Greater Effect of Highly Active Antiretroviral Therapy on Survival in People Aged ⩾50 Years Compared with Younger People in an Urban Observational Cohort

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Although human immunodeficiency virus–infected people aged ⩾50 years have a blunted CD4 cell recovery when receiving highly active antiretroviral therapy (HAART), there are few data on mortality. Mortality rates were studied for 253 individuals aged ⩾50 years and a younger group of 535 people in a retrospective cohort; for untreated persons in each age group, the proportions surviving at 3 years were 83% and 70% ($P < .01$), respectively. No significant difference in the survival rate was found between the older (83%) and younger (89%) patients who received HAART ($P = .29$). The hazard ratio for death in the older untreated group was 2.4 (95% confidence interval [CI], 1.4–3.9) when exposed to HAART. However, compared with older untreated patients, the hazard ratio for death decreased to 0.28 (95% CI, 0.15–0.52) for treated older adults. The effect of HAART substantially improves the survival rate for older individuals and supports the importance of treatment in this group.

As of December 2000, >774,000 cases of HIV infection in the United States had been reported to the US Centers for Disease Control and Prevention, and 58% of the affected patients had died [1]. During this time, the number of cases reported among those aged ⩾50 years was >84,000 (10.9%). Several cohort studies have shown that older people have progression to AIDS faster than younger people [2–7]. For example, a French cohort found that older age was associated with a more rapid progression to symptomatic disease [3]. In persons with hemophilia, the relative risk of developing AIDS after seroconversion is 1.45 for each 10-year increase in age [6]. The duration of survival is also significantly shorter for elderly persons [8–11], and older patients have poorer outcomes of opportunistic infections than do younger individuals [12, 13]. These data suggest that older patients might benefit from treatment more than do younger people.

HAART is effective in correcting CD4 lymphocytopenia and decreasing the virus load; this has been associated with a 50% decrease in morbidity and mortality associated with AIDS [14–16]. The degree of immune recovery is dependent on the regenerative capacity of the thymus, which is lost with advanced age [17, 18]. However, in one prospective cohort, the extent of CD4 recovery could be demonstrated in the oldest subjects in the cohort, although CD4 recovery was negatively correlated with age [19]. Although the median age was only 37 years in this cohort, it is reasonable to suspect that CD4 recovery may be slow, but present, as age increases [20, 21]. Recently, one case-control study examined 52 HIV-infected individuals aged ⩾50

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years and matched them to a random sample of 52 younger control subjects [22]. They found no differences in CD4 counts, virus loads, frequency of opportunistic infections, hospitalizations, drug-related side effects, and death. However, they did not include people who were untreated; thus, no estimate of the relative risk for death for treated versus untreated patients could be determined.

Given the question of meaningful immune restoration in older people and the significant toxicities of HAART, it is important to determine in a community-based setting whether HAART is effective in changing the level of HIV-related mortality in older people with HIV infection. We have conducted such an analysis by comparing the rate of survival for patients aged ⩾50 years with the rate for younger patients in a large urban HIV clinical cohort.

METHODS

Setting and database. Subjects for this analysis were enrolled at the Johns Hopkins HIV Clinic (Baltimore, Maryland), which provides primary and specialty care for HIV infection to ~2500 patients. In 1990, an observational clinical database was established [23] for patients receiving longitudinal primary care for HIV infection at the clinic. All patients were eligible for inclusion in the study if they enrolled during the period of 1 July 1990 through 28 February 2001. Baseline demographic characteristics were recorded for all patients enrolled in the clinic by clinicians and social workers during structured interviews, and the data were recorded on standardized forms. Clinical, laboratory, and pharmaceutical data from all subsequent clinic visits and hospitalizations were abstracted from the clinical record by trained technicians, who transcribed the information on structured data collection forms. All data were reviewed and updated at 6-month intervals. This information was subsequently entered into the database. Information concerning death was obtained from a death registry managed by the clinic. The registry received reports from families, funeral homes, other medical institutions, and local coroners. In addition, death records from the Maryland Bureau of Vital Records (Maryland Department of Health and Mental Hygiene, Baltimore) and the national Social Security death index were regularly searched. This research was approved by the Johns Hopkins Institutional Review Board, and the research followed the guidelines for human experimentation of the US Department of Health and Human Services.

