

Number of deaths among HIV-infected adults in France in 2000, three-source capture–recapture estimation

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SUMMARY

We estimated the number of deaths in France for the year 2000 in HIV-infected adults using three sources. The sources were (1) the ‘Mortalité 2000’ survey (M2000): 964 deaths were documented by 185 hospital wards involved in HIV management; (2) 1288 death certificates with a mention of HIV infection (INSERM-CèpiDc) and (3) the French hospital database on HIV infection (FHDH) identified 654 deaths. The capture–recapture method was used with log-linear modelling. Overall 1559 deaths were observed. Estimation of the number of deaths in France was 1699 (95% CI 1671–1727). The completeness of M2000, CèpiDc and FHDH were 55%, 76% and 38% respectively. Diversification of diseases and of causes of death in HIV-infected adults may explain: (1) the diversification of physicians involved in their management and incomplete coverage of M2000 and FHDH, and (2) why HIV infection was not mentioned in all death certificates.

INTRODUCTION

Causes of death have changed in HIV-infected adults since the dramatic decline in AIDS-related mortality due to highly active antiretroviral therapy (HAART) [1, 2]. Since mortality remains higher in HIV-infected persons than in the general population [3, 4], a description of the distribution of causes of death may provide a means of identifying priorities in the management of HIV infection and associated

comorbidities. Several sources are available in France for identifying deaths in HIV-infected persons. First, surveillance systems on HIV and AIDS record deaths after occurrence of AIDS. None of the other following sources alone allow for a valid estimation of the number of deaths in HIV-infected persons. Identification through death certificates involves a selection of certificates which mention HIV infection. Due to the increasing diversification of the causes of death, this source may omit non-HIV-related deaths. Cohort studies do not include the whole HIV-infected population, and do not currently use standardized determination of the causes of death. Finally, a specific survey, called ‘Mortalité 2000’, was planned in

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France in 2000 to describe the distribution of the causes of death in HIV-infected adults [5]. The participating physicians were those identified as currently involved in the management of HIV infection.

Using the capture–recapture method, the number of cases can be estimated according to several sources when complete census is not available and when random sampling is not easily applicable [6–8]. This method is based on cross-match between several databases in order to identify common cases. The availability of at least three sources makes it possible to verify hypotheses of the capture–recapture method.

The objective of this analysis was to estimate the number of deaths in France in 2000 in HIV-infected adults according to three sources representing different modes of collection of deaths in HIV-infected adults: the national death certificates database (CepiDc), the French hospital database on HIV infection (FHDH), a cohort of HIV-infected patients followed in hospitals, and the ‘Mortalité 2000’ survey (M2000). The completeness of each source was assessed.

METHODS

Data sources

Three sources of data were used, all approved by the French commission on informatics and liberties. First, the M2000 aimed at describing the distribution of the underlying cause of death in HIV-infected adults based on a standardized questionnaire [5]. All hospital wards known to be involved in the management of HIV infection in France were contacted. Physicians who agreed to participate were asked to report all deaths in HIV-infected adults (≥ 18 years) quarterly in 2000.

Second, death certificates for adults in 2000 with any mention of HIV infection were selected by the Epidemiological Center for Medical Causes of Death (INSERM-CepiDc).

Third, deaths of adults in 2000 were identified in FHDH, a cohort concerning HIV-infected patients followed in 29 HIV Information and Care Centers (CISIH) [9].

Cross-matches

The three databases were matched 2×2 using the following variables: gender, date of birth and date of death for M2000 and CepiDc; gender, month and year of birth, date of death and transmission group

for M2000 and FHDH; and gender, month and year of birth and date of death for CepiDc and FHDH. A first step retained exact cross-matches. Further steps accepted one or two differences after checking place of birth and place of death, when available. For these cross-matches accepting differences among matching variables, the causes of death had to be informative (other than unknown or an immediate cause of death) and belong to the same category of the *International Classification of Diseases – 10th revision* (ICD-10).

Capture–recapture method

The capture–recapture method was used to estimate the total number of cases according to the three sources of data. It is based on the following hypotheses [6, 7, 10]: cases must be true cases with common definition between sources; the population must be closed and the period and geographical areas must be the same between sources; the matching between sources must be accurate; the probability for each case to be identified must be the same within one source (homogeneity of capture); and identification by one source does not have to depend on identification by another (independence). Possible heterogeneity and dependence can be tested and taken into account using a log-linear model when more than two sources are available.

