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CLINICAL AND EPIDEMIOLOGICAL STUDY

Causes of death among Danish HIV patients compared with population controls in the period 1995–2008

M. Helleberg · G. Kronborg · C. S. Larsen · G. Pedersen · C. Pedersen · J. Gerstoft · N. Obel

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Abstract
Purpose To compare the mortality and causes of death in human immunodeficiency syndrome (HIV) patients with the background population.
Methods All adult HIV patients treated in Danish HIV centers from 1995 to 2008 and 14 controls for each HIV patient were included. Age-adjusted mortality rates (MR) and mortality rate ratios (MRR) were estimated using direct standardization and Poisson regression analyses. Up to four contributory causes of death for each person were included in analyses of cause-specific MR.
Results A total of 5,137 HIV patients and 71,918 controls were followed for 37,838 and 671,339 person-years (PY), respectively. Among non-injection drug use (IDU) HIV patients, the acquired immune deficiency syndrome (AIDS)-related MR/1,000 PY declined dramatically from 122.9 [95 % confidence interval (CI) 106.8–141.4] in 1995 to 5.0 (95 % CI 3.1–8.1) in 2008. The non-AIDS-related MR did not change substantially from 6.9 (95 % CI 3.8–12.5) to 5.6 (95 % CI 3.6–8.8). The MR of unnatural causes declined from 6.9 (95 % CI 3.8–12.5) to 2.7 (95 % CI 1.4–5.1). The MRR of infections declined from 46.6 (95 % CI 19.6–110.9) to 3.3 (95 % CI 1.6–6.6). The MRR of other natural causes of death remained constant.
Conclusions After the introduction of highly active antiretroviral therapy (HAART), the AIDS-related mortality has decreased substantially, but the long-term exposure to HIV and HAART has not translated into increasing mortality from malignancy, cardiovascular, and hepatic diseases.

Keywords Cause of death · Highly active antiretroviral therapy · HIV · Mortality

Abbreviations

AIDS	Acquired immune deficiency syndrome
AMR	Age-adjusted mortality rate
CD4	Cluster of differentiation 4
CI	Confidence interval
CMR	Crude mortality rate
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency syndrome
IDU	Injection drug use
IQR	Interquartile range
MR	Mortality rate
MRR	Mortality rate ratio
MSM	Men who have sex with men
PY	Person-years

M. Helleberg (✉) · J. Gerstoft · N. Obel
Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark
e-mail: mhelleberg@sund.ku.dk

G. Kronborg
Department of Infectious Diseases, Hvidovre Hospital, Hvidovre, Denmark

C. S. Larsen
Department of Infectious Diseases, Aarhus University Hospital, Aarhus C, Denmark

G. Pedersen
Department of Infectious Diseases, Aalborg University Hospital, Aalborg, Denmark

C. Pedersen
Department of Infectious Diseases, Odense University Hospital, Odense C, Denmark

Introduction

After the introduction of highly active antiretroviral therapy (HAART), the life expectancy of individuals infected with human immunodeficiency syndrome (HIV) has increased substantially [1–3], and several studies have shown that the proportion of deaths caused by acquired immune deficiency syndrome (AIDS) has decreased among HIV-infected individuals in high-income countries [4, 5]. Monitoring is needed in order to determine if long-term exposure to HAART is associated with side effects which could increase mortality. With aging of the HIV-infected population, cancer and cardiovascular diseases have become important causes of death. Some observational studies have indicated that the risk of myocardial disease increase for each year on HAART [6, 7], and it has been argued that the rate of deaths caused by cancer and cardiovascular diseases will increase more in HIV-infected individuals than in the background population due to immune activation and accelerated aging [8].

In the present study, we evaluated changes in the causes of death in a Danish HIV cohort over a 14-year period spanning 1995 to 2008. We further compared the changing trends in the causes of death among HIV patients with that of a cohort of age- and gender-matched individuals from the background population.

Materials and methods

We calculated the all-cause and cause-specific mortality rates (MR) in a nationwide population-based cohort of Danish HIV patients followed from 1 January 1995 to 31 December 2008. Mortality rate ratios (MRR) of HIV patients versus an age- and gender-matched control group were estimated.

Setting

Denmark had a population of 5.5 million as of 31 December 2008, with an estimated HIV prevalence of approximately 0.09 % in the adult population. Individuals with HIV infection are treated in one of the country's eight specialized medical centers, where they are seen on an outpatient basis at intended intervals of 12 weeks. Antiretroviral treatment is provided free of charge to all HIV-infected residents of Denmark.

