

INFECTIOUS DISEASES

Causes of death among human immunodeficiency virus (HIV)-infected adults in the era of potent antiretroviral therapy: emerging role of hepatitis and cancers, persistent role of AIDS

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Background In the era of highly active antiretroviral therapy (HAART) mortality has decreased substantially among human immunodeficiency virus (HIV)-infected people with access to HAART, but there are concerns regarding co-morbidities and adverse effects of HAART, which may impair vital prognosis. The Mortality 2000 study examined the causes of death in HIV-infected adults at a national level in France in the year 2000.

Methods All French hospital wards known to be involved in the management of HIV infection were asked to notify prospectively the deaths that occurred in 2000 among HIV-infected adults. The causes of death were documented using a standardized questionnaire.

Results The 185 participating wards notified 964 deaths. The main underlying causes of death were AIDS-related (47%, non-Hodgkin's lymphoma: 23%), viral hepatitis (11%, hepatitis C: 9%, hepatitis B: 2%), cancer not related to AIDS or hepatitis (11%), cardiovascular disease (7%), bacterial infections (6%), suicide (4%), and adverse effect of antiretroviral treatments (1%). Among AIDS-related deaths, HIV infection had been diagnosed recently in 20%. Smoking was recorded in 72% of cancer-related deaths and alcohol consumption in 54% of hepatitis-related deaths. Among non-HIV related deaths between 25 and 64 years, the proportion of infectious diseases (including HCV and HBV-related deaths) was higher in HIV-infected adults than in the general population.

Conclusions Improved strategies for detecting HIV infection before AIDS-defining complications occur are needed in the era of HAART. The prevention of non-AIDS related cancers, especially lung cancer, the management of non-Hodgkin's lymphoma, and of viral hepatitis are also important priorities.

Keywords Acquired immunodeficiency syndrome, antiretroviral therapy highly active, cause of death, epidemiology, HIV infections, national survey, mortality, cancer, hepatitis

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In countries where highly active antiretroviral therapy (HAART) is available, both mortality and the incidence of new AIDS-defining diseases have dramatically declined among human immunodeficiency virus (HIV)-infected people.^{1–3} Consequently, HIV infection has become a long-term chronic disease. In addition to concerns about failure of HAART in the long term, questions related to co-morbidities and adverse effects, which may impair vital prognosis have emerged. In this context, accurate data on the causes of death are of great importance and should help to define priorities in the prevention and management of lethal co-morbidities. Such data have come from prospective studies of HIV-infected patients.^{4–6} However, many cohort studies have not collected detailed information on causes of deaths and may not be representative of the HIV-infected population. The Mortality 2000 survey was set up to describe the distribution of causes of death among those infected with HIV at a national level in France in the year 2000.

Methods

Data collection

All hospital wards known to be involved in the management of HIV infection in France were contacted. The mailing list was compiled based on networks concerned with the management of HIV infection in France (Appendix).

Physicians who agreed to participate were contacted every 4 months in 2000 and were first asked to report all deaths and abstracted causes of death in HIV-infected adults (≥ 18 years) in 2000. Second, they were asked to precisely describe the causes of death using a standardized questionnaire, including all contributing causes of death, diseases present at death and to give a global assessment of the underlying cause of death. The questionnaire also covered socio-demographic characteristics (gender, date and place of birth, date and place of death and socio-economic condition), co-morbidities and risk factors (excessive alcohol consumption, smoking, drug use, hepatitis B [HBV] and C [HCV] serological status), and data on the HIV infection (date of diagnosis, transmission category, clinical stage, last plasma HIV-RNA, last CD4 cell count, previous antiretroviral treatment). HCV infection was defined as HCV-antibody positive or HCV-RNA positive. Poor socio-economic conditions were defined as one out of: no health insurance, no employment, no accommodation, income < 535 € per month, immigrant in illegal situation.

Determination of the underlying cause of death

Information contained in the questionnaire was used to determine one underlying cause of death according to the International Classification of Diseases, 10th Revision (ICD-10) rules.⁷ The underlying cause of death is the disease or injury which initiated the train of morbid events leading to death. The algorithm of determination was adapted to specific concerns in HIV infection and allowed categorization of deaths as follows: AIDS-related causes according to the 1993 clinical classification;⁸ deaths related to infection with HCV or HBV, including hepatocarcinoma; cancers and other causes not related to AIDS or HCV/HBV, and adverse effects of treatment. The latter was considered the underlying cause of death only when this was the explicit conclusion of the physician.

AIDS-defining causes were grouped in one underlying cause of death, followed by descriptions of individual AIDS-defining pathologies. If the standardized questionnaire was missing, the abstracted quarterly notifications were used to establish the underlying cause of death, if possible.

