

Prevalence of Intermediate-Stage Age-Related Macular Degeneration in Patients With Acquired Immunodeficiency Syndrome



DOUGLAS A. JABS, MARK L. VAN NATTA, EFE SEZGIN, JEONG WON PAK, AND RONALD DANIS, FOR THE STUDIES OF THE OCULAR COMPLICATIONS OF AIDS RESEARCH GROUP

- **PURPOSE:** To evaluate the prevalence of intermediate-stage age-related macular degeneration (AMD) in patients with acquired immunodeficiency syndrome (AIDS).
- **DESIGN:** Cross-sectional study of patients with AIDS enrolled in the Longitudinal Study of the Ocular Complications of AIDS.
- **METHODS:** Intermediate-stage AMD was determined from enrollment retinal photographs by graders at a centralized Reading Center, using the Age-Related Eye Disease Study grading system. Graders were masked as to clinical data.
- **RESULTS:** Of 1825 participants with AIDS and no ocular opportunistic infections, 9.9% had intermediate-stage AMD. Risk factors included age, with an odds ratio (OR) of 1.9 (95% confidence interval [CI] 1.6, 2.3, $P < .001$) for every decade of age; the prevalence of AMD ranged from 4.0% for participants 30–39 years old to 24.3% for participants ≥ 60 years old. Other risk factors included the human immunodeficiency virus (HIV) risk groups of injection drug use (OR = 2.4, 95% CI 1.5, 3.9, $P < .001$) or heterosexual contact (OR = 1.9, 95% CI 1.3, 2.8, $P = .001$). Compared with the HIV-uninfected population in the Beaver Dam Offspring Study, there was an approximate 4-fold increased age-adjusted prevalence of intermediate-stage AMD.
- **CONCLUSIONS:** Patients with AIDS have an increased age-adjusted prevalence of intermediate-stage AMD compared with that found in a non-HIV-infected cohort evaluated with similar methods. This increased prevalence is consistent with the increased prevalence of other age-related diseases in antiretroviral-treated, immune-restored, HIV-infected persons when compared to

non-HIV-infected persons. (*Am J Ophthalmol* 2015;159(6):1115–1122. Published by Elsevier Inc.)

AGE-RELATED MACULAR DEGENERATION (AMD) IS the leading cause of late-onset visual impairment and blindness in persons over 65 years of age.^{1,2} Age-related macular degeneration is staged as early, intermediate, or late. Small drusen are the hallmark of early-stage AMD; intermediate-stage AMD consists of extensive medium-size drusen or any large drusen, with or without pigment changes. Late-stage AMD is defined by either choroidal neovascularization or geographic atrophy.^{3–6} In the United States, it is estimated that ~1.2 million persons have neovascular AMD; 970 000 have geographic atrophy; and 8 million have intermediate-stage AMD.¹

Antiretroviral-treated, immune-restored, human immunodeficiency virus (HIV)-infected persons have a marked reduction in opportunistic infections and a substantially increased lifespan compared to those from the era before modern combination antiretroviral therapy.^{7–10} However, despite the improved immune function and increased lifespan, antiretroviral therapy does not fully restore health. Compared to similarly-aged, non-HIV-infected peers, antiretroviral-treated, immune-restored, HIV-infected persons have a substantially shortened lifespan, largely owing to an increased risk of non-acquired immunodeficiency syndrome (AIDS) diseases associated with aging.^{11–14} These diseases include cardiovascular disease, non-AIDS cancers, metabolic diseases, and neurocognitive decline, and collectively suggest that antiretroviral-treated, immune-restored HIV infection is associated with an “accelerated/accelerated aging” phenotype.¹¹ Therefore, we undertook to evaluate whether persons with AIDS had an increased prevalence of AMD, using retinal photographs taken at enrollment in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA) cohort.

