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Changes in Survival after Acquired Immunodeficiency Syndrome (AIDS): 1984–1991

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In a prospective cohort of 2,647 human immunodeficiency virus type 1 (HIV-1) seropositive homosexual men enrolled in Baltimore, Chicago, Los Angeles, and Pittsburgh, 891 developed clinical acquired immunodeficiency syndrome (AIDS) between June 1984 and January 1992. Cox proportional hazards models were used to examine temporal trends in survival after AIDS for specific diagnoses, controlling for level of immunosuppression at diagnosis, age, race, and geographic location. Median survival time following AIDS onset increased from 11.6 months in 1984–1985 to 19.5 months in 1988–1989; for those diagnosed in 1990–1991, the median survival time dropped to 17.2 months. Trends in improved survival were diagnosis-specific. Survival after *Pneumocystis carinii* pneumonia consistently improved from 1984 to 1991 ($p < 0.001$). Compared with men diagnosed in 1984–1985, those diagnosed with *P. carinii* pneumonia in 1990–1991 had one-tenth the hazard of dying. For men with ≥100 helper T-lymphocytes (CD4+ cells) when diagnosed with Kaposi's sarcoma, the relative hazards (95% confidence intervals) of dying after Kaposi's sarcoma were 0.8 (0.42–1.60) in 1986–1987, 0.7 (0.34–1.58) in 1988–1989, and 0.6 (0.19–1.61) in 1990–1991 compared with those diagnosed before 1986. Men with <100 CD4+ cells when diagnosed with Kaposi's sarcoma did not demonstrate a consistent change in their subsequent survival. After a nonsignificant ($p > 0.05$) initial improvement in prognosis, there has not been a significant improvement in survival for men who presented with other opportunistic infections. Observed increases in overall survival probably relate to improved treatment of patients who develop *P. carinii* pneumonia. Limited improvement in survival following other AIDS diagnoses indicates the need for developing effective treatment against these diseases. *Am J Epidemiol* 1993;138:952–64.

acquired immunodeficiency syndrome; antigens, CD4; cohort studies; HIV-1; immunosuppression; mortality; survival

In the epidemiologic examination of the natural history of disease, it is important to note changes related to the dissemination of efficacious interventions. In human immunodeficiency virus type 1 (HIV-1) disease, therapies have been developed recently and the onset of their use has been well documented to coincide with specific years, i.e., 1987 and onward (1, 2). Studies based on surveillance data have demonstrated early improvements in survival after acquired immunodeficiency syndrome (AIDS) (diag-

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Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV-1, human immunodeficiency virus type 1.

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noses that occurred after 1986 compared with those that occurred earlier) by using year of diagnosis as a proxy for the opportunity for receiving treatment (3–8). In this analysis, we capitalize on this approach in extending the examination of survival after AIDS to more recent years with the use of data collected in a large cohort study. Data collected prospectively from large cohorts offer the following advantages: 1) precision and specificity relating to disease occurrence, 2) concomitant information (e.g., level of immunosuppression) at the time of diagnosis, and 3) a close follow-up for the determination of vital status.

MATERIALS AND METHODS

The Multicenter AIDS Cohort Study is a prospective longitudinal study of the natural history of HIV-1 infection among homosexual men in the United States. A total of 5,579 homosexual men were enrolled, 4,954 between April 1984 and March 1985 and an additional 625 between April 1987 and September 1991. The study excluded men with clinically diagnosed AIDS prior to study entry. A detailed description of the study has been published previously (9) and therefore only methods relevant to this analysis will be elaborated.

The men return every 6 months to their study centers, located in Baltimore, Chicago, Los Angeles, and Pittsburgh. In addition to responding to an interview, they undergo a physical examination and provide specimens for laboratory analysis including complete blood counts and white blood cell differentials. Positive enzyme-linked immunoadsorbent assays with confirmatory Western blots are used to determine HIV-1 seropositivity. Among the 5,579 participants, 2,191 (39.3 percent) were HIV-1 seropositive on entry (seroprevalent); 456 (13.5 percent) of the 3,388 seronegatives were observed to seroconvert while in the study. T-lymphocyte subsets are determined by each center using flow cytometry (10). Laboratory data, collected from the visit closest to the AIDS diagnostic date, within a window of 9 months prior to diagnosis and 1 month post-diagnosis, were used to define markers at the time of the AIDS diagnosis.

AIDS diagnoses, as defined by the Centers for Disease Control's 1987 criteria (11), are ascertained for the cohort from self-reports and confirmed by medical records and/or death certificates. AIDS surveillance and reporting are conducted continuously. Men with less than 200 CD4+ lymphocytes and those who have been diagnosed with AIDS are contacted at least every 3 months to identify clinical events. As the men become sicker, more frequent contact is attempted. Reports by personal contacts and passive surveillance, reviewing obituaries and other public records, also are used to determine vital status. For each reported death, an attempt is made to obtain the corresponding death certificate; death certificates or autopsy reports were obtained for approximately 86 percent of all men dying with AIDS. This analysis included all men diagnosed with AIDS from June 1, 1984 through December 31, 1991.