Assessment of completeness of ascertainment and national coverage

The completeness of death ascertainment was assessed by examining the patients lost to follow-up and by reviewing hospital charts in a sample of wards, and coverage was assessed in a capture–recapture study using the national death registry.

We visited a random sample of wards to ascertain unreported deaths and patients lost to follow-up. Calculation of the number of wards needed to visit was based on the coefficient of variation of the number of deaths and done in three strata according to the number of patients followed.⁹ A patient lost to follow-up was defined as seen in 1999, not seen in 2000 or 2001, and not recorded in the survey database. Vital status of patients lost to follow-up was documented in the French National Repertory for Identification of Physical Persons.¹⁰

For deaths that occurred in January 2000, a cross-match was performed between the survey database and the French national database of death certificates based on gender, date of birth, and date of death. The total number of deaths in January 2000 was then estimated using the capture–recapture method,¹¹ assuming that these two sources were independent.

Comparison with the general population

We compared the distribution of non-HIV related causes of death to the causes of death in the general population, excluding HIV-related causes, as defined by AIDS-defining causes, specific HIV-related causes such as nephropathy, myelopathy, and cholangitis, and causes related to antiretroviral treatment or treatment of AIDS-defining pathologies. The population considered was the French general population in 1999 aged 25–64 years, stratified in 10-year age groups.¹²

Statistical analysis

We compared patient characteristics between causes of death using χ^2 and Kruskal-Wallis tests. We calculated exact 95% CI for the estimated completeness of death ascertainment and national coverage of the survey. All statistical analyses were performed using Statistical Analysis System software (SAS, version 8.2).

Results

A total of 185 wards participated in the survey and reported 64 000 HIV-infected patients with at least one contact in 2000, and 964 deaths. A questionnaire was completed for 924 deaths (96%).

Underlying causes of death

The underlying cause of death was an AIDS-defining illness in 456 patients (47%), non-AIDS related in 477 patients (50%), and unknown in 31 patients (3%). The distribution of underlying causes of death is shown in Figure 1. Among AIDS-related deaths, the mean number of AIDS-defining diseases reported at the time of death was 1.5 per case (range: 1–5). The