Data sources

We used the unique 10-digit civil registration number assigned to all individuals in Denmark at birth or upon immigration to avoid multiple registrations and to link data from the following registers:

- The Danish HIV cohort study described in detail elsewhere [9] is a population-based nationwide cohort study of all HIV-infected individuals who are treated at Danish HIV centers after 1 January 1995. Individuals are consecutively enrolled. Data are updated yearly and includes demographics, date of HIV infection, AIDS-defining events, and antiretroviral treatment. CD4 cell counts and HIV-RNA measurements are extracted electronically from laboratory data files.
- Data on vital status and migration were obtained from the Danish Civil Registration System [10], which is a national register established in 1967 that contains the demographic data and vital status of all Danish citizens. Data on causes of death were obtained from the Danish National Registry of Causes of Death, which contains information from all Danish death certificates [11]. When a Danish resident dies, the attending physician reports the cause of death; the train of morbid events leading to death can be described by specifying up to four diagnoses, according to the International Classification of Diseases, 10th Revision (ICD-10) [12].

Study population

All adult (>16 years of age) HIV-1-infected individuals in the Danish HIV cohort study, who attended an HIV care center at least once in the period 1 January 1995 to 31 December 2008 and had a Danish civil registration number were included. A control group was included by matching each HIV patient by gender and date of birth with 14 randomly selected individuals identified using the Danish Civil Registration System.

Statistics

MR for each calendar year were calculated as the number of deaths per 1,000 person-years (PY) and 95 % confidence intervals (CI) and MRR were estimated using conditional Poisson regression analyses. Age-adjusted death rates were estimated using the direct standardization method [13], with the age distribution of the HIV population in 1995 used as the standard. Analyses were stratified by injection drug use (IDU). HIV patients were followed from 1 January 1995, date of HIV diagnosis, or date of immigration to Denmark, whichever was the most recent. Individuals in the control group were followed from the same date as the HIV patient with whom they were matched. All individuals were followed until 31 December 2008, emigration, or death, whichever came first.

Analyses of causes of death were based on the diagnoses listed in the Danish National Registry of Causes of Death. First, we categorized causes of death as either AIDS-related, non-AIDS-related, or unnatural. Deaths were categorized as unnatural if caused by accidents, injury, suicide, or drug overdose; other causes were categorized as natural. Deaths were categorized as AIDS-related if the last CD4 count before and within 6 months of death was <200 and/or an AIDS-defining illness was diagnosed within 1 year of death.

Second, we estimated the MRR of deaths caused by infection, cancer, cardiovascular, hepatic, and renal disease among non-IDU HIV patients versus controls. We adopted the main categories used in the ICD-10 system, but deaths caused by respiratory tract infections, endocarditis, and infections in the central nervous system (ICD-10: J00–J32, I33, and G00–G08) were categorized as infections, and viral hepatitis (ICD-10: B15–B19) and esophageal varices (ICD-10: I85.0–I85.9) were categorized as hepatic disease. In the analyses of cause-specific MRR, up to four contributory causes of death could be entered for each patient and a patient could be represented with more than one contributory cause of death if multiple causes were noted on the death certificate. SPSS statistical software, version 15.0 (Norusis; SPSS Inc., Chicago, IL, USA) and Stata 8.0 (Stata Corporation, College Station, TX, USA) were used for the data analyses.

Results

A total of 5,137 HIV patients who attended HIV care between 1 January 1995 and 31 December 2008 were followed for 37,838 PY, with a median follow-up time of 7.1 years [interquartile range (IQR) 2.6–12.6] and 71,918 population controls were followed for 671,339 PY, with a median follow-up time of 10.5 years (IQR 5.2–14.0). Characteristics of the HIV patients are summarized in Table 1. There were 1,230 deaths among HIV patients and 2,934 deaths among population controls.

HAART and immune status

Among HIV patients who had initiated HAART, the median time of exposure to HAART increased linearly from 0.1 years (IQR 0.0–0.5) in 1995 to 7.8 years (IQR 3.8–11.3) in 2008. The proportion of HIV patients who had initiated HAART before death increased from 0 % in 1995 to 83.3 % in 2008.

