

RACE, SEX, DRUG USE, AND PROGRESSION OF HUMAN IMMUNODEFICIENCY VIRUS DISEASE

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Abstract Background. *The rates of progression of human immunodeficiency virus (HIV) infection and survival have been reported to differ among sociodemographic groups. It is unclear whether these differences reflect biologic differences or differences in access to medical care.*

Methods. *We measured disease progression and survival in a cohort of 1372 patients seropositive for HIV who were treated at a single urban center (median follow-up, 1.6 years). We calculated the rates of survival for the entire cohort and the rates of progression to the acquired immunodeficiency syndrome (AIDS) or death among the 740 patients who presented without AIDS. We used Cox proportional-hazards analysis to examine factors associated with progression to AIDS and death.*

Results. *Progression to AIDS or death was associated with a CD4 cell count of 201 to 350 per cubic millimeter (relative risk, 2.0; $P < 0.001$), the presence of symptoms at base line (relative risk, 2.0; $P < 0.001$), prior antiretroviral therapy (relative risk, 1.7; $P = 0.003$), and older age (relative risk per year of age, 1.02; $P = 0.03$). However, there*

was no relation between disease progression and sex, race, injection-drug use, income, level of education, or insurance status. In the entire cohort, a lower CD4 cell count, a diagnosis of AIDS, older age, and the receipt of antiretroviral therapy before enrollment were associated with an increased risk of death, whereas the use of prophylaxis against pneumocystis pneumonia, zidovudine use after enrollment, and having a job at base line were associated with lower risks of death. There was no significant difference in survival between men and women, blacks and whites, injection-drug users and those who did not use drugs, or patients whose median annual incomes were \$5,000 or less and those whose incomes were more than \$5,000.

Conclusions. *Among patients with HIV infection who received medical care from a single urban center, there were no differences in disease progression or survival associated with sex, race, injection-drug use, or socioeconomic status. Differences found in other studies may reflect differences in the use of medical care. (N Engl J Med 1995;333:751-6.)*

IN the United States, human immunodeficiency virus (HIV) disease is now a leading cause of death in adults 25 to 44 years old.¹ A large population of patients with HIV infection in the United States are members of racial or ethnic minorities, and a growing proportion of patients are women.^{2,3} The differences in survival between blacks and whites, men and women, and drug users and those who do not use drugs have led to speculation that HIV disease progresses more rapidly in some demographic groups than in others.⁴⁻⁶ The clinical course of the disease is variable, however, and a number of therapeutic and other factors may influence the natural history of the infection.⁷⁻¹⁰ Although differences in survival might result from biologically diverse responses to HIV infection,¹¹⁻¹³ differential access to medical care is another possible explanation for these findings.¹⁴ We have previously shown that blacks, women, and injection-drug users are significantly less likely to receive appropriate therapy for HIV infection.^{10,14} Whether providing medical care for all HIV-infected people can correct disparities in outcome is not known. A recent study in Canada, however, reported poor survival among HIV-infected patients with low incomes, in spite of presumably equal access to medical care.¹⁵

To examine the relation between demographic variables and survival among people with HIV infection receiving medical care, we analyzed data from the Johns Hopkins University HIV Clinic data base.^{14,16} This data base contains clinical, demographic, and socioeconomic information on a heterogeneous cohort of HIV-infected patients from an urban area who receive care at the Johns Hopkins HIV Clinic.

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METHODS

Patients and Data Collection

We analyzed data from a heterogeneous cohort of patients with HIV infection who presented for care at the Johns Hopkins HIV Clinic between July 1989 and April 1994. Patients in the cohort were those receiving ongoing medical care from the clinic; patients seen for only a single consultation who received no follow-up care at Johns Hopkins Hospital were excluded. All patients had serologically or clinically confirmed HIV infection and were enrolled in a longitudinal primary care program. All patients enrolling in the clinic during this period underwent a comprehensive base-line assessment, with collection of detailed demographic, social, behavioral, and clinical data. Information was obtained in structured interviews by social workers and clinicians using standardized forms. Data were abstracted from patients' charts and from the hospital's automated data bases at base line and every six months by trained monitors using standardized data-collection instruments. Items in the data abstraction included all base-line information and information on follow-up diagnoses, treatments, hospitalizations, and death. Definitions of disease progression were based on the 1993 revised surveillance case definition for the acquired immunodeficiency syndrome (AIDS) among adults and adolescents promulgated by the Centers for Disease Control and Prevention (CDC),¹⁷ which classifies AIDS on the basis of the occurrence of specific indicator opportunistic diseases or a CD4 cell count of less than 200 per cubic millimeter. Medical records from other institutions where patients may have received care were routinely sought. Information on death was obtained from patients' charts and from a separate death registry maintained by the clinic that receives reports from families, other medical institutions, funeral homes, and local coroners. In addition, the names of patients whose vital status was unknown for more than 12 months were searched for in death records of the Maryland Bureau of Vital Records and the National Death Index. A nurse or physician checked the validity of the data in a sample of 10 percent of the patients, and systematic problems were identified and corrected for all patients. Complete follow-up was maintained for 86 percent of the cohort.

