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Epidemiology of AIDS-related tumours in developed and developing countries

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Abstract

AIDS-associated illnesses include Kaposi's sarcoma (KS), non-Hodgkin's lymphoma (NHL), and, since 1993, invasive cervical cancer (ICC). Between 1988 and 1998, among AIDS cases reported in western Europe, 9.6% had KS and 3.9% had NHL as AIDS-defining illnesses. Between 1988 and 1998, the frequency of KS decreased from 13.4 to 6.4%, while NHL increased from 3.8 to 5.3%. Estimates of the relative risk (RR) of neoplasms in HIV-seropositive populations came from population-based cancer and AIDS registries linkage studies conducted in the United States, Italy and Australia and from a few cohort and case–control studies. In adults with HIV/AIDS, the RR was over 1000 for KS and ranged between 14 for low-grade NHL and over 300 for high-grade NHL. For Hodgkin's disease (HD), a consistent 10-fold higher RR was observed. For cervical and other anogenital tumours associated with human papilloma virus, risk increases were 2- and 12-fold, depending upon location. In Africa, the AIDS epidemic led to KS becoming the most common cancer type in men in several areas. The RR of AIDS-associated tumours were lower in Africa than those reported in western countries.

Keywords: HIV; AIDS; Kaposi's sarcoma; Non-Hodgkin's lymphoma; Hodgkin's disease; Invasive cervical cancer; Antiretroviral therapies

1. Introduction

Immunodeficiency, whether congenital, iatrogenic or due to infections, increases the risk of a few types of cancer. The investigation of cancer in the HIV-infected population follows the earlier research on patients iatrogenically immunosuppressed after organ transplantation [1], and it offers a unique opportunity to investigate on an unprecedented large scale the role of the immune system in the onset and growth of tumours.

The evidence for an increased risk of Kaposi's sarcoma (KS) and non-Hodgkin's lymphoma (NHL) in HIV-infected individuals is compelling [2]. Since the beginning of the epidemic, KS and NHL have been included among the AIDS-defining illnesses (i.e. diseases which in concurrence with HIV-seropositivity implied a diagnosis of AIDS). There have been several investigations on the relationship between HIV infection and cancers other than KS and NHL. These have been conducted in several countries and have shown weaker and less consistent results [2–5].

Different ways of quantifying an excess of cancer risk in persons with HIV/AIDS have been attempted. Several clinical series were published, but they were unable, on account of possible selection bias, to estimate accurately the HIV-associated relative risk (RR) of cancer [2]. Population-based cancer registration data first yielded indirect estimates of HIV-associated cancers based on surrogate indicators of groups at risk for HIV infection, such as never-married male adults for homosexual men [6]. Increases in RR of approximately 1000-fold for KS and between 2- and 20-fold for NHL were found in never-married men. However, these RRs tended to underestimate the actual risk increases, since surrogate groups included substantial proportions of uninfected individuals.

Although cohort studies of HIV-seropositive individuals often provided detailed information of risk correlates and

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follow-up data [2], they were generally based on too few cancer events to provide precise RR estimates. Thus, to have a better quantification of the spectrum of malignancies among HIV-infected individuals, linkage studies of AIDS and cancer registries have been conducted in western countries [3,5,7].

The highly active antiretroviral therapies (HAART) were introduced in developed countries during the end of 1996 and the beginning of 1997. Since then, mortality and morbidity rates from AIDS have fallen dramatically in developed countries, but the impact of HAART on cancer incidence rates in HIV-infected people is still ill defined.

The purpose of this paper is to summarise epidemiological findings on malignancies associated with HIV infection and AIDS, taking into account the strengths and weaknesses of the different study designs and temporal changes.

2. Kaposi's sarcoma

2.1. Background

Before the AIDS epidemic, KS had been described in immunosuppressed organ recipients [1], in Africa (the endemic type), and in the elderly population (mostly men) from Mediterranean countries (the classic type). In Italy, for instance, incidence rates of KS (approximately 10 cases/per million males) were intermediate between high (e.g. central Africa) and low risk areas (e.g. the United States (US)) [8]. In the pre-AIDS era, KS was a very rare cancer (incidence rates approximately 0.1 per million) [8] in Northern Europe and in the US, but, as a consequence of AIDS-related cases, KS incidence rates have risen, in men in the early 1990s, to over 10 per million in the US and in several European countries (i.e. France, Portugal, Spain, Switzerland and the United Kingdom) [9].

Relatively early on in the epidemic, it was hypothesised that KS was caused by a sexually transmitted agent [10], and the discovery of the human herpesvirus-8 (HHV8) [11] in all types of KS supported the possibility that this virus may be necessary, albeit not sufficient, to induce KS. Additional cofactors, most notably immune impairment, are probably required to develop KS [12]. A wide variation in HHV8 seroprevalence rates have been reported in healthy populations from different parts of the world (from 1% in the US to nearly 60% in Africa). However, the best serological methods to detect antibodies to HHV8 in the general population has still to be determined [12,13] and the lack of comparability among methods still limits the interpretation of such differences.

The transmission of HHV8 constitutes another open issue. In Western populations, the most important behavioural risk factor appears to be sexual intercourse between men [14]. However, data from Africa, French Guiana and from Italy support the possibility that HHV8 may be transmitted early in life, vertically from mother to child, or horizontally within the family [13,15–17].

2.2. KS as an AIDS-defining illness

AIDS surveillance data from developed countries has allowed the assessment of the spectrum of AIDS-defining illnesses since the beginning of the AIDS epidemic. AIDS surveillance data, however, underestimates the frequency of KS, as well as the frequency of NHL (see following section), since they do not include systematically diagnoses that occur after the first AIDS-defining illness(es).

As for other AIDS-defining illnesses, the most recent trends in KS can be evaluated only in Europe because in the US, since 1993, most AIDS cases have been reported based on immunological criteria (CD4+ T-lymphocyte count $<200/\mu l$). AIDS-defining illnesses have, therefore, stopped being reported systematically.

Information on KS in 17 western European countries, as of December 1999, was made available by the European Non-Aggregate AIDS Data Set (ENAADS) [18]. For comparability purposes, cases diagnosed and notified in the last available year (1999) were not considered due to incomplete notification and reporting delay.

Between 1988 and 1998, a total of 18 909 AIDS cases had KS as an AIDS-defining illness (9.6%). Table 1 shows that the number of cases of KS rose steadily from

Table 1
Number of all Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer as AIDS-defining illnesses and percent of all AIDS cases by year: Western Europe, 1988–1998[a]

Year	Kaposi's sarcoma	Non-Hodgkin's lymphoma	Invasive cervical cancer
	n (%)	*n* (%)	*n* (%)[b]
1988	1449 (13.4)	408 (3.8)	0
1989	1706 (12.1)	535 (3.8)	0
1990	1889 (11.6)	584 (3.6)	0
1991	2127 (11.4)	655 (3.5)	0
1992	2225 (10.8)	800 (3.9)	0
1993	2139 (9.6)	814 (3.6)	63 (1.5)
1994	2253 (8.9)	910 (3.6)	127 (2.6)
1995	1928 (7.9)	975 (4.0)	113 (2.3)
1996	1576 (7.5)	853 (4.1)	105 (2.4)
1997	980 (7.0)	700 (5.0)	82 (2.7)
1998	637 (6.4)	524 (5.3)	59 (2.8)
Total	18 909 (9.6)	7758 (3.9)	549 (2.3)[c]

[a] Data available from Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

[b] In females.

[c] Period 1993–1998.

1988 to 1992, then stabilised through 1994 and declined thereafter. As a percentage of AIDS-defining illnesses, however, KS decreased steadily throughout the examined period: from 13.4% in 1988 to 6.4% in 1998 (χ^2_1 for trend, adjusted for area, HIV-transmission group, gender and age = 147.0; $P < 0.001$).

Trends of KS as an AIDS-defining illness, stratified according to geographical area, age, gender and HIV-transmission group did not show significant heterogeneity. However, the proportion of KS seemed to be higher in Northern and Central European countries and among older individuals. This chiefly reflects the greater proportion of homosexual and bisexual men rather than intravenous (i.v.) drug users (IDU) or other HIV-transmission groups in certain countries and age groups [19].

