Risk Factors for Mortality in Patients with AIDS in the Era of Highly Active Antiretroviral Therapy

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Objective: To evaluate risk factors for mortality among patients with AIDS in the era of highly active antiretroviral therapy (HAART), particularly the effect of cytomegalovirus (CMV).

Design: Prospective cohort study of patients with AIDS, conducted from 1998 through 2003.

Participants: One thousand five hundred eighty-three patients with AIDS, of whom 374 had CMV retinitis.

Methods: Patients were contacted every 3 months, with examinations at least every 6 months, in which standardized data were collected on AIDS history and treatment, eye examinations, and hematologic, virologic, and immunologic laboratory data.

Main Outcome Measure: Mortality.

Results: The overall mortality rate was 0.07 deaths/person-year. In a multivariate analysis, the following baseline risk factors were associated with an increased mortality: higher human immunodeficiency virus (HIV) viral load (relative risk [RR] = 4.6 for HIV viral load >100 000 copies/ml vs. <400 copies/ml; $P<0.0001$), lower CD4+ T-cell count at enrollment (RR = 3.8 for CD4+ T cell count 0–49 cells/μl vs. ≥200 cells/μl; $P<0.0001$), CMV viral load ≥400 copies/ml (RR = 1.9; $P = 0.002$), lower hemoglobin (RR = 1.7 for hemoglobin <10 g/dl; $P = 0.009$), a history of cryptococcal meningitis (RR = 1.7; $P = 0.02$), CMV retinitis (RR = 1.6; $P = 0.0002$), and Karnofsky score ≤80 (RR = 1.4; $P = 0.008$).

Conclusions: In the era of HAART, CMV disease as manifested by CMV retinitis and a detectable CMV viral load were associated with an increased risk for mortality, even after adjusting for demographic, treatment, immunologic, and HIV virologic factors. *Ophthalmology 2005;112:771–779 © 2005 by the American Academy of Ophthalmology.*

In industrialized countries, the introduction of highly active antiretroviral therapy (HAART) has resulted in a substantial decline in the mortality associated with AIDS.[1–3] By suppressing human immunodeficiency virus (HIV) replication for extended periods, HAART can lead to improvements in immune function (immune reconstitution) and to restoration of immunity to specific pathogens.[4] As a consequence, the incidence of opportunistic infections has declined,[1,5] and if there is sufficient immune recovery, secondary prophylaxis, such as for *Pneumocystis carinii* pneumonia and for cytomegalovirus (CMV) retinitis, can be discontinued without relapse of the disease.[6–10]

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Nevertheless, not all patients respond to or can tolerate HAART,[11] and as such, the declines in mortality and the incidence of opportunistic infections seem to have leveled off.[3,12,13] Therefore, there remains a need to understand risk factors for mortality in patients with AIDS. The Longitudinal Studies of the Ocular Complications of AIDS (LSOCA) is an ongoing multicenter, prospective cohort study of patients with advanced HIV disease; all patients enrolled in LSOCA have a diagnosis of AIDS.[14] We evaluated risk factors for mortality in this cohort.

Patients and Methods

Patients with a diagnosis of AIDS who are 13 years of age or older are eligible for enrollment in LSOCA regardless of current immunologic status and regardless of the presence of previous or existing opportunistic infections. AIDS is diagnosed according to the 1993 Centers for Disease Control and Prevention Revised Surveillance Case definition.[15] Data collection at enrollment includes demographic information, ophthalmic and medical histories, a complete ophthalmologic examination, estimation of Karnofsky performance score,[16] lymphocyte subsets measured by flow cytometry, plasma HIV viral load, and plasma CMV viral load.[17] Patient follow-up occurs every 3 months, via either a face-to-face visit or a telephone contact. All patients are scheduled for face-to-face visits every 6 months. Information on mortality is collected on an ongoing basis, and confirmation of death is obtained.

