Association of Age-related Macular Degeneration With Mortality in Patients With Acquired Immunodeficiency Syndrome; Role of Systemic Inflammation

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• PURPOSE: To evaluate the relationships among age-related macular degeneration (AMD), mortality, and biomarkers of systemic inflammation in patients with acquired immunodeficiency syndrome (AIDS).

• DESIGN: Case-control study.

• METHODS: In participants with intermediate-stage AMD at enrollment in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) and 2:1 controls matched for age and sex, cryopreserved baseline plasma specimens were assayed for biomarkers of inflammation, including high-sensitivity C-reactive protein (CRP), interleukin (IL)-6, interferon-γ inducible protein (IP)-10, soluble CD14 (sCD14), soluble CD163 (sCD163), kynurenine/tryptophan (KT) ratio, and intestinal fatty acid binding protein (I-FABP). Main outcome measure was mortality.

• RESULTS: The study included 189 patients with AMD and 385 controls. In the unadjusted analysis, AMD was associated with mortality (hazard ratio [HR] 1.48; 95% confidence interval [CI] 1.02, 2.15; $P = .04$). In an adjusted analysis, CRP (HR 1.36; 95% CI 1.08, 1.71; $P = .009$), IL-6 (HR 1.45; 95% CI 1.11, 1.90; $P = .006$), and IP-10 (HR 1.41; 95% CI 1.08, 1.84; $P = .01$) were associated with mortality. In a Cox regression analysis adjusted for human immunodeficiency virus load, blood CD4+ T cell level, CRP, IL-6, and IP-10, the association of AMD with mortality was attenuated (HR 1.08; 95% CI 0.73, 1.59; $P = .70$), primarily by the addition of the inflammatory biomarkers.

• CONCLUSIONS: These data suggest that the increased mortality observed in patients with AIDS with AMD is, at least in part, a result of systemic inflammation. (Am J Ophthalmol 2019;199:230–237. © 2018 Elsevier Inc. All rights reserved.)

PERSONS WITH HUMAN IMMUNODEFICIENCY VIRUS (HIV) infection treated with modern combination antiretroviral therapy (ART) have suppression of HIV replication; reduction of the amount of HIV RNA circulating in the blood (HIV viral load); improvement in immune function, manifested as a rise in CD4+ T cells (immune recovery); decreased opportunistic infections; and an improved lifespan.[1–4] Nevertheless, they have a shortened lifespan compared to comparably aged HIV-uninfected persons, largely owing to age-related diseases,[5,6] and they have an increase in age-related diseases such as cardiovascular disease, metabolic disorders (eg, diabetes and osteoporosis), neurocognitive decline, and several age-related cancers not associated with acquired immunodeficiency syndrome (AIDS).[7–10] As such, they exhibit features of accentuated and accelerated aging.[9,10] They also exhibit features of immunosenescence, a state characterized by chronic immune activation and systemic inflammation, but a poor response to new antigenic challenges.[9–12]

Persons with AIDS also have an ~4-fold increased age- and sex-adjusted prevalence of intermediate-stage age-related macular degeneration (AMD) compared to HIV-uninfected persons[13] and an ~1.75-fold increased race/ethnicity- and sex-adjusted incidence of intermediate-stage AMD compared to HIV-uninfected persons,[14] a finding consistent with their accelerated and accentuated aging. Because of the association of AMD with C-reactive protein (CRP), a biomarker of systemic inflammation in HIV-uninfected persons,[15] the presence of circulating activated monocytes in patients with AMD,[16] and the elevations of several cytokines in the blood of patients with AMD,[17] we evaluated relationships among intermediate-stage AMD at enrollment, plasma biomarkers of systemic inflammation at enrollment, and mortality in

AJO.com Supplemental Material available at AJO.com.

Accepted for publication Dec 1, 2018.

