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CD4 Lymphocyte Decline and Survival in Human Immunodeficiency Virus Infection

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ABSTRACT

The loss of the CD4 lymphocyte is the central pathophysiologic event in the progression of human immunodeficiency virus (HIV) infection. This retrospective study, based on review of data from deceased HIV patients followed in a single HIV clinic, was conducted to determine if the rate of CD4 lymphocyte decline was predictive of survival. Forty of 172 patients met defined criteria for inclusion in this study. For each patient, CD4-cell counts showed approximate exponential decline over time. A Cox regression analysis was used to assess the association of CD4 cell decline (half-life), race, age, gender, initial CD4-cell count, and treatment (anti-*Pneumocystis carinii* pneumonia prophylaxis and/or zidovudine vs. no therapy) on total survival (from initial CD4 cell count) and on remaining survival time after reaching a CD4 cell count of 100 (estimated). For all patients, the rate of CD4 cell decline was predictive of total survival ($p = .009$) but not for survival after reaching a count of 100 ($p = .6$). For patients who had never received therapy (6 patients), however, the CD4 half-life remained associated with survival time from 100 CD4 cells ($p < .05$) as opposed to the treated patients. Therapy was the single variable most predictive of both survival endpoints, resulting in an increase in median total survival of 27.2 mo ($p < .00001$) and of 15.4 mo from a CD4 cell count of 100 ($p < .00004$). Nonwhites had a slight survival disadvantage compared to whites ($p = .08$ overall; $p = .02$ from CD4 cell count of 100). It was concluded that in the natural history of HIV infection, the rate of CD4 cell decline is predictive of total survival. Current therapy can alter the natural history by prolonging life and appears to negate the predictive value of CD4 cell decline on survival from 100 CD4 cells to death.

INTRODUCTION

The CENTERS FOR Disease Control in Atlanta has estimated that 1–1.5 million people in the United States are infected with the human immunodeficiency virus type 1 (HIV-1).[1] Infected individuals may remain asymptomatic for long periods of time before the development of the opportunistic infections and neoplasms characteristic of the acquired immunodeficiency syndrome (AIDS) toward the end of the natural history of the infection.[2] The forces involved in this progression of asymptomatic infection to full-blown AIDS and death are incompletely understood but are attended by such clinical findings as thrush,[3] weight loss,[4] and hairy oral leukoplakia.[5] Laboratory markers of disease progression include CD4 counts,[6,7] HIV-1 p24 antigen,[8] neopterin,[9] β_2-microglobulin,[10] and various combinations of these.[11]

In our clinical experience as in that of others,[12] it has been observed that some patients progress rapidly to AIDS and death,

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The views of the authors do not purport to be those of the U.S. Army or the Department of Defense.
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whereas others seem to have a much slower course. The importance of the CD4 cell as a target for HIV and as a key cell in the function of the immune system is well known.[13] Most opportunistic infections occur with greater frequency when the CD4 cell count is below 200 cells/mm^3.[14] Because of the central role of the CD4 cell in the pathophysiology of HIV infection,[15] we sought to examine the way CD4 cells change with time during the progression of disease with death as an endpoint.

If, for each patient, the pattern of CD4 cell counts over time could be approximated by a usable model, e.g., by simple exponential decline, then the rate of decline could then be investigated as a predictor of survival in the natural history of HIV infection. This patient-specific parameter could also be compared to other variables which may affect the natural history of HIV infection such as age, gender, race, and the use of therapy. The rate of CD4 cell decline could be an analogue of the inverse serum creatinine vs. time parameter which can predict the timing of the need for dialysis in patients with progressive renal failure.[16] We conducted a retrospective chart review of deceased patients followed in our clinic to determine if the pattern of CD4 cell count decline with time (to death) was consistent with approximate exponential decline, and if so, whether the rate of decline, as measured by the CD4 cell half-life is prognostic for overall survival (initial CD4 cell count to death) and survival after reaching a CD4 cell count of 100.

