Evaluation of the Effectiveness of Highly Active Antiretroviral Therapy in Persons with Human Immunodeficiency Virus using Biomarker-based Equivalence of Disease Progression

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The association of different CD4⁺ cell counts with the same disease risk in treated and untreated populations reflects the effectiveness of highly active antiretroviral therapy (HAART) in persons with human immunodeficiency virus (HIV). Clinical progression of disease following initiation of HAART was determined for 679 HIV-infected men in the Multicenter AIDS Cohort Study by means of Kaplan-Meier survival analyses. Cox proportional hazards models were used to assess the effects of markers of HIV disease, antiretroviral history, and demographic factors. Men who had been followed since January 1993 (pre-HAART) were used to identify CD4⁺ levels associated with the acquired immunodeficiency syndrome (AIDS)-free time equivalent to that of men starting HAART with CD4⁺ cell counts of <200 cells/µl. Within 3.5 years following HAART initiation, 11.3% of the subjects developed AIDS and 8.5% died. Determinants of AIDS were a CD4⁺ cell count of <200 cells/µl at initiation (relative hazard = 2.25, 95% confidence interval: 1.13, 4.49) and age >45 years at initiation (relative hazard = 1.92, 95% confidence interval: 0.98, 3.77). An increase in CD4⁺ cell count of >50 cells/µl immediately after HAART initiation also improved prognosis (relative hazard = 0.34, 95% confidence interval: 0.16, 0.71). AIDS risk in men starting HAART with CD4⁺ counts of <200 cells/µl (median = 132) was similar to that of non-HAART users with CD4⁺ counts of 375–475 cells/µl (median = 432). The equivalence of disease progression to that of nonusers with approximately 300 more cells per µl demonstrates that HAART users have a broader reconstitution of the immune system beyond that of observed increases in CD4⁺ cell count. Am J Epidemiol 2002;155:760–70.

In 1996, the use of highly active antiretroviral therapy (HAART) against human immunodeficiency virus (HIV) became widespread in the United States. Clinical trials have shown the efficacy of these regimens (1, 2), and cohort studies and data from registries have demonstrated the effectiveness of HAART in reducing the burden of acquired immunodeficiency syndrome (AIDS)-free time equivalent to that of men starting HAART with CD4⁺ cell counts of <200 cells/µl. Within 3.5 years following HAART initiation, 11.3% of the subjects developed AIDS and 8.5% died. Determinants of AIDS were a CD4⁺ cell count of <200 cells/µl at initiation (relative hazard = 2.25, 95% confidence interval: 1.13, 4.49) and age >45 years at initiation (relative hazard = 1.92, 95% confidence interval: 0.98, 3.77). An increase in CD4⁺ cell count of >50 cells/µl immediately after HAART initiation also improved prognosis (relative hazard = 0.34, 95% confidence interval: 0.16, 0.71). AIDS risk in men starting HAART with CD4⁺ counts of <200 cells/µl (median = 132) was similar to that of non-HAART users with CD4⁺ counts of 375–475 cells/µl (median = 432). The equivalence of disease progression to that of nonusers with approximately 300 more cells per µl demonstrates that HAART users have a broader reconstitution of the immune system beyond that of observed increases in CD4⁺ cell count. Am J Epidemiol 2002;155:760–70.

acquired immunodeficiency syndrome; antiviral agents; clinical protocols; cohort studies; disease progression; HIV protease inhibitors; reverse transcriptase inhibitors; treatment outcome

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Received for publication May 8, 2001, and accepted for publication November 1, 2001.

Abbreviations: AIDS: acquired immunodeficiency syndrome; HAART: highly active antiretroviral therapy; HIV: human immunodeficiency virus.

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inappropriate to defer HAART initiation until patients have reached a stage at which faster progression is documented. This is most important for therapies, such as HAART, that have been proven to be effective yet whose use has been associated with adverse events, toxicity, and viral resistance in cases where adherence is not optimal (13–18).

Improvement in immune function may translate into an effect of HAART on disease progression above and beyond the effect ascribed to the observed increase in CD4+ cell count (19–21). Cohort studies characterizing progression to disease according to markers of HIV infection prior to and after the introduction of HAART provide the opportunity to match disease progression in the two eras and determine the CD4+ cell counts associated with the matched progressions. A difference between these two CD4+ cell counts above the increase in CD4+ cell count observed after HAART initiation quantifies the added benefit of HAART. In addition, providing the CD4+ cell counts corresponding to the matched clinical progression in untreated individuals allows physicians to capitalize on their knowledge of disease progression acquired in clinical management during the pre-HAART era in their current monitoring of HIV patients.

