Mortality in HIV-Seropositive versus -Seronegative Persons in the Era of Highly Active Antiretroviral Therapy: Implications for When to Initiate Therapy

Cunlin Wang,¹ David Vlahov,¹ Noya Galai,¹ Joseph Bareta,¹ Steffanie A. Strathdee,¹ Kenrad E. Nelson,¹ and Timothy R. Sterling¹²

¹Department of Epidemiology, Johns Hopkins University Bloomberg School of Public Health, and ²Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland; ³Center for Urban Epidemiologic Studies, New York Academy of Medicine, New York, New York

(See the editorial commentary by Schechter, on pages 1043–5.)

Background. The optimal time to initiate highly active antiretroviral therapy (HAART) remains unclear.

Methods. Five hundred eighty-three human immunodeficiency virus (HIV)–seropositive and 920 HIV-seronegative injection drug users (IDUs) were followed from 1997 to 2000. HIV-seropositive participants were categorized according to receipt of HAART (either initiated or switched to HAART) and initial CD4 cell count. Survival analysis that included delayed-entry and Cox proportional-hazards models was used to evaluate the effect of HAART, with adjustments for factors associated with access to HAART.

Results. Compared with HIV-seronegative participants, overall survival was similar in HIV-seropositive participants who received HAART at ³500 CD4 cells/µL, but mortality was higher both in participants with ³500 CD4 cells/µL who did not receive HAART and in participants who received HAART at 200–350 CD4 cells/µL (mortality rates, 19.9, 24.0, 43.0, and 50.5/1000 person-years, respectively). In proportional-hazards models in which HIV-seronegative participants were the reference group and in which age, sex, race, frequency of drug use, substance-abuse treatment, and health-care utilization were adjusted for, hazard ratios were 1.01 (95% confidence interval [CI], 0.41–2.45), 2.28 (95% CI, 1.38–3.78), and 2.09 (95% CI, 1.07–4.10) for the latter 3 groups. In HIV-seropositive participants, HAART significantly improved survival when initiated at CD4 cell counts ³200 cells/µL.

Conclusions. Survival of HIV-seropositive participants receiving HAART approximated that of HIV-seronegative participants only when therapy was given at CD4 cell counts ³500 cells/µL. These data, restricted to IDUs, suggest initiating or switching to HAART at higher CD4 cell levels than are currently recommended.

Highly active antiretroviral therapy (HAART) significantly improves the prognosis of HIV-seropositive persons, both in delaying progression to AIDS and reducing mortality [1–4]. Among the predictors of HIV disease progression for persons receiving HAART, CD4 cell count is the most important [5–7]. Although current clinical guidelines recommend initiating HAART when CD4 cell counts are ³200 cells/µL—and possibly when 200–350 cells/µL [8, 9]—the most appropriate time to initiate HAART remains an open question.

Current treatment guidelines are based partially on data from observational cohort studies of HIV-seropositive persons who initiated HAART at different CD4 cell level strata, in which such end points as new AIDS-defining illness or death were compared [6, 7, 10–13]. Most of these studies did not compare clinical disease progression in HIV-seropositive persons receiving HAART to that in HIV-seropositive persons not receiving HAART. In addition, although the Swiss HIV Cohort Study has recently reported a comparison between mortality in HIV-seropositive patients and that in the general population [14], there is excess mortality associated with injection drug use, compared with the general population, which makes HIV-related comparisons with the general population problematic [15]. To date, no re-
ported study has compared the mortality rate in HIV-seropositive persons receiving HAART to that in HIV-seronegative persons who were in the same risk category (e.g., injection drug use). The purpose of such a comparison would be to demonstrate the degree to which survival rates in persons receiving HAART approximate uninfected populations with similar background mortality rates. Such information would provide an additional perspective when one considers at what CD4 cell level HAART should be initiated.