First, estimates of the total number of deaths were calculated for each pair of sources using unbiased formulae of Chapman [11] and Seber [12]. Dependence between sources comparing pairwise estimates can thus be detected [13], a lower estimate as compared to the others leading to suspected dependence between the sources of the concerned pair.

Second, the total number of deaths was estimated by log-linear modelling including all 2×2 interactions between the three sources, in order to take into account dependence between sources or heterogeneity of capture [6]. Statistical Analysis System software 8.2 PROC GENMOD was used (SAS Institute, Cary, NC, USA). A first step identified potential interaction between sources (dependence) and a second step stratified the analysis by gender and age in order to identify possible heterogeneity of capture. Age was considered in two classes: above or below 50 years. The choice of the final model was based on the Akaike Information Criterion [$AIC = G^2 - 2(D.F.)$] and on the Bayesian Information Criterion [$BIC = G^2 - (\log N_{obs}/2\pi)(D.F.)$] where G^2 is the deviance, D.F. the number of degrees

of freedom and N_{obs} the number of observed cases [7]. The 95% confidence intervals (95% CI) were based on variance.

Deaths from Metropolitan France (excluding over-sea areas) were stratified according to the place of death in two groups: Paris region (Ile-de-France) and other regions. The completeness of a source was defined as the number of deaths identified by this source divided by estimate of the total number of deaths.

In the death certificates' source, the underlying cause of death was determined by CapiDc according to ICD-10 rules [14]. In M2000, the underlying cause of death was determined using a coding adapted from the ICD-10 rules for specific concerns in HIV infection [5]. The underlying cause of death was not available in the FHDH source. The distribution of the underlying cause of death was described from the point of view of both M2000 and CapiDc, according to identification by other sources. Characteristics of patients were described according to the source and compared using χ^2 and Kruskal–Wallis tests.

RESULTS

Cross-matches

In 2000, 964 deaths were identified in HIV-infected adults in M2000, 1288 in CapiDc and 654 in FHDH. Pairwise matching retained 538, 451 and 276 exact cross-matches and accepted 717, 571 and 486 cross-matches between M2000–CapiDc, M2000–FHDH and CapiDc–FHDH respectively. Overall, 427 cases were common to all three sources and 1559 cases were identified by one source at least (Fig.).

Capture–recapture estimates

According to the two-source capture–recapture analysis, the estimate of the total number of deaths for the M2000–FHDH pair was about 1.6 times smaller (1104, 95% CI 1083–1125) than for the M2000–CapiDc (1731, 95% CI 1689–1774) and the CapiDc–FHDH (1733, 95% CI 1671–1794) pairs, leading us to suspect dependence between the two sources: M2000 and FHDH.

Log-linear modelling using the three sources selected the model with an estimate of the number of deaths given by the three sources and an interaction M2000*FHDH, confirming the dependence between M2000 and FHDH. Among the four models with the lowest values of both AIC and BIC, this model had the lowest number of parameters. At this step

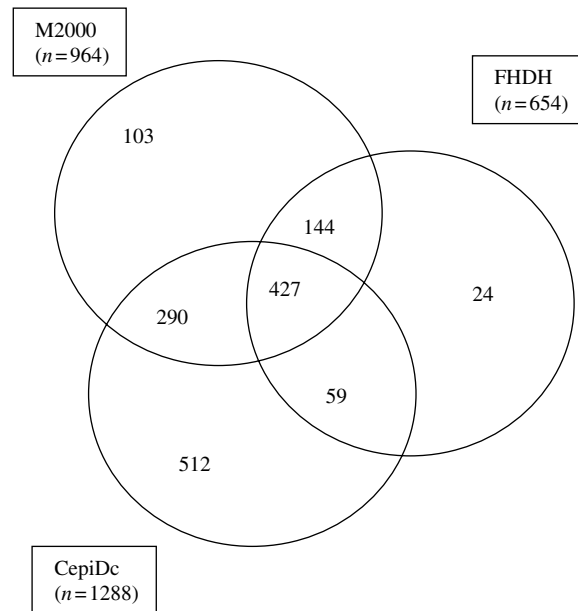


Fig. Number of deaths of HIV-infected adults in France in 2000, cross-matches between three sources of data: Mortality 2000 survey (M2000), death certificates (CapiDc) and French Hospital Database on HIV infection (FHDH).

estimation of the number of deaths was 1738 (95% CI 1711–1770).