Study design and definitions. We used a retrospective cohort design. The older group consisted of patients aged ⩾50 years at the time of enrollment in the clinic ($n = 259$), whereas the younger group consisted of patients aged 18–49 years ($n = 538$). The age cutoff of 50 years was chosen for 2 reasons: the World Health Organization does not report the prevalence of HIV infection among persons aged ⩾50 years, and previous studies have used this cutoff [2, 9, 13]. The younger group was chosen at random from the total cohort at a ratio of younger to older patients of approximately 2:1. The primary outcome of interest was all-cause mortality. Patients who were observed in the clinic for <90 days were excluded from the survival analysis ($n = 9$) to ensure an adequate follow-up time necessary to evaluate the effect of receipt of HAART. Of the 9 patients who were excluded, 8 died (3 in the younger group and 5 in the older group).

The CD4 cell count was recorded at enrollment in the clinic. The HIV-1 RNA level was measured by use of a standard RT-PCR assay (Roche Molecular Systems). Current guidelines were used to define HAART [24]. HAART was defined as use of ⩾2 nucleoside reverse-transcriptase inhibitors (NRTIs) with either (1) ⩾1 protease inhibitor (PI) or (2) a nonnucleoside reverse-transcriptase inhibitor (NNRTI). The PIs included indinavir, ritonavir, nelfinavir, amprenavir, and saquinavir (Fortovase [Roche], if this was the only PI, or Invirase [Roche], if ritonavir was added); the NNRTIs included efavirenz, nevirapine, and delavirdine, and the NRTIs included zidovudine, stavudine, zalcitabine, lamivudine, abacavir, and didanosine. Three NRTIs were considered to be HAART if abacavir was included. Monotherapy or dual antiretroviral therapy was not considered to be HAART, and patients who received such regimens were classified as untreated.

Use of HAART was defined as receipt of ⩾90 days of continuous therapy. The treatment time began when a HAART regimen was initiated, and ended when the patient stopped receiving ⩾1 drug or died. Drug substitutions were allowed during treatment as long as the new regimen met the definition of HAART. For the purpose of the analysis, an intent-to-treat principle was used such that once people were classified as exposed to HAART, they remained in this group, regardless of whether they discontinued therapy. The younger and older groups were then subdivided into 4 categories on the basis of HAART exposure: younger and older patients who were exposed or not exposed to HAART.

Statistical analysis. χ^2 Analysis for categorical variables and the Wilcoxon rank sum test for continuous, nonnormal variables were used to compare demographic characteristics between age categories and HAART exposure groups. For variables with normal distributions, Student's t test was used. Survival time was measured from the date of enrollment in the clinic to the last clinic visit, which could be as late as 31 July 2001. Patients were recorded as alive at their last clinic visit. Deaths were recorded after the last clinic visit or hospitalization by the methods detailed above. There was an inherent survival bias for the group exposed to HAART in the study. Those who survive long enough to initiate HAART may be healthier than those who never receive it.

Table 1. Demographic characteristics of HIV-1–infected patients enrolled in an urban HIV clinic, according to age group.

Characteristic	Patients aged <50 years	Patients aged ⩾50 years
No. of patients	535	253[a]
Age, mean years ± SD	36.5 ± 6.5	55.2 ± 5.8
Male sex	385 (72)	211 (83)[b]
Race		
White	135 (25)	65 (26)
Black	390 (73)	184 (73)
Other	10 (2)	4 (1)
Risk group		
MSM	182 (34)	67 (26)[b]
IDU	230 (43)	104 (41)
Patients with an infected partner	93 (17)	42 (17)
Patients with a high-risk partner	129 (24)	78 (31)
Date of enrollment, median year (IQR)	1997 (95–98)	1996 (95–98)
CD4 cell count at enrollment, median cells/mm^3 (IQR)	244 (75–421)	289 (120–481.5)[b]
HIV-1 RNA at enrollment, median $\log_{10}$ copies/mL (no. of patients who had the virus load measured at baseline)	4.5 (508)	4.3 (239)
Year patient began receiving HAART (IQR)	1997 (96–98)	1997 (96–98)
Receipt of HAART	342 (64)	152 (60)
Stage of HIV illness at enrollment		
Asymptomatic	181 (34)	96 (38)
Symptomatic	72 (13)	29 (11)
AIDS	282 (53)	128 (51)
AIDS at any time	361 (67)	166 (66)
Death[a]	63 (12)	50 (20)[b]