Cytomegalovirus retinitis was diagnosed on ophthalmologic examination by a study-certified ophthalmologist based on its characteristic presentation either as a necrotizing retinitis among those with active retinitis or as an atrophic and gliotic scar among those with quiescent retinitis resulting from anti-CMV treatment or from immune recovery.[6,18] The history of a diagnosis of other opportunistic infections was made according to the AIDS Clinical Trials Group guidelines, and confirmation of other opportunistic infections was obtained from the medical records. Highly active antiretroviral therapy (HAART) was defined as combination antiretroviral therapy with at least 3 drugs, containing at least 1 protease inhibitor or a nonnucleoside reverse transcriptase inhibitor.[1,14] Selected regimens with similar efficacy, such as triple nucleoside reverse transcriptase inhibitors (e.g., abacavir sulfate/lamivudine/zidovudine [Trizivir, GlaxoSmithKline, Brentford, United Kingdom]), also were classified as HAART. Karnofsky performance score was graded on a scale of 0 to 100 by 10-point decrements, with 100 being perfect health and 0 being death.[16] CD4+ T-cell counts were obtained at the individual clinical centers using standardized flow cytometry. Nadir CD4+ T-cell count was defined as the patient's lowest recorded CD4+ T-cell count at or before enrollment, determined from the patient's medical record. Human immunodeficiency virus viral load assays were performed at each clinical center. Ninety-two percent of these measurements were performed with a polymerase chain reaction assay using the Roche Amplicor system (Roche Molecular Systems, Pleasanton, CA). Only 4% of patients had their HIV viral load measured with a branch chain DNA method, and the remaining 4% had their HIV viral load measured with a second-generation or ultrasensitive polymerase chain reaction assay. For analysis, HIV viral load levels less than the assay lower limit of detection were assigned a value of one half of the lower limit, and values exceeding 750,000 copies/ml were assigned a value of 750,000 copies/ml. Plasma specimens for CMV viral load assays were processed at each clinical center and were shipped to a central laboratory for measurement using the Roche Amplicor system.[14,17] Using this assay, the lower limit of detection of CMV viral load is 400 copies/ml. Because of the high frequency of undetectable CMV viral load measurements, in the analyses it was treated as a binary variable rather than as a continuous one.

Data collected and reported to the coordinating center as of December 31, 2003, are included in this report. All enrolled patients with follow-up data as of that date are included in the analyses. Patients were classified as having CMV disease based on their reported medical history; the diagnosis of CMV retinitis was confirmed by an ophthalmologic examination. Follow-up time was calculated as the time from study entry to death for patients who died; to December 31, 2003, for patients under active follow-up; or to the date of the last study contact for patients who were lost to follow-up for mortality. Mortality rates were calculated as the number of deaths divided by the number of person-years at risk. Relative risks were estimated with Cox proportional hazards.[19] Survival analyses were performed with staggered entries based on time since diagnosis of AIDS.[20] This method allows for comparison of mortality among persons with similar duration of AIDS. The analysis of CMV retinitis as a risk factor for mortality was performed using time-dependent methods to account for the 18 patients in whom CMV retinitis developed during follow-up. An analysis in which these 18 patients were censored gave similar results (data not shown). For multivariate models, missing data for covariates were imputed to the most frequent category. An alternative analysis using multiple imputation methodology to address missing values did not alter the interpretation of the results (data not shown).[21] The baseline characteristic with the highest percentage of missing data was HIV viral load (96 observations; 6.1%). Variables were selected for inclusion in the multivariate model with stepwise regression; all models included CD4+ T-cell level, HIV viral load, and known predictors of mortality in AIDS. For inclusion of other covariates, $P = 0.05$ was used as the cutoff.[22] Backward and forward selection procedures were used, with both techniques yielding the same model. Analyses were performed with SAS software[22] and Stata software.[23] Analyses using only study follow-up time as the time scale, that is, without anchoring that time to the date of AIDS diagnosis, gave similar results.

This study was reviewed and approved by the institutional review boards at each of the participating centers, and all patients gave written informed consent.

Results

Enrollment, Baseline Characteristics, and Follow-up

Baseline characteristics of the study population are shown in Table 1; 1583 patients were enrolled from September, 1998, through March 31, 2003. The population was largely male, with a median age of 42 years. Nearly one half of the population was white, and there were substantial proportions of black and Hispanic patients. The predominant risk for HIV infection was men having sex with men, but there was also a substantial proportion of patients with heterosexual transmission as their risk factor. Nearly 90% of patients were receiving antiretroviral therapy, and nearly 80% were receiving HAART. Although the population typically had a history of severe immune compromise, as evidenced by the median nadir CD4+ T-cell count of 27 cells/μl, participants' immune function typically had improved, as evidenced by the median enrollment CD4+ T-cell count of 162 cells/μl. However, 25% of the population remained severely immune compromised, as evidenced by the lower quartile having CD4+ T-cell counts of less than 53 cells/μl. Despite the general improvement in immune function, as evidenced by the increased CD4+ T-cells, only 38.9% of participants had an HIV viral load of $<$400 copies/ml at enrollment.