Overall 1534 (98%) observations among the 1559 identified by at least one source had gender and age documented. Heterogeneity of capture was identified according to gender and age (Table 1, model 4). Finally the estimated number of deaths in France was 1699 (95% CI 1671–1727). The completeness of M2000, CapiDc and FHDH was, therefore, 55% (95% CI 54–56), 76% (95% CI 74–77) and 38% (95% CI 37–39) respectively (Table 2).

Considering deaths that occurred in Metropolitan France (excluding over-sea areas), 1433 cases with documented gender and age were recorded. Heterogeneity of capture was identified according to the region of death, and an interaction was identified between FHDH and the region. The final model took into account heterogeneity of capture according to gender, age and region of death (Table 1, model 6). In Metropolitan France, the estimated number of deaths was 1574 (95% CI 1548–1599) and the completeness of M2000, CapiDc and FHDH was 54% (95% CI 53–55), 78% (95% CI 77–80) and 36% (95% CI 35–36) respectively (Table 3). In FHDH, the completeness was higher in men aged <50 years who had died in the Paris region, and in M2000 the completeness was lower in men and

Table 1. Log-linear models and estimates of the number of deaths in HIV-infected adults in France in 2000, stratified by gender (SEXE) and age (AGE50) and in Metropolitan France (excluding overseas areas) stratified by gender, age and region of death (REG2)

	Models	N est.	D.F.	G ²	AIC	BIC
France						
1bis	M2000, CapiDc, FHDH, M2000 * FHDH	1696	2	3.143	-0.857	-19.954
2. Gender	M2000, CapiDc, FHDH, M2000 * FHDH, SEXE	1696	8	7.544	-8.456	-84.842
3. Age	M2000, CapiDc, FHDH, M2000 * FHDH, AGE50	1696	8	5.891	-10.109	-86.494
4. Gender and age	M2000, CapiDc, FHDH, M2000 * FHDH, SEXE, AGE50	1696	21	21.088	-20.912	-221.424
Metropolitan France						
1ter	M2000, CapiDc, FHDH, M2000 * FHDH	1574	2	2.109	-1.891	-20.987
4bis: gender and age	M2000, CapiDc, FHDH, M2000 * FHDH, SEXE, AGE50	1574	21	23.067	-18.933	-219.445
5. Region of death	M2000, CapiDc, FHDH, M2000 * FHDH, REG2, FHDH * REG2	1574	7	19.157	5.157	-61.681
6. Region of death, gender and age	M2000, CapiDc, FHDH, M2000 * FHDH, SEXE, AGE50, REG2, FHDH * REG2	1574	47	65.479	-28.521	-477.286

M2000, Mortalité 2000 survey; FHDH, French Hospital Database on HIV infection; CapiDc, Centre d'Epidémiologie sur les Causes de décès [Epidemiological Centre for Medical Causes of Death]; D.F., degrees of freedom; G², deviance; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion.

Table 2. Estimates of the number of deaths in HIV-infected adults in France in 2000 according to age and gender, and completeness of the three sources of data

Strata	N est.	95 % CI		Total		M2000		CapiDc		FHDH	
		Low	High	N obs.	%	N obs.	%	N obs.	%	N obs.	%
<50 years											
Men	981	964	1002	895	91	557	57	754	77	392	40
Women	288	278	303	258	90	160	56	217	75	106	37
≥50 years											
Men	358	344	377	312	87	179	50	256	72	126	35
Women	73	71	79	69	94	43	59	61	83	30	41
Total	1699	1671	1727	1534	90	939	55	1288	76	654	38

M2000, Mortalité 2000 survey; FHDH, French Hospital Database on HIV infection; CapiDc, Centre d'Epidémiologie sur les Causes de décès [Epidemiological Centre for Medical Causes of Death]; 95 % CI, variance-based 95 % confidence interval.

women aged >50 years who had died in the Paris region (Table 3).

Characteristics of patients according to the source

Because of the dependence between FHDH and M2000, the comparisons of patient characteristics

were carried out according to the following grouping: (1) common cases to CapiDc and (M2000 or FHDH), (2) (M2000 or FHDH) without CapiDc, (3) CapiDc only (Table 4). Age and gender did not differ according to the sources. Cases identified by M2000 or FHDH had died more frequently in overseas areas or abroad and more frequently at home (37%)

Table 3. Estimates of the number of deaths in HIV-infected adults in Metropolitan France (excluding overseas areas) in 2000 according to region of death, age and gender, and completeness of the three sources of data

