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Non-AIDS Defining Cancer Mortality: Emerging Patterns in the Late HAART Era

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Running head: Excess cancer death in Italian people with AIDS

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Abstract

Background. Non-AIDS defining cancers (non-ADCs) have become the leading non-AIDS-related cause of death among people with HIV/AIDS. We aimed to quantify the excess risk of cancer-related deaths among Italian people with AIDS (PWA), as compared to people without AIDS (non-PWA).

Methods. A nationwide, population-based, retrospective cohort study was carried out among 5285 Italian PWA, aged 15-74 years, diagnosed between 2006 and 2011. Date of death and multiple-cause-of-death (MCoD) data were retrieved up to December 2011. Excess mortality, as compared to non-PWA, was estimated using sex- and age-standardized mortality ratios (SMRs) and corresponding 95% confidence intervals (CIs).

Results. Among 1229 deceased PWA, 10.3% reported non-ADCs in the death certificate, including lung (3.1%) and liver (1.4%) cancers. A 7.3-fold (95% CI: 6.1-8.7) excess mortality was observed for all non-ADCs combined. Statistically significant SMRs emerged for specific non-ADCs, i.e., anus (5 deaths, SMR=227.6, 95% CI: 73.9-531.0), Hodgkin lymphoma (12 deaths, SMR=122.0, 95% CI: 63.0-213.0), unspecified uterus (4 deaths, SMR=52.5, 95% CI: 14.3-135.0, liver (17 deaths, SMR=13.2, 95% CI: 7.7-21.1), skin melanoma (4 deaths, SMR=10.9, 95% CI: 3.0-27.8), lung (38 deaths, SMR=8.0, 95% CI: 5.7-11.0), head and neck (9 deaths, SMR=7.8, 95% CI: 3.6-14.9), leukemia (5 deaths, SMR=7.6, 95% CI: 2.4-17.7), and colon-rectum (10 deaths, SMR=5.4, 95% CI: 2.6-10.0). SMRs for non-ADCs were particularly elevated among PWA infected through injecting drug use.

Conclusion. This population-based study documented extremely elevated risks of death for non-ADCs among PWA. These findings stress the need of preventive interventions for both virus-related and non virus-related cancers among HIV-infected individuals.

Keywords: HIV/AIDS, multiple causes of death, excess mortality, standardized mortality ratio

Introduction

The increasing survival of HIV-infected individuals with access to highly active antiretroviral therapy (HAART) has led to dramatic changes in mortality patterns of people with HIV/AIDS.[1,2] While mortality rates for AIDS-related conditions have been decreasing over time, those of non-AIDS-related ones remained unchanged or decreased very slightly.[3-5] In particular, non-AIDS defining cancers (non-ADCs, *i.e.*, cancers other than Kaposi sarcoma, non-Hodgkin lymphoma, and cervix uteri) have become the leading non-AIDS-related causes of death in the late HAART era, among both people with HIV[1,3] and people with AIDS (PWA).[6]

Nonetheless, the risk of death as compared to the HIV-uninfected population is still far from being assessed for each cancer site/type in the late HAART era, as only few studies quantified excess mortality for specific cancers among people with HIV[4] or PWA.[6] In addition, most mortality studies were solely based on the underlying cause of death (*i.e.*, the disease or injury which initiated the train of morbid events leading directly to death),[7] which is poorly informative of the complexity of the morbidity conditions that affect people with HIV/AIDS. Furthermore, such approach does not allow a direct comparison with the uninfected population because most death certificates of people with HIV/AIDS report 'HIV/AIDS' as the underlying cause of death.[6,8] To overcome such limits, several methods have been used.[3-6,8,9] For instance, in a previous Italian investigation aimed at quantifying the excess cancer mortality among PWA, as compared to the general population, we re-assigned the underlying cause of death by excluding HIV/AIDS reference in the death certificates.[10,11]

Currently, the availability in Italy of multiple-cause-of-death (MCoD) data (*i.e.*, all the conditions reported in death certificates ‑beyond the underlying cause of death) allows

making a direct comparison of the death certificates of people with HIV/AIDS with those of people without. Furthermore, it allows investigating in detail the presence at death of specific cancer sites/types and other diseases even if these conditions were not selected as the underlying cause. Using MCoD data, this nationwide population-based study aimed to assess excess risk of cancer-related deaths among Italian PWA, as compared to people without AIDS (non-PWA), in the late HAART era.