During the study period, the median CD4 count at the time of death [available in 986 (80 %) cases] increased from 14 (IQR 7–56) in 1995 to 301 (IQR 150–521) in 2008, and the proportion of individuals who had been

Table 1 Characteristics of the study population

	HIV patients		Population controls	
	n (%)	Interquartile range	*n* (%)	Interquartile range
Number of study subjects	5,137		71,918	
Total observation time (years)	37,838		671,339	
Observation time (years), median	7.1	2.6, 12.6	10.5	5.2, 14.0
Deaths	1,230 (23.9)		2,934 (4.1)	
Males	3,895 (75.8)		54,514 (75.8)	
Age at baseline (years), median	36	31, 44	36	31, 44
Origin				
Danish	3,734 (72.7)			
African	673 (13.1)			
Asian	233 (4.5)			
Other	497 (9.7)			
Route of infection				
Male homosexual	2,401 (46.7)			
Danish heterosexual	1,023 (19.9)			
Migrant heterosexual	868 (16.9)			
Injection drug use	556 (10.8)			
Other	289 (5.6)			
CD4 count at baseline (cells/μL), median	276	100, 480		
AIDS-defining illness at baseline	585 (11.4)			
Hepatitis C antibody-positive	823 (16.0)			
Hepatitis B core antibody-positive	575 (11.2)			
Hepatitis B surface antigen-positive	316 (6.2)			

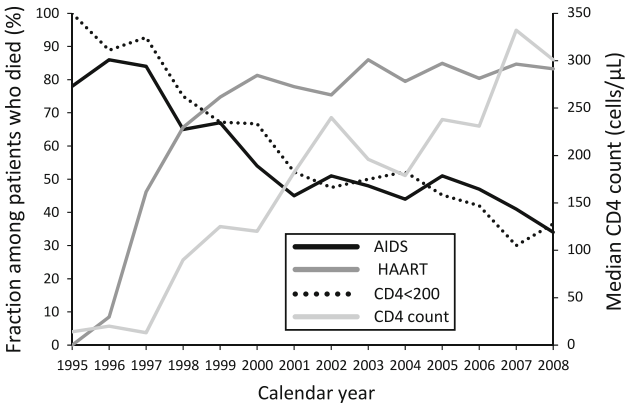

Fig. 1 Previous acquired immune deficiency syndrome (AIDS)-defining illness, highly active antiretroviral therapy (HAART) status (on the left *y*-axis) and CD4 count (on the right *y*-axis) at the time of death among human immunodeficiency syndrome (HIV) patients treated in Denmark in 1995–2008. The figure illustrates the fraction of patients having experienced an AIDS-defining illness, the fraction on HAART, and the last CD4 count prior to death

diagnosed with an AIDS-defining illness before death declined from 78.3 to 33.9 %. The proportion of patients who had been diagnosed with an AIDS-defining illness within 1 year of death declined from 39.1 to 8.7 % (Fig. 1). The median age increased during the study period from 37 years (IQR 31–45) in 1995 to 44 years (IQR 38–52) in 2008. The median age at the time of death was 41 years (IQR 34–50) in 1995 versus 58 years (IQR 50–65) in 2008.

All-cause mortality

The all-cause MR of HIV patients declined substantially from 1995 to 2008 (Table 2). The decline in MR during the study period was less pronounced among IDUs than non-IDUs (Fig. 2).

AIDS-related, non-AIDS-related, and unnatural causes of death

The rate of AIDS-related deaths declined dramatically after the introduction of HAART, and after the year 2000, the rate of AIDS-related deaths was of the same order as that of non-AIDS-related natural deaths. The rate of non-AIDS-related deaths did not change significantly in the study period. There was a very high rate of unnatural deaths among IDUs, but the rate declined among both IDUs and non-IDUs (Table 2).

Cause-specific mortality

In 1995, the MR of infectious diseases was 12.0/1,000 PY (95 % CI 7.6–18.8) in the non-IDU HIV population and substantially higher than the MR of other natural causes. During the study period, this rate declined and was 2.7/1,000 PY (95 % CI 1.4–5.1) in 2008, which did not exceed the rates of other natural causes of death. Infectious diseases also contributed the most to the excess mortality of HIV patients compared with controls. The MRR of infections declined from 46.6 (95 % CI 19.6–110.9) in 1995 to 3.3 (95 % CI 1.6–6.6) in 2008 (Fig. 3). The MRR of natural causes of death other than infections did not change significantly during the study period.

