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HIV-related excess mortality and age-related comorbidities in patients with HIV aged ≥60: a relative survival analysis in the French Dat'AIDS cohort

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ABSTRACT

Objective The objective was to evaluate the association between age-related comorbidities (ARCs) and 5-year HIV-related excess mortality in people living with HIV aged ≥60 years.

Design Cohort study using relative survival analysis (Estève's model).

Setting The French multicentre prospective Dat'AIDS cohort that involves 12 French hospitals.

Participants Inclusion of 1415 HIV-1 infected patients actively followed aged ≥60 years on January 2008, with a 5-year follow-up period in the late combination antiretroviral therapy era.

Results Among 1415 patients included, 154 died. By multivariable analysis, factors predictive of 5-year HIV-related excess mortality were non-AIDS-related cancer (adjusted excess HR (aEHR)=2.94; 95% CI 1.32 to 6.57), cardiovascular disease (aEHR=6.00; 95% CI 2.45 to 14.65), chronic renal disease (aEHR=4.86; 95% CI 2.24 to 10.53), cirrhosis (aEHR=3.58; 95% CI 1.25 to 10.28), hepatitis C co-infection (aEHR=3.63; 95% CI 1.44 to 9.12), body mass index<18.5 kg/m² (aEHR=4.10; 95% CI 1.61 to 10.48) and having a CD4 cell count ≤200/mm³ (aEHR=5.79; 95% CI 2.28 to 14.69).

Conclusions ARCs, particularly cardiovascular disease and chronic renal disease, are predictive of HIV-related excess mortality, with an increase in hazard similar to that of CD4 cell count.

Trial registration number NCT02898987.

Strengths and limitations of this study

► Inclusion of a large number of patients with HIV aged ≥60 in the late combination antiretroviral therapy era.

► As causes of death have become more diverse, relative survival methods are probably more appropriate than using cause-specific mortality.

► Since the HIV population differs from the general population not only in its HIV status but also in a wide range of sociodemographic and clinical factors, HIV-related excess mortality should not be interpreted as related only to the HIV infection but as related to the HIV population in general.

► As the data were based on a computerised medical record with no other ascertainment method, misclassification bias and underestimation of the prevalence of some comorbidities could not be excluded.

BACKGROUND

The population of people living with HIV (PLHIV) is ageing.[1] In France, the percentage of PLHIV aged ≥50 years increased from 8.0% in 1993 to 35.4% in 2011, including 11.2% who were aged ≥60 years.[2] Age-related comorbidities (ARCs) are significantly more common in HIV-infected patients, including younger age groups, compared with the general population.[3] Since the availability of combination antiretroviral therapy (cART), the impact of ARCs on all-cause mortality has become a major issue as we showed that they are independently associated with an increased risk of all-cause mortality[4] and that they could be significant predictors in a mortality risk index, even adjusted on immunovirological characteristics, in PLHIV aged ≥60.[5] However, whether ARCs are associated with the excess mortality related to HIV infection in aged PLHIV remains unclear.

As deaths in the HIV population become less and less AIDS-related,[6] what exactly is the HIV-related excess mortality nowadays? When a patient dies from AIDS-related disease such as pneumocystis pneumonia or Kaposi's sarcoma, it is easy to classify its death as HIV-related. But patients with HIV do not always die of AIDS. For example, when a patients dies of lung cancer, which is more frequent in the HIV population even when smoking is taken into account[7] and given that cancer-specific mortality is higher in the HIV population,[8] which part of the death is HIV-related?

Therefore, in aged patients with several ARCs, cause-specific survival analysis methods may not be adequate because information on cause of death is often unreliable or unavailable or is difficult to establish with certainty as it is frequently multifactorial in this population, leading to competing risks. Relative survival (RS), which is the ratio of observed survival in the population with the condition of interest to expected survival in the general population, could be a preferable approach. The observed mortality rate in the study cohort is made up of the background mortality rate in the general population plus the excess mortality rate associated with the disease of interest (HIV in our study).[9] Therefore, RS attempts to separate mortality from the disease of interest (namely, HIV in our population) from mortality due to all other causes without requiring specific knowledge of the cause of death. This removes the main problem associated with cause-specific mortality. RS is the method of choice for estimating patient survival using data collected by population-based cancer registries although its utility is not restricted to studying cancer.[10] For example, a research question in the cancer field using RS methodology could be: 'what is the impact of that comorbidity in a cancer-related mortality in a population that has the said cancer?' In the HIV field, RS could be used to measure deaths that are in excess among the HIV population beyond what would be expected for the study population if it did not have HIV (ie, the HIV-related excess mortality) using mortality rates observed in the general population (the expected mortality). The strength of this approach in HIV studies is that there is no need to assess the cause of death for each patient, for example, by using death certificates.[9 11] Relative survival could then be an approach for estimating specifically HIV-related mortality in the HIV population and some techniques, such as Estève's model, allow the analysis of the association between potential prognostic factors and the HIV-related excess mortality.[12]