Using data from a well-characterized cohort with close follow-up (22), we describe here the late 1990s “epidemic” of HAART initiation in the United States and provide estimates for the incidence of AIDS and death occurring within 3.5 years after initiation of HAART. Immunologic, virologic, and host characteristics were examined for their prognostic value in predicting clinical events. Using the comprehensive cohort data, we compared disease progression among individuals in 1993–1996 (the pre-HAART era) with that of individuals who initiated HAART between 1996 and 2000. This comparison permitted us to find the CD4+ cell count of men not treated with HAART that corresponded to the disease progression of men who initiated HAART at low CD4+ cell counts (e.g., <200 cells/µl).

MATERIALS AND METHODS

Population—Multicenter AIDS Cohort Study

The Multicenter AIDS Cohort Study is an ongoing cohort study of 5,622 homosexual men; 4,954 were enrolled in 1984–1985, and 668, mainly African Americans, were enrolled in 1987–1991. Study sites for the Multicenter AIDS Cohort Study are located in Baltimore, Maryland; Chicago, Illinois; Los Angeles, California; and Pittsburgh, Pennsylvania. Detailed information on the overall study design and descriptions of the cohort have been published elsewhere (22–25). Participants return to the study center every 6 months for a detailed interview regarding medical history (diagnoses, medication use, signs and symptoms), health care utilization, and behaviors engaged in since their last visit. The participants also undergo a physical examination and provide blood specimens for concurrent laboratory evaluations and for storage in local and national repositories. Study protocols for the Multicenter AIDS Cohort Study were approved by the institutional review boards at each of the participating centers, and informed consent was obtained from all of the men. The study questionnaires are available on the World Wide Web at the study’s website (www.statepi.jhsphs.edu/macs/macs.html).

Antiretroviral therapy

Use of antiretroviral therapy was summarized from the information reported by the participants at their semiannual follow-up visits. HAART was defined as: 1) two or more nucleoside reverse transcriptase inhibitors (zidovudine, stavudine (d4T), zalcitabine (ddC), didanosine (ddl), or lamivudine (3TC)) in combination with at least one protease inhibitor (indinavir, saquinavir, ritonavir, nelfinavir, amprenavir, or lopinavir) and/or one nonnucleoside reverse transcriptase inhibitor (nevirapine, efavirenz, or delavirdine); 2) one nucleoside reverse transcriptase inhibitor in combination with at least one protease inhibitor and at least one nonnucleoside reverse transcriptase inhibitor; 3) a regimen containing ritonavir and saquinavir in combination with one nucleoside reverse transcriptase inhibitor and no nucleoside reverse transcriptase inhibitors; and 4) an abacavir-containing regimen of three or more nucleoside reverse transcriptase inhibitors in the absence of both protease inhibitors and nonnucleoside reverse transcriptase inhibitors. Combinations of zidovudine and stavudine with either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor were not considered HAART. The date of HAART initiation was defined as the midpoint between the last visit with no reported HAART use and the first visit at which HAART use was reported. Only individuals who started using HAART between July 1995 and December 1999 and who had ≤1 year between the last no-HAART visit and the first HAART visit were included in the examination of time to AIDS and death.

Cofactors

Age at HAART initiation was determined from date of birth and was dichotomized as >45 years versus ≤45 years. Self-reported race was dichotomized as African-American versus other. Through analysis of fresh blood specimens, levels of T lymphocytes at each visit were determined by the study center, using standardized flow cytometry (26, 27). Number of CD4+ cells per µl prior to HAART initiation was defined as the average of CD4+ cell counts from the two semiannual visits prior to HAART initiation. The immediate change in CD4+ cell count after HAART initiation was defined as the change from the pre-HAART level to the count measured at the first post-HAART visit; the variable was dichotomized at ≤50 cells/µl versus >50 cells/µl. HIV RNA level was measured (retrospectively for visits prior to 1997 and concurrently thereafter) using the Roche Amplipcr assay (28). Pre-HAART level of HIV RNA was defined as the average of HIV RNA levels from the two visits prior to HAART initiation; the variable was dichotomized as ≤100,000 copies/ml versus >100,000 copies/ml. When we examined suppression of post-HAART HIV RNA level to <50 copies/ml as a predictive factor, we excluded men for whom HIV RNA level could only be determined as <400 copies/ml (without further specification), because the men
were tested only with the Roche second-generation assay, which had a detection limit of 400 copies/ml. Experience with antiretroviral therapy was defined as previous use of at least one of the medications in the initial HAART regimen (listed above).

