Course and Clinical Significance of CD8⁺ T-Cell Counts in a Large Cohort of HIV-Infected Individuals

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Objectives. To examine trajectories of CD8⁺ T-cell counts before and after combination antiretroviral therapy (cART) in human immunodeficiency virus (HIV)-infected individuals and associations with mortality.

Methods. CD8⁺ T-cell counts were measured in 3882 HIV-infected individuals who received care in Copenhagen during 1995–2012. Reference values were obtained from 1230 persons from the background population. Mortality rate ratios were estimated by Poisson regression.

Results. CD8⁺ T-cell counts were elevated during untreated HIV infection and remained elevated through 10 years of cART. A slight drop of 130 cells/µL (interquartile range, −160 to 410 cells/µL) in the median CD8⁺ T-cell count was observed after cART initiation. CD8⁺ T-cell counts stabilized at approximately 900 cells/µL (95th percentile of the background population, 835 cells/µL). Markedly elevated CD8⁺ T-cell counts at cART initiation were associated with a poor increase in the CD4⁺ T-cell count (relative risk, 2.22; 95% confidence interval [CI], 1.42–3.48). Individuals with a CD8⁺ T-cell count of <500 cells/µL 1 year after cART initiation had an increased mortality rate (mortality rate ratio, 1.73; 95% CI, 1.29–2.32) and a higher proportion of deaths attributable to AIDS-related conditions, compared with individuals with CD8⁺ T-cell counts of ≥500 cells/µL. After receiving cART for 10 years, a CD8⁺ T-cell count of >1500 cells/µL was associated with increased non–AIDS-related mortality (mortality rate ratio, 1.82; 95% CI, 1.09–3.22), compared with a CD4⁺ T-cell count of 500–1500 cells/µL.

Conclusions. CD8⁺ T-cell counts are elevated during HIV infection and do not normalize despite long-term cART. Low CD8⁺ T-cell counts are associated with increased AIDS-related mortality. Marked elevations in CD8⁺ T-cell counts after long-term cART are associated with increased non–AIDS-related mortality.

Keywords. HIV; CD8; immunological recovery; immune activation; mortality.
elucidated. Recent studies have shown that a low ratio of CD4+ to CD8+ T cells among treated HIV-infected individuals is associated with increased morbidity and mortality [11, 12]. The homeostasis of the CD4+ and CD8+ T-cell compartments are regulated differentially [5, 7]; thus, CD8+ T-cell counts may predict prognosis independently of CD4+ T-cell counts.

The aim of the present study was to describe changes in CD8+ T-cell counts during untreated HIV infection and during long-term cART in a large population-based cohort of HIV-infected individuals and to examine associations with CD4+ T-cell count increases and mortality.

METHODS

Data Sources
The Danish HIV Cohort Study, described in details elsewhere [13], is a population-based nationwide cohort study of all HIV-infected individuals who have received care in Danish HIV centers after 1 January 1995. CD4+ and CD8+ T-cell count and HIV RNA load measurements are extracted electronically from laboratory data files. Data on vital status and migration and causes of death were retrieved from the Danish Civil Registration System [14] and the National Registry of Causes of Death.

References values for CD8+ T-cell counts were obtained from a sample of 1230 persons from the background population. This group consisted of healthy staff, blood donors, and stem-cell donors.

CD4+ and CD8+ T-cell counts were measured by the single platform lyse-no-wash procedure, using Becton–Dickinson TRUcount beads and monoclonal antibodies against CD3, CD4, and CD8.

Study Population
We included all HIV-infected individuals aged ≥16 years at diagnosis, who received care in HIV centers in Copenhagen in the period 1 January 1995 to 31 December 2012. Individuals with no available data on CD8+ T-cell counts were excluded from the study. For specific analyses we included subsets of this population who fulfilled specified criteria as described in detail later.

