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# Association of Intermediate-Stage Age-Related Macular Degeneration with Plasma Inflammatory Biomarkers in Persons with AIDS

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***Purpose:*** To evaluate associations of plasma levels of inflammatory biomarkers with age-related macular degeneration (AMD) and cataract in persons with AIDS.

***Design:*** Nested case−control study (analysis 1) and nested cohort study (analysis 2).

***Participants:*** Analysis 1: persons with AIDS and incident intermediate-stage AMD (n = 26) and controls without AMD matched for age, race/ethnicity, and gender (n = 49) from The Longitudinal Study of Ocular Complications of AIDS. Analysis 2: 475 persons from LSOCA with baseline plasma biomarker levels followed prospectively for cataract.

***Methods:*** In both analyses, cryopreserved plasma specimens obtained at baseline were assayed for monocyte chemoattractant protein (MCP)-1 (CC motif chemokine ligand [CCL] 2), macrophage inflammatory protein (MIP)-1β (CCL4), soluble tumor necrosis factor receptor (sTNFR) 2, interleukin (IL)-18, and fractalkine (CX3 motif chemokine ligand 1 [CX3CL1]).

***Main Outcome Measures:*** Analysis 1: mean difference (cases − controls) in plasma biomarker levels. Analysis 2: incident cataract.

***Results:*** After adjusting for plasma human immunodeficiency virus RNA level, CD4+ T-cell count, and smoking, elevated baseline plasma levels of sTNFR2 and IL-18 (mean differences [cases − controls] 0.11 $\log_{10}$[pg/mL]; 95% confidence interval [CI], 0.01−0.20; $P = 0.024$ and 0.13 $\log_{10}$[pg/mL]; 95% CI, 0.01−0.24; $P = 0.037$, respectively) each were associated with incident AMD. In a competing risk (with mortality) analysis, elevated baseline standardized $\log_{10}$ plasma levels of MCP-1, sTNFR2, IL-18, and fractalkine each were associated with a decreased cataract risk.

***Conclusions:*** When combined with previous data suggesting that AMD is associated with elevated plasma levels of C-reactive protein, soluble CD14, and possibly IL-6, the association of elevated plasma levels of sTNFR2 and IL-18 with incident AMD, but not with incident cataract, suggests that innate immune system activation, and possibly NLRP3 inflammasome activation, may play a role in the pathogenesis of AMD in this population.

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Modern antiretroviral treatment (ART) of human immunodeficiency virus (HIV)-infected persons results in (1) suppression of HIV replication; (2) reduction of the amount of HIV RNA circulating in the blood (HIV viral load); (3) an increase in CD4+ T cells (immune recovery); (4) decreased incidence of opportunistic infections; and (5) a substantially improved lifespan compared with HIV-infected persons in the pre-ART era.[1−5] Nevertheless, ART-treated, immune-restored, HIV-infected persons have a shortened lifespan when compared with comparably aged HIV-uninfected persons,[6,7] and they have an increase in age-related diseases such as cardiovascular disease, metabolic disorders (e.g., diabetes and osteoporosis), neurocognitive decline, and age-related cancers not associated with AIDS.[8−11] Hence, they exhibit a phenotype characterized by accentuated aging.[10,11] Human immunodeficiency virus−infected persons, particularly those that initiate ART at more advanced disease stages, exhibit a chronic inflammatory state, which predicts many of these age-related complications.[10−13]

Compared with HIV-uninfected persons, people with AIDS have an approximately 4-fold increased age- and sex-adjusted prevalence of intermediate-stage age-related macular degeneration (AMD),[14] an approximately 1.75-fold increased race/ethnicity- and sex-adjusted incidence of intermediate-stage AMD,[15] and an increased prevalence of cataract and increased incidence of cataract surgery compared with similarly aged HIV-uninfected persons.[16] We previously demonstrated that elevated plasma levels of C-reactive protein (CRP), soluble CD14 (sCD14), and possibly interleukin (IL)-6 are associated with incident



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intermediate-stage AMD, but not with incident cataract.[17] In this study, we evaluated the relationships between incident AMD in persons with AIDS and plasma biomarkers IL-18 and soluble tumor necrosis factor receptor (sTNFR) 2, as well as with the following chemokines: monocyte chemoattractant protein-1 (MCP-1), also known as CC chemokine ligand (CCL) 2; macrophage inflammatory protein-1β (MIP-1β), also known as CCL4; and fractalkine, also known as CX3C chemokine ligand (CX3CL). In a second analysis, we investigated the relationship and between these plasma biomarkers and incident cataract in persons with AIDS.