The aim of this study was to investigate the relationship between ARCs and HIV-related excess mortality in our cohort of PLHIV aged ≥60 years,[13 14] in the context of a large French prospective cohort in the late cART era (from January 2008 to December 2012).

METHODS

As described in detail previously,[4 5] this study involved all HIV-1 infected patients aged ≥60 years on 1 January 2008 and followed up in the context of the Dat'AIDS cohort that involves 12 French hospitals. Dat'AIDS is a French multicentre prospective cohort that covers inpatients and outpatients treated in French public hospitals, including French overseas territories. It is based on a computerised medical record that is used by clinicians in real time during their consultations since 2000 (Nadis, Fedialis Medica, Marly le Roi, France).[15] All patients were included in the cohort after receiving oral information and giving written consent. All patient information was entered into a database using anonymous, coded identification numbers.

The DatAIDS cohort is registered on Clinicaltrials.gov under the identifier NCT02898987.

Patients were excluded if they were infected with HIV-2 or if they did not have at least one CD4 cell count available in the 12 months before or after 1 January 2008. For each patient, follow-up began on 1 January 2008 and stopped on the date of death, or date of last follow-up, or on 1 January 2013 (whichever came first).

The study endpoint was 5-year mortality. In patients lost to follow-up (defined as a date of last follow-up prior to 1 January 2013 and alive at last follow-up), vital status was systematically recorded via the Centre for Epidemiology and Population Health , by linkage with the French National Institute of Statistics and Economic Studies, which records nearly all deaths that occur in France by centralised reception of death certificates. Patients were handled in mortality analyses until their date of death, 1 January 2013, or the date of the last follow-up if it occurred before 1 January 2013 and if the patients were not deceased after the vital status recording.

The following data were collected at baseline (1 January 2008): age, gender, clinical centre, risk categories for HIV infection, duration of known HIV infection, AIDS status, CD4 cell count and CD4 nadir. The following ARCs were considered at baseline since they are known to be associated with mortality in the general population[16]: cardiovascular disease (CVD) (history of myocardial infarction, congestive heart failure, cerebrovascular disease), cancer (non-AIDS related), chronic pulmonary disease, diabetes, chronic renal disease (CRD) (defined as a composite criterion comprising documented history of CRD in the patient's medical file or an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² as calculated using the Modification of Diet in Renal Disease (MDRD) formula) and cirrhosis. The presence or the absence of ARCs was based on the data available in the Nadis computerised medical records. Although hepatitis C virus (HCV) co-infection and hepatitis B virus (HBV) co-infection are not ARCs, they were also assessed since liver-related deaths are the leading cause of death in HCV/HIV and/or HBV/HIV co-infected PLHIV.[17] HBV co-infection was defined as at least one positive hepatitis B surface antigen. HCV co-infection was defined as at least one positive anti-HCV antibody and/or detectable HCV-RNA viral load (recording the value from the assessment closest to the baseline date). Body mass index (BMI) was also assessed as it is significantly associated with mortality in the general aged population, even when adjusted for ARCs.[18] Where appropriate, adapted International Classification of Disease, 10th Revision (ICD-10) coding algorithms for Charlson comorbidities were used.[16] All other comorbidities were extracted using ICD-10 codes and diagnoses available before 1 January 2008.

To determine expected mortality, mortality rates were attributed to each individual by age (by year up to 84 years, then ≥85), sex, area of residence (by administrative regions) and year (by year, from 2008 to 2012); one mortality rate was attributed for each year of follow-up.