Stratifying by HAART status and stage of HIV infection at initiation of HAART, we evaluated survival after the initiation of HAART in a large cohort of injection drug users (IDUs) who have been followed for up to 14 years. HIV-seronegative IDUs served as the reference group. We accounted for all-cause mortality, AIDS-related mortality, and non–AIDS-related mortality and adjusted for factors associated with access to HAART [16]. Accounting for these differences provides information not only on the extent of HAART effectiveness, but also on when to initiate HAART.

**PARTICIPANTS, MATERIALS, AND METHODS**

**Population.** Participants were part of the AIDS Linked to the Intravenous Experience (ALIVE) study in Baltimore, MD, which has been described in detail elsewhere [17]. The study recruited IDUs through community outreach beginning in 1988–1989, with additional recruitment in 1994. Semiannual follow-up visits included comprehensive interviews (on sexual behavior, drug use, and medical history, including receipt of HAART during the preceding 6 months), a clinical exam, and phlebotomy. The present study included 1503 participants followed 1989, with additional recruitment in 1994. Semiannual follow-up visits included comprehensive interviews (on sexual behavior, drug use, and medical history, including receipt of HAART during the preceding 6 months), a clinical exam, and phlebotomy. The present study included 1503 participants followed from 1989 to 2001, during which time HAART was available for general use. Of the participants, 920 (61.2%) were HIV seronegative throughout the study period, 556 (37.0%) were HIV seropositive at baseline, and 27 (1.8%) seroconverted during the study period. By the end of follow-up, 314 (53.9%) HIV-seropositive participants reported receipt of HAART during the study period.

**Ascertainment of death, cause of death.** Death was ascertained as follows. First, study staffs were notified of deaths by family members or partners during contacts for routine follow-up. Then the death certificate was obtained from the Maryland State Archives for confirmation; 66% of deaths in the ALIVE study were identified in this way. Second, for participants lost to follow-up, we requested records from the National Death Index (NDI) and NDI-plus (maintained at the National Center for Health Statistics), for which measures of sensitivity are the highest among major national mortality-ascertainment services; they are the best sources for identifying cause of death [18]. Matches with NDI were based on name, Social Security number, birth date, sex, race, and mother’s maiden name. Confirmation that the ascertained matches were indeed

the same ALIVE participants was then sought by the review of death certificates, medical-examiner reports, and medical records. In the present study, we truncated at December 2000, because of the >1 year lag period for information from the NDI.

Causes of death were determined by NDI-plus (standardized nosology) according to immediate and underlying causes as well as by a supplemental review of death certificates and medical records by a clinical end-points committee. Cause of death was categorized [19] as AIDS related if the participant was HIV seropositive and (1) the primary cause of death was AIDS/HIV or included an AIDS-defining opportunistic infection or malignancy, according to the Centers for Disease Control and Prevention definition [20], or (2) the CD4 cell count at the last follow-up visit was ≥200 cells/μL and the primary cause of death was sepsis, bacteremia, pneumonia, or organ (kidney, heart, or lung) failure. Death was categorized as non-AIDS related if (1) the participant was HIV seronegative; (2) the participant was HIV seropositive but the primary cause of death was non-AIDS related (such as by accident, suicide, firearm, overdose, liver failure, or a non-AIDS-defining malignancy); or (3) the participant was HIV seropositive but the last CD4 cell count was ≥200 cells/μL and the primary cause of death was a non–AIDS-defining illness (such as cardiovascular, gastrointestinal, or central nervous system disease). Cause of death was classified as unknown if there was no death certificate available or if cause of death was not provided.

**HAART and group definition.** Determination of antiretroviral medication use was based on self-report during each follow-up interview. The definition of HAART was based on the International AIDS Society–USA panel’s guidelines [8, 9]. Self-report of receipt of HAART correlated with lower HIV load (data not shown). The date for initiation of HAART or switching from any other antiretroviral therapy to HAART (hereafter, both are considered to be the initiation of HAART) was estimated to be the midpoint between the visit at which receipt of HAART was first reported and the previous visit. CD4 cell counts at initiation of HAART were based on the average of the measurements from the last 2 visits before the first visit at which receipt of HAART was reported. Therefore, the CD4 cell count at this initial visit was not affected by receipt of HAART. CD4 cell counts for HIV-seropositive participants at study baseline were based on the average of the measurements from the 2 visits closest to 1 January 1997. For participants with only 1 CD4 cell count available, that value was used.