Statistical methods

Survival was defined as the time from the first AIDS diagnosis to death if the death was prior to July 1992. Men who died subsequently were censored at July 1, 1992, as were those men who were still alive at July 1, 1992, determined by subsequent contact ($n = 168$). Otherwise, they were censored at the date of last visit ($n = 14$). The vital status of 98.4 percent of the men with AIDS was known as of July 1992. AIDS diagnoses were examined individually or grouped according to agent or pathogenesis of disease. Year of diagnosis was categorized into four groups for examining temporal trends prior to and post-licensing of zidovudine and pentamidine: 1984–1985 and 1986–1987, corresponding to times when the availability of effective therapy was limited, and 1988–1989 and 1990–1991, representing times when zidovudine and anti-*Pneumocystis carinii* pneumonia therapies were available and used. To avoid assuming a linear effect

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of age on survival with AIDS, age at the time of presenting AIDS diagnosis was categorized into three groups: ≤30 years, 31–39 years, and ≥40 years. The number of helper T-lymphocytes (CD4+ cells) at the time of diagnosis was first categorized as <50 cells/mm^3, 51–100 cells/mm^3, 101–200 cells/mm^3, and >200 cells/mm^3 for examination by univariate methods, and then dichotomized into <100 cells/mm^3 and ≥100 cells/mm^3 when incorporated into the multivariate models.

For each covariate, time from AIDS to death was first examined univariately using Kaplan-Meier product-limit survival analyses. The log-rank test was used to test for significant differences in survival between groups. Cox proportional hazards models were used to examine time to death temporally while controlling for immunosuppression and demographic characteristics (12). Separate multivariate models were developed for Kaposi's sarcoma, for *P. carinii* pneumonia, and for other opportunistic infections; wasting syndrome, HIV-1-related encephalopathy, and lymphoma were excluded from this category since survival after these diagnoses differed from diseases with known infectious agents. Relative hazards of dying after AIDS with corresponding 95 percent confidence intervals were calculated using the results from the regression models.

RESULTS

As of January 1992, 883 (40.3 percent) of the seroprevalent men and 83 (18.2 percent) of the seroconverters had developed AIDS; 75 of the total AIDS cases have no clinical information regarding their AIDS diagnoses prior to death and therefore were omitted from the analysis. Table 1 shows the distribution of presenting AIDS diagnosis by year of diagnosis. Most of these men presented with *P. carinii* pneumonia (40 percent) and

TABLE 1. Percent distribution of presenting acquired immunodeficiency syndrome (AIDS) diagnosis in the Multicenter AIDS Cohort Study, by year of diagnosis, 1984–1991

Type of diagnosis	Year of diagnosis			
	1984–1985 (*n* = 93)	1986–1987 (*n* = 247)	1988–1989 (*n* = 284)	1990–1991 (*n* = 267)
Pneumocystis carinii pneumonia	36.6	53.8	41.2	27.0
Kaposi's sarcoma	37.6	16.6	22.5	19.9
Esophageal candidiasis	4.3	2.8	5.6	9.4
Cytomegalovirus				
Retinitis	0.0	2.8	2.1	3.4
Organ not specified	1.1	1.6	1.8	4.1
Mycobacterial				
Avium-intracellularity	1.1	2.8	2.8	5.6
Disseminated *Mycobacterium* tuberculosis	0.0	0.4	0.0	0.4
Lymphoma				
Non-Hodgkin's lymphoma	0.0	2.0	4.6	3.4
Primary lymphoma of brain	0.0	0.8	0.7	1.1
Wasting syndrome	0.0	0.8	2.5	6.4
Other single				
Cryptosporidiosis	3.2	2.0	1.1	3.0
Cryptococcal infection	4.3	2.0	1.4	1.9
HIV-1* encephalopathy	1.1	0.8	4.2	2.2
Toxoplasmosis	2.2	0.8	2.5	1.9
Progressive multifocal leukoencephalopathy	1.1	1.2	1.1	1.5
Herpes simplex	0.0	1.6	1.1	0.4
Histoplasmosis	0.0	0.4	0.4	0.7
Isosporiasis	1.1	0.4	0.0	0.0
Coccidioidomycosis	0.0	0.0	0.0	0.4
Salmonella septicemia	0.0	0.0	0.4	0.0
Multiple	6.5	6.1	4.2	7.5

* HIV-1, human immunodeficiency virus type 1.

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Kaposi's sarcoma (21.7 percent). *P. carinii* pneumonia comprised 37 percent, 54 percent, 41 percent, and 27 percent of all presenting AIDS conditions diagnosed in 1984–1985, 1986–1987, 1988–1989, and 1990–1991, respectively. For all men who presented with AIDS, the median survival time post-diagnosis was 16.4 months with 62.3 percent, 33.5 percent, 15.6 percent, 9.8 percent, and 5.7 percent surviving 1, 2, 3, 4, and 5 years post-AIDS, respectively. The median survival times after AIDS onset and probabilities of surviving 1 and 2 years after presenting with each AIDS diagnosis are shown in table 2.

Survival after AIDS differed by presenting diagnosis (table 2). Overall survival after Kaposi's sarcoma (median = 18.8 months) was similar to survival after presenting with *P. carinii* pneumonia (median = 19.1 months). Men who presented with lymphoma exhibited the worst survival, with only 18 percent surviving past 1 year. Men who presented with disseminated cytomegalovirus or mycobacterial infections fared slightly better; the median survival times for these men were 8.8 months and 8.3 months, respectively. Men who presented with other single AIDS diagnoses did not greatly differ in their overall survival, with median survival times of approximately 15 months.