2.3. Risk of HIV-associated KS in developed countries

A number of studies investigated the risk of KS in HIV-seropositive individuals, showing a prevalence 10- to 20-fold higher in homosexual and bisexual men than in other HIV-transmission groups [2].

Cohort studies of HIV-infected individuals showed marked KS excess [20,21]. The Pittsburgh component of Multicenter AIDS Cohort Study (MACS) included 769 HIV-seronegative participants and 430 seropositive subjects with a median follow-up of 7 years from 1985 through to 1993 [22]. The occurrence of KS among the HIV-seropositive individuals was over 400-fold higher than in the general population.

Investigators in the US [3,7], Europe [4] and Australia [5] have linked records of AIDS cases reported to AIDS registries to cancer registry records. Cancer incidence rates in the years subsequent to AIDS diagnosis (generally 2 or 3 years) were calculated and compared with rates expected among the general population of the same age, race, gender and area of residence as the persons with AIDS. Limitations and potential biases of registry linkage studies include missed linkages, increased or decreased medical surveillance in individuals with HIV/AIDS and survival bias in persons with HIV infection and cancer [7]. Furthermore, linkage studies do not allow adjustment for potential confounding factors (e.g. lifestyle factors, co-infection with other viruses, etc.) [2]. A strength of such methodology is represented, however, by the access to a large number of unselected cancers in HIV-positive individuals, both before and after AIDS diagnosis. Table 2 shows the findings of registry linkage studies with respect to KS.

Between 1981 and 1990, Biggar and colleagues [7] linked 83 434 AIDS cases reported to AIDS registries in seven regions in the US. Out of 8489 cases meeting the enrolment criteria, in 7351 of them KS was an AIDS-defining illness, whereas in 1045 it occurred 6–11 months after the onset of another AIDS-defining illness. From 6 to 11 months after AIDS, the RR of KS was, hence, 106 000 in homo/bisexual men with AIDS and 13 000 in men who belonged to other HIV-transmission groups (Table 2) and remained stable until 23 months after the diagnosis of AIDS.

Goedert and colleagues [3] matched 98 336 people with AIDS and 1 125 098 persons with cancer, ages less than 70 years, in seven regions of the US and in Puerto Rico. The RR for KS after AIDS diagnosis was 1000 from 6 months prior to and 3 months after the diagnosis of AIDS, and 310 between 4 and 27 months after the diagnosis of AIDS.

In Europe, a record linkage was carried out by Franceschi and colleagues [4] between the Italian Registry of AIDS (33 304 people with AIDS) and 13 Cancer Registries covering a population of approximately 8 million. The RR for KS after the diagnosis of AIDS was 1300 (Table 2).

In Australia, 778 cancer cases were identified in 3616 people with AIDS between 1980 and 1993 [5]. There were 511 KS cases, with a RR of approximately 72 700.

RRs in Table 2 are not as heterogeneous as they seem, since linkage studies differed mostly in the length of time around the diagnosis of AIDS when the cancer risk was evaluated.

Death rates offer another tool to investigate the increase of cancer risk in unselected populations with HIV infection. The first large study of this type was reported in the US by Selik and Rabkin [23]. They identified 22 275 persons 25–44 years old who had died from 1990 through 1995 and had cancer and HIV infection on their death certificates. By means of an estimate of HIV-seropositive individuals in the same age range in the US at the end of 1992 (i.e. 525 000 males and 120 000 females), the expected number of cancer deaths was estimated and compared with the observed one. RRs for death from KS and other skin cancers were 1322 in males and 555 in females (Table 3).

KS is rare as an AIDS-defining illness in children in the US (0.5%) and in Europe (0.2%) [24,25]. Granovsky and colleagues [26] described 65 malignancies in 64 HIV-infected children diagnosed at 84 member institutions of the Children's Cancer Group (in the US, Canada and Australia) and the Paediatric Branch of the National Cancer Institute (NCI), US. KS accounted for only three (5%) of tumours reported.

Only one population-based linkage study from the US published data on children (aged less than 14 years) with AIDS [27]. Eight KS were found out of 124 tumour cases which had arisen between 60 months prior to and 60 months after the diagnosis of AIDS. KS was the second most common malignancy after NHL.

2.4. HIV-associated KS in developing countries

The majority of information from developing countries is provided from Africa. KS was relatively frequent

Table 2
Relative risk (RR) and corresponding 95% confidence interval (CI) of Kaposi's sarcoma and haemolymphopoietic malignancies in people with AIDS from registry-linkage studies

Type of cancer	Country, Reference	Group	Time interval (months with respect to AIDS)		No. observed	RR (95% CI)
			From	To		
KS	US [7]	Homosexuals/bisexual	+6	+11	547	106 000
		Other men	+6	+11		13 000
	US [3]		−6	+3	5181	1 000
			+4	+27	1827	310 (292–330)
	Italy [4]		−60	+24	151	1300
	Australia [5]		0	Death	511	72 700 (66 800–79 600)
NHL	US [40]	High grade	0	+42	157	348
		Intermediate grade	0	+42	160	113
		Low grade	0	+42	10	14
		All NHL	0	+42	510	165
	US [3]		−6	+3	1276	325
			+4	+27	517	113 (104–123)
	Italy [39]		−12	+42	121	228 (189–272)
	Australia [5]		−60	Death	205	97 (84–112)
HD	US [3]		−60	−7	55	4.4
			−6	+3	72	42.4
			+4	+27	13	7.6 (4.1-13.1)
	Italy [4]		−60	+24	11	8.9 (4.4-16.0)
	Australia [5]		−60	Death	9	18.3 (8.4–34.8)
Multiple myeloma	US [3]		−60	−7	2	0.6
			−6	+3	11	14.5
			+4	+27	3	4.5 (0.9–13.2)
	Italy [4]		−60	+24	1	–
	Australia [5]		−60	Death	3	12.1 (2.5–35.4)
Leukaemia	US [3]		−60	−7	19	2.4
			−6	+3	27	13.9
			+4	+27	8	3.8
	Italy [4]		−60	+24	2	2.2 (0.2–8.1)
	Australia [5]		−60	Death	4	5.8 (1.6–14.7)

KS, Kaposi's sarcoma; NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease.

Table 3
Relative risk (RR) of death from Kaposi's sarcoma and haemolymphopoietic malignancies and corresponding 99% confidence interval (CI) in HIV-infected persons ages 25–44 years: United States, 1990–1995[a]

Type of cancer (ICD-9 codes)	Gender	No. observed	RR (99% CI)
Kaposi's sarcoma and other skin cancer (173)	Males	12 112	1322 (1209–1447)
	Females	158	555 (411–749)
Non-Hodgkin's lymphoma (200, 202)	Males	7813	136 (130–142)
	Females	650	112 (102–124)
Hodgkin's disease (201)	Males	280	11.3 (9.6–13.3)
	Females	27	9.7 (6.4–14.8)
Multiple myeloma (203)	Males	26	3.0 (1.8–5.0)
	Females	1	0.2 (0.0–63.5)
Leukaemia (204, 208)	Males	119	1.7 (1.3–2.1)
	Females	30	2.4 (1.5–3.9)

[a] ICD-9, International Classification of Diseases, 9th revision. Adapted from Selik and Rabkin (1998) [23].

in Africa even before the onset of the HIV epidemic, and showed marked geographical variation [8]. Striking increases in the KS incidence rates have been recorded subsequently to the spread of HIV infection in the 1970s and 1980s. Rates are at present highest between the age of 25 and 34 years in men, and between the age of 20 and 29 years in women. A small peak of KS has also been recorded in children below the age of 10 years [28,29].

In Kampala, Uganda, a population-based cancer registry had been active in 1954–1960 and was re-established in 1989–1991 [29,30]. Seropositivity for HIV was reported in approximately 10% of the rural population, and 8–30% of the urban population [30]. In the 1990s, KS had became the leading cancer in males (approximately 50% of all cancers) and the second most frequent in females (20%) after cervical cancer, with approximately a 20-fold increase since the 1960s. Incidence rates were 39/100 000 in males and 20/100 000 in females [29]. In another African cancer registry, Harare, Zimbabwe, KS was reported, in 1990–1992, as the most frequent cancer type in males (23% of all cancer incidence) and the third most frequent in females (10%) in 1990–1992 [28]. In 1991–1992, in the population-based cancer registry of Butare, Rwanda [31], KS accounted for 6% of all cancers in the two genders combined and the RR for KS in HIV-seropositive individuals was estimated to be 35.0 (95% confidence interval (CI): 8.2–206.7) (Table 4).

