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Mortality of people with AIDS in Italy: comparison of AIDS surveillance and multiple cause-of-death registries

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Abstract

Aims. To assess whether the use of multiple cause-of-death data could improve reporting of AIDS mortality in Italy.

Method. Population-based, record-linkage study, on 3,975,431 deaths recorded in the National Registry of Causes of Death (RCoD) and 4,530 deaths recorded in the National AIDS Registry (RAIDS), during 2006-2012.

Results. The record-linkage identified 3,646 AIDS-related deaths present in both registries, 884 deaths in the RAIDS without mention of HIV/AIDS in the RCoD, and 3,796 deaths in the RCoD with mention of HIV/AIDS that were not present in the RAIDS. In the latter, in-depth analysis of multiple cause-of-death allowed the identification of 1,484 deaths that were AIDS-related. On these results, we estimated 6,014 deceased people with AIDS. Of them, 14.7% (884) were not present in the RCoD and 24.7% (1,484) derived from the RCoD only.

Conclusions. The integration of different nationwide registries allowed a more comprehensive estimate of the impact of AIDS-associated mortality in Italy.

Key words

- AIDS
- HIV infection
- death certificates
- multiple cause-of-death
- Italy

INTRODUCTION

Estimates of AIDS related mortality vary considerably according to data source. In Europe, figures provided by HIV and/or AIDS surveillance systems have shown great across-country variability due to different approaches [1]. Moreover, mortality figures provided by surveillance systems are systematically lower than those reported by cause-of-death registries derived from death certificates [2].

Mortality patterns of people with HIV/AIDS have radically changed following the introduction of highly active antiretroviral therapy (HAART), resulting in an increased frequency of deaths due to non AIDS-related conditions [3]. New issues have therefore emerged, and various efforts have been put in place to assess causes of death among people with HIV/AIDS [4-6].

Despite well-known limits, death certificates remain of primary importance and one of the most useful tools for international comparisons of mortality. For people with HIV/AIDS, the cause of death classification system – e.g., the International Classification of Diseases, tenth revision (ICD-10) – lacks of specificity in the coding of AIDS defining conditions, and criteria adopted for the identification of people deceased for HIV/AIDS might differ from clinical definitions adopted by surveillance systems for the identification of HIV/AIDS cases. In particular, it is worth stressing that mortality statistics focus on the cause of death, i.e. on people deceased because of AIDS, whereas AIDS surveillance systems collect data on all people with AIDS (PWA), even if death is caused by other conditions.

The majority of the studies conducted to evaluate discrepancies among causes of death and clinical conditions in people with HIV/AIDS are based on the linkage between data from cause-of-death registries and surveillance systems [7-13]. In Italy, the only nationwide study [14] was conducted in 1997 and never updated. It was based on i) the National Registry of Causes of Death (RCoD) – where mortality data were coded according to the Ninth Revision of the International Classification of Diseases (ICD-9); and ii), the National AIDS

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Registry (RAIDS) fitting the 1987-CDC AIDS case definition.

In this investigation, by using a multiple cause of death (MCoD) approach, we carried out a record linkage between the RCoD and the RAIDS to assess whether the use of death certificates could contribute in identifying AIDS cases missed by the national surveillance system, and to identify possible sources of miscoding of AIDS deaths in RCoD.

METHODS

This study is part of a larger, nationwide, investigation on the survival and mortality patterns of Italian PWA included in the Italian National Statistical Plan, authorized by the Italian Data Protection Authority [15].

Source of data

Data were obtained from two Italian nationwide registries: the RAIDS, managed by the Italian National Institute of Health (Istituto Superiore di Sanità, ISS), and the RCoD, managed by the Italian National Institute of Statistics (Istituto Nazionale di Statistica, ISTAT). The RAIDS collects data on people newly diagnosed with AIDS according to the 1993 revised European definition [16], which requires the diagnosis of specific clinical conditions (AIDS-defining conditions) in people with a HIV-positive laboratory test *(Supplementary Table available online)*. The RCoD collects death certificates where the causes of death (i.e., sequence of conditions directly leading to death and other contributing causes) are registered.