Kaplan-Meier survival curves for each diagnostic year group are presented in figure 1. Survival after AIDS improved temporally over the period 1984–1985 to 1988–1989. The median survival time following an initial diagnosis of AIDS significantly increased from 11.6 months to 19.5 months from 1984–1985 to 1988–1989 ($p < 0.001$, log-rank test, table 2). For men diagnosed with AIDS in 1990–1991, the median survival time following their diagnosis was 17.2 months. The survival distribution for those diagnosed with AIDS in 1990–1991 was not significantly different ($p = 0.29$) compared with those diagnosed in 1988–1989.

Since overall survival differed by presenting diagnosis and the profile of presenting AIDS conditions has changed over time, prognostic trends were examined for each diagnostic group. The results describing the survival after AIDS by type and year of diagnosis are shown in table 3. There was a significant ($p < 0.001$, log-

TABLE 2. Overall survival probabilities† by presenting diagnosis and year of diagnosis for Multicenter AIDS Cohort Study participants diagnosed with acquired immunodeficiency syndrome (AIDS), 1984–1991

Category	No.	No. who died	Median survival time (months)	Cumulative probability of survival	
				1 year	2 years
Presenting diagnosis					
Pneumocystis carinii pneumonia	356	279	19.1	0.72 (0.67–0.77)‡	0.39 (0.34–0.45)
Kaposi's sarcoma	193	145	18.8	0.69 (0.62–0.76)	0.40 (0.33–0.48)
Esophageal candidiasis	52	36	15.9	0.60 (0.48–0.76)	0.38 (0.25–0.56)
Cytomegaloviral infection	43	38	8.8	0.39 (0.27–0.58)	0.20 (0.10–0.38)
Mycobacterial infections	33	26	8.3	0.42 (0.28–0.63)	0.10 (0.02–0.50)
Lymphoma	34	33	3.3	0.18 (0.09–0.37)	0.04 (0.01–0.26)
Wasting syndrome	26	17	16.1	0.65 (0.49–0.87)	0.29 (0.15–0.58)
Other single	101	77	14.1	0.55 (0.46–0.65)	0.30 (0.21–0.41)
Multiple	53	48	11.5	0.49 (0.37–0.65)	0.22 (0.13–0.37)
Year of diagnosis*					
1984–1985	93	91	11.6	0.49 (0.40–0.61)	0.13 (0.08–0.22)
1986–1987	247	239	15.7	0.59 (0.53–0.65)	0.32 (0.26–0.38)
1988–1989	284	229	19.5	0.69 (0.64–0.75)	0.41 (0.35–0.47)
1990–1991	267	140	17.2	0.63 (0.57–0.69)	0.35 (0.28–0.44)

* $p < 0.0001$.
† Probabilities were obtained by univariate Kaplan-Meier survival analyses.
‡ 95% confidence interval in parentheses.

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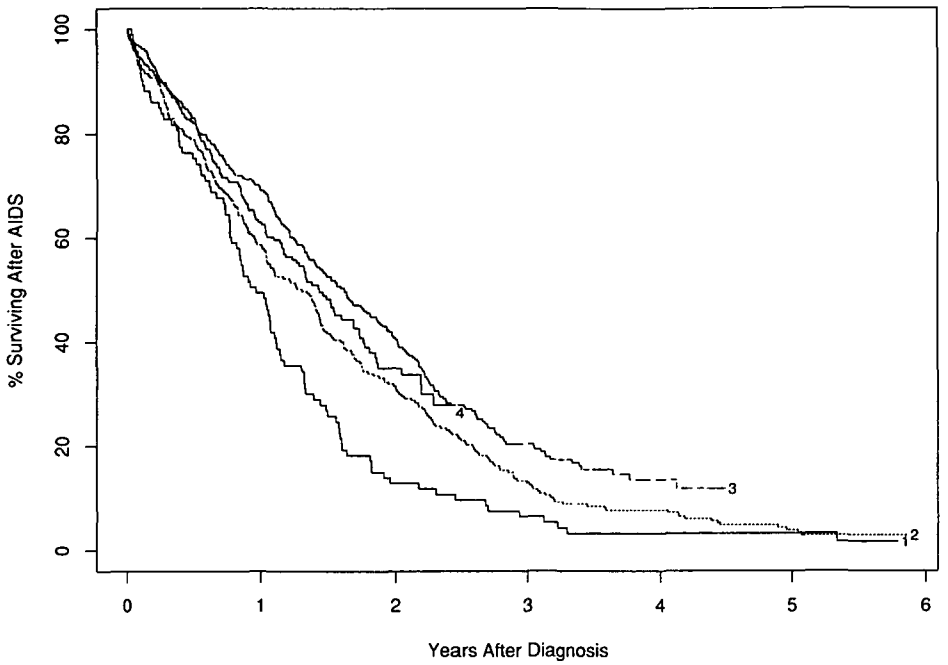

FIGURE 1. Percent of Multicenter AIDS Cohort Study participants surviving after acquired immunodeficiency syndrome (AIDS), by year of diagnosis, 1984–1991: results from univariate Kaplan-Meier survival analysis. 1 = the survival distribution for men diagnosed in 1984–1985, 2 = men diagnosed in 1986–1987, 3 = men diagnosed in 1988–1989, and 4 = men diagnosed in 1990–1991.