MATERIALS AND METHODS

This study was conducted under the auspices of an approved protocol by the Walter Reed Army Medical Center Human Use Committee and the Department of Clinical Investigation. The outpatient records of deceased HIV-infected patients who had died between July 1985 and July 1991 and had been followed in the Infectious Disease Clinic were reviewed. To be included for analysis several conditions had to be met (Fig. 1). The time of death had to be known and the cause of death had to be due to natural, HIV-associated mechanisms; patients who had suicidal, homicidal, and accidental deaths were excluded from analysis as were those with severe illnesses diagnosed prior to HIV infection. At least three independent CD4-cell counts over >150 days of observation were required. The minimum initial CD4-cell count was set arbitrarily at 125 cells/mm^3. The CD4 cell counts had been determined by fluorescence-activated cell analysis which has been part of the standard of care at Walter Reed since the onset of the epidemic.[17] These counts are determined every 6 mo as a minimum in patients with early disease and more frequently with progression. Clinical and demographic information was recorded from these charts particularly in regard to the use, timing, and types of therapy employed in treatment. Based on consistent exponential-like decline (semilog plots of counts vs. time were linear), ordinary (unweighted) least squares was used to estimate the rate of decline (slope of regression of the natural logarithm of the cell count vs. time) for each patient. The corresponding CD4 cell halflife (in months) was then estimated as ln 2 / m (m = slope). The fitted exponential decline model was used to estimate the time that cell counts would reach 100 (T100) and 25 (T25). These times were arbitrarily selected. Two survival measures were then estimated: (1) the survival time after reaching a cell count of 100 (T100-D) determined by subtracting T100 from the time of death, and (2) the survival from time of reaching a count of 25 (T25-D) determined in a similar manner using T25. These two measures of survival at low CD4 cell counts were analyzed in order to eliminate the possible influence of initial CD4 cell counts when assessing the effect of rate of cell decline on survival. A Cox life table regression model (proportional hazards model)[18] was used to assess the influence of several covariates (prognostic factors) on total survival time (initial CD4 cell count (entrance) to death) and on T100-D. Covariates included: treatment (treated vs. untreated), rate of CD4 cell decline (half-life) in months, initial CD4 cell count (cells/mm^3), age (years), gender, and race (white vs. nonwhite). This type of analysis attempts to model survival time data and provides a way to assess the influence of prognostic variables alone or after adjusting for effects of other variables. Computations were performed using BMDP program 2L.[19] Product limit (Kaplan-Meier) survival curves were also constructed. Both logrank and Wilcoxon statistics were used to test for differences in survival times.[20,21] The Wilcoxon test is more powerful than the log rank test in detecting differences in early survival (early deaths given more weight). Spearman's (rank) correlation was used to assess association of two quantitative variables. All reported p-values are two-sided.

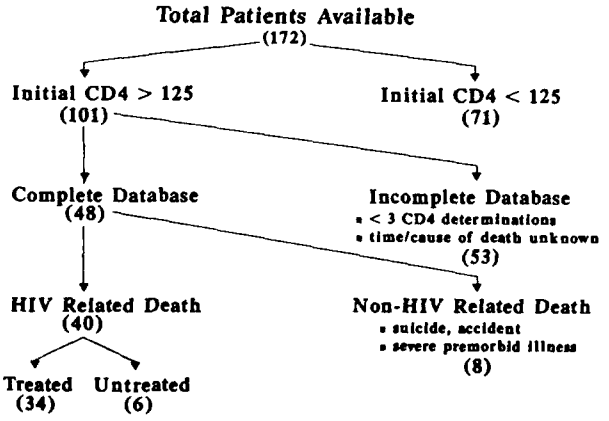

FIG. 1. Chart selection algorithm for 172 deceased HIV patients followed in the Infectious Disease Clinic (July 1985 to July 1991).

RESULTS

Of 172 deceased patients who had been seen in the clinic, 40 (23%) met criteria to be included for analysis (Fig. 1). The largest group of the deceased patients (41%) had presented to care at Walter Reed considerably late in their disease course as evidenced by low initial CD4 cell counts, often <25/mm^3. Thirty-one percent of the charts were incomplete because of an unknown time and cause of death and/or less than three discrete CD4 cell count determinations. The individuals in this category had left the geographic area covered by our clinic usually after one or two evaluations. No further information was readily available on these individuals for the purpose of the study. A small percentage (5%) were excluded from analysis for a non–HIV-related death (suicide, accident, severe premorbid

