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HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. — Source link

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Title page

HIV-infected adults with CD4 cell count above 500/mm^3 on long term combination antiretroviral therapy reach same mortality rates as the general population

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Running Head Survival in responders to HIV treatment

Abstract/ keyword page

Abstract

Objective. To compare mortality rates in combination antiretroviral therapy (cART) treated HIV-infected adults with mortality in the general population according to the level of CD4 reached and the duration of exposure to cART.

Methods. HIV-infected adults initiating a protease inhibitor-containing treatment between 1997 and 1999 were selected in the ANRS APROCO and AQUITAINE cohorts. CD4 counts were estimated during follow-up using a 2-phase mixed linear model. Standardized Mortality Ratios (SMRs) were computed in reference to the 2002 French population rates, overall and for the time period spent with CD4 cell count ≥ 500/mm^3. In order to identify if and when mortality rates reached values of the general population, SMRs were computed successively with truncation at each year of follow-up.

Results. The 2435 adults (77% men, baseline median age: 36 years, CD4: 270/mm^3) had a median follow-up of 6.8 years. SMR was 7.0 (95% confidence interval [CI]: 6.2-7.8). During the 5402 person-years spent with CD4 ≥500/mm^3, the mortality reached the level of the general population after the sixth year post-cART initiation (SMR: 0.5 [95%CI: 0.1-1.6]).

Conclusion. Although overall mortality was higher in cART-treated HIV-infected adults, a subgroup with especially good prognosis can be identified and these characteristics should be targeted for long-term treatment.

Keywords

antiretroviral therapy, highly active; CD4 cell count; HIV infection; mortality; response to treatment; standardized mortality ratio

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Introduction

The availability of combination antiretroviral therapy (cART) has resulted in immune restoration in the majority of treated HIV-infected patients and in a dramatic decrease in AIDS related mortality[1,2,3]. Providing treatment is taken daily and there is a regular follow-up, most cART treated individuals have a social life that may include working, having children or buying a house, since life expectancy has dramatically improved. Studies considering short-term or mid-term follow-up after cART initiation have shown that mortality remained higher in HIV-infected individuals in the cART period than in the general population, in France[4], in Switzerland[5,6] and in Denmark[7]. However, early favorable viro-immunologic response to treatment has proven to be associated with a longer survival regardless of the initial CD4 and plasma HIV-RNA values[8]. We hypothesized that high values of CD4 attained might allow these patients to reach the same mortality rates as those of the general population on the long term. We thus compared mortality rates in HIV-infected adults after the first cART prescription with the mortality of the general population of the same age and gender according to the level of CD4 reached and according to the duration of exposure to cART.

Methods

HIV-infected adults who started a cART containing a protease inhibitor (PI) for the first time in 1997-99 were identified from two well-established cohorts. Indeed, PI-containing regimens were the first available cART and exposure to this category of cART is therefore the longest that can be observed among treated patients. Patients selected for this study may have been previously exposed to mono- or dual-therapy of nucleoside reverse transcriptase inhibitors. The ANRS CO8 APROCO-COPILOTE cohort is a prospective observational study that enrolled consecutively 1281 HIV-1 infected adults in 47 hospital departments in France starting a PI-containing treatment for the first time in 1997-1999[9]. Standardized clinical and biological data were collected at baseline, after one and four months of cART and every four months thereafter. Investigators were requested to notify deaths to the data management centre as soon as known and regular monitoring rounds were organized in order to monitor consistency between hospital files and case report forms. The ANRS CO3 AQUITAINE Cohort was implemented in 1987 by the "Groupe d'Epidemiologie Clinique du Sida en Aquitaine" (GECSA) based on a public hospital surveillance system of HIV-infected adults in the Aquitaine region of southwest France[10]. Standardized clinical and biological data are collected at each hospital contact and at least every six months. An active search of patients lost-to-follow-up is performed yearly. In both cohorts, patients signed informed consent. Duplicate patient records between the two databases were excluded. We considered data on patients who remained alive up to December 31st, 2005 or until loss to follow-up or death. Death rates were calculated per 100 person-years (PY). Standardized mortality ratios (SMR) were estimated with reference to the 2002 French general population death rates stratified for gender and for every 10 years of age[11] and the 95% confidence intervals (CI) of the SMRs were estimated by Byar's approximation of the Poisson method[12].