Seven strata were defined based on HIV status, receipt of HAART, and CD4 cell count: (1) HIV seronegative; (2) HIV seropositive and HAART initiated at a CD4 cell count >350 cells/μL; (3) HIV seropositive, no receipt of HAART, and a CD4 cell count ≥350 cells/μL at baseline; (4) HIV seropositive and HAART initiated at a CD4 cell count of 200–350 cells/μL; (5) HIV seropositive, no receipt of HAART, and a CD4 cell...
count of 200–350 cells/µL at baseline; (6) HIV seropositive and HAART initiated at a CD4 cell count <200 cells/µL; and (7) HIV seropositive, no receipt of HAART, and a CD4 cell count <200 cells/µL at baseline. At the baseline visit, among HIV-infected participants who were not receiving HAART, 33.1% reported use of other antiretroviral therapy. Among participants who were receiving HAART at baseline or who initiated HAART later, 47.0% reported use of other antiretroviral therapy the visit before initiation of HAART.

**Laboratory assays.** HIV antibodies were assayed by use of commercial tests and were interpreted with standard criteria. T cell subsets were determined by flow cytometry. Baseline HIV load in plasma was determined on a subset of the cohort \( (n = 438) \) by reverse-transcriptase polymerase chain reaction (AmpliCor HIV-1 Monitor Test, version 1.5; Roche Molecular Systems); specimens were stored at \(-70^\circ\) C before virus load determination.

**Statistical analysis.** Mortality rates were calculated by use of person-time techniques. Kaplan-Meier survival curves and log-rank tests were used to compare time to death among groups. To account for potential selection bias, participants who changed groups (i.e., from the HIV-seronegative group to an HIV-seropositive group or from a non-HAART group to a HAART group) during the study period were handled by use of delayed entry [21], and the time spent by participants in each category was accounted for separately for the HIV-seronegative and -seropositive groups and for the non-HAART and HAART groups. Censoring occurred either at the last visit before changing from the HIV-seronegative group to an HIV-seropositive group or from a non-HAART group to a HAART group, at the end of the study (1 January 2001), or, if the visit was >1 year before 1 January 2001, at the last follow-up visit. Robust variances were estimated to account for the correlation between observations from the same participants. Cox proportional-hazards models were used to adjust for potential confounding factors measured at the visit closest to 1 January 1997 for the HIV-seronegative and HIV-seropositive participants not receiving HAART and at the visit at which receipt of HAART was first reported. These factors included demographic characteristics, alcohol and drug use, sex practices, substance-abuse treatment, insurance status, and history of hospitalization. Because the primary aim was to compare survival between HIV-seronegative participants and participants receiving HAART, we did not include factors uniquely associated with HIV status, such as previous antiretroviral therapy or *Pneumocystis carinii* pneumonia prophylaxis, in the models. The assumptions of proportionality were tested by use of both (1) the interaction of indicator category variables and survival time and (2) the graph method with Schoenfeld residuals [22].

**RESULTS**

Of the 1503 eligible participants, 1111 (73.9%) were male, and 1396 (92.9%) were African American. At baseline (1 January 1997), the median age was 41.5 years (interquartile range [IQR], 36.7–45.8 years); 73.9% were unemployed; and the median duration of drug use was 16.5 years (IQR, 9.5–23.5 years). In addition, 56.1% of the participants were active IDUs (i.e., injected any time within the 6 months before the study visit); 29.0% injected daily; and 6.5% reported methadone use. With regard to health-care utilization, 60.4% had insurance, but only 8.2% had private insurance; 14.1% had at least 1 hospital inpatient visit during the 6 months before the baseline study visit. Overall, there were 583 (38.8%) HIV-seropositive participants and 187 confirmed deaths during the 4-year period.