illness). Of the 40 evaluable patients, the 6 classified as untreated in this analysis had not received either zidovudine (AZT), anti-*Pneumocystis carinii* pneumonia (PCP) prophylaxis, or other related therapy in an effective manner. Reasons for nontreatment included: the refusal of all therapy by the patient; initiation only within the week prior to death; and discontinuance by the patient within 1 wk of starting therapy due to perceived side effects (nausea, nervousness). The other 34 patients classified as treated had received anti-PCP prophylaxis and/or AZT. Usually the two modalities were begun concurrently and in a few AZT was stopped later in the course for hematologic problems. Overall, 33 of 34 patients had received AZT (1 patient declined AZT) and all had received anti-PCP prophylaxis (pentamidine 22, Septra 1, Fansidar 5, Fansidar then pentamidine 6). Because of concurrent usage, comparisons between the two modalities could not be made. These therapies were instituted when the CD4 cell counts were $<200/mm^3$ in 33 of 34 patients. One patient had been initiated on low-dose AZT when the CD4 cell count fell $<500/mm^3$. Dideoxyinosine (ddI) was used briefly in one patient after hematologic problems with AZT developed near the end of his life. Four patients received the immunostimulator, Poly-ICLC, in concert with AZT for periods <6 mo in the terminal aspects of their illnesses. No conclusions considering these other individual antiretroviral therapies, immunostimulators or regimens directed against opportunists could be made given their variety and the small numbers of patients involved. Treated and untreated patients were similar in regard to sex ratio, age, ethnicity, and initial CD4 cell counts (Table 1). Treated patients had a mean of 10.3 CD4 cell determinations with a median interval of 3.75 mo between tests. The untreated group had a mean of 4.3 determinations with a median interval of 2.65 mo between tests.

The decline of CD4 cell count over time for each patient exhibited a form consistent with approximate exponential decay (semilog plots of the CD4 cell count vs. time were linear). Transient perturbations in the curves of patients initiated on AZT were noted and generally were of 4 mo or less in duration. Figure 2 portrays representative examples for an untreated and treated patient. Table 2 summarizes the results of estimating CD4 cell half-life and the two derived survival measures (T100-D and T25-D) as well as survival time from entrance to study.

The results of the Cox regression are summarized in Table 3. CD4 cell half-life, when considered alone, was predictive of overall survival ($p < .009$; model 2; Table 3A). When the survival time from 100 CD4 cells to death was considered (model 2, Table 3B), however, there was no relationship observed. Treatment was the most important single variable using either total survival time ($p < .00001$) or T100-D ($p < .00004$) (model 1; Table 3A and B) or T100-D. Treatment remained the most important variable when considered jointly with the other variables (models 7–10; Table 3A and B). For both survival measures, nonwhite race appeared to be associated with poorer survival either by itself ($p = .03$ and $p = .08$; model 3; Table 3A and B) or in combination with other variables (models 7–10). Age, gender, and initial CD4 cell count were not associated with overall survival.

Figures 3, 4, and 5 compare the Kaplan-Meier survival curves for both survival measures by treatment received (Fig. 3), race (Fig. 4), and CD4 cell half-life (Fig. 5). The nonparametric results concur with the proportional hazard analysis. A direct

TABLE 1. PATIENT DEMOGRAPHICS

	All	*Treated*	*Untreated*
N	40	34	6
Gender			
Male	36	31	5
Female	4	3	1
Race			
Black	14	11	3
Hispanic	4	3	1
White	22	20	2
Year of initial presentation			
1985	4	3	1
1986	19	16	3
1987	15	13	2
1988	1	1	0
1989	1	1	0
Age			
(yr)	34.4 ± 1.6 (31)	33.7 ± 1.6 (32)	38.5 ± 5.4 (30.5)
Initial CD4 cell count			
($cells/mm^3$)	342.7 ± 26 (294.5)	339.2 ± 28 (294.5)	362.8 ± 78 (289)
Amount of study time on AZT			
(percentage)	—	56.9	0
Amount of study time on anti-PCP prophylaxis:			
(percentage)	—	60.2	0

Demographic characteristics of patients included for analysis according to whether treated or not. Values reported as mean ± SEM and (median).

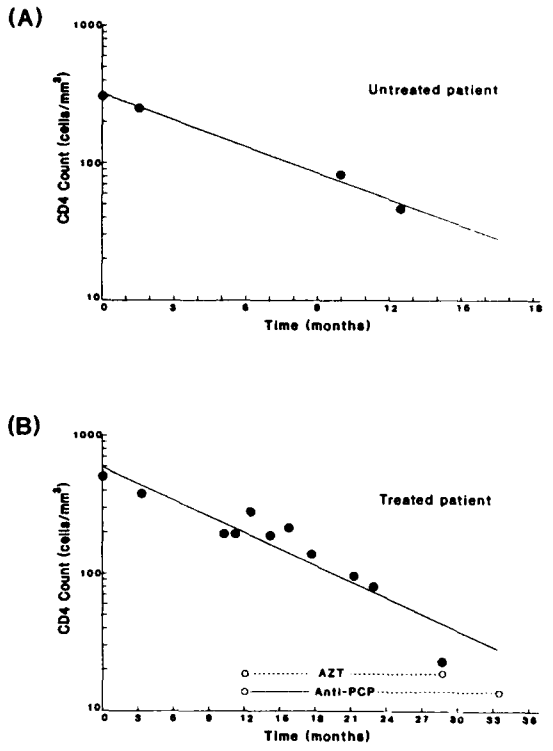

FIG. 2. Representative plots (semilog) of CD4 cell counts versus time (months) from study entrance: (A) untreated patient; (B) treated patient.