METHODS

THE LONGITUDINAL STUDY OF THE OCULAR COMPLICATIONS OF AIDS was a prospective, observational cohort study of patients with AIDS in the era of modern combination

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From the Departments of Ophthalmology (D.A.J.) and Medicine (D.A.J.), Icahn School of Medicine at Mount Sinai, New York, New York; Center for Clinical Trials, Department of Epidemiology, The Johns Hopkins University Bloomberg School of Public Health, Baltimore, Maryland (D.A.J., M.L.V.N., E.S.); and Department of Ophthalmology, University of Wisconsin, Madison, Madison, Wisconsin (J.W.P., R.D.).

Inquiries to Douglas A. Jabs, Department of Ophthalmology, The Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, Box 1183, New York, NY 10029; e-mail: douglas.jabs@mssm.edu

antiretroviral therapy.^{15,16} Enrollment began on September 1, 1998 and was completed on July 31, 2011. Eligible persons had AIDS diagnosed according to the 1993 Centers for Disease Control and Prevention revised criteria for the diagnosis of AIDS.¹⁷ Recruitment occurred at 19 clinical centers throughout the United States, typically located in large urban centers with a large HIV-infected population.¹⁵

Participants with and without ocular opportunistic infections were recruited. At enrollment all participants gave a detailed medical and HIV-related disease history; relevant findings were confirmed from the medical record. Wide-field retinal photographs were taken on all participants at enrollment, as previously described.^{15,16} Laboratory testing at enrollment included hematology and blood chemistry, lymphocyte subset analysis for CD4+ T cells, the amount of circulating HIV RNA in the blood (HIV load), and the presence of antibodies to hepatitis C.^{15,16}

Approval for the study and its procedures was obtained from the institutional review boards of the individual participating clinical centers and the 3 resource centers (chairman's office, coordinating center, and reading center). Written informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

• **GRADING OF RETINAL PHOTOGRAPHS:** Photographs were graded by graders at the Studies of the Ocular Complications of AIDS (SOCA) Reading Center at the University of Madison, Wisconsin from stereoscopic color photographs of the macula obtained at the baseline visit. Photographers and camera systems were certified for SOCA photographic procedures by Reading Center personnel. Images were graded either from 35 mm film, mounted in typical slide mounts and viewed on a light box with a Donaldson 5X stereoscopic viewer, or from digital images displayed on calibrated computer monitors and viewed with a stereoscopic viewer (PS Manufacturing, Portland, Oregon, USA). The Early Treatment Diabetic Retinopathy Study grid, measuring 7.2 mm on the retina, was placed on film slides using an acetate overlay sized for the camera type and degree of view.⁴ Digital image grading employed software tools to calibrate and locate the grid.⁶ Approximately 10% of the images were digital. Fundus photographs were graded for the features of intermediate-stage AMD, including the presence, size, and area of drusen and the presence and area of pigmentary abnormalities. Grading questions and procedures employed the Age Related Eye Disease Study (AREDS)-2 system for classifying AMD from retinal photographs.^{5,6} Graders were masked as to clinical information. The primary outcome of interest was intermediate-stage AMD, defined as at least 1 large druse (>150 μm using modern estimates of the average disc size or >125 μm using the traditional estimate) or extensive medium-sized drusen with or without pigment abnormalities (Figure).⁵ Quality control