In the 2006-2012 period, the ICD-10 was used [17] (incorporating WHO recommended updates until 2009), with an automated coding system that coded about 80% of all certificates without manual intervention. According to the MCoD coding process, all causes reported in the death certificates were analyzed, not only the underlying cause (the disease or external cause that initiated the train of events directly leading to death). For the MCoD analysis, AIDS-related deaths were defined by ICD-10 codes B20-B24 ("HIV disease") and/or R75 ("laboratory evidence of HIV").

Record-linkage procedure

For the 2006-2012-period, the records of the RAIDS and of the RCoD were linked using a validated, semi-automated software application that guarantees anonymity and high sensitivity [18] with the aim to identify deaths of PWA.

In this article we define as PWA a person included in the RAIDS and a PWA death a record from RAIDS successfully linked to RCoD.

Because the linkage procedure uses name, surname, and date of birth as matching criteria, in order to improve linkage effectiveness, we excluded: (a) the records from the provinces of Trento and Bolzano, because names/surnames and multiple causes of death are not available in the RCoD database; (b) the records of foreigners, because of the high frequency of spelling errors in names/surnames and the increased probability of losses to follow-up due to migration. For the aims of this analysis, only individuals deceased at an age greater than 15 years were considered. Details of the linkage procedure have been provided elsewhere [19]. The record-linkage procedure to identify deceased PWA was carried out through the following three steps.

All records from RAIDS linked to RCoD records are considered PWA deaths, irregardless from the cause of death reported in the RCoD.

Step 1

The record-linkage between the RAIDS and the RCoD databases allowed identifying three groups of deceased PWA *(Table 1)* taking into account also the cause of death reported in the death certificate:

- Group A: AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS (i.e., agreement between the two data sources); these deaths are considered PWA deaths;
- Group B: i.e. AIDS-related deaths for RCoD of people not notified to RAIDS; this group has been examined in further steps since potentially hides some PWA deaths;
- Group C: Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD (i.e they did not include mention of ICD-10 codes B20-B24 – HIV disease – or R75 – laboratory evidence of HIV); deaths in this group are considered PWA deaths although the cause of death is not AIDS-related.

Step 2

To evaluate the nature and the extent of the disagreement between the RAIDS and the RCoD, deaths in

Table 1

Distribution of deaths certificates in the RCoD, by mention of HIV/AIDS (ICD-10 codes: B20-B24, R75) and results of the record-linkage to the RAIDS. Italy, 2006-2012

Deaths in RCoD		Linked to RAIDS		
		Yes	No	Total
Mention of HIV/AIDS in death certificate	Yes	3,646 (Group A)[1]	3,796 (Group B)[2]	7,442
	No	884 (Group C)[3]	3,967,105	3,967,989
Total		4,530	3,970,901	3,975,431

RAIDS: National AIDS Registry; RCoD: National Registry of Causes of Death.
[1]Group A: AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS;
[2]Group B: AIDS-related deaths for RCoD of people not notified to RAIDS;
[3]Group C: Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD.

Group B (i.e. AIDS-related deaths for RCoD of people not notified to RAIDS) were individually assessed for AIDS by means of an in-depth analysis of ICD-10 codes derived from death certificates. Every ICD-10 code was flagged either as "certain", if the description matched an AIDS-defining disease, or "uncertain", if the code description was not specific enough to identify an AIDS-defining disease. Based on these criteria, and using the MCoD analysis, deaths in Group B were classified as follows: (a) "deaths fitting RAIDS criteria", when death certificates included an explicit mention of AIDS, or HIV disease, or HIV-positive status (ICD-10 codes: B20-B24, R75) together with at least one AIDS-defining condition (flagged as "certain" in *Supplementary Table available online*); (b) "deaths not fitting RAIDS criteria", when death certificates did not include the above mentioned patterns, therefore excluding a PWA death; (c) "AIDS uncertain": death certificates reporting ICD-10 codes for AIDS-defining conditions but not for HIV-positive status, therefore not certainly indicating a PWA-death (flagged as "uncertain" in *Supplementary Table available online)*.

