

# Incidence of AIDS-Defining Cancers After AIDS Diagnosis Among People with AIDS in Italy, 1986–1998

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**Abstract:** A record linkage was carried out between the Italian National Registry of AIDS and 19 cancer registries. The aim was to evaluate the 1986 through 1998 trends in incidence rate (IR) of AIDS-defining cancers (ADCs) among persons with AIDS (PWA) in Italy overall and according to various characteristics. A steady decrease in IRs was found for Kaposi sarcoma (KS) in men between 1986–1992 (2.5 per 100 person-years [py]) and 1997–1998 (1.0 per 100 py). Conversely, the first decrease in IRs of KS in women (from 0.9 to 0.6 per 100 py) and of non-Hodgkin lymphoma in both genders (from 1.7 to 0.7 per 100 py) was seen between 1993–1996 and 1997–1998, thus pointing to a favorable impact of highly active antiretroviral therapies. The decline was consistent across different age and HIV trans-

mission groups, but it was more marked in PWA with a CD4 count >50 cells/ $\mu$ L than in PWA with more severe immune suppression. As a proportion of AIDS cases, invasive cervical cancer increased from 1.5% in 1993–1996 to 2.4% in 1997–1998, but IRs after AIDS could not be evaluated. On account of the marked decline of KS in men in 1997–1998, the overall burden of ADCs in Italy became similar in both genders.

**Key Words:** AIDS, Kaposi sarcoma, non-Hodgkin lymphoma, invasive cervical cancer, linkage, incidence

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Since the mid-1990s, cancer incidence in HIV-infected populations has been investigated by some large population-based linkage studies of AIDS and cancer registries (CRs) in the United States,<sup>1–3</sup> Europe,<sup>4</sup> and Australia.<sup>5</sup> These studies have contributed to a better quantification of the burden of neoplasms in persons with HIV infection or AIDS and, together with clinical series and cohort studies,<sup>6–10</sup> have provided essential information on the frequency and characteristics of cancers during HIV infection. Incidence rates (IRs) were also evaluated using a large pooled analysis of HIV-infected subjects.<sup>7</sup>

The introduction of highly active antiretroviral therapies (HAART) after 1995 has greatly modified the natural history of AIDS and substantially decreased AIDS-associated morbidity and mortality.<sup>11,12</sup> Declining trends were observed for Kaposi sarcoma (KS) and for some subtypes of non-Hodgkin lymphoma (NHL). Conversely, no clear trend emerged for invasive cervical cancer (ICC) or other neoplasms.<sup>7,9</sup>

Italy offers a special research opportunity with respect to these issues, because the AIDS epidemic has been more severe and women constitute a larger proportion of persons with AIDS (PWA) than in most other developed countries.<sup>13,14</sup> Furthermore, a validated AIDS surveillance program<sup>15,16</sup> covers the whole population, and CRs cover nearly a quarter of it.<sup>4,17,18</sup>

The purpose of our study was to estimate the changes in the prevalence at AIDS diagnosis and subsequent incidence of AIDS-defining cancers (ADCs) among PWA in Italy overall and in different subgroups between 1986 and 1998.

## MATERIALS AND METHODS

The general design of our record linkage study has already been described.<sup>4,17,18</sup> Briefly, reporting of AIDS cases to the National Registry of AIDS (RAIDS) in Rome has been mandatory in Italy since 1986, and by the end of 2000, a total of 47,503 AIDS cases were recorded<sup>19</sup> according to clinical standard definitions.<sup>20</sup>

Nineteen independent CRs were active in Italy by the mid-1990s, covering a population of 12.6 million, corresponding to 23% of the total Italian population.<sup>21</sup> They served the regions of Romagna, Friuli-Venezia Giulia, and Umbria; a part of the Veneto region; the municipality of Turin; the provinces of Genoa, Biella, Varese, Parma, Modena, Ferrara, Macerata, Florence and Prato, Sassari, Trento, Alto Adige, Ragusa, and Latina; and a part of the province of Naples.<sup>18</sup> CRs varied in size, ranging from approximately 190,000 to nearly 1.9 million populations, and in number of registration years available. Routine indicators of data completeness and quality in Italian CRs were satisfactory.<sup>21-23</sup>

An ad hoc software application was developed to perform the record linkage procedure (Software for Automated Linkage in Italy [SALI])<sup>24</sup>. Briefly, records from RAIDS and CRs were linked by last and first names and by date of birth. Satisfaction of the name-date algorithm required (1) that the records were identical for at least 1 critical field and (2) that the other 2 critical fields, if not identical, differ only in prescribed ways. Personal identifiers were removed during linkage procedures; thus, the staff members of each registry were blinded to which persons had been linked. SALI has been shown to have a very high sensitivity and specificity in the Italian context, and it is available on request.<sup>24</sup>

The present study was restricted to people who (1) had a diagnosis of AIDS between 1986 and 1998; (2) were aged between 15 and 69 years at the time of AIDS diagnosis; (3) reported a legal residence in areas covered by CRs; and (4) had KS, NHL, and ICC reported in periods deemed complete in both registries.