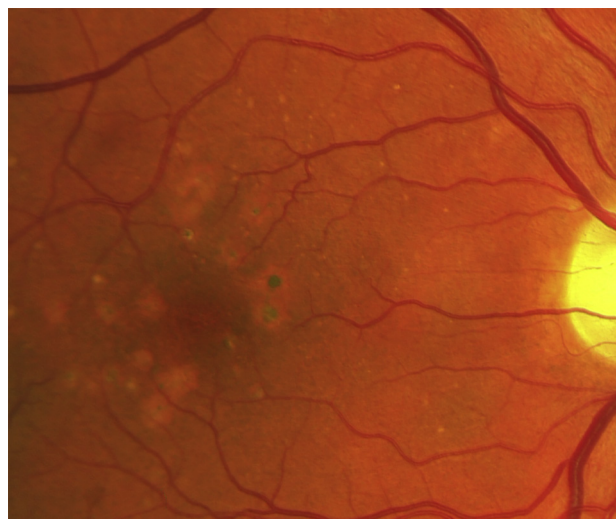


FIGURE. Retinal photograph of an HIV-infected participant in the Longitudinal Study of the Ocular Complications of AIDS, demonstrating large drusen and retinal pigment epithelial changes, characteristic of intermediate-stage age-related macular degeneration.

was provided by a resampling and regrading of 10% of the photographs by the reading center project ophthalmologist (R.P.D.). Because drusen are difficult to evaluate in the face of extensive retinal necrosis and scarring from cytomegalovirus (CMV) retinitis, eyes with ocular opportunistic infections were not graded, and these participants were not included in the study.¹⁸ The primary outcome was intermediate-stage AMD.

• **STATISTICAL METHODS:** Continuous variables were categorized into clinically meaningful categories or quartiles. Variables with moderate to large (>10%) amounts of missing data included a category for missing. The association of unadjusted participant characteristics with prevalence of intermediate-stage AMD was assessed using the χ^2 test (or Fisher exact test for small n's).¹⁹ Adjusted independent effects were assessed with a stepwise model selection procedure using Akaike's Information Criterion logistic regression.²⁰ The candidate set included all unadjusted participant characteristics except individual antiretroviral drugs. Odds ratios and confidence intervals were estimated using Wald's test.¹⁹ All statistical analyses were conducted with SAS/STAT version 9.3 (SAS Institute, Inc, Cary, North Carolina, USA) and Stata version 12.0 (Stata Statistical Software: Release 12, 2011; StataCorp LP, College Station, Texas, USA) software packages.

• **COMPARISON WITH THE BEAVER DAM OFFSPRING STUDY:** In order to compare the prevalence of intermediate-stage AMD among patients with AIDS to that seen in the non-HIV infected population, the prevalence of intermediate-stage AMD in LSOCA was

TABLE 1. Baseline Characteristics of the Study Population of Patients With Acquired Immunodeficiency Syndrome From the Longitudinal Study of the Ocular Complications of AIDS

Characteristic	Result
Number of participants	1825
Demographics	
Age (y)	
Mean	43.4
Standard deviation	8.8
Sex (%)	
Male	80.7
Female	19.3
Race (%)	
White, non-Hispanic	45.4
African American	37.7
Hispanic	13.3
Other	3.6
HIV transmission category (%)	
Male-to-male sexual contact	54.3
Injection drug use	14.1
Heterosexual contact	26.0
Other	5.6
Duration of AIDS at enrollment (y)	
Median	4.3
25th, 75th percentile	1.6, 7.3
Smoking (%)	
Current	18.0
Former	28.4
Nonsmoker	31.3
Missing	22.3
Immunology and virology	
Enrollment CD4+ T cells (cells/ μ L)	
Median	198
25th, 75th percentile	81, 360
Nadir CD4+ T cells (cells/ μ L)	
Median	44
25th, 75th percentile	13, 113
Enrollment HIV load (\log_{10} [copies/mL])	
Median	2.7
25th, 75th percentile	1.9, 4.6
Maximum prior HIV load (\log_{10} [copies/mL])	
Median	5.3
25th, 75th percentile	4.7, 5.7
HIV treatment	
Highly active antiretroviral therapy at enrollment ^a (%)	
Yes	84.9
No	15.1
Highly active antiretroviral therapy prior to or at enrollment (%)	
Yes	93.6
No	6.4
Comorbidities	
Diabetes (%)	
No	91.3
Yes	8.7

Continued

TABLE 1. Baseline Characteristics of the Study Population of Patients With Acquired Immunodeficiency Syndrome From the Longitudinal Study of the Ocular Complications of AIDS (Continued)

Characteristic	Result
Hyperlipidemia (%)	
No	78.4
Yes	21.6
Renal impairment (elevated serum creatinine) (%)	
No	93.9
Yes	6.1
Hypertension (%)	
No	79.1
Yes	13.7
Cardiovascular disease (%)	
No	86.3
Yes	13.7
Hepatitis C infection (%)	
Seronegative	66.4
Seropositive	19.0
Missing	14.6

AIDS = acquired immunodeficiency syndrome; HIV = human immunodeficiency virus.