Step 3

Deaths classified as "AIDS uncertain" in step 2 underwent an individual text analysis of the original death certificate: every certificate was manually reviewed to analyze in detail all causes of death and to assess whether they fitted with an AIDS diagnosis. Certificates containing medical entries indicating an AIDS-defining condition were considered "deaths fitting RAIDS criteria", whereas the others were considered "deaths not fitting RAIDS criteria". At the end of the evaluation process, we estimated the number of total PWA deaths in the 2006-2012 period by summing up the following:

1. the number of deaths of people notified to the RAIDS with also an AIDS-related cause of death reported in the RCoD (i.e., all Group A deaths, irregardless from the cause of death);
2. the number of deaths of people with an AIDS-related cause of death reported in the RCoD (i.e., "deaths fitting RAIDS criteria", derived from Group B), but not notified to the RAIDS; and
3. the number of deaths pertaining to people notified to the RAIDS, although without an AIDS-related cause of death reported in the RCoD (i.e., Group C).

RESULTS

In Italy, between 2006 and 2012, 3,975,431 death certificates were reported to the RCoD. HIV disease or HIV-positive status was mentioned in 7,442 cases *(Table 1)*. According to the linkage procedure, 3,646 (49.0%) of these 7,442 deceased people were identified in both RAIDS and RCoD (Group A), whereas 3,796 deaths (51.0%) were not found in the RAIDS (Group B). In addition, there were 884 deceased people recorded in the RAIDS without mention of HIV disease or HIV positive status in the RCoD (Group C) *(Table 1)*.

Table 2 shows the distribution of the most frequent MCoD mentioned in the death certificates for each of the three groups. The most frequently reported conditions in Group A and in Group B included unspecified HIV disease (mentioned in 93.9% of certificates in Group A and in 87.6% in Group B), liver diseases (41.2% in Group A and 58.7% in Group B), viral hepatitis (28.4% and 37.8%, respectively), influenza and pneumonia (17.7% and 15.0%, respectively), and renal failure (11.3% and 12.5, respectively). Other worth mentioning conditions included malignant neoplasms of lymphoid and hematopoietic tissue (13.7% in Group A and 7.9% in Group B), other bacterial diseases (17.7% in Group A and 15.1% in Group B), and other forms of heart diseases (14.2% in Group A and 14.5% in Group B) *(Table 2)*.

The most frequent causes of death listed in Group C (i.e., PWA whose death certificate did not mention HIV infection) included liver diseases (23.5%), other forms of heart diseases (20.8%), disorders involving the immune system (17.0%), and viral hepatitis (9.8%). External causes of death (ICD-10 codes: V01-Y98) were frequently reported (e.g., poisoning 4.5%, self-harm 4.6%), in contrast to the distribution observed in Group A and Group B.

According to the results of step 2, i.e. the MCoD analysis of 3,796 cases included in Group B by step 1 *(Table 3)*, 842 deaths (22.2%) were classified as "deaths fitting RAIDS criteria", and 216 cases as "deaths not fitting RAIDS criteria" (i.e., people with a laboratory evidence of HIV with no AIDS-defining disease). For the 2,738 (72.1%) remaining cases in Group B, the MCoD analysis evidenced ICD-10 codes not clearly identifying AIDS; therefore they were classified as "AIDS uncertain".