Methods

This retrospective cohort study is part of a larger epidemiological, population-based, nationwide investigation on the survival and mortality patterns of PWA in Italy.[12] The following data sources were used: 1) the National AIDS Registry (RAIDS) at the National Health Institute (ISS), which collects mandatory data on all people newly diagnosed with AIDS (according to the 1993 revised European definition[13]); 2) the National Register of Causes of Death (RCoD) at the National Institute of Statistics (ISTAT) which collects all death certificates mandatorily issued in Italy.[14] MCoD data are coded by RCoD, according to the International Classification of Diseases 10th revision, ICD-10 rules and provisions issued by the World Health Organization.[7]

In order to compare causes of death between PWA and non-PWA, RAIDS and RCoD data were linked for the concurrently available period, i.e., 2006-2011. The record-linkage procedure was conducted in observance of current laws regulating the use of RAIDS and RCoD data (*i.e.*, inclusion of the investigation in the Italian National Statistical Plan according to permission of the Data Protection Authority).[12] The record-linkage procedure was carried out by means of a validated, semi-automated, software application using names, surnames, and dates of birth that were blinded to the operator and removed from the output.[15,16] In order to guarantee the highest completeness of the record-linkage procedure, we

excluded: (a) PWA who were residing in the provinces of Trento and Bolzano, because their names were not available in RCoD; and (b) PWA who were foreign citizens, because of possible bias deriving by a higher frequency of spelling errors in their names when recorded at RAIDS and by a higher propensity of these people to migrate abroad and of being lost to follow-up.

For the aims of this study, 'PWA deaths' were identified by linked records in RAIDS and RCoD, whereas 'non-PWA deaths' were identified by RCoD records not linked with RAIDS. Furthermore, in order to avoid the inclusion of HIV-infected people in the comparison group, we excluded from the 'non-PWA deaths' category those records reporting AIDS/HIV-related conditions (*i.e.*, ICD-10 codes B20-B24).

To improve comparability between the study groups, the present analysis was restricted to PWA aged 15 to 74 years at diagnosis or at death. Furthermore, we excluded PWA with less than 1 month of follow-up, as the day (within the date) of AIDS diagnosis was often missing; this selection allowed also the exclusion of those PWA diagnosed at death. Our analysis finally included 1229 deaths occurred among 5285 PWA, and 952,019 non-PWA deaths.

Person-years at risk of death for PWA were calculated from the date of AIDS diagnosis to the date of death, or to December 31st, 2011, whichever came first. PWA who had been diagnosed within 74 years of age but who died thereafter were censored at their 75th birthday. The risk of death of PWA, as compared to non-PWA, was estimated using sex-and age-standardized mortality ratios (SMRs).[17] SMRs were calculated as the ratio between the observed number of deceased PWA who had a specific cancer to the expected one, estimated on the basis of sex- and age-specific (quinquennia) mortality rates among non-PWA, multiplied by the person-years at risk among PWA. Mortality rates for non-PWA were computed using, as numerator, the observed number of deceased non-PWA for that specific condition, and, as denominator the average resident Italian population of same sex and age in

the study period (after the exclusion of Trento and Bolzano provinces, and foreign citizens), as a proxy of person years at risk of death. Corresponding 95% confidence intervals (CIs) were computed using the exact Poisson method as appropriate for rare events (i.e., ≤5).[18] However, cancer sites with a total number of observed deaths below 4 were reported in the auxiliary Table A (see Supplemental Digital Content, http://links.lww.com/QAI/A820).