^aHighly active antiretroviral therapy = combination therapy including at least 1 potent antiretroviral drug (eg, a protease inhibitor).

compared to the published data from the Beaver Dam Eye Study, which also were obtained from grading retinal photographs at the same institution as the SOCA Reading Center and used similar grading protocols.²¹ Comparisons were stratified by age and adjusted for age and sex.²² In addition, because the Beaver Dam Offspring Study was a study of white participants, a comparison also was made with white participants in the LSOCA study.

RESULTS

• **CHARACTERISTICS OF THE STUDY POPULATION:** Of the 2392 participants enrolled in LSOCA, 535 had an intraocular opportunistic infection (primarily CMV retinitis), and 32 did not have enrollment photographs; 1825 had enrollment photographs and no intraocular infections and form the study population. Characteristics of the study population are listed in Table 1. The group had a mean age of 43.4 years and was 80.7% male. The plurality of participants were white, non-Hispanic (45.4%), but 37.7% were African American, and 13.3% were Hispanic. The largest transmission category for HIV infection was participants with male-to-male sexual contact (54.3%); 14.1% had injection drug use and 26.0% heterosexual transmission as the transmission category for HIV infection. The

TABLE 2. Univariate Analysis of Baseline Patient Characteristics and Intermediate-Stage Age-Related Macular Degeneration in Patients With Acquired Immunodeficiency Syndrome

Characteristic	Number	% With AMD ^a	P Value
Overall	1825	9.9	
Age (y)			<.0001
<30	98	8.2	
30–39	499	4.0	
40–49	794	9.3	
50–59	364	16.8	
≥60	70	24.3	
Sex			.30
Male	1472	9.5	
Female	353	11.3	
Race & ethnicity			.15
White, non-Hispanic	828	8.2	
African American	688	11.6	
Hispanic	243	9.9	
Other	66	12.1	
Smoking history			.02
Current	329	13.7	
Former	518	9.1	
Never	571	8.2	
Enrollment cohort (year of enrollment)			.36
1998–2000	663	8.8	
2001–2004	721	10.0	
2005–2012	441	11.3	
Time since AIDS diagnosis (y)			.37
Quartile 1 (<1.55)	445	10.1	
Quartile 2 (1.55–4.33)	457	7.9	
Quartile 3 (4.34–7.25)	448	10.0	
Quartile 4 (>7.25)	450	11.3	
HIV transmission category			.003
Male-to-male sexual contact	991	7.7	
Injection drug use	257	14.4	
Heterosexual contact	474	12.0	
Other	103	5.6	
Enrollment CD4+ T cells (cells/μL)			.98
<100	519	10.2	
100–199	389	10.3	
200–499	664	9.6	
≥500	238	9.7	
Nadir CD4+ T cells (cells/μL)			.25
<50	953	9.0	
≥50	845	10.7	
Enrollment HIV load (log ₁₀ [copies/mL])			.26
<2.6	627	8.3	
2.6–3.0	305	10.8	
≥3.0	786	10.7	
Maximum prior HIV load (log ₁₀ [copies/mL])			.98
<2.6	47	10.6	
2.6–3.0	49	10.2	
≥3.0	1645	9.8	

Continued

TABLE 2. Univariate Analysis of Baseline Patient Characteristics and Intermediate-Stage Age-Related Macular Degeneration in Patients With Acquired Immunodeficiency Syndrome (Continued)