relationship between the CD4 half-life and total study survival was found by Spearman's (rank) correlation for both treated ($r = 0.38$; $0.02 < p < 0.05$) and untreated patients ($r = 0.77$; $0.05 < p < 0.10$) (Fig. 6A). When considering estimated survival from a CD4 cell count of 100, there was no association with rate of decline in treated patients (Fig. 6B). However, there continues to be a positive association in untreated patients ($r = 0.83$; $0.02 < p < 0.05$) (Fig. 6B).

DISCUSSION

This study was performed to determine if CD4 cell decline fit a simple mathematical model such as exponential decay in an individual patient, and, if so, whether the patient-specific rate of CD4 cell decline is predictive of patient survival. In this group of patients the rate of CD4 cell decline over time could be approximated by a simple exponential model. The study is retrospective and suffers from the limitations of a retrospective analysis in addition to small numbers. The data, however, represents current clinical practice in a single clinic and was carefully screened by rigid criteria to ensure comparability. With the exception of excluded patients with pre-morbid illnesses, it is doubtful that the majority of the excluded patients were different from the included ones but this cannot be tested since the required detailed information on them is unavailable by definition. All patients had a comparable interval between CD4 cell determinations. Therefore we feel that the likelihood of substantial selection and/or detection bias is low. Cox regression was used to compare CD4 cell decline, race, age, gender, initial CD4 cell count, and treatment as variables with a known or potential effect on survival in HIV infection. Whether other unmeasured variables contributed to the observed associations is unknown.

In all of the patients, the rate of CD4 cell decline was approximately constant indicating the pattern of CD4 cell counts over time (to death) was exponential and could, therefore, be characterized in terms of the CD4 cell half-life. This decline, specific for each patient, is most likely determined by host–virus interplay in the individual patient. The initiation of therapy with zidovudine appeared to cause transient perturbations in the rate of decline of CD4 cells in some patients (Fig. 2). However, in all such cases the rate of decline returned to the baseline rate within 4 mo of initiation. This pattern in the CD4 cell counts of patients on chronic zidovudine has been noted before.[22] Patients on therapy experience a transient delay in decline or frank increase in CD4 cell count. Our data suggest that despite these perturbations, the overall rate of decline remains relatively constant over a long period of follow-up for an individual patient. To further test this observation numerically, the CD4 half-lives before and

TABLE 2. COMPARISON OF SURVIVAL PARAMETERS

	All	*Treated*	*Untreated*
N	40	34	6
CD4 cell half-life (*months*)	7.03 ± .5 (6.6)	7.68 ± .5 (7.0)	3.32 ± .6 (3.5)
Survival from entrance (mo)	34.4 ± 2.1 (36.2)	38.2 ± 1.8 (38.6)	12.9 ± 3.0 (11.4)
Survival from 100 CD4 cells (T100-D) (mo)	20.6 ± 1.7 (20.8)	23.1 ± 1.6 (22.3)	6.8 ± 1.6 (6.9)
Survival from 25 CD4 cells (T25-D) (mo)	6.6 ± 1.9 (5.0)	7.7 ± 2.2 (9.3)	0.14 ± 1.0 (−0.3)

Estimated CD4 cell half-life and three survival measures according to whether treated or not. Values reported as mean ± SEM and (median).