## Methods

The Longitudinal Study of Ocular Complications of AIDS (LSOCA) was a prospective cohort study of 2392 participants with AIDS conducted in the era of modern ART.[18] Enrollment occurred from 1998 to 2011, and follow-up continued through 2013. Of the 2392 participants, 535 had an ocular opportunistic infection (damage from which prevents evaluation of AMD) at enrollment, and 32 did not have baseline photographs. Hence, there were 1825 participants with baseline photographs available for evaluation of prevalent AMD. There were 730 participants without AMD at enrollment and with 5- and/or 10-year follow-up retinal photographs available for evaluation of incident AMD.[14,15] Participants were evaluated for the presence of intermediate-stage AMD (Age-Related Eye Disease Study [AREDS] stage 3 or greater) from photographs taken at enrollment (baseline) and at 5- and 10-year follow-up visits by graders at the Wisconsin Reading Center, masked to clinical data, as previously described.[14,15,19,20] The primary outcome was intermediate-stage AMD, determined using the AREDS classification system. Plasma specimens were obtained at enrollment (baseline) and cryopreserved. Cryopreserved specimens were thawed and assayed in duplicate on an MSD QuickPlex SQ 120 for biomarkers of inflammation using commercially available, electro-chemiluminescence-based immunoassay kits in the Hunt Laboratories at the University of California, San Francisco, School of Medicine.[17,21] Inflammatory biomarkers and chemokines known to be elevated in the plasma of HIV-infected persons and to predict morbidity and mortality in prior studies were assessed, including MCP-1, MIP-1β, sTNFR2, cleaved IL-18, and fractalkine (all Meso Scale Diagnostics).[22–24] Participants enrolled in LSOCA without an ocular opportunistic infection were seen every 6 months at semiannual follow-up visits until the common study close-out. At baseline and at each 6-month follow-up visit, participants underwent an ophthalmic examination, including detailed evaluation of the lens at the slit lamp for cataract, graded using standard semiquantitative grading systems.[16–19,25] For these analyses, cataract was defined as $\geq$ 1+ nuclear sclerosis or $\geq$ 1+ cortical spoking or $\geq$ 1+ posterior subcapsular cataract, or new onset pseudophakia or aphakia in a participant without cataracts at enrollment. Periodic surveys of each clinical center were conducted to identify deaths unreported to the coordinating center and deaths among participants lost to follow-up.[17,26]

The Longitudinal Study of Ocular Complications of AIDS adhered to the principles of the Declaration of Helsinki and was conducted with institutional board approval at each clinical and resource center. All participants gave written informed consent.

### Evaluation of Baseline Characteristics of the Cohorts

Baseline characteristics of participants with and without incident AMD were compared using a Wilcoxon rank sum test for continuous variables and a Pearson chi-square test or Fisher exact test (when an expected cell was $< 5$) for categorical variables. Baseline characteristics of participants in the incident cataract cohort were compared among 3 groups: (1) those developing incident cataract, (2) those who died during follow-up, and (3) those who neither developed cataract nor died. *P* values were calculated using a Kruskal–Wallis test for continuous variables and a Pearson chi-square test for categorical variables.

### Evaluation of Baseline Plasma Inflammatory and Incident AMD

Participants without AMD at enrollment but with incident AMD during follow-up (identified by the Reading Center on evaluation of either 5- or 10-year follow-up photographs) and at least 1 matched control (who had not developed AMD at the time a case developed AMD, individually matched on age [by decade of age], sex, and race/ethnicity) from LSOCA were selected for a case–control study of inflammatory biomarkers and incident AMD. Plasma inflammatory biomarker values were $\log_{10}$ transformed to achieve approximate normality. Mean differences in $\log_{10}$ plasma biomarker levels at baseline were compared between participants with incident AMD and their matched controls. These mean differences were adjusted for smoking status, CD4+ T-cell count, and $\log_{10}$ plasma HIV RNA level.[17]

### Evaluation of Baseline Inflammatory Biomarkers and Incident Cataract and Mortality

In an effort to evaluate if the relationship between inflammatory biomarkers and incident AMD was related specifically to AMD or to aging in general, we analyzed the relationship between the baseline inflammatory biomarkers and both incident cataract and mortality. As part of a prior evaluation of prevalent AMD and systemic inflammation, plasma inflammatory biomarker assays were performed on a nonoverlapping subset of 475 participants in LSOCA (166 with prevalent AMD at enrollment and 309 controls).[17,26] This sample was leveraged to evaluate predictors of incident cataract and mortality. Plasma inflammatory biomarker values were $\log_{10}$ transformed to achieve approximate normality and standardized by subtracting the mean $\log_{10}$(biomarker) and dividing by the standard deviation $\log_{10}$(biomarker). To account for mortality competing with an incident cataract event in the advanced population of HIV-infected persons, subdistribution hazard ratios (subHRs)[27,28] for cataract and mortality per standard deviation increase of each $\log_{10}$ transformed biomarker were used as the measure of association. All subHRs were adjusted for age, sex, race/ethnicity, and enrollment AMD status, and 95% confidence intervals [CIs] were used as a measure of precision. The data analyses were conducted using both SAS (SAS version 9.4, SAS Institute Inc) and Stata software (StataCorp. 2017. Stata Statistical Software: Release 15. StataCorp LLC).

