

RESEARCH ARTICLE

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Mortality by causes in HIV-infected adults: comparison with the general population

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Abstract

Background: We compared mortality by cause of death in HIV-infected adults in the era of combined antiretroviral therapy with mortality in the general population in the same age and sex groups.

Methods: Mortality by cause of death was analyzed for the period 1999-2006 in the cohort of persons aged 20-59 years diagnosed with HIV infection and residing in Navarre (Spain). This was compared with mortality from the same causes in the general population of the same age and sex using standardized mortality ratios (SMR).

Results: There were 210 deaths among 1145 persons diagnosed with HIV (29.5 per 1000 person-years). About 50% of these deaths were from AIDS. Persons diagnosed with HIV infection had exceeded all-cause mortality (SMR 14.0, 95% CI 12.2 to 16.1) and non-AIDS mortality (SMR 6.9, 5.7 to 8.5). The analysis showed excess mortality from hepatic disease (SMR 69.0, 48.1 to 78.6), drug overdose or addiction (SMR 46.0, 29.2 to 69.0), suicide (SMR 9.6, 3.8 to 19.7), cancer (SMR 3.2, 1.8 to 5.1) and cardiovascular disease (SMR 3.1, 1.3 to 6.1). Mortality in HIV-infected intravenous drug users did not change significantly between the periods 1999-2002 and 2003-2006, but it declined by 56% in non-injecting drug users ($P = 0.007$).

Conclusions: Persons with HIV infection continue to have considerable excess mortality despite the availability of effective antiretroviral treatments. However, excess mortality in the HIV patients has declined since these treatments were introduced, especially in persons without a history of intravenous drug use.

Background

The expansion of combined antiretroviral treatments in the developed countries has been followed by substantial reductions in the incidence of AIDS-defining conditions and mortality among HIV-infected persons [1,2]. With these treatments and in the absence of other risk factors, mortality in HIV-infected persons approaches that of similarly aged persons with chronic diseases and is becoming closer to mortality in the general population of a similar age [3-5].

Mortality in HIV-infected persons depends on the duration of infection, age at the time of seroconversion and the effectiveness of the antiretroviral treatment [6]; this, in turn, depends on when treatment was started, whether previous treatment responses have been suboptimal, and the presence of coinfections [7,8]. Combined

antiretroviral treatments were introduced when many countries had a considerable number of HIV- infection with long evolution of the disease and other comorbidities. These factors have meant that the real impact of these treatments on mortality has been less than what could be reached under ideal conditions. Various studies have related these treatments with substantial reductions in mortality from AIDS-defining conditions, but mortality from other causes may decrease to a lesser extent or may remain stable [8-10].

Many studies evaluating the effect of combined antiretroviral treatments on mortality in HIV-infected persons have been done in cohorts of patients during clinical follow-up [11], or who were being followed up regularly in HIV clinics [3,4,12,13], or who were beginning to receive combined antiretroviral treatment [14,15]. However, such studies may under-represent persons who died before the beginning medical follow-up, do not have regular check-ups, are difficult to recruit, or died from causes unrelated to HIV infection. Accordingly,

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such studies may describe scenarios that could be overly optimistic and not representative of the entire population of people living with HIV.

The objective of this study was to analyze total mortality and mortality by cause of death in a population-based cohort of adults diagnosed with HIV during a period of wide availability of combined antiretroviral treatments and to compare it with mortality in the general population of the same age and sex and living in the same region.

Methods

This study analyzed the population-based cohort of persons residing in the region of Navarre (approximately 600,000 inhabitants), Spain, with a diagnosis of HIV infection confirmed by Western blot. The information was obtained from the HIV epidemiological surveillance system that was launched in Navarre in 1991. All HIV-infected patients diagnosed by laboratories of the region were incorporated retrospectively, followed by a continuous active search of all new laboratory-confirmed cases and patients attended in clinical centers [16,17]. Information on AIDS diagnoses was completed by reviewing the AIDS case register [16], and information on vital status was completed by reviewing the regional mortality records [18]. These data sources include AIDS diagnoses and deaths among Navarre residents occurred both within and outside the region that are reported at national level. To rule out the possibility of undetected HIV cases, AIDS diagnoses or deaths outside the region, additional searches were made in the dataset of hospital discharges, in the national AIDS registry, and in the national death index of Spain [19] (Table 1). All individuals who maintained their residence in Navarre and who were not shown as dead in any of these sources were considered to be alive at the end of the follow-up.