Statistics
Differences in CD8+ T-cell counts between groups defined by origin, route of infection, age, CD4+ T-cell count, HIV RNA load, cytomegalovirus (CMV) serostatus, hepatitis B virus (HBV) coinfection, hepatitis C virus (HCV) coinfection, and HIV status were analyzed by the Mann–Whitney U test and the Kruskal–Wallis test. We included all variables from univariate analyses in multivariate linear regression analyses. Correlations between CD8+ T-cell counts and HIV RNA loads were assessed by Spearman rank correlation.

Relative risks (RRs) of a poor CD4+ T-cell count increase and of death were analyzed using Poisson regression. In analyses of CD4+ T-cell count increase, time was calculated from date of cART initiation until the date of the CD4+ T-cell count measurement 1 year thereafter (±30 days). We analyzed mortality in 3 separate analyses, defining baseline as the date of CD8+ T-cell count at cART initiation, 1 year after cART initiation, or 10 years after cART initiation. Time was calculated from the date of CD8+ T-cell count measurement until death, emigration, or 31 December 2012, whichever occurred first. Mortality rate ratios for individuals with CD8+ T-cell counts of <500 cells/µL, 500–1500 cells/µL, 1500–2000 cells/µL, or >2000 cells/µL versus 500–1500 cells/µL were estimated by Poisson regression, with adjustment for sex, age, route of HIV transmission, year of HIV diagnosis, and CD4+ T-cell count (measured the same date as the CD8+ T-cell count under analysis). The reference CD8+ T-cell count of 500–1500 cells/µL roughly corresponded to the 25th–75th percentile and a CD8+ T-cell count of >2000 cells/µL corresponded to the 90th percentile in the HIV-infected population at start of cART.

In sensitivity analyses of mortality, we replaced CD8+ T-cell counts in the analyses with total lymphocyte counts measured at the same date as the CD8+ T-cell count.

Stata 8.0 (StataCorp, College Station, Texas) and Excel 2010 (Microsoft; Redmond, Washington) were used for data analyses.

Ethics
The study was approved by the Danish Data Protection Agency. Ethics approval and individual consent are not required by Danish legislation governing this type of study.

RESULTS
A total of 4191 HIV-infected adults were followed in HIV centers in Copenhagen during the study period. Of these, 309 individuals were excluded because of lack of data on CD8+ T-cell counts. We thus included 3882 individuals, of whom 3060 (79%) were male; the median age at the time of the first CD8+ T-cell count measurement was 39 years (interquartile range [IQR], 32–47 years); 2012 (52%) were men who have sex with men (MSM), and 388 (10%) were infected through injection drug use; 3427 (88%) received cART during follow-up. Median follow-up was 8.6 years (IQR, 4.1–13.7 years). During 29 896 person-years of follow-up 94 344 CD8+ T-cell counts were measured; 14 129 (15%) were measured >5 years after cART initiation, and 47 293 (50%) were measured >5 years after cART initiation.

In the group of persons from the background population, 419 (52%) were male, and the median age was 33 years (IQR, 27–43 years). The median CD4+ and CD8+ T-cell counts in this group were 820 cells/µL (IQR, 630–1000 cells/µL) and 450 cells/µL (IQR, 340–570 cells/µL), respectively.
Distribution of CD8⁺ T-Cell Counts at the Start of cART

Table 1 summarizes CD8⁺ T-cell counts among 2284 HIV-infected individuals who had their CD8⁺ T-cell count measured at cART initiation. The median CD8⁺ T-cell count was 900 cells/µL (IQR, 590–1300 cells/µL; Table 1), which was slightly higher than the 95th percentile in the background population (835 cells/µL). Among HIV-infected individuals with a CD4⁺ T-cell count of <200 cells/µL at the start of cART, the median CD8⁺ T-cell count was 630 cells/µL (IQR, 380–950 cells/µL), compared with 1016 cells/µL (IQR, 740–1500 cells/µL) among those with a CD4⁺ T-cell count of ≥200 cells/µL. There were only slight differences between other subgroups: CD8⁺ T-cell counts were higher among MSM, compared with heterosexual men and women, and among individuals aged ≥50 years. CD8⁺ T-cell counts were significantly higher than in the background population in all subgroups (P < .001 for all comparisons). There was no correlation between CD8⁺ T-cell count and HIV RNA load (r = −0.01; P = .72).