NOTE. Data are no. (%) of patients, unless otherwise indicated. IQR, interquartile range; IDU, injection drug user; MSM, men who have sex with men.

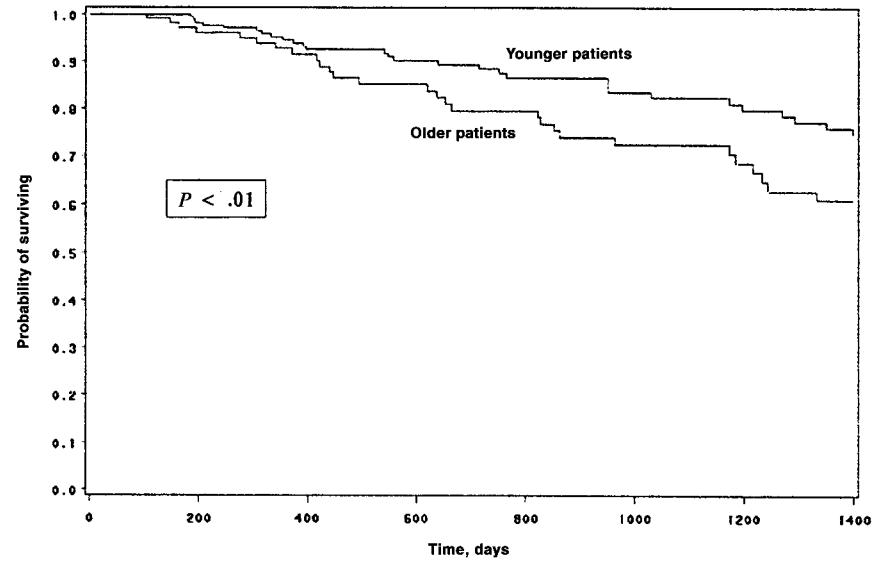
[a] Nine patients were excluded because they were observed for <90 days after enrollment.

[b] $P < .05$.

Without statistical adjustment for the survival bias, any difference in the survival rate between the treated and untreated groups may reflect the survival bias in the treated group, irrespective of HAART exposure status. The appropriate statistical adjustment for the survival bias is an extended Kaplan-Meier method that incorporates staggered entries [25]. Therefore, patients were not at risk for death until HAART was started. For patients receiving HAART, survival times were conditioned on the date of initiating HAART. Specifically, patients who were exposed to HAART after enrollment had a delayed entry time from enrollment in the analysis, and they did not become at risk for death until HAART was begun. Patients who received HAART before enrollment became at risk for death when HAART was initiated. This time is based on the elapsed time between the commencement of HAART and enrollment. People who never received HAART became at risk for death at enrollment. The maximum amount of time anyone was receiving HAART in our sample was 1828 days (5 years). Therefore, the maximum survival time was censored at 1828 days. Any deaths that occurred after 1828 days were censored. Demographic variables that were significantly different ($P < .05$) between the age categories on univariate analysis were adjusted for a multivariate Cox proportional hazard model with staggered entries [25]. The treatment groups were dummy coded, with the younger untreated patients used as the reference category. Variance inflation factors were used to determine whether multicollinearity between the independent variables was present. A value of >10 would be evidence of multicollinearity [26]. $P < .05$ was considered to be significant. All statistical analyses were performed by the Stata software package, version 7.0 (Stata).