Characteristic	Number	% With AMD ^a	P Value
HIV treatment			
Highly active antiretroviral therapy ^b			.21
No	276	12.0	
Yes	1548	9.5	
Nucleoside transcriptase inhibitor			.27
No	208	12.0	
Yes	1616	9.6	
Non-nucleoside transcriptase inhibitor			.24
No	1117	9.2	
Yes	707	10.9	
Protease inhibitor			.09
No	703	11.4	
Yes	1121	8.9	
Integrase inhibitor			.70
No	1781	9.8	
Yes	43	11.6	
Chemokine receptor 5 antagonist			.42
No	1818	9.9	
Yes	6	0	
Fusion inhibitor			.48
No	1795	9.8	
Yes	29	13.8	
Comorbidities			
Diabetes			.04
No	1666	9.4	
Yes	159	14.4	
Hyperlipidemia			.87
No	1428	9.9	
Yes	393	9.7	
Renal impairment (elevated serum creatinine)			.73
No	1714	9.8	
Yes	111	10.8	
Hypertension			.003
No	1442	8.8	
Yes	382	13.9	
Cardiovascular disease			.02
No	1258	8.9	
Yes	200	14.0	
Hepatitis C infection (seropositive)			.65
No	1211	9.8	
Yes	347	10.7	

AIDS = acquired immunodeficiency syndrome; AMD = age-related macular degeneration; HIV = human immunodeficiency virus.

^aPercentage with intermediate-stage AMD reported.

^bHighly active antiretroviral therapy = combination therapy including at least 1 potent antiretroviral drug (eg, a protease inhibitor).

TABLE 3. Multiple Regression of Risk Factors for Intermediate-Stage Age-Related Macular Degeneration in Patients With Acquired Immunodeficiency Syndrome

Covariate	Odds Ratio	95% Confidence Interval	P Value
Age (decade)	1.9	1.6, 2.3	<.001
HIV transmission category			
Male-to-male sexual contact (reference)	1.0		
Injection drug use	2.4	1.5, 3.9	<.001
Heterosexual contact	1.9	1.3, 2.8	.001
Other	1.4	0.7, 2.8	.31
Hepatitis C infection			
Seronegative or missing	1.0		
Seropositive	0.7	0.4, 1.1	.15
Smoking status			
Never	1.0		
Former	1.1	0.7, 1.7	.74
Current	1.5	0.9, 2.3	.09
Missing	1.4	0.9, 2.2	.17

HIV = human immunodeficiency virus.

median nadir CD4+ T cell count prior to enrollment was 44 cells/ μ L (25th, 75th percentiles, 11 cells/ μ L, 113 cells/ μ L), the median enrollment CD4+ T cell count was 198 cells/ μ L (25th, 75th percentiles, 81 cells/ μ L, 360 cells/ μ L). At enrollment 84.9% of participants were receiving combination antiretroviral therapy, and 93.6% had received combination antiretroviral therapy prior to or at enrollment. Comorbidities associated with aging included diabetes in 8.7%, hypertension in 20.9%, and cardiovascular disease in 13.7%.

• PREVALENCE OF AND RISK FACTORS FOR INTERMEDIATE-STAGE AGE-RELATED MACULAR DEGENERATION: The prevalence of intermediate-stage AMD in the entire study population was 9.9%. The associations of demographic, immunologic, and virologic comorbidity and antiretroviral treatment risk factors with intermediate-stage AMD in the univariate analysis are listed in Table 2. Age was a significant risk factor, with prevalences ranging from 4.0% for participants aged 30–39 years to 24.3% for participants 60 years of age and over ($P < .0001$). Smoking was associated with intermediate-stage AMD, with current smokers having a higher prevalence (13.7%) than former smokers (9.1%) and “never-smokers” (8.2%) ($P = .02$). Participants whose risk for HIV infection was either injection drug use (14.4%) or heterosexual contact (12.0%) had a greater prevalence of AMD than did men who had sex with men (7.7%) or other risk groups (5.6%) ($P = .003$). Diabetes (14.4% vs 9.4%, $P = .04$), hypertension (13.9% vs 8.8%, $P = .003$), and cardiovascular disease (14.0% vs 8.9%, $P = .02$) all were associated with intermediate-stage AMD.