The participants were stratified into 7 categories, according to HIV status, receipt of HAART, and CD4 cell count at initiation of HAART, as summarized in table 1. The median follow-up times for participants receiving HAART, participants not receiving HAART, and HIV-seronegative participants were 2.4, 2.0, and 4.0 years, respectively \( (P = .03, \text{ for the first } 2 \text{ groups}; P < .001, \text{ for both the first group vs. the HIV-seronegative group and the second group vs. the HIV-seronegative group}) \). The all-cause mortality rate was lowest in the HIV-seronegative group. This rate was significantly lower than the rates in all other groups, except the group of participants who began receiving HAART at CD4 cell counts >350 cells/µL \( (19.9 \text{ vs. } 24.1/1000 \text{ person-years [py]} \ (P = .76)) \). Among participants with CD4 cell counts >350 cells/µL, the mortality rate for those who received HAART was 56% of that for those who did not receive HAART.

Figure 1 shows the Kaplan-Meier survival curves for the 7 HIV/HAART/CD4 cell count categories. There was no significant difference in survival between the HIV-seropositive participants who began receiving HAART at CD4 cell counts >350 cells/µL and the HIV-seronegative participants \( (P = .71, \log-rank \text{ test}) \), but the HIV-seropositive participants with baseline CD4 cell counts >350 cells/µL who did not receive HAART had a significantly higher risk of death than did the HIV-seronegative participants \( (P < .001) \). In the HIV-seropositive participants with baseline CD4 cell counts of 200–350 cells/µL, survival was lower than that in the HIV-seronegative participants; this was true for both the HIV-seropositive participants who received HAART \( (P = .006) \) and those who did not \( (P < .001) \). Separately, univariate comparisons restricted to HIV-seropositive participants who did and did not receive HAART showed no significant difference in survival curves for CD4 cell counts >350 cells/µL \( (P = .27) \) or of 200–350 cells/µL \( (P = .32) \) but showed significant difference for CD4 cell counts <200 cells/µL \( (P = .01) \).

To return to the last column of table 1, we used Cox proportional-hazards models to adjust for putative confounding factors that had been identified in the univariate analysis (data
HIV seropositive, CD4 cell count at baseline during follow-up as either AIDS related ( ) or non–AIDS counts
pants not receiving HAART were similar, except at CD4 cell mortality rates in participants receiving HAART and partici-
AIDS-related mortality rate increased moderately with declines cell count, the higher the AIDS-related mortality rate; the non–
participants not receiving HAART, the lower the baseline CD4 related ( ). As shown in figure 2, in the HIV-seropositive hospitalization.

Table 1. Mortality rates (MRs) and hazard ratios (HRs) in HIV-seropositive injection drug users (IDUs), by receipt of highly active antiretroviral therapy (HAART) and CD4 cell count, compared with HIV-seronegative IDUs, in Baltimore, MD, 1997–2000.