TABLE 3. Survival times* (25th, 50th, 75th percentiles) in months after acquired immunodeficiency syndrome (AIDS) diagnosis, by type and year of diagnosis, for Multicenter AIDS Cohort Study participants diagnosed with AIDS

Presenting diagnosis	Year of diagnosis											
	1984–1985			1986–1987			1988–1989			1990–1991		
	25%	50%	75%	25%	50%	75%	25%	50%	75%	25%	50%	75%
Pneumocystis carinii pneumonia	8.6	12.8	15.8	9.5	16.6	26.1	12.6	24.2	33.9	16.0	26.3	NA
Kaposi's sarcoma	7.4	12.7	21.9	7.9	17.2	37.6	11.9	20.0	33.2	11.4	22.3	NA
Esophageal candidiasis	1.4	5.8	12.6	0.9	6.1	60.6	7.9	15.9	26.5	10.2	18.3	24.5
Cytomegalovirus		NA†		4.2	7.6	23.8	13.4	23.8	27.7	4.3	6.9	11.5
Mycobacterial *Avium*-intracellularity		NA		0.4	3.4	10.4	1.4	6.1	13.0	2.7	10.1	16.6
Lymphomas		NA		2.9	3.2	6.4	2.4	6.7	12.4	0.5	2.5	6.2
Wasting syndrome		NA			NA		1.9	6.1	14.6	15.4	17.9	NA
Other single	3.0	10.5	17.3	6.0	17.4	30.4	7.5	16.8	36.5	4.0	10.8	22.4
Multiple	0.6	2.0	4.6	4.6	16.4	27.8	8.3	15.8	31.9	6.5	10.2	15.9
Overall	6.2	11.6	18.7	7.0	15.7	27.5	8.7	19.5	31.9	7.7	17.2	NA

* Obtained by univariate Kaplan-Meier methods.
† NA, not applicable; survival estimates were computed for those diagnoses with at least 3 events.

rank test) improvement over time in the survival following *P. carinii* pneumonia, whereas the overall survival after Kaposi's sarcoma did not improve significantly ($p = 0.11$, log-rank test). Although there were trends for improved prognosis over time for each of the other single diagnoses, the numbers involved are not large and

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none of the differences were statistically significant ($p > 0.05$, log-rank test).

In this cohort, overall survival after AIDS did not differ according to demographics using univariate Kaplan-Meier survival analyses. There was no significant difference in survival according to study center ($p = 0.33$), potentially reflecting the standardization of medical practice and the achievement of standard methods of data collection and reporting by the centers. Race also did not modify overall survival after AIDS ($p = 0.52$). Although there was a trend in the median survival after AIDS by age, with younger men having the longest survival, survival distributions did not significantly differ between these age groups ($p = 0.31$).

The effect of the number of CD4+ lymphocytes on survival after AIDS was examined to determine the prognostic influence of immunosuppression at the time of diagnosis. Although CD4+ counts at the time of diagnosis were not available for all men who developed AIDS, survival was not significantly different for those with CD4+ data and those without. With the use of data contributed by the men with CD4+ measurements, the level of immunosuppression at the time of AIDS diagnosis was prognostic of survival; higher CD4+ counts substantially improved survival ($p < 0.001$, log-rank test). The median survival times were 11.3, 15.2, 17.4, and 23.8 months for those who had ≤50 CD4+ lymphocytes, 51–100 cells, 101–200 cells, and >200 CD4+ lymphocytes at the time of diagnosis, respectively. Since survival after AIDS differed by presenting diagnosis and the level of immunosuppression, improvement in survival over time was examined for each diagnosis adjusting for number of CD4+ lymphocytes at the time of diagnosis.

Kaplan-Meier curves for survival after Kaposi's sarcoma, *P. carinii* pneumonia, and all other opportunistic infections by year of diagnosis, stratified by CD4+ lymphocytes, clearly distinguished the prognostic value of CD4+ lymphocytes at the time of diagnosis (figure 2). For men who presented with *P. carinii* pneumonia and Kaposi's sarcoma, the survival curves are positively shifted for those with at least 100 CD4+ lymphocytes at the time of diagnosis compared with those who presented with less than 100 CD4+ cells. A residual improvement in survival with *P. carinii* pneumonia over time is evidenced after stratifying by CD4+ lymphocytes. This temporal trend is not as apparent for survival in men who presented with Kaposi's sarcoma or other opportunistic infections.

Cox proportional hazards models were used to examine the hazards of dying after presenting with *P. carinii* pneumonia, Kaposi's sarcoma, or another opportunistic infection by year of diagnosis. As noted in the survival distributions (figure 2), controlling for number of CD4+ lymphocytes, the survival curves overlapped in the first 4 months after AIDS. This observation suggests that the hazards during that period may not be proportional, and therefore only individuals observed to survive at least 4 months after diagnosis were used in the regression analyses. Age, race, and geographic location were included in the models in addition to the CD4+ lymphocyte category to control for potential confounding. Interaction terms were included in fitting the models but were not significant and were therefore excluded from the final models.