TABLE 4. Age-Stratified Prevalence of Intermediate-Stage Age-Related Macular Degeneration in Participants in the Longitudinal Study of the Ocular Complications of AIDS vs the Beaver Dam Offspring Study

	LSOCA ^a		Beaver Dam Offspring Study ^b	
	Number of Participants	% With AMD ^c	Number of Participants	% With AMD ^c
Age (y)				
21–34	244	5.3	168	0.6
35–44	782	5.9	822	1.3
45–54	605	12.9	1047	3.0
55–64	150	21.3	599	5.7
65–84	29	34.5	174	9.2
Total	1810	9.9	2810	3.3
Adjusted prevalences				
Age-adjusted		12.1		2.9
Age- and sex-adjusted		13.0		3.2
Age- and sex-adjusted, white subjects only		11.4		3.3

AMD = age-related macular degeneration; LSOCA = Longitudinal Study of the Ocular Complications of AIDS.

^aExcludes 15 participants aged ≤ 20 years, as this age group was not evaluated in the Beaver Dam Offspring Study.

^bData from Klein et al.²¹

^cPercentage with intermediate-stage AMD reported.

Neither combination antiretroviral therapy nor the use of any class of antiretroviral drugs at enrollment was associated with intermediate-stage AMD (Table 2). Details of the relationship of individual antiretroviral drugs to intermediate-stage AMD are listed in the Supplemental Table (available at AJO.com). The only individual antiretroviral drug statistically associated with intermediate-stage AMD was adefovir (33.3% in those taking it vs 9.7% in those not taking it, $P = .01$); however, only 15 participants were taking adefovir, and only 5 participants taking it had intermediate-stage AMD, so adefovir use had a minimal impact on the prevalence of AMD in this population. There was no association of the use of antiretroviral therapy prior to enrollment, the use of any class of antiretroviral drugs, or the use of any specific antiretroviral drugs prior to enrollment with the prevalence of intermediate-stage AMD at enrollment (data not shown).

The multiple regression analysis of risk factors for intermediate-stage AMD is listed in Table 3. Age was strongly associated with intermediate-stage AMD with an odds ratio of 1.9 for every decade of age (95% CI 1.6, 2.3, $P < .001$). HIV transmission category remained a risk factor with injection drug use (odds ratio 2.4, 95% CI 1.5, 3.9, $P = .01$) and heterosexual contact (odds ratio 1.9, 95% CI 1.3, 2.8, $P = .001$) associated with intermediate-stage AMD as compared to participants whose HIV risk factor was male-to-male sexual contact.

There was no evidence of effect modification between HIV risk group and sex on the risk of intermediate-stage AMD (interaction $P = .18$, data not shown).

• **COMPARISON WITH BEAVER DAM OFFSPRING STUDY:** The prevalence of intermediate-stage AMD compared to that published by the Beaver Dam Offspring Study,²¹ subgrouped by age, is given as Table 4. The crude prevalence of AMD is 3-fold higher in the LSOCA cohort (9.9% vs 3.3%), and the age-adjusted and age- and sex-adjusted prevalences were approximately 4-fold higher in LSOCA (12.1% vs 2.9% and 13.0% vs 3.2%, respectively).