Table 1 Baseline characteristics of the 1415 people living with HIV aged ≥60 years

	Baseline characteristics (n=1415)
Sex, male (n (%))	1093 (77.2)
Age (years) (mean (±SD))	65.7 (5.5)
Mode of HIV infection (n (%))	
Heterosexual	630 (44.5)
Homosexual	556 (39.3)
Injecting drug user	9 (0.6)
Other	220 (15.6)
Duration of known HIV infection (years) (mean (±SD))	11.9 (6.1)
ART-experienced (n (%))	1248 (88.2)
Duration on ART (years) (mean (±SD)) (n=1248)	9.6 (4.8)
CDC stage C (AIDS) (n (%))	426 (30.1)
Age-related comorbidities (n (%))	
Cancer	229 (16.2)
Non-AIDS-related cancer	94 (6.6)
Cardiovascular diseases	172 (12.2)
Cerebrovascular disease	77 (5.4)
Myocardial infarction	67 (4.7)
Congestive heart failure	42 (3)
Chronic pulmonary disease	112 (7.9)
Chronic renal disease*	285 (20.1)
Diabetes mellitus	201 (14.2)
Cirrhosis	39 (2.8)
HBV co-infection	54 (3.8)
HCV co-infection	92 (6.5)
Body mass index (n (%)) (missing=29)	
Obese (≥30 kg/m²)	98 (7.1)
Overweight (25–29.9 kg/m²)	389 (28.1)
Normal (18.5–24.9 kg/m²)	823 (59.4)
Low (<18.5 kg/m²)	76 (5.5)
CD4 cell count (cells/µL) (mean (±SD))	507 (245)
>500 cells/µL (n (%))	653 (46.2)
350–500 cells/µL	364 (25.7)
200–349 cells/µL	299 (21.1)
<200 cells/µL	99 (7)
CD4 nadir (cells/µL) (mean (±SD))	210 (174)
≥200 cells/µL (n (%))	619 (43.8)
<200 cells/µL	796 (56.2)
HIV viral load>50 copies/mL (n (%)) (missing=3)	331 (23.4)
Estimated glomerular filtration rate <60 mL/min/1.73 m² (MDRD) (n(%)) (missing=28)	260 (18.8)

*Defined as a composite criterion comprising documented history of chronic renal disease in the patient's medical file or an estimated glomerular filtration rate <60 mL/min/1.73 m² as calculated using the MDRD formula.
ART, antiretroviral treatment; CDC, Centers for Disease Control and Prevention; HBV, hepatitis B virus; HCV, hepatitis C virus; MDRD, Modification of Diet in Renal Disease.

Mortality tables were extracted from the Eurostat database (http://ec.europa.eu/eurostat/fr/data/database). Therefore, it was not required to include any control group in the present study.

Statistical analysis
Mean±SD and number (percentage) were used to describe population characteristics. Univariable and multivariable analysis were performed using Estève's model[12] to generate excess HRs (EHR) and associated 95% CIs, as opposed to the standard HRs obtained in Cox and other survival models.[9] For example, an EHR of 2 for a comorbidity would suggest that the excess mortality rate (HIV-related here) in patients presenting that comorbidity is twice as high as in patients who do not have that comorbidity. Thus, EHR should not be interpreted as the comorbidity is associated with a two-times higher all-cause mortality in HIV population than in HIV-uninfected population, which would be the result of an interaction test in a classical Cox model. The non-linear programming procedure was used in order to non-linearly optimise the log-likelihood of the Estève model. The multivariable models were systematically adjusted for age, gender, duration of HIV infection, baseline CD4 cell count and clinical centre. A manual, step-by-step descending selection of covariates was used. Interaction between HCV co-infection and cirrhosis was tested. Significance was reached when P<0.05. Statistical analyses were performed using SAS V.9.4 (SAS Institute).

Patient and public involvement
Patients and public were not involved in the present study.

RESULTS
Among 18 304 HIV-1 infected individuals actively followed up as of 1 January 2008, 1583 were aged ≥60 (8.6%). Among these, 168 were excluded due to the absence of available CD4 cell count within 1 year before or after baseline, and 1415 patients (89.4%) were included in the study. The baseline characteristics of the study population are presented in table 1. Most patients were male (77.2%); mean age was 65.7±5.5 years. ARC prevalence was high: 766 patients (54.1%) had at least one ARC and 314 (22.2%) had at least two. The most prevalent ARCs were CRD (20.1%), diabetes (14.2%) and CVD (12.2%). Cirrhosis, present in 39 patients (2.8%), was related to HCV and HBV co-infection in 11/39 (28.2%) and in 9/39 (23.1%) of cases, respectively. Among patients with eGFR <60 mL/min/1.73 m² (18.8% of all patients), mean eGFR was 48.4±11.5 mL/min/1.73 m².

