Death rates in HIV-positive antiretroviral-naive patients with CD4 count greater than 350 cells per μL in Europe and North America: a pooled cohort observational study

Study Group on Death Rates at High CD4 Count in Antiretroviral Naive Patients

Summary

Background Whether people living with HIV who have not received antiretroviral therapy (ART) and have high CD4 cell counts have higher mortality than the general population is unknown. We aimed to examine this by analysis of pooled data from industrialised countries.

Methods We merged data on demographics, CD4 cell counts, viral-load measurements, hepatitis C co-infection status, smoking status, date of death, and whether death was AIDS-related or not from 23 European and North American cohorts. We calculated standardised mortality ratios (SMRs) standardised by age, sex, and year, stratifying by risk group. Data were included for patients aged 20–59 years who had at least one CD4 count greater than 350 cells per μL while ART naive. All pre-ART CD4 counts greater than 350 cells per μL from January, 1990, to December, 2004, were included. We investigated mortality for four risk groups—men who have sex with men, heterosexual people, injecting drug users, and those at other or unknown risk. The association between CD4 cell count and death rate was investigated by use of Poisson regression methods.

Findings Data were analysed for 40 830 patients contributing 80 682 person-years of follow-up. Of 419 deaths, 401 were used in the SMR analysis: 100 men who have sex with men (SMR 1·30, 95% CI 1·06–1·58); 68 heterosexual people (2·94, 2·28–3·73); 203 injecting drug users (9·37, 8·13–10·75); and 30 in the other or unknown risk category (4·57, 3·09–6·53). Compared with CD4 counts of 350–499 cells per μL, death rate was lower in patients with counts of 500–699 cells per μL (adjusted rate ratio 0·77, 95% CI 0·61–0·95) and counts of 700 cells per μL (0·66, 0·52–0·85).

Interpretation In HIV-infected ART-naive patients with high CD4 cell counts, death rates were raised compared with the general population. In men who have sex with men this was modest, suggesting that a substantial proportion of the increased risk in other groups is due to confounding by other factors. Even though the increased risk is small, new studies of potential benefits of ART in this group are merited.


Introduction In people infected with HIV, risk of death increases as CD4 cell count declines, and this trend has been noted even in the high CD4 count range. Risk of death not attributable to AIDS is associated with CD4 cell count, although not as strongly as for AIDS deaths. The optimum CD4 cell count at which to start antiretroviral therapy (ART) in individuals infected with HIV is unclear. Most guidelines state that, in patients without a previous AIDS event, ART should be started when the CD4 count falls to 350 cells per μL. Evidence as to whether starting ART at greater CD4 cell counts might be beneficial is restricted to observational studies, and to a subanalysis of the SMART trial. Observational studies have attempted to mimic the comparison made in randomised trials, comparing outcomes from immediate versus deferred ART initiation, and have generally concluded that earlier initiation will probably lead to lower risk of death, although results are inconsistent. We sought to use observational data to address a more fundamental question about the potential benefit of early introduction of ART: are ART-naive patients with CD4 count greater than 350 cells per μL at higher risk of death than the general population?

We compared mortality in a large multinational collaborative cohort study of people with HIV with that expected for the general population, standardised by age, sex, country, and year. Furthermore, we considered whether death rates in these patients differed with CD4 cell count.

Methods

Data collection 23 cohorts and cohort collaborations contributed data for this analysis. 18 cohorts were based in Europe and five in North America. Data were requested in a standard format, and duplicate records were removed where patients were in more than one cohort. Data requested from participating cohorts included demographic information, CD4 cell counts, viral-load measurements, hepatitis C co-infection status, smoking status, date of death, and whether death was AIDS-related or not. This analysis was restricted to patients aged 20–59 years who had at least one CD4 count greater than 350 cells per μL while ART naive. All pre-ART ART naive patients.
CD4 counts greater than 350 cells per μL from January, 1990, to December, 2004, were included. The exclusion of CD4 cell counts after 2004 was to mitigate the effect of any delay in reporting of deaths. All CD4 cell counts measured during prospective follow-up were included—ie, after enrolment to a cohort while ART naive.

Statistical analysis

For each patient, the follow-up included was from the date of each eligible CD4 cell count until the earliest of next count, death, start of ART, or elapse of 1 year (figure 1).

Poisson regression methods were used to investigate the relation between death rate and CD4 cell count. Other factors included in the multivariate model were sex, risk group, age, current calendar year, and most recent viral-load measurement (no earlier than 6 months before the date of the included CD4 cell count). Hepatitis C co-infection and smoking status were also included as factors in models restricted to data from cohorts able to provide such data.

Three sensitivity analyses were done. In the first, follow-up was censored 6 months after each CD4 cell count instead of at 1 year, to test the assumption implicit in the main analysis that the most recent CD4 cell count was valid for up to 1 year. In the second, the main analysis was repeated but only follow-up after CD4 counts greater than 500 cells per μL was included, to establish whether there was a raised risk of death in this higher CD4 cell count range. In the third, to assess the effect of any possible underascertainment of deaths, the SMRs were calculated by use of data from only those cohorts that are known to be linked to national death registers.

