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Mortality associated with resistant cytomegalovirus among patients with cytomegalovirus retinitis and AIDS

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Abstract

Objective—To evaluate the effect of drug-resistant cytomegalovirus (CMV) on survival among patients with CMV retinitis.

Design—Prospective cohort study during 1993–2003.

Participants—266 patients with AIDS and newly diagnosed CMV retinitis treated with either ganciclovir or foscarnet.

Methods—Data on ganciclovir and foscarnet resistance were obtained from blood and urine specimens collected at regular, pre-determined intervals. The effect of resistant CMV on mortality was evaluated with a time-dependent Cox proportional hazard model.

Main outcome measure—Mortality

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Results—Median survival of the entire cohort was 12.6 months. Analysis of risk factors for mortality demonstrated that resistant CMV was associated with an increased mortality (hazard ratio = 1.65, 95% confidence interval=1.05–2.56, P=0.032). Among the other parameters tested, only time since AIDS diagnosis was associated significantly with mortality, with a hazard ratio of 1.10 per year since AIDS diagnosis (P=0.001).

Conclusions—Resistant CMV is associated with increased mortality among patients with AIDS being treated for CMV retinitis.

Keywords

AIDS; cytomegalovirus; retinitis; resistance; mortality

Disease due to cytomegalovirus (CMV) is among the most frequent opportunistic infections in patients with AIDS.[1–4] Retinitis accounts for ~80% of CMV disease.[1,2] Prior to the introduction of highly active antiretroviral therapy (HAART) in the mid 1990's, CMV retinitis affected an estimated 30% of patients with AIDS.[5] Although HAART has resulted in an 80% reduction in the incidence of CMV retinitis, this decrease has leveled off, and new cases continue to occur.[6–8] Unless there is immune recovery, long-term suppressive anti-CMV therapy is needed to prevent relapse of the retinitis, as relapse occurs promptly after discontinuation of anti-CMV therapy in immune compromised patients.[9,10] With chronic therapy, resistant CMV can occur, and resistant CMV is associated with retinitis relapse and worse visual outcomes.[11–14]

Cytomegalovirus retinitis is part of a systemic infection, as evidenced by positive blood and urine cultures and circulating CMV DNA in the blood of patients diagnosed with CMV retinitis.[15–17] Cytomegalovirus retinitis in patients with AIDS and immune compromise also is associated with an increased mortality.[18] This mortality is decreased by systemic (as opposed to intraocular only) anti-CMV therapy.[19] Because resistant CMV would allow CMV to resume replicating, which could result in an increased mortality, we evaluated the effect of resistant CMV on survival in the context of a prospective cohort study of patients with CMV retinitis who were systematically evaluated for resistant CMV.

PATIENTS AND METHODS

Study population

Patients with AIDS and newly diagnosed CMV retinitis were enrolled at one of three centers: the Johns Hopkins University School of Medicine in Baltimore, MD (1993–2003); the Northwestern University School of Medicine in Chicago, IL (1997–2003); and the University of Miami, School of Medicine in Miami, FL (1997–2003). Follow-up continued through June 2004.

Data collection

Before the start of anti-CMV therapy, blood and urine specimens were obtained for CMV culture. Treatment was determined by the best judgment of the treating clinician, but treatments were used in a standardized fashion. Follow-up cultures were performed 1 and 3 months after enrollment and every 3 months thereafter. CD4+ T cell counts were obtained at enrollment, and after May 1996 every 3 months during follow-up.[20] The amount of Human Immunodeficiency Virus (HIV) RNA in the blood ("HIV load") and CMV DNA in the plasma ("CMV load") at enrollment each were measured by quantitative PCR with the Amplicor HIV-1 monitor test (Roche Diagnostics) and Cobas Amplicor CMV monitor test (Roche Diagnostics), respectively, beginning in May 1996.[16,21] Information on anti-CMV and antiretroviral therapies were obtained at the regularly scheduled follow-up visits for CMV

cultures. Receipt of a protease inhibitor or of a non-nucleoside reverse transcriptase inhibitor was used to indicate HAART.