Most HIV infections in Navarre have occurred in intravenous drug users, although sexual transmission has predominated in recent years. The entire population

of the region has easy and free access to medical care and to the HIV test. Combined antiretroviral treatments are free and have been available since 1996 in accordance with internationally accepted treatment protocols [17].

The present analysis was limited to persons aged 20-59 years with stable residency in Navarre during the study period. The follow-up starting date was considered to be the date when HIV infection was diagnosed, the date when the person reached 20 years of age or 1 January 1999, whichever was latest. Follow-up of subjects was ceased at death or on 31 December 2006 for those who survived to that date. We calculated the mortality rates by cause of death, taking the number of person-years (PY) of follow-up as the denominator.

The reference population consisted of persons aged 20-59 years residing in Navarre according to the census data at the beginning of each study year, minus the number of person-years of follow-up corresponding to persons diagnosed with HIV infection. Deaths in the reference population were obtained from the regional mortality registry, and the number of deaths occurred in persons diagnosed with HIV were subtracted from it. The primary cause of death according to the International Classification of Diseases 10th edition was also obtained from this mortality registry [20].

The causes of death were grouped into the following categories: AIDS or HIV infection (B20-B24, R75), hepatic disease (B15-B19, B70, K73, K74, K769), non-AIDS defining cancers (C00-D48), drug addiction and overdose (F11, F16, F18, F19, X41, X42, X44, X45), cardiovascular disease (I00-I99), suicide (X60-X84), and other external causes (V01-Y89, excluding codes included in the preceding categories). Death certificates were reviewed from deaths coded as B20.3 and B23.8, and when the cause of death was liver disease or cirrhosis it was reclassified in the category of liver diseases rather than AIDS [20]. Deaths from acute pulmonary edema or other non-specific causes in parenteral drug users were reviewed taking the forensic report into account.

Mortality in persons diagnosed with HIV infection was compared with mortality in the rest of the population by calculating standardized mortality ratios (SMR) adjusted for sex and 5-year age groups; the 95% confidence intervals were obtained by applying the Poisson distribution. The analyses were stratified by sex and history of intravenous drug use to rule out the influence of such variables in the mortality comparisons.

Mortality in the HIV-infected cohort during the period of 1999-2002 was compared with that of during the period of 2003-2006 using Cox regression models, with age as the underlying time variable. Exit time was defined as the date of death or the end of the period, whichever came first.

Table 1 Information sources used

| Sources of information | Use |
|---|--|
| Epidemiological surveillance system of cases diagnosed with HIV-infection: active search of cases in records of laboratories and clinicians | Main source of HIV-infected cases |
| Hospital discharges database | Complementary source for quality control of HIV-infected cases |
| Regional AIDS-register | Main source of cases with AIDS-defining conditions |
| National AIDS-register | Complementary source for quality control of AIDS cases |
| Regional mortality register | Main source for deaths |
| National death index | Complementary source for quality control of deaths |

The χ^2 test was used to compare proportions and values of $P < 0.05$ were considered to be significant.

Results

Characteristics of the HIV-infected subjects who died

On 1 January 1999, there were 879 individuals aged 20-59 years in follow-up in Navarre who had been diagnosed with HIV infection, and 266 new cases were added by the end of 2006. Of all these cases, 68% were men, 63% had a history of intravenous drug use, and 35% had a previous diagnosis of AIDS or were diagnosed with AIDS during follow-up. Between 1999 and 2006, there were 210 deaths among individuals in follow-up (29.5 per 1000 person-years) with a higher rate of deaths in men (34.2 per 1000 PY), in intravenous drug users (33.5 per 1000 PY), and in persons previously diagnosed with AIDS (67.1 vs. 15.2 per 1000 PY, $P < 0.001$). Over half of those included in the cohort had been diagnosed with HIV infection at least 5 years before, and mortality was higher in this group (Table 2).

50.5% of deaths were due to AIDS-defining conditions, 17.1% due to liver diseases, 11.0% due to drug overdose

or addiction, 8.1% due to non-AIDS-defining cancers, 3.8% due to cardiovascular disease and 3.3% due to suicides.

The median time from HIV diagnosis to death was 11.4 years. About 5.2% ($n = 11$) of the deaths occurred in the first 3 months after the HIV diagnosis. This percentage was higher in parenteral drug users (16.3% vs. 1.9%, $P < 0.001$). Ten of these deaths were from AIDS-defining conditions and one from hepatic disease.

