIDS, and whether changes in vascular caliber indices over time are even stronger predictors of adverse events.

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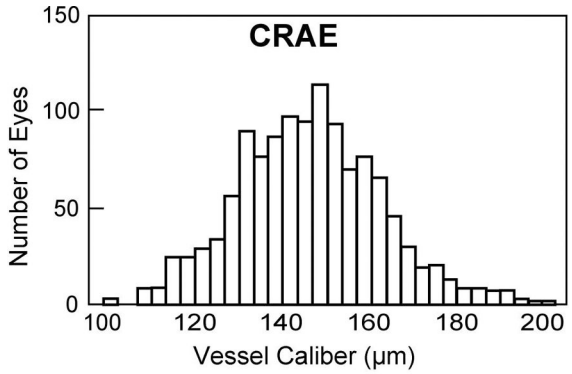

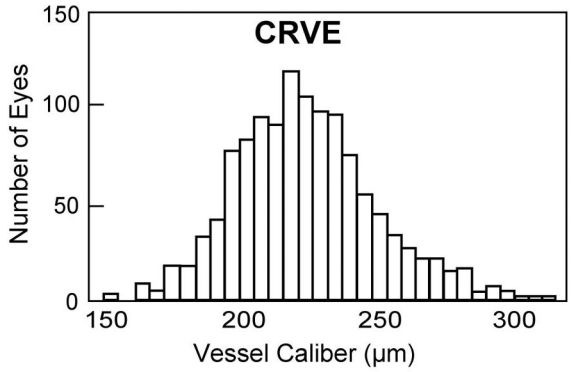

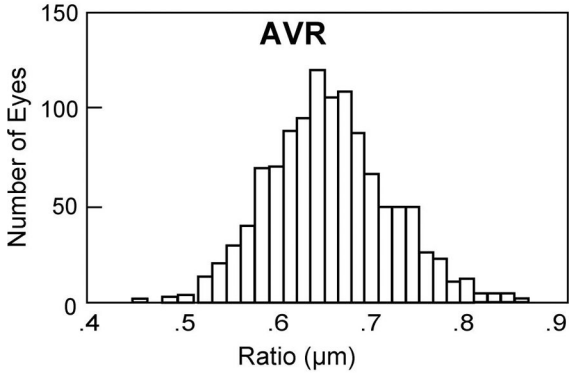

	QUARTILE			
	1	2	3	4
CRAE (μm)	<136	136-147	148-158	>158
CRVE (μm)	<206	206-221	222-238	>238
AVR (μm)	<0.62	0.62-0.66	0.67-0.70	>0.70

Figure.
Distribution of central retinal artery equivalents (CRAE), central retinal vein equivalents (CRVE), and arteriole:venule ratio (AVR) at study enrollment (baseline). The ranges of values for the quartiles of each index are indicated below the bar graphs.

TABLE 1

Relationships between Retinal Vessel Caliber Indices and Demographic and Laboratory Factors at Baseline for 1250 Study Participants without Ocular Opportunistic Infections in the Longitudinal Study of the Ocular Complications of AIDS

	Quartile				P Value	
	1	2	3	4	Crude	Adjusted[a]
Age (median, years)						
CRAE	45	44	42	41	<0.001	<0.001
CRVE	45	43	42	42	<0.001	<0.001
AVR	44	43	43	42	<0.001	<0.001
Gender (percent female)						
CRAE	13	17	19	26	<0.001	--
CRVE	12	19	23	23	<0.001	--
AVR	20	15	18	22	0.28	--
Race/ethnicity (percent black)						
CRAE	24	30	38	44	<0.001	<0.001
CRVE	21	28	38	49	<0.001	<0.001
AVR	41	35	29	32	0.008	0.009
Weight (median, kg)						
CRAE	77	74	75	74	0.02	--
CRVE	75	75	74	74	0.04	--
AVR	75	75	75	74	0.67	--
Smoking history (percent ever smoked cigarettes)						
CRAE	58	57	56	69	0.02	--
CRVE	49	59	66	65	<0.001	0.004
AVR	62	62	58	57	0.14	--
Hematology (medians)						
Hemoglobin (g/dL)						
CRAE	14.1	14.0	13.6	13.2	<0.001	--
CRVE	13.9	13.8	13.7	13.5	0.002	--
AVR	14.0	13.8	13.8	13.5	0.03	--