Secondary malignancies and malignant neoplasms not otherwise specified (*i.e.*, ICD-10 codes: C77-C80) were not considered in these analyses, as they were almost always (except in 8 cases out of 141 PWA deaths) reported in death certificates together with defined cancers and were, therefore, not relevant for the study aim.

Results

Table 1 shows the distribution of 5285 Italian PWA diagnosed during 2006-2011, and of the 1229 deceased who had died as of 31st December 2011, according to main characteristics at AIDS diagnosis. Mean follow-up time was 2.5 years, for a total of 14,180 person-years at risk of death. The proportion of observed deaths among PWA increased with age at AIDS diagnosis, whereas it decreased with increasing years of education; moreover, it was particularly high among PWA infected through injecting drug use (IDU) (31%), and it was the lowest among homosexual PWA (17%).

Table 2 shows the distribution of malignant neoplasms reported in death certificates of PWA and non-PWA, using MCoD data. AIDS-defining cancers (ADCs) were reported in 22.9% of death certificates of PWA: non-Hodgkin lymphoma in 18.0%, Kaposi sarcoma in 5.1%, and cervical cancer in 2.5%. Similar figures were found among PWA aged 15-49 and 50-74 years, with the exception of no mention of cervical cancer among female PWA aged 50 years or more. Conversely, these same malignancies were rarely reported as causes of death in non-PWA (<2% of total deaths, in all age groups).

Non-ADCs were reported in 10.3% of total deaths among PWA. The most frequent type was lung cancer (in 3.1% of death certificate, 38 deaths), followed by liver cancer (1.4%, 17 deaths), Hodgkin lymphoma (1.0%, 12 deaths). Among female PWA, unspecified uterine cancer was reported in 1.7% of death certificates (4 cases). Non-ADCs were more frequently observed in PWA who died between the ages of 50 and 74 years (13.8% of death certificates) than in younger ones (7.9%). As expected, non-ADCs were by far more frequently observed among non-PWA (46.8% of death certificates).

Tables 3 and 4 show the observed and the expected numbers of cancer-related deaths with the corresponding SMRs, overall and in selected sub-groups. ADCs, in particular Kaposi sarcoma, showed extremely high excess mortality, especially among PWA younger than 50 years (Table 3). When considering all non-ADCs together, a 7.3-fold excess risk of death was observed (95% CI: 6.1-8.7) with a higher excess in the youngest group of PWA (SMR=14.2, 95% CI: 10.8-18.5, for 15-49 years *vs*. 5.3, 95% CI 4.1-6.7, for 50-74 years). Remarkably elevated excess risks of death emerged for anal cancer (SMR=228) and Hodgkin lymphoma (SMR=122). Statistically significant excess mortality was also found for not otherwise specified uterine cancers (SMR=52.5, 95% CI: 14.3-135), liver (SMR=13.2, 95% CI: 7.7-21.1), skin melanoma (SMR=10.9, 95% CI: 3.0-27.8), lung (SMR=8.0, 95% CI: 5.7-11.0), head and neck (SMR=7.8, 95% CI: 3.6-14.9), leukemia (SMR=7.6, 95% CI: 2.4-17.7), and colon-rectum (SMR=5.4, 95% CI: 2.6-10.0). The SMRs were generally higher in the 15-49-years age group (Table 3). In particular, elevated excess risks among younger PWA emerged for liver (SMR=38.8 among PWA who died at ages 15-49 years *vs.* SMR=7.6 at ages 50-74 years) and lung cancers (SMR=22.0 and 5.7, respectively). The sex stratified analysis (see Table B, Supplemental Digital Content, http://links.lww.com/QAI/A820) showed similar SMRs for both ADCs (SMR=424, 95% CI: 372-482, in men; SMR=487, 95% CI: 358-647 in women) and non-ADCs (SMR=7.1, 95%

CI: 5.8-8.6, in men; SMR=9.1, 95% CI: 5.6-14.1 in women). Female PWA reported higher excess mortality than males for non-Hodgkin lymphoma (SMR=339, 95% CI: 292-392, in men; SMR=554, 95% CI: 386-771 in women) and lung cancer (SMR=7.4, 95% CI: 5.1-10.4 in men; SMR=17.3, 95% CI: 5.6-40.3 in women).