The MR of cancer, cardiovascular, hepatic, and renal diseases among non-IDU HIV patients did not change substantially with calendar time and were considerably higher than that among controls (Table 2).

Lung cancer accounted for the most malignant deaths. Hematological and gastrointestinal cancers were also prevalent. The MR of ischemic heart disease and stroke were also considerably higher among non-IDU HIV patients than in the control group. There was a rather high MR of suicide among non-IDU HIV patients, which was constant during the study period.

Discussion

In this nationwide population-based study of HIV patients followed in a 14-year period from 1995 to 2008, we found that mortality and causes of death changed dramatically after the introduction of HAART. In the pre- and early HAART period, the AIDS-related mortality among HIV patients was substantial, but after the year 2000, the rate of AIDS-related deaths had decreased to a level which was of the same order as that of non-AIDS-related deaths. Unnatural deaths accounted for a significant proportion of mortality among HIV patients, especially among IDUs. The rate of deaths caused by infectious diseases decreased during the study period, whereas the mortality due to other natural causes of death remained stable, in spite of aging of the study population and increasing time of exposure to HAART.

The finding of a substantial reduction in the all-cause mortality in the HIV population, which was almost entirely explained by a reduction in AIDS-related deaths, is in accordance with previous studies [4, 5, 14–16]. The reduction in the all-cause mortality was less pronounced among IDUs. In this group, the rate of unnatural deaths were as high as the rate of AIDS-related deaths and, thus, the impact of HAART on mortality was less pronounced.

Malignancies, infections, cardiovascular and hepatic diseases, accidents, and drug abuse were the most common causes of death in the late HAART era. Studies from other European countries, the US, and Canada have reached similar conclusions [4, 14–17]. Our study had a population-based, nationwide design, which makes the results

Table 2 Mortality rates (MR) among HIV patients and mortality rate ratios (MRR) of human immunodeficiency syndrome (HIV) patients versus a matched cohort from the background population

	MR/1,000 PY (95 % CI)		MRR (95 % CI)	
	1995	2008	1995	2008
All-cause mortality				
All	133.5 (118.0–151.0)	16.4 (12.8–21.2)	59.0 (44.8–77.7)	3.4 (2.5–4.5)
IDU	116.9 (84.3–162.0)	55.6 (33.5–92.2)	147.4 (50.9–426.7)	22.7 (10.1–51.0)
Non-IDU	136.7 (119.7–156.2)	13.3 (9.9–17.8)	53.5 (40.1–71.3)	2.6 (1.9–3.6)
IDU				
AIDS-related death	52.0 (31.8–84.8)	25.9 (12.4–54.4)	NA	NA
Non-AIDS-related death	6.5 (1.6–26.0)	14.8 (5.6–39.5)	7.0 (1.3–38.2)	10.3 (2.9–37.1)
Unnatural death	58.5 (36.8–92.8)	14.8 (5.6–39.5)	NA	13.9 (3.5–55.5)
Non-IDU				
AIDS-related death	122.9 (106.8–141.1)	5.0 (3.1–8.1)	NA	NA
Non-AIDS-related death	6.9 (3.8–12.5)	5.6 (3.6–8.8)	4.5 (2.3–9.0)	1.3 (0.8–2.1)
Unnatural death	6.9 (3.8–12.5)	2.7 (1.4–5.1)	5.3 (2.6–10.6)	3.2 (1.6–6.6)
Non-IDU	MR 1995–2008		MRR 1995–2008	
Cancer	3.5 (2.9–4.2)		2.7 (2.3–3.3)	
Lung cancer	0.8 (0.6–1.1)		2.7 (1.8–4.0)	
Hematological cancer	0.7 (0.4–1.0)		5.9 (3.7–9.3)	
Gastrointestinal cancer	0.6 (0.4–0.9)		1.7 (1.1–2.7)	
Cardiovascular disease	2.9 (2.4–3.5)		2.5 (2.0–3.1)	
Ischemic heart disease	1.1 (0.8–1.4)		2.4 (1.7–3.4)	
Stroke	0.6 (0.4–1.0)		2.6 (1.6–4.0)	
Hepatic disease	1.2 (0.8–1.6)		3.3 (2.4–4.6)	
Renal disease	0.5 (0.3–0.9)		5.8 (3.4–9.7)	
Suicide	1.2 (0.9–1.6)		4.2 (3.0–5.9)	