In step 3, the 2,738 cases classified as "AIDS uncertain" by step 2 underwent a text analysis of the medical description reported in every death certificate. Among them, we classified 642 certificates as "deaths fitting the RAIDS criteria", that summed to the 842 sorted in step 2 made up 1,484 "deaths fitting RAIDS criteria" derived from Group B (39.1% of the initial 3,796 cases identified as PWA deaths by RCoD but not by RAIDS) *(Table 3)*.

Thus, we estimated a total of 6,014 PWA deaths in the 2006-2012 period as the sum of deaths notified to the RAIDS (i.e., Group A + Group C, N=4,530, 75.3%) and deaths retrieved from the RCoD and confirmed as PWA deaths after the in-depth analysis of ICD-10 codes (N=1,484, 24.7%, from Group B after steps 2 and 3).

DISCUSSION

The present study based on MCoD analysis found that during the 2006-2012 period, in addition to the 4,530 people notified to the RAIDS and deceased, there were 1,484 (24.7%) additional people whose death certificate included AIDS-defining causes of death, but who were never notified to the RAIDS as PWA. The disagreement between the two registries may have been due to differences in the definition of AIDS death, inaccuracy in causes of death reporting in the RCoD, or underreporting of deceased PWA in the RAIDS.

Table 2
Distribution of death certificates in the RCoD, by mention of selected causes according to the three groups of deaths identified through the record-linkage between RCoD and RAIDS. Italy, 2006-2012

ICD-10 codes	Cause of death	Group A[1]		Group B[2]		Group C[3]		Total	
		N	%	N	%	N	%	N	%
Total		**3,646**	**100**	**3,796**	**100**	**884**	**100**	**8,326**	**100**
A30-A49	Other bacterial diseases	645	17.7	572	15.1	63	7.1	1,280	15.4
B15-B19	Viral hepatitis	1,034	28.4	1,436	37.8	87	9.8	2,557	30.7
B20-B23	Human immunodeficiency virus (HIV) disease (resulting in specified diseases)	53	1.5	23	0.6	0	0.0	76	0.9
B24	Unspecified human immunodeficiency virus (HIV) disease	3,424	93.9	3,326	87.6	0	0.0	6,750	81.1
B25-B34	Other viral diseases	231	6.3	73	1.9	33	3.7	337	4.0
B35-B49	Mycoses	259	7.1	107	2.8	13	1.5	379	4.6
B50-B64	Protozoal diseases	322	8.8	115	3.0	23	2.6	460	5.5
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx	25	0.7	31	0.8	9	1.0	65	0.8
C15-C26	Malignant neoplasms of digestive organs	243	6.7	467	12.3	66	7.5	776	9.3
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs	170	4.7	228	6.0	49	5.5	447	5.4
C43-C44	Melanoma and other malignant neoplasms of skin	7	0.2	27	0.7	6	0.7	40	0.5
C50	Malignant neoplasm of breast	6	0.2	30	0.8	3	0.3	39	0.5
C51-C58	Malignant neoplasms of female genital organs	52	1.4	34	0.9	16	1.8	102	1.2
C64-C68	Malignant neoplasms of urinary tract	14	0.4	35	0.9	11	1.2	60	0.7
C81-C96	Malignant neoplasms, stated or presumed to be primary, of lymphoid, haematopoietic and related tissue	500	13.7	301	7.9	58	6.6	859	10.3
D80-D89	Certain disorders involving the immune mechanism	93	2.6	78	2.1	150	17.0	321	3.9
E10-E14	Diabetes mellitus	176	4.8	231	6.1	30	3.4	437	5.3
F10-F19	Mental and behavioural disorders due to psychoactive substance use	149	4.1	225	5.9	31	3.5	405	4.9
I10-I15	Hypertensive diseases	94	2.6	148	3.9	18	2.0	260	3.1
I20-I25	Ischaemic heart diseases	165	4.5	273	7.2	114	12.9	552	6.6
I30-I52	Other forms of heart disease	519	14.2	551	14.5	184	20.8	1,254	15.1
I60-I69	Cerebrovascular diseases	171	4.7	238	6.3	50	5.7	459	5.5
J10-J18	Influenza and pneumonia	644	17.7	568	15.0	73	8.3	1,285	15.4
J40-J47	Chronic lower respiratory diseases	130	3.6	134	3.5	30	3.4	294	3.5
K70-K77	Diseases of liver	1,503	41.2	2,228	58.7	208	23.5	3,939	47.3
N17-N19	Renal failure	410	11.3	473	12.5	66	7.5	949	11.4
R75	Laboratory evidence of human immunodeficiency virus (HIV)	249	6.8	495	13.0	0	0.0	744	8.9
X40-X49	Accidental poisoning by and exposure to noxious substances	3	0.1	15	0.4	40	4.5	58	0.7
V01-W19, X58-X59	Other accidents	34	0.9	37	1.0	52	5.9	123	1.5
X60-X84	Intentional self-harm	5	0.1	8	0.2	41	4.6	54	0.6