Of the 1583 patients studied, 374 (23.6%) had a diagnosis of

Table 1. Baseline Characteristics of the Study Population

Characteristic	Total	No. of Observations
No. of patients	1583	
Gender (%)		1576
Men	80.8	
Women	19.2	
Age (yrs)		1552
Median	42	
Interquartile range	36–47	
Race (%)		1579
White, not Hispanic	49.3	
Black	32.5	
Hispanic	15.0	
Other	3.2	
HIV risk group (%)		1546
Men having sex with men	58.9	
Injection drug use	11.4	
Heterosexual	25.7	
Other	4.0	
Time since AIDS diagnosis (yrs)		1583
Median	4.1	
Interquartile range	1.8–6.6	
AIDS diagnosis (%)		1559
Opportunistic infection/syndrome	40.3	
CD4+ T cells <200 cells/μl	59.7	
Current HIV treatment		1581
None	13.0	
1 or 2 antiretroviral drugs	9.7	
Highly active antiretroviral therapy	77.3	
Karnofsky score		1566
Median	80	
Interquartile range	80–90	
Opportunistic infections (%)		1583
Pneumocystis carnii pneumonia	33.4	
Cerebral toxoplasmosis	2.2	
Cryptococcal meningitis	4.7	
Mycobacterium avium complex infection	8.7	
Cytomegalovirus disease	24.2	
Cytomegalovirus retinitis	23.6	
Visceral cytomegalovirus only	1.5	
Hemoglobin (g/dl)		1572
Median	13.6	
Interquartile range	12.2–14.8	
CD4+ T cells (cells/μl)		1561
Median	162	
Interquartile range	53–315	
Nadir CD4+ T cells (cells/μl)		1553
Median	27	
Interquartile range	8–81	
HIV viral load (copies/ml)		1487
Median	2129	
Interquartile range	187–7500	
% <400 copies/ml	38.9	
Cytomegalovirus load ≥400 copies/ml (%)	4.1	1510

HIV = human immunodeficiency virus.

CMV retinitis either at or before the time of enrollment or during follow-up. Other opportunistic infections included a history of *P. carinii* pneumonia in 33.4% of patients, cerebral toxoplasmosis in 2.2% of patients, cryptococcal meningitis in 4.7% of patients, and *Mycobacterium avium* complex infection in 8.7% of patients. Sixty-six of the 1583 patients had a history of extraocular (visceral) CMV disease, and 42 of these patients also had CMV retinitis. Only 1.5% of patients had extraocular CMV without CMV retinitis.

Median follow-up for the entire group was 2.3 years, and there was a total of 3714 person-years of follow-up. Of the 1583 patients enrolled, 8.4% were considered to have an unknown vital status as of December 31, 2003.

Mortality

There were 268 deaths, and the mortality rate for the entire patient population enrolled in LSOCA was 0.07 deaths/person-year. Baseline (enrollment) risk factors for mortality are listed in Table 2. Patients with CMV retinitis at enrollment had a significantly greater mortality than those without (Fig 1; relative risk [RR] = 2.3, $P<0.0001$). Because of the reduced mortality rate after immune recovery,[1] and because of the ability to discontinue anti-CMV therapy after sustained immune recovery to a CD4+ T-cell count of ≥100 cells/μl,[10] we evaluated whether the effect of CMV retinitis on mortality was different when there was immune recovery. There was an apparent difference in the effect of CMV retinitis, depending on the CD4+ T-cell count at enrollment. Among patients with a CD4+ T-cell count of 0 to 99 cells/μl at enrollment, the mortality for patients without CMV retinitis was 0.10/person-year (91 deaths/384 participants), whereas for those with CMV retinitis the mortality rate was 0.25/person-year (97 deaths/185 participants). The relative risk for mortality among those with CMV retinitis was 2.4 ($P<0.0001$) versus those without CMV retinitis. Conversely, among patients with an enrollment CD4+ T-cell count ≥100 cells/μl, the mortality rate was 0.03/person-year for those without CMV retinitis (59 deaths/805 participants) and 0.03/person-year for those with CMV retinitis (18 deaths/187 participants; $P = 0.96$).

Among other opportunistic infections, only a history of cryptococcal meningitis was associated with an increased risk for mortality (RR = 2.2; $P = 0.0004$). A history of *P. carinii* pneumonia, cerebral toxoplasmosis, or *M. avium* complex infection was not associated with a significantly increased risk of mortality. There was no significant difference in mortality whether the patient was diagnosed as having AIDS with an opportunistic infection or with T-cell lymphopenia ($P = 0.65$). Baseline Karnofsky score was associated with mortality (RR = 2.6 for ≤80 vs. 90–100; $P<0.0001$). Highly active antiretroviral therapy at enrollment was associated with a 60% reduction in the risk of mortality (RR = 0.4; $P<0.0001$).