Sitas and colleagues [32] used the case–control approach to estimate the risk of KS in a black population aged 18–49 years in South Africa (Table 4). The study resulted in an estimated RR for KS of 21.9 (95% CI: 12.5–38.6) in HIV-positive individuals.

The prevalence of HHV8 has been studied rather extensively in Africa, and prevalence rates are substantially higher than those reported in developed countries [13,33,34]. A high background risk of KS in HIV-negative individuals in Africa may explain the lower RRs for KS generally reported in this continent than in Europe or the US.

3. Non-Hodgkin's lymphoma and other lymphoid neoplasms

3.1. Background

NHL is the second commonest malignancy associated with HIV infection, and the spectrum of HIV-related lymphomas includes: (1) systemic NHL (i.e. immunoblastic and Burkitt's lymphoma); (2) primary brain lymphoma (PBL); and (3) body cavity-based lymphoma. Whether HIV infection is associated with an increased incidence of Hodgkin's disease (HD) has been a subject of considerable controversy [2].

Both primary and iatrogenic immunosuppression are associated with an increased risk for NHL [1,2]. Among NHL types, Burkitt's lymphoma incidence is increased in patients with X-linked lymphoproliferative disease and ataxia telangectasia, but not in iatrogenically immunosuppressed patients. Similarly, HD risk may be elevated in some primary immunodeficiencies, but increases in incidence have not been reported in studies of organ recipients [1]. Scanty information exists on specific NHL subtypes, body cavity-based lymphoma (a rare lymphoma linked to HHV8) [35], and other lymphoid neoplasms [36,37].

3.2. NHL as an AIDS-defining illness

PBL and Burkitt's lymphoma have been included among the AIDS-defining illnesses since 1982 whereas the immunoblastic NHL have been included since 1985. The frequent lack, in AIDS surveillance data, of inclusion of NHL subsequent to another AIDS-defining illness leads, however, to a 2- to- 3-fold underestimation of the NHL burden [2].

In contrast to what is reported for KS, the frequency of NHL varies very little by HIV exposure groups in developed countries [2]. This suggests that environmental cofactor(s) for AIDS-NHL are unlikely to be as important (or as unevenly distributed) as those for KS (e.g. HHV8) [35]. A modest excess among homosexual men (4%) compared with i.v. drug users (3%) in the US has been chiefly attributed to some underreporting of AIDS-related NHL in drug users [2].

As for KS, most recent trends in NHL as an AIDS-defining illness can be evaluated only in Europe. Information from ENAADS collected between 1988 and 1998 in 17 western European countries allowed us to evaluate 7758 AIDS cases that had NHL as an AIDS-defining illness (3.9%). Table 1 shows that NHL number rose steadily from 1988 to 1995, but declined there-

Table 4
Relative risk (RR) and corresponding 95% confidence interval (CI) of selected cancers among HIV-infected persons in developing countries

Type of cancer	Country [Ref.]	No. observed	RR (95% CI)
Kaposi's sarcoma	Rwanda [45]	11	35.0 (8.2–206.7)
	South Africa [32]	89	21.9 (12.5–38.6)
	Uganda [65]	–	19.2 (13.2–27.8)
Non-Hodgkin's lymphoma	Rwanda [45]	7	12.6 (2.2–54.4)
	South Africa [32]	23	5.0 (1.7–9.5)
	Uganda [65]	–	1.9 (1.0–3.5)
Hodgkin's disease	South Africa [32]	14	1.4 (0.7–2.8)
Invasive cervical cancer	Rwanda [45]	0	0.0
	South Africa [32]	167	1.6 (1.1-2.3)
	Uganda [65]	–	1.2 (0.8-1.8)

after. As a percentage of AIDS-defining illnesses, however, NHL increased from 3.6% in 1994 to 5.3% in 1998 (χ^2_1 for trend, adjusted for area, HIV-transmission group, gender and age = 61.4 years; $P < 0.001$).

Proportional increases of NHL as an AIDS-defining illness between 1994 and 1998 were found in northern (from 3.3 to 7.4%), central (from 4.8 to 7.4%), and southern Europe (from 2.8 to 4.1%) (Fig. 1). With respect to age, the proportion of NHL increased from 3.0 to 4.1% in AIDS cases age 39 years or less and from 5.3 to 7.5% in those aged 40 years or older. Upward trends were observed similarly in men (from 3.8 to 5.8%) and women (from 2.5 to 3.3%) and in the major HIV transmission groups (from 5.0 to 8.7% in homosexual and bisexual men; from 2.3 to 3.0% in i.v. drug users; and from 4.0 to 5.6% in other HIV transmission categories). Trends were, therefore, consistent across the different examined strata, although the proportion of NHL was highest among Northern European males, homosexual and bisexual men, and/or older individuals (Fig. 1).

3.3. Risk of HIV-associated lymphomas in developed countries

Many attempts have been made to estimate the RR of lymphomas in people with AIDS [2]. After a 12-year follow-up from the MACS prospective study [38], RRs in HIV-seropositive individuals versus the US general population were approximately 170 for NHL, based on 171 observed cases, and 7.0 for HD (95% CI: 2.5–15.1) based on 6 HD cases. Early evidence of an increase in HD came from the San Francisco City Clinic Cohort which was updated in a combined analysis (total 15 565 subjects) with the New York City hepatitis B natural history and vaccine trial cohorts [21]. The RR of HD was 2.5 (95% CI: 1.5–3.9).