RESULTS

A total of 253 patients aged ⩾50 years were identified from the clinic; for comparison, 535 younger patients were chosen



Younger patients							
No. at risk:	193	162	127	104	89	73	62
Cum Surv:	100	98	92	90	86	83	79
Older patients							
No. at risk:	101	84	68	58	51	40	32
Cum Surv:	100	95	91	84	78	70	66

Figure 1. Cumulative mortality rate for patients who were not exposed to HAART, according to age group (patients aged ⩾50 years [older patients] and patients aged <50 years [younger patients]). Survival estimates were conditioned on the date of initiation of HAART. Patients who received HAART some time after enrollment had a delayed entry time, and their data did not contribute to the risk sets until the time that HAART was started. Patients who received HAART before enrollment were left truncated on the basis of the time that had elapsed between beginning HAART and enrollment. Cum surv, cumulative survival as a percentage.

randomly among the 2500 people enrolled in the clinic. The demographic features of the 2 groups are shown in table 1. The mean age at enrollment was 36.5 years in the younger group (range, 18–49 years) and 55.2 years in the older group (range, 50–83 years; $P < .05$). Patients in the older group were more likely than patients in the younger group to be male (83% vs. 72%; $P < .05$) and to not be men who have sex with men (26% vs. 34%; $P < .05$).

At enrollment, there was no difference between the groups with regard to the stage of HIV disease. The median HIV RNA level at enrollment was lower in the older group (4.3 $\log_{10}$ copies/mL) than the younger group (4.5 $\log_{10}$ copies/mL; $P < .05$), but the median CD4 cell count for the older group (289 cells/mm^3) was significantly higher than that for the younger group (244 cells/mm^3; $P < .05$). The enrollment CD4 cell count was used because it establishes a comparable baseline for all the groups. There was no statistically significant difference between the older and younger groups with regard to the percentage of patients receiving HAART ($P = .30$), the year of enrollment ($P = .25$), or the year that HAART was initiated ($P = .23$). Among those who never received HAART, there was no significant difference between the older and younger groups in the median CD4 cell count (300 vs. 290 cells/mm^3, respectively; $P = .46$) or HIV RNA load at enrollment (4.4 vs. 4.4 $\log_{10}$ copies/mL, respectively; $P = .49$). However, among patients who received HAART, older patients had a significantly higher median enrollment CD4 cell count (273 vs. 224 cells/mm^3; $P < .05$) and a lower virus load (4.2 vs. 5.2 $\log_{10}$ copies/mL; $P < .05$) than did the younger patients.

There were more deaths in the older group (20%) than in the younger group (12%; $P < .01$). The median times to death in the older and younger groups were 663.5 and 828 days, respectively ($P = .29$). The conditional Kaplan-Meier survival analysis was performed by dividing the patients into 4 groups: young untreated patients ($n = 193$), young patients who were receiving HAART ($n = 342$), older untreated patients ($n = 101$), and older patients who were receiving HAART ($n = 152$). The median length of follow-up time for the cohort was 1095 days (3 years). As seen in figure 1, the cumulative proportions of patients who survived at 3 years were 83% in the