CMV cultures and susceptibility testing

Culture specimens were processed at each clinical center's virology laboratory using standardized methodology, and isolates were sent to the Virology Laboratory at the Johns Hopkins Hospital for susceptibility testing. Testing for ganciclovir and foscarnet susceptibility was performed with either a DNA hybridization assay (Hybriwix Probe System—CMV Susceptibility Test Kit, Diagnostic Hybrids) or the plaque reduction assay. We previously reported that there was an excellent correlation between the two methods.[12,22–24]

Definition of resistant CMV

Culture isolates, rather than directly PCR-amplified blood specimens, were used to detect resistant CMV, as culture isolates are more predictive of clinical behavior.[24] Phenotypic resistance was chosen as it is a direct measure of CMV resistance. For culture isolates, measures of phenotypic and genotypic resistance are highly correlated and similarly predictive of clinical behavior.[24] Phenotypic resistance to ganciclovir was defined as an inhibitory concentration 50% (IC_{50}) > 6 μM for a blood isolate and > 8 μM for a urine isolate.[23] Phenotypic resistance to foscarnet was defined as and IC_{50} > 600 μM. Because the thresholds for cidofovir resistance are less well established, only ganciclovir and foscarnet resistance were analyzed.[25]

HIV load

For the multivariate analysis including HIV load at enrollment, HIV load was treated as a categorical variable (detectable, i.e. > 400 copies/mL, or undetectable) and missing values prior to 1996 were imputed as detectable, as it was assumed that HIV replication was inadequately controlled in the pre-HAART era.

Mortality

Survival was calculated from the date of enrollment, which was at the time of diagnosis of CMV retinitis.

Statistical analysis

For characteristics of patients in the CRVR study, frequencies of categorical variables and medians and interquartile ranges of continuous variables were calculated on the period of enrollment as before 1996 or 1996 and after. The year 1996 was the year in which HAART use became widespread and the ganciclovir implant (Vitrasert®, Bausch & Lomb) was approved by the FDA.[26,27] We evaluated the effect of resistance on mortality with a time-dependent Cox proportional hazard model using the method of Andersen and Gill[28] in which patients' resistance status could initially be "susceptible" (resistant CMV is unusual at the diagnosis of CMV retinitis)[29] but could later change to "resistant" (resistance typically occurs with prolonged exposure to antiviral agents).[11–13] In each given time block after diagnosis of CMV retinitis in which resistance status was determined, the risk of death was compared between those who had evidence of resistant virus by that point in time and those who did not. Several baseline predictors of outcome (time since AIDS, use of HAART, CD4+ T-cell count, positive CMV culture, and detectable HIV load) were included in the model.

RESULTS

Study population

Of the 309 participants enrolled in the CRVR Study, 266 received either ganciclovir or foscarnet and had at least one follow-up visit. Of participants enrolled in the CRVR Study, 46

participants were co-enrolled in the Longitudinal Study of the Ocular Complications of AIDS (LSOCA)[18], and 199 were included in the Johns Hopkins Cytomegalovirus Retinitis Cohort study on mortality.19 The characteristics of the study population are listed as Table 1 (available at http://aaojournal.org). Secular demographic trends in the study population mirrored those of the AIDS epidemic, including an increasing proportion of women and non-white persons, as well as an increasing proportion of patients for whom heterosexual transmission was the mode of HIV acquisition. HAART use and use of the ganciclovir implant reflect their introduction and FDA-approval. The availability of HIV load and CMV load measurements at enrollment reflect the previously noted changes in the protocol after the widespread adoption of these technologies. Cytomegalovirus resistant to either ganciclovir or foscarnet was not present at enrollment (which was the time of diagnosis of CMV retinitis) in any of the 266 participants followed in this study. The risk of developing resistant CMV was 10.7% of patients by one-year and 17.2% by two years after diagnosis of CMV retinitis. Coincident with the introduction of HAART there was an apparent improvement in survival and a reduction in the incidence of resistant.[8,13]

Survival

One hundred eighty-eight of the 266 patients died. Median survival from the diagnosis of CMV retinitis was 12.6 months with an interquartile range of 5.8 to 24.9 months. For those patients who developed resistance, the median survival from time of CMV retinitis diagnosis was 7.0 months with an interquartile range of 5.1 to 13.1 months (Figure 1). Univariate analysis of survival from a time-dependent Cox model suggested that the occurrence of resistant CMV was associated with an increased mortality (Hazard Ratio [HR] = 1.61, 95% confidence interval [CI] = 1.04–2.48, P=0.033). A multivariate analysis, including resistant CMV, time since AIDS diagnosis, HAART use at diagnosis of retinitis, CD4+ T cells at diagnosis of retinitis, CMV culture results at diagnosis of retinitis, and HIV load at diagnosis of retinitis, is listed as Table 2. The effect of resistant CMV on mortality was relatively unaffected by these other variables (HR = 1.65, 95% CI = 1.05–2.56, P = 0.032). Of the other parameters, only time since AIDS diagnosis was significantly associated with mortality with a HR = 1.10 per year since AIDS diagnosis (P=0.001).