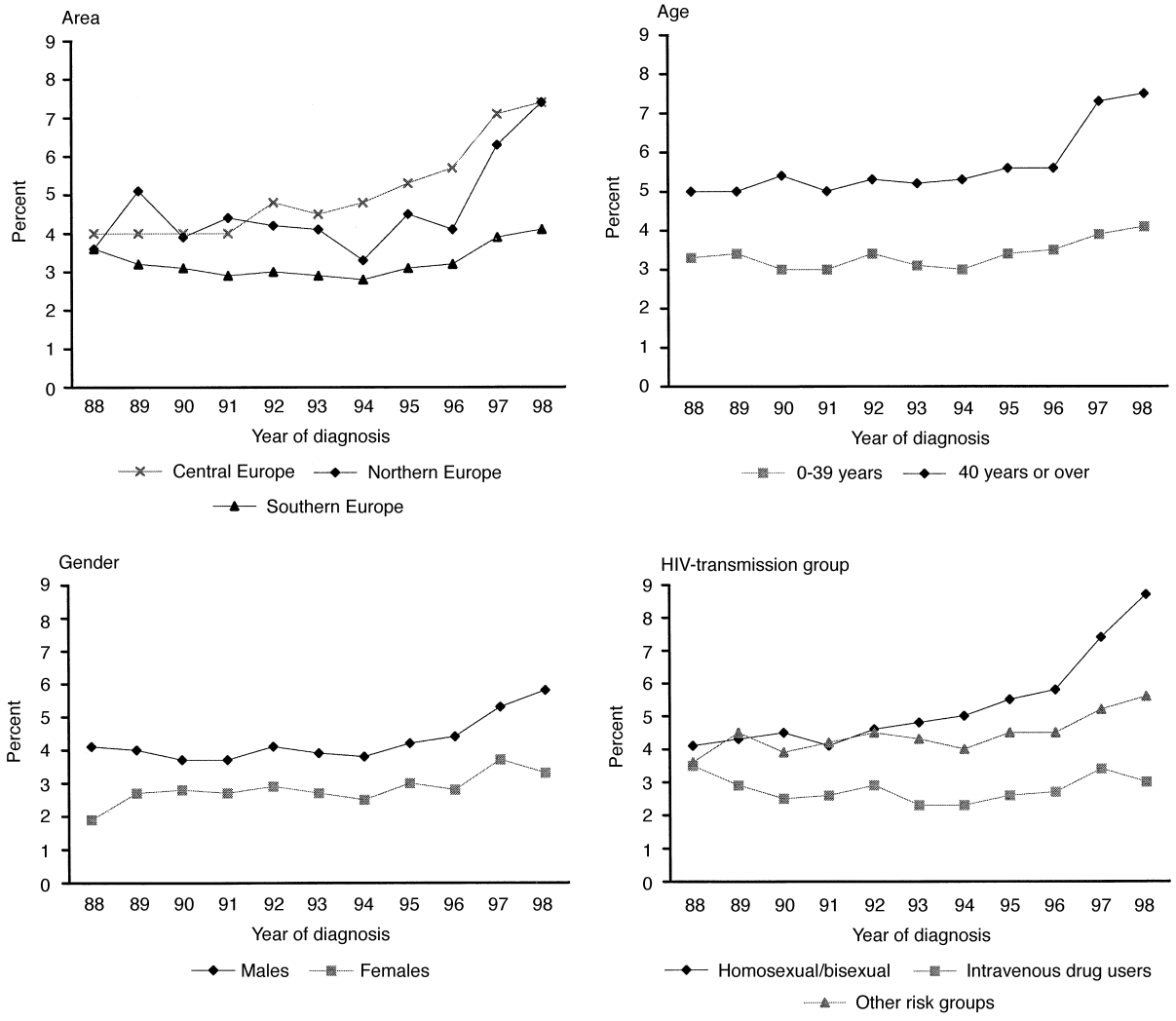

Fig. 1. Percent of AIDS cases with NHL as an AIDS-defining illness by area, age, gender and HIV-transmission group in western Europe, 1988–1998. Data available from Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, The Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

Findings from registry linkage studies [3–5,39,40] with respect to NHL, HD, and a few other lymphoid malignancies are shown in Table 2.

Among 83 434 AIDS cases reported to AIDS registries in seven regions of the US between 1981 and 1990 [7], 2031 NHL cases met the enrolment criteria and 335 occurred 6 through to 23 months after another AIDS-defining illness. The RR was 283 and nearly doubled between semesters 2 and 4 after the diagnosis of AIDS, pointing to a role of increasing immune impairment in NHL onset.

In the same US registration areas, Coté and colleagues [40] considered 2156 cases of NHL (4.3%) among 51 033 persons with AIDS and compared them with 4051 NHL cases without AIDS. Thirty-nine percent of NHLs were high grade (versus 12% among persons without AIDS), 40% were extranodal (versus 26% among people without AIDS) and 15% had brain NHL (versus 1% among persons without AIDS). Thus, RRs ranged between over 500 for diffuse immunoblastic NHL to 14 for low-grade NHL. One-year survival was approximately 30% (i.e. substantially lower than for NHL in the general population). Due to the high risk of other causes of death, tumour grade had little impact on the prognosis of NHL in people with AIDS [40].

The RRs for NHL after the diagnosis of AIDS, estimated by Goedert and colleagues [3] in the same US areas, were 325 around the time of the diagnosis of AIDS and 113 between 4 and 27 months afterwards (Table 2). The risk of HD was 4.4 between 60 and 7 months prior to AIDS, 42.4 in the period when AIDS was diagnosed, and 7.6 between 4 and 27 months after the development of AIDS. Thirteen (87%) of 15 HD tissues examined were positive for Epstein-Barr virus. People with AIDS seemed to be at a somewhat increased risk for multiple myeloma and leukaemia, too (Table 2). Some of these cases might be, however, leukaemoid transformations of AIDS-related NHL.

In Italy, the record linkage carried out by Franceschi and colleagues [39] allowed the estimation of RRs for NHL in people with AIDS aged 15–69 years for a time period that spanned from 1 year prior to and 3.5 years after AIDS diagnosis. Individuals with AIDS had a 228-fold increased risk of NHL (Table 2). The RR was somewhat more elevated in women (348) than in males (209), but similar among i.v.-drug users and other HIV risk groups. In Italian areas covered by a cancer registry, NHL in people with AIDS constituted 9% of all NHLs in men below the age of 50 years in 1985–1989 and 16% in 1990–1992. In women, the corresponding attributable fractions were 3 and 5% [39].

The risk of HD was also investigated in the time period between 60 months prior to and 24 months after AIDS diagnosis [4]. A nearly 10-fold increased risk was found in HIV-positive individuals (RR = 8.9) (Table 2). In contrast with the histological type predominating in HIV-negative young adults (i.e. nodular sclerosis), mixed cellularity type of HD was predominant in people with HIV/AIDS [4,41].

A registry linkage study conducted in Australia [5] found 205 NHL cases (RR = 97; 95% CI 84–112). The RR for HD was 18.3 (95% CI 8.4–34.8), after allowance for differential survival in AIDS patients. The incidence of HD increased significantly close to the time of AIDS diagnosis. Elevated RRs were also found for multiple myeloma (12.1; 95% CI: 2.5–35.4) and leukaemia (5.8; 95% CI: 1.6–14.7) (Table 2).

The comparative analysis of death rates reported in HIV-infected individuals [23] showed that RRs for NHL were 136 in males and 112 in females, and 11.3 and 9.7, respectively, for HD (Table 3). Mortality rates in HIV-seropositive individuals were also increased by approximately 2-fold for leukaemias and 3-fold for multiple myeloma in males.

Among 7629 children diagnosed with AIDS in the US by the end of December 1998, 156 (2%) had cancer as their AIDS-defining illness [42], including 50 Burkitt's lymphomas, 48 immunoblastic lymphomas and 30 PBL. A relatively high incidence of mucosa-associated lymphoid tumours (MALT) was also observed in the pulmonary or gastric mucosa, as well as in the parotid, salivary or lachrymal glands. Since lymphocytic interstitial pneumonitis is a common manifestation of paediatric HIV disease, it is possible that pulmonary mucosa-associated lymphoid tumours and lymphocytic interstitial pneumonitis are related [43].

In the Children's Cancer Group study conducted in the US, Canada and Australia [26], NHL accounted for 65% (42/65) of all tumours reported. Other lymphoid tumours included four acute lymphoblastic leukaemias, two HDs and one acute myeloid leukaemia. RR for NHL in HIV-infected children in the NCI series was 1203 (95% CI: 688–1949). At variance with the spectrum of malignancies in HIV-infected adults, leiomyosarcomas/leiomyomas were also frequent (11/65, 17%).

In the already mentioned linkage study on children with AIDS [27], a high RR (651) for NHL was noted (based on 28 cases). The RR was especially high (7143) for PBL (5 cases). There were also increased risks for HD (RR = 62, 1 case) and for leiomyosarcomas (RR = 1915, 2 cases).

3.4. HIV-associated risk of NHL in developing countries

It is unclear whether the risk for NHL in HIV-seropositive individuals in developing countries is the same as that observed in developed countries, since reliable data have emerged only recently, mainly from Africa.

In Uganda, a population-based cancer registry [29] has shown a stable incidence of NHL (3/100 000) in both sexes up to the early 1990s, but significant increases in 1995–1997 (6/100 000). Burkitt's lymphomas represented more than one third of NHL, but it was virtually restricted to children. In Harare, Zimbabwe

[44], incidence rates of NHL (4/100 000) were stable and relatively low in relation to the relatively high HIV prevalence in the study location.

In Butare, Rwanda, in 1991–1992 [31,45], NHL accounted for 3% of the total cancers and the RR for NHL in HIV-seropositive individuals was estimated to be 12.6 (95% CI: 2.2–54.4) (Table 4). In a case–control study conducted in South Africa by Sitas and colleagues [32], RRs were 5.0 (95% CI: 1.7–9.5) for NHL and 1.4 (95% CI: 0.7–2.8) for HD (Table 4). Since the HIV-associated risk seemed lower than in developed countries, the possibility was raised that early acquisition of Epstein-Barr virus (EBV) in childhood in Africa may impart immunity to subsequent EBV infection, or may lead to a lower lymphoma risk if the virus is reactivated following immunosuppression [47].

The possibility of a lower susceptibility to NHL in African rather than Caucasian populations has also been raised since, for instance in the US, between 1981 and 1994 the proportion of NHL as the AIDS-defining illness was lower in Blacks (1%) than Whites (3%) overall and in major HIV-transmission categories [2]. Most probably, however, the apparent lack of NHL in Africa may be explained by underascertainment and/or earlier deaths from other AIDS-associated causes. Patients with severe immunodeficiency in this part of the world tend to die from infectious diseases before manifesting NHL.