TABLE 3A. COX REGRESSION (PROPORTIONAL HAZARD) ANALYSES USING SURVIVAL TIME FROM ENTRANCE TO STUDY

Model	*Goodness of fit* χ^2	*d.f.*	*p*	*Variables included*	*Regression coefficient b*	*SE(b)*	*z = b/SE(b)*	*p*
1	41.1	1	<0.0001	Treatment (no vs. yes)	2.93	0.61	4.84	<0.00001
2	7.4	1	0.0064	Half-life (mo)	−0.189	0.072	−2.63	0.009
3	3.1	1	0.08	Race (nonwhite vs. white)	0.57	0.33	1.74	0.08
4	0.98	1	0.32	Initial CD4 (count)	−0.0009	0.0009	−0.99	0.32
5	0.96	1	0.33	Age (yr)	0.019	0.019	0.98	0.33
6	1.3	1	0.26	Sex (male vs. female)	−0.06	0.54	−1.11	0.27
7	44.2	2	<0.0001	Treatment	3.08	0.63	4.86	<0.00001
				Race	0.64	0.33	1.93	0.05
8	41.1	2	<0.0001	Treatment	2.51	0.64	3.90	0.0001
				Half-life	−0.120	0.066	−1.78	0.08
9	46.3	3	<0.0001	Treatment	2.70	0.66	4.06	0.00005
				Race	0.56	0.34	1.65	0.09
				Half-life	−0.102	0.066	−1.55	0.12
10	47.1	4	<0.0001	Treatment	2.72	0.67	4.02	0.00006
				Race	0.61	0.34	1.76	0.08
				Half-life	−0.099	0.066	−1.51	0.13
				Age	0.0206	0.0205	1.00	0.32

For explanation of columns, see Table 3B.

during AZT therapy were compared to the overall half-life by paired parametric and nonparametric statistical methods and no statistically significant differences were noted (data not shown). Also a direct linear relationship was determined between the half-life on AZT vs. the overall CD4 halflife ($p = .002$; data not shown).

Exponential decline of CD4-cells in early stage HIV disease has been previously described by Brundage and colleagues.[23] They studied a military cohort of HIV patients with early stage disease as a total population rather than as individuals and found a mean rate of decline of 5–10 CD4 cells/mo for those patients in the 500–800 cells/mm^3 range. Most cases in the current analysis, however, were patients who presented in the midstage of HIV disease (mean CD4 cell ~350/mm^3) and were followed until they died.

Phillips et al.[24] concluded that the trend of CD4 cell decline over time was linear. The rate of CD4 decline (slope of cell count versus time) derived from their study of hemophiliac patients was highly predictive of the development of AIDS as an endpoint with higher rates of decline associated with a more rapid development of AIDS. In that study the CD4 counts were not followed to death, so the flattening-out of the CD4 counts over time at low CD4 cell counts was not observed as in our study.

Our analysis revealed that the speed of CD4 cell decline in HIV patients as measured by CD4 cell half-life was predictive of the total survival time (from the initial CD4 cell count). This is not surprising, given the central pathophysiologic role of CD4 depletion in the progression of HIV infection. However, the analysis also suggested that once a patient's CD4 cell count reached 100, the CD4 half-life was no longer predictive of survival. We found the disparate predictive value of the CD4 cell half-life in regards to the survival interval used in our analysis to be of great interest. This effect was not due to alteration of the rate of CD4 decline by therapy in that no such alteration was observed. We postulate that current therapy may still be responsible for this effect by prolonging the interval of survival at very low CD4 cell counts, the duration of which may not be associated with the previous rate of decline. We have anecdotally observed this in many of our patients some of whom are still doing well after 3 years with CD4 cell counts <10/mm^3. This is also suggested in our study by the fact that patients on therapy had an increase of 9.6 months in the time from 25 CD4 cells to death compared to the untreated group (Table 2). Interestingly, in the untreated patients, the rate of decline of CD4 cells appears to be predictive of survival from a CD4 cell count of 100 (Fig. 6B). This should be interpreted with caution given the small numbers of untreated patients but suggests that in untreated HIV infection (natural history), the rate of decline may be predictive of survival regardless of which survival parameter is used.

The prolongation of survival at very low CD4 cell counts to account for this effect would be expected for anti-PCP prophylaxis which has already been shown to prolong survival in patients at risk (CD4 < 200 cells/mm^3). This therapy would exert a beneficial impact regardless of the rate of CD4 cell decline.[25] AZT, on the other hand, has been clearly demonstrated to prevent CD4 cell decline at least temporarily.[26] It has been suggested, however, that AZT may also work in a beneficial manner, independently of the CD4 cell count in patients with low CD4 cell counts.[27] Because both therapeutic modali-