The results from the final Cox proportional hazard models are presented in table 4. When adjusting for the other variables, age and geographic location still did not affect survival with AIDS. The effect of race, however, differed according to presenting diagnosis. For survival after Kaposi's sarcoma, nonwhite men had twice the hazard of dying ($p = 0.03$) compared with white men. Race was not significant for survival after *P. carinii* pneumonia or other opportunistic infections. Similarly, the effect of CD4+ cell counts differed by presenting diagnosis. Whereas there was no effect associated with survival with opportunistic infections, compared with those who presented with ≥100 CD4+ lymphocytes per mm^3, the relative

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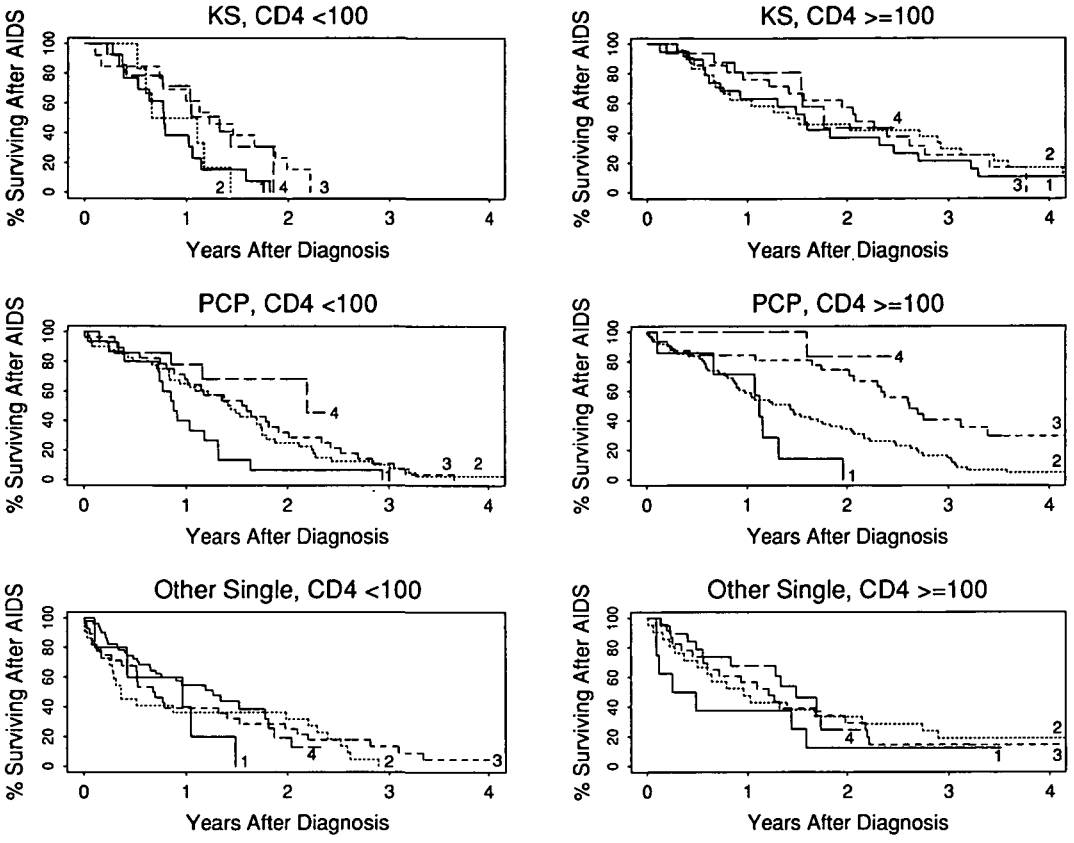

FIGURE 2. Percent of Multicenter AIDS Cohort Study participants surviving after acquired immunodeficiency syndrome (AIDS), by year of diagnosis, 1984–1991, stratified by presenting diagnosis and CD4+ cell count at time of diagnosis. 1 = men diagnosed in 1984–1985, 2 = men diagnosed in 1986–1987, 3 = men diagnosed in 1988–1989, and 4 = men diagnosed in 1990–1991. KS, presenting with Kaposi's sarcoma; PCP, presenting with *Pneumocystis carinii* pneumonia; Other Single, all other opportunistic infections.

hazards of dying were 1.6 ($p = 0.005$) and 3.2 ($p < 0.0001$) for those with <100 CD4+ lymphocytes per mm^3 when presenting with *P. carinii* pneumonia and Kaposi's sarcoma, respectively.

Controlling for these demographic characteristics and CD4+ lymphocyte count, the trend for improved prognosis over time became more striking for men who presented with *P. carinii* pneumonia. This trend is consistent with those diagnosed in each subsequent year group having a significantly better prognosis than those diagnosed earlier. Although it appears that the survival of men diagnosed with either Kaposi's sarcoma or opportunistic infections in 1986 and subsequently was better than for those diagnosed earlier, the improvement was not significant ($p > 0.05$). The temporal trends in the relative hazards of dying by CD4+ lymphocyte count observed for those diagnosed with *P. carinii* pneumonia and Kaposi's sarcoma are illustrated in figure 3.