## Results

### Plasma Inflammatory Biomarkers and Incident AMD

Of the 26 cases with incident AMD and available plasma specimens, there were 23 with 2 matched controls and 3 with 1 matched control. Characteristics of the 26 cases and 49 controls are shown in Table 1. Cases and controls were reasonably comparable, except for the following: suggestion of greater smoking use in cases (46% vs.

Table 1. Enrollment Characteristics of Study Population of Persons with AIDS with and without Incident Intermediate-Stage AMD

| Enrollment Characteristics | Incident AMD* Cases | No AMD Controls | *P* Value |
|---|---|---|---|
| Number of participants | 26 | 49 | |
| Matching variables | | | |
| Age (yrs), median (IQR) | 44 (37–48) | 44 (39–47) | 0.77 |
| Sex (%) | | | 0.75 |
| Men | 81 | 84 | |
| Women | 19 | 16 | |
| Race (%) | | | 0.87 |
| White | 31 | 33 | |
| Non-White | 69 | 67 | |
| Current smoker (%) | 46 | 30 | 0.13 |
| Comorbidities (%) | | | |
| Hypertension | 19 | 20 | 0.90 |
| Hyperlipidemia | 27 | 24 | 0.82 |
| Diabetes | 12 | 4 | 0.22 |
| Hepatitis C | 12 | 6 | 0.41 |
| HIV transmission risk factor (%) | | | 0.78 |
| Men having sex with men only | 62 | 53 | |
| Injection drug use only | 4 | 8 | |
| Men having sex with men and injection drug use | 4 | 2 | |
| Heterosexual/other | 31 | 37 | |
| Time since AIDS diagnosis (yrs), median (IQR) | 1.7 (0.5–6.6) | 4.3 (2.8–6.6) | 0.08 |
| AIDS-defining illness (%) | | | 0.38 |
| CD4+ T cell lymphopenia† | 62 | 73 | |
| AIDS-defining opportunistic infection‡ or cancer | 38 | 27 | |
| HIV treatment (%) | | | |
| Receiving ART at enrollment | 88 | 98 | 0.12 |
| Receiving NRTI‖ therapy at enrollment | 88 | 98 | 0.12 |
| Received ART at or before enrollment | 100 | 100 | 0.99 |
| Received ART during follow-up | 100 | 100 | 0.99 |
| Received NRTI therapy during follow-up | 100 | 100 | 0.99 |
| Virology/immunology | | | |
| Enrollment HIV load, $\log_{10}$(copies/mL), median (IQR) | 2.3 (1.9–3.7) | 2.2 (1.4–3.7) | 0.36 |
| Enrollment CD4+ T cells, cells/μL, median (IQR), | 143 (81–300) | 211 (154–372) | 0.10 |
| Nadir CD4+ T cells, cells/μL, median (IQR), | 22 (7–68) | 52 (9–125) | 0.15 |

AMD = age-related macular degeneration; ART = antiretroviral therapy; HIV = human immunodeficiency virus; IQR = interquartile range; NRTI = nucleoside reverse transcriptase inhibitor.
*AMD defined as intermediate-stage AMD.
†CD4+ T cell lymphopenia = CD4+ T cells < 200 cells/μL.
‡AIDS-defining illnesses include Pneumocystis pneumonia, Kaposi sarcoma, cerebral toxoplasmosis, cytomegalovirus gastroenteritis, systemic histoplasmosis, and cryptococcal meningitis.

30%), suggestion of lower median CD4+ T cells at enrollment among cases (149 cells/μL vs. 211 cells/μL), and a suggestion of a lower nadir CD4+ T-cell count before enrollment among cases (22 cells/μL vs. 52 cells/μL). Although there was a slightly lower use of nucleoside reverse transcriptase inhibitors (NRTIs) use at baseline in cases (88% vs. 98%), there was no difference in ART use (100% in cases and controls) or NRTI use (100% in cases and controls) during follow-up.

The results of the paired comparisons of baseline $\log_{10}$ plasma inflammatory biomarkers between cases with incident AMD and controls without incident AMD are shown in Table 2. Cases with incident AMD has significantly higher baseline levels of sTNFR2 (adjusted mean difference [cases − controls] = 0.11 $\log_{10}$(pg/mL); 95% confidence interval [CI], 0.01–0.20; $P = 0.024$) and IL-18 (adjusted mean difference = [cases − controls] = 0.13 $\log_{10}$(pg/mL); 95% CI, 0.01–0.24; $P = 0.037$). Incident AMD was not associated with baseline plasma levels of MCP-1, MIP-β, or fractalkine.