CD8⁺ T-Cell Counts and Other Viral Infections

There were no significant associations between CD8⁺ T-cell count and HBV or HCV coinfection at the time of cART initiation (Table 1). Individuals who were seropositive for CMV had higher CD8⁺ T-cell counts than those who were seronegative, but the difference was small and not statistically significant in multivariate analysis. A year after cART initiation, when 71% of the HIV-infected individuals had an HIV RNA load of <40 copies/mL, CMV-seropositive status was associated with a higher median CD8⁺ T-cell count, compared with the CMV-seronegative group (943 cells/µL [IQR, 680–1300 cells/µL; n = 1976] vs 789 cells/µL [IQR, 499–1100 cells/µL; n = 387]; P < .01).

Trajectories of CD4⁺ and CD8⁺ T-Cell Counts and Ratio of CD4⁺ to CD8⁺ T Cells

In analyses of trajectories of CD8⁺ T-cell counts, we included 865 individuals for whom CD8⁺ T-cell counts were available at least 2 years before and 1 year after cART. A total of 28,442 CD8⁺ T-cell counts were measured for these patients, with a median interval of 98 days (IQR, 83–127 days). CD8⁺ T-cell counts were stable during chronic, untreated HIV infection. Within the first 2 years after cART initiation, the median change in CD8⁺ T-cell count was −130 cells/µL (IQR, −160 to 410 cells/µL; Figure 1). CD8⁺ T-cell counts remained high, compared with data for the background population, with no change the following 8 years (median change, 0 cells/µL; 95% confidence interval [CI], −240 to 250 cells/µL). There was a strong correlation between CD8⁺ T-cell counts 2 years before cART initiation and 5 years after cART initiation (r = 0.42; P < .001).

If individuals without serial CD8⁺ T-cell count measurements 2 years before and 1 year after cART initiation were included in analyses (n = 2284), the median CD8⁺ T-cell count at cART initiation was lower (Table 1), while CD8⁺ T-cell counts at other time points were not significantly different (data not shown). The lower CD8⁺ T-cell count at cART initiation was explained by inclusion of individuals who had advanced HIV disease and severe lymphopenia at the time of HIV diagnosis and cART initiation.

Figure 2 shows the distributions of CD4⁺ and CD8⁺ T-cell counts at cART initiation and 10 years thereafter. The variance in CD8⁺ T-cell counts decreased, but the mean changed only little after cART initiation, which is in contrast to the significant increase in both mean and variance of CD4⁺ T-cell counts. Even