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0002-9394/$36.00
https://doi.org/10.1016/j.ajo.2018.12.002

TABLE 1. Characteristics of the Study Population of Patients With AIDS With and Without Age-related Macular Degeneration

Enrollment Characteristic	AMD (Cases)	No AMD (Controls)	*P* Value
Number of participants	189	385	
Matching variables			
Age			
Number of participants	189	385	
Mean ± standard deviation, years	47.9 ± 9.7	47.3 ± 8.9	.47
Sex, n (%)			.98
Male	146 (77.2)	297 (77.1)	
Female	43 (22.8)	88 (22.9)	
Race, n (%)			.99
White	72 (38.1)	148 (38.4)	
Black	81 (42.9)	163 (42.3)	
Other	36 (19.0)	74 (19.2)	
AIDS-defining illness, n (%)			.21
CD4+ T-cell lymphopenia[a]	121 (64.0)	264 (69.3)	
Opportunistic infection	68 (36.0)	117 (30.7)	
HIV treatment, n (%)			
On ART at enrollment	155 (82.0)	331 (86.0)	.22
Received ART at or before enrollment	174 (92.1)	362 (94.0)	.37
Virology/immunology			
HIV load (log_{10} (copies/mL))			
Number	181	366	
Mean ± standard deviation	3.2 ± 1.5	2.9 ± 1.5	.07
Distribution, n (%)			
≤2.6	79 (43.6)	191 (52.2)	
>2.6 to 3.0	17 (9.4)	26 (7.1)	
>3.0	85 (47.0)	149 (40.7)	
CD4+ T cells (cells/μL)			
Number	189	382	
Median (25^{th}, 75^{th} percentile)	179 (82, 325)	220 (96, 387)	.12
Distribution, n (%)			
<100	58 (30.7)	99 (25.9)	
100-199	42 (22.2)	77 (20.2)	
200-499	66 (34.9)	159 (41.6)	
≥500	23 (12.2)	47 (12.3)	
CD8+ T cells (cells/μL)			
Number	188	380	
Median (25^{th}, 75^{th} percentile)	761 (488, 1033)	810 (504, 1128)	.30
Inflammatory biomarkers			
CRP (log_{10}(mg/L))			
Number	158	328	
Mean ± standard deviation	0.39 ± 0.62	0.32 ± 0.58	.20
IL-6 (log_{10}(pg/mL))			
Number	185	381	
Mean ± standard deviation	0.39 ± 0.42	0.32 ± 0.36	.06
IP-10 (log_{10}(pg/mL))			
Number	185	376	
Mean ± standard deviation	2.42 ± 0.39	2.37 ± 0.37	.20
sCD14 (log_{10}(μg/mL))			
Number	185	383	
Mean ± standard deviation	0.44 ± 0.14	0.43 ± 0.13	.31
sCD163 (log_{10}(ng/mL))			
Number	187	383	
Mean ± standard deviation	2.83 ± 0.27	2.84 ± 0.23	.84
KT ratio (log_{10}(ratio))			
Number	175	354	
Mean ± standard deviation	1.76 ± 0.27	1.77 ± 0.31	.86
I-FABP (log_{10}(pg/mL))			
Number	184	382	
Mean ± standard deviation	3.15 ± 0.28	3.16 ± 0.33	.67

AMD = age-related macular degeneration; ART = combination antiretroviral therapy; CRP = C-reactive protein; I-FABP = intestinal fatty acid binding protein; IL-6 = interleukin-6; IP-10 = interferon-γ inducible protein-10; KT ratio = kynurenine tryptophan ratio; sCD14 = soluble CD14; sCD163 = soluble CD163.
[a]CD4+ T-cell lymphopenia = CD4+ T cells <200 cells/ART μL.

participants enrolled in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA).