## Plasma Inflammatory Biomarkers and Incident Cataract and Mortality

Enrollment characteristics of the 475 participants in the cataract study (166 with prevalent AMD at enrollment and 309 without AMD at enrollment) are shown in Table 3. In general, the subpopulation used for this analysis appeared to have reasonably similar characteristics to the subpopulation used for the AMD analysis. Of this population, 182 participants (38%) developed incident cataract, 112 participants (24%) died, and 181 (38%) were free of both events. The median age of the participants who developed cataract was greater than that of those who did not (Table 3), and there appeared to be a greater proportion of participants with hypertension and

Table 2. Difference in Enrollment Plasma Biomarker Levels between Cases with Incident Intermediate-stage Age-Related Macular Degeneration and Matched Controls* in Persons with AIDS

| | Mean $Log_{10}$(Plasma Biomarker Cases) − $Log_{10}$(Plasma Biomarker Controls) | | |
|---|---|---|---|
| **Biomarker** | *Adjusted*† *Mean Difference* | *95% Confidence Interval* | *P Value* |
| MCP-1 | −0.07 | −0.16 to 0.01 | 0.101 |
| MIP-1β | 0.06 | −0.04 to 0.15 | 0.246 |
| sTNFR2 | 0.11 | 0.01 to 0.20 | 0.024 |
| IL-18 | 0.13 | 0.01 to 0.24 | 0.037 |
| Fractalkine | 0.03 | −0.03 to 0.11 | 0.379 |

Fractalkine = CX3C motif chemokine ligand 1(CX3CL1); IL-18 = interleukin-18; MCP-1 = monocyte chemoattractant protein -1 (chemokine CC motif ligand [CCL] 2); MIP-1β = macrophage inflammatory protein -1β (CCL4); sTNFR2 = soluble tumor necrosis factor receptor 2.
*Cases with incident intermediate-stage age-related macular degeneration (n = 26) and controls (n = 49) individually matched for age (within decade of age), race/ethnicity, and sex.
†Adjusted for enrollment plasma human immunodeficiency virus RNA level, CD4+ T-cell count, and smoking status.

hyperlipidema among participants developing cataract compared with those who did not develop cataract and did not die (Table 3). Participants who died without developing cataract appeared to be less likely to have been ART-treated at or before enrollment than the other 2 groups, but nearly all participants received ART during

Table 3. Enrollment Characteristics of the Population of Persons with AIDS Evaluated for Incident Cataract and Mortality

| Enrollment Characteristic | Entire Cohort | Incident Cataract | Alive without Cataract | Died without Cataract | *P* Value |
|---|---|---|---|---|---|
| Number of participants | 475 | 182 | 181 | 112 | |
| Age (yrs), median (IQR) | 47 (41–52) | 50 (44–54) | 44 (40–51) | 45 (40–51) | < 0.0001 |
| Sex (%) | | | | | 0.49 |
| Men | 76 | 77 | 76 | 71 | |
| Women | 24 | 23 | 24 | 29 | |
| Race (%) | | | | | 0.78 |
| White | 40 | 42 | 39 | 40 | |
| Non-White | 60 | 58 | 61 | 60 | |
| Current smoker (%) | 27 | 29 | 29 | 22 | 0.39 |
| Comorbidities (%) | | | | | |
| Hypertension | 24 | 30 | 16 | 28 | 0.01 |
| Hyperlipidemia | 23 | 34 | 18 | 15 | < 0.0001 |
| Diabetes | 9 | 9 | 7 | 12 | 0.31 |
| Hepatitis C | 12 | 15 | 12 | 4 | 0.02 |
| Time since AIDS diagnosis (yrs), median (IQR) | 4.8 (1.8–7.5) | 5.4 (2.0–8.9) | 4.3 (1.5–7.1) | 4.3 (1.6–7.4) | 0.02 |
| HIV transmission risk factor (%) | | | | | 0.72 |
| Men having sex with men only | 43 | 46 | 42 | 41 | |
| Injection drug use only | 10 | 7 | 12 | 13 | |
| Men having sex with men and injection drug use | 4 | 5 | 4 | 4 | |
| Heterosexual/other | 42 | 42 | 42 | 42 | |
| AIDS-defining illness (%) | | | | | 0.61 |
| CD4+ T cell lymphopenia* | 67 | 69 | 65 | 65 | |
| AIDS-defining opportunistic infection† or cancer | 33 | 31 | 35 | 35 | |
| HIV treatment (%) | | | | | |
| Receiving antiretroviral therapy at enrollment | 84 | 90 | 84 | 80 | 0.05 |
| Receiving NRTI§ therapy at enrollment | 84 | 89 | 84 | 80 | 0.05 |
| Antiretroviral therapy at or before enrollment | 94 | 98 | 92 | 90 | 0.02 |
| Received antiretroviral therapy during follow-up | 99 | 100 | 99 | 98 | 0.24 |
| Received NRTI therapy during follow-up | 99 | 99 | 99 | 97 | 0.16 |
| Virology/immunology | | | | | |
| Enrollment HIV load, median (IQR), $log_{10}$(copies/mL) | 2.61 (1.59–4.21) | 2.30 (1.41–3.29) | 2.30 (1.41–4.31) | 3.92 (2.61–5.01) | < 0.0001 |
| Enrollment CD4+ T cells, median (IQR), cells/μL | 211 (91–378) | 261 (142–417) | 221 (96–388) | 102 (23–238) | < 0.0001 |
| Nadir CD4+ T cells, median (IQR), cells/μL | 44 (13–111) | 49 (19–113) | 52 (14–112) | 23 (9–100) | 0.06 |