Because HAART had a substantial effect on the course of AIDS, and because the CRVR study spanned the pre-HAART and HAART eras, survival of patients with resistant CMV from the time of development of resistance was compared between those in the pre-HAART era (diagnosis CMV retinitis prior to 1996) and those in the HAART era (diagnosis of CMV retinitis in 1996 or later). As shown in figure 2, there were no substantial differences between the two groups (Hazard ratio = 1.22, P=0.64).

DISCUSSION

In several studies of the interaction between CMV and HIV, CMV infection appears to worsen the outcome of HIV infection. In those populations of patients with relatively lower rates of latent CMV infection (e.g., pediatric HIV infection and transfusion-related HIV infection), latent CMV infection accelerates the disease process and shortens the time from acquisition of HIV to AIDS.[30–32] In the Longitudinal Study of the Ocular Complications of AIDS, CMV disease, as detected by CMV retinitis, was associated with a 60% increase in mortality overall and a 110% increase in mortality among those without immune recovery.18 Cytomegalovirus transactivates HIV, which would result in higher HIV loads and a worse prognosis.[33,34] Furthermore, infection with CMV is itself immunosuppressive. Cytomegalovirus: 1) produces an IL-10 homolog, which binds to the host IL-10 receptor and suppresses Th1 (cell-mediated) immune responses;[35,36] 2) produces chemokine receptors, which bind chemokines and inhibit the recruitment of inflammatory/immune cells; and 3) interferes with NK cells, thereby

inhibiting the ability to clear viruses.37,38 All of these mechanisms could contribute to an increased rate of HIV disease progression and mortality.

Among patients with CMV retinitis, there is evidence that the CMV "burden" is associated with increased mortality. Positive blood or urine cultures at diagnosis of retinitis are associated with an increased mortality.15 Detectable plasma CMV load (vs undetectable) at diagnosis of retinitis is associated with increased mortality and there are greater mortality rates with higher CMV loads.[17] Furthermore, among patients with CMV retinitis without immune recovery, systemic anti-CMV therapy (vs intraocular only) is associated with a reduced mortality, suggesting that inhibiting systemic CMV replication decreases mortality.19 The occurrence of CMV resistant to the anti-CMV agent being administered would result in systemically replicating CMV and presumably an effect on mortality similar to a greater CMV burden at diagnosis.

Although the study was prospective, had a moderate sample size, and a substantial mortality rate, there are several caveats to the analysis. Data on CMV load and HIV load were incomplete. The multivariate analysis imputed the HIV load data. Although it was a reasonable assumption, analyses using quantitative levels of HIV load were not possible. Cytomegalovirus load at diagnosis of CMV retinitis is known to associate with mortality and with the subsequent development of resistance.[17] Because of the incomplete data, we were not able to accurately include it in the model; unlike HIV load, which was detectable in most patients with CMV retinitis at diagnosis of the retinitis, CMV load is detectable in only 55% of those with retinitis at the diagnosis of retinitis. However, CMV culture results at diagnosis, the results of which correlate with CMV load,[16] with mortality[17] and with subsequent CMV resistance,[13] were available on all patients and were included in the multivariate model instead. Furthermore, the multivariate model gave a very similar HR for the effect of resistant CMV to the univariate analysis.

Although the rate of resistant CMV was moderate, the number of events was insufficient to analyze the impact of switching therapy to an alternate one. Furthermore, because of the delay in obtaining resistance results, they were not used in clinical management, and most patients remained on the same drug, at least initially.39 Because the CRVR study was an observational study, treatment decisions were made at the discretion of the treating physicians at the local sites. Changes in anti-CMV treatment made on clinical grounds, generally for rapidly-relapsing retinitis,20 would be expected to blunt the effect of resistant CMV on mortality. Changes in treatment to a drug to which the virus was susceptible, by controlling replicating CMV, might be expected to improve survival and result in underestimating the effect of resistant CMV on mortality. Newer methods of identifying resistant CMV, such as direct PCR amplification and sequencing the CMV genome, allow for faster identification of ganciclovir resistance and would permit changing treatment after the identification of resistance.[24] We previously have shown in data from this cohort study that direct PCR amplification of blood specimens and sequencing the CMV genome correlates well with genotypic and phenotypic culture results and, therefore, have clinical utility in this situation. Nevertheless, culture results correlate slightly better with clinical outcomes (which is why they were chosen for this analysis).[24] Given the poorer ocular outcomes with resistant CMV,12,14,24 one would anticipate that in the future most patients with identified resistant CMV would have therapy changed.[40] It is conceivable that changes in systemic drug therapy (as opposed to only changing "local" ocular therapy) would not only improve visual outcomes, but also, by controlling systemic CMV replication, possibly improve survival.