Several laboratory measures were associated with an increased risk for mortality, including: low hemoglobin (<10 g/dl; RR = 2.9; $P<0.0001$); low CD4+ T-cell count at enrollment (RR = 9.0 for the lowest group [0–49 cells/μl] compared with that for the highest group [≥200 cells/μl]; $P<0.0001$); and low nadir CD4+ T-cell count (RR = 2.8 for 0–99 cells/μl vs. ≥100 cells/μl; $P<0.0001$). Higher HIV viral load at enrollment was associated with a greater risk for mortality ($P<0.0001$); the relative risk for the highest category (>100 000 copies/ml) was 11.1 compared with the lowest category (<400 copies/ml). Cytomegalovirus viral load also was associated with an increased risk of mortality; the RR for mortality for a CMV viral load of ≥400 copies/ml compared with a CMV viral load of <400 copies/ml was 5.2 ($P<0.0001$). Of the 268 deaths, 1 was the result of homicide, and all others seemed to be related to complications of HIV infection. There were no substantial differences in the causes of death between patients with and without CMV retinitis (data not shown).

The results of the multivariate analysis of risk factors for mortality are shown in Table 3. Overall, CMV retinitis was associated with a 1.6-fold increase in the risk of mortality when compared with that for those patients without retinitis ($P = 0.0002$). A history of cryptococcal meningitis was associated with an increased risk for mortality (RR = 1.7; $P = 0.02$). A lower Karnofsky score (≤80) was associated with an increased risk for mortality (RR = 1.4; $P = 0.008$), as was lower hemoglobin (<10

Table 2. Baseline Risk Factors for Mortality

Baseline Characteristics	Rate (Person-Year)*	No. Deaths/ No. at Risk	Relative Risk*	*P* Value†
Overall	0.07	268/1583		
Demographics				
Gender				
Male	0.07	206/1274	0.8	0.07
Female	0.09	61/302	1.0	
Age (yrs)				
<42	0.07	138/830	1.0	0.68
≥42	0.07	127/722	1.1	
Race				
White, not Hispanic	0.07	132/779	1.0	0.06
Black	0.09	96/513	1.4	
Hispanic	0.06	32/237	0.9	
Other	0.07	8/50	1.0	
HIV risk group				
MSM	0.06	146/911	1.0	0.05
IDU	0.10	34/176	1.5	
Heterosexual	0.08	68/397	1.2	
Other	0.10	15/62	1.6	
AIDS diagnosis				
Opportunistic infection/syndrome	0.07	113/628	1.0	0.65
CD4+ T-cell count <200 cells/μl	0.07	154/931	0.9	
AIDS diagnosis date				
July 1996 or earlier	0.07	162/843	1.0	0.93
August 1996 or later	0.07	106/740	1.0	
Karnofsky score				
90–100	0.04	82/777	1.0	<0.0001
≤80	0.11	185/789	2.6	
Treatment				
Baseline antiretroviral treatment				
No HAART	0.14	90/359	1.0	<0.0001
HAART	0.06	178/1222	0.4	
Opportunistic infections				
No *Pneumocytis carinii* pneumonia	0.07	163/1054	1.0	0.07
Pneumocystis carinii pneumonia	0.08	105/529	1.3	
No cerebral toxoplasmosis	0.07	261/1548	1.0	0.37
Cerebral toxoplasmosis	0.10	7/35	1.4	
No cryptococcal meningitis	0.07	246/1509	1.0	0.0004
Cryptococcal meningitis	0.16	22/74	2.2	
No MAC infection	0.07	234/1445	1.0	0.19
MAC infection	0.09	34/138	1.3	
No CMV retinitis	0.05	153/1209	1.0	<0.0001
CMV retinitis	0.12	115/374	2.3	
Laboratory				
Hemoglobin (g/dl)				
≥10	0.07	239/1499	1.0	<0.0001
<10	0.19	29/73	2.9	
CD4+ T-cell count (cells/μl)				
≥200	0.02	40/670	1.0	<0.0001
100–199	0.05	37/322	2.2	
50–99	0.07	31/194	3.2	
0–49	0.20	157/375	9.0	
Nadir CD4+ T-cell count (cells/μl)				
≥100	0.03	22/313	1.0	<0.0001
0–99	0.08	246/1240	2.8	
HIV viral load (copies/ml)				<0.0001
<400	0.02	20/410	1.0	
400–10 000	0.03	37/456	1.6	
10 001–100 000	0.09	69/316	4.7	
>100 000	0.21	126/305	11.1	
CMV viral load (copies/ml)				<0.0001
<400	0.07	232/1448	1.0	
≥400	0.30	33/62	5.2	

CMV = cytomegalovirus; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency virus; IDU = injection drug user; MAC = *Mycobacterium avium* complex; MSM = men having sex with men.
*Of deaths as compared to reference group.
†Unadjusted *P* value for RRs.