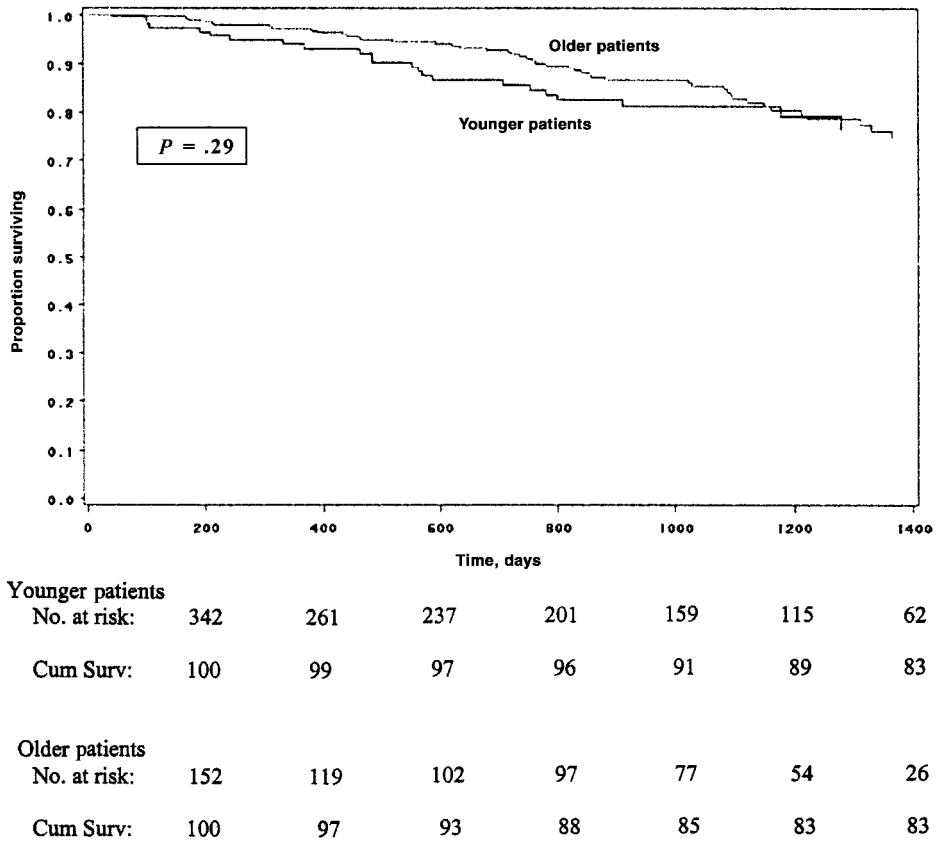


Figure 2. Cumulative mortality rate for patients who were exposed to HAART, according to age group (patients aged ⩾50 years [older patients] and patients aged <50 years [younger patients]). Survival time was measured from the date of enrollment in the cohort to a maximum of 1828 days. Cum surv, cumulative survival as a percentage.

younger group and 70% in the older group ($P < .01$). However, there was no significant difference in the cumulative survival rates between the older and younger treated groups at 3 years (83% vs. 89%, respectively; $P = .29$; figure 2).

Table 2 lists the Cox proportional hazard model for the data. After controlling for sex, homosexual behavior, CD4 cell count at enrollment, and the year of enrollment (centered on 1996), older patients had 2.36 (95% CI, 1.422–3.929) times the hazard of dying than did younger untreated patients. Younger patients treated with HAART had a hazard of 0.415 (95% CI, 0.248–0.695), which represents a 58.5% decrease in the hazard for death compared with younger untreated patients. Exposure to HAART decreased the hazard of death to 0.669 relative to the younger untreated group, but this was not significant. Note that the estimated hazard ratio for the older treated group is <1.0 as opposed to the older untreated group.

The Cox proportional hazard analysis was repeated with the younger group excluded, but the variable coding was identical to that of the first Cox model. The hazard ratio for the older treated group was 0.283 (95% CI, 0.153–0.524) after controlling for the other covariates. The hazard ratio for sex was 0.992 (95% CI, 0.433–2.272); for homosexual behavior, it was 1.501 (95% CI, 0.793–2.842); for CD4 cell count at enrollment, it was 0.997 (95 CI, 0.995–0.998); and for year of enrollment into the cohort, it was 1.209 (95% CI, 1.040–1.405). Thus, there was a 72% decrease in the hazard for older treated people compared with older untreated people. To check for multicollinearity, the mean variance inflation factor was calculated for the model, and it was 1.27 (range, 1.03–1.60). Because values of ⩾10 are associated with multicolinearity, there was no evidence of this problem in this data set.

DISCUSSION

In the present study, we have shown that HIV-infected individuals aged ⩾50 years and unexposed to HAART had double the hazard rate for death than did younger, untreated, HIV-infected people. Older patients receiving HAART had >2-fold reduction in the hazard for death after controlling for enrollment CD4 cell count and demographic variables. However, among patients who had been treated with HAART for ⩾90 days, there were no statistically or clinically significant differences in the survival rate between the younger and older groups. When the sample was restricted to just the older group, the

Table 2. Results of the Cox proportional hazard regression analysis of predictors of survival in patients, according to age group and HAART status.