In conclusion, these data suggest that among patients with CMV retinitis the occurrence of resistant CMV is associated with an increased risk for mortality in addition to the previously noted increased risk of poor visual outcomes.

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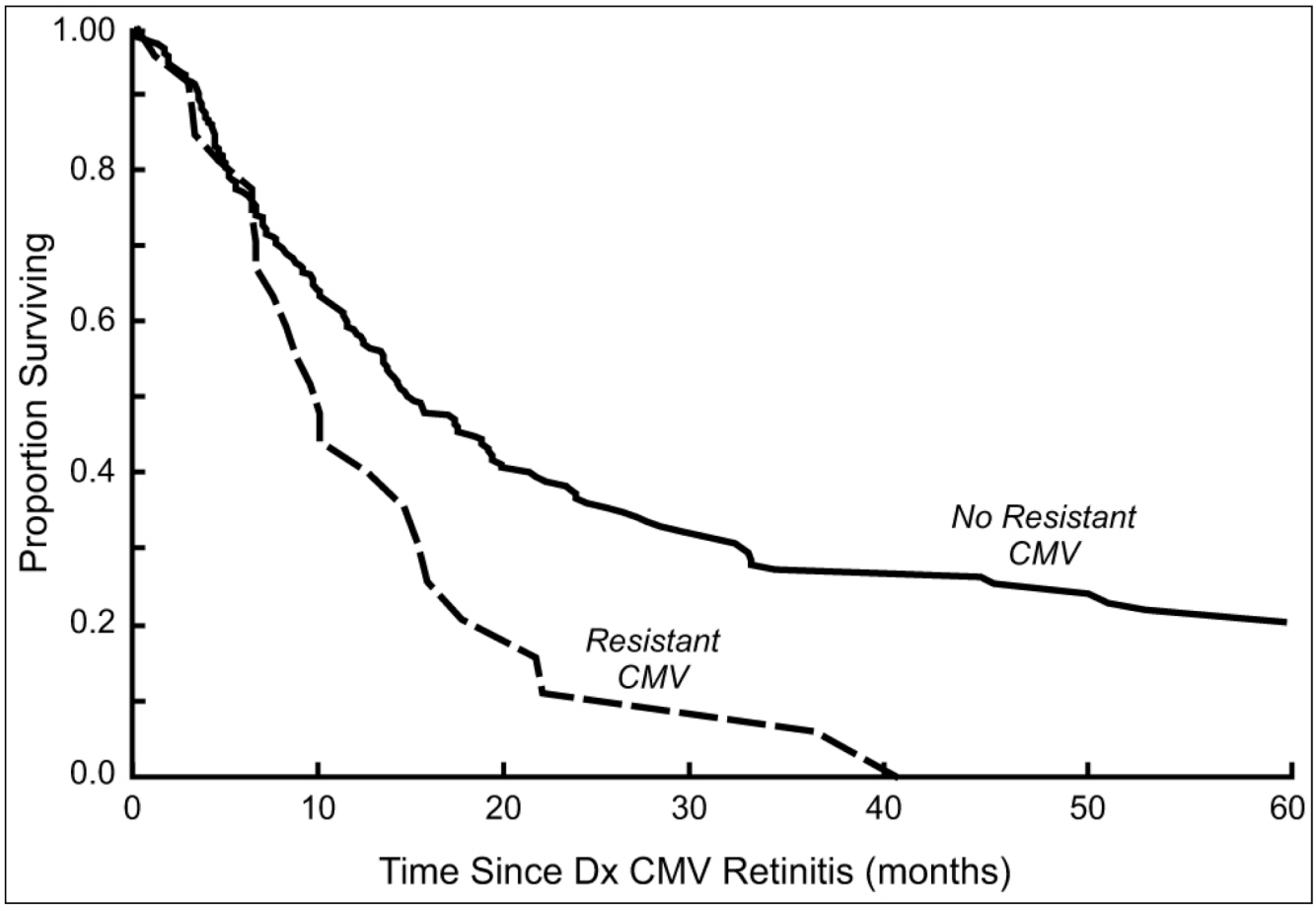

Figure 1.
Survival from cytomegalovirus (CMV) retinitis diagnosis by development of resistant CMV status.