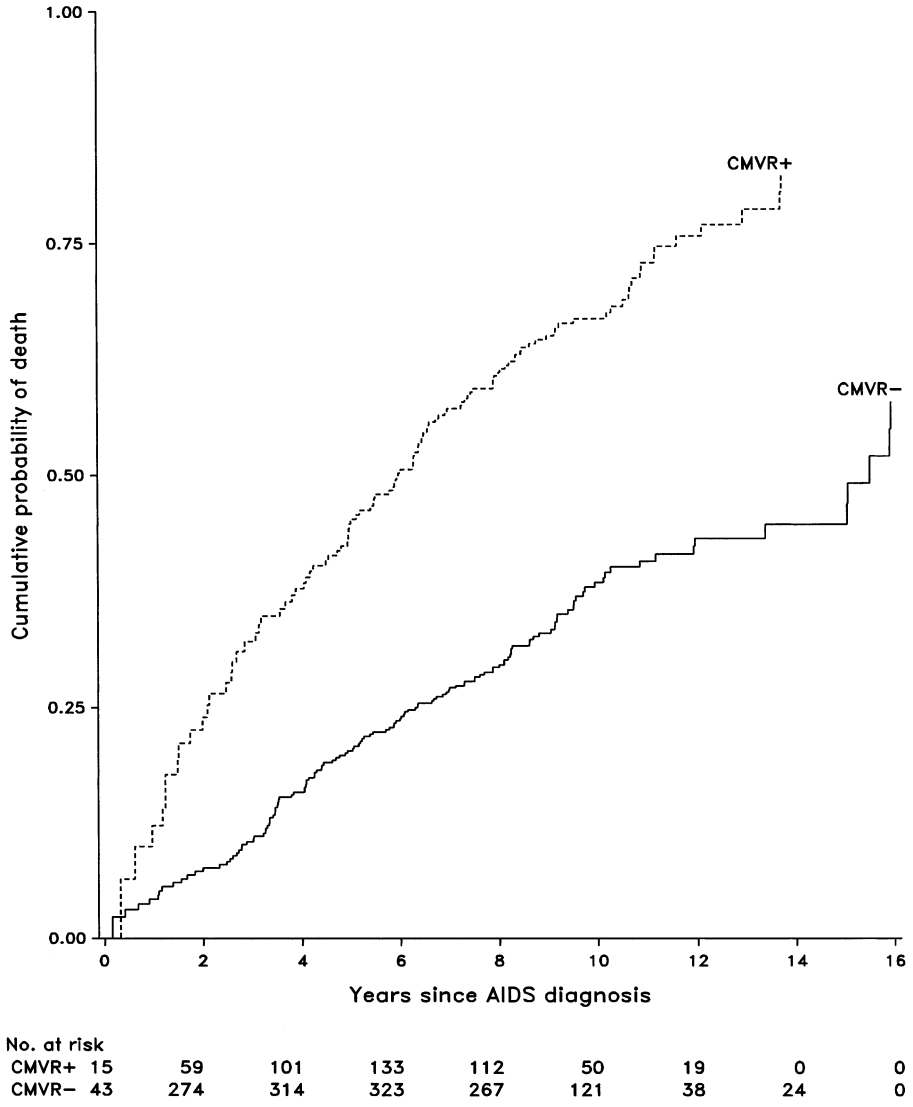

Figure 1. Kaplan–Meier analysis of mortality comparing patients with (+) and without (−) cytomegalovirus retinitis (CMVR).

mg/dl; RR = 1.7; $P = 0.009$). Lower CD4+ T-cell count at enrollment was associated with an increased risk of mortality ($P<0.0001$); the RR for the lowest group (0–49 cells/μl) was 3.8 compared with that for the highest group (≥200 cells/μl). Higher HIV viral load at enrollment was associated with an increased risk of mortality ($P<0.0001$); the RR for the highest group (>100 000 copies/ml) was 4.6 compared with that for the lowest group (<400 copies/ml). The CMV viral load remained associated with increased mortality; the RR for mortality for patients with a CMV viral load ≥400 copies/ml was 1.9 compared with that for those patients with a CMV viral load <400 copies/ml ($P = 0.002$).