Outcomes—AIDS and death

After the onset of AIDS (29), men in the Multicenter AIDS Cohort Study are contacted at least every 3 months for information on new or recent clinical events. Reports by proxy contacts and passive surveillance, such as monitoring of obituaries and other public records, are also used to determine vital status. Medical records are reviewed to confirm AIDS events, and death certificates and/or autopsy reports are obtained for reported deaths. Here we defined AIDS as the presence of opportunistic illnesses or malignancies diagnostic of AIDS; individuals who met the Centers for Disease Control and Prevention’s definition of AIDS but whose diagnosis was attributable only to their CD4+ cell count were not considered to have clinical AIDS.

Statistical analyses

The incidence rate of HAART initiation was defined as the number of individuals beginning HAART per 100 person-years observed in each 6-month calendar period from the second semester of 1995 (denoted by 95-2) to the second semester of 1999 (denoted by 99-2). All HIV-positive men were considered “at risk” for HAART use up to the time of study attrition, December 1999, or the date of HAART initiation. If \( p_i \) denotes the incidence rate in the \( i \)th 6-month calendar period (\( j = 95-2, 96-1, ..., 99-2 \)), the cumulative incidence by calendar period \( i \) is determined by

\[
1 - \prod_{j=95-2}^{i} \{1 - p_j\}, i = 95-2, 96-1, ..., 99-2.
\]

For the survival analyses, if a participant developed the event (AIDS, death) prior to April 2000, he contributed time from the date of HAART initiation to the date of diagnosis. Men who withdrew from the study prior to April 1999 were censored at the time of attrition; otherwise they were considered event-free and were administratively censored at April 2000. Men who developed the event after April 1, 2000, were also censored at this date. Kaplan-Meier survival probabilities were used to plot the distributions of times to events. Cox proportional hazards models were used to determine the relative hazard of each clinical event. Variables with \( p \) values less than 0.10 univariately were assessed as independent predictors using a multivariate Cox proportional hazards model.

RESULTS

Incidence of HAART

A total of 679 participants in the Multicenter AIDS Cohort Study initiated HAART use between July 1995 and December 1999. The cumulative incidence of HAART use was 85.3 percent (figure 1). Many of the participants immediately started HAART when it became available, as evidenced by the sharp rise in incidence in 1996, peaking at 34.5 percent in July–December 1996; subsequently, new use of HAART slowed. Although the overall temporal trend of HAART incidence was similar for men who had AIDS when initiating HAART and men who were free of AIDS when initiating HAART, the sizes of the risk populations and the magnitudes of the incidence rates differed. Since, prior to HAART, individuals with AIDS had a short survival time (30), there were fewer men with AIDS who were at risk of initiating HAART at any given time, but the incidence of starting HAART among them was dramatically higher from 1996 through early 1998. By the end of 1998, practically all individuals with AIDS had started using HAART. Although most AIDS-free participants who initiated HAART as of December 1999, 130 HIV-positive AIDS-free men had not begun such treatment (i.e., they remained “susceptible” for the initiation of HAART).

The composition of the initial HAART regimen has changed over time. Although the majority of men in this cohort who started HAART used one protease inhibitor and two nucleoside reverse transcriptase inhibitors (56.3 percent), use of this regimen has decreased over time; it was the initial HAART regimen for 64.1 percent, 52.3 percent, and 48.3 percent of men who started HAART in 1995–1996, 1997, and 1998–1999, respectively. Similarly, the use of one protease inhibitor with three nucleoside reverse transcriptase inhibitors (10.7 percent overall) and the use of two protease inhibitors and two nucleoside reverse transcriptase inhibitors (8.7 percent overall) as the initial regimen have decreased over time. In contrast, a regimen of one nonnucleoside reverse transcriptase inhibitor with two nucleoside reverse transcriptase inhibitors has increasingly been used as the initial regimen—by 0.7 percent, 9.5 percent, and 16.8 percent of HAART initiators in 1995–1996, 1997, and 1998–1999, respectively. The specific protease inhibitor used has also changed. Whereas in 1995–1996 saquinavir and indinavir were used by 39.2 percent and 56.0 percent of HAART initiators, respectively, in subsequent years only 19.3 percent of initial HAART regimens comprised saquinavir and 42.5 percent contained indinavir. Concurrent with this decrease, nelfinavir use has increased—from 0.4 percent in 1995–1996 to 28.1 percent after 1996. In this cohort, most HAART initiators remained on HAART, although the specific HAART regimen may have changed over time.