Both PWA infected trough IDU or through sexual intercourses reported extremely elevated excess mortality for ADCs (Table 4). PWA who had been infected through IDU showed particularly high excess mortality for non-ADCs, being the overall SMR equal to 20.0 (95% CI: 15.1-26.1). Of note, 14 out of 17 (82%) liver cancers occurred among IDU PWA, corresponding to a SMR of 74.7 (95% CI: 40.8-125.3). Also the SMRs of anus (SMR=440.4, 95% CI: 53.3-1591), not otherwise specified uterus (SMR=156.8, 95% CI 32.3-458.2), lung (SMR=29.3, 95% CI: 17.4-46.3), and head and neck cancers (SMR=23.6; 95% CI: 7.6-55.0) were extremely elevated in this group.

Considering PWA infected through sexual intercourses, the SMR for non-ADCs overall was 4.9 (95% CI: 3.8-6.2). Very high SMRs emerged especially for anal cancer (SMR=189.5; 95% CI: 39.1-553.9), Hodgkin lymphoma (SMR=115.9; 95% CI: 50.0-228.4), but significant excess mortality was detected also for leukemias (SMR=8.2; 95% CI: 2.2-21.0), lung (SMR=5.1; 95% CI: 3.1-8.0), and colorectal cancer (SMR=3.5; 95% CI: 1.1-8.3).

Discussion

This study provided nationwide, population-based estimates of the excess cancer mortality among Italian PWA, as compared to people without HIV/AIDS, in the late-HAART era. In addition to extremely elevated risks of death for ADCs, the study documented a statistically significant higher mortality also for cancers not directly associated with HIV/AIDS, with an overall 7.3-fold excess risk for all non-ADCs combined. This latter figure

can be interpreted as a combination of the increased incidence of such malignancies[15,19-22] and of the reduced cancer survival of people with HIV/AIDS.[16,23,24]

Overall, significant excess mortality emerged for cancers associated with viruses, for which HIV-infected individuals are likely to lose the immune control of infections, and for cancers associated to unhealthy behaviors, like tobacco smoking. All these risk factors have been shown to be more common among HIV-infected individuals than among uninfected ones.[1,4,5,25,26] Furthermore, mortality in HIV patients without such risk factors was found to be very similar to that of the non-HIV-infected individuals in a Danish cohort.[26] In particular, the poorer survival observed among HIV-infected people via IDU was recently reported to be mostly due to HCV co-infection.[27] In our study, PWA infected via IDU reported also very high SMRs.

As expected, extremely high SMRs were documented for the three ADCs, which were strongly associated with viruses.[28] Very high excess risk emerged also for the group of not otherwise specified uterine cancers where several misclassified cervical cancers are included.[29]

Among non-ADCs, very high excess risks were registered for Hodgkin lymphoma (associated to EBV[28]) and anal carcinoma (associated to HPV[28]), two cancers that deserve particular attention as the elevated corresponding SMRs were due to the combination of their relative paucity in the general population and to their increased incidence among HIV-infected people.[15,19,22] Of note, 2 out of 5 PWA death certificates reporting anal cancer mentioned also Kaposi sarcoma, in line with findings of a large prospective cohort of HIV-positive individuals.[21] This cancer was also found to be more frequent among homosexual PWA[19] (3 out of 5 cases, in our study). Liver cancer, which is strongly associated to infection with hepatitis C and B viruses,[28] showed a particularly high SMR, especially among IDU PWA, similarly to other studies.[19] This tumor was reported together with liver cirrhosis (ICD-

10 code K74.6) in 10 out of 17 death certificates (59%) and with chronic viral hepatitis C (HCV, ICD-10 code B18.2) in 5 cases (29%). Highly significant excess risks of death were also seen for lung and head and neck cancers -associated with tobacco smoking- [28] in particular among PWA infected through IDU but also among PWA who died at age 50-74 years (an age period in which lung cancer is very common also among the general population[14]). On the other hand, colorectal cancer, leukemia, and skin melanoma -which also reported significant SMRs- were not generally found to be at increased incidence risk among HIV/AIDS patients.[15,19] The excess death risk observed for these cancers can be explained by a poorer survival of HIV/AIDS patients after cancer onset.[15,23] Some misclassification of anal cancer into rectal cancer in death certificates cannot be excluded (SMR=19.0; 95% CI: 7.6-39.1 for rectal cancer, see Table A, Supplemental Digital Content, http://links.lww.com/QAI/A820).