Because of the suggestion in the univariate analysis that the effect of CMV retinitis on mortality was different for different CD4+ T-cell counts, a multivariate analysis was performed of the mortality risk by CMV retinitis and CD4+ T-cell count (Table 4). Among patients with an enrollment CD4+ T-cell count of 0 to 99 cells/μl, CMV retinitis was associated with an adjusted RR for mortality of 2.1 ($P<0.0001$). Conversely, among patients with an enrollment CD4+ T-cell count of 100 cells/μl or more, the adjusted RR for mortality among patients with CMV retinitis was 1.0 ($P = 0.94$). The P value for the interaction was 0.02, which, given the number of subgroups examined, and therefore the large number of potential interactions, is considered moderate evidence for an interaction, that is, that the effect of CMV retinitis on mortality is modified by CD4+ T-cell count.

A multivariate analysis of risk factors for mortality also was performed including all CMV disease diagnoses. This analysis included both ocular and nonocular diagnoses of CMV disease and did not alter any of the conclusions (data not shown). A subgroup analysis restricted to patients with a nadir CD4+ T-cell count <50 cells/μl gave results similar to those from the entire population (data not shown).

Discussion

Although all patients enrolled in LSOCA were diagnosed as having AIDS, there was a diversity of immunologic function at the time of enrollment. Nearly 80% of patients

Table 3. Multivariate Analysis of Risk Factors for Mortality

Risk Factor	RR*	95% Confidence Interval	P Value
Cytomegalovirus retinitis			0.002
No retinitis	1.0	—	
Cytomegalovirus retinitis	1.6	1.3, 2.2	
History of cryptococcal meningitis			0.02
No	1.0		
Yes	1.7	1.1, 2.7	
Karnofsky score			0.008
90–100	1.0		
≤80	1.4	1.1, 1.9	
Hemoglobin (g/dl)			0.009
≥10	1.0		
<10	1.7	1.1, 2.6	
CD4+ T-cell count (cells/μl)			<0.0001
≥200	1.0	—	
100–199	1.7	1.1, 2.6	
50–99	1.9	1.2, 3.2	
0–49	3.8	2.6, 5.7	
HIV viral load (copies/ml)			<0.0001
<400	1.0	—	
400–10 000	1.9	1.1, 3.2	
10 001–100 000	3.2	1.9, 5.3	
>100 000	4.6	2.7, 7.6	
CMV viral load (copies/ml)			0.002
<400	1.0		
≥400	1.9	1.3, 2.8	

CMV = cytomegalovirus; HIV = human immunodeficiency virus.
*RR = Adjusted relative risk from proportional hazard regression.

enrolled were receiving HAART; more than one half had experienced some degree of immune reconstitution; and there was a wide range of CD4+ T-cell counts at the time of enrollment. Approximately one fourth of the patients had CMV retinitis at the time of enrollment. As such, the study cohort contained a broad spectrum of immunologic function, virologic status, and functional status among patients with AIDS. In part because of our interest in ocular complications, primarily CMV retinitis, the study cohort had a substantial proportion of patients with CMV retinitis. However, studies from the pre-HAART era suggested that approximately 30% of patients with AIDS would experience CMV retinitis,[18,24] and 1 prevalence study suggested that 30% of patients with CD4+ T-cell counts <50 cells/μl would have CMV retinitis when routine ophthalmologic examinations were performed.[25] Therefore, given the low nadir CD4+ T-cell count of this cohort, a substantial proportion of patients would be expected to have CMV retinitis.

In the univariate analysis, several baseline factors were associated with increased mortality, including lower Karnofsky performance score, anemia, lower CD4+ T-cell count at enrollment, lower nadir CD4+ T-cell count, higher HIV viral load at enrollment, CMV viral load ≥400 copies/ml at enrollment, a history of cryptococcal meningitis, and the presence of CMV retinitis. Highly active antiretroviral therapy at enrollment was associated with decreased mortality. Several of these factors previously have been associated with an increased risk for either mortality or progression of HIV disease, including anemia, lower CD4+ T-cell count, lower nadir CD4+ T-cell count, and higher HIV viral load,[2,26–29] whereas HAART has been associated with improved survival.[1,2,26–29] However, in the multivariate analysis, some of the factors detected in the univariate analysis no longer were associated significantly with mortality; their influence presumably was mediated via other factors. Hence, HAART no longer was associated with a decreased mortality risk in the multivariate model, presumably because the effect of HAART was mediated through increased CD4+ T-cell counts and decreased HIV viral load.