Comparison with the general population

Mortality among persons diagnosed with HIV was 14 times higher than mortality in the general population of the same sex and age groups (SMR, 14.0; 95% CI, 12.2 to 16.1); after excluding deaths from AIDS, high mortality in individuals with HIV persisted and was 6.9 times higher (5.7 to 8.5). Such high mortality in persons diagnosed with HIV was mainly from the liver disease (SMR 69.0, 48.1 to 78.6), drug overdose or addiction (SMR 46.0, 29.2 to 69.0) and suicide (SMR 9.6, 3.8 to 19.7) and, in lesser measure, from non-AIDS defining cancers (SMR 3.2, 1.8 to 5.1), cardiovascular disease (SMR 3.1,

Table 2 Characteristics of persons included in the cohort of HIV-infected subjects, and number and rate of deaths according to these characteristics; Navarre, Spain, 1999-2006

| | HIV-infected subjects | | | Deaths | | P-value |
|-------------------------|-----------------------|-----|--------------|--------|----------------------------|---------|
| | N | % | Person-years | N | Rate per 1000 person-years | |
| Sex | | | | | | <0.001 |
| Male | 781 | 68 | 4734 | 162 | 34.2 | |
| Female | 364 | 32 | 2379 | 48 | 20.2 | |
| Risk categories | | | | | | <0.001 |
| Injecting drug users | 721 | 63 | 4839 | 162 | 33.5 | |
| Homo-/bisexual men | 85 | 7 | 478 | 5 | 10.5 | |
| Heterosexual | 263 | 23 | 1328 | 34 | 25.6 | |
| Other/unknown | 76 | 7 | 877 | 9 | 10.3 | |
| Country of origin | | | | | | 0.398 |
| Spain | 1024 | 89 | 6655 | 200 | 30.0 | |
| Other | 121 | 11 | 458 | 10 | 21.8 | |
| AIDS-defining condition | | | | | | <0.001 |
| Yes | 402 | 35 | 1967 | 132 | 67.1 | |
| No | 743 | 65 | 5146 | 78 | 15.2 | |
| Year of HIV diagnosis | | | | | | <0.001 |
| 1990 or before | 307 | 27 | 1744 | 76 | 43.6 | |
| 1991-1995 | 354 | 31 | 1779 | 75 | 42.2 | |
| 1996-1999 | 242 | 21 | 1787 | 35 | 19.6 | |
| 2000-2006 | 242 | 21 | 1802 | 24 | 13.3 | |
| Total | 1145 | 100 | 7113 | 210 | 29.5 | |

P value for comparison of rates within categories.

1.3 to 6.1) and other causes (SMR 5.1, 2.3 to 9.7). Excess mortality in persons diagnosed with HIV was more pronounced in those who had a history of intravenous drug use (SMR 17.7, 15.2 to 20.8) than in those who did not (SMR 8.2, 6.0 to 11.0). Among the former group, there was notably increased mortality from causes other than AIDS (SMR 9.6, 7.7 to 12.0); especially from liver disease (SMR 96.6, 65.2 to 138.1) and from drug overdose or addiction (SMR 63.4, 40.2 to 95.1) (Table 3).

Among non-injecting drug users, mortality from causes other than AIDS (SMR 2.7, 1.6 to 4.4) was still higher than the general population but less than that among the intravenous drug users. In non-injecting drug users the increase in mortality was again primarily due to liver diseases (SMR 28.4, 10.4 to 62.0) (Table 3).

Cox regression models were used to compare mortality in the cohort of HIV-infected persons between the periods of 1999-2002 and of 2003-2006, adjusted for sex, age, intravenous drug use and country of origin. AIDS mortality in HIV-infected persons decreased by 37% (adjusted hazard ratio [HR] 0.63; 95% CI 0.42-0.95; $P = 0.026$). Mortality in intravenous drug users remained high with a non-statistically significant change between the two periods (HR 0.85; 95% CI 0.60-1.19; $P = 0.336$), whereas mortality in non-injecting drug users decreased by 56% (HR 0.44; 95% CI 0.24-0.79; $P = 0.007$), with a 51% reduction in mortality caused by AIDS (HR 0.49; 95% CI 0.24-1.02; $P = 0.057$) and 67% reduction in mortality from causes other than AIDS (HR 0.33; 95% CI 0.11-0.96; $P = 0.041$) (Table 4).

Discussion

Persons diagnosed with HIV infection had considerable excess mortality in comparison with the general population of the same age group and sex, despite wide availability of combined antiretroviral treatments. This excess mortality was largely due to deaths from AIDS-defining conditions, but other causes of death were also important, such as drug overdose or addiction, hepatic disease, non-AIDS-defining cancers, and cardiovascular disease. Excess mortality associated with HIV infection was observed in both men and women, and in persons with and without a history of injecting drug use.