RAIDS: National AIDS Registry; RCoD: National Registry of Causes of Death.
[1]AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS;
[2]AIDS-related deaths for RCoD of people not notified to RAIDS;
[3]Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD.

The definition of AIDS death used by the RAIDS is "the death of a person diagnosed with AIDS" whereas the one used by RCoD is "a death for which AIDS was among the causes reported on the death certificate". As a consequence, it is reasonable that PWA who die for causes other than AIDS (such as external causes, non AIDS-related neoplasms, drug addiction, heart disease, chronic liver disease) are not found in the RCoD as AIDS deaths. The profile by cause of death for the 884 cases in Group C (i.e., notified to RAIDS but with no mention of AIDS in RCoD) suggests that most of them could indeed be included in this latter case, since they show higher frequencies of non AIDS-related causes compared to other groups *(Table 3)*.

Also, an inaccurate classification of causes of death may occur in this group of deaths. Some cases notified to RAIDS but not found in RCoD include sometimes causes of death such as AIDS-related neoplasms, infections generally occurring in PWA, or ill-defined diseases referring to virosis or immunodeficiencies. For instance, in this group, lymphomas and other lymphoid tumours were observed in 6.6% of cases, protozoal diseases, especially toxoplasmosis, in 2.2%, non-specific retroviruses in 3.7%, and unspecified immunodeficiency in 17%. In addition, the lack of mention of HIV or AIDS in the RCoD can be intentional to prevent relatives and acquaintances from knowing about the deceased's infection and avoid the stigma associated with HIV [20, 21].

Finally, underreporting of deceased AIDS cases to the RAIDS may explain the remaining disagreement between the two registers. The present study estimates about 25% underreporting of deceased AIDS cases to the RAIDS based on 1,484 people who had HIV/AIDS mentioned in the death certificate but that were not reported in RAIDS. This estimate is consistent with the findings from other previous studies carried out in Italy: Barchielli *et al.* [7] estimated in one region 23% of underreporting of deaths to RAIDS in the period 1987-91; in the same period a nationwide study conducted by Conti, *et al.* [14] in 1992 estimated 21.7% underreporting of AIDS deaths for RAIDS.

Some factors may be associated with underreporting of deceased PWA to the RAIDS. Firstly, delayed reporting of new AIDS diagnoses to RAIDS may hinder the linkage with death certificates because a number of AIDS case reports may have not yet been recorded in RAIDS [21]. Secondly, a concurrent first diagnosis of both HIV and AIDS may lead to only one report sent to either the RAIDS or the HIV registry (in Italy these two registries are separated), thus resulting in underreporting to the other registry. Thirdly, a missed notification of AIDS may occur when the AIDS diagnosis is performed at/or close to death; in this case, the physician could certify the death without reporting the case to RAIDS.