TABLE 3B. COX REGRESSION (PROPORTIONAL HAZARD) ANALYSES USING SURVIVAL TIME FROM REACHING AN ESTIMATED CD4 COUNT OF 100

Model	*Goodness of fit* χ^2	*d.f.*	*p*	*Variables included*	*Regression coefficient b*	*SE(b)*	*z = b/SE(b)*	*p*
1	38.1	1	<0.0001	Treatment (no vs. yes)	3.47	0.85	4.11	0.00004
2	0.28	1	0.60	Half-life (mo)	0.036	0.069	0.53	0.60
3	5.0	1	0.02	Race (nonwhite vs. white)	0.77	0.34	2.22	0.03
4	0.47	1	0.49	Initial CD4 (count)	0.0006	0.0009	0.68	0.50
5	1.2	1	0.28	Age (yr)	0.021	0.019	1.07	0.28
6	0.01	1	0.90	Sex (male vs. female)	−0.07	0.54	−0.12	0.90
7	42.0	2	<0.0001	Treatment	4.06	0.91	4.48	0.00001
				Half-life	0.057	0.069	2.12	0.03
8	41.8	2	<0.0001	Treatment	3.43	0.87	3.96	0.00007
				Race	0.69	0.35	1.96	0.05
9	49.3	3	<0.0001	Treatment	4.13	0.93	4.42	0.00001
				Half-life	0.198	0.069	2.76	0.02
				Race	0.96	0.37	2.59	0.01
10	49.6	4	<0.0001	Treatment	4.08	0.96	4.25	0.00002
				Half-life	0.195	0.072	2.74	0.01
				Race	0.96	0.37	2.59	0.01
				Age	0.0036	0.0205	0.17	0.87

Explanations of columns: (1) model identification; (2–5) the χ^2 goodness-of-fit measure for overall significance of all covariates included in the model, corresponding degrees of freedom (number of variables), p-value, and list of included variables; columns (6–9) give the regression coefficients (*b*) for each included variable (a measure of predictive value of the variable), its standard error, test of significance, and corresponding p-value. The table includes the assessment of each individual prognostic variable (models 1–6); the two best two-variable models (models 7 and 8); and the best three-variable (model 9) and four-variable (model 10) model. A negative regression coefficient indicates a variable is positively associated with survival (decreased hazard).

ties were administered to our patients, comments about the relative contributions of each to the increased survival remain to be determined. AZT is currently recommended for patients with CD4 cells <500/mm^3.[28] Only 1 of the 34 treated patients had received AZT in that fashion inasmuch as these patients had had significant CD4 cell decline by the time those recommendations were made. A similar analysis of patients who had received early AZT may reveal more profound changes of the natural history of HIV infection. One would anticipate a slowing of CD4 cell decline or a delay such that survival would be lengthened. The recent Veteran's Administration Hospital study, however, demonstrates that this may not be the case with early AZT treatment, since overall survival was not prolonged in the early AZT recipients relative to later use.[29] Whether the CD4 cell halflife would retain a predictive relationship to total survival in that situation also remains to be seen and is the subject of ongoing study at this institution.

The results of our analysis demonstrate a survival advantage of being on current therapy as demonstrated by an estimated median increase in life span of 15.4 mo from reaching a CD4 cell count of 100 for treated patients and a 27.2-mo increase in total survival from the initial CD4 cell count. This beneficial effect is independent of age, gender, rate of CD4 cell decline, and initial CD4 cell count. These figures are also consistent with the 19.3 mo observed in a large retrospective study of AZT-treated individuals.[30] In that study as in ours, the role of anti-PCP prophylaxis could not be determined separately from that of AZT. Survival at low CD4 cell counts was also substantially prolonged in our patients due to current therapy. The 9.6-mo median increase in life span at CD4 cell counts <25/cm^3 is also consistent with the results of another group of well-studied patients.[31] In that study, a CD4 cell count of 50 or less was associated with an increased risk of dying. When our data was analyzed in that fashion, we found similar results and also found treatment prolonged the interval from the last CD4 cell count to death.[32]

Race also had an influence on outcome in this group of patients, although quantitatively to a much lesser degree than therapy. Nonwhites had a somewhat shorter survival compared to whites (7 mo). This trend has been noted before in other studies in which the differences were attributed to socioeconomic differences.[30,33] In that all of the patients studied herein had equal access to medical care and current drug therapy in the military system, it suggests that the observed difference may be due to variables beyond access to treatment and care. The difference in survival persists when treatment is accounted for in the proportional hazard model. The nature of this observed racial difference in survival (biological vs. risk factor, etc.) is the subject of ongoing study at our institution. Older age has previously been reported to have a negative influence on sur-