	Quartile				P Value	
	1	2	3	4	Crude	Adjusted[a]
Hematocrit (percentage)						
CRAE	41.4	41.2	40.0	38.8	<0.001	0.002
CRVE	41.0	40.8	40.1	39.5	0.005	--
AVR	41.2	40.9	40.0	39.6	0.008	0.001
Mean corpuscular volume (fL)						
CRAE	99.8	98.6	96.8	97.1	0.005	--
CRVE	101.5	98.6	96.5	96.0	<0.001	0.001
AVR	97.0	98.4	97.8	100.1	0.009	0.04
Platelet count (×1000 cells/μL)						
CRAE	214	215	210	214	0.73	--
CRVE	212	213	222	211	0.34	--
AVR	220	214	209	215	0.42	--
Leukocyte count (×1000 cells/μL)						
CRAE	5.0	4.7	4.6	4.4	0.11	--
CRVE	4.6	4.9	4.8	4.5	0.85	--
AVR	4.8	4.7	4.8	4.4	0.24	--
Absolute neutrophil count (×1000 cells/μL)						
CRAE	2.6	2.4	2.3	2.2	0.32	--
CRVE	2.3	2.5	2.5	2.2	0.87	--
AVR	2.5	2.4	2.4	2.2	0.83	--

AVR=arteriole:venule ratio
CRAE=central retinal arteriolar equivalent
CRVE=central retinal venular equivalent
HAART=highly active antiretroviral therapy

[a]Variables selected from three separate ordered logistic regression models, regressing quartiles of CRAE, CRVE, and AVR on a candidate list of all baseline characteristics (n=1181 complete cases), using forward-selection entry criterion p<0.05. Significant variables for regression of CRAE are age, black race, hematocrit, HAART (ever used), and CD4+ T-lymphocyte count; for regression of CRVE, they are age, black race, history of smoking, mean corpuscular volume, HAART (ever used and current use); for regression of AVR, they are age, black race, hematocrit, mean corpuscular volume and current use of HAART.

TABLE 2

Relationships between Retinal Vessel Caliber Indices and AIDS-Specific Medical and Laboratory Factors at Baseline for 1250 Study Participants without Ocular Opportunistic Infections in the Longitudinal Study of the Ocular Complications of AIDS

	Quartile				P Value	
	1	2	3	4	Crude	Adjusted[a]
AIDS history						
Time since AIDS diagnosis (median, years)						
CRAE	4.5	4.4	4.4	3.4	0.15	--
CRVE	4.6	4.5	3.9	3.6	0.05	--
AVR	4.1	4.5	4.0	4.4	0.49	--
Lymphocytopenia as AIDS-defining illness (percentage)						
CRAE	65	67	68	60	0.16	--
CRVE	68	66	66	60	0.03	--
AVR	66	60	65	68	0.28	--
Immunology and virology						
CD4+ T-lymphocyte count (median, cells/μL)						
CRAE	201	194	200	172	0.73	0.04
CRVE	207	197	184	182	0.13	--
AVR	191	197	190	186	0.59	--
Nadir CD4+ T-lymphocyte count (median, cells/μL)						
CRAE	42	38	44	42	0.50	--
CRVE	45	41	41	42	0.21	--
AVR	39	41	46	42	0.33	--
CD8+ T-lymphocyte count (median, cells/μL)						
CRAE	784	773	798	747	0.09	--
CRVE	756	753	808	766	0.78	--
AVR	786	767	787	751	0.14	
Peak HIV RNA blood level (median, log copies/mL)						
CRAE	5.3	5.3	5.3	5.3	0.50	--
CRVE	5.3	5.3	5.3	5.4	0.37	--