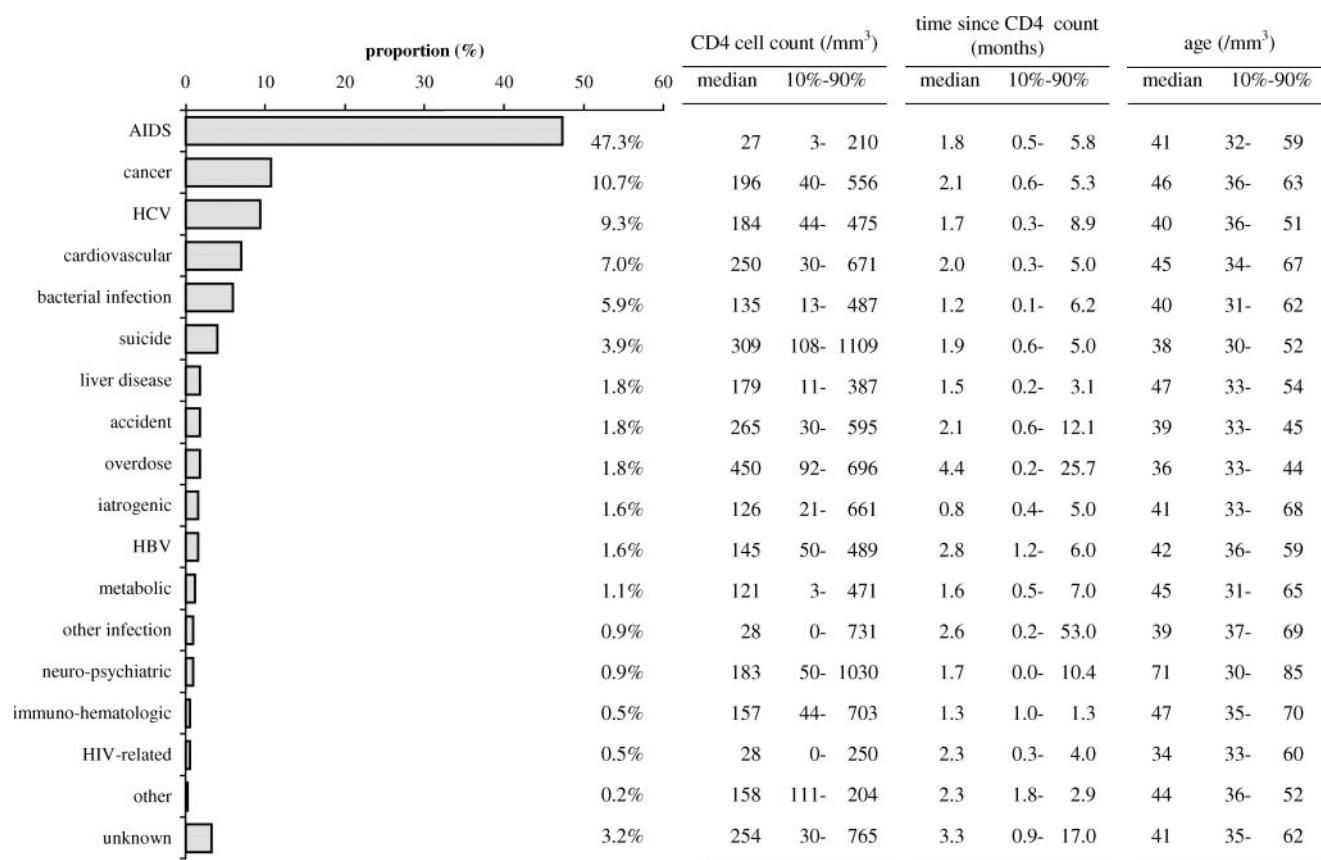


Figure 1 Distribution of the underlying causes of death in 964 HIV-infected people in 2000 in France

AIDS: acquired immunodeficiency syndrome; HCV: hepatitis C virus; HBV: hepatitis B virus; Cancer: other than AIDS and HCV-HBV-related cancer; Bacterial infection: confirmed or probable, non-AIDS related; Liver disease: alcohol (n = 12), other than HCV, HBV or alcohol-related (n = 5); Iatrogenic: antiretroviral: lactic acidosis (n = 6), hepatitis (n = 2), pancreatitis (n = 1), allergy (n = 1); other treatment (n = 4), haemothorax (n = 1); Metabolic: metabolic acidosis following surgical intervention (n = 1), diabetes mellitus (n = 4), renal (n = 4), pancreatic (n = 2); other than iatrogenic and HIV-related; Other infection: viral, fungal, parasitic infection: herpes zoster (n = 3), aspergillosis (n = 2), pulmonary toxoplasmosis (n = 2), HTLV-I (n = 1), influenza (n = 1); Immuno-hematologic: Castleman disease (n = 1), refractory anaemia (n = 1), erythrophagocytosis (n = 1), thrombotic microangiopathy (n = 1), antiphospholipid syndrome (n = 1); HIV-related disease: non-AIDS related: nephropathy (n = 3), myelopathy (n = 1), cholangitis (n = 1); Other: gastro-duodenal ulcer (n = 1), emphysema (n = 1)

most frequent underlying causes were non-Hodgkin's lymphoma (23%) and cytomegalovirus disease (20%, Table 1). Among patients whose HIV infection was diagnosed within 6 months of their death, the most frequent AIDS-defining cause was *Pneumocystis carinii* pneumonia (38%, Table 1).

Frequent non AIDS-related causes of death included cancers not related to AIDS or HCV/HBV infection (103, 11%), HCV infection (90, 9%), cardiovascular disease (67, 7%), bacterial infections (57, 6%), and suicide (38, 4%). The two most frequent types of cancers in this category were lung cancer (41) and Hodgkin's lymphoma (12). Other cancers included digestive (9), eye-nose-throat (6), anal (6), central nervous system (4), myeloid leukaemia (4), pleural (3), prostate (3), breast (3), hepatocarcinoma (2), skin (2), sarcoma (2), uterus (1), bladder (1), penis (1), multiple myeloma (1), and unknown (3).

Among the 90 HCV-related deaths and the 15 HBV-related deaths, 10 and 7 were related to hepatocellular carcinoma, respectively. Among the 67 cardiovascular-related deaths, 22 were related to coronary artery disease, 12 to a cerebrovascular accident, 9 were related to heart failure, 6 to pulmonary

hypertension, 4 to venous thrombosis or pulmonary embolism, 4 to valvular disease or endocarditis, 2 to pericardial disease, 1 to arrhythmia, 1 to aortic aneurysm, and 6 suspected without more precision. Among the 57 non-AIDS bacterial infections reported as the underlying cause of death, the most frequent were pulmonary infections (26, including 12 *Pneumococcus pneumoniae* infections). In 10 patients (1%), antiretroviral treatment was considered the underlying cause of death leading to lactic acidosis (6), hepatitis (2), pancreatitis (1), or an allergic reaction (1). In 47 additional cases, antiretroviral treatment was mentioned as having contributed to the death, with the following underlying causes of death: AIDS (23), HCV (8), cardiovascular (7), cancer (2), infection (2), nephropathy (2), accident (1), overdose (1), and suicide (1). Overall 7% of deaths were related to accident, overdose, or suicide.