During the 5 years of follow-up (6225 patient-years), 154 (10.9%) patients died (observed mortality rate 2.47/100 patient-years). The expected mortality rate in this population was 1.67/100 patient-years. Mean age at death was 70.5±7.4 years. In total, 1053 surviving PLHIV were fully followed until the end of the study period, and 208

Table 2 Factors associated with 5-year HIV-related excess mortality among people living with HIV aged ≥60 years by univariable and multivariable analysis (n=1415)

	Univariable analysis		Multivariable analysis (n=1385)	
	EHR (95% CI)	P value	aEHR* (95% CI)	P value
Age (years), per additional year	1.01 (0.91 to 1.13)	0.839	0.98 (0.92 to 1.04)	0.536
Male sex	0.49 (0.18 to 1.31)	0.154	1.16 (0.51 to 2.65)	0.72
AIDS	3.19 (1.22 to 8.33)	0.018		
Non-AIDS-related cancer	5.93 (2.63 to 13.38)	$<10^{-4}$	2.94 (1.32 to 6.57)	0.008
Cardiovascular disease	7.73 (3.39 to 17.61)	$<10^{-4}$	6 (2.45 to 14.65)	$<10^{-4}$
Chronic renal disease	12.07 (3.58 to 40.71)	$<10^{-4}$	4.86 (2.24 to 10.53)	$<10^{-4}$
Chronic pulmonary disease	1.11 (0.19 to 6.45)	0.906		
Diabetes	2.41 (1.00 to 5.81)	0.05		
Cirrhosis	11.63 (5.26 to 25.74)	$<10^{-4}$	3.58 (1.25 to 10.28)	0.018
HCV co-infection	4.88 (2.11 to 11.29)	0.0002	3.63 (1.44 to 9.12)	0.006
HBV co-infection	0.00004 (0.0000 –)	0.988		
Body mass index				
Low	10.61 (3.79 to 29.71)	$<10^{-4}$	4.1 (1.61 to 10.48)	0.003
Overweight	0.85 (0.16 to 4.59)	0.854	0.9 (0.32 to 2.57)	0.85
Obese	2.72 (0.74 to 9.94)	0.131	2.71 (0.81 to 9.03)	0.105
CD4 cell count (cells/µL), ≤200	4.94 (2.12 to 11.53)	0.0002	5.79 (2.28 to 14.69)	0.0002
CD4 nadir (cells/µL), ≤200	4.32 (0.75 to 24.77)	0.19		
HIV viral load (copies/mL), >50	2.39 (1.05 to 5.45)	0.039		
Duration of known HIV infection, per year	1 (0.93 to 1.08)	0.938		

*Also adjusted for duration of HIV infection and clinical centre.
aEHR, adjusted excess HR; EHR, excess HR; HBV, hepatitis B virus; HCV, hepatitis C virus.

(14.7%) patients were lost to follow-up (median follow-up among these patients was 2.3 years IQR (2.0–3.4)).

By univariable analysis, factors predictive for HIV-related excess mortality were CRD, non-AIDS-related cancer, CVD, cirrhosis, HCV co-infection, low BMI, AIDS status, CD4 cell count (<200 cells/µL) and detectable HIV viral load (>50 copies/mL). By multivariable analysis, CRD, non-AIDS-related cancer, CVD, cirrhosis, HCV co-infection, low BMI and CD4 cell count (<200 cells/µL) remained significantly associated with HIV-related excess mortality (table 2). There was no significant interaction between HCV co-infection and cirrhosis (p=0.34).

DISCUSSION

In a large population of PLHIV aged ≥60 followed up for 5 years in a multicentre prospective cohort representative of French PLHIV in the late cART era in France, we found that CRD, non-AIDS-related cancer, CVD, cirrhosis, HCV co-infection and low BMI were predictive of HIV-related excess mortality, with EHRs ranging from 2.9 to 6.

Finding these ARCs to be predictive of HIV-related excess mortality is consistent with the fact that ARCs have both higher prevalence and higher mortality in PLHIV compared with the general population.[3 8 19–22] For

example, in an Italian study, the prevalence of chronic kidney disease was higher (24.3%) compared with age-matched uninfected controls aged ≥60 (0.49%).[3] Furthermore, several studies have shown a higher mortality in patients with HIV compared with HIV-seronegative patients with acute myocardial infarction,[20 21] and higher cancer-specific mortality for prostate, breast, hepatocarcinoma or lung cancers, independent of cancer stage or receipt of cancer treatment.[8 22] Interestingly, age, which is linked with all-cause mortality in the HIV population,[4] was not linked to the HIV-related excess mortality, highlighting the difference between relative survival analysis and traditional survival analysis.