PATIENTS AND METHODS

LSOCA WAS A PROSPECTIVE COHORT STUDY OF PATIENTS with AIDS conducted in the era of modern ART.[18] Participants were evaluated for the presence of intermediate-stage AMD (AREDS stage 3) or greater from photographs taken at enrollment (baseline).[13,14,19] Photographs were evaluated for AMD at the Reading Center in the Department of Ophthalmology and Visual Sciences at the

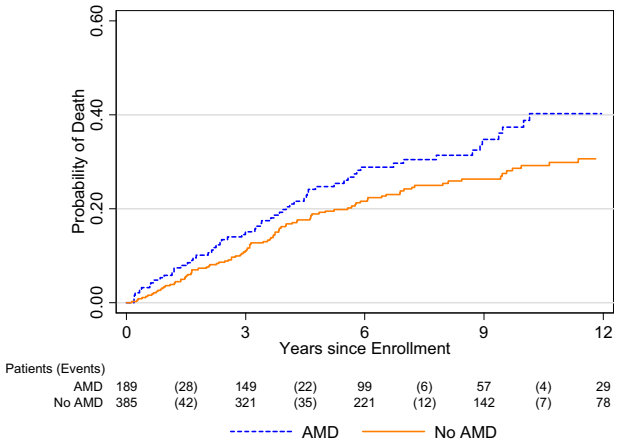

FIGURE 1. Kaplan-Meier curve of mortality by age-related macular degeneration status in patients with AIDS.

University of Wisconsin, Madison, School of Medicine and Public Health by graders masked as to clinical data, as previously described.[13,14] Of the 1825 participants without an ocular opportunistic infection, 9.9% had prevalent AMD at enrollment.[13] Patients with AMD at enrollment were age group-, race/ethnicity-, and sex-matched with 2 controls from LSOCA for a case-control study of inflammatory biomarkers and AMD. For age matching, AMD cases and controls were grouped by decade of age (ie, 20s, 30s, 40s, 50s, 60s+). Phlebotomy was performed at enrollment and plasma specimens cryopreserved. Cryopreserved specimens were thawed and assayed for biomarkers of inflammation using commercially available immunoassay kits in the Core Immunology Laboratories of the University of California, San Francisco, School of Medicine, as previously described.[20] Inflammatory biomarkers included high-sensitivity CRP (UBI Magiwel, Mountain View, California, USA), interleukin (IL)-6 (R&D Systems, Minneapolis, Minnesota, USA), soluble CD14 (sCD14, R&D Systems), soluble CD163 (sCD163, R&D Systems), and interferon-γ inducible protein (IP)-10. Intestinal fatty acid binding protein (I-FABP), a marker of impaired gut epithelial integrity (R&D Systems), and plasma kynurenine to tryptophan (KT) ratio, a marker of dendritic cell indoleamine 2,3 dioxygenase (IDO) upregulation,[21] also were assessed. The KT ratio was assayed using liquid chromatography–tandem mass spectrometry.[22] Participants enrolled in LSOCA without an ocular opportunistic infection were seen every 6 months for follow-up until the common study close-out in 2013, with periodic surveys of each clinical center to identify deaths unreported to the coordinating center and deaths among patients lost to follow-up.

• **STATISTICS:** Comparisons between cases with AMD and controls without AMD used the χ^2 test for categorical variables and t test and Wilcoxon rank sum test for normally and non-normally distributed continuous variables, respectively. Plasma inflammatory biomarker values were $\log_{10}$ transformed for normality (values = 0 were imputed with 0.5 × smallest nonzero value). For comparisons among different biomarkers with different dynamic ranges results were standardized to the standard deviation (SD) units of the $\log_{10}$(biomarker plasma concentration). Quartiles were used to compare the levels within the biomarker. Adjusted hazard ratios (HR) and 95% confidence intervals (95% CI) for mortality were estimated using multiple Cox regression adjusted for the following: level of HIV RNA in plasma ("HIV viral load"), CD4+ T cell count, and biomarkers of inflammation listed above. The data analyses were generated using both SAS (SAS version 9.4, SAS Institute Inc, Cary, North Carolina, USA) and Stata software (Stata Statistical Software: Release 15, 2017; StataCorp LLC, College Station, Texas, USA).