<table>
<thead>
<tr>
<th>Category, variable</th>
<th>Receipt of HAART (n)</th>
<th>py at risk, no.</th>
<th>MR (95% CI), deaths/1000 py</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV seronegative</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV seropositive, CD4 cell count at baseline or initiation of HAART</td>
<td>3060.7</td>
<td>19.9 (15.5–25.6)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>&gt;350 cells/μL</td>
<td>Yes (99)</td>
<td>207.9</td>
<td>24.1 (10.0–57.8)</td>
<td>1.15 (0.46–2.88)</td>
</tr>
<tr>
<td></td>
<td>No (222)</td>
<td>534.5</td>
<td>43.0 (28.6–64.8)</td>
<td>2.19 (1.36–3.55)</td>
</tr>
<tr>
<td>200–350 cells/μL</td>
<td>Yes (87)</td>
<td>217.6</td>
<td>50.5 (28.0–91.3)</td>
<td>2.44 (1.28–4.65)</td>
</tr>
<tr>
<td></td>
<td>No (159)</td>
<td>317.3</td>
<td>59.9 (38.2–93.9)</td>
<td>3.10 (1.85–5.20)</td>
</tr>
<tr>
<td>&lt;200 cells/μL</td>
<td>Yes (127)</td>
<td>323.1</td>
<td>86.7 (59.8–125.5)</td>
<td>4.22 (2.69–6.62)</td>
</tr>
<tr>
<td></td>
<td>No (150)</td>
<td>240.8</td>
<td>166.1 (121.9–226.5)</td>
<td>8.70 (5.80–13.03)</td>
</tr>
<tr>
<td>Total</td>
<td>... (1791)</td>
<td>4901.9</td>
<td>38.1 (33.1–44.0)</td>
<td>...</td>
</tr>
</tbody>
</table>

NOTE.  CI, confidence interval; py, person-years.
* Adjusted for age, race, sex, and the following covariates measured at the baseline visit closest to 1 January 1997, referring to the prior 6 months: employment, active drug use, duration of drug use, IDU sex partner, alcohol or drug treatment, multivitamin treatment, insurance status, regular source of health care, and hospitalization.
not shown) and for factors that had been associated with access to HAART in previous analyses [16, 23–25]. The participants who began receiving HAART at CD4 cell counts >350 cells/μL had a similar risk for all-cause mortality as did the HIV-seronegative participants (adjusted hazard ratio [HR], 1.01 [P = .99]); in contrast, compared with that for the HIV-seropositive participants, the risk for all-cause mortality was significantly higher in the participants with baseline CD4 cell counts of 200–350 cells/μL and <200 cells/μL (regardless of whether they received HAART) and in the participants with baseline CD4 cell counts >350 cells/μL who did not receive HAART (adjusted HR, 2.28 [P = .001]).

To distinguish the effect that HAART has on AIDS- and non–AIDS-related mortality, we classified the 187 deaths observed during follow-up as either AIDS related (n = 58) or non–AIDS related (n = 129). As shown in figure 2, in the HIV-seropositive participants not receiving HAART, the lower the baseline CD4 cell count, the higher the AIDS-related mortality rate; the non–AIDS-related mortality rate increased moderately with declines in CD4 cell count. Within CD4 cell count strata, AIDS-related mortality rates in participants receiving HAART and participants not receiving HAART were similar, except at CD4 cell counts <200 cells/μL; in contrast, the non–AIDS-related mortality rate was higher in the participants not receiving HAART than in the participants receiving HAART in both the CD4 cell counts >350 cells/μL stratum and the 200–350 cells/μL stratum, with marginal significance for CD4 cell counts >350 cells/μL (37.4 vs. 14.4 deaths/1000 py [P = .09]). Table 2 details the non–AIDS-related deaths and shows that, for both CD4 cell count strata, HAART was associated with a reduction in death from viral/bacterial infection.

Of the 583 HIV-seropositive participants in the present study, who had an overall median CD4 cell count of 296 cells/μL (IQR, 168–442/μL), 438 (75.1%) had HIV plasma-load measurements at study baseline or HAART initiation; the median virus load was 2196 copies/mL (IQR, 455–7987 copies/mL). In a subanalysis that categorized both baseline HIV load (≥ or <55,000 copies/mL, as per the guidelines [8]) and baseline CD4 cell count (>350 and 200–350 cells/μL), we reevaluated the effect that HAART has on survival. At CD4 cell counts >350 cells/μL, the HIV load did not effect a lack of a difference in survival between the participants receiving HAART and the HIV-seronegative participants. However, a distinction was noted for participants receiving HAART who had CD4 cell counts of 200–350 cells/μL—participants with baseline HIV loads <55,000 copies/mL had a survival rate similar to that for HIV-seronegative participants (HR, 1.21 [95% CI, 0.48–3.10] [P = .68]), whereas the participants with baseline HIV loads ≥55,000 copies/mL had a significantly higher risk of death than did the HIV-seropositive participants (HR, 5.3 [95% CI, 2.2–13.0] [P < .001]). In addition, of the 1436 participants who were tested for hepatitis C virus (HCV), 91.9% were seropositive at baseline. Adjustment for HCV status in the model did not change the results (data not shown).