4. Invasive cervical cancer and other HPV-related cancers

4.1. Background

The vast majority of cervical tumours are caused by human papillomavirus (HPV) [47]. Immunosuppression (e.g. in organ recipients) has been shown to be able to enhance the onset and progression of HPV-related tumours [2].

Although invasive cervical cancer (ICC) has been included among the AIDS-defining conditions since January 1993, the contribution of HIV to the development of cervical tumours is still ill quantified [2]. Several studies have documented an increased risk for cervical intraepithelial neoplasm (CIN), the precursor lesion of ICC, among HIV-infected women, but smaller increases have been noted in incidence rates of cervical cancer, in the US [2]. Conversely, an association between HIV and cervical cancer has been found in Italy and France [4,46].

4.2. Invasive cervical cancer as an AIDS-defining illness

Between January 1993 and December 1998, 23 561 women were diagnosed with AIDS in the World Health Organization (WHO) European region (Table 5). ICC was the AIDS-defining illness in 549 (2.3%) of them, and the proportion of AIDS cases with ICC remained substantially stable between 1994 and 1998 (Table 1).

The distribution of AIDS cases in France, Italy, and Spain (i.e. the three European countries mostly affected by the epidemic), according to the presence of ICC at AIDS diagnosis and HIV-exposure category, is shown at Table 5. Overall, the proportion of cases with ICC was higher among women who were i.v. drug users than among those who acquired HIV infection through heterosexual intercourse (3.2 and 1.8%, respectively). Women who were i.v. drug users had more than twice the frequency of ICC as AIDS-defining conditions than heterosexual women ($P<0.001$), in France (3.9 and 1.7%, respectively) and Italy (3.2 and 1.2%), whereas in Spain the frequency ICC as an AIDS-defining illness was similar in heterosexual women (3.7%) and women who were i.v. drug users (3.6%). Sexual promiscuity (e.g. practice of prostitution) [2,48] and/or lack of appropriate screening may explain the more frequent occurrence of ICC among women who were i.v. drug users.

4.3. Risk of HIV-associated cervical cancer in developed countries

In western countries, the few epidemiological studies investigating whether HIV-infected women were at increased risk for ICC were not totally consistent. Since HPV and HIV share the sexual route of transmission, it is obviously difficult to disentangle their respective contribution in the development of ICC [2].

A cohort study conducted among 2141 HIV-infected women in Italy and France [46] showed a significant 13-fold higher risk for ICC. Such risk was particularly elevated among i.v. drug users. A record linkage between the National AIDS Registry and 13 population-based Italian cancer registries yielded a RR of 15.5 (95% CI 4.0–40.1) for ICC in women with HIV/AIDS [4]. RRs for cervical tumours tended to be lower in linkage studies conducted in the US [3]. The risk of *in situ* cervical carcinoma among women with AIDS was low in the early pre-AIDS interval (RR = 0.7), but increased over time to a figure slightly above the incidence in the general population (post-AIDS RR = 1.7). In the already mentioned study from the US [3], a different pattern occurred in the risk of ICC with higher risk in the early pre-AIDS period (RR = 5.4) than in the post-AIDS period (RR = 2.9; CI: 0.7–16.0). Among the different patterns, it may be hypothesised that the lower RR for ICC in the US than in Southern European countries may be partly attributable to differences in cervical cancer screening practices in these two areas.

Mandelblatt and colleagues [49] carried out a meta-analysis of 15 cross-sectional studies published between 1986 and 1998 and which included information on the

presence of cervical neoplasia and infection with HPV and HIV. A significant interaction was found between HPV and HIV strengthening the suggestion that HIV is a cofactor in the association between HPV and cervical neoplasia. This effect seemed to vary according to the level of immune function.

Ahdieh and colleagues [50] evaluated HPV positivity and time to HPV clearance according to HIV serostatus and CD4+ cell count in a cohort of 268 black IDU women (184 HIV-positive) in Baltimore (USA). Of 187 participants who had at least one HPV-positive cervicovaginal lavage specimen, the probability of subsequent HPV-positivity was 48% among HIV-negative women, 79% among HIV-positive women with a CD4+ count $\geqslant$200 cells/μl, and 93% among HIV-positive women with a CD4+ count $<$200 cells/μl. HPV clearance was reduced 71 and 90% in the HIV-positive women with the aforementioned CD4+ cell thresholds, respectively.

Frisch and colleagues [51] studied invasive and *in situ* HPV-associated cancers among 309 365 US patients, of whom 51 760 were women. Risks were significantly increased for cervical (RR = 4.6), vulvar/vaginal (RR = 3.9), anal (RR = 7.8 in females and 60.1 in males), and penile (RR = 6.9) *in situ* carcinomas. For invasive cancer, RRs were 5.4 for the cervix, 5.8 for the vulva/vagina, 6.8 and 37.9, respectively, in females and males, for the anus and 3.7 for the penis. All increases were statistically significant, but the authors noticed that, for invasive cancers, RRs changed little during the 10 years spanning AIDS onset (i.e. ±60 months). The finding by Frish and colleagues [51] suggests: (1) that HPV persistence, but not late-stage cancer invasion, is strongly influenced by the immune status; and (2) that the 'dose–response' relationship between HIV-induced immunosuppression and HPV-related tumours is substantially different from the one observed for KS and NHL.

4.4. HIV and cervical cancer in Africa

Further information on the association between HIV and ICC comes from some African countries where, among female adults, cervical cancer is the commonest neoplasm in the general female population and the prevalence of HIV infection is high [52]. In none of the case–control studies conducted in Rwanda [45], South Africa [32] and Coté d'Ivoire [53] did ICC appear to be clearly associated with HIV infection. In Zambia, neither an upward trend in the incidence of cervical cancer nor changes in age at presentation of the disease were observed subsequent to the spread of HIV infection [54]. RRs for ICC in HIV-infected women compared with HIV-negative women were generally close to unity (Table 4) but a statistically significant excess emerged in South Africa [32]. However, a high background risk of ICC among African women may have, to some extent, blurred the impact of HIV on those incidence trends in the 1980s and 1990s and on the RR estimates in case–control studies.

4.5. Anal cancer

The occurrence of anal cancer has been strongly associated with HPV infection, particularly types 16 and 18 [47], and there is evidence that such HPV types are found more frequently in the anal area in HIV-positive than in HIV-negative homosexuals [55]. Furthermore, it has been shown that homosexual men with a history of receptive anal intercourse are at a higher risk of developing anal cancer than men in the general population [56].

Significant increases in the incidence of anal cancer, however, had begun in the US and Northern Europe decades before the AIDS epidemic [57–59]. Such increases were more apparent in urban than in rural areas and among never-married men than in ever-married men, suggesting that some changes in homosexual behaviours had occurred before the spread of HIV infection.

Most studies showing a positive association between HIV infection and anal cancer risk were carried out in the metropolitan areas of the US (i.e. San Francisco and New York City). A linkage study of AIDS and cancer registries showed anal cancer 14- to 27-fold more common among HIV-infected individuals (depending upon the time since diagnosis of AIDS) than in the general

Table 5
Number of women with invasive cervical cancer (ICC) as AIDS-defining illness, according to HIV-exposure category and country: WHO European region, 1993–1998

	Transmission group				All transmission groups	
	Intravenous drug users		Heterosexuals			
Country	AIDS cases	% with ICC	AIDS cases	% with ICC	AIDS cases	% with ICC
France	1492	3.9	2713	1.7	4905	2.2
Italy	3295	3.2	2417	1.2	6249	2.2
Spain	4151	3.7	2051	3.6	6805	3.4
All Europe	10 723	3.2	10 385	1.8	23 561	2.3

WHO, World Health Organization.

population [60]. Studies from Italy [4] and Africa [30] have failed to demonstrate a clear positive association, or an increase in incidence rates of such neoplasms following the AIDS epidemic [28]. They had, however, low statistical power, chiefly on account of the relatively low proportions of homosexual and bisexual men among HIV-infected individuals.

The already mentioned linkage study from the US [51] showed an overall risk of developing invasive anal cancer of 6.8, based on 7 women with AIDS and 37.9 for men, based on 214 cases with AIDS. However, the risk of anal cancer was not clearly correlated with decreases in CD4+ cell counts.