RESULTS

THE STUDY INCLUDED 189 CASES WITH AMD AND 385 CONtrols without AMD. Enrollment characteristics of cases with AMD and controls without AMD are listed in Table 1. There were no significant differences between the 2 groups in enrollment characteristics. HIV viral load was borderline significantly higher in cases with AMD (mean ± SD = 3.2 ± 1.5 $\log_{10}$(copies/mL)) than in controls without AMD (mean ± SD = 2.9 ± 1.5 $\log_{10}$(copies/mL), $P = .07$). Plasma IL-6 levels were borderline significantly higher in cases with AMD (mean ± SD = 0.39 ± 0.42 $\log_{10}$(pg/mL)) than in controls without AMD (mean ± SD = 0.32 ± 0.36 $\log_{10}$(pg/mL); $P = .06$).

During follow-up there were 44 (23%) deaths among participants with AMD at enrollment and 62 (16%) deaths among controls without AMD at enrollment. Cases with AMD had a 48% higher mortality rate (Figure 1) than controls without AMD (HR 1.48; 95% CI 1.02, 2.15; $P = .04$). Among the plasma biomarkers analyzed (Table 2 and Figure 2), CRP (HR adjusted for HIV viral load and CD4+ T cells 1.46 per quartile; 95% CI 1.23, 1.74; $P < .001$), IL-6 (HR 1.45 per quartile; 95% CI 1.23, 1.71; $P < .001$), IP-10 (HR 1.33 per quartile; 95% CI 1.11, 1.59; $P = .002$), and sCD14 (HR 1.20 per quartile; 95% CI 1.02, 1.40; $P = .02$) were associated with an increased mortality, whereas the association of KT ratio (HR 1.14 per quartile; 95% CI 0.98, 1.33; $P = .10$) was of borderline significance, and sCD163 (HR 1.03 per quartile; 95% CI 0.88, 1.20; $P = .74$) and I-FABP (HR 0.97 per quartile; 95% CI 0.84, 1.12; $P = .67$) were not associated with an increased risk of mortality.

In the multiple Cox regression of mortality including demographic, virologic, immunologic, and biomarker risk factors (Table 3), the increased risk of mortality for cases with AMD vs controls without AMD was attenuated and no longer significant (adjusted HR 1.14; 95% CI 0.77, 1.70; $P = .51$). The associations of HIV viral load (adjusted

TABLE 2. Plasma Inflammatory Biomarkers and Mortality in Patients With AIDS

	Quartiles	Mortality					
		Mortality per Quartile			4th vs 1st Quartile		
Biomarker	25th, 50th, 75th Percentiles	HR[a]	95% CI	*P* Value	HR[a]	95% CI	*P* Value
CRP (mg/L)	0.8, 2.3, 5.6	1.46	1.23, 1.74	<.001	2.46	1.20, 4.16	.001
IL-6 (pg/mL)	1.3, 2.2, 3.7	1.45	1.23, 1.71	<.001	3.42	1.96, 5.95	<.001
IP-10 (pg/mL)	128, 238, 460	1.33	1.11, 1.59	.002	2.47	1.35, 4.51	.003
sCD14 (μg/L)	2.2, 2.7, 3.3	1.20	1.02, 1.40	.02	1.55	0.94, 2.54	.09
sCD163 (ng/L)	469, 685, 1006	1.03	0.88, 1.20	.74	0.99	0.61, 1.60	.97
KT ratio	25, 40, 61	1.14	0.98, 1.33	.10	1.35	0.81, 2.23	.25
I-FABP (pg/mL)	901, 1419, 2288	0.97	0.84, 1.12	.67	0.86	0.53, 1.37	.52

CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; I-FABP = intestinal fatty acid binding protein; IL-6 = interleukin-6; IP-10 = interferon-γ inducible protein-10; KT ratio = kynurenine tryptophan ratio; sCD14 = soluble CD14; sCD163 = soluble CD163.
[a]Adjusted for HIV load and CD4+ T cell count.