Characteristics of patients who died from different causes

The characteristics of patients who died, based on the 924 completed questionnaires, are shown in Table 2. Median age at

Table 1 Number and frequency of AIDS-defining illnesses among 456 human immunodeficiency virus (HIV)-infected people with AIDS-related underlying cause of death in 2000 in France

	Total (<i>n</i> = 456)		Time since diagnosis of HIV infection			
			≤6 months (<i>n</i> = 81)		6 months (<i>n</i> = 358)	
	<i>n</i>	(%)	<i>n</i>	(%)	<i>n</i>	(%)
Non-Hodgkin's lymphoma	105	(23.0)	11	(13.6)	89	(24.9)
Cytomegalovirus disease	89	(19.5)	17	(21.0)	72	(20.1)
Atypical mycobacterial infection	65	(14.3)	7	(8.6)	56	(15.6)
<i>Pneumocystis carinii</i> pneumonia	64	(14.0)	31	(38.3)	30	(8.4)
Toxoplasma encephalitis	55	(12.1)	14	(17.3)	40	(11.2)
Multifocal leukoencephalopathy	49	(10.7)	5	(6.2)	43	(12.0)
Kaposi's sarcoma	46	(10.1)	9	(11.1)	36	(10.1)
Oesophageal or pulmonary candidiasis	38	(8.3)	6	(7.4)	32	(9.0)
Tuberculosis	35	(7.7)	6	(7.4)	28	(7.8)
HIV encephalopathy	35	(7.7)	5	(6.2)	30	(8.4)
Cryptococcosis	22	(4.8)	5	(6.2)	16	(4.5)
Cryptosporidiosis	21	(4.6)	3	(3.7)	18	(5.0)
Wasting	18	(3.9)	4	(4.9)	14	(3.9)
Histoplasmosis	11	(2.4)	4	(4.9)	7	(2.0)
Herpes	8	(1.8)	1	(1.2)	7	(2.0)
Cervical cancer	5	(1.1)	–		5	(1.4)
Isosporidiosis	1	(0.2)	–		1	(0.3)
Recurrent bacteria pneumopathy	1	(0.2)	–		1	(0.3)

death was 41 years; the last CD4+ cell count was >200/mm³ in 291 patients (32%) and HIV-1 RNA <500 copies/ml in 285 (33%); 149 patients (17%) had both a CD4 count >200/mm³ and a HIV-RNA measurement <500 copies/ml. The median time between last CD4 measurement and death was 1.9 months (interquartile range: 0.9–3.6). Overall 263 patients (29%) never reached the AIDS stage. About one-third had HCV co-infection and 12% were HBs antigen positive. Half of the patients were smokers and one-third were exposed to poor socio-economic conditions.

Patients dying from AIDS-related causes had lower median CD4+ cell counts than those dying from other causes (27 versus 212 cells/mm³) and higher median HIV-RNA (5.0 versus 3.1 log₁₀ copies/ml). They were less likely to be intravenous drug users, died more frequently in French overseas areas and more frequently had HIV infection diagnosed within the last 6 months.

Patients dying from cancers were older than those dying from another cause, were more frequently male and smokers, had a higher median CD4+ cell count (196 versus 80 cells/mm³) and a longer known duration of HIV infection.

Compared to patients dying from another cause, patients dying from a cause related to HCV and/or HBV hepatitis more frequently had a history of excessive alcohol and tobacco consumption. They had higher median CD4+ cell count (180 versus 78 cells/mm³) and a longer known duration of HIV infection. Patients dying from cardiovascular disease were older than those dying from other causes and had a higher median CD4+ cell count (250 versus 83 cells/mm³); 24% had dyslipidaemia compared with 11% among patients dying from other causes. Among patients committing suicide, 43% had a history of excessive alcohol consumption and 19% were active

drug users. Among patients whose cause of death was unknown, 30% were active drug users, 54% had excessive alcohol consumption, and 50% had poor socio-economic conditions.

Causes in patients dying free of AIDS and with no antiretroviral treatment

The main causes of death in patients dying without having reached the AIDS stage were cancer (22%), HCV (21%), cardiovascular disease (13%), and suicide (10%). In this group the median CD4+ cell count was high (296 cells/mm³) and the median HIV-RNA low (2.9 log₁₀ copies/ml). Half were HCV co-infected, 69% were smokers, and 45% had a history of excessive alcohol consumption.