IQR = interquartile range; HIV = human immunodeficiency virus; NRTI = nucleoside reverse transcriptase inhibitor.
*CD4+ T cell lymphopenia, defined as CD4+ T cells < 200 cells/μL.
†AIDS-defining illnesses include Pneumocystis pneumonia, Kaposi sarcoma, cerebral toxoplasmosis, cytomegalovirus gastroenteritis, histoplasmosis, and cryptococcal meningitis.

follow-up. Participants who died during follow-up had significantly higher baseline plasma levels of HIV RNA (HIV load) and lower CD4+ T cells compared with the other 2 groups (Table 3). Because of the known association of systemic inflammation with mortality in persons with HIV infection and the high mortality rate in our population,[17,21,26] we analyzed the subdistributions of hazards of cataract and mortality simultaneously in an effort to account for the competing risk of mortality.[27,28] The relationships between enrollment plasma inflammatory biomarker levels and incident cataract and between enrollment plasma inflammatory biomarker levels and mortality are shown in Table 4. Each standard deviation increase in $\log_{10}$ baseline levels of MCP-1 (subHR = 0.73; 95% CI, 0.62−0.86; $P < 0.001$), sTNFR2 (subHR = 0.76; 95% CI, 0.64−0.90; $P = 0.002$), IL-18 (subHR = 0.75; 95% CI, 0.64−0.88; $P < 0.001$), and fractalkine (subHR = 0.78; 95% CI, 0.67−0.92; $P = 0.002$) was associated with a decreased risk of cataract. Elevated baseline levels of all of the plasma biomarkers studied were associated with a significantly increased risk of mortality. The subHRs per standard deviation increase in $\log_{10}$(plasma biomarker concentration) were as follows: MCP-1 = 1.77 (95% CI, 1.42−2.22; $P < 0.001$), MIP-1β = 1.20 (95% CI, 1.02−1.41; $P = 0.030$), sTNFR2 = 1.57 (95% CI, 1.33−1.85; $P < 0.001$), IL-18 = 1.62 (95% CI, 1.35−1.094; $P < 0.001$), and fractalkine = 1.69 (95% CI, 1.39−2.05; $P < 0.001$).

To further evaluate the association of elevated plasma levels of inflammatory biomarkers with a decreased risk of cataract and the impact of missed visits on this association, we performed a sensitivity analysis in which cataracts were imputed to have occurred in those patients without a visit with an eye examination within 1 year before death or censoring. This sensitivity analysis attenuated the magnitude of the associations of the plasma inflammatory biomarkers with a reduced risk of cataract somewhat but did not alter the conclusion that elevated levels of plasma inflammatory biomarkers were associated with a decreased risk of cataract and an increased risk of mortality (data not shown).

We also evaluated the use of oral corticosteroids on the relationship between plasma inflammatory biomarkers and cataract among the 443 participants with corticosteroid use data. Of the 175 participants with incident cataract, 18 (10%) reported corticosteroid use, and of the 268 participants without cataract, 24 (9%) reported corticosteroid use. Adding corticosteroid use to the adjusted model made a minimal difference in the subHRs and did not alter any of the conclusions about the relationships among inflammatory biomarkers, cataract, and mortality (data not shown).

## Discussion

Previous data from our group have shown that persons with AIDS have an increased age- and sex-adjusted prevalence and an increased sex- and race/ethnicity-adjusted incidence of intermediate-stage AMD[14,15] and that incident AMD is associated with increased baseline plasma levels of CRP, sCD14, and possibly IL-6 (Table 5).[17] In these previous studies, AMD was associated with age and smoking but not with sex, race/ethnicity, time since AIDS diagnosis, hepatitis C infection, nadir or enrollment CD4+ T cells, maximum or enrollment HIV viral load, ART use, and use of any class of ART, including NRTIs.[14,15] In this study, we evaluated the relationship between several additional baseline plasma biomarkers of systemic inflammation and incident intermediate-stage AMD, and our data indicate that elevated baseline plasma levels of sTNFR2 and IL-18 were associated with incident intermediate-stage AMD in persons with AIDS. Because the association of elevated plasma inflammatory biomarkers with incident AMD could be due to an association with AMD or with aging in general, we also evaluated the relationship of these biomarkers to another age-related eye disease, namely incident cataract. If the association of these biomarkers with AMD was due to aging in general, one might expect them to be associated with both incident AMD and incident cataract, but if these biomarkers were associated specifically with AMD and not just the aging eye in general, then one might expect no association of these biomarkers with incident cataract. Our data demonstrate that incident cataract was not associated with elevated plasma levels of MCP-1, MIP-1β, sTNFR2, IL-18, or fractalkine, and suggest that elevated plasma levels of sTNFR2 and IL-18 are associated specifically with incident AMD and not just with aging in general.