CD4 cell counts during follow-up were estimated using a mixed linear model to take into account unbalanced data due to missing at random measurements[13] and measurement error[14]. Square root of CD4+ values were fitted using a piecewise linear model allowing for a change of slope at four months[15] and adjusted for baseline covariates: age, clinical AIDS

stage, plasma HIV-RNA, history of antiretroviral treatment and HIV transmission (injecting drug use versus others). For each year of age during follow-up, three values of CD4 cell count were estimated (every four months) and the lowest value of the year was classified in the following categories: ≥ 500/mm^3, 350 to 499/mm^3, 200 to 349/mm^3 or <200/mm^3. Death rates and SMRs were estimated for the cumulated time period spent within each category of CD4 cell count.

In order to identify if and when during follow-up mortality rates reached values of the general population, we performed successive selections of patients with long term follow-up. SMRs were computed successively with truncation at each year of follow-up for the two highest categories of CD4 cell count (≥ 500 and 350 to 499/mm^3). For instance, for the analysis of time spent with CD4 cell count ≥ 500/mm^3 and truncation at six years, a patient still followed eight years after cART initiation may contribute to the analysis for the time spent with CD4 cell count ≥ 500/mm^3 only after the sixth year of follow-up.

SMRs were also estimated according to HIV transmission group (injecting drug use versus others) and hepatitis C virus (HCV) co-infection as defined by the presence of HCV antibody or plasma HCV-RNA at baseline, since similar types of analyses reported higher mortality ratios in these groups[5,6].

The underlying cause of death was ascertained with data available in the hospital file according to the International Classification of Diseases (ICD)-10th revision (ICD-10) rules[16] and adapted to the specificities in HIV infection[17].

Statistical analyses were performed using Statistical Analysis System software (SAS, version 9.1).

Results

A total of 2435 patients (1281 from the APROCO-COPILOTE cohort, 1154 from the AQUITAINE cohort) were included in the analysis. Median age was 36 years, 77% were men, HIV transmission categories were homo-bisexual in 38%, heterosexual in 35%, and injecting drug use in 21% of cases. Overall, 29% of patients were HCV-infected (88% among patients infected through injecting drug use). The median CD4 cell count was 270/mm^3 at the time of cART initiation, 16% had CD4 cell count ≥500 /mm^3 and 19% had CD4 cell count between 350 and 499 /mm^3. At baseline, 22% had a previous AIDS-defining clinical event, 39% had previously received an antiretroviral treatment with one or two drugs and the first PI prescribed was indinavir in 43%, nelfinavir in 31%, saquinavir in 16% and ritonavir in 15%. Estimated CD4 cell counts were ≥500/mm^3 in 39% of the 1949 patients still followed at three years after cART initiation and in 49% of the 1430 still followed at six years (figure 1). During a median follow-up of 6.8 years (interquartile range IQR 4.1 to 7.9; 13970 PY), 288 individuals died, 2.1 deaths per 100 PY (95%CI: 1.8 to 2.3). Overall mortality was 7.0 times higher than in the general population, 4.8 in men and 13.0 in women, 16.3 in injecting drug users and 13.9 in HCV co-infected patients (table 1). Considering the total time spent within each category of CD4 cell count, mortality remained higher than in the general population in all categories and SMR were gradually higher as CD4 cell counts were lower (table 2). However, in patients with CD4 cell count ≥500/mm^3, mortality reached the level of the general population after the sixth year following initiation of cART: SMR: 0.5 (95% CI: 0.1 to 1.6), (table 3). Considering the time spent in the category of CD4 cell count from 350 to 499, SMR was lower after six years, but remained around twice the mortality of the general population (table 4). Overall, the underlying cause of death was AIDS-related in 35% of cases, and in 52%, 21%, 15% and 8% when CD4 cell count at the age of death was <200/mm^3, 200 to 349/mm^3, 350 to 499/mm^3 and ≥ 500/mm^3, respectively.

Discussion

In this study with a median follow-up of seven years after cART initiation, age and gender-adjusted overall mortality remained seven-fold higher in HIV-infected adults than in the general population. However, the mortality rate became similar to that of the general population after the sixth year of follow-up among patients whose CD4 cell counts had reached 500/mm^3.

Since we aimed at identifying if and when during follow-up mortality rates reached values of the general population, we selected patients that had the highest CD4 cell count and were followed on the long term. Therefore, we cannot exclude a survivor bias and we acknowledge that these results only apply to a specific subgroup. Nevertheless, identifying patients with the best prognosis, regardless of their history, may help identifying therapeutic objectives and formulate guidelines. That is the reason why we did not adjust for potential confounding factors such as previous ARV exposure, baseline CD4 cell count and HIV-RNA, type of treatment received as we would have done in a classical prognosis study.

We acknowledge that our analysis may have some limitations. For this analysis, we considered that the two cohorts studied were similar enough to be pooled since they took place in the same country where guidelines for the case management of HIV-infected are generally well known and followed by physicians[18]. Moreover, epidemiological and biostatistical support, as well as data management, are coordinated by the same epidemiology unit.