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	Quartile				P Value	
	1	2	3	4	Crude	Adjusted[a]
AVR	5.3	5.4	5.2	5.3	0.22	--
HIV RNA blood level (median, log copies/mL)						
CRAE	2.6	2.7	2.6	3.2	<0.001	--
CRVE	2.6	2.6	2.9	3.5	<0.001	--
AVR	2.9	2.6	2.8	2.7	0.37	--
Antiretroviral treatment history (percent individuals)						
Ever on HAART						
CRAE	93	94	87	85	<0.001	<0.001
CRVE	94	92	90	83	<0.001	<0.001
AVR	89	91	88	90	0.82	--
Current HAART						
CRAE	89	88	82	80	<0.001	--
CRVE	91	87	83	77	<0.001	0.01
AVR	79	85	88	86	0.01	0.004

AVR=arteriole:venule ratio
CRAE=central retinal arteriolar equivalent
CRVE=central retinal venular equivalent
HAART=highly active antiretroviral therapy

[a]Variables selected from three separate ordered logistic regression models, regressing quartiles of CRAE, CRVE, and AVR on a candidate list of all baseline characteristics (n=1181 complete cases), using forward selection entry criterion p<0.05. Significant variables for regression of CRAE are age, black race, hematocrit, HAART (ever used), and CD4+ T-lymphocyte count; for regression of CRVE, they are age, black race, history of smoking, mean corpuscular volume, HAART (ever used and current use); for regression of AVR, they are age, black race, hematocrit, mean corpuscular volume and current use of HAART.

TABLE 3

Relationships between Retinal Vessel Caliber Indices and Selected Co-Morbidities at Baseline for 1250 Study Participants without Ocular Opportunistic Infections in the Longitudinal Study of Ocular Complications of AIDS

	Quartile				Comparisons			
	1	2	3	4	Crude		Adjusted[a]	
					OR[b]	P	OR[b]	P
Co-morbidities								
Hypertension (percent individuals)								
CRAE	27	21	17	14	0.76	<0.001	0.75	<0.001
CRVE	21	22	19	17	0.89	0.09	0.88	0.08
AVR	27	21	16	15	0.79	<0.001	0.83	0.007
Diabetes mellitus (percent individuals)								
CRAE	9	8	10	6	0.89	0.23	0.92	0.41
CRVE	7	11	8	7	0.91	0.34	0.96	0.73
AVR	11	8	7	8	0.93	0.47	0.93	0.47
Renal disease (percent individuals)								
CRAE	5	4	6	5	1.03	0.83	1.00	0.97
CRVE	6	4	5	6	1.00	0.94	1.00	0.97
AVR	6	3	5	7	1.06	0.64	1.03	0.77
Coronary heart disease (percent individuals)								
CRAE	8	7	6	8	0.98	0.88	1.05	0.69
CRVE	8	7	7	8	1.01	0.90	1.04	0.77
AVR	7	7	8	6	0.98	0.88	1.00	0.97
Peripheral vascular disease (percent individuals)								
CRAE	5	3	5	3	0.89	0.45	0.90	0.52
CRVE	4	2	4	7	1.31	0.07	1.26	0.15
AVR	5	5	5	1	0.73	0.04	0.79	0.12
Stroke (percent individuals)								
CRAE	6	6	3	4	0.82	0.15	0.85	0.26
CRVE	7	4	6	4	0.86	0.27	0.88	0.38

	Quartile				Comparisons			
	1	2	3	4	Crude		Adjusted[a]	
					OR[b]	P	OR[b]	P
AVR	3	9	5	3	0.95	0.73	0.96	0.77

AVR=arteriole:venule ratio
CRAE=central retinal arteriolar equivalent
CRVE=central retinal venular equivalent

[a] Analyses involving CRAE were adjusted for age, race, hematocrit, time since diagnosis of AIDS, HAART (ever used), and CD4+ T-lymphocyte count; analyses involving CRVE were adjusted for age, race, mean corpuscular volume, history of smoking, and HAART (ever used and current use); analyses involving AVR were adjusted for age, race, mean corpuscular volume, hematocrit, and current use of HAART.