Time to AIDS

There were 434 men who were AIDS-free when they initiated HAART and who had a HAART initiation window of ≤1 year. As is shown by the Kaplan-Meier curve in figure 2, 11.3 percent developed AIDS in the subsequent 3.5 years. Only 11 (2.8 percent) of the men not observed to develop AIDS withdrew from the study prior to April 1999. Table 1 provides a description of the men at HAART initiation. Overall, the men had a median CD4+ cell count of 341 cells/μl and a median
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FIGURE 1. Overall cumulative and period incidence of highly active antiretroviral therapy (HAART) initiation among men infected with human immunodeficiency virus in the Multicenter AIDS Cohort Study, by calendar time, July 1995–December 1999. Calendar time is represented by the last two digits of the year, followed by a semester indicator (1 = January–June; 2 = July–December). Men who had not used HAART by the start of each semester were considered “at risk” for initiating HAART. Incidence rates are presented per 100 person-semesters at risk.

HIV RNA level of 26,281 copies/ml; 128 (30.3 percent) of the men were inexperienced in the use of antiretroviral therapy, and the median age at HAART initiation was 43 years. The men who developed AIDS post-HAART had median values of 196 CD4+ cells/µl and 67,900 HIV RNA copies/ml; 128 (30.3 percent) of the men were inexperienced in the use of antiretroviral therapy, and the median age at HAART initiation was 46 years.

The results from the univariate Cox proportional hazards models are shown in table 2. Significant (p < 0.05) determinants of developing AIDS were older age (for age >45 years, relative hazard = 2.11), low CD4+ cell count (for <200 cells/µl, relative hazard = 2.99), and high HIV RNA level (for >100,000 copies/ml, relative hazard = 2.02) at the time of HAART initiation. When we stratified CD4+ cell counts into three categories of <200, 200–349, and ≥350 cells/µl, men with counts of 200–349 CD4+ cells/µl were at no greater risk of AIDS than men with counts of ≥350 cells/µl (p = 0.575) (figure 3). Similarly, when we stratified men with ≤100,000 copies of HIV RNA per ml, the risk of AIDS was not significantly greater for those with 25,001–100,000 copies/ml (relative hazard = 1.53, p = 0.297) compared with those with ≤25,000 copies/ml.

Neither experience with the use antiretroviral therapy nor race was a statistically significant predictor, although the relative hazard of AIDS was 4.55 (p = 0.135) for non-African Americans compared with African Americans (table 2). AIDS was less likely to occur (relative hazard = 0.31) among men who had gained >50 CD4+ cells/µl by their first visit after HAART initiation. Although results were not statistically significant (p = 0.156), men whose HIV RNA levels were suppressed to ≤50 copies/ml were less likely to develop AIDS (relative hazard = 0.42). In the multivariate analysis, CD4+ cell count at HAART initiation and change in CD4+ cell count after HAART initiation remained significant independent determinants of AIDS, with slightly diminished magnitudes of association (table 2).

Equivalence between HAART and non-HAART CD4+ cell counts

Figure 3 shows time to AIDS for users of HAART, stratified by CD4+ cell count at the time of HAART initiation. We also present time to AIDS for control groups, defined as men who were HIV-seropositive and AIDS-free as of January 1993. Only time without HAART up to July 1996 was used for these controls. As the figure shows, although the HAART users starting therapy with low CD4+ cell counts were at higher risk of developing AIDS among users, their prognosis was better than that of non-HAART users whose CD4+ cell counts were ≥200 cells/µl. This improved prognosis was not due to increased use of prophylaxes against opportunistic infections, since the use of prophylaxes in this cohort actually decreased during the HAART era (31).
FIGURE 2. Overall proportion of men in the Multicenter AIDS Cohort Study who remained free of acquired immunodeficiency syndrome (AIDS) after initiating highly active antiretroviral therapy (HAART), July 1995–April 2000. The numbers of men at risk of AIDS and cumulative numbers of AIDS cases by each half-year period after HAART initiation are provided at the bottom of the graph.