The spectrum of non-ADCs, for which we found excess mortality, and the magnitude of SMRs are in line with our previous investigation[11] and with other studies conducted in high-income countries.[1,4,6,20] The proportion of deaths associated to non-ADCs was higher in the present study, referring to the period 2006-2011, than in the previous one conducted in the period 1999-2006[11] (10.3% *vs.* 7.4%). This difference did not seem attributable to the use of MCoD: among the 17 death certificates of PWA that reported more than one cancer, the majority were ADCs. The increasing proportion of non-ADCs at death is in agreement with findings of other investigations.[1,3,6] Indeed, this proportion increased from 9% in 1999-2000 to 23% in 2009-2011 among HIV-positive individuals under treatment in a large multi-cohort collaboration,[3] and from 7% to 16.9% between 1996-1997 and 2006-2011 among PWA in San Francisco.[6]

Among the main strengths of this study is the use of MCoD data, which allowed direct comparisons with non-PWA for all the conditions contributing to death without the need to

resort to a manual review of death certificates, as customary in earlier studies;[10,11] thus, improving reproducibility. Comparisons based on the underlying cause may be affected by poor detail and would prevent to identify specific conditions.[6,8] Indeed, in our data 73% (293 cases) of PWA reporting a cancer in death certificate had HIV/AIDS codes as the underlying cause of death (*i.e.*, ICD-10 codes B20-B24) –a value similar to that observed in other investigations,[8] often with a poor level of detail (*e.g.*, 50% had ICD-10 code B22.7="HIV disease resulting in multiple diseases", 7% had unspecific cancer codes B21.7-21.8).

Issues of reliability regarding causes of death derived from death certificate statistics are well known,[30] including a possible lack of specificity and/or underreporting due to the limited knowledge of the certifying physician regarding the medical history of the deceased. This could have differently affected the compilation of death certificates of people with or without HIV infection. Nonetheless, in our investigation, the same coding rules were applied to both study groups, thus limiting information bias.

It is worth remembering that our data included only HIV-infected individuals having already had an AIDS diagnosis. Thus, study results cannot be referred to HIV-infected people at an earlier stage of immunodeficiency. In particular, given that AIDS diagnosis can be a consequence of the diagnosis of an ADC, SMRs for ADCs could be much lower in the case of HIV-infected people without AIDS (in our data, approximately 84% of PWA reporting ADCs at death reported also ADCs at diagnosis).

The limited number of person-years at risk, resulting in a low number of observed deaths for specific cancer types, was also a study limitation. However, given that most of PWA deaths occurred within the first 6 months after AIDS diagnosis,[12] the median follow-up of 2.5 years was sufficiently long for observing most of the events of interest. Nonetheless, SMRs for very a low number of deaths should be interpreted with caution.

Completeness was the main strength of this investigation. The full coverage of the Italian population by the two used data sources allowed robust comparisons between PWA and the general population. Furthermore, the high sensitivity of the record-linkage procedure,[15,16] allowed to keep the number of losses to follow-up very limited.

In conclusion, study findings stress the need of monitoring the burden of both virus-related and non virus-related cancers among PWA in the late HAART era, as they are at still at a higher risk of death than the HIV-negative population. This applies in particular to PWA who acquired HIV infection through IDU. Indeed, our results call for taking primary and secondary preventive actions to reduce both cancer incidence and mortality among people with HIV or AIDS.