The present study highlights some limits of the ICD-10 in the classification of AIDS deaths, especially in distinguishing full-blown AIDS from HIV-positive status (the expression "HIV" is often used to indicate HIV-positive status, nevertheless AIDS and "HIV" are both classified in the same ICD-10 code B24). This factor can contribute in overestimating AIDS cases in RCoD when considering multiple causes. In this paper, in order to overcome these limits, a methodology for the evaluation of cases mentioning HIV/AIDS (ICD-10 codes B20-B24 or the R75) to identify full-blown AIDS and HIV-positive status only was developed.

It is worth noting that more comprehensible and precise rules for AIDS classification, in particular for the selection of underlying cause in PWA and in identifying AIDS-defining causes, have been introduced in the 2016 ICD-10 version [22].

Table 3
Classification of deaths into PWA or non-PWA deaths after the analysis of the multiple causes of death (MCoD), according to the three groups of deaths identified through the record-linkage between RCoD and RAIDS. Italy 2006-2012

	Group A[1]		Group B[2]		Group C[3]		Total
MCoD Group	N	%	N	%	N	%	N
Total	3,646	100.0	3,796	100.0	884	100.0	8,326
(a) Deaths fitting RAIDS criteria	3,646	100.0	842	22.2	-	-	4,488
(b) Deaths not fitting RAIDS criteria	-	-	216	5.7	-	-	216
(c) AIDS uncertain, manual revision:	-	-	2,738	72.1	-	-	2,738
(c.1) Deaths fitting RAIDS criteria	-	-	*642*	*16.9*	-	-	*642*
(c.2) Deaths not fitting RAIDS criteria	-	-	*2,096*	*55.2*	-	-	*2,096*
(d) Deaths in RAIDS					884	100.0	884
PWA deaths (a + c.1 + d)	3,646	100.0	1,484	39.1	884	100.0	6,014
(Row %)	(60.6)		(24.7)		(14.7)		(100.0)
Non-PWA deaths (b + c.2)	0	0.0	2,312	60.9	0	0.0	2,312
(Row %)	(0.0)		(100.0)		(0.0)		(100.0)

PWA: people with AIDS; RAIDS: National AIDS Registry; RCoD: National Registry of Causes of Death.
[1]AIDS-related deaths identified by the RCoD and pertaining to people notified to the RAIDS;
[2]AIDS-related deaths for RCoD of people not notified to RAIDS;
[3]Deaths pertaining to people notified to the RAIDS but who were not considered as AIDS-related deaths by the RCoD.

The strengths of the study are the following: 1) the national coverage of the two population-based registries (RAIDS and RCoD), which allowed not to miss any notified case of AIDS or any death occurred in Italy; 2) the high sensitivity of the record-linkage procedure [18], which allowed to link also people reported with spelling errors in names/surnames or errors in the dates of birth; and 3) the use of multiple causes of death, which allowed the study of all the conditions mentioned in the death certificates, rather than a single cause identified as responsible for the death. The proposed methodology that links the ICD-10 MCoD with the diagnoses from RAIDS provides a generalized basis for further studies of the same type.

In summary, by integrating the two nationwide registries, a total of 6,014 PWA deaths were estimated for the 2006-2012 period, of which 14.7% were not present in the RCoD, whereas 24.7% were of individuals not included in the RAIDS. Thus, the integration of different national data sources allowed a more comprehensive estimate of the impact of AIDS on mortality. The study findings stress the urgent need, in Italy, for a combined HIV/AIDS surveillance and a more accurate ICD coding for HIV and AIDS-defining conditions.

Authors' contribution

BS, LF and DS designed the study; FG, EG, and BS drafted the manuscript; FG, EG, and MP analyzed data; VR, and LP managed the National AIDS Registry data used in this study; EG, FG, and MP managed data of the National Register of Causes of Death used in this study; AZ and MT performed the record-linkage and managed the final database used in this study. All Authors contributed to data interpretation and revised the manuscript for intellectual content.

Conflict of interest statement

All Authors declare that they have no conflicts of interest.

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