Separate models were fitted for the two levels of immunosuppression (<100 CD4+ cells and ≥100 CD4+ cells), with 1984–1985 being the baseline category in each case. The estimates were adjusted for demographics specified in the Cox proportional hazards models. Among men with <100 CD4+ lymphocytes, the relative hazards (95 percent confidence interval) of dying after being diagnosed with *P. carinii*

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TABLE 4. Relative hazards* (95% confidence intervals (CI)) of dying after acquired immunodeficiency syndrome (AIDS) for Multicenter AIDS Cohort Study participants, 1984–1991

Model covariate	Presenting AIDS condition					
	P. carinii pneumonia		Kaposi's sarcoma		Other opportunistic infections	
	Relative hazard	95% CI	Relative hazard	95% CI	Relative hazard	95% CI
Year of diagnosis						
1984–1985	1.0		1.0		1.0	
1986–1987	0.5	0.28–0.81	0.8	0.48–1.45	0.7	0.24–2.21
1988–1989	0.3	0.15–0.48	0.6	0.33–1.11	0.8	0.25–2.74
1990–1991	0.1	0.04–0.34	0.6	0.30–1.20	0.9	0.26–2.79
CD4+ lymphocytes (per mm^3)						
≥100	1.0		1.0		1.0	
<100	1.6	1.16–2.28	3.2	1.94–5.21	1.2	0.68–2.10
Race						
White	1.0		1.0		1.0	
Nonwhite	1.7	0.93–3.24	2.0	1.08–3.64	0.7	0.28–1.66
Age (years)						
≤30	1.0		1.0		1.0	
31–39	0.7	0.45–1.03	1.2	0.58–2.41	1.0	0.44–2.16
≥40	1.0	0.60–1.60	0.8	0.39–1.71	1.0	0.42–2.37
Study site						
Baltimore	1.0		1.0		1.0	
Chicago	1.2	0.72–1.94	1.0	0.43–2.52	1.1	0.47–2.58
Los Angeles	1.1	0.69–1.74	1.1	0.64–1.96	1.1	0.60–2.16
Pittsburgh	1.5	0.86–2.72	1.0	0.41–2.49	1.1	0.46–2.89

* Relative hazards were obtained using separate multivariate Cox proportional hazards models for each diagnosis.

pneumonia in 1986–1987, 1988–1989, and 1990–1991 were 0.40 (0.20–0.81), 0.25 (0.11–0.58), and 0.14 (0.04–0.52), respectively, compared with those diagnosed in 1984–1985. An even greater continued improvement in survival was observed for those less immunosuppressed at the time of diagnosis, with relative hazards (95 percent confidence interval) of 0.40 (0.16–1.01), 0.14 (0.05–0.39), and 0.04 (0.005–0.37) for diagnoses occurring in 1986–1987, 1988–1989, and 1990–1991 compared with those who presented with *P. carinii* pneumonia in 1984–1985.

For men diagnosed with Kaposi's sarcoma, there is a trend for improved survival although the hazard estimates for those diagnosed after 1985 are not statistically different from those diagnosed earlier and are of lesser magnitude when compared with men with *P. carinii* pneumonia. This lack of significant improvement is independent of the immune state at the time of diagnosis. However, for men with at least 100 CD4+ lymphocytes per mm^3, survival has been consistently improving with time.

DISCUSSION

In this cohort of homosexual men, overall survival with AIDS has improved since 1985. The increase in AIDS survival time has occurred concomitantly with a change in the relative frequencies of the different AIDS-defining clinical events (table 1), and with changes in the use of antiretroviral drugs and *P. carinii* pneumonia prophylaxis (table 5).

The changes in the frequency of AIDS-defining events suggest two possible explanations for this increased AIDS survival: 1) the diseases that have increased in frequency as *P. carinii* pneumonia frequency decreased have a longer survival expectation than does *P. carinii* pneumonia; and 2) the survival expectation for *P. carinii* pneumonia has increased sufficiently to increase overall survival despite a decrease in *P. carinii*

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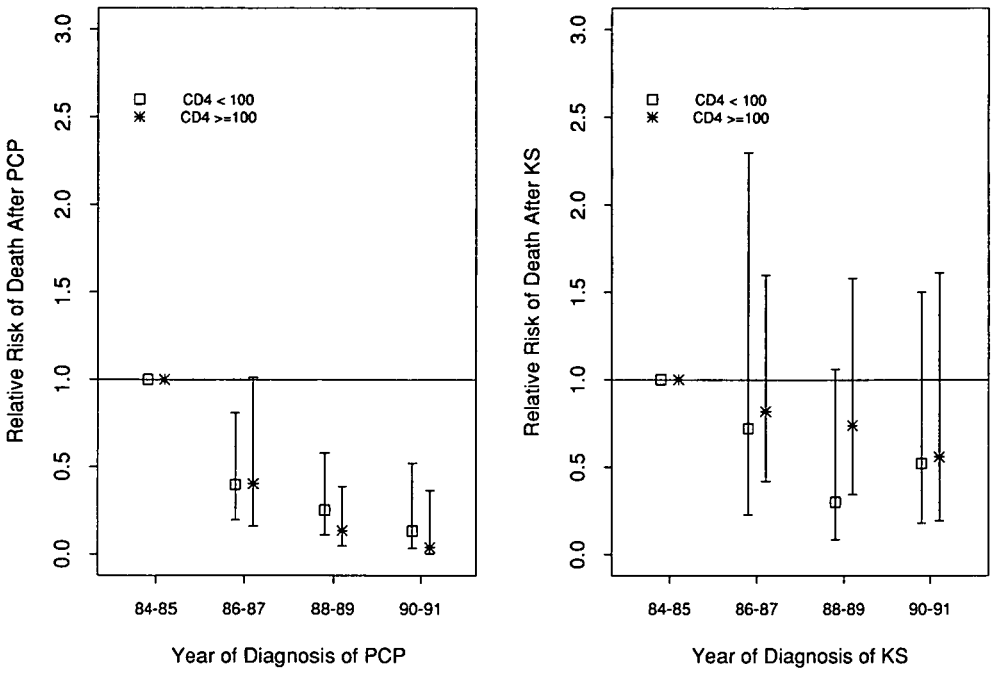