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Table 1. Distribution of 5285 Italian people with AIDS (PWA) and of 1229 PWA deceased between 15 and 74 years of age, by selected characteristics at AIDS diagnosis. Italy, 2006-2011

	Total PWA N=5285	PWA deaths* N=1229	
Characteristics at AIDS diagnosis	No. (%)	No.	% of deaths among PWA
Sex			
Male	4215 (79.8)	992	23.6
Female	1070 (20.2)	237	22.1
Age at AIDS diagnosis (years)			
15-39	1566 (29.6)	227	14.5
40-49	2273 (43.0)	527	23.2
50-59	976 (18.5)	298	30.5
60-74	470 (8.9)	177	38.5
Calendar year at AIDS diagnosis			
2006-2007	2110 (39.9)	593	28.3
2008-2009	1780 (33.7)	396	22.3
2010-2011	1395 (26.4)	240	17.3
Residence area°			
North	2808 (53.1)	652	23.3
Center	1326 (25.1)	278	21.0
South	1065 (20.2)	273	25.6
Education (years)			
<6	593 (11.2)	168	28.3
6-8	2216 (41.9)	547	24.7
≥9	1601 (30.3)	296	18.5
Unknown	875 (16.6)	218	25.3
HIV transmission mode			
Heterosexual intercourse	2093 (39.6)	446	21.5
Homosexual male intercourse	1316 (24.9)	223	17.0
Injecting drug use	1533 (29.0)	473	30.9
Other/undetermined	343 (6.5)	87	25.7
CD4 (cell count/mm^3)°			
≥350	493 (9.3)	97	19.7
200-349	585 (11.1)	161	27.7
50-199	1891 (35.8)	449	23.9
▪ 50	2177 (41.2)	476	21.9

* Deceased up to 31st Dec 2011; ° The sum does not add up to the total because of missing values

Table 2. Distribution of 1229 deceased people with AIDS (PWA) and 952,019 without AIDS (non-PWA), according to malignant neoplasms reported in death certificates[*], by age at death. Italy, 15-74 years, 2006-2011

	PWA deaths			Non-PWA deaths		
	Total N=1229	15-49 yrs N=713	50-74 yrs N=516	Total N=952,019	15-49 yrs N=115,199	50-74 yrs N=836,820
Cancer site/type (ICD-10 codes)[*]	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
AIDS-defining	*282 (22.9)*	*173 (24.3)*	*109 (21.1)*	*16,661 (1.8)*	*2191 (1.9)*	*14,470 (1.7)*
Kaposi sarcoma (C46)	63 (5.1)	36 (5.0)	27 (5.2)	170 (<0.1)	7 (<0.1)	163 (<0.1)
Cervix uteri (C53)	6 (2.5[§])	6 (3.8[§])	0 (0.0[§])	1540 (0.4[§])	405 (1.0[§])	1135 (0.4[§])
Non-Hodgkin lymphoma (C82-88, C96)	221 (18.0)	137 (19.2)	84 (16.3)	14,966 (1.6)	1779 (1.5)	13,187 (1.6)
Non AIDS-defining[°,^]	*127 (10.3)*	*56 (7.9)*	*71 (13.8)*	*445,944 (46.8)*	*37,384 (32.5)*	*408,560 (48.8)*
Head and neck (C00-14, C30-32)	9 (0.7)	4 (0.6)	5 (1.0)	19,652 (2.1)	1790 (1.6)	17,862 (2.1)
Stomach (C16)	4 (0.3)	3 (0.4)	1 (0.2)	27,759 (2.9)	2346 (2.0)	25,413 (3.0)
Colon-rectum (C18-20)	10 (0.8)	4 (0.6)	6 (1.2)	49,807 (5.2)	3092 (2.7)	46,715 (5.6)
Anus (C21)	5 (0.4)	3 (0.4)	2 (0.4)	554 (0.06)	64 (0.1)	490 (0.1)
Liver and bile ducts (C22)	17 (1.4)	9 (1.3)	8 (1.6)	30,110 (3.2)	1489 (1.3)	28,621 (3.4)
Bronchus and lung (C34)	38 (3.1)	15 (2.1)	23 (4.5)	109,198 (11.5)	5132 (4.5)	104,066 (12.4)
Skin melanoma (C43)	4 (0.3)	1 (0.1)	3 (0.6)	6726 (0.7)	1627 (1.4)	5099 (0.6)
Uterus, not otherwise specified (C55)	4 (1.7[§])	1 (0.6[§])	3 (3.7[§])	5721 (1.6[§])	681 (1.7[§])	5046 (1.6[§])
Hodgkin lymphoma (C81)	12 (1.0)	6 (0.8)	6 (1.2)	1962 (0.2)	657 (0.6)	1305 (0.2)
Leukemia (C91-95)	5 (0.4)	1 (0.1)	4 (0.8)	16,847 (1.8)	2435 (2.1)	14,412 (1.7)