We then compared AIDS risk in the men who initiated HAART with CD4+ cell counts of <200 cells/µl with the risk for control groups defined by their CD4+ cell counts at the start of 1993. The relative hazards were 0.58 (p = 0.047), 0.70 (p = 0.203), 0.97 (p = 0.916), and 1.32 (p = 0.360) for men who started HAART with <200 cells/µl as compared with controls with counts of 325–425, 350–450, 375–475, and 400–500 cells/µl, respectively. Thus, the HAART users who started HAART with CD4+ cell counts under 200 cells/µl (median = 132) had a progression to AIDS, within 3.5 years, that was equivalent (nonsignificant relative hazard closest to 1.0) to that of men with counts of 375–475 cells/µl (approximately 300 more cells per µl) in the pre-HAART era.

Time to death

In addition to the 434 AIDS-free men, there were 124 men with AIDS who initiated HAART and contributed follow-up time to the analysis of time to death. Using Kaplan-Meier survival analysis, 8.5 percent of the men were found to have died within 3.5 years after initiating HAART. Only 13 (2.5 percent) of the survivors were lost to follow-up before April 1999. Those who had AIDS when they initiated HAART had the lowest CD4+ cell counts and the highest HIV RNA levels at the time of HAART initiation; this was particularly true for those who died during the subsequent 3.5 years (table 1).

AIDS at the time of HAART initiation strongly determined subsequent survival (relative hazard = 4.00, p < 0.001) (table 3). Similarly, men with CD4+ cell counts under 200 cells/µl had a relative hazard of 3.74 (p = 0.001) as compared with those with counts of ≥200 cells/µl at the time of initiation. Given the strong correlation between low CD4+ cell count and AIDS, we wished to assess the role of CD4+ cell count among men who were AIDS-free. Compared with AIDS-free men with CD4+ counts of ≥200 cells/µl, the relative hazard of death was 3.10 (p = 0.02) for men with <200 cells/µl and no AIDS-defining complications. The effect of CD4+ cell count at HAART initiation was no longer significant (p > 0.05) upon adjustment for the immediate change in CD4+ cell count following HAART (table 3).

As was shown for time to AIDS, age at HAART initiation and CD4+ cell response to HAART initiation predicted subsequent survival (table 3). However, the magnitude of the age effect was smaller and only marginally significant (p = 0.068). HIV RNA level at HAART initiation had little effect for subsequent prognosis, but suppression of HIV RNA level (i.e., <50 copies/ml) immediately following HAART, though not statistically significant (p = 0.218), was associated with survival (relative hazard = 0.40). When we examined age, AIDS and CD4+ cell count at HAART initiation,
### Table 1. Characteristics of 558 HIV*-infected men with known dates (±6 months) of initiation of highly active antiretroviral therapy between July 1995 and December 1999, Multicenter AIDS* Cohort Study

<table>
<thead>
<tr>
<th></th>
<th>AIDS-free at HAART* initiation</th>
<th></th>
<th>AIDS at HAART initiation</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total (n = 434)</td>
<td>AIDS† (n = 41)</td>
<td>Deaths† (n = 19)</td>
<td>Total (n = 124)</td>
</tr>
<tr>
<td></td>
<td>Median or no.</td>
<td>IQR* or %</td>
<td>Median or no.</td>
<td>IQR* or %</td>
</tr>
<tr>
<td><strong>CD4</strong>+ cell count (cells/µl) at visit preceding HAART initiation §</td>
<td>341</td>
<td>203, 491</td>
<td>196</td>
<td>88, 400</td>
</tr>
<tr>
<td><strong>HIV RNA level (copies/ml) at visit preceding HAART initiation §</strong></td>
<td>26,281</td>
<td>6,580, 86,585</td>
<td>67,900</td>
<td>17,819, 175,569</td>
</tr>
<tr>
<td>Inexperienced in the use of antiretroviral therapy at HAART initiation (no.) ¶</td>
<td>128</td>
<td>30.3%</td>
<td>10</td>
<td>25.0%</td>
</tr>
<tr>
<td>Age (years) at HAART initiation</td>
<td>43.0</td>
<td>38.5, 48.0</td>
<td>46.0</td>
<td>40.8, 51.0</td>
</tr>
<tr>
<td>Race (no.)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>46</td>
<td>10.6%</td>
<td>1</td>
<td>2.4%</td>
</tr>
<tr>
<td>White</td>
<td>366</td>
<td>84.3%</td>
<td>38</td>
<td>92.7%</td>
</tr>
<tr>
<td>Latino</td>
<td>22</td>
<td>5.1%</td>
<td>2</td>
<td>4.9%</td>
</tr>
<tr>
<td>Follow-up time (years) after HAART initiation</td>
<td>3.21</td>
<td>2.43, 3.74</td>
<td>1.51#</td>
<td>0.72, 2.21</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy; IQR, interquartile range (25th and 75th percentiles).
† Events occurring after initiation of HAART and prior to April 2000.
‡ 30 AIDS-free participants and five participants with AIDS at the time of HAART initiation were missing data on CD4**+ cell count pre-HAART.
§ 40 AIDS-free participants and 23 participants with AIDS at the time of HAART initiation were missing data on HIV RNA level pre-HAART.
¶ 12 AIDS-free participants and six participants with AIDS at the time of HAART initiation had insufficient data for us to determine whether they were inexperienced in the use of antiretroviral therapy.
# Follow-up time to AIDS; all other times are total follow-up time.
and CD4+ response to HAART in the same multivariate model, AIDS and post-HAART CD4+ response remained strong independent predictors of survival (table 3). The effect of age remained marginally significant ($p = 0.079$).