Compared with patients with previous antiretroviral treatment, patients dying with CD4+ cell counts <200 cells/mm³ and no previous antiretroviral treatment had HIV infection diagnosed within 6 months in 54% (versus 5%), were born abroad in 44% (versus 23%), and died in French overseas areas in 25% (versus 8%). Overall 92% had reached the AIDS stage (versus 72%) and 84% died from AIDS (versus 45%). The main reasons given for the absence of treatment were recent admission to clinic (60%) and irregular follow-up (26%).

Completeness of ascertainment and national coverage of survey

The completeness of ascertainment of deaths was examined in a sample of 27 wards which had reported 114 deaths. Among the 186 patients identified as lost to follow-up, the vital status of 118 could be documented through the National Repertory for Identification of Physical Persons, which identified 4 additional

Table 2 Characteristics of human immunodeficiency virus (HIV)-infected people dying in 2000 in France according to cause of death, analysis based on 924 questionnaires

	All causes (n = 924)	AIDS ^a (n = 441)	HCV ^b or HBV ^c (n = 105)	Cancer ^d (n = 98)	Cardio vascular (n = 65)	Other (n = 215)
Male gender (%)	78	77	73	87	82	77
Median age (years)	41	41	40	46	45	40
(inter-quartile range)	(36–49)	(35–49)	(38–44)	(40–54)	(37–56)	(35–48)
Known duration of HIV infection (years)	7.6	6.5	11.1	8.6	7.5	7.8
(inter-quartile range)	(3.3–11.6)	(1.5–10.2)	(7.3–13.8)	(5.8–12.2)	(3.7–11.7)	(4.0–11.7)
HIV infection diagnosed within 6 months (%)	11	18	2	7	3	5
HIV transmission group (%)						
Heterosexual	34	40	15	37	32	32
Homo-bisexual	27	32	10	31	23	25
Injecting drug use	28	16	67	22	28	35
Other/undetermined	11	12	8	10	17	8
AIDS ^a stage (%)	71	100	40	42	46	50
Median CD4+ cell count (/mm ³)	94	27	180	196	250	229
(inter-quartile range)	(19–260)	(8–90)	(96–345)	(89–356)	(123–456)	(73–417)
Median HIV-RNA (log ₁₀ copies/ml)	4.2	5.0	3.2	2.6	2.7	3.6
(inter-quartile range)	(2.3–5.3)	(3.5–5.6)	(1.9–4.6)	(1.7–4.2)	(1.7–4.3)	(1.9–4.9)
No prior antiretroviral treatment (%)	14	19	6	8	12	14
HAART ^e (%)	78	78	77	84	83	75
HCV ^b antibodies (%)	35	21	88	24	41	37
HBs antigen (%)	12	8	29	13	11	10
Excessive alcohol consumption (%)	29	14	54	27	30	45
Smoking (%)	52	42	74	72	58	53
Active drug use (%)	11	8	19	1	15	19
Poor socio-economic conditions ^f (%)	33	32	39	22	26	40
Non-native from France (%)	25	30	15	9	26	26
Death in French overseas areas (%)	10	14	4	8	9	7
Death at hospital (%)	83	91	94	91	63	63

^a AIDS: acquired immunodeficiency syndrome; AIDS stage: 1993 CDC clinical stage C.

^b Hepatitis C virus.

^c Hepatitis B virus.

^d Cancer: other than AIDS and HCV-HBV-related cancer.

^e HAART: highly active antiretroviral therapy.

^f Poor socio-economic conditions: at least one of the following items: no health insurance, no employment, no accommodation, income below 535 € per month, immigrants in illegal situation.

deaths in 2000. Incorrect identification made it impossible to check the vital status of the remaining 68 patients. Moreover, during these visits, seven additional deaths were identified after checking hospital files. Therefore, the estimated completeness of death ascertainment for these wards was 91% (114 of 125, 95% CI: 85%, 96%). The underlying causes of the 11 additional deaths were AIDS (n = 7), cancer (n = 1), HCV (n = 1), suicide (n = 1), and unknown (n = 1).

The capture–recapture exercise for January 2000 showed that 17 of 104 deaths identified in the survey could not be matched to deaths in the national death registry whereas 38 of 120 deaths whose death certificate in the national registry mentioned HIV infection were not included in the survey database. Based on

these two sources, the estimated number of deaths in January 2000 was 149 (95% CI: 142, 156), resulting in an estimated national coverage of the survey of 69% (95% CI: 62%, 78%). Most of the 38 additional deaths identified in the national death registry were reported by physicians not routinely involved in the management of HIV infection. The underlying causes of death included AIDS in 19 patients, cancer in 6, HCV in 4, and non-specified sepsis or pneumonia in 3 patients.