**DISCUSSION**

The major finding of the present study was that survival in the HIV-seropositive IDUs with CD4 cell counts >350 cells/μL who received HAART was similar to that in the HIV-seronegative IDUs. Both groups had better survival rates than did the HIV-seropositive participants with CD4 cell counts >350 cells/μL who did not receive HAART and the participants with CD4 cell counts between 200 and 350 cells/μL who reported receiving HAART. Assuming that the goal of HIV treatment is to produce outcomes similar to those seen in HIV-seronegative persons,
Figure 1. Kaplan-Meier survival curves, by HIV/highly active antiretroviral therapy (HAART)/CD4 cell count categories, for injection drug users in Baltimore, MD, 1997–2000. CD4 cell counts indicate cells per microliter. Neg., negative.
our results provide information that suggests that HAART should be initiated or switched to at higher CD4 cell levels than currently recommended.

Several observational cohort studies have assessed the effect that HAART has on HIV disease progression and mortality [6, 7, 11–13, 26, 27]. However, all of these studies were comparisons of either HIV-seropositive persons who began receiving HAART at different CD4 cell levels or HIV-seropositive persons who did or did not receive HAART. In the present study, we used HIV-seronegative IDUs as the comparison group, to measure the extent to which survival in persons receiving HAART approximates that of an uninfected peer group with similar background mortality. This provides a more accurate assessment of the effect that HAART has on survival, because, when all-cause mortality is used as the measurement of outcome, the risk for mortality that is unrelated to HIV (and therefore is not affected by HAART but can happen in both HAART and non-HAART groups) can dilute the effect of HAART as measured by an HR closer to 1 and result in the underestimation of HAART’s benefits on survival. In addition, we considered that the lower risk of death associated with HAART might be due simply to selection bias: the characteristics of IDUs that are associated with lower mortality may also be characteristics associated with access to HAART. IDUs who have not used drugs recently, have enrolled in alcohol- or drug-treatment programs, or have insurance and a regular source of care are more likely to receive HAART [16, 23–25]. Therefore, in our multivariable models that examined the effect that HAART has on mortality, we adjusted for all of these factors, to minimize potential confounding.

HIV-seronegative IDUs may have higher non–AIDS-related mortality rates than do other HIV risk groups (e.g., homosexual men). Although this would affect comparisons of mortality rates among such groups, it would not affect comparisons between HIV-seropositive and HIV-seronegative persons within the same risk group, as was done in the present study. However, the extent to which results from this cohort can be extended to other populations requires further study.

Despite differences in the outcome assessed, the comparison groups studied, and the confounding factors considered, our findings on survival in persons who began receiving HAART at CD4 cell counts >350 cells/μL are similar to those reported from some, but not all, cohorts that were restricted to HIV-seropositive persons [26, 27]. The Swiss HIV Cohort Study compared HAART-treated and -untreated persons who had the same CD4 cell level and found that providing HAART at CD4 cell counts >350 cells/μL significantly improved the prognosis of HIV infection [26]. The HIV Outpatient Study found that the mortality rate in persons who began receiving HAART at

![Figure 2. AIDS-related and non–AIDS-related mortality rates (MRs), by HIV/highly active antiretroviral therapy (HAART)/CD4 cell count categories, for injection drug users in Baltimore, MD, 1997–2000. CD4 cell counts indicate cells per microliter. py, Person-years.](https://academic.oup.com/jid/article-abstract/190/6/1046/918201)
CD4 cell counts between 351 and 500 cells/µL was lower than that in persons who delayed therapy until reaching a lower CD4 cell count stratum, but this difference was not statistically significant [27]. In another study, initiation of HAART at CD4 cell counts >350 cells/µL also did not significantly improve survival, compared with that in persons who did not receive HAART, and persons receiving HAART had high rates of drug toxicity and nondurable virologic suppression [28].