Statistical Analysis

The primary outcomes of interest were progression of disease and survival after enrollment in the clinic. The frequencies and distributions of base-line variables within demographic and clinical subgroups were compared with Fisher's exact test and the Wilcoxon rank-sum test. Comparisons of disease progression and survival were performed

for demographic variables stratified according to initial CD4 cell counts with Kaplan–Meier estimates.¹⁸ Differences between groups were assessed by the log-rank test. A Cox proportional-hazards model was constructed to determine independent predictors of disease progression and death.¹⁹ Both fixed and time-dependent covariates were included in the model.²⁰ The fixed covariates were the base-line demographic variables, whereas the time-dependent covariates were the use of antiretroviral therapy, the use of prophylaxis against pneumocystis pneumonia, and the CD4 cell count. For disease progression, we analyzed data on patients with initial CD4 cell counts above 200 per cubic millimeter who did not have a diagnosis of AIDS and used progression to AIDS or death as the dependent variable. For the survival analysis, we included all patients. The assumption of a constant risk ratio over time for the proportional-hazards analysis was tested and found to be valid for the variables modeled.

RESULTS

Between July 1989 and April 1994, 1372 patients with HIV infection who underwent initial comprehensive evaluations and for whom follow-up data were available were entered in the data base. Follow-up was complete through October 1994, with 2170 person-years of observation and a median follow-up of 1.6 years. There were no significant differences in the length of follow-up or in loss to follow-up among demographic subgroups. The base-line demographic and clinical characteristics of the cohort are presented in Table 1. Thirty percent of the patients were women, 77 percent were black, and 21 percent were white. Risk factors for HIV included homosexual contact in 27 percent, injection-drug use in 29 percent, injection-drug use and sexual contact with an HIV-infected partner in 25 percent, heterosexual contact in 14 percent, and other risk factors in 5 percent. The median age was 34 years, with a range of 17 to 72 years. The median annual income of the cohort at presentation was \$5,000, and the median level of education was 12 years. Fifty-four percent of the patients were insured by Medicaid or Medicare, 15 percent had private insurance, 25 percent

Table 1. Base-Line Characteristics of the 1372 Patients in the Johns Hopkins HIV Clinic Cohort.

CHARACTERISTIC	NUMBER	PERCENT
Sex		
Male	958	70
Female	414	30
Race or ethnic group		
White	295	21
Black	1053	77
Hispanic	12	1
Other	12	1
Risk factors for HIV		
Homosexual contact	364	27
Heterosexual contact	194	14
Injection-drug use	392	29
Injection-drug use and sexual contact with HIV-infected partner	346	25
Other	76	5
Type of insurance		
Medicaid or Medicare	745	54
Private or commercial	208	15
None	338	25
Other	81	6
Active heroin or cocaine use	617	45
Homelessness	74	5
History of psychiatric treatment	356	26

Table 2. Clinical Characteristics of the Patients in the Johns Hopkins HIV Clinic Cohort.

CHARACTERISTIC	NUMBER	PERCENT
CD4 cell count at enrollment (per mm ³)		
>500	346	25
351–500	244	18
201–350	244	18
≤200	538	39
1993 CDC AIDS category		
AIDS	632	46
Symptomatic	194	14
Asymptomatic	546	40
Antiretroviral therapy		
Before enrollment	523	38
During follow-up	961	70
Pneumocystis prophylaxis		
Before enrollment	392	29
During follow-up	468	34
Death during follow-up	427	31
Development of AIDS during follow-up*	134	18
Death or development of AIDS during follow-up*	171	23

*For the 740 patients without AIDS at entry.

had no insurance, and 6 percent had other types of health insurance.