If an ADC was mentioned in both RAIDS and a CR, the date of cancer diagnosis was defined as the earliest one. We backdated AIDS when KS (99 cases) or NHL (109 cases) was recorded by a CR up to 5 years before the onset date recorded at RAIDS. To ensure that all cancers were associated with HIV, 4 cases of NHL that had occurred more than 5 years before AIDS diagnosis were excluded from the analyses. All NHL types in PWA were considered in the present analysis in agreement with previous studies.<sup>2</sup> Trends of primary brain lymphoma (PBL) were also evaluated separately from other

types of NHL to identify specific time patterns.<sup>7,25-27</sup> All medical and histologic records on KS, NHL, and ICC were reviewed by CR coordinators.

The proportion of PWA who had an ADC at AIDS notification was computed. Person-years (py) were then computed between AIDS diagnosis and date of cancer diagnosis or death. The period was censored 5 years after AIDS diagnosis to reduce inaccuracies from losses at follow-up. To take into account changes in the demographic characteristics of PWA, IRs were standardized for gender and age based on the AIDS population in the overall period, using the direct method.<sup>28</sup> Corresponding 95% confidence intervals (CIs) were computed according to the Poisson distribution.<sup>29</sup>

To evaluate temporal trends, IRs were computed separately for ADCs occurring during 3 periods: (1) 1986 through 1992 (ie, spread of AIDS in Italy), (2) 1993 through 1996 (ie, introduction of combination therapies and inclusion of ICC in AIDS definition), and (3) 1997 through 1998 (ie, introduction of HAART).<sup>30</sup>

## RESULTS

Table 1 shows the proportion of PWA with KS at AIDS diagnosis and the IRs of KS by period and overall. KS declined between 1986-1992 and 1997-1998 as a proportion of AIDS cases (from 4.1% to 2.5%) and in respect to IRs (from 2.0 to 0.9 per 100 py). In men, a decrease in incidence was already present in 1993-1996, whereas in women, it appeared only in 1997-1998. It was proportionally similar in homosexual and bisexual men compared with the other transmission categories, despite the approximately 7-fold difference in IRs. A greater decrease in KS emerged among PWA aged 35 years or older than among younger PWA as well as among those with CD4 counts above 50 cells/ $\mu$ L (see Table 1).

Corresponding trends for NHL are shown in Table 2. The proportion of PWA with NHL at AIDS diagnosis increased from 2.6% to 3.4% between 1986-1992 and 1993-1996 and then remained stable. The NHL IR also increased between the first and second periods considered but declined in 1997-1998. PBL seemed to have stopped increasing earlier than other types of NHL. NHL trends were similar in different strata of gender, age, and CD4 count. In the first 2 periods, but not in 1997-1998, IRs seemed lower among intravenous drug users than other transmission groups (see Table 2).

A more detailed evaluation of IRs of KS and NHL in the 2-year periods between 1989-1990 and 1997-1998 combining both genders is shown in Figure 1. The NHL IR reached the level of the KS rate in 1993-1994 and then showed a similar downward trend (see Fig. 1). By 1997-1998, IRs for the combination of ADCs had become similar in men and women (see Tables 1, 2).