In summary, increases in the incidence rates of anal cancer preceded the AIDS epidemic, at least in the US, and anal cancer is more common in homosexual and bisexual men than in heterosexual ones, even in the absence of HIV infection. Still, a contribution of HIV-induced immunosuppression to HPV-related malignancies of the anus is well documented [51].

5. Other HIV-related cancers

5.1. Hepatocellular carcinoma

Rising trends of hepatocellular carcinoma in young never-married men in the US in the first years of the AIDS epidemic led to the hypothesis that HIV infection may increase the risk of developing such neoplasms [6]. An increased frequency of hepatocellular carcinoma among individuals with HIV infection may be expected also because such cancers are primarily caused by persistent infection with hepatitis B virus (HBV) and/or with hepatitis C virus (HCV) — two agents sharing the same routes of transmission as HIV. However, later observations did not clearly show a rise in the incidence rates of hepatocellular carcinoma as a consequence of HIV infection in the US [61], Italy [4] or Africa [30].

In a linkage study between AIDS and cancer registries in the US, Goedert and colleagues [3] found, in the interval between 5 years prior to and 27 months after the diagnosis of AIDS, a RR of 13 (non-significant) for hepatocellular carcinoma. A cohort study conducted among HIV-positive men in Italy and France suggested an elevated RR [62], but the observation, however, was based on 2 cases only. Longer follow-up studies will help in elucidating whether uncertain results are attributable to the effects of the long latency of HBV or HCV, even in the presence of HIV, or whether immunosuppression does not increase the risk of hepatocellular carcinoma.

5.2. Lung cancer

Some clinical reports suggested that lung cancer might be more frequent among HIV-positive than HIV-negative individuals [63,64], and a small increase in lung cancer was reported among never-married men in the US [20]. AIDS and cancer registry linkage studies [3–5] showed an approximately 2-fold higher risk of lung cancer in people with HIV/AIDS, but allowance for cigarette smoking as a contributing factor was not possible.

In an Italian/French cohort study, a significant excess of lung cancer emerged among HIV-positive i.v. drug users (RR = 6.2, 95% CI: 1.3–18.1), but not in the other HIV-transmission groups. A similarly elevated RR was found, however, among HIV-negative i.v. drug users (RR = 14.3, 95% CI: 1.4–52.8) [62]. Therefore, it appears that lifestyle habits unrelated to HIV infection in i.v. drug users (i.e. heavy cigarette smoking) are responsible for the reported risk increase.

5.3. Other cancers

Many case-reports and case-series have suggested that various cancers may be increased among HIV-infected individuals or that they may have among them unusual presentations [52]. These cancers include squamous cell carcinoma of the conjunctiva, a rare cancer related to HPV. The evidence of an association with HIV infection is very strong, and it comes from studies in the US [51] and especially African reports [65]. Leiomyosarcoma, an extremely rare tumour apparently linked to EBV infection, has been found to be greatly in excess in HIV-infected children [26] (see Section 3.3). Testicular cancer [3,38] and non-melanoma skin cancers [4] have also been reported to occur with an increased frequency in HIV-infected individuals. For non-melanoma skin cancers the association is consistent with, but much less strong than, the one reported among organ recipients [1]. A 7.5-fold increase risk of brain cancers has emerged, but this may be attributable to the misdiagnosis of brain NHL in the absence of a histological confirmation [4]. Thus, no excess of mortality for brain cancer was observed in the US (RR = 1.1 in men and 1.0 in women) [23].

In Western countries, individuals with HIV infection show an overall cancer risk (excluding KS and NHL) approximately 2-fold higher than that registered in the general population of the same age and gender [3,4].

6. Antiretroviral therapy and incidence of HIV-associated malignancies

Between the end of 1995 and 1996, antiretroviral agents that inhibit HIV protease became available for clinical use [66]. HAART rapidly became a standard care for HIV infection in developed countries [67], with more than 60% of HIV-positive cases having used it as therapy since 1995 in the US [67,68]. Combination of protease inhibitors with other agents, mainly with

nucleoside analogues, has substantially modified the natural history and clinical manifestation of HIV infection and prolonged life expectancy. The incidence of opportunistic infections and AIDS mortality has consistently declined after HAART, both in the US [69] and in Europe [70].

Time trends in the incidence of HIV-related neoplasms (and other conditions) has been investigated by comparing the pre-HAART period with the years when the new therapies had been introduced. A reduction in KS incidence cases has been reported by several authors using different study designs [68,71,72]. The more convincing evidence came from a pooled-analysis conducted by the International Collaboration on HIV and Cancer [73], using cancer incidence data from 23 prospective studies that included 47 936 HIV-seropositive individuals from North America, Europe and Australia. For the period between 1992 and 1999, 2702 incident cancers were reported in 138 148 person-years (p-y) of observation. The overall adjusted incidence of KS declined from 15.2 per 1000 p-y in 1992–1996 to 4.9 in 1997–1999 with a rate-ratio of 0.32 [73]. The ratio of the KS incidence rates in 1997–1999 compared with 1992–1996 did not vary significantly between cohorts and the decline was seen in each single cohort examined. Presently, the KS decrease suggests either a direct effect of HAART on HHV8 replication or an indirect effect through immune recovery.

The effect of HAART on the incidence of NHL was less consistent [68,71,72,74]. Pooling data from 23 cohort studies [73], the incidence rates for NHL declined significantly after the spread of HAART from 6.2 per 1,000 p-y to 3.6 (RR = 0.58). Significant differences, however, emerged when the analysis was conducted separately among the three types of NHL. The RRs were 0.42 for PBL (the type of NHL which is associated with the severest level of immunodepression), 0.57 for immunoblastic, and 1.18 for Burkitt's lymphoma.

Jones and colleagues [72] compared HD incidence in 7 cases treated with HAART and 15 untreated ones. Differences and temporal trends are not significant even if, in the first semester of 1997 they showed an HD incidence of 4.7/1000 p-y in persons treated with HAART versus 0.7/1000 p-y among untreated persons. However, a larger database including Jones' study [73] found no statistically significant trend in incidence rates for HD.

Different levels of CD4+ counts associated with different tumours may be important in order to explain the different effect of HAART on KS and NHL. The median CD4+ count at systemic NHL diagnosis in 1994–1997 (61 cells/μl for immunoblastic lymphoma and 177 for Burkitt's lymphoma) was more than 2-fold higher than the median CD4+ count at KS (30) and PBL diagnosis (24) [72]. Thus, the partial immune reconstitution induced by HAART may be sufficient to prevent KS and PBL, but not other NHL types [69].

No clear change in the incidence of ICC (RR = 1.87) and all other malignancies combined (RR = 0.96) were associated with the use of HAART [73]. Some data [50] suggest that at least the risk of carcinoma *in situ* of the cervix may be crucially dependent upon the degree of immunosuppression.

7. Conclusions

AIDS has substantially changed the epidemiology of cancers most closely associated with immunosuppression. KS has become one of the commonest cancers in Africa and has substantially increased in many developed countries. As a percentage of the AIDS-defining illnesses, however, KS has shown a tendency to decrease since the late 1980s. Reasons for this are not fully understood, but they include the relative decline in the proportion of homosexual and bisexual men, particularly the most promiscuous ones, among AIDS cases.

Conversely, after many years of substantial stability, NHL as percentage of AIDS-defining illnesses has shown a tendency to increase in Western Europe since 1995. It has already been suggested that improvements in therapy of HIV which decrease the burden of opportunistic infections and prolong life expectancies may lead to an increase in HIV-associated NHL [2]. The favourable impact of HAART may thus have smaller effect upon NHL than other AIDS-defining illnesses including KS [75,76].

Registry-linkage studies have allowed estimates of RR of HIV-associated neoplasms on large, non-selected population with HIV/AIDS. RRs for KS were above 1000 in adults with HIV/AIDS in all studies from developed countries [7] while those for NHL ranged between 14, for low-grade NHL, and over 300, for high-grade NHL [40]. For HD, the RR was approximately 10. In Africa, with a HHV8 seropositivity above 50% in some areas [13] and an elevated KS incidence, some strategies (preventive and therapeutic) to prevent or curtail the disease are urgently needed.

The definition of the actual impact of the HIV infection on ICC and, possibly, anal cancer has important implications, both at individual and at public health levels, since there are effective screening programmes for anogenital tumours [2]. The role of HIV on ICC risk varies according to the population group (e.g. i.v. drug users) [51], geographical area, and/or success of the screening programmes to interrupt the transition from *in situ* to ICC in HIV-infected women. Possible excesses of other types of cancer, such as non-melanomatous skin cancer, leukaemia and multiple myeloma, need to be confirmed.