HR 1.28 $\log_{10}$(copies/mL); 95% CI 1.11, 1.47; $P = .001$), CD4+ T cells (HR 0.87; 95% CI 0.76, 0.99; $P = .04$), CRP (HR 1.36 per SD $\log_{10}$(mg/L); 95% CI 1.08, 1.71; $P = .009$), IL-6 (HR 1.45 per SD $\log_{10}$(pg/mL); 95% CI 1.11, 1.90; $P = .006$), and IP-10 (HR 1.41 per SD $\log_{10}$(pg/mL); 95% CI 1.08, 1.84; $P = .01$) all remained significantly associated with mortality. Therefore, we performed stepwise modeling of the association of AMD with mortality using Cox regression (Table 4). As can be seen from Table 4, the addition of HIV viral load has little effect on the association of AMD with mortality, and the addition of CD4+ T cells had a modest effect, but it was the addition of the inflammatory biomarkers to the model that substantially reduced the risk of AMD for mortality (adjusted HR 1.08; 95% CI 0.73, 1.59; $P = .70$).

Forty-four cases with AMD and 114 controls without AMD had suppressed HIV viral load at baseline (<2.6 $\log_{10}$(copies/mL), the lower limit of detection for assays used at the initiation of LSOCA). Restricting the analysis to participants with suppressed HIV replication gave qualitatively similar results as the entire analysis (Supplemental Table 1; Supplemental Material available at www.ajo.com). Compared to the analysis using the entire data set, there were no significant interactions ($P < .01$) between other variables and suppression of HIV viral load as risk factors. A sensitivity analysis using multiple imputation for missing data (HIV load, CD4+ T cells, CRP, IL-6, IP-10) also gave qualitatively similar results to the primary Cox regression model (Supplemental Table 2; Supplemental Material available at www.ajo.com). Correlations among the inflammatory biomarkers (Supplemental Table 3; Supplemental Material available at www.ajo.com) were minimally to moderately positive (Spearman correlation coefficients 0.07 to 0.53), as were the correlations with HIV viral load (Spearman correlation coefficients -0.01 to 0.37). Inflammatory biomarkers were minimally to modestly negatively correlated with CD4+ T cells (Spearman correlation coefficients -0.04 to -.036), and, as expected, HIV viral load and CD4+ T cells were negatively correlated (Spearman correlation coefficient -0.47).

Causes of death were grouped as AIDS-related, cardiopulmonary, other non-AIDS-related, and unknown. Although there was a greater proportion of deaths attributable to cardiopulmonary disease among cases with AMD (25%) than among controls without AMD (16%), the overall distribution of cause of death did not differ between the 2 groups ($P = .455$, Supplemental Table 4; Supplemental Material available at www.ajo.com).

DISCUSSION

OUR DATA DEMONSTRATE AN INCREASED MORTALITY among patients with AIDS and AMD compared to those with AIDS but no AMD. The hazard ratio for the increased mortality with AMD is not attenuated and attenuated slightly by the inclusion of HIV load and CD4+ T cells in the model, respectively, but substantially by the inclusion of the plasma inflammatory biomarkers, CRP, IL-6, and IP-10. Although the baseline cross-sectional associations between inflammatory biomarkers and AMD were limited, the development of AMD is a multiyear process, suggesting that a history of sustained inflammation may be more important than the current level of inflammation, as evidenced by systemic inflammation's association with incident AMD in HIV-uninfected persons. Our previous work has demonstrated an increased incidence of intermediate-stage AMD among participants in LSOCA vs a sex- and race-matched HIV-uninfected cohort.[14] In HIV-uninfected populations,