FIGURE 3. Relative risk of Multicenter AIDS Cohort Study participants dying after *Pneumocystis carinii* pneumonia and Kaposi's sarcoma by year of diagnosis compared with men diagnosed in 1984–1985, stratified by CD4+ cell count at time of diagnosis. PCP, *P. carinii* pneumonia; KS, Kaposi's sarcoma. Years of diagnosis: 84–85 = 1984–1985, 86–87 = 1986–1987, 88–89 = 1988–1989, 90–91 = 1990–1991. Bars denote 95% confidence intervals and horizontal line at 1.0 is reference indicating no difference.

TABLE 5. Percent of Multicenter AIDS Cohort Study participants with acquired immunodeficiency syndrome (AIDS) reporting antiretroviral and/or *Pneumocystis carinii* prophylaxis, by year of diagnosis and number of CD4+ lymphocytes, 1988–1991

Category and year of diagnosis	No. of CD4+ lymphocytes									
	≤50		51–100		101–200		>200		Unknown	
	No.	%	No.	%	No.	%	No.	%	No.	%
Antiretroviral prophylaxis										
1988	20	70	15	40	19	42	22	14	61	8
1989	22	64	17	76	22	45	15	47	71	35
1990	26	81	17	94	10	100	14	64	70	49
1991	32	88	13	77	11	82	14	86	60	48
P. carinii pneumonia prophylaxis										
1988	20	10	15	7	19	5	22	0	61	2
1989	22	50	17	29	22	9	15	7	71	11
1990	26	65	17	82	10	50	14	29	70	33
1991	32	84	13	62	11	73	14	29	60	33

pneumonia frequency and an increase in the frequency of other AIDS-defining events with shorter associated survival times.

The changes in the median survival times by AIDS-defining conditions (table 3) as well as the diminishing hazards of dying following diagnosis suggest that most of the overall increase in survival did result from a marked improvement in AIDS survival following a diagnosis of AIDS due to *P. carinii* pneumonia. The median survival time following the first diagnosis of *P. carinii*

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pneumonia more than doubled between 1984–1985 and 1990–1991, with more than 50 percent surviving at least 2 years since 1988. Although prognosis following Kaposi's sarcoma was better than for *P. carinii* pneumonia earlier in the epidemic ($p = 0.02$, log-rank test), since 1988, the survival for men who have developed *P. carinii* pneumonia has surpassed that for those diagnosed with Kaposi's sarcoma, after controlling for immune status at the time of diagnosis. The improvement in survival with *P. carinii* pneumonia extends the findings of other studies in which survival for individuals diagnosed with *P. carinii* pneumonia in 1986 and 1987 was demonstrated to be better when compared with earlier cases (3, 5, 6).

There are several potential explanations for the increasing survival after *P. carinii* pneumonia. Closer follow-up and earlier detection of the disease may result in a lead time bias where the survival time appears greater despite no actual difference for similar disease stages. However, after controlling for level of immunosuppression at the time of diagnosis, there remains a residual improvement in post-*P. carinii* pneumonia survival with time. In addition, after 1985 the level of CD4+ lymphocytes at the time of presenting with *P. carinii* pneumonia has decreased with time in the Multicenter AIDS Cohort Study; these median CD4+ lymphocyte counts were 74, 132, 108, and 87 in 1984–1985, 1986–1987, 1988–1989, and 1990–1991, respectively. The lower CD4+ cell counts in 1984–1985 probably reflect *P. carinii* pneumonia being diagnosed at later disease stages very early in the epidemic due to diagnostic difficulties and limited awareness of disease among patients and health care providers. The overall decrease in CD4+ lymphocyte counts at the time of AIDS diagnosis is consistent with increasing use of antiretroviral and anti-*P. carinii* pneumonia prophylaxis by these men (table 5) and argues against lead time bias as an explanation for prolonged survival in more recent times. However, an increased sensitivity to *P. carinii* pneumonia signs and symptoms, in combination with improved diagnostics, may have resulted in an earlier diagnosis of *P. carinii* pneumonia following disease onset. *P. carinii* pneumonia diagnosed at a less fulminant stage, prior to widespread pulmonary involvement, may make it more responsive to treatment despite its onset in individuals with greater HIV-related immune suppression (as manifested by lower CD4+ cell counts). Increased availability and utilization of effective chemotherapy also may be key factors for improving the survival after *P. carinii* pneumonia (1, 13–17).