Several other cohort studies of HIV-infected patients from the HAART era, including the French Hospital Database for HIV, the combined Swiss HIV, Frankfurt HIV, and EuroSIDA cohorts, and the British Columbia Centre for Excellence in HIV/AIDS cohort have reported mortality rates in the range of 0.02 to 0.03/person-year for patients treated with HAART.[2,28,29] The greater mortality rate in the LSOCA study likely reflects several factors, including the more advanced stage of HIV infection of patients in LSOCA (all patients in LSOCA had a diagnosis of AIDS) than in some of those studies. In the multivariate analysis of the British Columbia study, only a lower CD4+ T-cell count at baseline was associated with mortality, and HIV viral load was not associated with mortality. Conversely, in the multivariate analysis of the LSOCA study, both higher HIV viral load at enrollment and lower CD4+ T-cell count at enrollment were associated with an increased risk of mortality.

Cytomegalovirus retinitis remained a risk factor for mortality in the multivariate analysis, which also included CD4+ T-cell count and HIV viral load. The only other opportunistic infection associated with increased mortality was a history of cryptococcal meningitis, which occurs in a substantially smaller proportion of patients with AIDS in the United States than does CMV disease,[29] as it did in our cohort. Disease resulting from CMV is among the most common opportunistic infections in patients with AIDS,[18,23,30–32] and retinitis accounts for 75% to 85% of CMV disease among patients with AIDS.[31,32] In the era before HAART, the lifetime probability of a patient with AIDS developing cytomegalovirus was estimated to be 30%.[24] Highly active antiretroviral therapy has resulted in approximately a 75% decline in the number of new cases of CMV retinitis per year compared with that seen during the peak era of opportunistic infections among patients with

Table 4. Mortality Risk by Cytomegalovirus Retinitis and CD4+ T-Cell Count

CD4+ T cell (cells/μl)	Cytomegalovirus Retinitis	Relative Risk*	95% Confidence Interval	P Value†
0–99	No	1.0	—	<0.0001
	Yes	2.1	1.5, 2.8	
≥100	No	1.0		0.94
	Yes	1.0	0.6, 1.7	

*Adjusted relative risk from proportional hazard model.
†Interaction P value = 0.02.

AIDS,[1,12,13] but this decline seems to have leveled off, and new cases of CMV retinitis continue to occur.[14]

Cytomegalovirus retinitis is a late-stage manifestation of HIV infection and typically occurs among patients with CD4+ T-cell counts <50 cells/μl.[14,25,31,32] Because of the level of immune deficiency associated with CMV retinitis, mortality among these patients in the era before HAART was substantial. Median survival among these patients typically was estimated to be 1 year.[18,33–36] With the advent of HAART, there has been an improvement in survival[37,38] and an increasing, prevalent population of patients with CMV retinitis.[14]

Although CMV retinitis was a risk factor for mortality in the multivariate analysis, there was a suggestion of an interaction between the presence of CMV retinitis and the enrollment CD4+ T-cell count. Mortality was increased among those with a CD4+ T-cell count <100 cells/μl, but did not seem to be increased among those with a CD4+ T-cell count ≥100 cells/μl. A threshold CD4+ T-cell count of 100 cells/μl typically is used as the cutoff for discontinuation of maintenance anti-CMV therapy among patients with sustained immune recovery.[10] Data from The Johns Hopkins Cytomegalovirus Retinitis Cohort demonstrated that the use of systemic anti-CMV therapy (as opposed to only local, ocular, anti-CMV therapy) is associated with a 20% reduction in the risk of mortality.[39] The increased mortality among patients with CD4+ T-cell counts <100 cells/μl, coupled with the ability of systemic anti-CMV therapy to reduce this mortality, suggests that continued use of such treatment is appropriate. The similar mortality rates among patients with an enrollment CD4+ T-cell count ≥100 cells/μl, regardless of whether CMV was present, suggests that anti-CMV maintenance therapy (secondary prophylaxis) can be discontinued safely after a sustained immune recovery to a CD4+ T-cell count level of ≥100 cells/μl. Not only is the retinitis unlikely to progress,[5–10] but the beneficial effect of systemic anti-CMV therapy likely no longer will be necessary for those with such immune recovery.

Cytomegalovirus viral load also was associated with an increased mortality in the multivariate model. Cytomegalovirus viremia, detected as a positive CMV viral load, was a recognized predictor of CMV disease and death among patients with AIDS in the era before HAART.[40–42] Improved immune function resulting from HAART decreases CMV replication and can clear CMV viremia, as evidenced by changing CMV viral load from detectable to undetectable among patients receiving HAART.[43–45] The widespread use of HAART in the study cohort presumably explains the low prevalence of detectable CMV viral load at enrollment.