The surprising result was that systemic inflammation, as evidenced by several plasma inflammatory biomarkers, was not just unassociated with incident cataract but was associated with a decreased risk of cataract, despite accounting for the association between systemic inflammation and mortality. This negative association remains unexplained but striking, all the more so as intraocular inflammation (i.e., active uveitis) is associated with incident cataract.[29] In this study, elevated levels of the plasma biomarkers MCP-1, sTNFR2, IL-18, and fractalkine and in our previous study (Table 6), elevated levels of the plasma biomarkers IL-6, interferon inducible protein-10 (IP-10), sCD14, and sCD163 all were associated with a decreased risk of cataract even after accounting for the competing risk of mortality.[17] In the Physician's Health Study, there was an association between elevated plasma CRP levels and incident cataract but only at levels of CRP above the 97.5% percentile for normal persons.[30] Conversely, in the Singapore Malay Study, there was no association between plasma CRP and prevalent cataract.[31] In our work, after adjustment for age, race/ethnicity, sex, and AMD status, CRP levels were not associated with the risk of incident cataract, whereas elevated levels of multiple other inflammatory biomarkers, including IL-6, IP-10, sCD14, sCD163, IL-18, MCP-1, sTNFR2, and fractalkine, all were associated with a decreased risk of incident cataract.[17] These data suggest that CRP as a single biomarker may be inadequate to evaluate the relationship between systemic inflammation and cataract risk.

The population of participants with AIDS and AMD differs from that of HIV-uninfected persons with AMD in that patients with AIDS and AMD are younger and have a greater proportion of non-White persons than HIV-uninfected persons with AMD.[14,15] The younger age of

Table 4. Multivariate Association of Plasma Biomarkers of Inflammation with Incident Cataract and Mortality in Persons with AIDS (n = 475)

| | Event = Incident Cataract | | | Event = Mortality | | |
|---|---|---|---|---|---|---|
| **Biomarker*** | *subHR*† | *95% CI* | P *Value* | *subHR*† | *95% CI* | P *Value* |
| MCP-1 (CCL2) | 0.73 | 0.62–0.86 | < 0.001 | 1.77 | 1.42–2.22 | < 0.001 |
| MIP-1β (CCL4) | 0.88 | 0.75–1.04 | 0.125 | 1.20 | 1.02–1.41 | 0.030 |
| sTNFR2 | 0.76 | 0.64–0.90 | 0.002 | 1.57 | 1.33–1.85 | < 0.001 |
| IL-18 | 0.75 | 0.64–0.88 | < 0.001 | 1.62 | 1.35–1.94 | < 0.001 |
| Fractalkine (CX3CL1) | 0.78 | 0.67–0.92 | 0.002 | 1.69 | 1.39–2.05 | < 0.001 |

CI = confidence interval; CX3CL1 = CX3C chemokine ligand 1; IL=18 = interleukin-18; MCP-1 = monocyte chemoattractant protein -1 (chemokine CC ligand [CCL] 2); MIP-1β = macrophage inflammatory protein -1β (CCL4); subHR = subdistribution hazard ratio; sTNFR2 = soluble tumor necrosis factor receptor 2.
*subHR = cause-specific hazard ratio, adjusted for age, race/ethnicity, sex, and age-related macular degeneration status; expressed as /standard deviation unit $\log_{10}$(concentration biomarker). Hazard ratios > 1.0 are associated with an increased risk and those < 1.0 with a decreased risk.

persons with AIDS and AMD is consistent with the accelerated/accentuated aging in ART-treated, immunorestored, HIV-infected persons.[10,11] Moreover, in our prevalence study,[14] the prevalence of AMD increased with age, and there was an increased age- and sex-adjusted prevalence of intermediate-stage AMD compared with HIV-uninfected persons. The racial/ethnic distribution of our patients with AMD is at least in part reflective of the evolution of the AIDS epidemic, and the diagnosis of intermediate-stage AMD was made by graders masked to clinical features at a reading center with extensive experience with grading AMD and using the AREDS grading system.[14,15,19,20] There were several nonsignificant differences in baseline characteristics between cases and controls with and without AMD, possibly suggestive of initiation of ART at a more advanced stage of HIV infection (e.g., lower nadir CD4+ T-cell count) and with a less robust response to ART (e.g., lower baseline CD4+ T cells). However, in previous work, none of these features were associated with AMD in persons with AIDS.[14,15] Furthermore, it is that population of patients who initiate ART at more advanced stages of HIV infection and have a less robust immunologic response to ART who are most likely to experience accelerated/accentuated aging.[10,11]