Numerous studies have reported substantial reductions in mortality in HIV-infected persons after the introduction of combined antiretroviral treatments [21,22], the same as we found in Navarre [9]. Nonetheless, mortality in this group is still 14 times higher than in the general population after adjusting for sex and age group. Some studies have found somewhat lower excess mortality [23], but different results could be explained by the epidemiological characteristics of those infected, time of evolution of the infection, and whether or not persons who are not receiving antiretroviral treatment

are included. Health authorities should be alert not only to those causes with relative excess mortality, but also to those that are responsible for the largest absolute number of deaths.

In the era of combined antiretroviral treatments, mortality among persons diagnosed with HIV has continued to decline, mainly in those without a history of injecting drug use [21], but is still a long way from reaching mortality levels similar to those in the general population [5].

We found that the weight of AIDS-defining diseases has decreased in favor of other causes, although they continue to be the leading cause of death in HIV-infected persons [24]. Possible explanations for this include delayed diagnosis of HIV infection, HIV-infected subjects who refuse to receive antiretroviral treatment, and low adherence to these treatments. Delayed diagnosis has been detected in 37% of cases of HIV-infection diagnosed in Spain [25]. People who are unaware of their infection probably have a higher risk of death than diagnosed subjects, thus earlier diagnosis would reduce the excess mortality. Some misclassification is also possible since doctors may be prone to certify deaths in HIV-infected subjects as due to AIDS; however, this is unlikely because classification of a death as due to AIDS requires the presence of an AIDS-defining condition.

Liver diseases were the second cause of death in persons living with HIV, which may be explained by coinfections with hepatitis B or C viruses, which share the same sexual and parenteral mechanisms of transmission as HIV, and by high levels of alcohol and drug use [26]. Of note is the high mortality associated with drug overdose or addiction [14,27], which could have previously been partly masked by AIDS mortality and may only now be coming to the fore due to improved survival in HIV infection [4]. Excess cardiovascular mortality has been related with some antiviral treatments [28], but recent studies suggest an effect of the infection itself [29]. Non-AIDS-defining cancers play a larger than expected role as a cause of death in HIV-infected persons [30], comprising 8% of deaths, a percentage close to that found in other studies [31]. Among the explanations offered for these types of cancer are HIV-induced immunosuppression and the high frequency of unhealthy habits like smoking [32]. Combined antiretroviral treatments may be reducing the mortality of both AIDS-defining and non-AIDS-defining cancers [33]. In agreement with other studies, we found a high mortality from suicide among HIV-infected persons [34]. Despite advances in the treatment of HIV infection and increased survival in these patients, their mortality rates remain higher than those in the general population [35]. Only by investigating the factors that determine these causes of death will we be able to act on them.

Table 3 Standardized mortality ratio by cause of death, injecting-drug status and sex in HIV-infected subjects compared with persons in the general population not diagnosed with HIV infection; Navarre, Spain, 1999-2006