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**Table 1. Stratified Analyses of CD8⁺ T-Cell Counts Among Human Immunodeficiency Virus (HIV)-Infected Patients at the Start of Combination Antiretroviral Therapy**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients, No.</th>
<th>CD8⁺ T-Cell Count, Cells/µL, Median (IQR)</th>
<th>P Valueᵃ</th>
<th>P Valueᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>2284</td>
<td>900 (590–1300)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Origin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Danish</td>
<td>1665</td>
<td>912 (594–1340)</td>
<td>&lt;.01</td>
<td>.98</td>
</tr>
<tr>
<td>African</td>
<td>241</td>
<td>835 (570–1190)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>378</td>
<td>870 (555–1217)</td>
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<tr>
<td><strong>Transmission route</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male-male sex</td>
<td>1262</td>
<td>969 (641–1400)</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
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<tr>
<td>Heterosexual sex</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Males</td>
<td>444</td>
<td>830 (470–1300)</td>
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</tr>
<tr>
<td>Females</td>
<td>387</td>
<td>860 (580–1200)</td>
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<tr>
<td>Injection drug use</td>
<td>191</td>
<td>766 (490–1100)</td>
<td></td>
<td></td>
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<tr>
<td><strong>Age, y</strong></td>
<td></td>
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<td></td>
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<tr>
<td>≤50</td>
<td>1836</td>
<td>890 (590–1300)</td>
<td>.09</td>
<td>&lt;.01</td>
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<tr>
<td>&gt;50</td>
<td>448</td>
<td>950 (576–1400)</td>
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<tr>
<td><strong>CD4⁺ T-cell count, cells/µL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;200</td>
<td>794</td>
<td>630 (380–950)</td>
<td>&lt;.01</td>
<td>&lt;.01</td>
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<tr>
<td>≥200</td>
<td>1490</td>
<td>1016 (740–1500)</td>
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<tr>
<td><strong>HIV RNA load, copies/mL</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;1000</td>
<td>136</td>
<td>795 (550–1053)</td>
<td>.88</td>
<td>.26</td>
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<td>1000–100 000</td>
<td>1158</td>
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<td>&gt;100 000</td>
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<td>890 (520–1400)</td>
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<tr>
<td><strong>CMV antibody status</strong></td>
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<tr>
<td>Positive</td>
<td>1911</td>
<td>910 (597–1317)</td>
<td>&lt;.01</td>
<td>.21</td>
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<tr>
<td>Negative</td>
<td>373</td>
<td>840 (500–1200)</td>
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<td><strong>HCV RNA status</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Positive</td>
<td>224</td>
<td>840 (558–1183)</td>
<td>.06</td>
<td>.84</td>
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<tr>
<td>Negative</td>
<td>2060</td>
<td>900 (590–1300)</td>
<td></td>
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<td><strong>HbsAg status</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>141</td>
<td>845 (540–1200)</td>
<td>.15</td>
<td>.27</td>
</tr>
<tr>
<td>Negative</td>
<td>2143</td>
<td>900 (590–1300)</td>
<td></td>
<td></td>
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</tbody>
</table>

Abbreviations: CMV, cytomegalovirus; HbsAg, hepatitis B virus surface antigen; HCV, hepatitis C virus; IQR, interquartile range.

ᵃ By univariate analysis.
ᵇ By multivariate analysis.
after 10 years of cART, CD8+ T-cell counts were significantly higher and CD4+ T-cell counts lower among HIV-infected individuals, compared with the background population ($P < .001$ in both analyses).

Changes in the ratio of CD4+ to CD8+ T-cell counts during the first 2 years of cART had a closer correlation to changes in CD4+ T-cell counts than changes in CD8+ T-cell counts ($\rho = 0.49$ [$P < .001$] and $\rho = 0.39$ [$P < .001$], respectively).

We assessed CD8+ T-cell counts by viral load 1 year after cART initiation and found no differences in CD8+ T-cell counts between different viral load strata (Supplementary Figure 1).

Trajectories of CD8+ T-Cell Counts, by Immune Status Before cART Initiation

To examine the impact of immune status before cART initiation, we analyzed CD8+ T-cell count trajectories from the time of cART initiation onward in 3 separate analyses in which HIV-infected patients were grouped on the basis of their last CD4+ T-cell count, their last CD8+ T-cell count, and their total lymphocyte count before the start of cART (Figure 3A–C). The measurement by which patients were grouped was not included in analyses, to avoid regression toward the mean. In these analyses, we included patients who had CD8+ T-cell count measurements before and at the time of cART initiation and at least once thereafter ($n = 1235$). In all 3 analyses, there was a tendency toward stabilization of CD8+ T-cell counts at a level of approximately 900 cells/µL 1–2 years after cART initiation. Within the first year of cART initiation, CD8+ T-cell counts dropped among individuals with higher baseline CD8+ T-cell counts, whereas they increased among individuals with lower baseline CD8+ T-cell counts. This trend was similar in the 3 analyses.