Combining the data from this study with those from our previous study suggests possible systemic inflammatory pathways associated with an increased risk of AMD in ART-treated people with HIV. Although all of the biomarkers assessed on our studies have been associated with morbidity and mortality in persons with AIDS, only a subset of these predicted incident AMD.[17,21,22,32–34] One pathway potentially suggested by our studies is NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome activation. Like pro-IL-1β, pro-IL-18 requires proteolytic cleavage by NLRP3 inflammasome-induced caspase-1 (or possibly other inflammatory enzymes),[35–37] before the active form can be released into the extracellular space. Thus, increased plasma levels of both IL-1β and IL-18 are observed with systemic NLRP3 inflammasome activation, but we chose to measure IL-18 as it is more reliably measured in plasma than IL-1β. Although other inflammatory pathways may certainly play a role, IL-6 can be induced by IL-1β, and CRP is, in turn, induced by IL-6,[37] so our finding that IL-18, CRP, and possibly IL-6 seem to predict incident AMD in persons with AIDS may be consistent with NLRP3 inflammasome activation.[17] Our finding that TNFR2 also predicts incident AMD in this setting also may be linked to this same pathway as TNF-α signaling

Table 5. Plasma Inflammatory Biomarkers at Enrollment in Cases with Incident AMD and Controls without Incident AMD (n = 60) in Persons with AIDS

| | Adjusted Mean $\text{Log}_{10}$(Plasma Biomarker) (Standard Deviation)* | | |
|---|---|---|---|
| **Biomarker level at enrollment** | *Incident AMD* | *No AMD* | **P Value**† |
| C-reactive protein (mg/mL) | 0.52 (0.60) | 0.20 (0.43) | 0.01 |
| Interleukin-6 (pg/mL) | 0.24 (0.33) | 0.11 (0.29) | 0.10 |
| Interferon-γ inducible protein-10 (pg/mL)‡ | 2.47 (0.36) | 2.42 (0.39) | 0.59 |
| Soluble CD14 (μg/mL) | 6.31 (0.11) | 6.23 (0.14) | 0.008 |
| Soluble CD163 (ng/mL) | 2.85 (0.25) | 2.81 (0.29) | 0.59 |

AMD = age-related macular degeneration.
*Adjusted for age, sex, race, smoking status, hypertension status, and CD4+ T cells.
†*P* value for unpaired analysis between participants with AIDS and incident AMD (n = 26) and participants without AMD (n = 60).
‡CXC chemokine ligand 10 (CXCL10). Adapted from Jabs et al.[17]

Table 6. Multivariable Relationship of Inflammatory Biomarker Levels at Enrollment with Incident Cataract and Mortality

| Biomarker | Number of Participants | Event = Incident Cataract | | | Event = Mortality | | |
|---|---|---|---|---|---|---|---|
| | | *subHR** | *95% CI* | P *Value* | *subHR** | *95% CI* | P *Value* |
| C-reactive protein | 465 | 0.92 | 0.80–1.06 | 0.27 | 1.56 | 1.25–1.95 | < 0.001 |
| Interleukin-6 | 544 | 0.83 | 0.73–0.95 | 0.01 | 1.66 | 1.35–2.03 | < 0.001 |
| Interferon-γ inducible protein-10† | 539 | 0.69 | 0.59–0.81 | < 0.001 | 1.65 | 1.35–2.02 | < 0.001 |
| Soluble CD14 | 546 | 0.78 | 0.68–0.88 | < 0.001 | 1.51 | 1.27–1.81 | < 0.001 |
| Soluble CD163 | 548 | 0.82 | 0.71–0.94 | 0.005 | 1.31 | 1.10–1.55 | 0.002 |

CI = confidence interval; subHR = subdistribution hazard ratio.
*subHR = cause-specific hazard ratio, adjusted for age, race, sex/ethnicity, and age-related macular degeneration status; expressed as /standard deviation unit $\log_{10}$(concentration biomarker). Hazard ratios > 1.0 are associated with an increased risk and those < 1.0 with a decreased risk.
†CXC chemokine ligand 10 (CXCL10). Adapted from Jabs et al.[17]

has been shown to increase inflammasome activation and IL-18 production.[38]

The NLRP3 inflammasome is a critical component of the innate immune system. Triggered by pattern recognition receptors that respond to either pathogen-associated molecular patterns or damage-associated molecular patterns, the NLRP3 inflammasome activates caspase 1, which proteolytically cleaves pro-IL-1β and pro-IL-18 into their activated forms, allowing for their secretion from the responding cell and driving an inflammatory response.[39] Although the NLRP3 inflammasome is involved in host immune defense against acute infections, chronic NLRP3 inflammasome dysregulation has been linked to other diseases of aging, including Alzheimer's disease and atherosclerosis.[37,40,41] The CANTOS Trial demonstrated that a monoclonal antibody directed against NLRP3 inflammasome-derived IL-1β significantly reduced cardiovascular events and mortality.[42] The association of NLRP3 activation with other aging-related diseases is consistent with our observations, suggesting an association of NLRP3 activation with incident AMD. Indeed, NLPR3 inflammasome activation has been implicated in the pathogenesis of AMD in vitro and in animal models,[43–45] and a recent cross-sectional study also found elevated NLRP3 inflammasome-associated proteins in plasma (including IL-18) in HIV-uninfected people with AMD of indeterminate stage.[46] Our finding that plasma IL-18 is associated with subsequent intermediate-stage AMD risk in a prospective study provides stronger evidence for the relevance of this pathway to AMD risk and for its role early in the development of AMD. Furthermore, the development of selective inhibitors of NLRP3 activation suggests a potential interventional target for decreasing AMD risk.[47]

Our previous study demonstrated an association of elevated plasma levels of sCD14, a marker of monocyte activation, with incident AMD, again implicating systemic activation of the innate immune system in the pathogenesis of AMD.[17] Although our prior study found that elevated plasma levels of the monocyte activation marker sCD14 were associated with incident AMD, this study suggested that elevated plasma levels of chemokines associated with activated monocyte trafficking to inflamed tissues, including MIP-1β, MCP-1, and fractalkine, were not associated with incident AMD.