Variable	Hazard ratio	SE	95% CI
Younger group, no HAART (yes, 1; no, 0)	1.0	—	—
Younger group, HAART (yes, 1; no, 0)	0.415[a]	0.109	0.248–0.695
Older group, no HAART (yes, 1; no, 0)	2.364[a]	0.613	1.422–3.929
Older group, HAART (yes, 1; no, 0)	0.669	0.200	0.372–1.201
Sex (male, 1; female, 0)	1.111	0.287	0.694–1.844
MSM (yes, 1; no, 0)	1.038	0.228	0.674–1.597
CD4 cell count at time of enrollment (1 cell/mm^3)	0.996[a]	0.0006	0.995–0.997
Year of enrollment in years (centered on 1996)	1.155[a]	0.058	1.046–1.276

NOTE. MSM, men who have sex with men; older group, patients aged ⩾50 years; younger group, patients aged <50 years.

[a] $P < .01$.

hazard for death in the treated group was reduced by 71.7% after controlling for confounding variables.

These results are consistent with those of earlier studies, which showed that older patients have a higher mortality rate than do younger patients and that age is inversely correlated with the time of AIDS diagnosis [2–7, 9, 10, 12, 13]. AIDS-defining illnesses have also been shown to be present at higher CD4 cell counts in people aged >30 years [2]. The magnitude and speed of CD4 cell count recovery after the initiation of HAART is also negatively correlated with age in people with AIDS [2] and in elderly persons with malignancies that occur after they have undergone marrow ablative chemotherapy [18]. The observation that the ability of the thymus to repopulate CD4 cells is inversely correlated with age has been proposed as a mechanism for the blunted T cell response to HAART in elderly individuals [19]. These findings imply that treatment of elderly persons may not lead to clinically meaningful responses. However, our study used a direct measure of treatment response (mortality) rather than surrogate markers (CD4 cell count and virus load). By means of this approach, we have now demonstrated that patients aged ⩾50 years have a great mortality benefit associated with HAART. The reason for the discrepancy between the CD4 cell count and the survival rate may be the lag between diagnosis of HIV/AIDS and death and the subsequent follow-up required for cohort studies.

Several potential limitations to this study should be noted. First, older patients who received HAART had a higher median enrollment CD4 cell count (273 vs. 224 cells/mm^3) and a lower median baseline virus load (4.3 vs. 4.5 $\log_{10}$ copies/mL; $P < .05$) than did younger patients; these are both favorable prognostic factors. However, the CD4 cell counts at enrollment are well within the range noted in current guidelines for the initiation of treatment. Therefore, it is unclear how important the CD4 cell count difference between the groups is within the observed ranges. Second, we do not have information on treatment compliance, a factor that has been shown to be critical in predicting treatment outcome [27, 28]. Poor compliance has resulted in a rapid rate of resistance to antiretroviral drugs [29]. Compliance of >95% with all pill doses has been found to correlate with success in antiretroviral therapy [30]. The standard clinical practice is to actively work at reducing barriers to compliance (e.g., drug addiction) before initiating HAART. Clinicians need to feel that the patients could be reasonably compliant with HAART regimens before treatment is started, regardless of the patients' ages.

The number of comorbidities increases with age, a factor that may influence the decision whether to initiate HAART; this deciding factor was not examined directly in our study. Among the older patients, one would expect that direct contraindications to HAART were not present in those who received treatment. In addition, antiretroviral therapy would not be expected to treat non–HIV-related diseases. Indeed, diabetes and hyperlipidemia would be expected to be worse if a PI had been used. Therefore, the effect of comorbidities would bias the survival against the treated elderly; instead, this group benefited the most from treatment.

We have shown here that administration of HAART to older HIV-positive patients produced a greater reduction in the mortality rate than it did for younger patients. Untreated older patients have more than double the mortality rate of younger patients. These data highlight the importance of treatment of older patients. Further studies are needed in this area to confirm our results. Pharmacokinetic studies of antiretroviral drugs are necessary to optimize safety in HIV-positive patients aged ⩾50 years.

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