In the late cART era, as causes of death have become more diverse and as the survival and follow-up have been extended, RS methods are probably more appropriate than using specific mortality since RS makes it possible to study the impact of ARC on HIV-related excess mortality. RS methodology does not require including a comparator group in the study as expected mortality rates could be obtained from widely available mortality tables. Therefore, we believe relative survival to be of increasing usefulness in the future. To the best of our knowledge, the present study is the first to evaluate the association

of ARCs with HIV-related excess mortality using this methodology. CRD and CVD were predictive of excess mortality (eHR 4.86 and 6.0, respectively), with a magnitude of effect similar to that of a CD4 cell count below 200 cells/µL (eHR 5.79). It means that in the late cART era these ARCs may predict HIV-related excess mortality to the same extent as CD4 cell count.

As these ARCs are predictive of all-cause mortality among aged PLHIV[4] but also of HIV-related excess mortality as we have shown, HIV physicians should provide global care to aged PLHIV, with special considerations for CVD and CRD as their prevalence is high and they have a strong impact on HIV-related excess mortality and global mortality.[4] Prevention should be organised early in PLHIV's medical history, with cardiovascular risk factors control, and poor cardiovascular profile drugs and nephrotoxic drugs avoidance.[23]

Our study has some limitations that deserve to be underlined. Evaluating RS requires a reference population exempt from the disease of interest to estimate the real excess mortality. In this study, HIV-related excess mortality was included in the mortality rates for the general population used to build the mortality tables. However, HIV prevalence is low enough in French general population for its impact to be negligible. Indeed, it was estimated that 153 400 patients (95% CI 150 300 to 156 200) were living with HIV in France in 2013[24] where the French population was about 66 000 000 people, yielding to a crude prevalence rate of 0,23%. Another limitation is that, for ethical reasons, there are no existing mortality tables comprising mortality rates by ethnicity or socioeconomic characteristics in France. Ethnicity may differ widely between PLHIV and the general population, in particular in France, as with socioeconomic status, which has been found to be associated with subsequent mortality.[24] Assigning individual mortality rates from the general population to the HIV-infected population may therefore not be adequate. Their impact could be somewhat attenuated by the fact that we took into account administrative regions to assign individual mortality rates.[25] HIV-related excess mortality could be also explained by other factors that could differ from the general population, such as the prevalence of intravenous drug users. Indeed, a fourfold higher excess risk of mortality throughout the cART era has been observed in intravenous drug users.[26] However, in our study, the number of injecting drug users was low (0.6%) and does not necessarily reflect active drug injecting and, therefore, could not predict the excess mortality. The HIV population also differs from the general population in terms of tobacco use, exposure to sexually transmitted infections, recreational drug use, and so on, that may also be related to ARCs and mortality. Since the HIV population differs from the general population not only in its HIV status but also in a wide range of sociodemographic and clinical factors, HIV-related excess mortality should not be interpreted as related only to the HIV infection but as related to the HIV population in general. Another limitation is that data are collected before 2013, because the vital status update on patients lost to follow-up was done at that time, which may look a little outdated at the time of the publication of the present study. However, extending the study without doing another vital status update would have introduced bias and it was not expected that doing another vital status update was likely to change the results. Moreover, to date, no other study has investigated this association, leaving our findings novel. As the data were based on a computerised medical record with no other ascertainment method, misclassification bias and underestimation of the prevalence of some comorbidities could not be excluded. Finally, using CD4 cell count up to 1 year after the study baseline could have led to immortal time bias. However, this period of 'immortality' is not expected to be different in the low CD4 cell count than in the high CD4 cell count. Moreover, the CD4 count is not expected to change sufficiently to induce a CD4 group change between the study baseline and the next months for most patients as most patients had a CD4 cell count >200/mm^3 (93%) and were undetectable (77%).

CONCLUSIONS

Using relative survival methods, we showed that ARCs, particularly CVD and CRD, are predictive of HIV-related excess mortality, with approximately the same weight as CD4 cell count. RS methods seem to be more adequate to evaluate the impact of ARCs on HIV-related excess mortality in PLHIV.

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