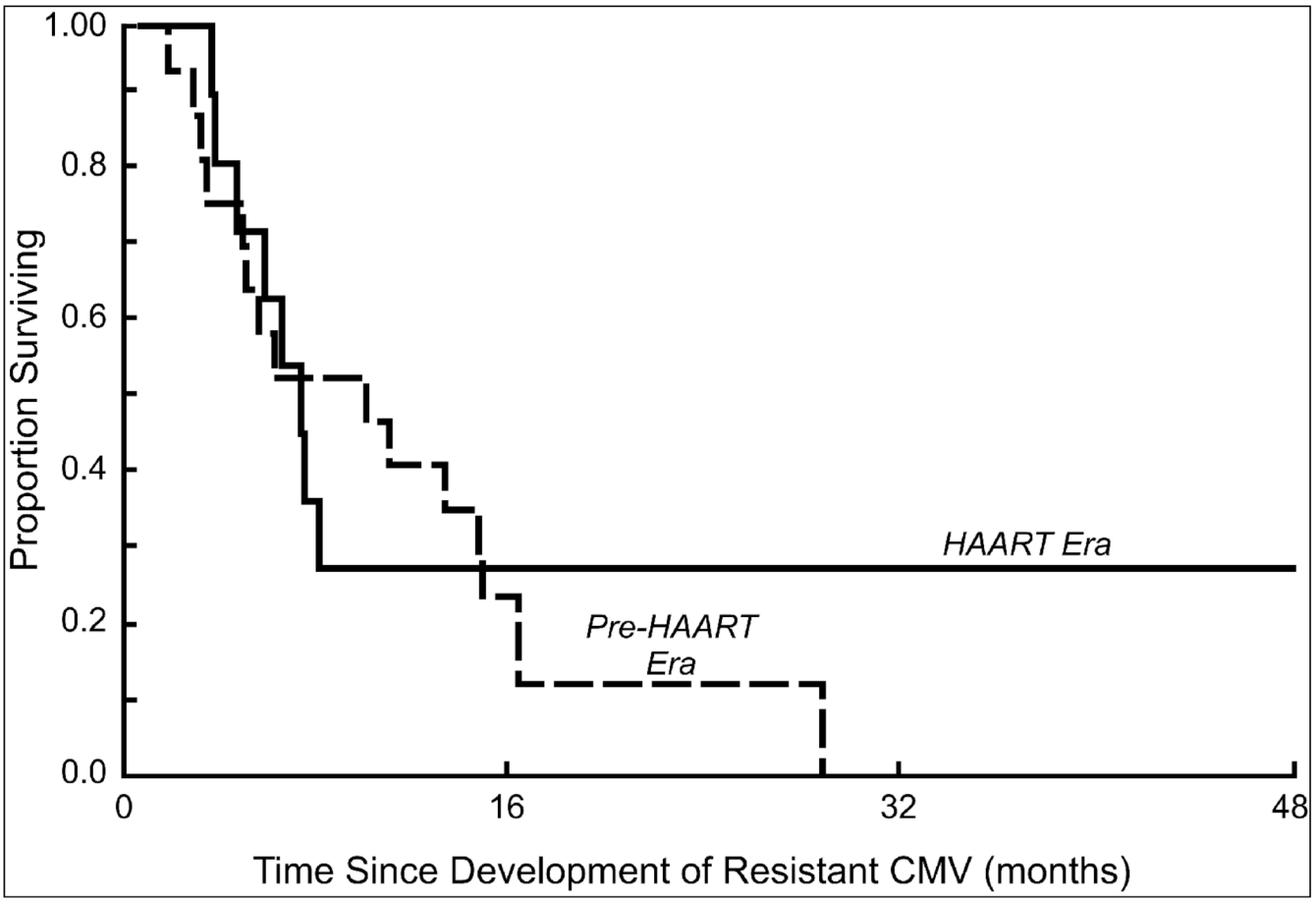

Figure 2.
Survival from development of resistant cytomegalovirus (CMV) for patients with CMV retinitis, comparing patients in the pre-HAART* and HAART eras.
*HAART = highly active antiretroviral therapy.