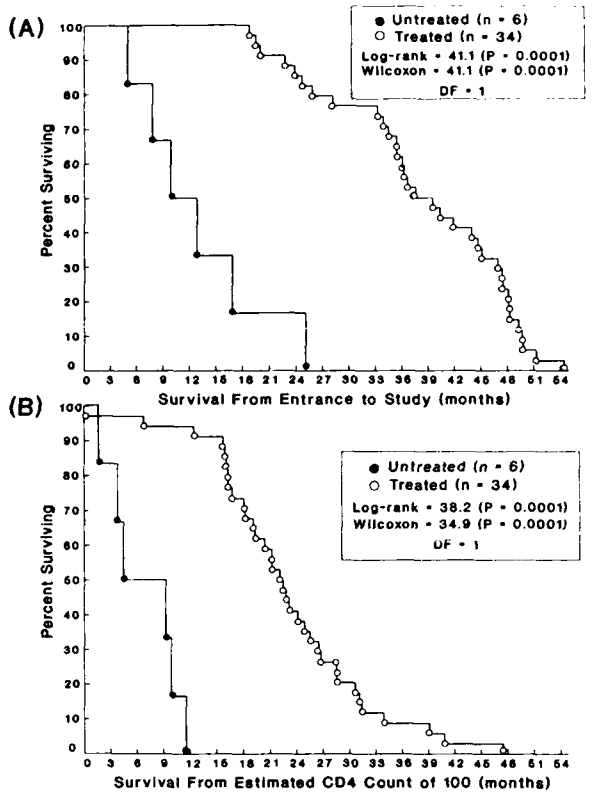

FIG. 3. Product limit (Kaplan-Meier) survival curves for untreated and treated patients: (A) using survival time from entrance; (B) using T100-D, estimated survival time after reaching a CD4 cell count of 100.

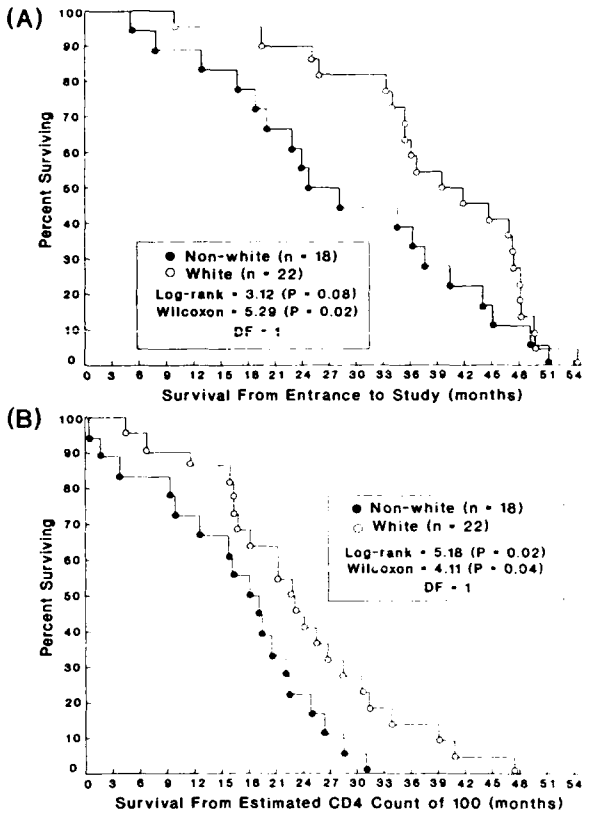

FIG. 4. Product limit (Kaplan-Meier) survival curves for nonwhite and white patients: (A) using survival time from entrance; (B) using T100-D, estimated survival time after reaching a CD4 cell count of 100.

vival in HIV infection.[3,4] This was not observed in our group of patients, but it should be pointed out that the number of patients was small with a narrow age range. A larger, more powerful study may have demonstrated an effect due to age. The same argument can be applied to gender, because there were few females in the study.

Because the rate of CD4 cell decline was not predictive of remaining survival after reaching a CD4 cell count of 100, there is a need for other prognostic parameters which may better predict ultimate outcome in patients with advanced HIV infection on therapy. With the availability of current therapy, this subset ideally should be nearly 100% of all such patients, considering the survival advantage of such therapy demonstrated here and in numerous other studies.[30] The CD4 cell half-life was predictive of outcome from the initial CD4 cell count to death. This period of time included periods on no treatment. This measure of cell decline may be a useful one to consider in trials of novel therapies for patients not on current therapy such as those with earlier stages of disease. Relying only on initial CD4 cell counts in defining entry criteria and not taking into account the rate of CD4 cell decline may give both false-positive and -negative indications of efficacy to a new treatment. The CD4 cell half-life may be a useful prognostic parameter regardless of current therapy if an endpoint less stringent than actuarial survival is used such as the development of an opportunistic infection or thrush. More complex models (Markovian), which attempt to incorporate current and past time-varying predictors (CD4 cell count, rate of decline, etc.), could also be used to predict survival. Cox regression models exist which can incorporate time-varying covariates. Such attempts to model survival would require a large population with an attendent large database per subject. All of these issues remain unanswered and are the focus of ongoing study at our institution. All of the findings of the current study need confirmation in larger patient populations.