All p values are two-sided. Analyses were done with SAS version 9.1 (Cary, NC, USA).

Role of the funding source

The study sponsors had no role in the study design, analysis, interpretation of data, writing of the report, or in the decision to submit the paper for publication. Final responsibility for the decision to submit for publication was held by the Analysis and Writing Committee.
Results

40 830 patients were included in the analysis, contributing 20 620 CD4 cell counts and 80 682 person-years of follow-up with a median of three CD4 cell counts per patient (IQR 1–6). Data for 11 713 (28.7%; 5.8% of CD4 counts) patients were censored because of ART initiation. The distribution of follow-up according to characteristics of patients is described in table 1. Most follow-up was from men (39 732 person-years, 74.1%), about half of follow-up was from men who have sex with men (39 732 person-years, 49.2%), and about half of follow-up was from patients age 30–39 years (38 112 person-years, 47.2%). 50 375 person-years of follow-up (62.4%) were in people with CD4 counts greater than 500 cells per μL. The most recent viral load was available for 48 478 person-years of follow-up (60.1%). Around a third of follow-up was from patients within cohorts linked to national death registers (27 206 person-years, 33.7%). Data on hepatitis C co-infection status were available from 16 of the 23 participating cohorts (37 322 person-years; 90.9% of total follow-up) and on smoking from nine cohorts (30 332 person-years; 33.7% of total follow-up).

419 (1.0%) patients died during follow-up, giving an overall mortality of 5.2 per 1000 person-years (95% CI 4.7–5.7). Of these, 61 (15%) deaths were categorised as AIDS-related, 188 (45%) were categorised as non-AIDS-related, and the cause was unknown for 170 deaths (41%).

The SMR analysis for pre-ART CD4 counts greater than 350 cells per μL included 38 997 patients (95.5% of the total): the SMR was 1.03 (95% CI 0.76–1.37). For CD4 counts greater than 350 cells per μL but with follow-up censored at 6 months after each CD4 cell count instead of at 1 year, the SMRs were slightly lower than in the main analysis at 0.75 (95% CI 0.60–0.93) for homosexual men, 2.74 (95% CI 2.05–3.60) for the heterosexual risk group, 9.35 (95% CI 7.93–10.94) for injecting drug users, and 3.30 (95% CI 1.96–5.22) for the other or unknown risk group. Restriction of the analysis to follow-up from patients within cohorts linked to national death registers resulted in slightly higher SMRs than in the main analysis, at 1.52 (95% CI 1.10–2.04) for men who have sex with men, 3.29 (95% CI 2.09–4.94) for the heterosexual risk group, 15.85 (95% CI 11.27–21.67) for injecting drug users, and 6.99 (95% CI 3.99–11.35) for the other or unknown risk group.

In a Poisson regression model fitted to the full dataset, a CD4 count greater than 500 cells per μL was associated with a lower risk of death than CD4 count between 350 cells per μL and 499 cells per μL (figure 2). The unadjusted risk ratios were 0.75 (95% CI 0.60–0.93) for CD4 counts of 500–699 cells per μL and 0.67 (95% CI 0.52–0.86) for counts of 700 cells per μL or greater, compared with 350–499 cells per μL (table 3). Significant predictors of death in univariate analyses were risk group, age, calendar year, and viral load. Sex and calendar year of CD4 cell count were not associated with the rate of death in univariate analyses, but were significant factors in the multivariate model. Viral load, which was available for only 60.1% of total follow-up, was not associated with death rate. After adjustment for the other factors in the model, the rate ratios for the CD4 cell count remained largely unchanged at 0.77 (95% CI 0.61–0.95) for counts of 500–699 cells per μL and 0.66 (95% CI 0.52–0.85) for counts of 700 cells per μL or greater, compared with 350–499 cells per μL.

Table 2: Observed death rates and standardised mortality ratios based on 77 936 person-years of follow-up from 38 997 patients

<table>
<thead>
<tr>
<th>Risk group</th>
<th>Observed deaths</th>
<th>Follow-up (person-years)</th>
<th>Death rate* (95% CI)</th>
<th>Expected deaths</th>
<th>SMR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men who have sex with men</td>
<td>100</td>
<td>38 764</td>
<td>2.58 (2.07–3.09)</td>
<td>76.79</td>
<td>1.30 (1.06–1.58)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>68</td>
<td>18 311</td>
<td>3.71 (2.83–4.60)</td>
<td>23.43</td>
<td>2.94 (2.28–3.73)</td>
</tr>
<tr>
<td>Other or unknown</td>
<td>30</td>
<td>4137</td>
<td>7.25 (4.66–9.85)</td>
<td>6.56</td>
<td>4.57 (3.09–6.53)</td>
</tr>
</tbody>
</table>

SMR=standardised mortality ratios. *Death rate per 1000 person-years.
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In the two models fitted to subsets of the data to include hepatitis C and smoking covariates respectively, the associations between CD4 cell count and death rate were consistent with those in the main model.