CD8+ T-Cell Counts and Increases in CD4+ T-Cell Counts After cART Initiation

Among individuals with a viral load of <400 copies/mL 1 year after cART, the median increase in CD4+ T-cell count during the first year of cART was significantly lower among individuals with a CD8+ T-cell count of >2000 at cART initiation, compared with those with a CD8+ T-cell count of $\leq$2000 cells/µL (100 cells/µL [IQR, 15–200 cells/µL; $n = 91$] vs 150 cells/µL [IQR, 70–260 cells/µL; $n = 1304$]; $P < .01$). The RR of having a poor CD4+ T-cell count gain (defined as an increase of <50 cells/µL) was 2.22 (95% CI, 1.42–3.48). The estimate was attenuated after adjustment for CD4+ T-cell count at cART initiation (RR, 1.60; 95% CI, 1.00–2.55). Results were similar in analyses using a viral load of $<$50 copies/mL as a cutoff (RR, 2.21 [95% CI, 1.37–3.57] and 1.63 [95% CI, .99–2.68], respectively). In analyses replacing CD8+ T-cell counts with total lymphocyte counts, there was no association with CD4+ T-cell count gain after adjustment for CD4+ T-cell count at cART initiation (RR, 1.32; 95% CI, .78–2.24).

CD8+ T-Cell Counts and Mortality

The association between CD8+ T-cell count and risk of death changed over time of cART receipt (Table 2). Individuals with CD8+ T-cell counts of <500 cells/µL at the time of cART initiation had increased mortality, compared with those with CD8+ T-cell counts of 500–1500 cells/µL. Both individuals with CD8+ T-cell counts of <500 cells/µL and those with CD8+ T-cell counts of >2000 cells/µL 1 year after cART initiation had increased mortality. Individuals with CD8+ T-cell counts of >1500 cells/µL 10 years after cART initiation had increased mortality, whereas low CD8+ T-cell counts were not
Figure 2. Distributions of CD8+ and CD4+ T-cell counts (dark grey) at initiation of combination antiretroviral therapy (cART; A and B, respectively) and 10 years after cART initiation (C and D, respectively), compared with the background population (light grey). Abbreviation: HIV, human immunodeficiency virus.
associated with an increased risk of death. All analyses were adjusted for CD4+ T-cell count. Analyses stratified by CD4+ T-cell count (<200, 200–500, and >500 cells/µL) yielded similar results (data not shown).

In analyses restricted to individuals with a fatal outcome, time to death was markedly shorter for individuals with CD8+ T-cell counts of <500 cells/µL, compared with those with higher CD8+ T-cell counts (Table 2), and a higher proportion of deaths were AIDS related. Among individuals with CD8+ T-cell counts of <500 cells/µL at cART initiation, 24 deaths (22% of all deaths) were AIDS related, compared with 36 deaths (13%) among those with CD8+ T-cell counts of ≥500 cells/µL (P = .04). Among individuals with CD8+ T-cell counts of <500 cells/µL 1 year after cART initiation, the corresponding values were 15 (24%) and 20 (8%), respectively (P < .01). There were no AIDS-related deaths >10 years after cART initiation.

To examine whether associations between CD8+ T-cell counts and mortality were explained by virological failure, we reanalyzed the data while censoring individuals at the time of virological failure (defined as an HIV RNA load of >1000 copies/mL >180 days after cART initiation). Results did not differ significantly from results of the original analyses (Supplementary Table 1).

We repeated the analyses by using total lymphocyte counts instead of CD8+ T-cell counts. Findings were quite different from findings of associations between CD8+ T-cell counts and mortality. Low total lymphocyte counts were associated with increased mortality, and the association became stronger after long-term cART receipt, while there was no association between high total lymphocyte count and mortality (Table 3).

**DISCUSSION**

In this study examining trajectories of CD8+ T-cell counts in HIV-infected individuals before and after long-term cART, we found that CD8+ T-cell counts were significantly elevated in untreated HIV-infected individuals and decrease only slightly after cART initiation. CD8+ T-cell counts were elevated in all subgroups examined. Individuals with markedly elevated CD8+ T-cell counts at treatment initiation had an increased risk of having a poor CD4+ T-cell count gain. After cART initiation, CD8+ T-cell counts converged toward levels above the 95th percentile in the background population and remained there despite >10 years of cART. Low CD8+ T-cell counts within the first year after cART initiation were associated with increased mortality, with a high proportion of AIDS-related deaths. After long-term cART, markedly elevated CD8+ T-cell counts were associated with increased non–AIDS-related mortality.