In summary, for this group of military patients, individual CD4 cell decline to death appeared to be approximately exponential. Transient perturbations occurred due to AZT, but CD4 cell loss remained constant for each patient. The corresponding rate of CD4 cell decline (CD4 cell half-life) provided prognostic information when survival from the initial CD4 cell count to death was used as an endpoint. This measure of survival time included untreated periods and time on current therapy. The survival from 100 CD4 cells to death in treated patients did not seem to be related to the CD4 cell decline. In untreated patients, however, a persistent relationship was suggested although the numbers were small.

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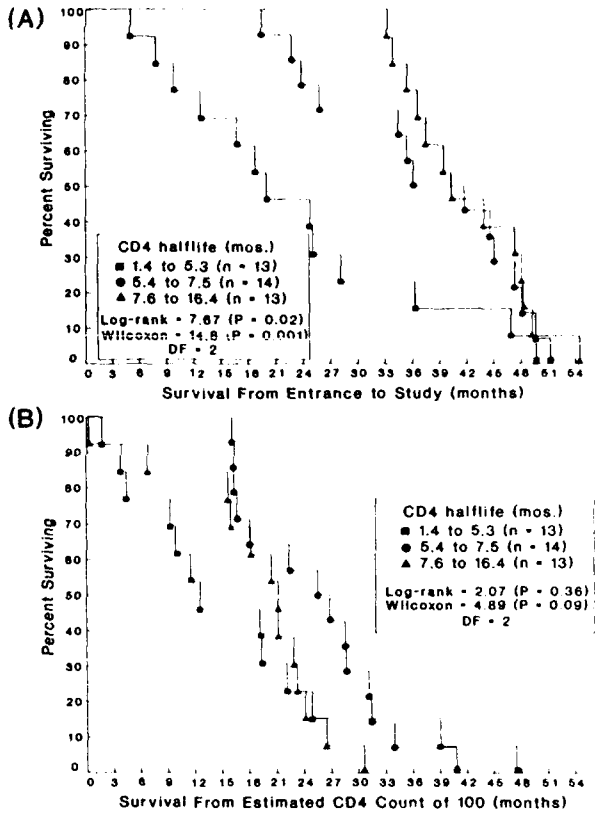

FIG. 5. Product limit (Kaplan-Meier) survival curves for the low, middle, and upper thirds of CD4-cell half-lives: (A) using survival time from entrance; (B) using T100-D, estimated survival time after reaching a CD4 cell count of 100.

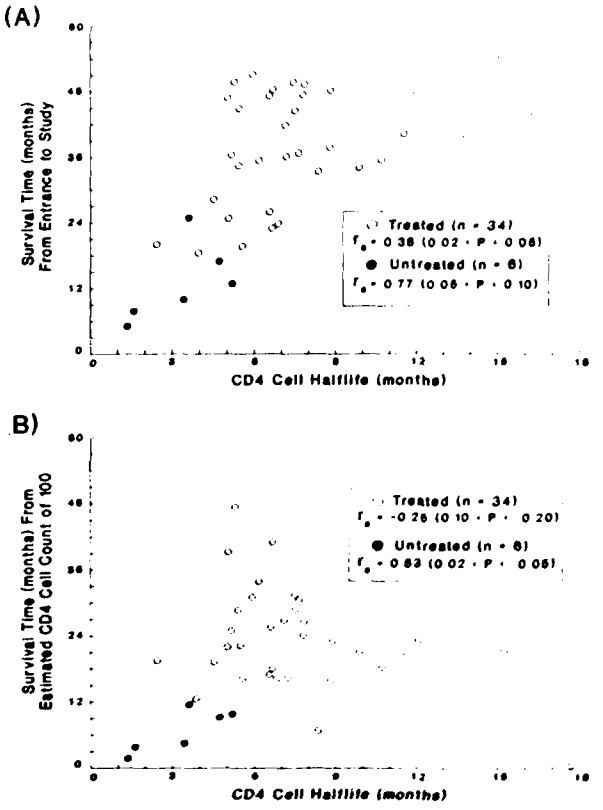

FIG. 6. Relationship between CD4 cell half-life (months) and survival time: (A) using survival time from entrance; (B) using T100-D, estimated survival time after reaching a CD4 cell count of 100.

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