Consistent with the results of other studies [6, 7, 11–13], our analysis within the HIV-seropositive participants showed that the risk of death decreased as the CD4 cell level before initiation of HAART increased. HAART significantly reduced the risk of death in HIV-seropositive participants with baseline CD4 cell counts <200 cells/µL but did not reduce it in participants with baseline CD4 counts of 200–350 or >350 cells/µL.

It is also noteworthy that, in the present study, participants who received HAART had lower rates of non–AIDS-related death than did participants who did not receive HAART, particularly in those with CD4 cell counts >350 cells/µL at baseline. The effect that HAART had on non–AIDS-related mortality appeared to be greater than the effect it had on AIDS-related mortality in persons who began receiving HAART at CD4 cell counts >200 cells/µL. The explanation for this finding is unclear, but it could be due to several factors. A more stable lifestyle (e.g., less illicit-drug use and regular health care) increases the likelihood of receiving HAART and could be associated with lower rates of drug-related deaths (e.g., overdose, trauma/homicide, endocarditis, and sepsis) [23, 29]. IDUs not receiving HAART are more likely to be active drug users, to not be enrolled in alcohol- or drug-treatment programs, and to be without usual sources of care [16, 23–25]. Thus, factors that select against receipt of HAART may also be associated with higher mortality, independent of the direct effects of HAART. However, in our data, comparison of participants who did and did not receive HAART revealed no key differences in factors associated with treatment selection (e.g., active drug use); in our final models, we adjusted for other treatment-selection factors (e.g., enrollment in an alcohol- or drug-treatment program and employment status) as well as treatment-access factors (e.g., health insurance and having routine care).

Another factor to consider that might explain lower non–AIDS-related mortality in patients receiving HAART is that HAART would also reduce HIV-associated non–AIDS-related mortality, which could happen before the patients progressed to CD4 cell counts <200 cells/µL or clinical AIDS. Studies have shown that mortality rates preceding AIDS are higher in IDUs than in other populations composed of HIV patients [30–32]. Among pre-AIDS deaths, HIV progression has not been shown to be associated with death from overdose and violence, but it has been shown to be associated with bacterial infection, liver disease, and non–AIDS-related malignancies [29, 30, 33–35].

These results make sense in context, because advancing immunodeficiency may increase susceptibility to infection [31]. In addition, several studies have addressed the beneficial effects that HAART has on the recovery of the immunologic system when initiated at an early stage of HIV infection; these effects include restoring CD8 cells, both physically and functionally [36]; maintaining normal structure and function of lymphoid thymus [37, 38]; and restoring the immune function more completely [39]. Also, by further analyzing the causes of death among non–AIDS-related mortality in the strata composed of participants with CD4 cell counts >350 and of 200–350 cells/µL, the present study has shown that, in both strata, HAART is associated with a reduction in death from viral/bacterial infection.

As in other studies [6, 11], we observed that HIV load at the time HAART was initiated did not predict mortality when base-

Table 2. Cause-specific mortality rates (MRs) for injection drug users with and without receipt of highly active antiretroviral therapy (HAART), by 2 CD4 cell count categories (>350 and 200–350 cells/µL), Baltimore, MD, 1997–2000.