As with most research studies, the survival estimates from the LSOCA cohort are subject to potential survival bias—the study participants may have better survival than the general population of AIDS patients. The survival analysis with staggered entry partially addresses this bias by comparing the risks of death among patients with similar duration of AIDS.[46,47] The Centers for Disease Control and Prevention's estimates of the survival after a diagnosis of AIDS[3] generally are lower than those for the LSOCA cohort, especially for patients diagnosed with AIDS before 1996. Hence, the estimates of median survival for patients with and without CMV retinitis from this study may be optimistic. However, if the analysis is restricted to participants diagnosed with AIDS after 1996, the estimates of median survival times are similar, suggesting comparability with patients with more recently diagnosed AIDS.

As with most research studies, the cohort also is subject to potential selection bias. As compared with the Centers for Disease Control and Prevention's estimate of all persons living with AIDS in the United States as of December, 2002, the LSOCA cohort has slightly more men (81% vs. 78%), has more white persons (49% vs. 37%), is older (35% ≥40 years of age vs. 22%), and has relatively fewer people exposed to HIV via injection drug use (11% vs. 32%). However, we saw no evidence that the effect of CMV retinitis on mortality was different among any of these subgroups, suggesting that these factors did not greatly bias our results.[46] We do not know whether patients with CMV retinitis enrolled in LSOCA are representative of all patients in the United States with a diagnosis of AIDS and CMV retinitis, although the entire LSOCA cohort experienced longer survival compared with national trends. It is likely that their survival is longer because of a healthy participant effect, that is, they survived long enough after diagnosis to be enrolled in LSOCA. Hence, we believe that reasons for patient selection into LSOCA are likely to have operated similarly in patients with and without CMV retinitis and that the estimate of effect of CMV retinitis on mortality is relatively unbiased.

In this study, CMV retinitis was chosen as the CMV disease variable because it represents the vast majority of CMV disease in patients with AIDS and because its diagnosis can be made with a high degree of certainty. An experienced ophthalmologist can make the diagnosis of CMV retinitis reliably.[18,33–36] Nonocular CMV diagnoses were obtained from patient histories, with confirmation from medical records. Although attempts were made in the interview process to elicit symptoms related to CMV disease and to refer appropriate patients for evaluation, CMV retinitis remained the most frequent and most certain end-organ CMV diagnosis. The multivariate model defining CMV disease as all CMV diagnoses (including ocular and visceral CMV disease) did not change the conclusion that CMV disease was associated with an increased mortality. The overlap between patients with CMV retinitis and those with visceral CMV disease and the similar results for risk factors for mortality between the CMV retinitis and any CMV disease groups may reflect the fact that CMV retinitis typically is a manifestation of systemic infection. In the pre-HAART era, autopsy studies of patients with CMV retinitis suggested that nearly all such patients had CMV infection elsewhere in the body.[48]

Cytomegalovirus and HIV are known to transactivate each other in vitro.[49,50] Hence, it is conceivable that HIV and CMV would have additive or even synergistic deleterious effects on the immune system. Cytomegalovirus infection has been reported to be associated with an increased risk of progression of HIV disease among pediatric patients and among those with transfusion-associated HIV infection.[51–53] Because the effect of CMV on mortality was

independent of HIV viral load in the LSOCA cohort, this result suggests that CMV's effect on mortality was not mediated strictly through increasing HIV viral replication via transactivation. The CMV genome contains an interleukin-10 homolog.[54,55] Interleukin-10 is a cytokine that suppresses Th1 type immune responses, such as cell-mediated immunity, and the CMV homolog also has immunosuppressive effects.[55] Hence, it is possible that the CMV interleukin-10 homolog adds to or synergizes with the immune deficiency caused by HIV infection and increases mortality.

In conclusion, in the era of HAART, CMV end-organ disease, as manifested by retinitis, is associated with increased mortality that is present even after adjusting for immunologic status, as manifested by CD4+ T-cell count; virologic status, as manifested by HIV viral load; and antiretroviral therapy. There was a suggestion that the excess mortality among patients with CMV retinitis was seen primarily among those with a low CD4+ T-cell count (<100 cells/μl), suggesting that discontinuation of anti-CMV maintenance therapy among those with sustained increases in CD4+ T-cell counts to a level ≥ 100 cells/μl also is safe from a systemic perspective. However, patients with newly diagnosed CMV retinitis may well benefit from systemic and anti-CMV therapy in terms of improved survival.[39] Because there are an increasingly large prevalent population of patients with previously diagnosed CMV retinitis and ongoing new cases of CMV retinitis,[14] these data suggest that CMV disease remains an important factor in the AIDS epidemic even in the era of HAART.

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