Strata	N est.	95% CI		Total		M2000		CepiDc		FHDH	
		Low	High	N obs.	%	N obs.	%	N obs.	%	N obs.	%
Ile-de-France											
<50 years											
Men	342	333	354	315	92	195	57	264	77	157	46
Women	113	108	123	102	90	61	54	87	77	38	34
≥50 years											
Men	121	114	135	106	87	57	47	87	72	40	33
Women	29	27	35	27	95	13	46	25	88	8	28
Other region											
<50 years											
Men	591	577	609	538	91	322	55	464	79	198	34
Women	148	142	159	135	91	80	54	119	80	49	33
≥50 years											
Men	197	189	210	178	90	99	50	157	80	61	31
Women	33	32	37	32	96	22	66	29	87	13	39
Total	1574	1548	1599	1433	91	849	54	1232	78	564	36

Ile-de-France, Paris region; M2000, Mortalité 2000 survey; FHDH, French Hospital Database on HIV infection; CepiDc, Centre d'Epidémiologie sur les Causes de décès [Epidemiological Centre for Medical Causes of Death]; 95% CI, variance-based 95% confidence interval.

Table 4. Characteristics of HIV-infected persons dying in France in 2000 according to the source of identification

	Total (n = 1559)	CepiDc and (M2000 or FHDH) (n = 776)	(M2000 or FHDH) only (n = 271)	CepiDc only (n = 512)
Male gender (%)	79	79	79	78
Median age (years)	42	41	42	42
(Inter-quartile range)	(36–50)	(36–49)	(36–50)	(36–51)
Place of death (%)				
France	93	93	75	99
Overseas areas	7	7	20	1
Abroad	1	—	5	—
Region of death (%)				
Ile-de-France	35	37	31	35
Provence-Alpes-Côte d'Azur	15	15	16	15
Overseas departments	7	7	20	1
Languedoc-Roussillon	6	6	5	6
Rhône-Alpes	5	6	3	5
Aquitaine	5	5	3	5
Other	27	24	22	33
Localization of death (%)				
Hospital short stay	76	82	60	73
Domicile, public area	18	11	37	20
Other	6	7	3	7

compared to those identified by CepiDc only (20%) and by both sources (11%).

In a sample of 215 death certificates among the 570 not identified by M2000, the speciality of the certifying physician was unknown for 26%. Among the 160 cases for whom it was documented, 86% did not belong to the specialities that were contacted for participation in M2000, i.e. infectious diseases and internal medicine.

Causes of death according to the source

From the M2000 source, the underlying cause of death was AIDS-related in 55, 50, 35 and 25% of cases identified by (1) three sources, (2) M2000 and CepiDc, (3) M2000 and FHDH and (4) M2000 only. From the CepiDc source, the underlying cause of death was HIV-related in 87, 81, 93 and 78% and AIDS-related in 44, 39, 39 and 31% of cases identified by (1) three sources, (2) CepiDc and M2000, (3) CepiDc and FHDH and (4) CepiDc only. Overall AIDS-related deaths were less frequent among cases identified by only one source.

DISCUSSION

Using log-linear modelling and three sources, we estimated the number of deaths in HIV-infected adults in 2000 in France as 1699 (95% CI 1671–1727). Considering only Metropolitan France, the estimation was 1574 (95% CI 1548–1599). Overall, the completeness was 55% (95% CI 54–56) for M2000, 76% (95% CI 74–77) for Cepi-DC and 38% (95% CI 37–39) for FHDH.

We acknowledge several limitations to our analysis when considering the hypotheses of the capture–recapture method [6, 7, 10]. The definition of case is in our opinion straightforward, because we sought to identify deaths from all causes and because diagnosis of HIV infection in France is based on Western blot testing.

Closed population

The population cannot be considered as closed since some HIV-infected persons may have migrated between France and other countries. Nevertheless, as in most epidemiological studies, we considered that the size of the population of HIV-infected adults was constant within the period of study [8].

Accuracy of matching

Because no complete identifier was available for patients, cross-match was performed according to a set of characteristics and accepted some differences. For that reason we can assume that there are both false-positive matches and false-negative matches. Concerning matches that accept potential differences in dates, verification of other available variables made them acceptable. When these verifications could not be made, the correspondence between the two records was not accepted. For this reason we assume that the most likely are false-negative matches resulting in an underestimation of the number of cross-matches, overestimating the total number of deaths and underestimating the completeness.

Independence between sources

We identified dependence between M2000 and FHDH. Indeed, most of the physicians who participated in M2000 were involved in the management of HIV infection in hospital wards participating in FHDH. This dependence has been taken into account in the log-linear model. On the contrary, we did not identify dependence between mention of HIV infection on the death certificate and participation in both M2000 and FHDH.