A total of 28 ICCs were identified among PWA (data not shown). All but 1 ICC was found at AIDS diagnosis. The pro-

**TABLE 1.** Proportion at AIDS and Incidence Rates<sup>a</sup> per 100 Person-Years of Kaposi Sarcoma in Persons With AIDS in Italy According to Calendar Period and Selected Variables (1986–1998)

Variable		Calendar Period			1986–1998
		1986–1992	1993–1996	1997–1998	
	Obs	183	255	35	473
	proportion (%) of AIDS cases	4.1	4.7	2.5	4.5
Incidence					
Person-years at diagnosis of AIDS		3,339	6,716	2,323	12,377
All	Obs	56	103	16	175
	rate	2.0	1.7	0.9	1.5
	(95% CI)	(1.5–2.7)	(1.4–2.1)	(0.4–1.6)	(1.3–1.8)
Gender					
Men	Obs	52	90	14	156
	rate	2.5	1.9	1.0	1.8
	(95% CI)	(1.8–3.3)	(1.5–2.3)	(0.4–1.8)	(1.5–2.1)
Women	Obs	4	13	2	19
	rate	0.4	0.9	0.6	0.7
	(95% CI)	(0.1–1.1)	(0.4–1.7)	(0.0–2.6)	(0.4–1.1)
Age (years)					
15–34	Obs	29	44	9	82
	rate	0.9	0.7	0.7	0.7
	(95% CI)	(0.5–1.4)	(0.5–1.0)	(0.3–1.4)	(0.5–0.9)
35–69	Obs	27	59	7	93
	rate	1.4	1.1	0.3	1.0
	(95% CI)	(0.9–2.0)	(0.8–1.4)	(0.1–0.7)	(0.8–1.2)
Transmission groups					
Homo-bisexual men	Obs	30	54	7	91
	rate	7.9	6.3	3.4	6.1
	(95% CI)	(5.1–11.7)	(4.4–8.6)	(1.2–7.3)	(4.8–7.7)
Others <sup>b</sup>	Obs	26	49	9	84
	rate	1.3	0.9	0.5	0.9
	(95% CI)	(0.8–2.0)	(0.6–1.2)	(0.2–0.9)	(0.7–1.1)
CD4 count/ $\mu\text{L}$ <sup>c,d</sup>					
<50	Obs	9	50	9	68
	rate	1.6	2.0	1.5	1.7
	(95% CI)	(0.6–3.2)	(1.4–2.7)	(0.6–3.1)	(1.3–2.2)
$\geq 50$	Obs	16	49	7	72
	rate	2.4	1.5	0.4	1.3
	(95% CI)	(1.3–4.0)	(1.1–2.0)	(0.1–0.8)	(1.0–1.7)

Obs, observed cases; CI, confidence intervals.

<sup>a</sup>Rates are standardized (direct method) on age and gender based on persons with AIDS.

<sup>b</sup>Unknown transmission category included.

<sup>c</sup>Thirty-five missing values excluded.

<sup>d</sup>Information on CD4 has been systematically collected only since 1988.

portion of women with ICC at AIDS was higher in 1997–1998 (2.4%; CI: 0.8–4.0) than in 1993 to 1996 (1.5%; CI: 0.8–2.2). Only 5 women with ICC had a CD4<sup>+</sup> level below 50 cells/ $\mu\text{L}$ .

### DISCUSSION

We have estimated incidence trends for KS and NHL in all PWA in approximately a quarter of the Italian population using a validated record linkage between RAIDS and the com-

**TABLE 2.** Proportion at AIDS and Incidence Rates<sup>a</sup> per 100 Person-Years of Non-Hodgkin Lymphoma<sup>b</sup> (NHL) in Persons With AIDS in Italy According to Calendar Period and Selected Variables (1986–1998)