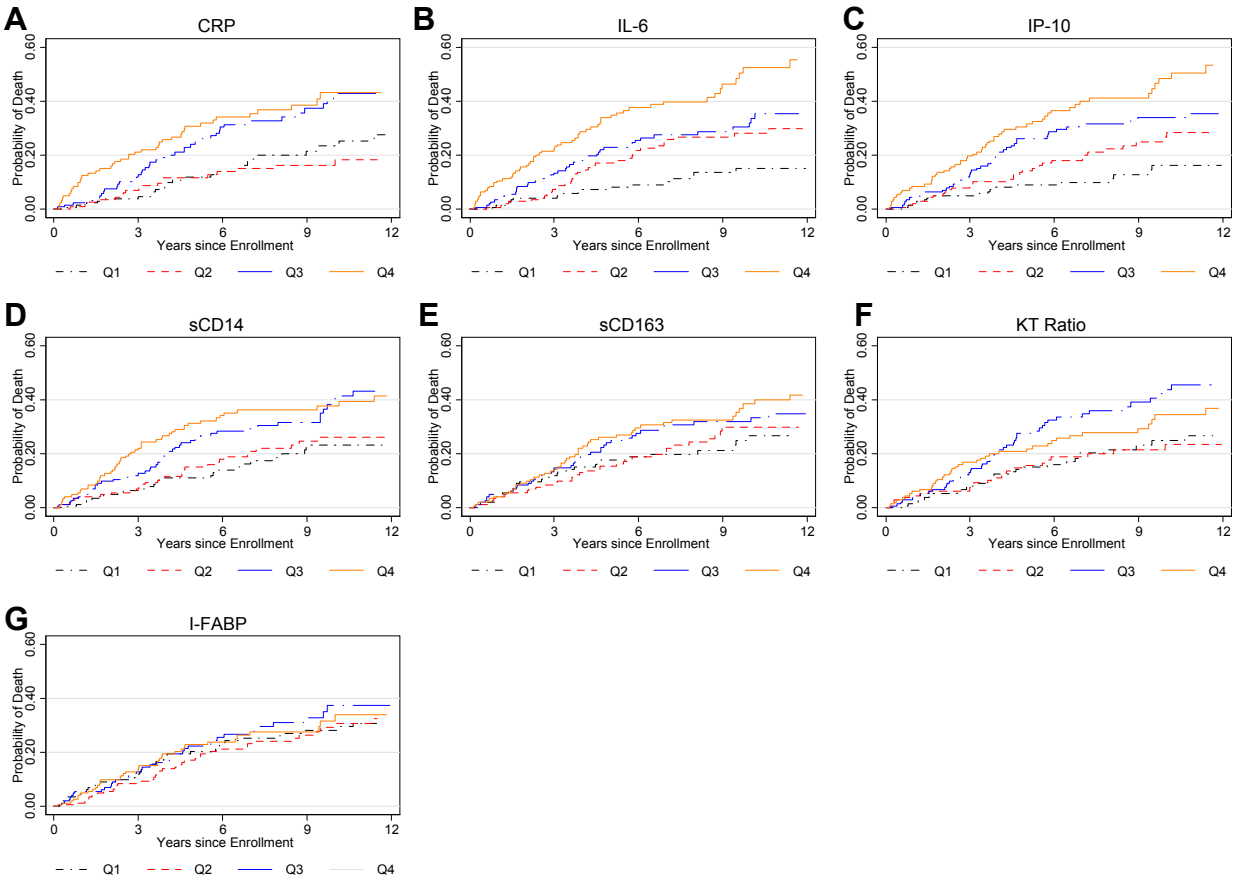

FIGURE 2. Kaplan-Meier curves of mortality per biomarker quartile at enrollment in patients with AIDS: (A) C-reactive protein (CRP); (B) interleukin-6 (IL-6); (C) interferon-γ inducible protein-10 (IP-10); (D) soluble CD14 (sCD14); (E) soluble CD163 (sCD163); (F) kynurenine tryptophan ratio (KT ratio); (G) intestinal fatty acid binding protein (I-FABP).