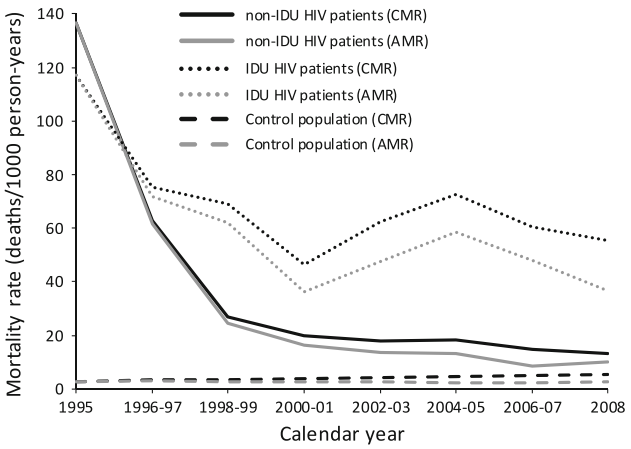

Fig. 2 Crude and age-adjusted all-cause mortality rates (MR) in HIV patients treated in Denmark and a gender- and age-matched population control cohort 1995–2008. *AMR* age-adjusted mortality rate, *CMR* crude mortality rate, *IDU* injection drug use

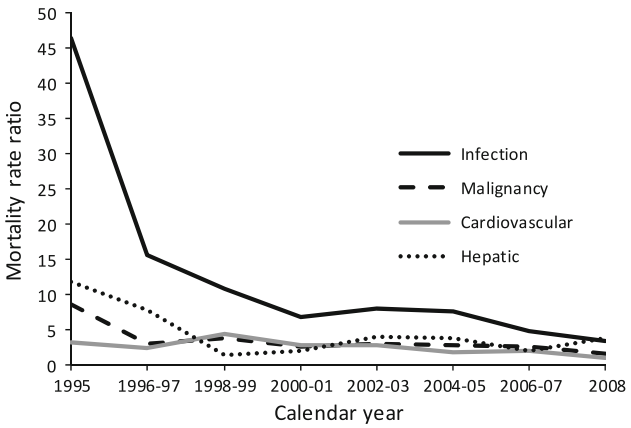

Fig. 3 Cause-specific mortality rate ratios (MMR) of natural causes of death among HIV patients treated in Denmark who were not infected through injection drug use (IDU) compared with population controls during the period 1995–2008. The MRR of renal diseases were omitted due to the limited number of events that did not allow analyses by calendar year

generalizable. Since all HIV centers in the country were included and because of the high quality of the Danish Civil Registration System, study subjects were not lost to follow-up unless they emigrated.

The present study has certain limitations. We defined the cause of death as AIDS-related if the last CD4 count before and within 6 months of death was <200 cells/μL and/or an AIDS-defining illness was diagnosed within 1 year of

death; we may, thereby, have misclassified some deaths. Even though individuals with CD4 <200 cells/μL have significantly increased risk of infections and malignancy, they do not necessarily die of AIDS-related disease. On the other hand, in a few cases of AIDS-related disease which ultimately caused death may have occurred at CD4 counts >200 cells/μL and been diagnosed more than 1 year prior to death. In 20 % of the cases, no CD4 count was available within 6 months of death, but in Denmark, where healthcare is free and very few HIV patients are lost to follow up from HIV care [18], we believe that it is unlikely that many individuals died of an AIDS-related disease which was not diagnosed prior to death or at autopsy.

It is a challenging task to determine the underlying cause of death, as several diseases and risk factors may contribute in the train of events leading to death and in the discernment of which is the determining one; there is a risk of bias. In analyses of cause-specific MR, we included all contributory death causes listed in the death certificate, in order to reduce the risk of bias and avoid the underestimation of specific death causes. It is likely that, among IDUs, deaths without an obvious cause would be considered as being caused by an overdose and, thus, the rate of unnatural deaths may be overestimated in this group. We have, however, no reason to believe that there was a systematic bias in the assessment of causes of death among non-IDU HIV patients or the control group. We used the Danish National Registry of Causes of Death as it allowed us to compare causes of death among a large number of HIV patients with a matched control group from the background population. Thereby, our assessment of the effect of HIV on causes of death was not biased by changes in screening, diagnostic procedures, or treatment during the study period. The duration of the study period of 14 years allowed us to assess the effects of long-term exposure to HIV and HAART.