At enrollment CD4 cell counts were more than 500 per cubic millimeter in 25 percent of the patients, 351 to 500 per cubic millimeter in 18 percent, 201 to 350 per cubic millimeter in 18 percent, and ≤200 per cubic millimeter in 39 percent (Table 2). According to the 1993 CDC surveillance case definition for AIDS, 46 percent of the patients had AIDS; 14 percent were symptomatic, with CD4 cell counts exceeding 200 per cubic millimeter; and 40 percent were asymptomatic, with CD4 cell counts exceeding 200 per cubic millimeter. Before enrollment in the clinic, 38 percent of the patients had been treated with zidovudine or another antiretroviral agent and 29 percent had received prophylaxis against pneumocystis pneumonia. As previously reported, black patients were significantly less likely than whites to have received these treatments before enrollment in the clinic, but the racial differences in drug therapy were eliminated within six months after enrollment.¹⁴ During follow-up, 70 percent of the patients received antiretroviral therapy and 34 percent received pneumocystis prophylaxis. Use of pneumocystis prophylaxis was reported at base line by 60 percent of the patients with CD4 cell counts below 200 per cubic millimeter and during follow-up by 83 percent of such patients ($P < 0.001$).

During the follow-up period, 427 of the 1372 patients died (31 percent). Kaplan–Meier survival estimates stratified according to the CD4 cell count at enrollment and demographic variables are shown in Figure 1. After stratification for the CD4 cell count at base line, there were no significant differences in survival between men and women (Fig. 1A), injection-drug users and those who did not use injection drugs (Fig. 1B), whites and nonwhites (Fig. 1C), or patients with median annual incomes of \$5,000 or less and those with incomes of more than \$5,000 (Fig. 1D). There were also