late-stage AMD, particularly neovascular AMD, is associated with an increased risk of all-cause mortality and cardiovascular mortality, whereas early-stage AMD is not. In our study, intermediate-stage AMD was associated with an increased risk of mortality.[23–25] Because the effects of immunosenescence and inflammation may be more pronounced in HIV-infected populations, it may be easier to see their consequences in HIV-infected populations than in HIV-uninfected populations. Although a greater proportion of deaths were attributable to cardiopulmonary disease in LSOCA participants with AMD, the overall distribution of causes of death were not significantly different between cases with AMD and controls without AMD.

The attenuation of the AMD mortality association after adjustment for inflammatory biomarkers suggests that systemic inflammation may be causally linked to both AMD and mortality risks. Persistent inflammation and immune activation are commonly observed in ART-treated, immunorestored HIV-infected persons and in HIV-uninfected older persons, suggesting that similar pathways may contribute to AMD risk in HIV infection and in aging.[9,10,20–22,26–28]

The inflammatory biomarkers chosen for this study were chosen because their association with increased mortality is seen in both HIV-infected persons and HIV-uninfected older persons.[20,29,30] C-reactive protein is an acute-phase reactant, which is elevated in a variety of inflammatory conditions, including infection and autoimmune diseases. IL-6 is a proinflammatory cytokine, secreted by several innate immune cells and B cells, and is a key inducer of CRP synthesis in the liver. The fact that both IL-6 and CRP predicted mortality in this study and attenuated the association between AMD and mortality strengthens the inferences from our study, since these biomarkers are mechanistically linked in vivo. IP-10 is a marker of type I and type II interferon responses often induced by viral or bacterial infection, consistent with the possibility that HIV or other co-pathogens might contribute to this inflammatory state. The attenuation of the AMD mortality risk by these markers of systemic inflammation may provide clues to the

TABLE 3. Multiple Cox Regression of Mortality in Patients With AIDS

Risk Factor	Adjusted HR	95% CI	*P* Value
AMD status (AMD vs no AMD)	1.14	0.77, 1.70	.51
Demographics			
Age (/decade)	1.01	0.82, 1.25	.92
Sex (female vs male)	1.46	0.92, 2.32	.10
Race (white vs nonwhite)	1.40	0.92, 2.14	.12
AIDS history			
AIDS-defining illness (CD4+ lymphopenia vs opportunistic infection)	1.16	0.76, 1.77	.48
On ART at enrollment (yes vs no)	1.24	0.72, 2.12	.44
Virology/immunology			
HIV load (/$\log_{10}$(copies/mL))	1.28	1.11, 1.47	.001
CD4+ cells (/100 cells/μL)	0.87	0.76, 0.99	.04
Biomarkers			
CRP (/SD $\log_{10}$(mg/L))	1.36	1.08, 1.71	.009
IL-6 (/SD $\log_{10}$(pg/mL))	1.45	1.11, 1.90	.006
IP-10 (/SD $\log_{10}$(pg/mL))	1.41	1.08, 1.84	.01
sCD14 (/SD $\log_{10}$(μg/mL))	1.04	0.83, 1.32	.72
sCD163 (/SD $\log_{10}$(ng/mL))	0.86	0.68, 1.09	.22
KT ratio (/SD $\log_{10}$(ratio))	1.16	0.94, 1.42	.17
I-FABP (/SD $\log_{10}$(pg/mL))	0.93	0.77, 1.13	.46

CRP = C-reactive protein; HR = hazard ratio; I-FABP = intestinal fatty acid binding protein; IL-6 = interleukin-6; IP-10 = interferon-γ inducible protein-10; KT ratio = kynurenine tryptophan ratio; sCD14 = soluble CD14; sCD163 = soluble CD163; SD = standard deviation.