Even if it is well established that immunosuppression predisposes an individual to the development of a variety of cancers, the specific mechanism(s) need to be

better elucidated. There is, for instance, strong evidence [3,4,22] that, the excess of some cancers (e.g. cervix) may develop earlier than KS and NHL, thus suggesting different cancers can develop at different levels of immune impairment.

As therapies improve the survival of AIDS patients, the cumulative risk of developing, or dying from cancer, is likely to increase. Large and well designed population-based studies will be essential in order to better define the spectrum of AIDS-associated malignancies and the most effective strategies for screening and treatment.

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References

1. Kinlen L. In Immunologic factors, inclunding AIDS. Schottenfeld D, Fraumeni JF, eds. *Cancer Epidemiology and Prevention*, 2nd edn. New York, Oxford University Press, 1996, 532–545.
2. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Human Immunodeficiency Viruses and Human T-Cell Lymphotropic Viruses. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, vol. 67. Lyon, IARC, 1996.
3. Goedert JJ, Coté TR, Virgo P, *et al*. Spectrum of AIDS-associated malignant disorders. *Lancet* 1998, **351**, 1833–1839.
4. Franceschi S, Dal Maso L, Arniani S, *et al*. Risk of cancer other than Kaposi's sarcoma and non-Hodgkin's lymphoma in persons with AIDS in Italy. *Br J Cancer* 1998, **78**, 966–970.
5. Grulich AE, Wan X, Law MG, Coates M, Kaldor JM. Risk of cancer in people with AIDS. *AIDS* 1999, **13**, 839–843.
6. Biggar RJ, Horm J, Goedert JJ, Melbye M. Cancer in a group at risk of acquired immunodeficiency syndrome (AIDS) through 1984. *Am J Epidemiol* 1987, **126**, 578–586.
7. Biggar RJ, Rosenberg PS, Coté T. Kaposi's sarcoma and non-Hodgkin's lymphoma following the diagnosis of AIDS. *Int J Cancer* 1996, **68**, 754–758.
8. Franceschi S, Geddes M. Epidemiology of classic Kaposi's sarcoma, with special reference to Mediterranean population. *Tumori* 1995, **81**, 308–314.
9. Franceschi S, Dal Maso L, Lo Re A, Serraino D, La Vecchia C. Trends of Kaposi's sarcoma at AIDS diagnosis in Europe and the United States, 1987–1994. *Br J Cancer* 1997, **76**, 114–117.
10. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? *Lancet* 1990, **335**, 123–128.
11. Chang Y, Cesarman E, Pessin MS. Identification of herpesvirus-like DNA sequences in AIDS-associated Kaposi's sarcoma. *Science* 1994, **265**, 1865–1869.
12. Boshoff C. Kaposi's sarcoma associated herpesvirus. In Newton R, Beral V, Weiss RA, eds. *Infections and Human Cancer*. Cancer Surveys 1999, vol. 33, 157–190.
13. Olsen SJ, Chang Y, Moore PS, Biggar RJ, Melbye M. Increasing Kaposi's sarcoma-associated herpesvirus seroprevalence with age in a highly Kaposi's sarcoma endemic region, Zambia in 1985. *AIDS* 1998, **12**, 1921–1925.
14. Melbye M, Cook PM, Hjalgrim H, *et al*. Risk factors for Kaposi's-sarcoma-associated herpesvirus (KSHV/HHV-8) seropositivity in a cohort of homosexual men, 1981–1996. *Int J Cancer* 1998, **77**, 543–548.
15. Sitas F, Newton R, Boshoff C. Increasing probability of mother-to-child transmission of HHV-8 with increasing maternal antibody titer for HHV-8. *N Engl J Med* 1999, **340**, 1923.
16. Plancoulaine S, Abel L, van Beveren M, *et al*. Human herpervirus 8 transmission from mother to child and between siblings in an endemic population. *Lancet* 2000, **356**, 1062–1065.
17. Serraino D, Locatelli M, Songini M, *et al*. Human herpes virus-8 infection among pregnant women and their children: results from the Sardinia-IDDM Study 2. *Int J Cancer* 2001, **91**, 740–741.
18. ENAADS European Centre for the Epidemiological Monitoring of AIDS. *HIV/AIDS Surveillance in Europe*. End-year report 1999, no. 62. Saint-Maurice, France, 2000.
19. Dal Maso L, Franceschi S, Negri E, Serraino D, La Vecchia C, Ancelle-Park RA. Trends of AIDS incidence in Europe and the United States. *Soz Präventivmed* 1995, **40**, 239–265.
20. Rabkin CS, Yellin F. Cancer incidence in a population with a high prevalence of infection with human immunodeficiency virus type I. *J Natl Cancer Inst* 1994, **86**, 1711–1716.
21. Koblin BA, Hessol NA, Zauber AG, *et al*. Increased incidence of cancer among homosexual men, New York City and San Francisco, 1978–1990. *Am J Epidemiol* 1996, **144**, 916–923.
22. Lyter DW, Bryant J, Thackeray R, Rinaldo CR, Kingsley LA. Incidence of human immunodeficiency virus-related and non-related malignancies in a large cohort of homosexual men. *J Clin Oncol* 1995, **13**, 2540–2546.
23. Selik RM, Rabkin CS. Cancer death rates associated with human immunodeficiency virus infection in the United States. *J Natl Cancer Inst* 1998, **90**, 1300–1302.
24. Serraino D, Franceschi S. Kaposi's sarcoma in children with AIDS in Europe and the United States. *Eur J Cancer* 1996, **32A**, 650–651.
25. Dal Maso L, Parazzini F, Lo Re A, Favero A, La Vecchia C, Franceschi S. Paediatric AIDS incidence in Europe and the USA, 1985–96. *J Epidemiol Biostat* 1999, **4**, 75–81.
26. Granovsky MO, Mueller BU, Nicholson HS, Rosenberg PS, Rabkin CS. Cancer in human immunodeficiency virus-infected children: a case series from the Children's Cancer Group and the National Cancer Institute. *J Clin Oncol* 1998, **16**, 1729–1735.
27. Biggar RJ, Frisch M, Goedert JJ. Risk of cancer in children with AIDS. *JAMA* 2000, **284**, 205–209.
28. Bassett MT, Chokunonga E, Mauchaza B, Levy L, Ferlay J, Parkin DM. Cancer in the African population of Harare, Zimbabwe, 1990–1992. *Int J Cancer* 1995, **63**, 29–36.
29. Parkin DM, Wabinga H, Nambooze S, Wabwire-Mangen F. AIDS-related cancers in Africa: maturation of the epidemic in Uganda. *AIDS* 1999, **13**, 2563–2570.
30. Wabinga HR, Parkin DM, Wabwire-Mangen F, Kugerwa JW. Cancer in Kampala, Uganda, in 1989–91: changes in incidence in the era of AIDS. *Int J Cancer* 1993, **54**, 26–36.
31. Newton R, Ngilimana P-J, Grulich A, *et al*. Cancer in Rwanda. *Int J Cancer* 1996, **66**, 75–81.
32. Sitas F, Pacella-Norman R, Carrara H, *et al*. The spectrum of HIV-1 related cancers in South Africa. *Int J Cancer* 2000, **88**, 489–492.