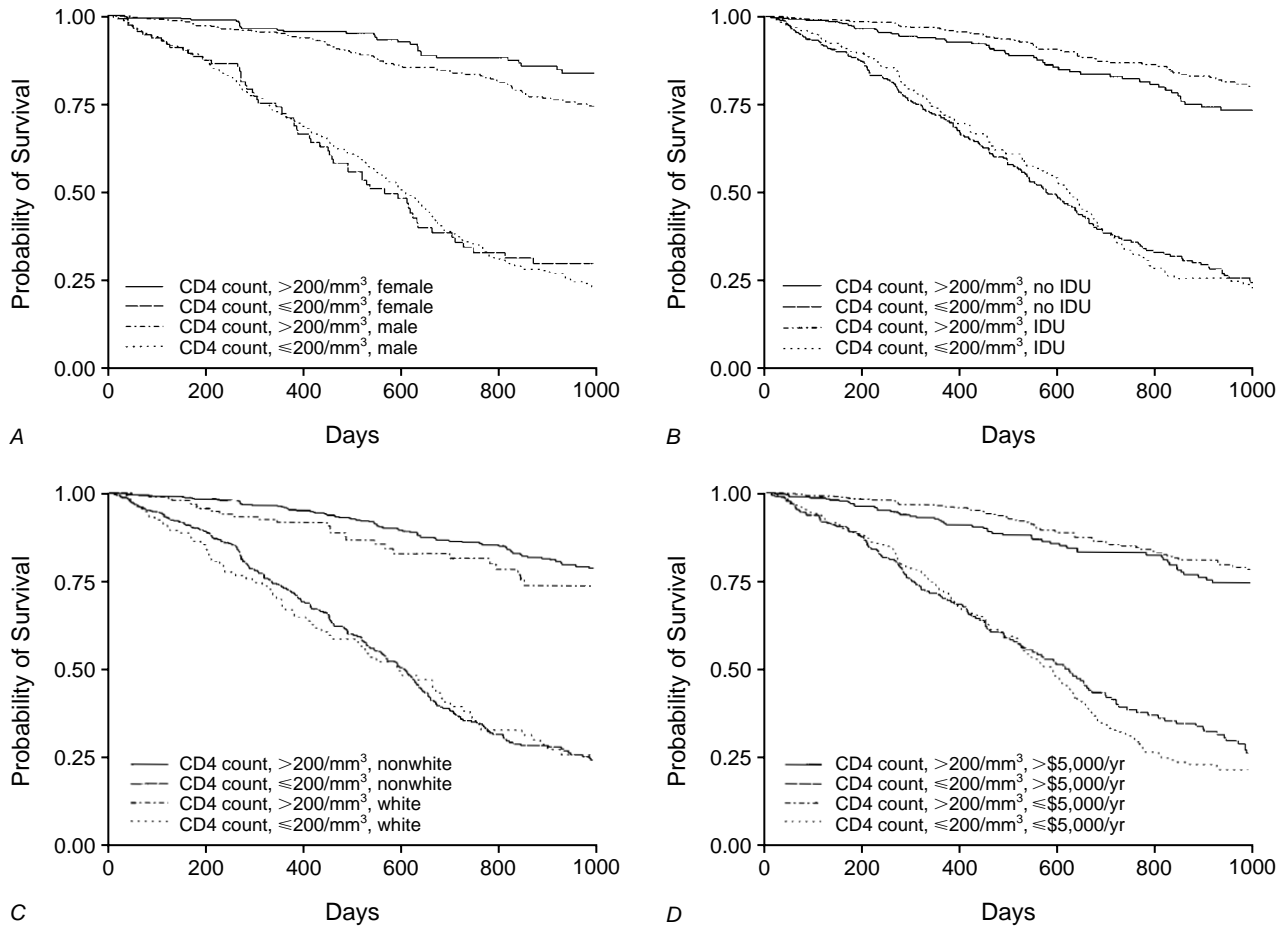


Figure 1. Kaplan-Meier Estimates of Survival According to the CD4 Cell Count and Sex (Panel A), Injection-Drug Use (Panel B), Race (Panel C), and Annual Income (Panel D).

IDU denotes injection-drug use.

no significant differences in survival according to the type of health insurance carried by patients at enrollment, the active use of injection drugs, housing status (homeless or not homeless), or level of education (<12 years or ≥12 years) (data not shown).

The mortality rate was significantly higher among patients who had received antiretroviral therapy before enrollment in the clinic than among patients who had not received such therapy (Fig. 2). Patients with initial CD4 cell counts of ≤200 per cubic millimeter who had a history of treatment with zidovudine or other antiretroviral drugs had a median survival of 600 days, as compared with 820 days for patients with CD4 cell counts of ≤200 per cubic millimeter who had not been treated previously with antiretroviral agents ($P<0.001$). The results were similar for patients with CD4 cell counts of 201 to 500 per cubic millimeter at enrollment.

The results of a Cox proportional-hazards analysis of factors associated with mortality among all 1372 patients are shown in Table 3. A CD4 cell count of ≤200 per cubic millimeter at enrollment was associated with an increased risk of death (relative risk, 7.8; 95 percent confidence interval, 4.9 to 12.5; $P<0.001$), as was a CD4 cell count of 201 to 350 per cubic millimeter (rel-

ative risk, 2.6; 95 percent confidence interval, 1.5 to 4.4; $P=0.006$). A diagnosis of AIDS at enrollment was associated with a risk of death of 2.9 (95 percent confidence interval, 2.1 to 3.9; $P<0.001$). Older age was associated linearly with a greater risk of death (relative risk per year of age, 1.02; 95 percent confidence interval, 1.01 to 1.03; $P=0.01$). Having a job at enrollment was associated with a decreased risk of death (relative risk, 0.77; 95 percent confidence interval, 0.67 to 0.89; $P<0.001$). Sex, race, income level, and a history of injection-drug use were not significantly associated with mortality. Patients who had received antiretroviral therapy before enrollment had a significantly increased risk of death (relative risk, 1.4; 95 percent confidence interval, 1.2 to 1.8; $P<0.001$), whereas treatment with antiretroviral therapy after entry was associated with a lower risk of death (relative risk, 0.65; 95 percent confidence interval, 0.52 to 0.83; $P=0.004$). Use of pneumocystis prophylaxis during follow-up was also associated with a significantly decreased risk of death (relative risk, 0.71; 95 percent confidence interval, 0.56 to 0.91; $P=0.006$).

Among the 740 patients with CD4 cell counts above 200 per cubic millimeter and without AIDS at enroll-

ment, AIDS subsequently developed in 134 (18 percent). In addition, AIDS subsequently developed or death occurred in 171 of the 740 (23 percent). After stratification according to the initial CD4 cell count, there were no significant differences in disease progression between men and women, blacks and whites, and injection-drug users and those who did not use injection drugs. A Cox proportional-hazards analysis with disease progression as the dependent variable showed an increased risk of progression associated with a CD4 cell count of 201 to 350 per cubic millimeter, prior antiretroviral therapy, older age, and symptomatic disease at base line (Table 4). Race, sex, previous use of injection drugs, current use of injection drugs, income level, type of insurance at enrollment, and housing status (homeless or not homeless) were not associated with disease progression or death in these patients ($P > 0.10$ for all comparisons).