<table>
<thead>
<tr>
<th>Variable</th>
<th>CD4 cell count of &gt;350 cells/µL</th>
<th>CD4 cell count of 200–350 cells/µL</th>
<th>HIV seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Receipt of HAART</td>
<td>No receipt of HAART</td>
<td>Receipt of HAART</td>
</tr>
<tr>
<td>Person-years at risk, no.</td>
<td>207.9</td>
<td>534.5</td>
<td>217.6</td>
</tr>
<tr>
<td>Deaths, no.</td>
<td>5</td>
<td>23</td>
<td>11</td>
</tr>
<tr>
<td>AIDS-related death MR</td>
<td>9.6</td>
<td>5.6</td>
<td>27.6</td>
</tr>
<tr>
<td>Non–AIDS-related death MR</td>
<td>14.4</td>
<td>37.4</td>
<td>23.0</td>
</tr>
<tr>
<td>Overdose</td>
<td>0</td>
<td>5.0</td>
<td>9.2</td>
</tr>
<tr>
<td>Accident/violence</td>
<td>14.4</td>
<td>3.7</td>
<td>0</td>
</tr>
<tr>
<td>Viral/bacterial infection</td>
<td>0</td>
<td>11.2</td>
<td>0</td>
</tr>
<tr>
<td>Other natural cause</td>
<td>0</td>
<td>7.5</td>
<td>13.8</td>
</tr>
</tbody>
</table>

NOTE. Data are deaths/1000 person-years, unless otherwise noted.
line CD4 cell counts were >350 cells/µL. However, at CD4 cell counts of 200–350 cells/µL, survival was lower for the participants with HIV loads ≥55,000 copies/mL. This finding is consistent with that of recent studies demonstrating that high virus load can be an independent predictor of disease progression for patients receiving HAART [7, 40] and supports the current treatment guidelines indicating that virus load should be taken into consideration when CD4 cell counts are >200 cells/µL.

Although the ALIVE cohort is one of the few large, well-characterized HIV cohorts with extensive follow-up, the median length of follow-up for participants receiving HAART was ~2.4 years. This relatively short follow-up period and the limited number of outcomes identified among study participants are mainly due to the lag time for the reporting of mortality and the delayed availability of HAART for IDUs, compared with other HIV-seropositive populations, especially at relatively high CD4 cell levels [28, 41]. Another limitation of the present study was that receipt of HAART was determined by self-report and reflected “any use” in the 6 months before each study visit. Duration of adherence to, and toxicity of HAART during that 6-month period were not assessed; if adherence to HAART were suboptimal, it would underestimate the potential benefits of HAART. Furthermore, this study cohort consisted entirely of IDUs; the generalizability of our results to other HIV risk groups is, therefore, unclear. Finally, HAART regimens in current use (e.g., those that include efavirenz- or ritonavir-boosted protease inhibitors) may be more potent and/or have a better pharmacokinetic profile (allowing for less-frequent dosing and perhaps better adherence) than were the HAART regimens used during the study period. Such newer regimens could potentially lower rates of disease progression and death in patients with lower baseline CD4 levels. Future studies of HAART that have longer follow-up and that assess sustainability of treatment, toxicities, disease progression, and cost-effectiveness will be beneficial. In the present analysis, >95% of the visits at which CD4 cell counts were used to estimate CD4 cell levels occurred within 2 years of the initiation of HAART, and all visits occurred within 4 years of the initiation of HAART; therefore, the misclassification of participants in CD4 cell count strata at treatment initiation was minimal. The low baseline HIV load in this study population is notable. It may be associated with the broad range of CD4 cell levels included in the present study and with receiving non-HAART antiretroviral treatment at baseline.

Our study demonstrates that, among IDUs, HAART initiated at CD4 cell counts >350 cells/µL was associated with a survival rate comparable to that of HIV-seronegative IDUs, even after accounting for factors associated with access to care. This result suggests that, to optimize survival in HIV-seropositive IDUs, initiation of HAART at CD4 cell levels higher than the current treatment guidelines indicate might be considered.

Acknowledgments

We acknowledge Joseph B. Margolick, for CD4 cell count assays; Homayoon Farzadegan and Thomas Quinn, for HIV load assays; and Lisette Johnson and Lisa Purvis, for project management.

References


17. Vlahov D, Anthony JC, Munoz A, et al. The ALIVE study, a longitudinal study of HIV-1 infection in intravenous drug users: description of meth-