| | Observed deaths | Expected deaths | Standardized mortality ratio | (95% CI) |
|----------------------------------|-----------------|-----------------|------------------------------|--------------|
| All HIV-infected subjects | | | | |
| All-cause deaths | 210 | 15.0 | 14.0 | (12.2-16.1) |
| Non-AIDS deaths | 104 | 15.0 | 6.9 | (5.7-8.5) |
| Liver disease | 36 | 0.5 | 69.0 | (48.1-78.6) |
| Non-AIDS defining cancer | 17 | 5.4 | 3.2 | (1.8-5.1) |
| Drug overdoses or addiction | 23 | 0.5 | 46.0 | (29.2-69.0) |
| Cardiovascular disease | 8 | 2.6 | 3.1 | (1.3-6.1) |
| Suicide | 7 | 0.7 | 9.6 | (3.8-19.7) |
| Other external causes | 4 | 3.0 | 1.3 | (0.4-3.4) |
| All other causes | 9 | 1.8 | 5.1 | (2.3-9.7) |
| Injecting drug users | | | | |
| All-cause deaths | 162 | 9.1 | 17.7 | (15.2-20.8) |
| Non-AIDS deaths | 88 | 9.1 | 9.6 | (7.7-12.0) |
| Liver disease | 30 | 0.3 | 96.6 | (65.2-138.1) |
| Non-AIDS defining cancer | 12 | 3.0 | 4.0 | (2.1-7.0) |
| Drug overdoses or addiction | 23 | 0.4 | 63.4 | (40.2-95.1) |
| Cardiovascular disease | 6 | 1.5 | 4.0 | (1.5-8.6) |
| Suicide | 5 | 0.5 | 10.8 | (3.5-25.3) |
| Other external causes | 4 | 2.0 | 2.0 | (0.5-5.1) |
| All other causes | 8 | 1.1 | 7.3 | (3.2-14.4) |
| Non-injecting drug users | | | | |
| All-cause deaths | 48 | 5.9 | 8.2 | (6.0-11.0) |
| Non-AIDS deaths | 16 | 5.9 | 2.7 | (1.6-4.4) |
| Liver disease | 6 | 0.2 | 28.4 | (10.4-62.0) |
| Non-AIDS defining cancer | 5 | 2.3 | 2.1 | (0.7-5.0) |
| Drug overdoses or addiction | 0 | 0.1 | 0 | |
| Cardiovascular disease | 2 | 1.1 | 1.8 | (0.2-6.6) |
| Suicide | 2 | 0.3 | 7.4 | (0.89-26.6) |
| Other external causes | 0 | 1.0 | 0 | |
| All other causes | 1 | 0.7 | 1.5 | (0.04-8.2) |
| Male | | | | |
| All-cause deaths | 162 | 12.5 | 12.9 | (11.0-15.1) |
| Non-AIDS deaths | 78 | 12.5 | 6.2 | (4.9-7.9) |
| Liver disease | 25 | 0.5 | 54.1 | (35.0-80.1) |
| Non-AIDS defining cancer | 13 | 4.1 | 3.1 | (1.7-5.4) |
| Drug overdoses or addiction | 20 | 0.5 | 43.3 | (26.5-66.7) |
| Cardiovascular disease | 6 | 2.4 | 2.5 | (0.9-5.6) |
| Suicide | 4 | 0.5 | 7.3 | (2.0-18.7) |
| Other external causes | 3 | 2.7 | 1.1 | (0.2-3.3) |
| All other causes | 7 | 1.4 | 5.0 | (2.0-10.2) |
| Female | | | | |
| All-cause deaths | 48 | 2.5 | 19.5 | (14.2-26.1) |
| Non-AIDS deaths | 26 | 2.5 | 10.6 | (6.9-15.5) |
| Liver disease | 11 | 0.1 | 183.3 | (91.5-328.1) |
| Non-AIDS defining cancer | 4 | 1.2 | 3.3 | (0.9-8.3) |
| Drug overdoses or addiction | 3 | 0.04 | 78.5 | (16.2-229.3) |

Table 3 Standardized mortality ratio by cause of death, injecting-drug status and sex in HIV-infected subjects compared with persons in the general population not diagnosed with HIV infection; Navarre, Spain, 1999-2006 (Continued)

| | | | | |
|------------------------|---|-----|------|------------|
| Cardiovascular disease | 2 | 0.2 | 8.0 | (1.0-29.0) |
| Suicide | 3 | 0.2 | 16.4 | (3.4-47.8) |
| Other external causes | 1 | 0.3 | 2.9 | (0.1-16.4) |
| All other causes | 2 | 0.4 | 5.5 | (0.7-20.0) |

Our study provides a population-based view of mortality by causes of death in HIV-infected people, including cases and events that could be not detected in clinical cohorts. Therefore, we have not included some baseline variables such as antiretroviral treatments, viral load and CD4 cell count which are relevant from a clinical perspective.

Losses to follow-up are one of the main sources of bias in follow-up studies. We tried to reduce such losses in our study by searching for subjects in a variety of information sources in order to detect or rule out their death. AIDS-related deaths included those due to AIDS-defining conditions, including opportunistic infections, some cancers and tuberculosis, which are the most frequent but not exclusive causes of death in persons with HIV-infection. We partly overcame this problem of comparability with the general population by not

including deaths from liver disease in HIV-infected persons as deaths from AIDS. However, it was not possible to compare persons with HIV and the general population with respect to deaths from AIDS-defining diseases. Our results are marked by the epidemiological pattern in the study area, which is characterized by a predominance of HIV infections acquired in relation with injecting drug use [17]. Thus, they may not be generalized to other areas with a different epidemiological pattern.