Comparison with general population

Considering non-HIV related deaths in patients aged 25–64 years (426 deaths), the proportion of infectious diseases (including HCV and HBV-related deaths) was higher in HIV-infected adults than in

the general population in all age groups, and the proportion of cardiovascular disease was higher <35 years (Figure 2). The proportion of tumoural causes of death was higher in the general population >35 years and the proportion of external causes of death was higher in the general population <45 years.

Discussion

This collaborative survey of the causes of death among HIV-infected adults in the era of HAART found that 47% of 964 deaths in France in 2000 were AIDS-related. Two reasons were identified for the high proportion of AIDS-related causes: a late diagnosis of HIV infection, particularly in immigrants and those living in French overseas areas, and the persistence of non-Hodgkin's lymphoma. The most frequent non AIDS-related deaths were cancer (11%), HCV infection (9%), and cardiovascular diseases (7%). Smoking and excessive alcohol consumption was present in many of these patients.

Strengths and weaknesses

Our survey was based on physicians involved in the routine management of HIV infection, but the capture–recapture study using the national death registry indicated that about 30% of deaths among HIV-infected people were missed. The more diverse morbidity in HIV-infected people in the HAART era may have widened the number of physicians and specialties involved. The distribution of the causes of death was similar for reported and missed deaths and our sample may thus nevertheless be representative of the target population.

The comparison of non-HIV related deaths with the general population should be interpreted with caution, since the number of cases was small in each age category. We acknowledge that summarizing the course of events leading to death in one underlying cause, according to ICD-10 rules, is problematic. The use of an internationally standardized definition will, however, facilitate comparisons with other studies and populations. Moreover, we presented detailed information on individual AIDS-related pathologies and on causes related to antiretroviral treatment.

Relationship to other studies

Compared to a previous study performed in France in 1992 based on a sample of death certificates that mentioned HIV or AIDS,¹³ death occurred at a younger age in 1992 (38 versus 41 years) and mean CD4 cell count was lower in 1992 than in 2000 (43 versus 117 cells/mm³). The higher age may reflect two mechanisms: ageing of HIV-infected people due to improving prognosis or occurrence of new infections at a higher age. Considering the higher CD4 cell count in 2000, improved management of HIV infection appears to be the dominant factor.

Poor socio-economic conditions were reported in one of three deaths. Despite universal health care in France, poor socio-economic conditions are associated with higher mortality among the HIV-infected as well as in the general population.^{14–16} A decrease in the proportion of AIDS-related deaths since 1995 has been reported among those with AIDS,¹⁷ and in cohort studies of HIV-infected adults,^{5,6} reflecting the improved prognosis in the era of HAART.^{1–3} Nevertheless, AIDS remains a frequent cause of death, partly due to the late diagnosis of HIV: in France in 2001, half of those with a new AIDS diagnosis were simultaneously diagnosed with HIV infection.¹⁸

Since the advent of HAART, the incidence of non-Hodgkin's lymphoma has decreased,^{19,20} but less than the incidence of other AIDS-defining diseases.² Although its prognosis has improved in the HAART era,¹⁹ non-Hodgkin's lymphoma is the most frequent cause of AIDS-related death.⁴ Before HAART, an excess of non-AIDS cancers (Hodgkin's lymphoma and anal cancer) was demonstrated among homosexual men.²¹ Nevertheless, among non-HIV related deaths, the proportion of cancers was lower in HIV-infected adults than in the general population. In this survey, the most frequent non-AIDS and non-HCV/HBV related cancer was cancer of the lung, in accordance with other studies.^{17,22} These results will at least partly be the consequence of the high prevalence of smoking among HIV-infected people.²³ Finally, one can anticipate that the incidence of cancer will increase in parallel with the ageing of the HIV-infected population.

HBV and HCV infection accounted for 11% of deaths and 21% of non-HIV related deaths. Shared modes of transmission of HIV, HCV, and HBV partly explain the higher proportion of infectious causes of death not related to HIV infection in HIV-infected adults compared with the general population. Because of the dramatic improvement in the survival of HIV-infected people, the long-term exposure to HCV infection required for complications to develop in co-infected people is becoming more common. Moreover, progression to HCV-related fibrosis is accelerated by HIV infection.^{24,25}

Although cardiovascular diseases accounted for only 7% of deaths and coronary artery disease for 2%, they accounted for 14% of non-HIV related deaths. The proportion of deaths due to cardiovascular disease among HIV-infected patients was similar to the proportion in the general population, except for a higher proportion in HIV-infected people <35 years (Figure 2). Cardiovascular deaths will probably increase during the coming years, as HIV-infected people age, and exposure to lipid abnormalities associated with HAART accumulates.²⁶ Coronary risk is higher among HIV-infected adults than in the general population.^{23,27,28} Fortunately, newer treatment combinations may have fewer metabolic side effects than those including protease inhibitors.²⁹