DISCUSSION

OUR DATA SUGGEST AN INCREASED AGE-ADJUSTED PREVALENCE of intermediate-stage AMD when compared to a non-HIV-infected cohort. These results are consistent with the increase in other age-related diseases, such as cardiovascular disease, osteoporosis, metabolic disorders, non-AIDS-related cancers, and neurocognitive decline, seen in HIV-infected, antiretroviral-treated, immune-restored persons and with the associations of AMD with the age-related diseases, diabetes, hypertension, and cardiovascular disease, in the LSOCA population. In the non-HIV-infected population, AMD also has been associated with cardiovascular disease and, in some studies, with diabetes.^{23–26} Similar to the HIV-uninfected population, in the LSOCA population age was strongly and significantly associated with the prevalence of AMD, with a near-doubling of the risk for each decade of age.

Antiretroviral-treated, immune-restored, HIV-infected persons do not have normal immune systems; instead they have immunologic changes similar to those seen in HIV-uninfected persons over 70 years of age, a phenomenon termed immunosenescence.^{11,27} In addition, antiretroviral-treated, immune-restored, HIV-infected persons are characterized by a state of chronic immune activation with ongoing systemic inflammation.^{11,27,28} This increase in age-related diseases in HIV-infected persons is not related to any drug or class of drugs, and it occurs to a greater degree among those with less complete immune recovery, suggesting that it is a consequence of HIV infection itself and/or the state of chronic inflammation it induces.^{11,27} Studies in non-HIV-infected persons demonstrate that systemic inflammation is a risk factor for AMD.^{29–31} Therefore, the apparent increased prevalence of intermediate-stage AMD in persons with AIDS may relate to their state of chronic immune activation and systemic inflammation, although immunosenescence also could contribute.

Similar to non-HIV-infected populations, several risk factors were associated with AMD in the univariate analysis, including smoking and cardiovascular disease.^{23–26,32}

However, all of these risk factors were not independently associated in the multiple regression model. The only other risk factor, besides age, associated with AMD was the HIV risk group with those participants whose transmission category for HIV acquisition was either injection drug use or heterosexual contact, having a greater prevalence than those whose risk was male-to-male sexual contact. Whether this increased risk represents access to care with less antiretroviral therapy adherence and less complete immune recovery in the past or greater inflammation is uncertain. However, injection drug use itself is associated with immune activation and inflammation, and HIV-infected injection drug users have greater immune activation and inflammation than HIV-infected noninjection drug users,³³ again suggesting systemic inflammation as a possible link in the increased prevalence of AMD. In the LSOCA cohort, there was no difference in the prevalence of intermediate-stage for different racial/ethnic groups, whereas in HIV-uninfected persons there is a greater prevalence among European Americans than among African Americans. In the Multi-Ethnic Study of Atherosclerosis (MESA), a cohort study in which AMD also was graded from photographs, and in which the mean age was ~63 years, AMD prevalences were 2.4% among African Americans and 5.4% among whites.³⁴ One possible explanation for this difference between the LSOCA cohort and non-HIV-infected persons is that the immunologic and inflammatory drivers, which are increasing the overall risk of AMD in persons with AIDS, may be sufficiently strong to overcome any inherent racial differences in AMD risk.

Caution should be taken in interpreting our data. Although the AMD lesions seen in the LSOCA population are clinically and photographically identical to those seen in non-HIV-infected populations, we do not have histology to confirm the nature of the lesions. In order to compare the prevalence of intermediate-stage AMD among persons with AIDS to that in the non-HIV-infected population, we used published data from a cohort evaluated with similar methodology. We were able to adjust the comparison for some recognized non-HIV-related risk factors, but not all, as we were working from published data. As such, the magnitude of the apparent increased risk for AMD among persons with AIDS may be somewhat different from our estimates. Nevertheless, adjustments for those risk factors where we had data do not alter the conclusion that there appears to be an increased risk of intermediate-stage AMD among persons with AIDS. However, a better method (but one not available to us) would have been a cross-sectional study employing concurrently collected persons with and without HIV infection. Follow-up of HIV-infected persons with intermediate-stage AMD for the occurrence of late-stage AMD (ie, choroidal neovascularization or geographic atrophy) also would be important, although the potential effect of nucleoside reverse-transcriptase inhibitors on inhibiting the progression of late-stage AMD³⁵ might reduce the rate

of progression to late-stage AMD among antiretroviral-treated, HIV-infected persons with intermediate-stage AMD.