Conclusions

In the era of combined antiretroviral treatments, we still find considerable excess mortality in persons living with HIV. Since these treatments were introduced, advances have continued to be made in reducing this excess mortality, especially in persons without a history of injecting drug use. Further reduction will require improvements

Table 4 Comparison of mortality by cause of death in HIV-infected cohort in the periods 1999-2002 and 2003-2006; Navarre, Spain.

| | Period 1999-2002 | | Period 2003-2006 | | Hazard ratio* | (95% CI) | P-value |
|----------------------------------|------------------|------------------|------------------|------------------|---------------|-------------|---------|
| | Cases | Rate per 1000 PY | Cases | Rate per 1000 PY | | | |
| All HIV-infected subjects | | | | | | | |
| All-cause deaths | 115 | 32.6 | 95 | 26.5 | 0.72 | (0.54-0.96) | 0.024 |
| AIDS deaths | 62 | 17.6 | 44 | 12.3 | 0.63 | (0.42-0.95) | 0.026 |
| Non-AIDS related deaths | 53 | 15.0 | 51 | 14.2 | 0.82 | (0.54-1.23) | 0.325 |
| Liver disease | 14 | 4.0 | 22 | 6.1 | 1.34 | (0.66-2.72) | 0.420 |
| Non-AIDS defining cancer | 10 | 2.8 | 7 | 2.0 | 0.47 | (0.17-1.30) | 0.145 |
| Drug overdoses or addiction | 14 | 4.0 | 9 | 2.5 | 0.63 | (0.26-1.53) | 0.307 |
| Cardiovascular disease | 3 | 0.9 | 5 | 1.4 | 1.12 | (0.25-5.06) | 0.880 |
| Suicide | 3 | 0.9 | 4 | 1.1 | 1.26 | (0.26-6.04) | 0.776 |
| Other external causes | 3 | 0.9 | 1 | 0.3 | 0.21 | (0.02-2.16) | 0.190 |
| All other causes | 6 | 1.7 | 3 | 0.9 | 0.58 | (0.13-2.50) | 0.461 |
| Injecting drug users | | | | | | | |
| All-cause deaths | 85 | 33.5 | 77 | 33.5 | 0.85 | (0.60-1.19) | 0.336 |
| AIDS deaths | 43 | 16.9 | 31 | 13.5 | 0.68 | (0.41-1.13) | 0.132 |
| Non-AIDS related deaths | 42 | 16.5 | 46 | 20.2 | 1.02 | (0.65-1.61) | 0.933 |
| Non-injecting drug users | | | | | | | |
| All-cause deaths | 30 | 30.4 | 18 | 14.0 | 0.44 | (0.24-0.79) | 0.007 |
| AIDS deaths | 19 | 19.3 | 13 | 10.1 | 0.49 | (0.24-1.02) | 0.057 |
| Non-AIDS related deaths | 11 | 11.2 | 5 | 3.9 | 0.33 | (0.11-0.96) | 0.041 |

PY, person-years. CI, confidence interval.

*Hazard ratio obtained in Cox regression models with age as underlying time variable and adjusted for sex, country of origin (Spain or others) and injecting drug use.

in early diagnosis of HIV and compliance with treatment as well as special emphasis on measures to prevent cancer, cardiovascular disease, and the whole range of problems related with injecting drug use.

List of abbreviations

HIV: human immunodeficiency virus; AIDS: acquired immunodeficiency syndrome; SMR: standard mortality ratio; PY: person-year; HR: hazard ratio.

Acknowledgements

No outside funding was provided for this analysis. No conflict of interest exists for any of the authors.

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Authors' contributions

All the authors participated in the data preparation and analysis, and also contributed to and approved the final manuscript. Additionally, PA, JC and CMI designed the original cohort study, planned the statistical analysis and wrote the draft.

Competing interests

The authors declare that they have no competing interests.