To have an adequate number of outcomes, our study evaluated the association of systemic inflammation with intermediate-stage AMD, which is approximately 4-fold more common than late-stage AMD,[48] and has a high rate of progression to late-stage AMD in HIV-uninfected persons.[49] We do not have data on the rate of progression of intermediate-stage AMD to late-stage AMD in HIV-infected persons, and there are some data both in animal models and humans to suggest NRTI use is associated with a decreased incidence of late-stage AMD,[50,51] possibly reducing the number of late-stage AMD cases in an HIV-infected population treated with NRTIs. With the increasing use of NRTI-sparing regimens for the treatment of HIV, particularly intermittent injectable therapy,[52] it remains to be seen whether late-stage AMD may emerge among persons with AIDS treated with these regimens.

## Limitations

The population of persons in our study all were diagnosed with AIDS.[18] Therefore, these data may not be directly applicable to persons who start ART at earlier stage of HIV infection and never develop the level of immune compromise necessary to be diagnosed as having AIDS. However, the characteristics of the participants in LSOCA are similar to those diagnosed with AIDS in the United States and, therefore, seem to have relevance for this population.[18] Our study did not include HIV-uninfected persons, but it did demonstrate an association among persons with AIDS between elevated plasma levels of selected biomarkers and incident AMD. There are immunologic similarities between immunosenescence in HIV-uninfected persons and the changes seen in ART-treated, immunorestored, HIV-infected persons.[10,11] The elevated plasma levels of biomarkers evaluated in our studies are known to be associated with age-related diseases and mortality in HIV-uninfected persons,[9,10,21,53] which suggests that these results may be relevant to HIV-uninfected persons as well, and there are some data suggesting a relationship between systemic inflammation and monocyte activation with late-stage AMD in HIV-uninfected persons.[54–56]

The small sample size for the incident AMD analysis necessitated the use of a different, larger subset of the cases in the LSOCA cohort for the cataract and mortality analyses.

Despite the different study populations in the 2 analyses, the baseline characteristics were similar between the 2 study populations, suggesting some degree of comparability. Although our analysis of immunologic predictors of cataract (largely significant inverse correlations) attempted to account for the substantial competing risk of mortality (significant positive correlations) by using the ratio of the subhazards of the cumulative incidences as the key measure of association, it is difficult to be certain that the competing risk has been fully accounted for. Nevertheless, the extreme-case sensitivity analysis did not alter the conclusions that systemic inflammation is associated with a decreased risk of cataract in this population.

The LSOCA cohort did not have ocular specimens, so we cannot assess whether the plasma inflammatory biomarkers associated with AMD also are elevated in the eye. In addition to the systemic components of the innate immune system implicated by our results, resident cells within the eye may produce these inflammatory mediators. Although the absence of intraocular data does not invalidate the significant associations found, we cannot distinguish between a systemic process affecting AMD pathogenesis indirectly or a direct effect within the eye.

Our data, coupled with our previous work, suggest that among ART-treated persons with AIDS, systemic inflammatory biomarkers related to monocyte activation (sCD14) and possibly to NLRP3 inflammasome activation (IL-18, CRP, sTNFR2) are associated with incident intermediate-stage AMD but not with incident cataract, another age-related eye disease. These data suggest a role for systemic innate immune system activation, including monocyte activation and possibly NLRP3 inflammasome activation, in the pathogenesis of AMD in this population.

## Footnotes and Disclosures

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Author Contributions:

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Analysis and interpretation: Jabs, Schneider, Hunt

Obtained funding: Jabs, Hunt

Overall responsibility: Jabs, Hunt

Abbreviations and Acronyms:
**AMD** = age-related macular degeneration; **AREDS** = Age-Related Eye Disease Study; **ART** = antiretroviral treatment; **CCL** = CC chemokine ligand; **CX3CL** = CX3C chemokine ligand; **CI** = confidence interval; **CRP** = C-reactive protein; **HIV** = human immunodeficiency virus; **LSOCA** = Longitudinal Study of Ocular Complications of AIDS; **MCP-1** = monocyte chemoattractant protein; **MIP-1β** = macrophage inflammatory protein-1β; **NRTI** = nucleoside reverse transcriptase inhibitor; **sCD14** = soluble CD14; **STNFR** = soluble tumor necrosis factor receptor; **subHR** = subdistribution hazard ratio.

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