DISCUSSION

We have shown that in patients with HIV infection who receive consistent medical care, disease progression and survival are not related to race, sex, drug use, or income. When the data were stratified according to the CD4 cell count, no significant demographic differences in mortality were observed in our patient population. In addition to the CD4 cell count, an increased risk of death was associated with older age and use of antiretroviral therapy before enrollment in the clinic, whereas improved survival was associated with the initiation of antiretroviral therapy after enrollment, the use of prophylaxis against pneumocystis, and being employed at enrollment.

Previous studies have found that survival among patients with advanced HIV disease may vary according to demographic characteristics. Rothenberg and coworkers examined survival among patients with AIDS

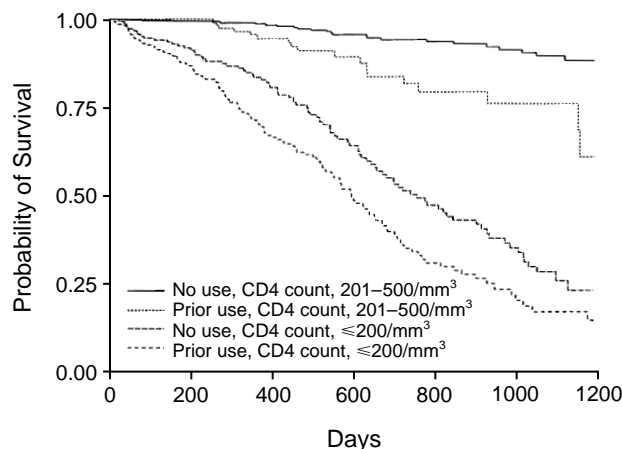


Figure 2. Kaplan-Meier Estimates of Survival According to the Use of Antiretroviral Therapy (Primarily Zidovudine) before Enrollment and the CD4 Cell Count.

$P < 0.001$ for the differences between patients with and those without exposure to antiretroviral drugs in both CD4-cell strata (by the log-rank test).

Table 3. Results of a Cox Proportional-Hazards Analysis of Factors Associated with Death among the 1372 Patients in the Johns Hopkins HIV Clinic Cohort.

CHARACTERISTIC	RELATIVE RISK	95% CI*	P VALUE
AIDS at base line	2.9	2.1-3.9	<0.001
Age (per year of age)	1.02	1.01-1.03	0.01
CD4 cell count, $\leq 200/\text{mm}^3$	7.8	4.9-12.5	<0.001
CD4 cell count, 201-350/ mm^3	2.6	1.5-4.4	0.006
Prior antiretroviral therapy	1.4	1.2-1.8	<0.001
Antiretroviral therapy after enrollment	0.65	0.52-0.83	0.004
Pneumocystis prophylaxis	0.71	0.56-0.91	0.006
Male sex	1.1	0.87-1.40	0.42
White race	1.06	0.83-1.35	0.63
Injection-drug use	0.98	0.79-1.21	0.83
Income $\leq \$5,000/\text{yr}$	0.98	0.78-1.22	0.83
Employed at base line	0.77	0.67-0.89	<0.001
High-school graduate	1.15	0.92-1.43	0.21

*CI denotes confidence interval.

in New York City between 1981 and 1985 and found that homosexual men and whites survived significantly longer than women, blacks, and injection-drug users.⁶ In a study of patients with AIDS who received Medicaid in Maryland, we found that survival was significantly shorter among women, blacks, and injection-drug users than among homosexual men and whites.¹⁰ The most important predictor of survival in our earlier study was the use of zidovudine, indicating that women, blacks, and injection-drug users had poorer access to medical care for HIV disease. Friedland and coworkers reported several demographic differences in survival among patients at a hospital-based clinic in the Bronx, New York,²¹ and suggested that differences in treatment may have contributed to these findings. Some recent studies have reported the absence of demographic differences in survival among patients with HIV disease in Europe and in the United States, after adjustment for treatment or degree of immunosuppression.^{12,22} However, a recent multicenter study found that women had higher mortality rates, but not more rapid disease progression, than men.⁴ Our study involved a heterogeneous population of patients receiving clinical care for HIV disease and had a large number of clinical end points. Our results provide strong evidence that earlier reports of differences in survival were a result of inadequate medical care rather than biologic differences in the natural history of HIV infection.