Table 1

Characteristics of the Study Population

Characteristic		Year of CMV* retinitis diagnosis		
		Overall	1993–1995	1996 & after
Number patients		266	84	182
Age at study entry (years)	Median	39.0	39.0	39.0
	Interquartile range	34.0 to 44.0	33.0 to 44.0	34.0 to 44.0
Gender (%)	Men	69.2	76.2	65.9
	Women	30.8	23.8	34.1
Race (%)	White	30.4	45.2	23.6
	Non-white	69.6	54.8	76.4
HIV† exposure (%)	MSM‡	48.1	54.9	45.0
	IDU§	17.8	20.7	16.4
	MSM & IDU	1.6	1.2	1.8
	Heterosexual	28.1	19.5	32.2
	Other	4.6	3.7	4.6
Time since AIDS diagnosis (months)	Median	23.1	18.9	28.8
	Interquartile range	10.1 to 44.6	10.5 to 33.7	10.1 to 48.2
CD4+ T cells at study entry	Median (cells/μL)	12	8	14
	Interquartile range	4 to 32	3 to 22	6 to 38
	% < 50 cells/μL	82.9	92.7	78.1
HAART¶ (%)	Prior to study entry	45.1	1.2	65.4
	At study entry	32.7	1.2	47.3
Bilateral CMV retinitis at study entry (%)		32.0	23.8	35.9
Area of CMV retinitis at study entry (%)	≥ 25% retinal area	30.1	17.9	35.7
Positive blood or urine culture for CMV at study entry (%)		69.7	82.0	63.7
Plasma CMV load at study entry	Median (copies/mL)**	1035	-	1035
	Interquartile range**	0 to 6475	-	0 to 6675
	< 400 copies/mL (%)**	39.9	-	39.9
	≥ 400 copies/mL (%)**	60.1	-	60.1
	Missing (%)	44.3	100	15.1
Log_{10} HIV load at study entry	Median (copies/mL)**	5.3	-	5.3
	Interquartile range**	4.7 to 5.8	-	4.7 to 5.8
	< 400 copies/mL (%)**	11.0	-	11.0
	≥ 400 copies/mL (%)**	89.0	-	89.0
	Missing (%)	54.7	100	36.0

Characteristic		Year of CMV* retinitis diagnosis		
		Overall	1993–1995	1996 & after
Initial CMV treatment (%)	Systemic ganciclovir or valganciclovir	50.7	63.1	45.1
	Implant & systemic ganciclovir	21.1	1.2	30.2
	Implant only	12.0	0	17.6
	Other	16.2	35.7	7.1
Follow-up time (months)	Median	10.5	8.0	12.8
	Interquartile range	5.4 to 22.7	4.7 to 13.7	6.0 to 25.9
Survival time (months)	Median	12.6	9.7	13.6
	Interquartile range	5.8 to 22.9	5.0 to 16.7	6.4 to 27.0
Retinitis progression rate (/person-year)		1.15	2.74	0.60
Resistance (%)	At 1 year	10.7	20.7	7.0
	At 2 years	17.2	37.5	10.6

*CMV = cytomegalovirus

†HIV = Human Immunodeficiency Virus

‡MSM = men having sex with men

§IDU = injection drug use

¶HAART = highly active antiretroviral therapy

**Median, interquartile range, % <400 copies/mL, and % ≥ 400 copies/mL of those participants tested.

Table 2

Risk Factors for Mortality

Risk factor	HR*	95% CI†	P-value
Time since AIDS diagnosis (/year)	1.10	1.04 – 1.16	0.001
HAART‡ at diagnosis cytomegalovirus (CMV) retinitis	1.30	0.86 – 1.96	0.212
CD4+ T cells < 50 cells/μL at diagnosis CMV retinitis	1.42	0.84 – 2.38	0.190
CMV culture positive at diagnosis CMV retinitis	1.16	0.81 – 1.68	0.638
HIV§ load ≥ 400 copies/mL	1.18	0.47 – 2.99	0.127
Resistant CMV	1.65	1.05 – 2.56	0.032

*HR = hazard ratio

†CI = confidence interval

‡HAART = highly active antiretroviral therapy

§HIV = Human Immunodeficiency Virus