Variable		Calendar Period			
		1986–1992	1993–1996	1997–1998	1986–1998
	Obs	116	187	49	352
	proportion (%) of AIDS cases	2.6	3.4	3.5	3.1
<b>Incidence</b>					
Person-years at diagnosis of AIDS		3,499	6,991	2,373	12,863
All	Obs	40	117	18	175
	rate	1.2	1.7	0.7	1.4
	(95% CI)	(0.8–1.6)	(1.4–2.1)	(0.4–1.1)	(1.2–1.6)
<b>Presentation site</b>					
Brain	Obs	15	35	7	57
	rate	0.4	0.5	0.3	0.4
	(95% CI)	(0.2–0.7)	(0.3–0.7)	(0.1–0.6)	(0.3–0.6)
All other	Obs	25	82	11	118
	rate	0.8	1.2	0.4	0.9
	(95% CI)	(0.5–1.2)	(1.0–1.5)	(0.2–0.7)	(0.8–1.1)
<b>Gender</b>					
Men	Obs	33	96	12	141
	rate	1.2	1.8	0.6	1.5
	(95% CI)	(0.8–1.8)	(1.4–2.2)	(0.3–1.1)	(1.2–1.7)
Women	Obs	7	21	6	34
	rate	0.9	1.4	0.9	1.1
	(95% CI)	(0.3–2.0)	(0.8–2.2)	(0.3–2.1)	(0.8–1.6)
<b>Age (years)</b>					
15–34	Obs	31	70	10	111
	rate	1.1	1.1	0.5	0.9
	(95% CI)	(0.6–1.9)	(0.8–1.4)	(0.2–0.8)	(0.8–1.2)
35–69	Obs	9	47	8	64
	rate	0.5	0.8	0.3	0.6
	(95% CI)	(0.2–1.0)	(0.6–1.1)	(0.1–0.7)	(0.5–0.8)
<b>Transmission group</b>					
Intravenous drug users	Obs	27	63	12	102
	rate	0.8	1.4	0.7	1.1
	(95% CI)	(0.5–1.2)	(0.9–2.1)	(0.3–1.3)	(0.9–1.4)
Others <sup>c</sup>	Obs	13	54	6	73
	rate	1.7	2.5	0.5	1.7
	(95% CI)	(0.7–3.1)	(1.8–3.4)	(0.1–1.2)	(1.3–2.3)
<b>CD4 count/μL<sup>d,e</sup></b>					
<50	Obs	10	54	9	73
	rate	1.5	2.1	0.9	1.7
	(95% CI)	(0.7–2.9)	(1.6–2.8)	(0.4–1.8)	(1.4–2.2)
≥50	Obs	9	54	9	72
	rate	0.8	1.4	0.5	1.2
	(95% CI)	(0.3–1.5)	(1.0–1.8)	(0.2–1.1)	(0.9–1.5)

Obs, observed cases; CI, confidence intervals.

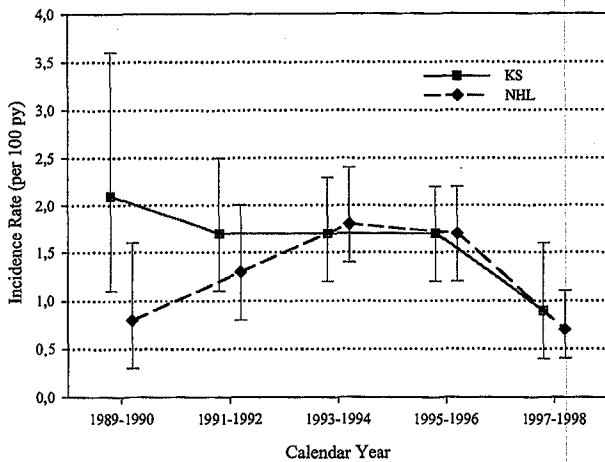
<sup>a</sup>Rates are standardized (direct method) on age and gender based on persons with AIDS.

<sup>b</sup>Primary brain lymphoma included.

<sup>c</sup>Unknown transmission category included.

<sup>d</sup>Thirty missing values excluded.

<sup>e</sup>Information on CD4 has been systematically collected only since 1988.



**FIGURE 1.** Incidence rates and 95% confidence intervals of Kaposi sarcoma (KS) and non-Hodgkin lymphoma (NHL) in both genders in Italy (1989–1998) per 100 person-years. Rates are standardized (direct method) on age and gender based on PWA.

bination of Italian CRs.<sup>4,24</sup> Our major findings are as follows: (1) the incidence of KS in men was already decreasing in 1993–1996, but decreases in KS in women and in NHL (both genders) first emerged in 1997–1998; (2) by 1997–1998, the IRs of the combination of ADCs had become similar in both genders; and (3) no excess of NHL incidence in men versus women is present among PWA, which is at variance with a male-to-female ratio of at least 1.5 in the general population.<sup>31</sup>

The standardized incidence ratios (SIRs) for KS and NHL after AIDS diagnosis compared to the general Italian population were 497 (CI: 412–595) and 125 (CI: 105–149), respectively, for the whole period from 1986–1998.

The IRs and the time pattern we observed for KS and NHL are similar to those reported by cohort studies of HIV-infected individuals<sup>7,10</sup> and PWA.<sup>32</sup> Also in agreement with a previous work,<sup>32</sup> the incidence of KS and NHL was approximately 2-fold more elevated in PWA with a CD4 count below 50 cells/ $\mu$ L than in those with less severe immune suppression. The apparent benefit of HAART in the last considered period also seemed more marked in PWA who showed CD4 counts above 50 cells/ $\mu$ L. A greater decline in PBL than in immunoblastic and Burkitt lymphoma has been reported by some studies.<sup>7</sup> The number of PBLs in PWA, in our study, was too small to draw definite conclusions, and the greatest difference between the incidence of PBLs and other NHLs was actually seen in 1993–1996 (ie, prior to HAART).