Hogg and coworkers recently reported significantly shorter survival among low-income Canadian patients infected with HIV than among those with higher incomes.¹⁵ Because Canada has universal health care, they concluded that access to medical care was probably not a factor in this difference. We found no significant differences in survival according to income or the type of health insurance at enrollment in our study. Our patients were impoverished, however, with few having incomes near the median in the Canadian study. Nonetheless, our data suggest that the use of HIV-related health care services may be independent of

Table 4. Results of a Cox Proportional-Hazards Analysis of Disease Progression or Death among the 740 Patients with HIV Infection but without AIDS at Enrollment.*

VARIABLE	RELATIVE RISK	95% CI	P VALUE
CD4 cell count, 201–350/mm ³	2.0	1.4–2.7	<0.001
Symptoms at entry	2.0	1.5–2.7	<0.001
Age (per year of age)	1.02	1.00–1.04	0.03
Prior antiretroviral therapy	1.7	1.2–2.4	0.003

*The following variables were not associated with the hazard of disease progression or death: race, sex, injection-drug use (ever or currently), income level, level of education, base-line insurance status, and homelessness. CI denotes confidence interval.

health insurance in influencing survival. Indeed, as noted above, we previously found marked demographic differences in the use of zidovudine among patients with AIDS whose care was covered by Medicaid, which provides prescription-drug coverage.¹⁰

Although having a job at base line was not associated with disease progression in patients without AIDS initially, it was associated with a lower risk of death. We have previously reported that impaired functional status is independently associated with an increased risk of death.²³ Because functional status affects the ability to work, it is likely that the survival advantage associated with employment is a result of better overall health.

In this study, the CD4 cell count was the most important predictor of survival, which is consistent with numerous previous reports. Yarchoan and associates reported that median survival in a small cohort of patients enrolled in trials of antiretroviral therapy was 12.1 months after the CD4 cell count dropped below 50 per cubic millimeter and that virtually all deaths occurred in patients with low counts.²⁴ Ehmann and co-workers recently reported that survival among patients with hemophilia and low CD4 cell counts was age-related but similar to that found in this study.²⁵ Our data support the findings of a low mortality rate among patients with high CD4 cell counts and shorter survival in very advanced HIV disease.

Our finding that the use of antiretroviral therapy (principally zidovudine) before enrollment in the clinic was associated with poorer survival is consistent with the observation that the survival advantage conferred by zidovudine is constrained by time. Although zidovudine clearly prolongs survival in advanced HIV disease,⁷ recent studies have indicated that survival is prolonged only for one to two years.^{26–29} Our previous study of access to therapy for HIV disease indicated that after adjustment for the CD4 cell count, whites were more likely than nonwhites to receive antiretroviral therapy and pneumocystis prophylaxis before their initial visit to the Johns Hopkins HIV Clinic.¹⁴ This subsequent analysis has shown no difference in survival between whites and nonwhites, yet has shown a significantly increased risk of death for persons receiving antiretroviral therapy before enrollment. We believe that this finding reflects the limited duration of the efficacy of antiretroviral therapy. Patients in our cohort who began receiving zidovudine before enrollment had al-

ready obtained a partial survival benefit from the drug, whereas those who started treatment after enrollment obtained all the benefit during the follow-up period of the study. A recent analysis from our clinic indicates that the duration of the survival advantage conferred by zidovudine in this population is approximately 18 months.³⁰

In our proportional-hazards analysis prophylaxis against pneumocystis was also associated with improved survival, with a 29 percent reduction in the risk of death after adjustment for other variables. We have previously reported a significantly reduced risk of death with the use of pneumocystis prophylaxis in a different patient population, as have others.^{8,9,31} In this analysis, pneumocystis prophylaxis was correlated with the use of antiretroviral therapy and the CD4 cell count, and the magnitude of the benefit may be somewhat muted by adjustment for these factors.

In our study, age was associated with a higher rate of death from HIV, with an increased risk of death of 2 percentage points per year of age. Bacchetti and colleagues³² first reported age-related differences in survival among patients with AIDS in San Francisco, and these findings have been confirmed in studies of other populations.^{25,33} The reason for this difference in survival is not known, although increased susceptibility to immunosuppression from HIV infection has been suggested. These data underscore the importance of adjustment for age in the comparison of survival in different populations of people with HIV infection.

Our data demonstrate that the outcome of treated HIV disease is not influenced by important demographic variables. Nonetheless, analyses of large populations of people with AIDS or advanced HIV disease show sometimes striking differences in survival.³⁴ Although it may be speculated that biologic differences between the sexes, racial or ethnic groups, or other groups (e.g., users and nonusers of injection drugs) may underlie these disparities, our findings suggest that access to medical care is a more important predictor of survival. Improved access to adequate medical care for HIV infection is essential to achieve better clinical outcomes.

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