TABLE 4. Variable Selection for Cox Regression Models of Mortality on Age-related Macular Degeneration in Patients With AIDS

Models[a]	AMD HR[b]	95% CI	*P* Value
AMD	1.48	1.02, 2.15	.04
AMD + IP-10	1.27	0.87, 1.85	.21
AMD + IP-10 + HIV load	1.29	0.89, 1.88	.18
AMD + IP-10 + HIV load + CRP	1.16	0.79, 1.70	.45
AMD + IP-10 + HIV load + CRP + IL-6	1.13	0.77, 1.66	.54
AMD + IP-10 + HIV load + CRP + IL-6 + $CD4^+$ T cells	1.08	0.73, 1.59	.70

AMD = age-related macular degeneration; CI = confidence interval; CRP = C-reactive protein; HR = hazard ratio; IL-6 = interleukin-6; IP-10 = interferon-γ inducible protein-10.

[a]Intermediate steps of Cox regression model using forward selection with P value for entry = .05, forcing AMD into the model and ending with final selected model.

[b]AMD HR = AMD (AMD vs no AMD) hazard ratio for mortality adjusted for factors in the model.

common immunologic mechanisms that drive AMD and mortality in HIV infection and perhaps aging.

Increased levels of sCD14 and sCD163 are markers of macrophage/monocyte activation. Elevation of I-FABP levels is associated with gut epithelial cell death and/or turnover linked to microbial translocation in HIV-infected persons. Elevations of the KT ratio are a measure of IDO upregulation,[21] which results in T cell proliferative defects, loss of gut barrier integrity, and neurotoxicity.[20–22] Although sCD14, sCD163, I-FABP, and KT ratio were not associated with mortality in this study, they have been strongly linked to mortality in other studies, particularly among ART-treated HIV-infected persons with suppressed HIV viral replication,[20–22,26–32] including a previous study of LSOCA participants with suppressed HIV replication.[20] In contrast to these previous studies, a minority of our patients had suppressed HIV replication (and this subset is relatively underpowered), which may account for some of these differences.

Caution should be exercised in interpreting these data. LSOCA enrolled patients with AIDS and not with earlier stages of HIV infection, so the generalizability to the entire HIV epidemic is unknown. We did not evaluate HIV-uninfected persons, so the generalizability of our results to the HIV-uninfected population is inferential, based on similar immune phenomena being present in ART-treated, immunorestored HIV-infected persons and in HIV-uninfected older persons.[9,10] Nevertheless, the association of elevations of CRP with incident AMD[15] and of prevalent AMD with other proinflammatory cytokines[17] in HIV-uninfected persons suggests that these mechanisms may be operative in the HIV-uninfected. Furthermore, the persistent inflammatory state in HIV-infected persons and the increased prevalence of AMD in patients with AIDS suggest that these associations may be easier to detect in populations such as LSOCA.[20] Nevertheless, given the prolonged time frame (years to decades) to develop AMD, cross-sectional associations with prevalent AMD may be less relevant than sustained systemic inflammation is for incident AMD.[15]

In conclusion, our data demonstrate an increased mortality among patients with AIDS and AMD, compared to patients with AIDS but without AMD, and suggest that the observed increased mortality may be the result of systemic inflammation, a feature of immunosenescence, seen in both ART-treated, immunorestored HIV-infected persons and HIV-uninfected older persons.[9,10,23,25,27,29,30,33]

FUNDING/SUPPORT: SUPPORTED BY GRANT EY025093 FROM THE NATIONAL EYE INSTITUTE, THE NATIONAL INSTITUTES OF Health, Bethesda, Maryland, USA. Financial Disclosures: The following authors have no financial disclosures: Douglas A. Jabs, Mark L. Van Natta, Garrett Trang, Norman G. Jones, Jeffrey M. Milush, Ryan Cheu, Nichole R. Klatt, Ronald P. Danis, and Peter W. Hunt. All authors attest that they meet the current ICMJE criteria for authorship.

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