Caution also should be taken in extrapolating our data to all HIV-infected persons. The LSOCA cohort enrolled persons with AIDS and not earlier stages of HIV infection.^{15,16} As such, the prevalence of AMD in HIV-infected patients with earlier stage of HIV infection remains uncertain. Nevertheless, because of late diagnosis, as many as 45% of patients diagnosed with HIV infection will progress to AIDS within 3 years of the diagnosis of HIV infection.³⁶ Furthermore, among patients with HIV infection retained in follow-up care, nearly 30% will not have suppressed HIV replication in the blood.³⁷ As such, there remains a substantial population of HIV-infected patients who will progress to AIDS and for whom these results are relevant.

Participants were enrolled at AIDS ophthalmology clinics, so it is possible that patients with visual symptoms were more likely to enroll and that the prevalence of eye disease is overestimated. However, the LSOCA population is

very similar to the AIDS epidemic in terms of demographic and other features, decreasing the likelihood of a referral bias. In that regard, the only HIV risk group underrepresented in the LSOCA cohort is injection drug use,^{15,16} a group with a higher prevalence of AMD, suggesting the possibility of underestimation of the prevalence of AMD in the AIDS epidemic.

In conclusion, persons with AIDS appear to have an approximately 4-fold increased prevalence of intermediate-stage AMD when compared to a similarly aged HIV-uninfected population. As in the HIV-uninfected population, the prevalence is strongly and significantly related to age. This finding also is consistent with the “aging phenotype” identified in antiretroviral-treated, immune-restored, HIV-infected persons.^{11,27} Reasons for this increased prevalence are not fully explained, but it may relate to the state of chronic immune activation and systemic inflammation seen in these patients,^{11,27,28} which would be consistent with the association of AMD with systemic inflammation seen in the HIV-uninfected population.^{29–31}

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Members of the SOCA Research Group are listed in [Supplemental Material](#) at www.ajo.com.

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SUPPLEMENTAL TABLE. Association of Baseline Individual Antiretroviral Drug Use With Intermediate-Stage Age-Related Macular Degeneration in Patients With Acquired Immunodeficiency Syndrome

Drug	Number of Patients	AMD ^a (%)	P Value
Combovir (zidovudine, lamivudine)			.34
No	1491	9.5	
Yes	333	11.7	
Zidovudine			.44
No	1757	10.0	
Yes	67	7.5	
Didanosine			.43
No	1561	10.1	
Yes	263	8.4	
Zalcitabine			.30
No	1814	9.9	
Yes	10	0	
Stavudine			.11
No	1340	10.5	
Yes	484	8.1	
Lamivudine			.90
No	1309	9.8	
Yes	515	9.9	
Abacavir			.66
No	1528	9.7	
Yes	296	10.8	
Adefovir			.01
No	1809	9.7	
Yes	15	33.3	
Hydroxyurea			.35
No	1776	10.0	
Yes	48	6.2	
Tenofovir			.29
No	1664	9.7	
Yes	160	11.9	
Trizavir (zidovudine, lamivudine, abacavir)			.51
No	1805	9.9	
Yes	19	5.3	
Epzicom (abacavir, lamivudine)			.44
No	1782	9.8	
Yes	42	14.3	
Emtricitabine			.89
No	1816	9.9	
Yes	8	12.5	
Truvada (emtricitabine, tenofovir)			.61
No	1687	10.0	
Yes	137	8.8	
Atripla (emtricitabine, tenofovir, efavirenz)			NA
No	1824	9.9	
Yes	0	NA	

AMD = age-related macular degeneration; NA = not applicable.

^aPercentage with intermediate-stage AMD reported.