[*]Using the multiple cause of death data (i.e., each death certificate reports more than one cause), the sum can exceed the total. Causes of death reported in the same death certificate within the same ICD-10 group were counted only once; [°]Secondary malignant neoplasms or unspecified cancers (C77-80) excluded; [^] It includes also sites/types with less than 4 observed deaths among total PWA, which were not shown in table; [§] Percentages were calculated on females only.

Table 3. Standardized mortality ratios according to malignant neoplasms reported in death certificates[*] of people with AIDS (PWA), as compared to people without AIDS, by age at death. Italy, PWA 15-74 years, 2006-2011

	Total (14,180 person-years)		15-49 yrs (10,080 person-years)		50-74 yrs (4100 person-years)	
Cancer site/type (ICD-10 codes)[*]	Obs./Exp.	SMR (95% CI)	Obs./Exp.	SMR (95% CI)	Obs./Exp.	SMR (95% CI)
AIDS-defining	*282/0.7*	*433.4 (384.3-487.0)*	*173/0.2*	*821.4 (703.6-953.4)*	*109/0.4*	*247.7 (203.4-298.8)*
Kaposi sarcoma (C46)	63/<0.1	10,108 (7767-12,932)	36/<0.1	38,426 (26,913-53,197)	27/<0.1	5098 (3360-7417)
Cervix uteri (C53)	6/<0.1	179.4 (65.9-390.6)	6/<0.1	281.0 (103.1-611.6)	0/<0.1	0.0 (0.0-247.8)
Non-Hodgkin lymphoma (C82-88, C96)	221/0.6	361.5 (315.4-412.4)	137/0.2	727.5 (610.8-860.0)	84/0.4	198.6 (158.4-245.8)
Non AIDS-defining[°,^]	*127/17.3*	*7.3 (6.1-8.7)*	*56/3.9*	*14.2 (10.8-18.5)*	*71/13.4*	*5.3 (4.1-6.7)*
Head and neck (C00-14, C30-32)	9/1.1	7.8 (3.6-14.9)	4/0.3	14.4 (3.9-37.0)	5/0.9	5.7 (1.9-13.4)
Stomach (C16)	4/1.2	3.5 (0.9-8.8)	3/0.3	10.6 (2.2-30.9)	1/0.9	1.1 (0.0-6.4)
Colon-rectum (C18-20)	10/1.8	5.4 (2.6-10.0)	4/0.4	11.1 (3.0-28.4)	6/1.5	4.0 (1.5-8.8)
Anus (C21)	5/<0.1	227.6 (73.9-531.0)	3/<0.1	491.1 (101.3-1435.2)	2/<0.1	126.1 (15.3-455.4)
Liver and bile ducts (C22)	17/1.3	13.2 (7.7-21.1)	9/0.2	38.8 (17.7-73.6)	8/1.1	7.6 (3.3-14.9)
Bronchus and lung (C34)	38/4.7	8.0 (5.7-11.0)	15/0.7	22.0 (12.3-36.2)	23/4.1	5.7 (3.6-8.5)
Skin melanoma (C43)	4/0.4	10.9 (3.0-27.8)	1/0.2	5.8 (0.1-32.3)	3/0.2	15.3 (3.2-44.7)
Uterus, not otherwise specified (C55)	4/<0.1	52.5 (14.3-134.5)	1/<0.1	26.7 (0.7-148.7)	3/<0.1	78.2 (16.1-228.5)
Hodgkin lymphoma (C81)	12/<0.1	122.0 (63.0-213.0)	6/<0.1	119.6 (43.9-260.2)	6/<0.1	124.5 (45.7-270.9)
Leukemia (C91-95)	5/0.7	7.6 (2.4-17.7)	1/0.2	4.7 (0.1-26.1)	4/0.4	8.9 (2.4-23.0)