For men who presented with Kaposi's sarcoma, a trend for improvement in survival was demonstrated. Although not statistically significant ($p > 0.05$), the median survival time has steadily improved. The lack of significant improvement may reflect the limited availability of effective therapy specifically for this disease during the time frame of the analysis. This situation may also explain the overall poorer prognosis for men diagnosed with other AIDS-related malignancies where there is again an absence of temporal improvement in survival.

After controlling for type of diagnosis and level of immunosuppression at the time of diagnosis, survival did not differ significantly by study center or age. Although overall there was no difference in survival by race, when examining survival with specific diagnoses, the effect of race differed. Nonwhite men diagnosed with Kaposi's sarcoma had a worse prognosis than white men. This racial difference may reflect differences in either disease stage at the time of diagnosis or differential access to the health care system and use of therapies. The lack of any difference in survival following other opportunistic infections favors these arguments rather than a genetic disposition. Results from other studies have not been consistent (4, 6, 8, 18). Individuals in different sociodemographic groups may vary in their use of the health care system and, thus, present with disease at different stages.

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When examining survival trends, it is important to stratify by type of presenting diagnosis and adjust for level of immunosuppression. In a recent study, neither age nor race predicted progression to death after controlling for CD4+ lymphocyte counts at the time of disease (19). In studies conducted by Lemp et al. (3) and Rothenberg et al. (4), survival according to age was U-shaped. In the Multicenter AIDS Cohort Study, the overall effect of age was in accordance with studies in which older age was related to an increased risk of mortality (8). However, when examining survival with specified conditions, a U-shaped hazard trend by age remained for those with *P. carinii* pneumonia, although it was not significant. For survival with the other diagnoses, no trend by age existed. The lack of differences by geographic location suggests that access to health care and the receipt of adequate treatment were similar in this sample of homosexual men in the United States.

These data furnish strong evidence for the prognostic value of CD4+ lymphocytes in projecting survival after an initial diagnosis of AIDS. The percentage of men with less than 100 CD4+ lymphocytes when diagnosed with opportunistic infections other than *P. carinii* pneumonia went from 42 percent, 49 percent, 67 percent, to 80 percent for those diagnosed in 1984–1985, 1986–1987, 1988–1989, and 1990–1991, respectively. Therefore, year of diagnosis in the multivariate models was highly correlated with CD4+ count and no additional information was contributed by these markers of the immune state. CD4+ lymphocyte count may not best distinguish severely advanced stages, and, therefore, other variables such as the number of CD8 lymphocytes may better differentiate the state of the immune system at the time of diagnosis. The need for including the immune state when examining survival trends corroborates the findings of other studies (19–22).

Decreasing CD4+ lymphocyte counts at the time of diagnosis have been observed previously in a study by Schwartländer et al. (23). This change together with changes in the profile of the incidence of AIDS (2) and the trends for improvement in survival shown in this paper are concomitant with increased use of prophylaxis and treatment against diseases with known infectious agents (table 5).

The improved overall prognosis is similar to that shown by Lemp et al. (24, 25), indicating that increases in survival may be specific to certain diagnoses. Certain AIDS conditions may be more susceptible to the effect of antiretroviral therapy on the immune system and directed treatments; the interaction of combination therapy may enable the immune system to suppress, if not eradicate, these infectious agents. Malignancies and dementia are more difficult to treat and therefore demonstrate less prognostic change. Continued effort in the development of effective disease-specific therapies is necessary.

Despite the dramatic increases in survival after AIDS demonstrated in this analysis, the expectations for future improvement may be limited. As evidenced in figure 3, individuals who presented with *P. carinii* pneumonia when their CD4+ cell counts were at least 100 showed the largest increases in survival. Use of antiretroviral therapy and primary prophylaxis against *P. carinii* pneumonia (17, 26) probably resulted in the decreasing level of CD4+ cells seen at the time of the initial AIDS-defining *P. carinii* pneumonia diagnosis. As the use of these therapies becomes more widespread and refined, a greater proportion of initial AIDS-defining diagnoses may occur in persons with lower CD4+ cell numbers. Eventually, AIDS survival may plateau, or even decrease, as initial AIDS-defining events occur in individuals with more advanced stages of HIV-related immune dysfunction. The lack of improvement in survival for those diagnosed in 1990–1991 may reflect this evolution. This may explain also the conflicting results observed in clinical tri-

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als of zidovudine use when comparing time to AIDS with time to death (27–29). Ideally, such a trend should be accompanied by an even greater increase in the overall duration of the asymptomatic stage of HIV-1 infection prior to AIDS. A trend of this nature would provide evidence that intensive systematic and widespread AIDS prophylactic use has succeeded in transforming HIV-1 infection into a condition more analogous to chronic diseases than to the more rapidly fatal condition with which it is now associated. It further emphasizes the need to examine carefully overall HIV-1 survival, from seroconversion or early infection until death, to more accurately assess the ultimate impact of new therapeutic agents and regimens. The results from this analysis provide insight for performing this next step when sufficient events are observed among seroconverters.

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