Received: 28 October 2010 Accepted: 11 May 2011

Published: 11 May 2011

References

1. Palella FJ, Delaney K, Moorman A, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD: Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Eng J Med* 1998, **338**:853-860.
2. Mocroft A, Ledergerber B, Katlama C, Kirk O, Reiss P, d'Arminio Monforte A, Knysz B, Dietrich M, Phillips AN, Lundgren JD, EuroSIDA Study Group: Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003, **362**:22-29.
3. Jäggy C, von Overbeck J, Ledergerber B, Schwarz C, Egger M, Rickenbach M, Furrer HJ, Telenti A, Battegay M, Flepp M, Vernazza P, Bernasconi E, Hirschel B, Swiss HIV Cohort Study: Mortality in the Swiss HIV Cohort Study (SHCS) and the Swiss general population. *Lancet* 2003, **362**:877-878.
4. Keiser O, Taffé P, Zwahlen M, Battegay M, Bernasconi E, Weber R, Rickenbach M, the Swiss HIV Cohort Study: All cause mortality in the Swiss HIV cohort study from 1990 to 2001 in comparison with the Swiss population. *AIDS* 2004, **18**:1835-1843.
5. Lohse N, Hansen AB, Pedersen G, Kronborg G, Gerstoft J, Sørensen HT, Vaeth M, Obel N: Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med* 2007, **146**:87-95.
6. Pérez-Hoyos S, del Amo J, Muga R, del Romero J, García de Olalla P, Guerrero R, Hernández-Aguado I, GEMES (Spanish Multicenter Study Group of Seroconverters): Effectiveness of highly active antiretroviral therapy in Spanish cohorts of HIV seroconverters: differences by transmission category. *AIDS* 2003, **17**:353-359.
7. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, Brooks JT, Holmberg SD, HIV Outpatient Study Investigators: Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006, **43**:27-34.
8. Pineda JA, García-García JA, Aguilar-Guisado M, Ríos-Villegas MJ, Ruiz-Morales J, Rivero A, del Valle J, Luque R, Rodríguez-Baño J, González-Serrano M, Camacho A, Macías J, Grilo I, Gómez-Mateos JM, Grupo para el Estudio de las Hepatitis Virales de la Sociedad Andaluza de Enfermedades Infecciosas (SAEI): Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. *Hepatology* 2007, **46**:622-630.
9. Aldaz P, Castilla J, Moreno-Iribas C, Irisarri F, Floristán Y, Sola-Boneta J, Martínez-Artola V, Fernández-Jáuregui C, Dorronsoro I: Trends in mortality and causes of death among persons with HIV infection, 1985-2004 (in Spanish). *Enferm Infecc Microbiol Clin* 2007, **25**:5-10.
10. Lewden C, Salmon D, Morlat P, Bèvilacqua S, Jouglu E, Bonnet F, Héripret L, Costagliola D, May R, Chêne G, Mortality 2000 study group: Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancer, persistent role of AIDS. *Int J Epidemiol* 2005, **34**:121-130.
11. Neuhaus J, Angus B, Kowalska JD, La Rosa A, Sampson J, Wentworth D, Mocroft A, INSIGHT SMART and ESPRIT study groups: Risk of all-cause mortality associated with nonfatal AIDS and serious non-AIDS events among adults infected with HIV. *AIDS* 2010, **24**:697-706.
12. Jensen-Fangel S, Pedersen L, Pedersen C, Larsen CS, Tauris P, Møller A, Sørensen HT, Obel N: Low mortality in HIV-infected patients starting highly active antiretroviral therapy: a comparison with the general population. *AIDS* 2004, **18**:89-97.
13. Mocroft A, Vella S, Benfield TL, Chiesi A, Miller V, Gargaliano P, d'Arminio Monforte A, Yust I, Bruun JN, Phillips AN, Lundgren JD: Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998, **352**:1725-1730.
14. Wang C, Vlahov D, Galai N, Cole SR, Baretta J, Pollini R, Mehta SH, Nelson KE, Galea S: The effect of HIV infection on overdose mortality. *AIDS* 2005, **19**:935-942.
15. The Antiretroviral Therapy Cohort Collaboration: Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries. *Int J Epidemiol* 2009, **38**:1624-1633.
16. Caro-Murillo A, Moreno-Iribas C, Irisarri F, Aldaz P, Napal V, Varela Santos C, Castilla J: Evaluation of the surveillance system for human immunodeficiency virus infections of Navarra, Spain, 1985-2003 (in Spanish). *Rev Esp Salud Pública* 2007, **81**:387-389.
17. Moreno-Iribas C, Irisarri F, Elizalde L, Urriaga M, Sola J, Fernández Jauregui C, Martínez De Artola V, Sáinz de Murieta J, Dorronsoro I, Rubio T, Castilla J: Progress in the control of HIV infection and AIDS in Navarre, 1985-2003 (in Spanish). *An Sist Sanit Navar* 2004, **27**:221-231.
18. Moreno-Iribas C, Floristán Y, Egués N: Recent trends of the main causes of death in Navarre, 1995-2004 (in Spanish). *An Sist Sanit Navar* 2006, **29**:399-414.
19. Navarro C: The National Death Index: a largely expected advance in the access to mortality data (in Spanish). *Gac Sanit* 2006, **20**:421-423.
20. World Health Organization: International statistical classification of diseases and related health problems: ICD-10. Geneva, Switzerland: World Health Organization; 1992.
21. Sterne JA, Hernan MA, Ledergerber B, Tilling K, Weber R, Sendi P, Rickenbach M, Robins JM, Egger M, Swiss HIV Cohort Study: Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005, **366**:378-384.
22. Crum NF, Riffenburgh RH, Wegner S, Agan BK, Tasker SA, Spooner KM, Armstrong AW, Fraser S, Wallace MR, Triservice AIDS Clinical Consortium: Comparisons of causes of death and mortality rates among HIV-infected persons: analysis of pre-, early, and late HAART (highly active antiretroviral therapy) eras. *J Acquir Immune Defic Syndr* 2006, **41**:194-200.
23. Bhaskaran K, Hamouda O, Sannes M, Boufassa F, Johnson AM, Lambert PC, Porter K, CASCADE Collaboration: Changes in the risk of death after HIV seroconversion compared with mortality in the general population. *JAMA* 2008, **300**:51-59.
24. Krentz HB, Kliever G, Gill MJ: Changing mortality rates and causes of death for HIV-infected individuals living in Southern Alberta, Canada from 1984 to 2003. *HIV Med* 2005, **6**:99-106.
25. Oliva J, Galindo S, Vives N, Arrillaga A, Izquierdo A, Nicolau A, Castilla J, Lezaun ME, Álvarez M, Rivas A, Diez M: Delayed diagnosis of HIV infection in Spain (in Spanish). *Enferm Infecc Microbiol Clin* 2010, **28**:583-589.
26. Hessamfar-Bomarek M, Morlat P, Salmon D, Cacoub P, May T, Bonnet F, Rosenthal E, Costagliola D, Lewden C, Chêne G, Mortalité 2000 & 2005 Study Groups: Causes of death in HIV-infected women: persistent role of AIDS. The 'Mortalité 2000 & 2005' surveys (ANRS EN19). *Int J Epidemiol* 2010, **39**:135-146.