It should be borne in mind that the incidence of NHL is more elevated in men than in women in virtually all populations and ethnic groups, regardless of 2- to -3-fold variations in standardized NHL IRs worldwide.<sup>22,23,31,33</sup> Male excesses were reported for B-cell and T-cell NHL and for different histologic types, but they seemed greater for high-grade lym-

phoma (male-to-female ratios from 2.0 to 3.1 among whites) than for follicular lymphomas (ratios between 1.0 and 1.2).<sup>31,34</sup> Our present findings suggest that in the presence of AIDS, NHL becomes equally frequent in both genders, as if HIV-induced immune depression/dysregulation would implicate the loss of some protective features linked to the female gender.<sup>35</sup>

A few problems may affect the present study. The periods examined were not completely comparable for a number of reasons. Diagnostic standards in HIV-infected persons have improved in more recent periods,<sup>20</sup> and the consequence of these modifications have generally been an anticipation of AIDS diagnosis and an increase in py of observation after AIDS. Conversely, the introduction of prophylaxis against several AIDS-defining illnesses and of new antiretroviral drugs significantly delayed the date of AIDS diagnosis.<sup>36</sup> The last considered period (1997–1998) included only observations close in time to AIDS diagnosis, thus leading to fewer py of follow-up. Furthermore, because a large (but unknown) proportion of HIV-infected persons in Italy in 1997–1998 had probably received HAART only after AIDS diagnosis,<sup>19</sup> our population-based estimates of the benefit of HAART on KS and NHL chiefly apply to the use of HAART relatively late in the course of HIV infection.<sup>37</sup>

A different incubation period for different AIDS-defining diseases might affect the apparent changes in the proportion of ADCs at AIDS and subsequently.<sup>38</sup> Nevertheless, some authors have recently demonstrated that risks of AIDS-defining illnesses obtained using competing risk models<sup>39</sup> were similar to those obtained from illness-specific models.<sup>38</sup> The linkage of personal identifiers between RAIDS and CRs may have failed in a few instances, and an overestimation of the number of people thought to be under observation may have been produced by unreported deaths or migration of PWA outside cancer registration areas. The Italian population is, however, a relatively stable one: CRs tend to be located in areas with good medical standards, and treatment to PWA is provided free of charge all over the country. A surveillance bias is possible, but it may operate in either direction, because ADCs, notably NHL,<sup>40</sup> can be either under- or overdiagnosed in PWA compared with the general population.<sup>41,42</sup>

More important, two thirds of KS and NHL and virtually all ICC in PWA in our study had occurred at AIDS, also because AIDS definition in Italy is clinical and not based on CD4 count. Although the inclusion of KS and NHL that led to AIDS diagnosis would have biased the incidence of such cancers in a cohort of PWA, their exclusion has entailed a substantial loss of statistical power in the evaluation of incidence trends.

In conclusion, the findings of our present linkage of RAIDS and CRs suggest that, whereas the decline in KS incidence in men antedated the introduction of HAART and may thus have alternative explanations (eg, changes in the compo-

sition of PWA), the decreases seen in the incidence of KS in women and of NHL in both genders are likely attributable to the favorable impact of new treatments.<sup>43,44</sup> On account of the substantial decrease of KS in men and the inclusion of ICC, the burden of all ADCs in Italy in 1997–1998 became similar in men and women, as shown in other areas.<sup>10</sup>

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#### APPENDIX: CANCER AND AIDS REGISTRY LINKAGE STUDY

The members of the Cancer and AIDS Registry Linkage Study not included in the first page are as follows: Gary Clifford (IARC Lyon, France); Eugenio Paci and Emanuele Crocetti (Registro Tumori Toscano, Firenze, Italy); Silvia Patriarca and Stefano Rosso (Registro Tumori Piemonte, Torino, Italy); Fabio Falcini and Rosa Vattiato (Registro Tumori della Romagna, Forlì, Italy); Paola Contiero (Registro Tumori Lombardia-Provincia di Varese, Italy); Marina Vercelli and Maria Antonietta Orengo (IST, Università di Genova and Registro Tumori Regione Liguria, Genova, Italy); Paola Zambon and Stefano Guzzinati (Registro Tumori del Veneto, Padova,

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