33. Gao S-J, Kingsley L, Li M, *et al*. KSHV antibodies among Americans, Italians and Ugandas with and without Kaposi's sarcoma. *Nat Med* 1996, **2**, 925–928.
34. Mayama S, Cuevas LE, Sheldon J, *et al*. Prevalence and transmission of Kaposi's sarcoma-associated herpesvirus (human herpesvirus 8) in Ugandan children and adolescents. *Int J Cancer* 1998, **77**, 817–820.
35. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *Epstein-Barr Virus and Kaposi's Sarcoma Herpesvirus/Human Herpesvirus 8*. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol. 70. Lyon, IARC, 1997.
36. Franceschi S, Dal Maso L, La Vecchia C. Advance in the epidemiology of HIV-associated non-Hodgkin's lymphoma and other lymphoid neoplasms. *Int J Cancer* 1999, **83**, 481–485.
37. Tirelli U, Spina M, Gaidano G, Vaccher E, Franceschi S, Carbone A. Epidemiology, biological and clinical features of HIV-related lymphomas in the era of highly active antiretroviral therapy. *AIDS* 2000, **14**, 1675–1688.
38. Lyter DW, Bryant J, Thackeray R, *et al*. Non-AIDS defining malignancies in the multicenter AIDS cohort study (MACS), 1984–96. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, **17**, A13 (abstr).
39. Franceschi S, Dal Maso L, Orengo MA, Tagliabue G, Zambon P, Rezza G. Non-Hodgkin lymphoma among people with AIDS: incidence and attributable fraction in Italy. *J Acquir Immune Defic Syndr* 2000, **23,** A26 (abstract).
40. Coté TR, Biggar RJ, Rosenberg P, *et al*. Non-Hodgkin's lymphoma among people with AIDS: incidence, presentation and public health burden. *Int J Cancer* 1997, **73**, 645–650.
41. Serraino D, Pezzotti P, Dorrucci M, Alliegro MB, Sinicco A, Rezza G. Cancer incidence in a cohort of human immunodeficiency virus seroconverters. *Cancer* 1997, **79**, 1004–1008.
42. Mueller BU. Cancer in children infected with the human immunodeficiency virus. *Oncologist* 1999, **4**, 309–317.
43. Kingma DW, Weiss A, Sorbara L, Raffeld M, Mueller BU, Jaffe ES. Is lymphocytic interstitial pneumonitis an early stage of MALT lymphoma in HIV-infected pediatric patients? *J Acquir Immune Defic Syndr Hum Retrovirol* 1997, **14**, A54 (abstr).
44. Chokunonga E, Levy LM, Bassett MT, *et al*. Aids and cancer in Africa: the evolving epidemic in Zimbabwe. *AIDS* 1999, **13**, 2583–2588.
45. Newton R, Grulich A, Beral V, *et al*. Cancer and HIV infection in Rwanda. *Lancet* 1995, **i**, 1378.
46. Serraino D, Carrieri P, Pradier C, *et al*. Risk of invasive cervical cancer among women with, or at risk for, HIV infection. *Int J Cancer* 1999, **82**, 334–337.
47. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. *IARC Monographs on the Evaluation of Carcinogenic Risks for Humans from the Human Papillomaviruses*, vol. 64. Lyon, IARC, 1995.
48. Parazzini F, Chatenoud L, La Vecchia C, Negri E, Franceschi S, Bolis G. Determinants of risk of invasive cervical cancer in young women. *Br J Cancer* 1998, **77**, 838–841.
49. Mandelblatt JS, Kanetsky P, Eggert L, Gold K. Is HIV infection a cofactor for cervical squamous cell neoplasia? *Cancer Epidemiol Biomarkers Prev* 1999, **8**, 97–106.
50. Ahdieh L, Muñoz A, Vlahov D, Trimble CL, Timpson LA, Shah K. Cervical neoplasia and repeated positivity of human papillomavirus infection in human immunodeficiency virus-seropositive and-seronegative women. *Am J Epidemiol* 2000, **151**, 1148–1157.
51. Frisch M, Biggar RJ, Goedert JJ. Human papillomavirus-associated cancers in patients with human immunodeficiency virus infection and acquired immunodeficiency syndrome. *J Natl Cancer Inst* 2000, **92**, 1500–1510.
52. Newton R, Beral V, Weiss RA. Human immunodeficiency virus infection and cancer. In Newton R, Beral V, Weiss RA, eds. *Infections and Human Cancer*. Cancer Surveys vol. 33, 1999, 237–262.
53. La Ruche G, You B, Mensah-Ado I, *et al*. Human papillomavirus and human immunodeficiency virus infections: relation with cervical dysplasia–neoplasia in African women. *Int J Cancer* 1998, **76**, 480–486.
54. Patil P, Elem B, Zumla A. Pattern of adult malignancies in Zambia (1980–1989) in the light of the human immunodeficiency virus type 1 epidemic. *J Trop Med Hyg* 1995, **98**, 281–284.
55. Breese PL, Judson FN, Penley KA, Douglas Jr JM. Anal human papillomavirus infection among homosexual and bisexual men: prevalence of type-specific infection and association with human immunodeficiency virus. *Sex Transm Dis* 1995, **22**, 7–14.
56. Palefsky JM. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. *AIDS* 1994, **8**, 283–295.
57. Goldman S, Glimelius B, Nilsson B, Pahlman L. Incidence of anal epidermoid carcinoma in Sweden, 1970–1984. *Acta Chir Scand* 1989, **155**, 191–197.
58. Frisch M, Melbye M, Moller H. Trends in incidence of anal cancer in Denmark. *BMJ* 1993, **306**, 419–422.
59. Melbye M, Coté TR, Kessler L, Gail M, Biggar RJ. High incidence of anal cancer among AIDS patients. *Lancet* 1994, **343**, 636–639.
60. Melbye M, Rabkin C, Frisch M, Biggar RJ. Changing patterns of anal cancer incidence in the United States, 1940–1989. *Am J Epidemiol* 1994, **139**, 772–780.
61. Rabkin CS, Biggar RJ, Horm JW. Increasing incidence of cancers associated with the human immunodeficiency virus epidemic. *Int J Cancer* 1991, **47**, 692–696.
62. Serraino D, Boschini A, Carrieri P, *et al*. Cancer risk among men with, or at risk for, HIV infection in southern Europe. *AIDS* 2000, **14**, 553–559.
63. Tirelli U, Spina M, Sandri S, *et al*. Lung carcinoma in 36 patients with human immunodeficiency virus infection. *Cancer* 2000, **88**, 563–569.
64. Parker MS, Leveno DM, Campbell TJ, Worrell JA, Carozza SE. AIDS-related bronchogenic carcinoma: fact or fiction? *Chest* 1998, **113**, 154–161.
65. Newton R, Ziegler J, Mbidde E, *et al*. HIV and cancer in Kampala, Uganda. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, **17**, A12 (abstr).
66. Sparano JA, Anand K, Desai J, Mitnick RJ, Kalkut GE, Hanau LH. Effect of highly active antiretroviral therapy on the incidence of HIV-associated malignancies at an urban medical center. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl.), S18–S22.
67. Moore RD, Chiasson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS* 1999, **13**, 1933–1942.
68. Jacobson LP, Yamashita TE, Detels R, *et al*. Impact of potent antiretroviral therapy on the incidence of Kaposi's sarcoma and non-Hodgkin's lymphomas among HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S34–S41.
69. Palella FJ, Delaney KM, Moorman A, *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1998, **338**, 853–860.
70. Mocroft A, Vella S, Benfield TL, *et al*. Changing patterns of mortality across Europe in patients infected with HIV-1. *Lancet* 1998, **352**, 1725–1730.
71. Rabkin CS, Testa MA, Huang J, Von Roenn JH. Kaposi's sarcoma and non-Hodgkin's lymphoma incidence trends in AIDS Clinical Trial Group study participants. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S31–S33.
72. Jones JL, Hanson DL, Dworkin MS, Ward JW, Jaffe HW. Effect of antiretroviral therapy on recent trends in selected cancers among HIV-infected persons. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S11–S17.

73. International Collaboration on HIV and Cancer. Highly active antiretroviral therapy and incidence of cancer in human immunodeficiency virus-infected adults. *J Natl Cancer Inst* 2000, **92**, 1823–1830.
74. Buchbinder SP, Holmberg SD, Scheer S, Colfax G, O'Malley P, Vittinghoff E. Combination antiretroviral therapy and incidence of AIDS-related malignancies. *J Acquir Immune Defic Syndr* 1999, **21**(Suppl. 1), S23–S26.
75. Pezzotti P, Dal Maso L, Serraino D, Franceschi S, Rezza G. Has the spectrum of AIDS-defining illnesses been changing since the introduction of new treatments and combination of treatments? *J Acquir Immune Defic Syndr* 1999, **20**, 515–516.
76. Pezzotti P, Serraino D, Rezza G, *et al*. The spectrum of AIDS-defining diseases: temporal trends in Italy prior to the use of highly active anti-retroviral therapies, 1982–1996. *Int J Epidemiol* 1999, **28**, 975–981.