27. Prins M, Hernández Aguado I, Brettle RP, Robertson JR, Broers B, Carré N, Goldberg DJ, Zangerle R, Coutinho RA, van den Hoek A: **Pre-Aids mortality from natural causes associated with HIV disease progression: evidence from the European Seroconverter Study among injecting drug users.** *AIDS* 1997, **11**:1747-1756.
28. Boccard F: **Cardiovascular complications and atherosclerotic manifestations in the HIV-infected population: type, incidence and associated risk factors.** *AIDS* 2008, **22**(Suppl 3):S19-26.
29. Francisci D, Giannini S, Baldelli F, Leone M, Belfiori B, Guglielmini G, Malincarne L, Gresele P: **HIV type infection, and not short-term HAART, induces endothelial dysfunction.** *AIDS* 2009, **23**:589-596.
30. Patel P, Hanson DL, Sullivan PS, Novak RM, Moorman AC, Tong TC, Holmberg SD, Brooks JT, Adult and Adolescent Spectrum of Disease Project and HIV Outpatient Study Investigators: **Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003.** *Ann Intern Med* 2008, **148**:728-736.
31. Engels E, Pfeiffer R, Goedert JJ, Virgo P, McNeel TS, Scoppa SM, Biggar RJ, for the HIV/AIDS Cancer Match Study: **Trends in cancer risk among people with AIDS in the United States 1980-2002.** *AIDS* 2006, **20**:1645-1654.
32. Frisch M, Biggar RJ, Engels EA, Goedert JJ, AIDS-Cancer Match Registry Study Group: **Association of cancer with AIDS-related immunosuppression in adults.** *JAMA* 2001, **285**:1736-1745.
33. Crum-Cianflone N, Hullsiek KH, Marconi V, Weintrob A, Ganesan A, Barthel RV, Fraser S, Agan BK, Wegner S: **Trends in the incidence of cancers among HIV-infected persons and the impact of antiretroviral therapy: a 20-year cohort study.** *AIDS* 2009, **23**:41-50.
34. Keiser O, Spoerri A, Brinkhof MW, Hasse B, Gayet-Ageron A, Tissot F, Christen A, Battegay M, Schmid P, Bernasconi E, Egger M, Swiss HIV Cohort Study; Swiss National Cohort: **Suicide in HIV-infected individuals and the general population in Switzerland, 1988-2008.** *Am J Psychiatry* 2010, **167**:143-150.
35. Lai D, Hardy RJ: **An update of the impact of HIV/AIDS on life expectancy in the United States.** *AIDS* 2004, **18**:1732-1734.

Pre-publication history

The pre-publication history for this paper can be accessed here:
<http://www.biomedcentral.com/1471-2458/11/300/prepub>

doi:10.1186/1471-2458-11-300

Cite this article as: Aldaz et al.: Mortality by causes in HIV-infected adults: comparison with the general population. *BMC Public Health* 2011 **11**:300.

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