Although the all-cause MRR decreased markedly during the study period, HIV-infected patients continued to have increased mortality compared with the control group in the late HAART period. Both natural and unnatural causes of death contributed to this excess mortality. The MRR of infectious diseases declined substantially during the study period and reached the level of MRR of cancer, cardiovascular, and hepatic diseases. The high mortality among the HIV patients may be partly explained by risk-taking behavior, factors associated with lifestyle, and co-morbidities, but our data do not allow any conclusions to be made as to whether the excess mortality was caused by HIV or non-HIV-related factors. However, a recent study demonstrated that the survival of Danish HIV patients who had initiated HAART had undetectable viral load and no co-morbidities or alcohol/drug abuse was almost identical to the background population without co-morbidity or alcohol/drug abuse [19], indicating that co-morbidities and abuse account for a large proportion of the excess mortality among Danish HIV-infected individuals.

In the present study, there was a high rate of deaths caused by malignancies. The rate of deaths caused by malignancies did not increase during the study period and, thus, long-term exposure to HAART did not seem to increase the risk of cancer. We found high MR and MRR of lung cancer among HIV patients. A large proportion of Danish HIV patients are smokers [20]. It has previously been documented that there is a strong association between smoking and lung cancer among HIV-infected individuals [15, 20] and that lung cancer is one of the most common malignancies among HIV patients [4, 15]. It has also been shown that the risk of lung cancer is increased among parents of Danish HIV patients, indicating that lifestyle, social, and/or genetic factors may have a marked effect on the excess risk of lung cancer among HIV patients. It is likely that some malignant deaths might be averted by addressing risk factors such as smoking, improving adherence to screening programs, and keeping a high level of vigilance when HIV patients attend regular follow-up visits.

In the late HAART period, a large proportion of deaths were caused by cardiovascular disease. It is well known that HIV patients have increased risk of cardiovascular disease [21] and that some antiretroviral drugs alter cholesterol and lipids towards a more atherogenic profile [22]. Whether the increased risk of cardiovascular disease is caused by HIV, HAART, or non-HIV-related factors are debated. Rasmussen et al. [23] found that parents of HIV patients also have increased risk of myocardial infarction compared with the background population, indicating that lifestyle factors play an important role. Previous studies have reached different conclusions regarding the association between long-term exposure to HAART and the risk of myocardial infarction. In a large prospective, observational, European collaborative cohort study (DAD study), HAART was associated with a 26 % relative increase in the rate of myocardial infarction per year of exposure [6], whereas there was no increase in the risk of serious cardiovascular events with long-term HAART in a study from the Veterans Affairs Research Initiative [24]. In the present study, there was no increase in the rate or the relative risk of cardiovascular deaths during the study period, in spite of the increasing time of exposure to HAART. Our findings do not, thereby, support the dramatic effect of HAART on cardiovascular risk observed in the DAD study. In the present study, the MRR of hepatic disease did not increase with calendar time either and, thus, we did not see any indication of an association between several years of HAART and major hepatic toxicity.

Several groups have studied inflammatory markers in HIV patients and found immune activation and elevated levels of cytokines even in patients on HAART. On the

basis of these findings, it has been argued that HIV patients have accelerated aging and, as a consequence, may have increased risk of death due to cancer and cardiovascular disease [8, 25–27]. In a recent study, the prevalence of non-infectious co-morbidities among HIV patients aged 41–50 years was similar to that among controls aged 51–60 years [28]. In the present study, the MRR of cancer and cardiovascular disease among HIV patients compared with HIV-negative individuals were unchanged during the study period, in spite of increasing age. If aging was accelerated among HIV patients compared with HIV-negative individuals, one would expect a larger increase in the MR of cancer and cardiovascular disease among HIV patients than among the population controls during the study period and, thus, our findings do not suggest that HIV infection accelerates the process of aging markedly.

We conclude that, after the introduction of HAART, there has been a marked decrease in mortality among HIV patients, almost exclusively due to a substantial reduction in the rate of AIDS-related deaths, but the long-term exposure to HIV and HAART has not translated into increasing mortality from malignancy, cardiovascular, and hepatic diseases.

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Conflict of interest N.O. has received research funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Glaxo-SmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag, and Swedish Orphan. C.P. has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Glaxo-SmithKline, Swedish Orphan, Jansen Pharma/Tibotec, and Boehringer Ingelheim. J.G. has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, ViiV, Swedish Orphan, and Gilead. M.H., G.K., C.S.L., and G.P. report no conflicts of interest.

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