**DISCUSSION**

In this cohort, few major clinical events occurred within 3.5 years after HAART initiation; only 11.3 percent of the men developed AIDS and only 8.5 percent died. Most clinical events occurred among men with low CD4+ cell counts (<200 cells/µl) and a history of AIDS at the time of initiation and a poor CD4+ cell response immediately following initiation. The prognostic value of a low CD4+ cell count for the development of AIDS following treatment has been shown by other investigators (32, 33). There has been controversy as to when HAART should be initiated. Given the limited number of distinct treatment options and the occurrence of cross-resistance among regimens in the same therapy class, current clinical guidelines suggest caution when considering the initiation of HAART in asymptomatic individuals with higher CD4+ cell counts and lower HIV RNA levels (34). In this cohort, men who started HAART with CD4+ cell counts of ≥350 cells/µl did not differ in terms of time to AIDS from men who started HAART with counts of 200–349 cells/µl; this finding supports the suggestion that it may not be inappropriate to defer treatment initiation. This should be viewed with caution, since these men were not randomized with regard to treatment. As has been shown elsewhere, the sickest individuals in the population, as represented in cohorts, start new treatments as they become available (35).

To our knowledge, this study was the first to determine non-HAART CD4+ cell equivalence based on disease progression for men who initiated HAART with low CD4+ cell counts. AIDS risk for men who initiated HAART with CD4+ counts of <200 cells/µl (median = 132) was not significantly different from that of controls with counts of $<200$ copies/ml; 99 of these men had $<400$ copies/ml using the standard Roche assay.
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FIGURE 3. Acquired immunodeficiency syndrome (AIDS)-free survival times for users (U) of highly active antiretroviral therapy (HAART) and nonusers (NU) of HAART in the Multicenter AIDS Cohort Study, according to CD4+ cell count. Follow-up time was time after HAART initiation (July 1995–April 2000) for users and January 1993–July 1996 for nonusers. Relative hazards (RH) and p values (see inset) were obtained from Cox proportional hazards models. Nonusers with CD4+ counts of 350–500 cells/µl comprised the reference group for model 1; model 2 was restricted to HAART users, with those initiating HAART at CD4+ counts of ≥350 cells/µl comprising the reference group.

375–475 cells/µl (median = 432). This observation is of interest, since this group of HAART users exhibited an average CD4+ cell increase of <100 cells/µl 3–6 months following HAART initiation (36). Thus, the observed prognosis is improved beyond what might be expected on the basis of rise in CD4+ count only. We examined average CD4+ cell counts in the 3.5 years of follow-up for these two groups and observed that men not treated with HAART who had counts of 375–475 cells/µl in 1993 had an overall mean count of 368 cells/µl in 1993–1996.5, as compared with a mean of 268 cells/µl in the 3.5 years following HAART among men who started HAART with counts of <200 cells/µl. Thus, the equivalent AIDS prognosis did not correspond to an equivalent average of subsequent CD4+ cell counts (i.e., the area under the curve). Other investigators have noted that HAART may have immunologic effects not reflected by T-lymphocyte counts (19–21). Indeed, our results reinforce the evidence that HAART has a beneficial effect beyond its effect on CD4+ cell count. Furthermore, we quantified this effect, which is likely to be due in great part to the improved function of the immune system.