Homogeneity of capture

We identified heterogeneity of capture according to age, gender and region of death. In M2000 and FHDH, lower completeness in persons >50 years may indicate that older patients are followed by various physicians, not only those specializing in the management of HIV infection. This especially seems to occur in the Paris region.

Completeness

Overall 45% of the estimated number of deaths has not been identified by M2000. According to analysis of a sample of death certificates, the majority of certificates concerning these non-identified cases were filled in by physicians not identified by the M2000 protocol as being currently involved in the management of HIV infection. The diversification of diseases in HIV-infected adults has widened the number of physicians and specialities involved in their management. In a future survey, one might extend the speciality of participants in order to increase the

number of identified cases. Nevertheless, this choice can result in greater difficulties in obtaining exhaustive participation and standardized collection of data.

Although death certificates collect information on all deaths in France, the identification of HIV-infected people was not complete. The implementation of electronic certification may resolve this problem in the future, allowing more precise data on HIV infection to be collected from certification during a specific period.

The completeness of FHDH was lower than for M2000, as was expected by the participating hospital wards. This is lower than the completeness of FHDH for AIDS cases that was estimated at 48% for 1990–1993 [9]. This may be explained by either a lower completeness of death notification in FHDH in the HAART period compared to the pre-HAART period because of a diversification of involved physicians, or by a lower notification of deaths in FHDH compared to AIDS cases. This will be explored by matching lost-to-follow-up patients in FHDH and deaths in the two other sources. Lack of correct determination of the underlying cause of death means that the distribution of the causes in this database cannot be described. Further standardization of data collection on deaths to be implemented will make it possible to evaluate the role of this database in the surveillance of the causes of death in HIV-infected adults in France.

Cause of death according to the source

From the CepiDc source, the ICD-10 rules led to classification of the underlying cause of death as HIV-related in a majority of cases when HIV infection was mentioned in the certificate. For this reason the comparison of distribution of the causes of death in cases identified only by the death certificate and in cases identified by both the death certificate and another source does not lead to straightforward conclusions. Proportions of cases related to HIV/AIDS are quite similar in these groups and the proportion of AIDS-related deaths is lower in cases identified only by the death certificate. One reason may be that AIDS is most frequent in cases followed by physicians specializing in HIV infection, or that the AIDS diagnosis is stated more frequently, and that in cases followed elsewhere, HIV infection is involved but the diagnosis is less precise.

From the M2000 source, the proportion of AIDS-related deaths was lower in cases not identified by a

death certificate, and this corresponds to cases in which the mention of HIV infection was not recorded on the death certificate.

These differences in the distribution of the causes of death may suggest heterogeneity of capture according to the cause of death. Nevertheless, differences in the coding of the cause of death between sources and unavailability of the underlying cause of death in one source did not allow us to stratify our analysis according to this information.

Characteristics according to the source

We did not stratify the analysis according to the place of death defined as hospital, home or public area because of lack of this information in one source. However, people who died at home were less likely to be identified by both M2000 and CepiDc, and were more likely to be identified either by M2000, or by CepiDc. Different interpretations of this phenomenon may be possible: (1) cases deceased at home may have been more frequently reported by a physician not specializing in HIV infection, and have been identified by death certificate alone; (2) cases identified only by M2000 died more frequently of non-AIDS defining causes, and more frequently at home; (3) documentation of deaths occurring at home may have been less complete in M2000 making cross-matching impossible.

Specific interest of each source

In order to identify deaths occurring in HIV-infected adults in the HAART period, death certificates had the best completeness but they underestimated non-HIV-related deaths. Hospital databases may be representative of deaths occurring among patients currently followed in hospital. The completeness of M2000 was between the two other sources. Specific surveys like M2000 can reach high level of standardization of data collection and they can be adapted to specific concerns related to the pathology studied, like HIV infection in the HAART period.

CONCLUSION

Using a capture–recapture method, we estimated that a total of 1699 deaths occurred in France in 2000 among HIV-infected adults, leading to an 1.9% annual mortality rate (95% CI 1.0–3.3) according to

estimation of prevalence of HIV infection in France at the end of 2000 [15]. None of the three sources studied is complete and the interest of a source in identifying deaths in HIV-infected persons will depend on research objectives. Regular estimations of the number of deaths in HIV-infected persons according to several sources are needed since treatment strategies are changing and pathologies are diversifying in this population. This will contribute to an evaluation both of the completeness of surveillance systems that may change and of the completeness of specific surveys like the M2000.

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DECLARATION OF INTEREST

None.

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