In a sensitivity analysis with follow-up censored at 6 months after each CD4 cell count instead of at 1 year, the association between CD4 cell count and the risk of death was similar. Compared with 350–499 cells per μL, the adjusted rate ratio for CD4 count 500–699 cells per μL was 0·71 (95% CI 0·55–0·92), and for CD4 count of 700 cells per μL was 0·67 (95% CI 0·50–0·89). When the analysis was restricted to CD4 counts greater than 500 cells per μL, there was no significant difference in the risk of death between the count categories (adjusted rate ratio for CD4 count 700 cells per μL or greater compared with 500–699 cells per μL: 0·84, 95% CI 0·65–1·10, p=0·22).

**Discussion**

Death rates in ART-naive people infected with HIV who have CD4 counts greater than 350 cells per μL tend to be higher than in the general population of industrialised countries. The increase in risk was substantial in injecting drug users and the heterosexual group but was small in men who have sex with men. This finding suggests that much of the raised risk in the former two risk groups probably results from confounding by socioeconomic and lifestyle factors,22 rather than being an effect of HIV infection itself. Consistent with this finding, an increased risk of death has been noted in the siblings of people with HIV infection compared with the siblings of a control population without HIV infection.23 We also noted that a higher CD4 cell count was associated with a lower risk of death, even in this high range, a trend that has previously been seen in patients on ART.24 There seems to be a moderate HIV-related risk of death in antiretroviral-naive people with high CD4 cell counts. This risk increase applies despite the very low risk of AIDS-related diseases at this CD4 cell count.24,25 This finding is consistent with the hypothesis that in people with high CD4 cell counts, HIV causes increased mortality risk.2–4,6–17

We identified a higher risk of death in men than in women, which is consistent with the situation in the general population. When investigating the association between CD4 cell count and risk of death, in multivariate models fitted to subsets of our data we were able to adjust for two potential confounding factors, hepatitis C co-infection and smoking history; the relation between death rate and CD4 cell count remained. We did not identify an association between plasma viral load and risk of death in the subset of patients for whom this information was available. This finding seems inconsistent with data suggesting an association between viral suppression and risk of non-AIDS-related diseases,4 although here we are comparing people with various unsuppressed viral loads.

To our knowledge there have been no substantive studies restricted to ART-naive people; however, several studies have compared death rates in individuals infected with HIV, including those on ART, with those for the general population. When investigating the association between CD4 cell count and risk of death, in multivariate models fitted to subsets of our data we were able to adjust for two potential confounding factors, hepatitis C co-infection and smoking history; the relation between death rate and CD4 cell count remained. We did not identify an association between plasma viral load and risk of death in the subset of patients for whom this information was available. This finding seems inconsistent with data suggesting an association between viral suppression and risk of non-AIDS-related diseases, although here we are comparing people with various unsuppressed viral loads.

To our knowledge there have been no substantive studies restricted to ART-naive people; however, several studies have compared death rates in individuals infected with HIV, including those on ART, with those for the general population, matched for factors such as age and sex.20–21 Although all such studies have shown an excess risk of death in people with HIV infection, some successfully treated subgroups of patients have been identified for whom death rates approach that of the general population. A study combining data from two French cohorts26 found that the death rate in patients with CD4 counts greater than 500 cells per μL reached that of the general population by the sixth year after starting ART, whereas a study on a collaboration of HIV seroconverter cohorts27 noted that, in the most recent period of follow-up (in which 73% of person-time was on ART), there was no excess mortality during the first 5 years after seroconversion in patients infected sexually when compared with the general population.

Patients included in this analysis had been diagnosed earlier than most HIV-positive people in these settings. Of patients presenting with HIV infection from 1996 to 2006 at selected clinics in the UK, 39% had an initial CD4 count greater than 350 cells per μL.22 Patients who are
diagnosed earlier might differ from patients diagnosed later in their attitudes towards health and access to health-care services.

Although several included cohorts are linked to national death registers, a further limitation is that possible underascertainment of deaths might have resulted in underestimation of death rates. This possibility is supported by the slightly higher SMRs seen in the sensitivity analysis restricted to data from cohorts linked to national death registers. The decrease in risk of death over calendar time identified in the multivariate model (table 3) could be due, at least partly, to a delay in the reporting of deaths.

Patients included in this study were under care at clinics linked to cohort studies and collaborations in Europe and North America. Results from this study might not be generalisable to all settings, either in clinics in these regions without research links, or in resource-limited settings.

In conclusion, these data suggest that people with HIV who have not taken ART and have CD4 count greater than 350 cells per μL have a raised risk of death compared with the general uninfected population, although the increase seems to be small. Because ART might reduce risk of death, underascertainment of deaths might have resulted in underestimation of death rates. This possibility is supported by the slightly higher SMRs seen in the sensitivity analysis restricted to data from cohorts linked to national death registers.

Contributors
All members of the analysis and writing committee participated in discussions on the design of the study, the choice of statistical analyses and interpretation of the findings, and were involved in the preparation and review of the final paper for submission. Additionally, Rebecca Lodwick and Andrew Phillips are responsible for doing all analyses, and Rebecca Lodwick acts as guarantor for the analyses and has full access to the dataset.

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References