[*]Using the multiple cause of death data (i.e., each death certificate reports more than one cause), the sums can exceed the total. Causes of death reported in the same death certificate within the same ICD-10 group were counted only once; [°] Secondary malignant neoplasms or unspecified cancers (C77-80) excluded; [^] It includes sites/types with less than 4 observed deaths among total PWA, which were not shown in table.
SMR: sex and age-standardized mortality ratio; CI: confidence interval; obs./exp.: observed/expected deaths.

Table 4. Standardized mortality ratios according to malignant neoplasms reported in death certificates[*] of people with AIDS (PWA), as compared to people without AIDS, by mode of HIV transmission. Italy, PWA 15-74 years, 2006-2011

	Injecting drug use (473 deaths) (4048 person-years)		Sexual intercourse[§] (669 deaths) (9302 person-years)	
Cancer site/type (ICD-10 codes)[*]	Obs./Exp.	SMR (95% CI)	Obs./Exp.	SMR (95% CI)
AIDS-defining	*69/0.1*	*571.7 (444.8-723.5)*	*186/0.5*	*388.8 (334.9-448.8)*
Kaposi sarcoma (C46)	11/<0.1	14,784 (7380-24,453)	50/<0.1	10,203 (7573-13,451)
Cervix uteri (C53)	2/<0.1	201.1 (24.4-726.4)	4/<0.1	188.9 (51.5-483.7)
Non-Hodgkin lymphoma (C82-88, C96)	58/0.1	526.8 (400.0-681.0)	137/0.5	302.7 (254.1-357.8)
Non AIDS-defining[°,^]	*55/2.7*	*20.0 (15.1-26.1)*	*64/13.1*	*4.9 (3.8-6.2)*
Head and neck (C00-14, C30-32)	5/0.2	23.6 (7.6-55.0)	3/0.9	3.5 (0.7-10.3)
Stomach (C16)	1/0.2	5.2 (0.1-29.0)	3/0.9	3.4 (0.7-10.1)
Colon-rectum (C18-20)	3/0.3	11.0 (2.3-32.1)	5/1.4	3.5 (1.1-8.3)
Anus (C21)	2/<0.1	440.4 (53.3-1591)	3/<0.1	189.5 (39.1-553.9)
Liver and bile ducts (C22)	14/0.2	74.7 (40.8-125.3)	3/1.0	3.0 (0.6-8.8)
Bronchus and lung (C34)	18/0.6	29.3 (17.4-46.3)	19/3.7	5.1 (3.1-8.0)
Uterus, not otherwise specified (C55)	3/<0.1	156.8 (32.3-458.2)	1/<0.1	19.8 (0.5-110.4)
Hodgkin lymphoma (C81)	4/<0.1	176.1 (48.0-450.9)	8/<0.1	115.9 (50.0-228.4)
Leukemias (C91-95)	0/0.1	0.0 (0.0-24.3)	4/0.5	8.2 (2.2-21.0)

[*]Using the multiple cause of death data (i.e., each death certificate reports more than one cause), the sums can exceed the total. Causes of death reported in the same death certificate within the same ICD-10 group and were counted only once; [°] Secondary malignant neoplasms or unspecified cancers (C77-80) excluded; [^] It includes sites/types with less than 4 observed deaths among total PWA, which were not shown in table; [§] Including both men having sex with men and heterosexuals.
SMR: sex and age-standardized mortality ratio; CI: confidence interval; obs./exp.: observed/expected deaths.