The level of CD4 cell count is known as a strong prognostic factor for the occurrence of AIDS-defining events and death. In our study, the proportion of non AIDS-related causes of death increased with higher CD4 cell count. Achieving the level of 500 /mm^3 appeared to be associated with the same rates of mortality as among the general population after six years following cART, whereas it was still higher during shorter time of follow-up. Among patients who spent time with CD4 cell count between 350 and 499 /mm^3, mortality remained higher than in the general population. Several interpretations of these observations are possible. First, the level of CD4 is associated with mortality even above 200/mm^3 because of the

persistence of AIDS-defining or HIV-associated morbidities. For instance non-Hodgkin's lymphoma remains a frequent cause of death among treated HIV-infected patients[17]. Second, non-AIDS defining morbidities such as bacterial infections or cancers may occur more frequently at an intermediate level of CD4 cell count[19]. Nevertheless, even among patients with the highest category of CD4 cell count, the reason for the long period of time needed to reach the same mortality rates as in the general population remains to be clarified. We hypothesize that immune restoration after HIV infection may be a long lasting process and that time is necessary to recover immune functions able to reduce mortality to the same level as in the general population. Another hypothesis may be that patients without severe co-morbidities succeed more frequently in reaching a high CD4 cell count and maybe a longer time of follow-up.

Published studies reported higher mortality in HIV-infected persons compared with the general population[4,6,7]. Van Sighem et al found higher mortality in HIV-infected patients in the Netherlands even after having selected patients followed up for at least six months and taking into account the CD4 cell count six months after cART initiation[20]. In the Swiss cohort, Jaggy et al reported a moderate excess of death rates, compared with the general population, when the CD4 cell count reached 250/mm^3 at least once after cART[5].

Our analysis does not take into account some confounding factors that might at least partly explain differences in mortality rates. Firstly, the risk of death from cardiovascular diseases or cancer might be related to the high proportion of smokers among HIV-infected individuals[21,22]. Secondly, injecting drug users have a higher risk of death from overdose and violence[23]. They are frequently co-infected by HCV that exposes them to cirrhosis and hepatocarcinoma. In fact mortality was higher among injecting drug users and HCV-infected patients in our analysis, in agreement with other studies[5,6,24]. None of these characteristics was available in databases of the general population, nor were socioeconomic conditions or levels of education, which are associated with higher mortality both in the general population[25] and in treated HIV-infected patients[26]. Confounding factors may thus explain the higher overall mortality compared with the general population and the higher SMR in women

than in men, agreeing with a previous analysis in the APROCO-COPILOTE cohort[4] and with other reports[6]. The less favorable prognosis observed in HIV-infected women as compared to women of the general population could reflect a less favorable socio-demographic status of HIV-infected women as well as a higher frequency of co-morbidities (29% of women were infected through injecting drug use and 30% were HCV-infected). Other time-dependent markers of HIV progression, e.g. HIV-RNA, are associated with mortality in the long term. Nevertheless, to our knowledge, the additional effect of HIV-RNA on mortality in patients with high CD4 cell count was not reported so far and would probably be weak.

Although patients who started a PI-containing cART may not be representative of patients having started cART with more recent combinations, they can be considered as representative of the large number of patients, approximately 35,000 in France, who started cART in the years 1997-99, who have currently the longest follow-up under cART. We excluded the year 1996 since it was the first year of cART being available in France and an intermediate period of implementation with heterogeneous practices. We can hypothesize that patients who started cART later than 1999 may have a better prognosis as therapeutic strategies have improved[2] and that they may reach more rapidly the same mortality than the general population.

These results remain to be confirmed in other populations and cohort collaborations may address this question with a larger sample size and a longer follow-up. Nevertheless, we believe that communicating these results to patients and physicians is already crucial to assist them in maintaining their efforts to achieve and sustain high CD4 cell counts through sustained adherence to cART. We acknowledge that our results are derived from a method using a selection of subgroups of patients and may therefore be only generalized to this specific population.

In countries where a certificate of health status is required to obtain insurance contracts and loans, HIV infection with a favorable response to treatment in the long term might no longer be considered as an obstacle based on our observations. In order to improve prognosis in the majority of HIV-infected patients, medical teams should go through all known factors

associated with suboptimal response to treatment, i.e. tolerance, adherence, social support or care of depression, to achieve the goal of sustained immune reconstitution. In addition to identifying factors that may hinder this objective[27], operational tools to improve complete therapeutic success should be developed and evaluated.

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ANRS CO8 APROCO-COPILOTE Study Group (see Appendix)

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ANRS CO3 AQUITAINE Cohort (see Appendix)

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Appendix

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