Future research could extend our results in two ways. First, the equivalence between “treated” CD4+ count and “natural” CD4+ count could be determined using the continuous scale of the CD4+ cell count. Second, other variables (e.g., HIV RNA level and age) could be incorporated into the characterization of AIDS risk. Both objectives are amenable to parametric survival regression, which is beyond the scope of this report.

Although HIV RNA level at HAART initiation was prognostic for subsequent development of AIDS, it was less informative for predicting death. These observations are consistent with those of Ledergerber et al. (12); they showed that baseline HIV RNA level was predictive of developing AIDS within 6 months of HAART initiation but did not differentiate those who developed AIDS subsequently (12). Similarly, in an earlier analysis of this cohort, prior therapy was a significant predictor of the immediate CD4+ cell count and HIV RNA response to HAART but had little effect on long-term CD4+ cell response (36). The lack of an effect of prior therapy on the development of AIDS over the 3.5 years following HAART initiation is consistent with this earlier observation.

We have previously documented adherence to HAART in this cohort (37). Although we did not record adherence to HAART at the time the regimens were initiated and thus
could not directly estimate its effect on prognosis, there is no reason to believe that adherence to the initial regimen would be any lower than the 77.7 percent complete adherence observed approximately 2 years later (37). This adherence measure was significantly associated with suppression of HIV RNA levels (37); therefore, the effect of suppressed viral replication incorporates the effect of adherence on the development of AIDS within 3 years after starting HAART.

A rise in CD4+ cell count by the first visit after HAART initiation was associated with a lower incidence of clinical outcomes. Whereas the ability to immediately suppress virus levels may be a more universal consequence of HAART, CD4+ cell response may be more variable, and thus it provides a means of classifying the heterogeneous risk of clinical progression. A competent immune system may provide the environment needed to keep the virus in check, allowing the immune system to continue to function. Equally, it may be the competent immune system that can generate a rise in CD4+ cells. As was shown in the natural history of HIV infection, most opportunistic conditions and malignancies occur at low CD4+ cell counts. The positive feedback between inhibition of virus replication and immune system function would mechanistically prevent the subsequent development of AIDS and death. Thus, whereas most users of HAART may decrease their HIV RNA levels, only those whose immune system can recover sufficiently to control the virus and prevent opportunistic infections may exhibit a healthier prognosis.

Although age has been shown to be predictive of clinical progression in the natural history of HIV (38), our results indicate that older men also progress more quickly to AIDS

TABLE 3. Relative hazard for time to death among 558 HIV*-positive participants initiating highly active antiretroviral therapy with a known date (±6 months) of initiation, Multicenter AIDS* Cohort Study, 1995.5–2000.25

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of men</th>
<th>Univariate models</th>
<th>Multivariate model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Relative hazard</td>
<td>95% confidence interval</td>
</tr>
<tr>
<td>Age (years) at HAART* initiation</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤45</td>
<td>345</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;45</td>
<td>213</td>
<td>1.76</td>
<td>0.96, 3.22</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>51</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Non-African-American</td>
<td>507</td>
<td>3.69</td>
<td>0.51, 26.85</td>
</tr>
<tr>
<td>Experienced in the use of antiretroviral therapy†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>149</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>391</td>
<td>2.17</td>
<td>0.85, 5.56</td>
</tr>
<tr>
<td>History of clinical AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>434</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>124</td>
<td>4.00</td>
<td>2.18, 7.35</td>
</tr>
<tr>
<td>CD4+ cell count (cells/µl) prior to HAART initiation‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥200</td>
<td>345</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&lt;200</td>
<td>178</td>
<td>3.74</td>
<td>1.93, 7.26</td>
</tr>
<tr>
<td>HIV RNA level (copies/ml) prior to HAART initiation§</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤100,000</td>
<td>369</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>&gt;100,000</td>
<td>126</td>
<td>1.38</td>
<td>0.66, 2.86</td>
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<tr>
<td>Change (cells/µl) in CD4+ cell count¶</td>
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<td></td>
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</tr>
<tr>
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<td>1</td>
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<tr>
<td>&gt;50</td>
<td>262</td>
<td>0.28</td>
<td>0.13, 0.59</td>
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<tr>
<td>Suppression of HIV RNA level to &lt;50 copies/ml#</td>
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<td></td>
</tr>
<tr>
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<td>298</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Yes</td>
<td>70</td>
<td>0.40</td>
<td>0.10, 1.71</td>
</tr>
</tbody>
</table>

* HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; HAART, highly active antiretroviral therapy.
† 18 participants had insufficient data for us to determine whether they were experienced in the use of antiretroviral therapy.
‡ 35 participants were missing data on CD4+ cell count in the year prior to starting therapy.
§ 63 participants were missing data on HIV RNA level in the year prior to starting therapy.
¶ 56 participants were missing data on change in CD4+ cell count.
# 190 participants had insufficient data for determining suppression to HIV RNA levels below 50 copies/ml; 110 of these men had <400 copies/ml using the standard Roche assay.
in the era of HAART. Aging is associated with thymus involution and has been shown to play a role in cell regeneration (39, 40). Douek et al. (41) have shown that although thymic output of cells declines with age, the thymus contributes to immune reconstitution post-HAART. Since older individuals chronically infected with HIV are less likely to increase their number of naive CD4+ T lymphocytes, they are more likely to develop infectious complications in the short term following use of HAART.

These data also provide information needed for the design of clinical trials addressing treatment issues related to prognosis. Since very few events occur within 3 years after HAART initiation, clinical trials must enroll very large cohorts and must follow participants for long periods of time to examine meaningful prognostic differences. This needed size will be even greater if recruitment is not restricted to HIV-infected persons in the later stages of disease (i.e., those with low CD4+ cell counts or opportunistic infections).

Since the “epidemic” of HAART use in this cohort originated in the latter half of 1995, the relatively short follow-up time limits inferences that can be made about long-term outcomes. It will be important to continue to follow these men and other cohorts to determine whether these low rates of clinical events can be maintained and whether the characteristics related to the development of events in the first 3.5 years predict future prognosis. In addition, it is interesting that approximately 18 percent of the AIDS-free men in the Multicenter AIDS Cohort Study who have been infected with HIV for a relatively long time have not yet initiated potent therapy. Although these men should be studied further to identify determinants of nonuse of HAART, they can serve as possible controls or as a “deferment arm” in analogy to a clinical trial.

ACKNOWLEDGMENTS

The Multicenter AIDS Cohort Study is funded by the National Institute of Allergy and Infectious Diseases, with supplemental funding from the National Cancer Institute (grants U01-AI-35042, S-M01-RR-00722 (GCRC), U01-AI-35043, U01-AI-37984, U01-AI-35039, U01-AI-35040, U01-AI-37613, and U01-AI-35041).

The Multicenter AIDS Cohort Study includes the following researchers: Baltimore, Maryland—Johns Hopkins University, Bloomberg School of Public Health: Joseph B. Margolick (Principal Investigator), Haroutune Armenian, Barbara Crain, Adrian Dobs, Homayoon Farzadegan, Nancy Kass, Shenghan Lai, Justin McArthur, and Ellen Taylor; Chicago, Illinois—Howard Brown Health Center and Northwestern University Medical School: John P. Phair (Principal Investigator), Joan S. Chmiel, Bruce Cohen, Maurice O’Gorman, Daina Vhariakojis, and Steven M. Wolinsky; Los Angeles, California—University of California, Los Angeles, School of Public Health and School of Medicine: Roger Detels and Beth Jamieson (Principal Investigators), Barbara R. Visscher (Co-Principal Investigator), Anthony Butch, John Fahey, Otoniel Martínez-Maza, Eric N. Miller, John Oishi, Paul Satz, Elyse Singer, Harry Vinters, Otto Yang, and Stephen Young; Pittsburgh, Pennsylvania—University of Pittsburgh, Graduate School of Public Health: Charles R. Rinaldo (Principal Investigator), Lawrence Kingsley (Co-Principal Investigator), James T. Becker, Phalguni Gupta, John Mellors, Sharon Riddler, and Anthony Silvestre; Data Coordinating Center—Johns Hopkins University, Bloomberg School of Public Health: Alvaro Muñoz (Principal Investigator), Lisa P. Jacobson (Co-Principal Investigator), Linda Adhieh, Stephen Cole, Stephen Gange, Cynthia Kleeberger, Rui Li, Eric Seaberg, Sol Su, and Patrick Tarwater; National Institutes of Health—National Institute of Allergy and Infectious Diseases: Carolyn Williams; National Cancer Institute: Sandra Melnick.

REFERENCES