[b] Odds ratio defined as change in odds of event per quartile of vascular measurement.

TABLE 4

Retinal Vessel Caliber indices at Baseline as Predictors of Mortality among 1250 Study Participants without Ocular Oportunistic Infections in the Longitudinal Study of Ocular Complications of AIDS[a]

Index	Crude			Adjusted[b]		
	RR[c] death / quartile	95% CI	P	RR[c] death / quartile	95% CI	P
CRAE	0.98	0.89–1.09	0.77	0.95	0.86–1.06	0.40
CRVE	1.15	1.04–1.27	0.006	1.07	0.96–1.20	0.21
AVR	0.84	0.76–0.93	<0.001	0.88	0.79–0.98	0.02

AVR=arteriole:venule ratio
CRAE=central retinal arteriolar equivalent
CRVE=central retinal venular equivalent
RR=relative risk

[a] 304 deaths among 1250 study participants; median follow-up, 6.8 years; rate, 3.6/100person-years.

[b] Adjusted for the following variables at baseline: current use of HAART, CD4+ T-lymphocyte count, HIV RNA blood level; age, black race, mean corpuscular volume, hematocrit, time since diagnosis of AIDS, and hypertension (n=1152 because of missing values).

[c] Relative risk estimated from Cox regression per increasing quartile.

TABLE 5

Relationships between Retinal Vessel Caliber Indices and Causes of Death during Follow-Up among 304 Study Participants in the Longitudinal Study of Ocular Complications of AIDS

	Quartile			
	1	**2**	**3**	**4**
Number of deaths[a]				
CRAE	78	81	66	79
CRVE	64	72	77	91
AVR	96	73	76	59
Number of participants for whom death certificates were available				
CRAE	30	22	23	17
CRVE	20	20	24	28
AVR	36	28	18	10
Attributed causes of, or contributors to, death				
Diseases characterized by vasculopathy[b]				
Cardiovascular disease				
CRAE	4	2	0	0
CRVE	2	2	2	0
AVR	3	3	0	0
Renal disease				
CRAE	1	0	1	1
CRVE	1	0	0	2
AVR	1	0	2	0
Stroke				
CRAE	1	1	0	0
CRVE	0	0	2	0
AVR	1	1	0	0
Liver disease				
CRAE	4	0	0	3
CRVE	3	0	2	2
AVR	4	1	2	0
Other specified diseases[c]				
CRAE	4	3	2	4
CRVE	3	4	3	3
AVR	5	4	1	3
AIDS-related opportunistic infection or malignancy				
CRAE	9	6	7	4
CRVE	7	5	5	9
AVR	9	8	5	4

	Quartile			
	1	**2**	**3**	**4**
AIDS-related, not otherwise specified				
CRAE	7	9	11	5
CRVE	4	9	7	12
AVR	13	9	7	3
Trauma				
CRAE	0	1	2	0
CRVE	0	0	3	0
AVR	0	2	1	0

AVR=arteriole:venule ratio
CRAE=central retinal arteriolar equivalent
CRVE=central retinal venular equivalent

[a] P-values comparing quartiles are 0.59, 0.77, and 0.81 for CRAE, CRVE, and AVR respectively.

[b] P-values for the comparison of diseases characterized by vasculopathy vs. other causes are 0.08, 0.54, and 0.31 for CRAE, CRVE and AVR, respectively.

[c] Includes organ diseases other than those listed in the table, plus sepsis and shock.