The observed lack of normalization of CD8+ T-cell counts after long-term cART is somewhat surprising, since previous studies have shown that CD8+ T-cell proliferation is correlated with HIV replication and decreases markedly after initiation of cART [15, 16], and is in contrast to the fact that the majority of HIV-infected patients experience CD4+ T-cell count recovery toward levels comparable to those of the background population. CD8+ T-cell counts were slightly higher in MSM and in individuals with CMV infection. These findings are similar to results of previous studies [17, 18] and indicate that ongoing infections other than HIV infection may exacerbate elevations of CD8+ T-cell counts; however, their contribution first becomes evident once HIV replication is controlled.

There was a clear association between CD8+ T-cell counts before and after cART initiation. Previous studies have shown that CD8+ T-cell counts correlate with proviral DNA [19] and that
The increase in CD8+ T-cell counts during primary HIV infection coincides with expansion of the HIV reservoir [20, 21]. Together, these findings could suggest that the CD8+ T-cell count reflects the size of the viral reservoir. In contrast, we found no correlation between CD8+ T-cell counts and HIV RNA loads.

Our finding of an association between high CD8+ T-cell counts and a poor CD4+ T-cell count response to cART is in line with previous studies showing that poor CD4+ T-cell count gain is associated with hyperactivation of CD8+ T cells, increased rates of peripheral CD8+ T-cell proliferation, and depletion of naive cells [22].

HIV-infected individuals with relatively low CD8+ T-cell counts during the first year of cART had increased mortality. Low CD8+ T-cell counts were associated with increased mortality, independently of age and CD4+ T-cell count. The association persisted even when individuals were censored at virological failure and is therefore not explained by uncontrolled HIV replication. CD8+ T cells have important functions in the control of infections and for immune surveillance. CD8+ T cells inhibit and kill tumor cells through production of interferon γ and through cytotoxic effects [23]. Thus, depletion of CD8+ T cells may cause an increased risk of cancer. Approximately one
fourth of the deaths among HIV-infected individuals with low CD8$^+$ T-cell counts during the first year of cART occurred within a year. This reflects the high risk of AIDS-related events among individuals with severe immunodeficiency at cART initiation. It is possible that redistribution of lymphocytes from blood to tissues with ongoing pathological processes is part of the explanation for the observed association between low CD8$^+$ T-cell counts and increased short-term mortality.

Markedly elevated CD8$^+$ T-cell counts after long-term cART were associated with a moderate increase in non–AIDS-related mortality. An association between high CD8$^+$ T-cell counts and increased mortality has previously been observed in HIV-negative populations [24, 25]. Elevated CD8$^+$ T-cell counts are associated with immune activation [26]. Whether there is an association between immune activation and an increased risk of non–AIDS-related mortality in the long term (eg, deaths due to cardiovascular disease, cancer, and liver disease) needs to be explored in future studies.

The present study is limited in that we did not have data on the subsets of CD8$^+$ T cells or proportions of activated CD8$^+$ T cells. Strengths of the study include the large study population with data on CD8$^+$ T-cell counts and long-term follow-up.

We conclude that CD8$^+$ T-cell counts are continuously elevated in HIV-infected individuals and not normalized despite 10 years of cART. Individuals with CD8$^+$ T-cell counts below the median of the background population during the first year of cART have increased mortality, with an elevated risk of AIDS-related death within a year. Marked elevations in CD8$^+$ T-cell counts after long-term cART are associated with increased non–AIDS-related mortality.

**Supplementary Data**

Supplementary materials are available at The Journal of Infectious Diseases online (http://jid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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