Non-AIDS defining bacterial infections were the underlying cause in 6% of deaths. Despite the decrease in the incidence of bacterial pneumonia since the advent of HAART, pneumonia still occurs, particularly in injecting drug users or patients in hospital care.³⁰ Further research is warranted on the need to maintain prophylaxis with trimetoprim-sulfamethoxazole in specific populations, like in resource-limited settings.³¹

Only few underlying causes were related to antiretroviral therapy. This may be an underestimate since antiretroviral treatment was mentioned as having contributed to death in an additional 5% of deaths, bringing the figure close to that reported by Valdez *et al.*, who reported 4 deaths related to the treatment of HIV infection among 52 patients (8%).³² External causes of death (overdose, accident, and suicide) accounted for 7% of cases and 15% of non-HIV related causes. Interestingly, the proportion of external causes was higher in the general population <45 years (Figure 2).

Implications for prevention and research

The late diagnosis of HIV infection calls for increased screening efforts, particularly in marginalized populations in France and those living in the French overseas areas. Furthermore, specific programmes for smoking and alcohol cessation should be

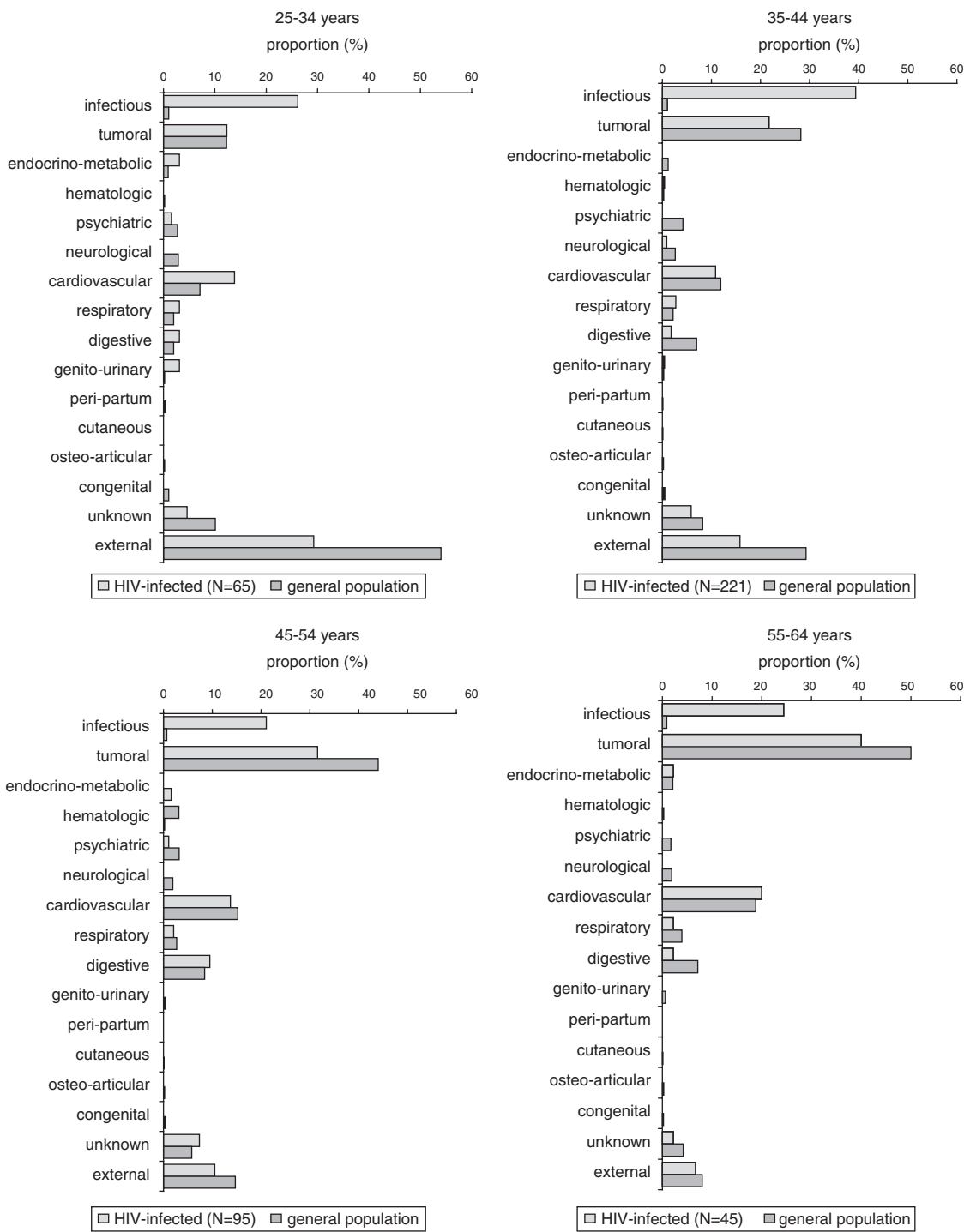


Figure 2 Distribution of the underlying causes of non-human immunodeficiency virus (HIV) related deaths in 426 HIV-infected adults aged 25–64 (France, 2000) compared with the distribution of the causes of death in the general population (France, 1999)

developed for HIV-infected people. More research is needed on early biological markers for non-Hodgkin's and Hodgkin's lymphoma and on treatment strategies of HCV infection in HIV-infected patients, as responses rates are half those reported in non-HIV infected patients.³³ Prevention policies set up in France to decrease the transmission of both HIV and HCV infection through injecting drug use may have led to a decrease

in the number of new co-infections. The adverse effects of HAART did not appear to markedly affect vital prognosis in 2000, but ongoing surveillance is required and the development of less toxic treatments is warranted.

HIV infection may be causally involved in other pathologies such as cancer, bacterial infection, viral and parasitic infections, cardiovascular disease, and aggravation of HCV infection.

Further data are needed to quantify the exact role of HIV. In the context of surveillance, clinical trials, and cohort studies, our results should be useful when developing algorithms for determining the underlying cause of death in HIV-infected patients, and in particular for distinguishing between HIV- and non-HIV related deaths.

Finally, even in regions where HAART is currently available, the distribution of the causes of death may vary considerably between countries.⁵ Indeed, regional variations in the distribution of the causes of death are likely considering the differing prevalence of co-morbidities like HCV and HBV infections or risk factors for cancers and cardiovascular diseases, such as smoking.

Conclusion

Improved strategies are urgently needed to ensure timely detection of HIV infection, particularly in vulnerable and marginalized populations in France and its overseas territories.

Moreover, prevention, screening, and management of non-Hodgkin's lymphoma and of non-AIDS related cancers, especially lung cancer, prevention of cardiovascular diseases, and management of viral hepatitis should be considered public health priorities.

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KEY MESSAGES

- Mortality has decreased substantially among human immunodeficiency virus (HIV) infected people with access to potent antiretroviral therapy, but there are concerns regarding co-morbidities and adverse effects of HAART, which may impair vital prognosis.
- The three main underlying causes of death in HIV-infected adults in France in 2000 were AIDS in 47% (of whom 23% were non-Hodgkin lymphoma), viral hepatitis in 11%, and non-AIDS and non-hepatitis related cancer in 11%.
- Among AIDS-related deaths, 20% had HIV infection recently diagnosed.
- Smoking was recorded in 72% of cancer-related deaths and alcohol consumption in 54% of hepatitis-related deaths.

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Appendix

Mortality 2000 Study Group

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Commentary: Death in the era of potent antiretroviral therapy: shifting causes, new challenges

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Several studies have shown that the introduction of highly active antiretroviral therapies (HAART) has led to a substantial reduction in HIV-associated mortality.^{1–4} This in turn has resulted in a notable shift in causes of death among adults who died with or due to HIV infection.^{5–11} In this issue Lewden *et al.* present the results of a nation-wide survey of the causes of death of 964 HIV-infected individuals who died in the year 2000 in 185 wards in France.¹²

Their study has several strengths. The investigators made extensive efforts to ascertain all deaths among HIV-infected individuals cared for in hospitals known to be involved in the management of HIV infection in France. They visited sites to check and enhance the completeness and accuracy of the available information. Finally, they collected an array of important and detailed information on the deceased HIV-infected

individuals, going far beyond what is available from routine hospital records or death certificates.

AIDS/HIV infection was attributed to be the underlying cause of the death in about half the cases, and cancer, cardiovascular diseases, hepatitis C, and bacterial infections in a third. Of note, only three quarters of deceased patients had received HAART treatment prior to death and the excess of infections among the causes of death of HIV-infected people compared with the background population is remarkable. Most of these infections are preventable by using HAART and effective chemoprophylaxis, including *Pneumocystis* pneumonia and tuberculosis. One in nine had the HIV infection diagnosed only recently and a third lived in poor socio-economic conditions. Clearly, HIV-associated mortality is increasingly affecting individuals with multiple risk factors, including social deprivation and reduced access to health services. These important results reinforce the notion that implementing equitable access to HIV diagnosis and treatment is not only a challenge for the less developed countries but also for economically developed societies, many of whom suffer from substantial health and social disparities.

There are important concerns whether longer duration of antiretroviral therapy, known to affect various metabolic

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